Doctoral Dissertation

Studies on Insertion of C_1 Unit into Carbon–Carbon/Carbon–Halogen Bond: Lewis Acid-Promoted Carbon Chain Elongation of Benzylic Ethers, Acetates, Acetals, or Halides with Diazo Compounds

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Preface and Acknowledgements

The study of this doctoral dissertation was carried out under the guidance of Prof. Dr. Makoto Yasuda at the Department of Applied Chemistry, Graduated School of Engineering, Osaka University from October 2019 to September 2022. The thesis describes the development of Lewis acid-catalyzed insertion of a C_1 unit into carbon–carbon or carbon–halogen bond.

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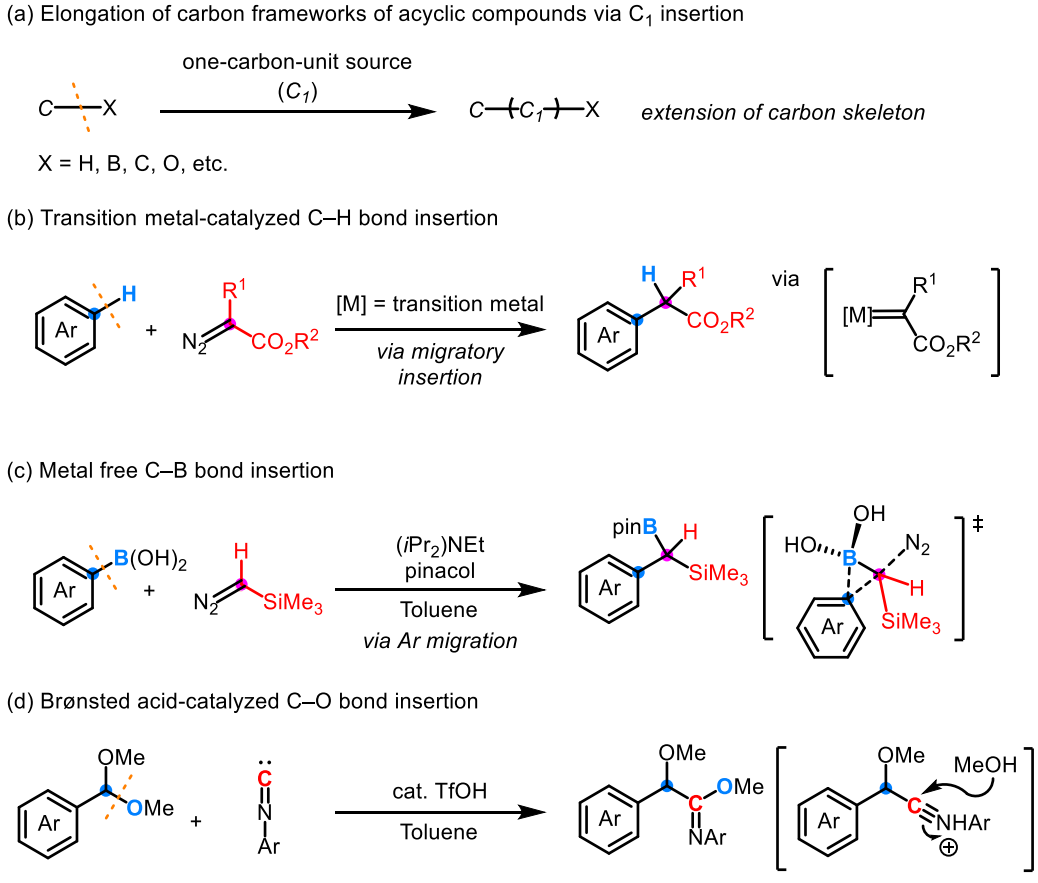
Contents

General Introduction

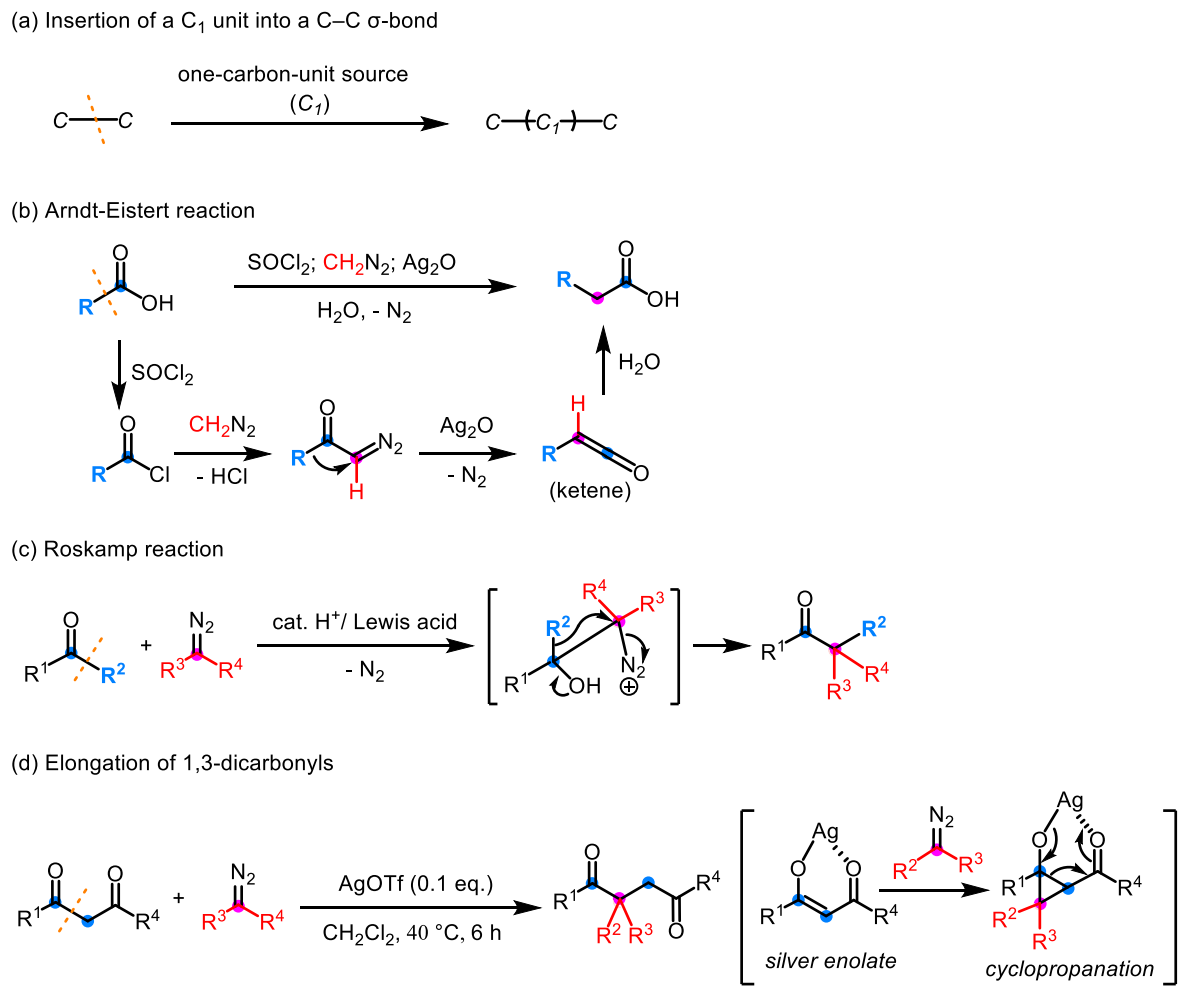
An insertion of one-carbon-unit (C_1 unit) into a chemical bond is a powerful method to elongate carbon frameworks and diversify the structural complexity of organic molecules (Scheme 1a).[1] This efficient method is accompanied with the introduction of functional groups and provides opportunities to streamline the synthetic routes of natural products in pharmaceutical chemistry and agrochemistry. Many C_1 sources have been widely applied in this field, such as CO,[2a] ylides,[2b-d] isocyanides,[1g] and *N*-tosylhydrazones.[2e,f] Among which the diazo compounds have been recognized as the most efficient one due to their diversity and ready availability.[2e,f,3] The insertion into C–H bond using metal carbenoids generated from transition metal catalysts and diazo compound has been well established (Scheme 1b).[1e,i] Ley's group[1f] reported an insertion of diazo compounds into C–B bonds of boronic acids to prepare elongated organoboron compounds (Scheme 1c). Although not an example of using diazo compounds, Chatani and Tobisu developed an insertion of isocyanides into C–O bonds of acetals catalyzed by a Brønsted acid (Scheme 1d).[1g]



Scheme 1. Insertion of C_1 unit into C–H, C–B, and C–O bonds

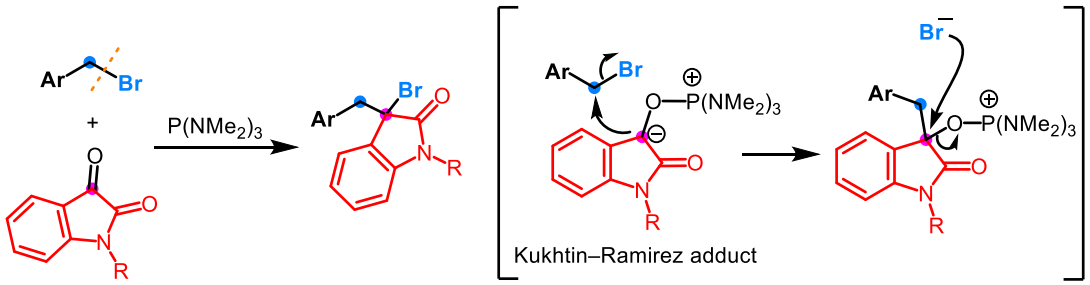
The insertion of a C_1 unit into a C–C σ-bond can realize the effective construction of complex carbon skeletons.[4] Many ring-expansion processes via the insertion of a C_1 unit have been well established using promoters such as transition metal catalysts and Lewis acids due to the release of ring strain in cyclic compounds working as a driving force for C–C bond cleavage.[1a,b] However, the insertion of C_1 unit into C–

C bonds of acyclic compounds has remained a challenging issue (Scheme 2a). The multi-step homologation process of carboxylic acid using CH_2N_2, $SOCl_2$, Ag_2O, and H_2O is known as Arndt-Eistert reaction.[4a] This process includes an insertion of CH_2N_2 into a C–C bond and Wolff rearrangement of in situ generated ketene (Scheme 2b). Various types of Roskamp reaction have been developed to achieve the elongation of ketones or aldehydes in recent years (Scheme 2c).[1d,4b–e] Bi's group[1c] established an elongation of 1,3-dicarbonyl compounds via silver carbenoids generated from AgOTf and diazo compounds (Scheme 2d). In this reaction, silver-catalyzed enolate formation and cyclopropanation of diazo compound achieved C_1 insertion into C–C σ-bond. As mentioned above, it is essential that a carbonyl group works as a foothold and affords a driving force by re-establishment of the carbonyl group. It obviously limits the diversity of applicable substrates and has hampered progress in this field.



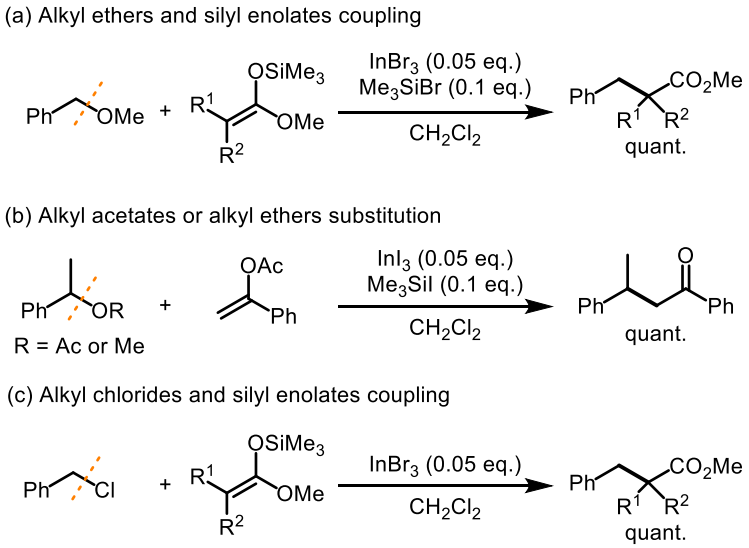
Scheme 2. Insertion of C_1 unit into C–C σ-bond

The insertion of a C_1 unit into a carbon–halogen bond is also challenging and remains underdeveloped. There is only one report for the reaction of isatins with benzylic bromides or chlorides (Scheme 3).[5] $P(NMe_2)_3$ adds to isatin to generate a Kukhtin–Ramirez adduct. Then, S_N2 reaction of this adduct with benzylic bromide and subsequent nucleophilic attack of Br^- to complete C–Br bond insertion. However, the generality of this reaction is quite narrow.



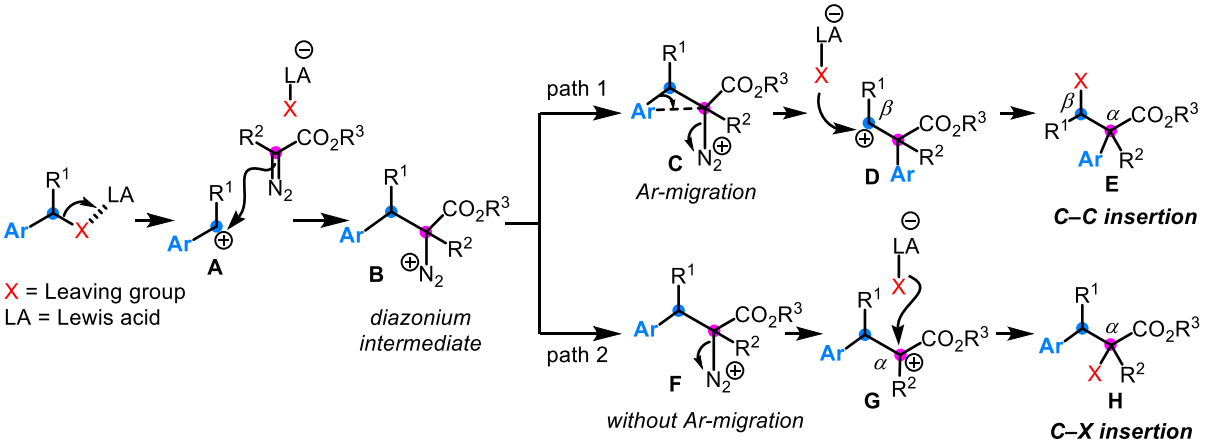
Scheme 3. Insertion of C_1 unit into C–Br bond

In previous works of Yasuda's group, indium-catalyzed nucleophilic substitutions of alkyl ethers, alkyl acetates, and alkyl chlorides with organosilicon reagents or alkenyl acetates have been developed (Scheme 4).[6,7] The indium catalysts present appropriate Lewis acidity to abstract oxygen-containing groups or halogen groups from benzylic ethers, acetates, or halides to generate the corresponding carbocation intermediates, respectively.



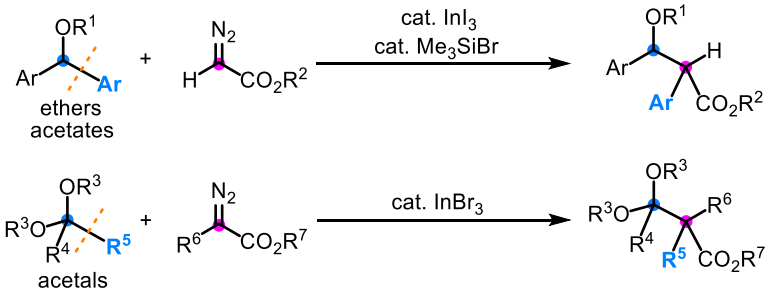
Scheme 4. Our works: coupling or nucleophilic substitution via indium-catalyzed carbocation formation

Based on these researches, I suggested a working hypothesis for a novel C–C and C–X bond insertions in this study (Scheme 5). A Lewis acid abstracts a leaving group (X) to form a carbocation intermediate **A**. Then, the nucleophilic addition of a diazo compound to cation **A** gives diazonium intermediate **B**. In path 1, N_2 elimination and Ar-migration affords carbocation **D**, followed by the nucleophilic attack of a leaving group to cation **D** generates C–C bond insertion product **E**. If the Ar-migration is inhibited (path 2), the leaving group is installed at *α*-position of a carbonyl group to give a C–X bond insertion product **H**. Therefore, the control of Ar-migration process is a key point.



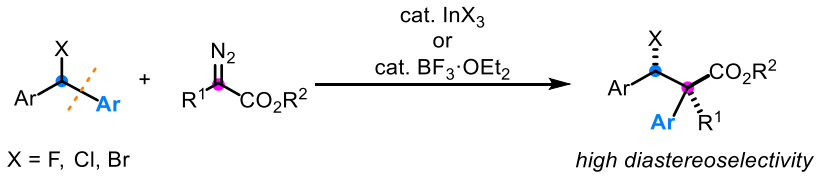
Scheme 5. Working hypothesis for Lewis acid-catalyzed insertion of diazo compound into C–C or C–X bond

Chapter 1 describes an elongation of benzylic acetates and ethers catalyzed by a combined Lewis acid InI_3/Me_3SiBr and an elongation of acetals catalyzed by $InBr_3$ via the insertion of diazo compounds into C–C σ-bonds (Scheme 6). Various types of benzylic ethers, acetates, acetals, and diazo compounds were applicable. In these elongations, the abstraction of alkoxy or acetoxy group by an indium catalyst, the electrophilic addition of a carbocation or an oxonium ion to diazoesters followed by the rearrangement of aryl group proceeds to provide a cation intermediate. The leaving group is re-captured by the carbocation intermediate to furnish the elongated products.



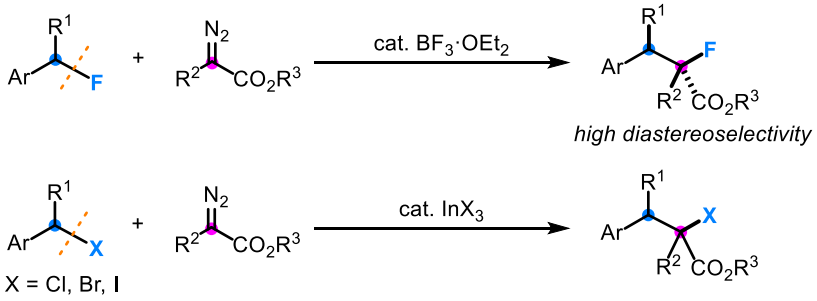
Scheme 6. Insertion of diazoesters into C–C bond of benzylic ethers, acetates, and acetals

Chapter 2 describes a Lewis acid-catalyzed elongation of benzylic halides via the insertion of diazoesters into C–C σ-bonds (Scheme 7). This reaction proceeds via C–X (X = F, Cl, Br) bond cleavage and C–X bond re-formation at the benzylic position. *α*,*β*-Diaryl-*β*-haloesters were obtained with a high level of diastereoselectivity. DFT study revealed that the diastereoselectivity was determined by the aryl migration step. The high functional compatibility of the present elongation demonstrated its potential for use in the synthesis of pharmaceutical building blocks.



Scheme 7. Insertion of diazoesters into C–C bond of benzylic halides

Chapter 3 describes a BF_3-catalyzed insertion of diazoesters into C−F bonds of benzylic fluorides (Scheme 8). This elongation exhibited high level of diastereoselectivity, and various benzylic fluorides and diazoesters were applicable to afford *α*,*β*-diaryl-*α*-fluoroesters. DFT study suggested that the abstraction of F^- by BF_3 and the re-formation of a C−F bond mediated by BF_4^- led to the unique catalytic activity of BF_3. In contrast to the C–C bond insertion mentioned in previous chapters, this reaction proceeds without aryl rearrangement and enables the re-capture of F^- at *α*-position of a carbonyl group. Moreover, the present strategy was successfully applied to synthesize other organic halides via C–Cl, C–Br, and C–I bond insertions.



Scheme 8. Insertion of diazoesters into C–F, C–Cl, C–Br, and C–I bonds of benzylic halides

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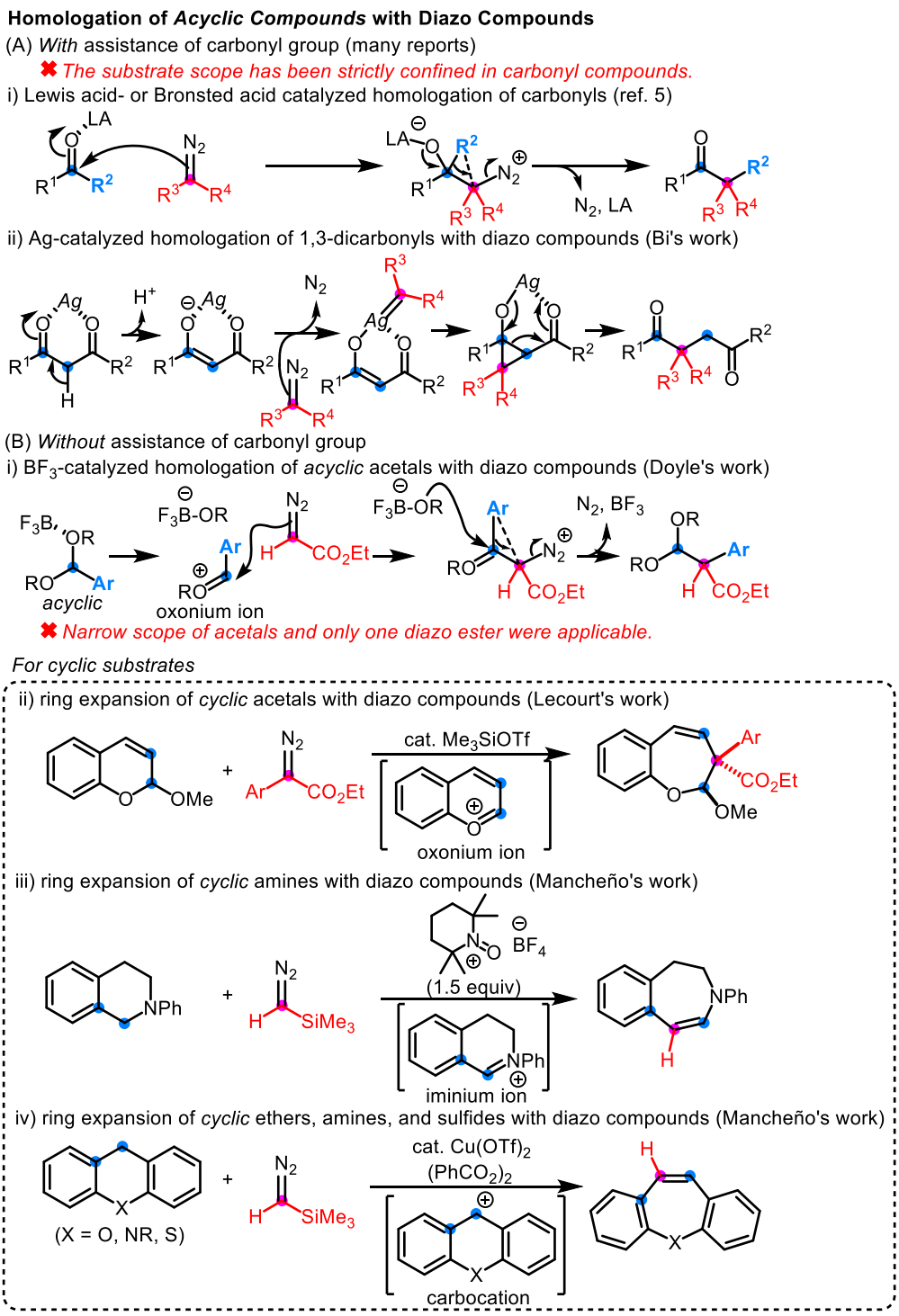
Chapter 1: Homologation of Alkyl Acetates, Alkyl Ethers, Acetals, and Ketals by Formal Insertion of Diazo Compounds into a Carbon–Carbon Bond

1-1. Introduction

Homologation of organic compounds by selective one-carbon-insertion into C–C σ-bonds is a powerful tool that is used to construct carbon frameworks with two new carbon–carbon bonds that form simultaneously.[1–3] Diazo compounds have been recognized as the most efficient one-carbon source due to their diversity and ready availability.[4] Many ring-expansion processes via one-carbon insertions have been well established using promoters such as transition metal catalysts and Lewis acids[1] due to the release of ring strain in cyclic compounds working as a driving force for C–C bond cleavage. By contrast, insertion into the carbon chains of acyclic compounds has remained a challenging issue, and reported systems are limited to homologation of either aldehydes or ketones (Scheme 1A). Most reports are categorized as either Lewis acid or Brønsted acid mediated reactions (Schemes 1A-i), wherein the addition of a diazo compound to a carbonyl group followed by 1,2-rearrangement of a carbon substituent (R^2) gives the homologated product.[5] Bi and co-workers established the Ag-catalyzed reaction of diazo compounds with 1,3-dicarbonyls, in which cyclopropanation between enolate isomers of 1,3-dicarbonyls and silver carbenoids followed by retro-aldol fragmentation completes the formal insertion (Scheme 1A-ii).[1c,d,6] It is essential in both reaction systems that a carbonyl group works as a foothold and re-establishment of the carbonyl group is a driving force, which obviously limits the diversity of applicable substrates and has hampered progress in this field. On the other hand, the BF_3-catalyzed homologation of acyclic acetals is the only one report detailing the system without the assistance of a carbonyl group, which was authored by Doyle in 1983 (Scheme 1B-i).[7] After the addition of a diazoester to an oxonium ion, the reforming of a C–O σ-bond by the release of RO group from BF_3 leads to the rearrangement of a carbon substituent and N_2 extrusion. The scope of acetals, however, was narrow and only simple ethyl diazoacetate was applicable. As far as ring expansion of cyclic substrates, there are only a few reports. Lecourt developed the Me_3SiOTf-catalyzed ring expansion of cyclic acetals via the mechanism similar to Doyle's system.[8] Recently, Mancheño reported the synthesis of 3-benzazepines from tetrahydroisoquinolines under oxidative conditions,[9] wherein the generation of iminium ions via oxidation, the addition of Me_3SiCHN_2, and the rearrangement occur. Mancheño also established the ring expansion of xanthenes, acridanes, and thioxanthenes via the addition of Me_3SiCHN_2 to carbocations generated by the C–H oxidation of the benzylic position.[10] The reaction mechanisms involving cationic intermediates like oxonium ions, iminium ions, and carbocations as mentioned above could offer the promise of a system that would function without the assistance of a carbonyl group. The homologation of acyclic substrates, however, has been limited to Doyle's system.

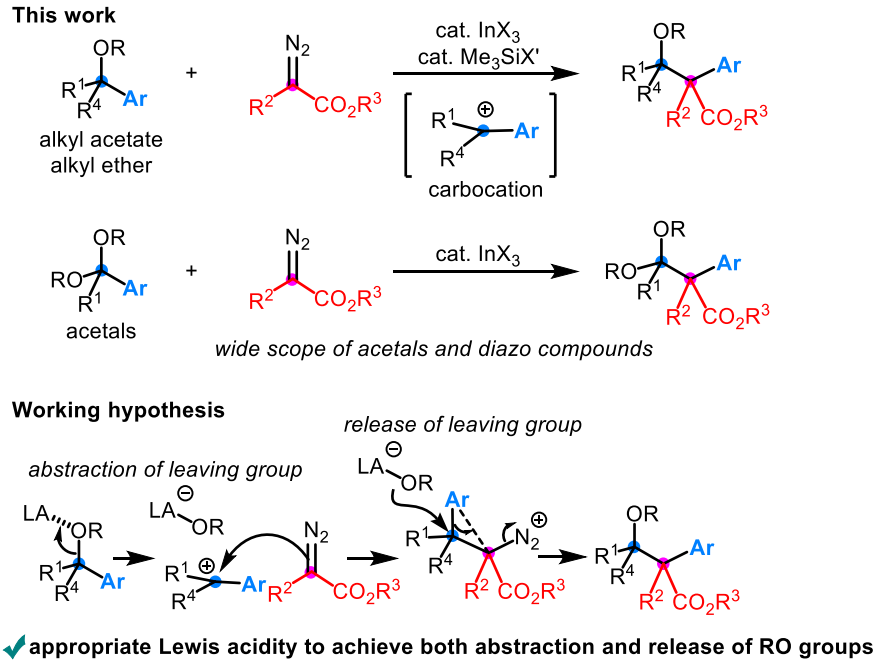
Herein, we report the InI_3/Me_3SiBr-catalyzed homologation of acyclic alcohol derivatives with diazoesters (Scheme 2). This is the first report of the homologation of alkyl acetates and alkyl ethers. In addition, it has been discovered that $InBr_3$ effectively catalyzes homologation of acetals and ketals. Scopes of acetals, ketals, and diazoesters were remarkably wide. The working hypothesis for homologation of



Scheme 1. Homologation of acyclic compounds by selective one-carbon-insertion into C–C σ-bonds

alcohol derivatives is illustrated in Scheme 2. A Lewis acid abstracts RO group to provide a carbocation, which reacts with a diazo compound. Then, N_2-extrusion, rearrangement of the carbon substituent, and re-composition of the C–OR σ-bond completes the homologation. The present homologation would be much more difficult than that of acetals reported by Doyle. The generation of carbocations requires a stronger Lewis acid than that offered by oxonium ions, but a stronger Lewis acidity would disturb the release of RO groups. For the homologation of alcohol derivatives, therefore, it would be necessary for a Lewis acid to

exercise conflicted abilities that could generate carbocations via the abstraction of poor leaving groups (OR), and would release the OR groups under certain circumstances. Actually, the use of $BF_3{\cdot}OEt_2$ in the reaction of benzhydryl acetate (**1a**) with diazoester **2a** resulted in a low yield (Table 1, entry 1).



Scheme 2. Working hypothesis for homologation of alkyl acetates and ethers with diazoesters via carbocation intermediate

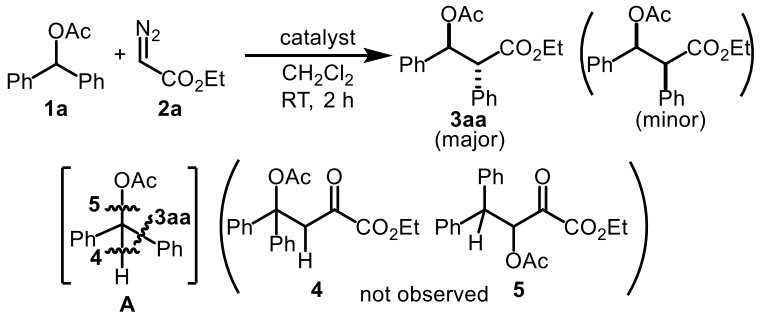
1-2. Results and Discussion

We discovered that a combination of the Lewis acids of indium trihalides with silyl halides exhibited an efficient catalytic activity in the direct substitutions of HO, AcO, and Me_3SiO groups.[11] The combined Lewis acid catalyst activates oxygen-containing substrates to give carbocation intermediates and regenerates as catalysts via dissociation from the oxygen-containing functional groups. When investigating the reaction of **1a** with **2a**, the combination of InI_3 with Me_3SiBr achieved the desired homologation to give **3aa** in 67% yield with a high level of diastereoselectivity (90:10) (Table 1, entry 2). The relative stereochemistry of the major isomer, ethyl (2*R*,3*S*)/(2*S*,3*R*)-3-acetoxy-1-phenyl-3-phenylpropanoate (**3aa**), was determined via X-ray crystallographic analysis.[12] Undesired products **4** and **5**, which would be the result of formal insertion into C–H and C–O bonds, respectively, were not observed. The sole use of InI_3 or Me_3SiBr was ineffective (entries 3 and 4). A smaller amount of catalyst (10 mol% of InI_3 and 10 mol% of Me_3SiBr) led to a poor result (entry 5). Other combinations between indium halides and trimethylsilyl halides resulted in lower yields than that of InI_3/Me_3SiBr (entries 6–9). Other group 13 Lewis acids such as AlI_3 and GaI_3 exhibited a much lower level of catalytic activity than InI_3 (entries 10 and 11).

The scope of alkyl acetates was investigated using diazoester **2b** and a InI_3/Me_3SiBr catalyst (Table 2). Methylsubstituted benzhydryl acetate **1b** gave the corresponding homologation product **3bb** in 49% yield with a high level of diastereoselectivity (Table 2, entry 1). The electronwithdrawing effect of the Cl group completely retarded the present reaction (entry 2). The homologation of dinaphthyl-substituted methyl acetate **1d** occurred in 27% yield (entry 3). The sluggish result of phenethyl acetate **1e** suggests the

importance of the stabilization of a carbocation intermediate by two aryl groups on the reaction progress (entry 4). Benzhydryl ether **1f** was also applicable to this homologation to afford the desired product **3af**, although the yield was low (entry 5). Triphenylmethyl ether underwent homologation and afforded a high yield without the use of Me_3SiBr (entry 6).

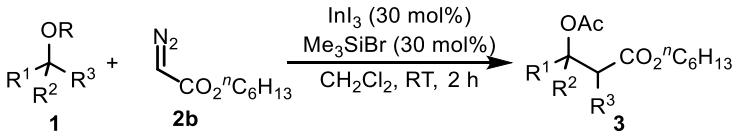
Table 1. Effect of catalysts in the homologation of alkyl acetate **1a** with diazoester **2a**[a].



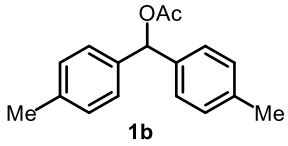
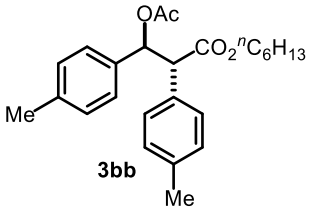
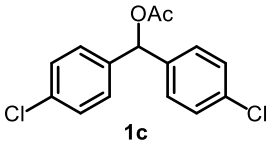
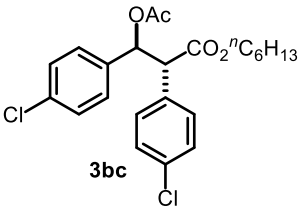
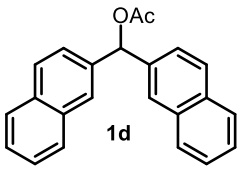
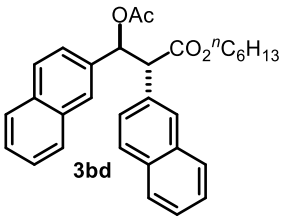
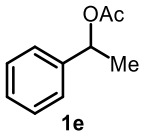
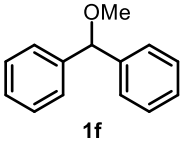
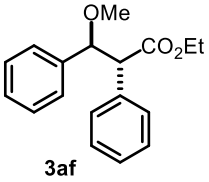
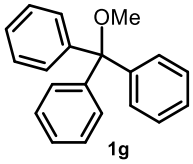
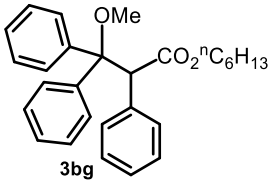
entry	catalyst (mol%)	yield of **3aa**	d.r.
1	$BF_3{\cdot}OEt_2$ (30)	27%	83:17
2	InI_3 (30) + Me_3SiBr (30)	67%	90:10
3	InI_3 (30)	8%	-
4	Me_3SiBr (30)	0%	-
5	InI_3 (10) + Me_3SiBr (10)	2%	-
6	InI_3 (30) + Me_3SiCl (30)	20%	85:15
7	InI_3 (30) + Me_3SiI (30)	25%	86:14
8	$InBr_3$ (30) + Me_3SiBr (30)	55%	88:12
9	$InCl_3$ (30) + Me_3SiBr (30)	11%	81:19
10	AlI_3 (30) + Me_3SiBr (30)	0%	-
11	GaI_3 (30) + Me_3SiBr (30)	2%	-

[a]**1a** (0.5 mmol), **2a** (1.0 mmol), CH_2Cl_2 (1 mL), room temperature, 2 h. The yields and dr values of **3aa** were measured by ^1H NMR analysis of the crude mixture.

Table 2. Scope of alkyl acetates and ethers in the homologation with diazoester **2b** using InI_3/Me_3SiBr catalyst[a].



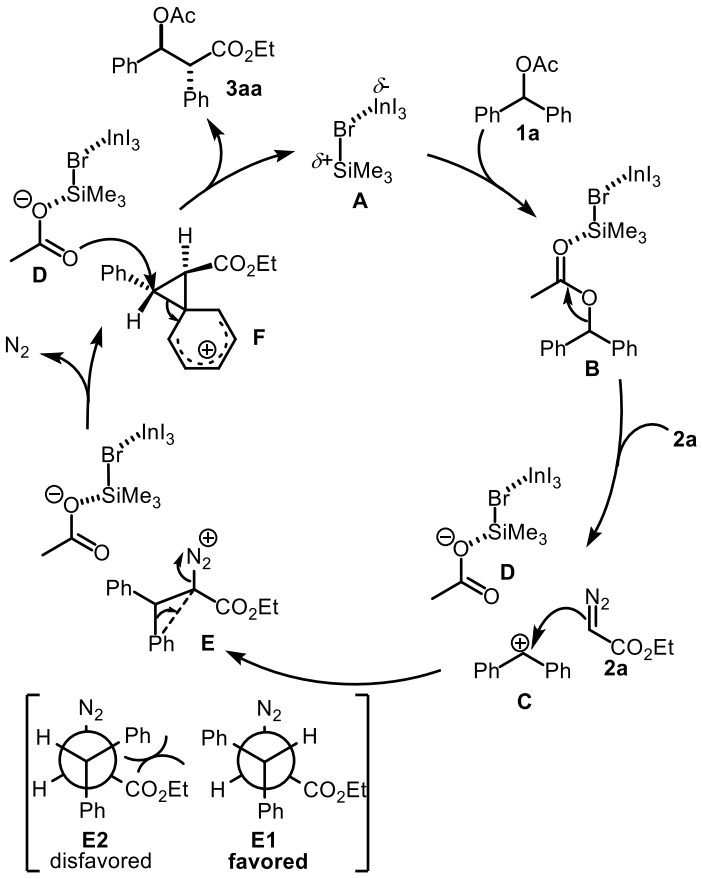
1 **2b** **3**

entry	alcohol derivatives **1**	product **3**	yield
1	 **1b**	 **3bb**	49% (83:17)
2	 **1c**	 **3bc**	0%
3	 **1d**	 **3bd**	27% (87:13)
4	 **1e**	no reaction	-
5	 **1f**	 **3af**	18% (93:7)
6	 **1g**	 **3bg**	89%

[a]**1** (0.5 mmol), **2b** (1.0 mmol), InI_3 (0.15 mmol), Me_3SiBr (0.15 mmol), CH_2Cl_2 (1 mL), room temperature, 2 h. The yield and diastereselectivity of **3** were measured by ^1H NMR analysis of the crude mixture. A diastereomeric ratio is shown in parentheses. The isolated yields were shown in the experimental section. [b]Diazoester **2a** instead of **2b** was used. [c]Without Me_3SiBr.

A plausible mechanism for the homologation of alkyl acetate **1a** with diazoester **2a** is illustrated in Scheme 3. First, the combined Lewis acid **A** is formed, in which the Br atom of Me_3SiBr coordinates to InI_3 and the Lewis acidity on the Si atom is enhanced.[11,13] A carbonyl oxygen atom of **1a** interacts with the Si

center of **A**, and then the abstraction of an AcO group leads to carbocation **C** and InI_3-Me_3SiBr-OAc complex **D**. The electrophilic addition of cation **C** to **2a** gives intermediate **E**. The migration of a Ph group with inversion of the configuration at the diazonium carbon and denitrogenation occurs in concert to afford phenonium intermediate **F**. The AcO^- trapped in **D** attacks at the α-carbon atom of the Ph group in **F**, which inverts its configuration, and combined Lewis acid **A** releases AcO^- to yield homologated product **3aa**. The diastereoselectivity is determined at the migration step in **E**, in which the conformation of **E1** with less steric repulsion than **E2** gives the major diastereomer of **3aa**.

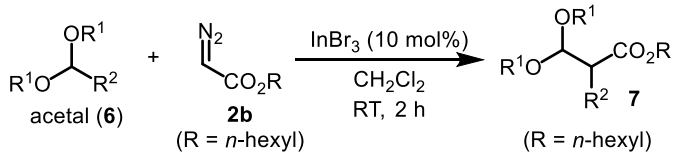


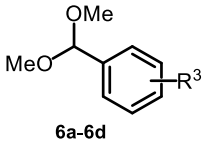
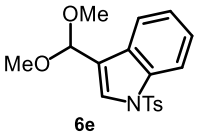
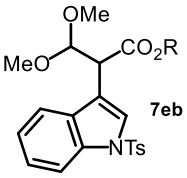
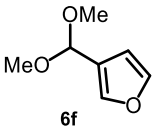
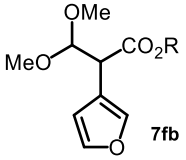
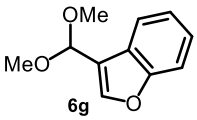
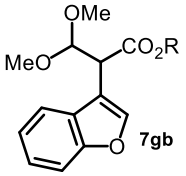
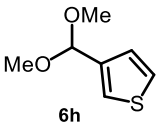
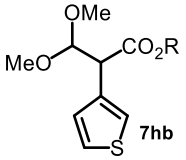
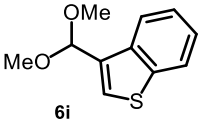
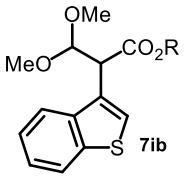
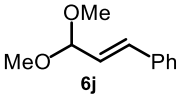
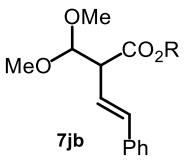
Scheme 3. Proposed reaction mechanism of homologation of **1a** with **2a** catalyzed by InI_3/Me_3SiBr

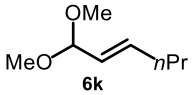
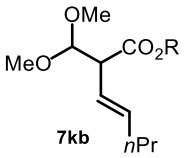
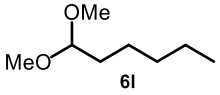
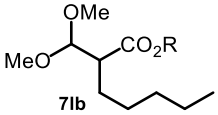
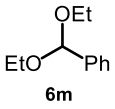
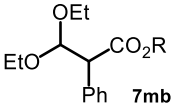
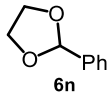
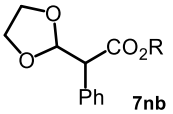
Next, we shifted our attention to acetals and ketals. As far as acyclic substrates, Doyle's method[7] is the only one report and applicable substrates are limited to a few types of acetals, acetophenone dimethyl ketal, and ethyl diazoacetate. When the optimal conditions for homologation of alkyl acetates with InI_3 (30 mol%) and Me_3SiBr (30 mol%) were applied to benzaldehyde dimethyl acetal (**6a**), the desired homologation occurred (Table 3, entry 1). However, **7ab** was produced in only 26% yield, and unidentified products were observed. After further investigation, the milder conditions with $InBr_3$ (10 mol%) led to an excellent yield of **7ab** (entry 2).[14–16] Electron-rich and -deficient arylaldehyde acetals[6b–d] smoothly gave high yields (entries 3–5). Heteroaromatic aldehyde acetals underwent the present homologation to provide the corresponding indolyl-, furyl-, benzofuranyl-, thienyl-, and benzothienyl-substituted compounds in high yields (entries 6–10). α,β-Unsaturated aldehyde acetals **6j** and **6k** were also applicable to the present reaction system, and the stereochemistry of the alkene moieties in **6j** and **6k** was maintained (entries 11 and 12).

Unfortunately, the homologation of alkyl aldehyde acetal **6l** did not proceed (entry 13). Homologations using diethyl acetal **6m** (entry 14) and cyclic acetal **6n** (entry 15), which are more stable than dimethyl **6a**, were also accomplished via the optimal conditions.

Table 3. $InBr_3$-catalyzed homologation of acetals **6** with diazoester **2b**[a].

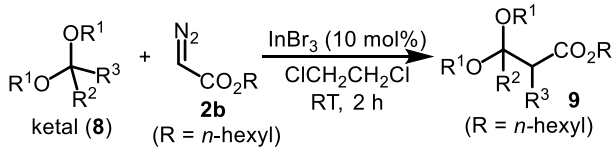


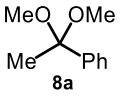
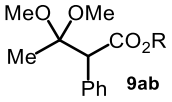
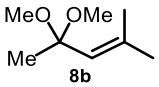
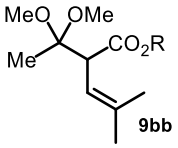
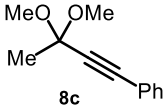
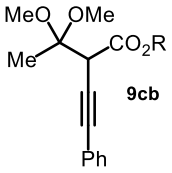
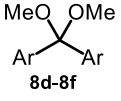
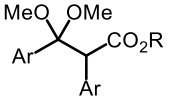
entry	acetal **6**	product **7**	yield (%)
1[b]		R^3 = H (**7ab**)	26
2		H (**7ab**)	99
3		4-Me (**7bb**)	93
4		2-Me (**7cb**)	99
5		4-Cl (**7db**)	89
6			78
7			71
8			65
9			71
10			80
11			66

12	 **6k**	 **7kb**	67
13	 **6l**	 **7lb**	0
14	 **6m**	 **7mb**	99
15	 **6n**	 **7nb**	79

[a]Reaction conditions: **6** (0.5 mmol), **2b** (0.6 mmol), $InBr_3$ (0.05 mmol), CH_2Cl_2 (1 mL), RT, 2 h. The yields of product **7** were measured by ^1H NMR analysis of the crude mixture. The isolated yields are shown in the experimental section. [b]InI_3 (0.15 mmol) and Me_3SiBr (0.15 mmol) were used instead of $InBr_3$ with **2b** (1 mmol).

Table 4. $InBr_3$-catalyzed homologation of ketals **8** with diazoester **2ba**[a].



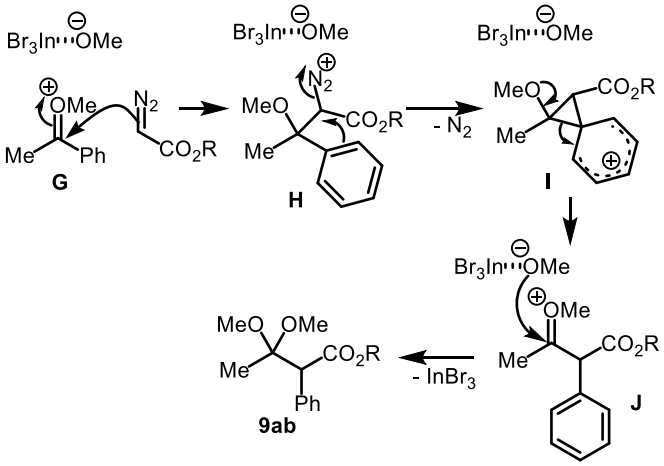
entry	ketal **8**	product **9**	yield (%)
1	 **8a**	 **9ab**	91
2	 **8b**	 **9bb**	39
3	 **8c**	 **9cb**	77
4[b]	 **8d-8f**		Ar = Ph (**9db**)	65
5[b]			4-MeC_6H_4 (**9eb**)	63
6[b]			4-ClC_6H_4 (**9fb**)	14

[a]**8** (0.5 mmol), **2b** (1.0 mmol), $InBr_3$ (0.05 mmol), $ClCH_2CH_2Cl$ (1 mL), room temperature, 6 h. The yields of product **9** were measured by ^1H NMR analysis of the crude mixture. The isolated yields were shown in the experimental section. [b]InI_3 (30 mol%) and Me_3SiBr (30 mol%) were used instead of $InBr_3$.

As shown in Table 4, many types of ketals were also applicable. In the reactions using alkyl aryl ketone ketal **8a** and alkenyl alkyl ketone ketal **8b**, a one-carbon insertion into $(MeO)_2C–Csp^2$ bonds selectively

occurred (Table 4, entries 1 and 2). The $(MeO)_2C$–Csp bond of **8c** underwent insertion to selectively give the homologated product **9cb** (entry 3). Benzophenone dimethyl ketal **8d** and its analogues **8e** and **8f** reacted with diazoester **2b** in the presence of InI_3 (30 mol%) and Me_3SiBr (30 mol%), instead of $InBr_3$, to afford the homologated products **9db**, **9eb**, and **9fb** (entries 4–6). The low yield of **9fb** suggests that an electron withdrawing group decreases the reactivity of ketals toward homologation (entry 6).

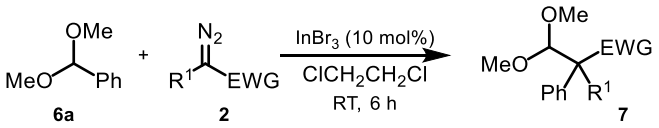
The regioselectivity of the formal insertion of **2b** into a C–C bond in unsymmetrical ketal **8a** is explained in Scheme 4. $InBr_3$ abstracts MeO group from **8a** to give oxonium ion **G** and, the electrophilic addition of **G** to **2b** affords diazonium **H**. Then, the migration of Ph group via the phenonium intermediate **I** occurs in prior to Me group, and at last **9ab** is selectively generated. The present selectivity is the same as that of homologation of **8a** reported by Doyle.[7] The migration magnitude is similar to that in other rearrangement such as semipinacol rearrangement.[17] In fact, alkenyl and alkynyl groups favorably migrate rather than alkyl groups (Table 4, entries 2 and 3).

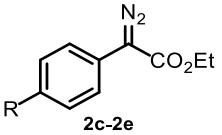
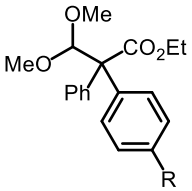
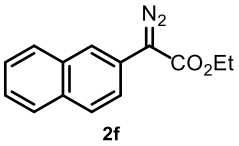
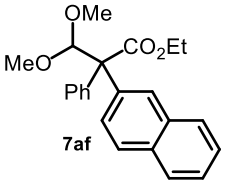
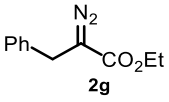
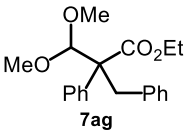
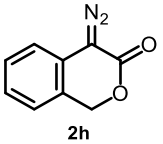
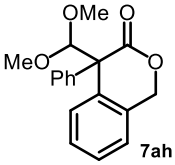
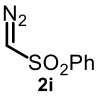
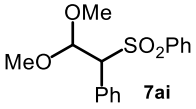


Scheme 4. Proposed reaction mechanism of homologation of **8a** with **2b** catalyzed by $InBr_3$

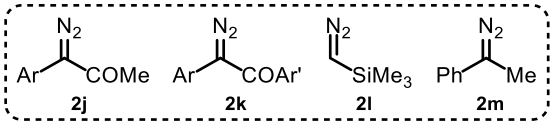
The scope of diazoesters **2** in the homologation of acetal **6a** was then investigated (Table 5). *α*-Aryl *α*-diazoesters **2c**–**f** were feasible substrates, giving moderate to high yields of the corresponding products (Table 5, entries 1–4). The reaction using *α*-alkyl *α*-diazoester **2g** resulted in a low yield of the desired product **7ag** because considerable competitive insertions into C–H bonds occurred (entry 5). Using cyclic substrate **2h** allowed access to the cyclic homologated product **7ah** (entry 6). Various *α*-diazo ketones like **2j** and **2k**, which would possess lower nucleophilicity than *α*-diazoesters, were examined, but meaningful results were not obtained. Also electron-rich diazo compounds **2l** and **2m** were not applicable because of the rapid decomposition under the present reaction conditions. On the other hand, *α*-diazo sulfone **2i** was applicable to the present homologation (entry 7).

Table 5. Scope of diazoesters in $InBr_3$-catalyzed homologation of acetal **6a**[a].



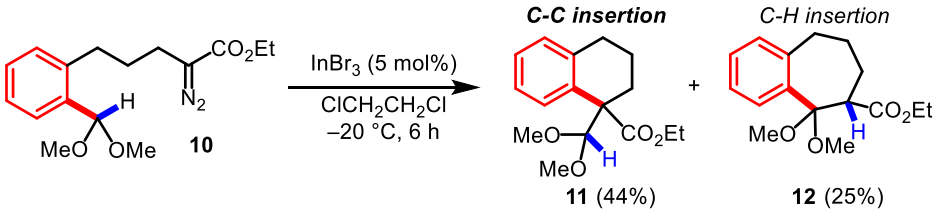
entry	diazo compound **2**	product **7**	yield (%)
1		 R = H (**7ac**)	92
2		Me (**7ad**)	68
3		Cl (**7ae**)	94
4			47
5			40
6[b]			69
7[c]			53

inapplicable diazo compounds



[a]**6a** (0.5 mmol), 2 (1.0 mmol), $InBr_3$ (0.05 mmol), $ClCH_2CH_2Cl$ (1 mL), room temperature, 2 h. The yields of product **7** were measured by ^1H NMR analysis of the crude mixture. The isolated yields were shown in the experimental section. [b]40 °C, 12 h. [c]0 °C, overnight.

Cyclization by the present one-carbon insertion into a C–C σ-bond was demonstrated (Scheme 5). When substrate **10** possessing both dimethyl acetal and diazoester moieties was exposed to a catalytic amount of $InBr_3$, the desired intramolecular C–C insertion mainly occurred to furnish product **11** in 44% yield. Although the C–H insertion of product **12** was competitively obtained in 25% yield, products **11** and **12** were easily separated via silica gel column chromatography.



Scheme 5. Cyclization by one-carbon-insertion into C–C σ-bond

1-3. Conclusion

In summary, homologation of alkyl acetates and alkyl ethers catalyzed by the combination of InI_3 and Me_3SiBr as well as homologation of acetals and ketals catalyzed by $InBr_3$ have been accomplished via the formal insertion of diazoesters into carbon–carbon σ-bonds. Various types of alkyl acetates, alkyl ethers, acetals, ketals, and diazoesters were applicable. In these homologations, the abstraction of a leaving group by an indium catalyst and the electrophilic addition of carbocations or oxonium ions to diazoesters is followed by the rearrangement of carbon substituents, which provides the corresponding cation intermediates. The leaving group kept by the Lewis acid bonds to carbocation intermediates to furnish the homologated products. A key point of the present study must be the appropriate level of Lewis acidity shown by the indium catalysts, which allowed both the abstraction and the release of leaving groups.

1-4. Experimental Section

General Information

NMR spectra were recorded on a JEOL-AL400 and a JEOL-ECS400 spectrometers (400 MHz for 1H and 100 MHz for 13C). Chemical shifts were reported in ppm on the δ scale relative to TMS (δ = 0 for ^{1}H NMR) and residual $CDCl_3$ (δ = 77.0 for ^{13}C NMR) as an internal reference. Coupling constants (J) are quoted in hertz (Hz). Standard abbreviations are used to designate splitting patterns. New compounds were characterized by ^{1}H, ^{13}C, ^{13}C off-resonance techniques, COSY, HMQC, and HMBC. IR spectra were recorded on a JASCO FT/IR-6200 Fourier transform IR spectrophotometer. Column chromatographies were performed with silica gel. Purification by recycle HPLC was performed on SHIMADZU recycle HPLC system (SPD-20A, RID-10A, DGU-20A, LC-6AD, and FCV-20H2) and Japan Analytical Industry Co. (NEXT recycling preparative HPLC). Reactions were carried out in anhydrous solvents under N_2 atmosphere, unless otherwise stated. Reagents were purchased from Aldrich or Tokyo Chemical Industry Co., Ltd. (TCI), FUJIFILM Wako Pure Co., Ltd., and used after purification by distillation or used without purification for solid substrates. X-ray diffraction analysis was carried out by Rigaku XtaLAB Synergy with Hypix-6000HE.

Materials

Compounds **1a**,[18] **1c**,[19] **1e**,[20] **1f**,[21] **1g**,[22] **2a**,[23] **2b**,[24] **2c**,[25] **2d**,[26] **2e**,[27] **2f**,[28] **2g**,[29] **2h**,[30] **2i**,[31] **6a**,[32] **6b**,[33] **6c**,[34] **6d**,[35] **6e**,[36] **6f**,[37] **6i**,[38] **6j**,[38] **6k**,[32] **6m**,[39] **6n**,[40] **8a**,[41] **8b**,[42] **8d**,[43] **8e**,[44] **8f**[45] were known compounds.

Homologation of alkyl acetates and alkyl ethers with diazoester 2b; General Procedure A

To a solution of InI_3 (0.15 mmol, 30 mol%), *n*-hexyl diazoacetate **2b** (1.0 mmol, 2 equiv), and an alkyl acetate or an alkyl ether **1** (0.5 mmol, 1 equiv) in CH_2Cl_2 (1.0 mL) was added Me_3SiBr (0.15 mmol, 30 mol%) at RT (25 °C) under N_2 atmosphere. The resultant solution was stirred at this temperature for 2 h. Then, the reaction was quenched with sat. aq $NaHCO_3$ (5 mL) and the mixture was extracted with $CHCl_3$ (3 x 10 mL). The collected organic layers were dried ($MgSO_4$). The volatiles were evaporated and the residue was purified by silica gel column chromatography to give the desired product.

Homologation of acetals 6 with diazoester 2b; General Procedure B

To a solution of $InBr_3$ (0.05 mmol, 10 mol%), *n*-hexyl diazoacetate **2b** (0.6 mmol, 1.2 equiv) in CH_2Cl_2 (1.0 mL) was added the respective acetal **6** (0.5 mmol, 1 equiv) at 0 °C under N_2 atmosphere. The resultant solution was stirred at 0 °C for 5 min and then warmed to RT for 2 h. Then, the reaction was quenched with sat. aq $NaHCO_3$ (5 mL) and the mixture was extracted with $CHCl_3$ (3 x 10 mL). The collected organic layers were dried ($MgSO_4$). The volatiles were evaporated and the residue was purified by silica gel column chromatography to give the desired product.

Homologation of acetal 6a with diazoesters 2c–i; General Procedure C

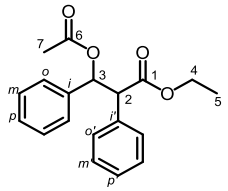
To a solution of $InBr_3$ (0.05 mmol, 10 mol%) and a diazoester **2** (1.0 mmol, 2 equiv) in 1,2-dichloroethane (1.0 mL) was added benzaldehyde dimethyl acetal (**6a**; 0.5 mmol, 1 equiv) at 0 °C under N_2 atmosphere. The resultant solution was stirred at 0 °C for 5 min and then warmed to RT for 6 h. Then, the reaction was quenched with Et_3N (0.5 mL) and sat. aq $NaHCO_3$ (5 mL), and the mixture was extracted with $CHCl_3$ (3 x 10 mL). The collected organic layers were dried ($MgSO_4$). The volatiles were evaporated and the residue was purified by silica gel column chromatography to give the desired product.

Homologation of ketals 8 with diazoester 2b; General Procedure D

Procedure D1 with the combination catalyst of InI_3/Me_3SiBr: To a solution of InI_3 (0.15 mmol, 30 mol%), *n*-hexyl diazoacetate **2b** (1.0 mmol, 2 equiv), and a ketal **8d**–**f** (0.5 mmol, 1 equiv) in 1,2-dichloroethane (1.0 mL) was added Me_3SiBr (0.15 mmol, 30 mol%) at 0 °C under N_2 atmosphere. The resultant solution was stirred at 0 °C for 5 min and then warmed to RT for 6 h. Then, the reaction was quenched with Et_3N (0.5 mL) and sat. aq $NaHCO_3$ (5 mL), and extracted with $CHCl_3$ (3 x 10 mL). The collected organic layers were dried ($MgSO_4$). The volatiles were evaporated and the residue was purified by silica gel column chromatography to give the desired product.

Procedure D2 with $InBr_3$: To a solution of $InBr_3$ (0.05 mmol, 10 mol%), *n*-hexyl diazoacetate (**2b**; 1.0 mmol, 2 equiv) in 1,2-dichloroethane (1.0 mL) was added the corresponding ketal **8** (0.5 mmol, 1 equiv) at 0 °C under N_2 atmosphere. The resultant solution was stirred at 0 °C for 5 min and warmed to RT for 6 h. Then, the reaction was quenched with Et_3N (0.5 mL) and sat. aq $NaHCO_3$ (5 mL) and extracted with CHCl3 (3 x 10 mL). The collected organic layers were dried ($MgSO_4$). The solvent was evaporated and the residue was purified by silica gel column chromatography to give the desired product.

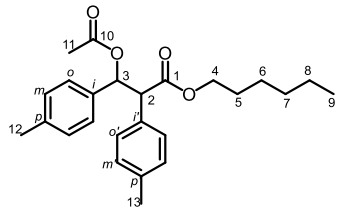
Ethyl 3-acetoxy-2,3-diphenylpropanoate (3aa)



General procedure A with benzhydryl acetate **1a** (0.500 mmol, 0.113 g), ethyl diazoacetate **2a** (1.00 mmol, 0.114 g), InI_3 (0.152 mmol, 0.075 g), and Me_3SiBr (0.150 mmol, 22 μL). The yield and the diastereoselectivity in the crude product were determined by ^1H NMR using 1,1,2,2-tetrachloroethene as an internal standard (67%, dr = 90:10). The title compound was obtained after silica gel column chromatography (hexane/ethyl acetate = 95:5, column length 11 cm) as a colorless solid (major diastereomer, *dr* >99:1, 0.0875 g, 56%).

^1H NMR: (400 MHz, $CDCl_3$) 7.15-7.10 (m, 10H, Ar), 6.24 (d, J = 11.1 Hz, 1H, 3-H), 4.22-4.17 (m, 2H, 4-H_2), 4.04 (d, J = 11.1 Hz, 1H, 2-H), 2.04 (s, 3H, 7-H_3), 1.25 (t, J = 7.2 Hz, 3H, 5-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 171.3 (s, C-1), 169.4 (s, C-6), 137.4 (s), 133.8 (s), 128.7, 128.4, 128.1, 128.0, 127.7, 127.2, 77.2 (d, C-3), 61.1 (t, C-4), 57.8 (d, C-2), 21.0 (q, C-7), 14.1 (q, C-5); mp. 100–103 °C; IR: (KBr) 1743 (C=O) cm^{-1}; HRMS: (ESI+) Calculated ($C_{19}H_{20}O_4Na$) 335.1254 ($[M+Na]^+$) Found: 335.1247

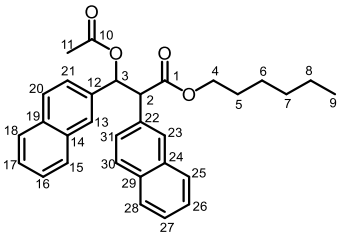
Hexyl 3-acetoxy-2,3-di-*p*-tolylpropanoate (3bb)



General procedure A with 4,4'-dimethylbenzhydryl acetate **1b** (0.500 mmol, 0.127 g), *n*-hexyl diazoacetate **2b** (0.969 mmol, 0.165 g), InI_3 (0.152 mmol, 0.075 g), and Me_3SiBr (0.150 mmol, 22 μL). The yield and the diastereoselectivity in the crude product were determined by ^1H NMR using 1,1,2,2-tetrachloroethene as an internal standard (49%, dr = 87:13). The title compound was obtained after silica gel column chromatography (hexane/ethyl acetate = 95:5, column length 11 cm) as a colorless oil (major diastereomer, *dr* >99:1, 0.0640 g, 32%).

^1H NMR: (400 MHz, $CDCl_3$) 7.05-6.95 (m, 8H, Ar), 6.23 (d, J = 11.1 Hz, 1H, 3-H), 4.14-4.07 (m, 2H, 4-H_2), 4.03 (d, J = 11.1 Hz, 1H, 2-H), 2.22 (s, 6H, Ar-Me x 2), 2.01 (s, 3H, 11-H_3), 1.62-1.58 (m, 2H, 5-H_2), 1.30-1.26 (m, 6H, 6-H_2, 7-H_2 and 8-H_2), 0.88-0.85 (m, 3H, 9-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 171.6 (s, C-1), 169.4 (s, C-10), 137.7 (s), 137.3 (s), 134.5 (s), 130.9 (s), 129.1, 128.8, 128.6, 127.3, 76.9 (d, C-3), 65.1 (t, C-4), 57.3 (d, C-2), 31.3 (t, C-7), 28.5 (t, C-5), 25.4 (t, C-6), 22.5 (t, C-8), 21.09 (q), 21.05 (q), 21.0 (q), 13.9 (q, C-9); IR: (neat) 1739 (C=O) cm^{-1}; HRMS: (ESI) Calculated ($C_{25}H_{32}O_4Na$) 419.2193 ($[M+Na]^+$) Found: 419.2168

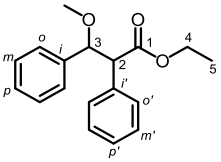
Hexyl 3-acetoxy-2,3-di(naphthalen-2-yl)propanoate (3bd)



General procedure A with di(naphthalen-2-yl)methyl acetate **1d** (0.500 mmol, 0.163 g), *n*-hexyl diazoacetate **2b** (1.00 mmol, 0.170 g), InI_3 (0.152 mmol, 0.076 g), and Me_3SiBr (0.150 mmol, 22 μL). The yield and the diastereoselectivity in the crude product were determined by ^1H NMR using 1,1,2,2-tetrachloroethene as an internal standard (27%, dr = 87:13). The title compound was obtained after silica gel column chromatography (hexane/ethyl acetate = 95:5, column length 11 cm) as a colorless oil (major diastereomer, *dr* >99:1, 0.0539 g, 23%).

^1H NMR: (400 MHz, $CDCl_3$) 7.70-7.59 (m, 8H, Ar), 7.38-7.22 (m, 6H, Ar), 6.65 (d, *J* = 11.0 Hz, 1H, 3-H), 4.44 (d, *J* = 11.0 Hz, 1H, 2-H), 4.21-4.10 (m, 2H, 4-H_2), 2.08 (s, 3H, 11-H_3), 1.64-1.60 (m, 2H, 5-H_2), 1.26-1.22 (m, 6H, 6-H_2, 7-H_2 and 8-H_2), 0.84-0.81 (m, 3H, 9-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 171.4 (s, C-1), 169.4 (s, C-6), 134.7, 133.1, 133.0, 132.73, 132.66, 131.3, 128.2, 128.0, 127.9, 127.8, 127.4, 127.1, 126.3, 126.1, 126.0, 125.9, 124.6, 77.1 (d, C-3), 65.3 (t, C-4), 57.7 (d, C-2), 31.3 (t, C-7), 28.5 (t, C-5), 25.4 (t, C-6), 22.4 (t, C-8), 21.1 (q, C-11), 13.9 (q, C-9); IR: (neat) 1739 (C=O) cm^{-1}; HRMS: (ESI+) Calculated ($C_{31}H_{32}O_4Na$) 491.2193 ($[M+Na]^+$) Found: 491.2184

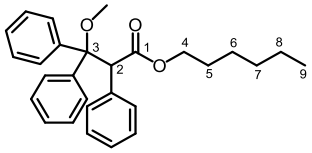
Ethyl 3-methoxy-2,3-diphenylpropanoate (3af)



General procedure A with benzhydryl methyl ether **1f** (0.496 mmol, 0.098 g), ethyl diazoacetate **2a** (1.00 mmol, 0.114 g), InI_3 (0.151 mmol, 0.075 g), and Me_3SiBr (0.150 mmol, 22 μL). The yield and the diastereoselectivity in the crude product were determined by ^1H NMR using 1,1,2,2-tetrachloroethene as an internal standard (18%, dr = 93:7). The title compound was obtained after silica gel column chromatography (hexane/ethyl acetate = 95:5, column length 11 cm) as a white solid (major diastereomer, *dr* >99:1, 0.0241 g, 17%).

^1H NMR: (400 MHz, $CDCl_3$) 7.15-7.02 (m, 10H, Ar), 4.68 (d, *J* = 10.5 Hz, 1H, 3-H), 4.27-4.17 (m, 2H, 4-H_2), 3.79 (d, *J* = 10.5 Hz, 1H, 2-H), 3.24 (s, 3H, OMe), 1.27 (t, *J* = 7.0 Hz, 3H, 5-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 172.6 (s, C-1), 138.3 (s), 134.7 (s), 128.7, 128.2, 127.9, 127.8, 127.5, 127.3, 85.9 (d, C-3), 60.9 (t, C-4), 59.7 (d, C-2). 57.0 (q, OMe), 14.1 (q, C-5); mp. 57–58 °C; IR: (KBr) 1730 (C=O) cm^{-1}; HRMS: (ESI+) Calculated ($C_{18}H_{20}O_3Na$) 307.1305 ($[M+Na]^+$) Found: 307.1296

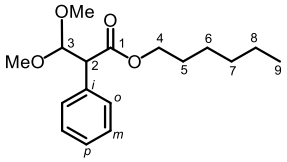
Hexyl 3-methoxy-2,3,3-triphenylpropanoate (3bg)



General procedure A with triphenylmethyl methyl ether **1g** (0.500 mmol, 0.137 g), *n*-hexyl diazoacetate **2b** (1.00 mmol, 0.170 g), and InI_3 (0.151 mmol, 0.075 g). The yield in the crude product was determined by ^1H NMR using 1,1,2,2-tetrachloroethene as an internal standard (89%). The title compound was obtained after silica gel column chromatography (hexane/ethyl acetate = 95:5, column length 11 cm) as a colorless oil (0.1771 g, 85%).

^1H NMR: (400 MHz, $CDCl_3$) 7.34-7.13 (m, 11H, Ar), 7.07 (t, J = 8.0 Hz, 2H, Ar), 6.90 (d, J = 7.9 Hz, 2H, Ar), 4.94 (s, 1H, 2-H), 4.04-3.87 (m, 2H, 4-H_2), 2.92 (s, 3H, OMe), 1.50-1.45 (m, 2H, 5-H_2), 1.22-1.20 (m, 6H, 6-H_2, 7-H_2 and 8-H_2), 0.85 (t, J = 6.8 Hz, 3H, 9-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 171.1 (s, C-1), 140.0 (s), 138.8 (s), 134.8 (s), 130.6, 130.2, 129.5, 127.5, 127.2, 127.15, 127.12, 127.0, 126.7, 85.9 (s, C-3), 64.6 (t, C-4), 59.9 (d, C-2), 51.9 (q, OMe), 31.3 (t, C-7), 28.3 (t, C-5), 25.4 (t, C-6), 22.5 (t, C-8), 13.9 (q, C-9); IR: (neat) 1740 (C=O) cm^{-1}; HRMS: (ESI+) Calculated ($C_{28}H_{32}O_3Na$) 439.2244 ($[M+Na]^+$) Found: 439.2236

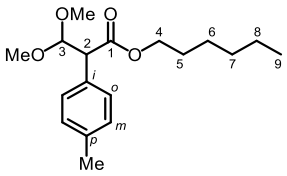
Hexyl 3,3-dimethoxy-2-phenylpropanoate (7ab)



General procedure B with benzaldehyde dimethyl acetal **6a** (0.500 mmol, 0.076 g), *n*-hexyl diazoacetate **2b** (1.00 mmol, 0.170 g), and $InBr_3$ (0.050 mmol, 0.017 g). The yield in the crude product was determined by ^1H NMR using 1,1,2,2-tetrachloroethene as an internal standard (99%). The title compound was obtained after silica gel column chromatography (hexane/ethyl acetate/Et_3N = 94.5:5:0.5, column length 11 cm) as a colorless oil (0.1472 g, 99%).

^1H NMR: (400 MHz, $CDCl_3$) 7.41-7.26 (m, 5H, Ar), 4.98 (d, J = 8.8 Hz, 1H, 3-H), 4.11-4.05 (m, 2H, 4-H_2), 3.88 (d, J = 8.8 Hz, 1H, 2-H), 3.46 (s, 3H, OMe), 3.18 (s, 3H, OMe), 1.60-1.55 (m, 2H, 5-H_2), 1.29-1.23 (m, 6H, 6-H_2, 7-H_2 and 8-H_2), 0.87-0.84 (m, 3H, 9-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 171.0 (s, C-1), 134.6 (s, C-*i*), 128.5, 128.4, 127.5, 104.9 (d, C-3), 64.8 (t, C-4), 55.4 (d, C-2), 54.9 (q, OMe), 53.1 (q, OMe), 31.2 (t, C-7), 28.3 (t, C-5), 25.2 (t, C-6), 22.4 (t, C-8), 13.8 (q, C-9); IR: (neat) 1736 (C=O) cm^{-1}; HRMS: (ESI+) Calculated ($C_{17}H_{26}O_4Na$) 317.1723 ($[M+Na]^+$) Found: 317.1712

Hexyl 3,3-dimethoxy-2-(*p*-tolyl)propanoate (7bb)



General procedure B with 4-methylbenzaldehyde dimethyl acetal **6b** (0.500 mmol, 0.083 g), *n*-hexyl

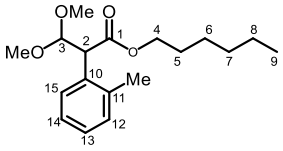
diazoacetate **2b** (0.579 mmol, 0.098 g), and $InBr_3$ (0.050 mmol, 0.017 g). The yield in the crude product was determined by ^1H NMR using 1,1,2,2-tetrachloroethene as an internal standard (93%). The crude product was purified by distillation under reduced pressure (0.57 torr, 130 °C) to give the title compound as a colorless oil (0.1249 g, 81%).

^1H NMR: (400 MHz, $CDCl_3$) 7.20 (d, J = 7.7 Hz, 2H, Ar), 7.06 (d, J = 7.7 Hz, 2H, Ar), 4.89 (d, J = 8.9 Hz, 1H, 3-H), 4.05-3.94 (m, 2H, 4-H_2), 3.77 (d, J = 8.9 Hz, 1H, 2-H), 3.36 (s, 3H, OMe), 3.09 (s, 3H, OMe), 2.24 (s, 3H, Ar-Me), 1.50 (m, 2H, 5-H_2), 1.21 (m, 6H, 6-H_2, 7-H_2 and 8-H_2), 0.79 (m, 3H, 9-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 171.3 (s, C-1), 137.2 (s, C-*p*), 131.6 (s, C-*i*), 129.2 (d, C-*o*), 128.4 (d, C-*m*), 104.9 (d, C-3), 64.9 (t, C-4), 55.0 (d, C-2), 55.0 (q, OMe), 53.0 (q, OMe), 31.3 (t, C-7), 28.4 (t, C-5), 25.3 (t, C-6), 22.4 (t, C-8), 21.0 (q, Ar-Me), 13.9 (q, C-9).

IR: (neat) 1736 (C=O) cm^{-1}

HRMS: (EI, 70 eV) Calculated ($C_{18}H_{28}O_4$) 308.1988 (M^+) Found: 308.1982

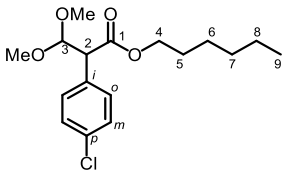
Hexyl 3,3-dimethoxy-2-(*o*-tolyl)propanoate (7cb)



General procedure B with 2-methylbenzaldehyde dimethyl acetal **6c** (0.500 mmol, 0.083 g), *n*-hexyl diazoacetate **2b** (0.617 mmol, 0.105 g), and $InBr_3$ (0.056 mmol, 0.019 g). The yield in the crude product was determined by ^1H NMR using 1,1,2,2-tetrachloroethene as an internal standard (99%). The crude product was purified by distillation with glass tube oven under reduced pressure (0.57 torr, 130 °C) to give the title compound as colorless oil (0.0981 g, 63%).

^1H NMR: (400 MHz, $CDCl_3$) 7.45 (d, J = 6.3 Hz, 1H, Ar), 7.18-7.17 (m, 3H, Ar), 5.05 (d, J = 9.0 Hz, 1H, 3-H), 4.17 (d, J = 9.0 Hz, 1H, 2-H), 4.11-4.00 (m, 2H, 4-H_2), 3.49 (s, 3H, OMe), 3.13 (s, 3H, OMe), 2.43 (s, 3H, Ar-Me) 1.58-1.55 (m, 2H, 5-H_2), 1.27-1.19 (m, 6H, 6-H_2, 7-H_2 and 8-H_2), 0.87-0.83 (m, 3H, 9-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 171.4 (s, C-1), 136.9 (s), 133.2 (s), 130.5 (d), 127.2, 126.1, 105.8 (d, C-3), 64.8 (t, C-4), 55.4 (q, OMe), 53.9 (q, OMe), 50.8 (d, C-2), 31.2 (t, C-7), 28.4 (t, C-5), 25.3 (t, C-6), 22.4 (t, C-8), 19.9 (q, Ar-Me), 13.9 (q, C-9); IR: (neat) 1736 (C=O) cm^{-1}; HRMS: (EI, 70 eV) Calculated ($C_{18}H_{28}O_4$) 308.1988 (M^+) Found: 308.1981

Hexyl 2-(4-chlorophenyl)-3,3-dimethoxypropanoate (7db)

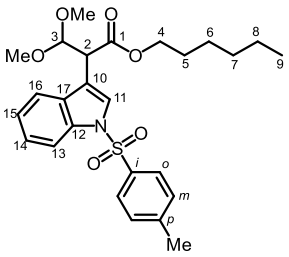


General procedure B with 4-chlorolbenzaldehyde dimethyl acetal **6d** (0.551 mmol, 0.103 g), *n*-hexyl diazoacetate **2b** (0.637 mmol, 0.109 g), and $InBr_3$ (0.055 mmol, 0.018 g). The yield in the crude product was determined by ^1H NMR using 1,1,2,2-tetrachloroethene as an internal standard (89%). The crude product was purified by distillation with glass tube oven under reduced pressure (0.57 torr, 130 °C) to give the title

compound as a colorless oil (0.1151 g, 70%).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.34-7.27 (m, 4H, Ar), 4.92 (d, J = 8.8 Hz, 1H, 3-H), 4.14-4.03 (m, 2H, 4-H_2), 3.86 (d, J = 8.8 Hz, 1H, 2-H), 3.45 (s, 3H, OMe), 3.19 (s, 3H, OMe), 1.60-1.57 (m, 2H, 5-H_2), 1.29-1.25 (m, 6H, 6-H_2, 7-H_2 and 8-H_2), 0.88-0.84 (m, 3H, 9-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.8 (s), 133.5 (s, C-*p*), 133.2 (s, C-*i*), 130.0 (d, C-*o*), 128.6 (d, C-*m*), 104.9 (d, C-3), 65.1 (t, C-4), 55.1 (q, OMe), 54.9 (d, C-2), 53.5 (q, OMe), 31.2 (t, C-7), 28.4 (t, C-5), 25.3 (t, C-6), 22.4 (t, C-8), 13.9 (q, C-9); IR: (neat) 1735 (C=O) cm^{-1}; HRMS: (CI, 70 eV) Calculated ($C_{17}H_{26}ClO_4$): 329.1520 ([M+H]$^+$) Found: 329.1519

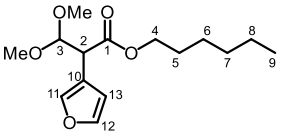
Hexyl 3,3-dimethoxy-2-(1-tosyl-1*H*-indol-3-yl)propanoate (7eb)



General procedure B with 2-(dimethoxymethyl)-1-tosyl-1H-indole **6e** (0.509 mmol, 0.176 g), *n*-hexyl diazoacetate **2b** (0.599 mmol, 0.102 g), and $InBr_3$ (0.050 mmol, 0.018 g). The yield in the crude product was determined by ^{1}H NMR using 1,1,2,2-tetrachloroethene as an internal standard (78%). The title compound was obtained after silica gel column chromatography (hexane/ethyl acetate/Et_3N = 94.5:5:0.5, column length 11 cm) as a brown oil (0.1853 g, 76%).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.96 (d, J = 7.5 Hz, 1H, Ar), 7.74 (d, J = 8.0 Hz, 2H, *o*), 7.65-7.63 (m, 2H, 11-H and Ar), 7.30 (t, J = 7.2 Hz, 1H, Ar), 7.25-7.18 (m, 3H, Ar), 4.99 (d, J = 8.5 Hz, 1H, 3-H), 4.12-4.06 (m, 3H, 2-H and 4-H_2), 3.46 (s, 3H, OMe), 3.12 (s, 3H, OMe), 2.32 (s, 3H, Ar-Me), 1.58 (m, 2H, 5-H_2), 1.25 (m, 6H, 6-H_2, 7-H_2 and 8-H_2), 0.86 (m, 3H, 9-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.4 (s, C-1), 144.8 (s, C-*p*), 135.1 (s), 134.8 (s), 130.1, 129.7, 126.7, 124.8, 124.7, 123.2, 120.0, 116.2 (s, C-10), 113.5 (d, C-11), 104.6 (d, C-3) 65.2 (t, C-4), 55.1 (q, OMe), 53.6 (q, OMe), 47.1 (d, C-2), 31.2 (C-7), 28.4 (t, C-5), 25.3 (t, C-6), 22.4 (t, C-8), 21.4 (q, Ar-Me), 13.9 (q, C-9); IR: (neat) 1735 (C=O) cm^{-1}; HRMS: (EI, 70 eV) Calculated ($C_{26}H_{33}NO_6S$) 487.2029 (M$^+$) Found: 487.2023

Hexyl 2-(furan-3-yl)-3,3-dimethoxypropanoate (7fb)

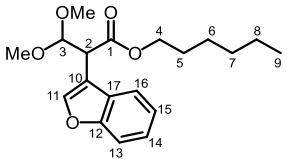


General procedure B with 3-dimethoxymethylfuran **6f** (0.623 mmol, 0.088 g), *n*-hexyl diazoacetate **2b** (0.653 mmol, 0.111 g), and $InBr_3$ (0.053 mmol, 0.019 g). The yield in the crude product was determined by ^{1}H NMR using 1,1,2,2-tetrachloroethene as an internal standard (71%). The crude product was purified by distillation with glass tube oven under reduced pressure (0.57 torr, 130 °C) to give the title compound as a colorless oil (0.0807 g, 57%).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.43 (s, 1H), 7.38 (s, 1H), 6.44 (s, 1H, 11-H), 4.79 (d, J = 8.5 Hz, 1H, 3-H), 4.13 (t, J = 5.3 Hz, 2H, 4-H_2), 4.84 (d, J = 8.5 Hz, 1H, 2-H), 3.43 (s, 3H, OMe), 3.28 (s, 3H, OMe), 1.65-

1.61 (m, 2H, 5-H_2), 1.32-1.29 (m, 6H, 6-H_2, 7-H_2 and 8-H_2), 0.90-0.86 (m, 3H, 9-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.8 (s, C-1), 142.8 (d), 140.5 (d), 118.7 (s, C-10), 110.3 (d, C-11), 104.5 (d, C-3), 65.1 (t, C-4), 54.7 (q, OMe), 53.3 (q, OMe), 46.5 (d, C-2), 31.3 (t, C-7), 28.3 (t, C-5), 25.4 (t, C-6), 22.5 (t, C-8), 13.9 (q, C-9); IR: (neat) 1737 (C=O) cm^{-1}; HRMS: (EI, 70 eV) Calculated ($C_{15}H_{24}O_5$) 284.1624 (M^+) Found: 284.1627

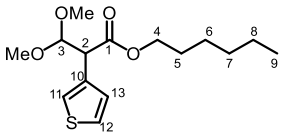
Hexyl 2-(benzofuran-3-yl)-3,3-dimethoxypropanoate (7gb)



General procedure B with 3-dimethoxymethylbenzofuran **6g** (0.574 mmol, 0.110 g), *n*-hexyl diazoacetate **2b** (0.588 mmol, 0.100 g), $InBr_3$ (0.049 mmol, 0.017 g). The yield in the crude product was determined by ^{1}H NMR using 1,1,2,2-tetrachloroethene as an internal standard (65%). The crude product was purified by distillation with glass tube oven under reduced pressure (1.30 torr, 140 °C) to give the title compound as a colorless oil (0.1087 g, 57%).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.53 (d, J = 7.7 Hz, 1H, 13-H), 7.46 (d, J = 8.2 Hz, 1H, 16-H), 7.28-7.18 (m, 2H, Ar), 6.72 (s, 1H, 11-H), 5.10 (d, J = 8.7 Hz, 1H, 3-H), 4.21-4.14 (m, 3H, 2-H and 4-H_2), 3.47 (s, 3H, OMe), 3.31 (s, 3H, OMe), 1.64-1.61 (m, 2H, 5-H_2), 1.28-1.25 (m, 6H, 6-H_2, 7-H_2 and 8-H_2), 0.87-0.83 (m, 3H, 9-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 168.6 (s, C-1), 154.7 (s, C-12), 151.2 (s, C-10), 128.2 (s, C-17), 124.0 (d, Ar), 122.7 (d, Ar), 120.8 (d, C-13), 111.2 (d, C-16), 105.1 (d, C-11), 103.4 (d, C-3), 65.5 (t, C-4), 54.9 (q, OMe), 53.5 (q, OMe), 49.9 (d, C-2), 31.3 (t, C-7), 28.4 (t, C-5), 25.4 (t, C-6), 22.5 (t, C-8), 13.9 (t, C-9); IR: (neat) 1741 (C=O) cm^{-1}; HRMS: (EI, 70 eV) Calculated ($C_{19}H_{26}O_5$) 334.1780 (M^+) Found: 334.1780

Hexyl 3,3-dimethoxy-2-(thiophen-3-yl)propanoate (7hb)

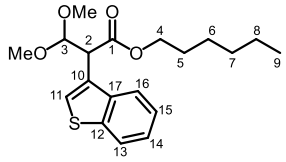


General procedure B with 3-dimethoxymethylthiophen **6h** (0.623 mmol, 0.089 g), *n*-hexyl diazoacetate **2b** (0.653 mmol, 0.111 g), and $InBr_3$ (0.054 mmol, 0.019 g). The yield in the crude product was determined by ^{1}H NMR using 1,1,2,2-tetrachloroethene as an internal standard (71%). The crude product was purified by distillation with glass tube oven under reduced pressure (1.30 torr, 140 °C) to give the title compound as a yellow oil (0.0807 g, 57%).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.29-7.26 (m, 2H, 11-H and 12-H), 7.13 (d, J = 4.7 Hz, 1H, 13-H), 4.87 (d, J = 8.5 Hz, 1H, 3-H), 4.11-4.10 (m, 2H, 4-H_2), 4.03 (d, J = 8.5 Hz, 1H, 2-H), 3.43 (s, 3H, OMe), 3.22 (s, 3H, OMe), 1.63-1.59 (m, 2H, 5-H_2), 1.31-1.27 (m, 6H, 6-H_2, 7-H_2 and 8-H_2), 0.89-0.86 (m, 3H, 9-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.8 (s, C-1), 134.6 (s, C-10), 127.6 (d, C-13), 125.5 (d, C-12), 123.0 (d, C-11), 104.9 (d, C-3), 65.1 (t, C-4), 54.9 (q, OMe), 53.5 (q, OMe), 51.1 (d, C-2), 31.3 (t, C-7), 28.4 (t, C-5), 25.4 (t, C-6), 22.5 (t, C-8), 13.9 (q, C-9); IR: (neat) 1737 (C=O) cm^{-1}; HRMS: (CI, 70 eV) Calculated ($C_{15}H_{25}O_4S$)

301.1474 ([M+H]$^+$) Found: 301.1470

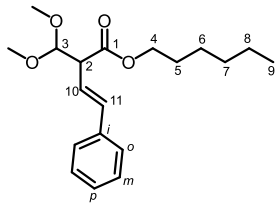
Hexyl 2-(benzothiophen-3-yl)-3,3-dimethoxypropanoate (7ib)



General procedure B with 3-dimethoxymethylbenzothiophen **6i** (0.493 mmol, 0.103 g), *n*-hexyl diazoacetate **2b** (0.608 mmol, 0.104 g), and $InBr_3$ (0.058 mmol, 0.021 g). The yield in the crude product was determined by ^{1}H NMR using 1,1,2,2-tetrachloroethene as an internal standard (80%). The crude product was purified by distillation with glass tube oven under reduced pressure (1.30 torr, 140 °C) to give the title compound as a yellow oil (0.0903 g, 52%).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.78 (d, J = 7.3 Hz, 1H, Ar), 7.72 (d, J = 6.8 Hz, 1H, Ar), 7.32-7.27 (m, 3H, 11-H, 14-H and 15-H), 4.95 (d, J = 9.8 Hz, 1H, 3-H), 4.25 (d, J = 9.8 Hz, 1H, 2-H), 4.16-4.15 (m, 2H, 4-H_2), 3.46 (s, 3H, OMe), 3.30 (s, 3H, OMe), 1.62 (m, 2H, 5-H_2), 1.27 (m, 6H, 6-H_2, 7-H_2 and 8-H_2), 0.85-0.83 (m, 3H, 9-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 169.9 (s, C-1), 139.8 (s), 139.2 (s), 137.2 (s), 124.2 (s, C-10), 124.1, 123.4, 123.3 (s), 122.1 (s), 104.9 (d, C-3), 65.5 (t, C-4), 55.0 (q, OMe), 53.9 (q, OMe), 51.8 (d, C-2), 31.3 (t, C-7), 28.4 (t, C-5), 25.4 (t, C-6), 22.5 (t, C-8), 13.9 (q, C-9); IR: (neat) 1736 (C=O) cm^{-1}; HRMS: (ESI+) Calculated ($C_{19}H_{26}O_4NaS$) 373.1444 ([M+Na]$^+$) Found: 373.1439

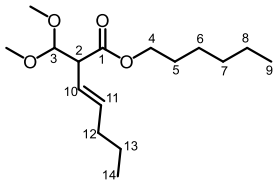
Hexyl (*E*)-2-(dimethoxymethyl)-4-phenylbut-3-enoate (7jb)



General procedure B with (*E*)-cinnamaldehyde dimethyl acetal **6j** (0.493 mmol, 0.103 g), *n*-hexyl diazoacetate **2b** (0.608 mmol, 0.104 g), and $InBr_3$ (0.058 mmol, 0.021 g). The yield in the crude product was determined by ^{1}H NMR using 1,1,2,2-tetrachloroethene as an internal standard (66%). The crude product was purified by distillation with glass tube oven under reduced pressure (0.65 torr, 150 °C) to give the title compound as a colorless oil (0.0491 g, 32%).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.39-7.23 (m, 5H, Ar), 6.56 (d, J = 15.5 Hz, 1H, 11-H), 6.23-6.17 (dd, J = 15.5, 8.5 Hz, 1H, 10-H), 4.75 (d, J = 8.5 Hz, 1H, 3-H), 4.13 (t, J = 6.3 Hz, 2H, 4-H_2), 3.55 (t, J = 8.5 Hz, 1H, 2-H), 3.41 (s, 3H, OMe), 3.35 (s, 3H, OMe), 1.66-1.63 (m, 2H, 5-H_2), 1.33-1.28 (m, 6H, 6-H_2, 7-H_2 and 8-H_2), 0.89-0.85 (m, 3H, 9-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.9 (s, C-1), 136.5 (s, C-*i*), 134.0 (d, C-11), 128.5, 127.7, 126.4, 122.7 (d, C-10), 104.1 (d, C-3), 65.0 (t, C-4), 54.7 (q, OMe), 53.5 (q, OMe), 53.0 (d, C-2), 31.3 (t, C-7), 28.5 (t, C-5), 25.4 (t, C-6), 22.5 (t, C-8), 13.9 (q, C-9); IR: (neat) 1735 (C=O) cm^{-1}; HRMS: (EI, 70 eV) Calculated ($C_{19}H_{28}O_4$) 320.1988 (M$^+$) Found: 320.1982

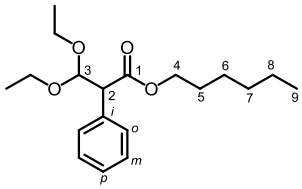
Hexyl (*E*)-2-(dimethoxymethyl)hept-3-enoate (7kb)



General procedure B with *trans*-2-hexenal dimethyl acetal **6k** (0.528 mmol, 0.076 g), *n*-hexyl diazoacetate **2b** (0.653 mmol, 0.112 g), $InBr_3$ (0.065 mmol, 0.023 g). The yield in the crude product was determined by ^1H NMR using 1,1,2,2-tetrachloroethene as an internal standard (67%). The title compound was obtained after silica gel column chromatography (hexane/ethyl acetate/Et_3N = 94.5:5:0.5, column length 11 cm) as a colorless oil (0.0571 g, 38%).

^1H NMR: (400 MHz, $CDCl_3$) 5.68-5.61 (m, 1H, 11-H), 5.46-5.40 (dd, J = 15.5, 8.5 Hz, 1H, 10-H), 4.64 (d, J = 8.5 Hz, 1H, 3-H), 4.11 (t, J = 6.3 Hz, 2H, 4-H_2), 3.37-3.32 (m, 7H, OMe x 2 and 2-H), 2.05-2.00 (m, 2H, 12-H_2), 1.63-1.61 (m, 2H, 5-H_2), 1.42-1.26 (m, 8H, 6-H_2, 7-H_2, 8-H_2 and 13-H_2), 0.90-0.86 (m, 6H, 9-H_3 and 14-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 171.4 (s, C-1), 135.5 (d, C-11), 123.0 (d, C-10), 104.0 (d, C-3), 64.7 (t, C-4), 54.6 (q, OMe), 53.1 (q, OMe), 52.4 (d, C-2), 34.5 (t, C-12), 31.3 (t, C-7), 28.5 (t, C-5), 25.4 (t, C-6), 22.5 (t, C-8), 22.1 (t, C-13), 14.0 (q, C-9), 13.5 (q, C-14); IR: (neat) 1737 (C=O) cm^{-1}; HRMS: (CI, 70 eV) Calculated ($C_{16}H_{31}O_4$) 287.2222 ($[M+H]^+$) Found: 287.2226

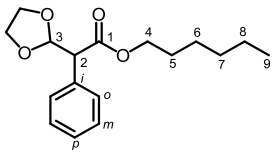
Hexyl 3,3-diethoxy-2-phenylpropanoate (7mb)



General procedure B with benzaldehyde diethyl acetal **6m** (0.506 mmol, 0.091 g), *n*-hexyl diazoacetate **2b** (0.603 mmol, 0.103 g), and $InBr_3$ (0.050 mmol, 0.018 g). The yield in the crude product was determined by ^1H NMR using 1,1,2,2-tetrachloroethene as an internal standard (99%). The title compound was obtained after silica gel column chromatography (hexane/ethyl acetate/Et_3N = 94.5:5:0.5, column length 11 cm) as a colorless oil (0.1596 g, 99%).

^1H NMR: (400 MHz, $CDCl_3$) 7.41-7.25 (m, 5H, Ar), 5.05 (d, J = 8.8 Hz, 1H, 3-H), 4.15-4.00 (m, 2H, 4-H_2), 3.87 (d, J = 8.8 Hz, 1H, 2-H), 3.83-3.75 (dq, J = 9.3, 7.0 Hz, 1H, OCH_2CH$_3$), 3.64-3.56 (dq, J = 9.3, 7.0 Hz, 1H, OCH_2CH$_3$), 3.49-3.43 (dq, J = 9.3, 7.0 Hz, 1H, OCH_2CH$_3$), 3.32-3.24 (dq, J = 9.3, 7.0 Hz, 1H, OCH_2CH$_3$), 1.61-1.57 (m, 2H, 5-H_2), 1.34-1.18 (m, 9H, 6-H_2, 7-H_2, 8-H_2 and OCH$_2$CH_3), 0.95-0.91 (t, J = 7.0 Hz, 3H, OCH$_2$CH_3), 0.89-0.84 (m, 3H, 9-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 171.3 (s, C-1), 134.9 (s), 128.7, 128.3, 127.4, 103.6 (d, C-3), 64.8 (t, C-4), 63.4, (t, O*C*H$_2$CH$_3$), 62.2 (t, O*C*H$_2$CH$_3$), 56.4 (d, C-2), 31.3 (t, C-7), 28.4 (t, C-5), 25.3 (t, C-6), 22.4 (t, C-8), 15.1 (q, OCH$_2$*C*H$_3$), 14.9 (q, OCH$_2$*C*H$_3$), 13.9 (q, C-9); IR: (neat) 1733 (C=O) cm^{-1}; HRMS: (ESI+) Calculated ($C_{19}H_{30}O_4Na$) 345.2036 ($[M+Na]^+$) Found: 345.2023

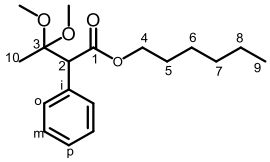
Hexyl 2-(1,3-dioxolan-2-yl)-2-phenylacetate (7nb)



A modified procedure B with InI_3 (30 mol%) and Me_3SiBr (30 mol%). To a solution of InI_3 (0.150 mmol, 0.074 g), *n-hexyl* diazoacetate **2b** (1.003 mmol, 0.170 g), and 2-phenyl-1,3-dioxolane **6n** (0.513 mmol, 0.077 g) in dichloromethane (1.0 mL) was added Me_3SiBr (0.150 mmol, 22 μL) at 0 °C. The resultant solution was stirred at 0 °C for 5 min and then warmed to room temperature for 6 h. Then, the reaction was quenched by saturated $NaHCO_3$ (5 mL) and the mixture was extracted with chloroform (10 x 3 mL). The collected organic layers were dried over $MgSO_4$ and the solvent was evaporated. The yield in the crude product was determined by ^1H NMR using 1,1,2,2-tetrachloroethene as an internal standard (79%). The title compound was obtained after silica gel column chromatography (hexane/ethyl acetate/Et_3N = 94.5:5:0.5, column length 11 cm) as a colorless oil (0.1067 g, 73%).

^1H NMR: (400 MHz, $CDCl_3$) 7.40-7.28 (m, 5H, Ar), 5.48 (d, J = 7.2 Hz, 1H, 3-H), 4.14-4.09 (m, 2H, 4-H_2), 3.92-3.73 (m, 4H, OCH_2CH_2O), 3.72 (d, J = 7.2 Hz, 1H, 2-H), 1.59-1.57 (m, 2H, 5-H_2), 1.25-1.23 (m, 6H, 6-H_2, 7-H_2 and 8-H_2), 0.85-0.83 (m, 3H, 9-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.7 (s, C-1), 134.2 (s, C-*i*), 128.6, 128.5, 127.7, 104.5 (d, C-3), 65.1 (t, O*C*H_2*C*H_2O), 65.0 (t, C-4), 56.5 (d, C-2), 31.2 (t, C-7), 28.3 (t, C-5), 25.3 (t, C-6), 22.4 (t, C-8), 13.9 (q, C-9); IR: (neat) 1734 (C=O) cm^{-1}; HRMS: (EI, 70 eV) Calculated ($C_{17}H_{24}O_4$) 292.1675 (M^+) Found: 292.1669

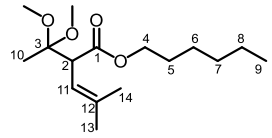
Hexyl 3,3-dimethoxy-2-phenylbutanoate (9ab)



Modified general procedure D2 with acetophenone dimethyl ketal **8a** (0.554 mmol, 0.092 g), *n*-hexyl diazoacetate **2b** (1.080 mmol, 0.185 g), and $InBr_3$ (0.054 mmol, 0.019 g). The yield in the crude product was determined by ^1H NMR using 1,1,2,2-tetrachloroethene as an internal standard (91%). The title compound was obtained after silica gel column chromatography (hexane/ethyl acetate/Et_3N = 94.5:5:0.5, column length 11 cm) as a colorless oil (0.144 g, 83%).

^1H NMR: (400 MHz, $CDCl_3$) 7.46 (d, J = 6.3 Hz, 2H, *o*), 7.34-7.26 (m, 3H, Ar), 4.17 (s, 1H, 2-H), 4.18-4.06 (m, 2H, 4-H_2), 3.30 (s, 3H, OMe), 3.22 (s, 3H, OMe), 1.63-1.60 (m, 2H, 5-H_2), 1.43 (s, 3H, 10-H_3), 1.27-1.24 (m, 6H, 6-H_2, 7-H_2 and 8-H_2), 0.88-0.84 (m, 3H, 9-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.8 (s, C-1), 134.8 (s, C-*i*), 129.5 (d, C-*o*), 128.0 (d, C-*m*), 127.3 (s, C-*p*), 102.4 (s, C-3), 64.8 (t, C-4), 56.2 (d, C-2), 48.7 (q, OMe), 48.2 (q, OMe), 31.3 (t, C-7), 28.4 (t, C-5), 25.5 (t, C-6), 22.5 (t, C-8), 18.1 (q, C-10), 14.0 (q, C-9); IR: (neat) 1738(C=O) cm^{-1}; HRMS: (FAB+) Calculated ($C_{18}H_{28}NaO_4$) 331.1885 ([M+Na]$^+$) Found: 331.1885

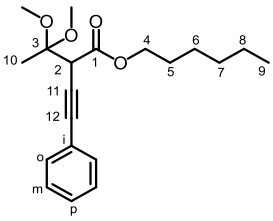
Hexyl 4-(1,1-dimethoxyethyl)-2-methylpent-2-enoate (9bb)



Modified general procedure D2 with 4-methyl-3-penten-2-one dimethyl ketal **8b** (0.508 mmol, 0.073 g), *n*-hexyl diazoacetate **2b** (1.031 mmol, 0.176 g), and $InBr_3$ (0.050 mmol, 0.018 g). The yield in the crude product was determined by ^1H NMR using 1,1,2,2-tetrachloroethene as an internal standard (39%). The title compound was obtained after column chromatography (hexane/ethyl acetate/Et_3N = 94.5:5:0.5, column length 11 cm) as a colorless oil (0.054 g, 38%).

^1H NMR: (400 MHz, $CDCl_3$) 5.27 (d, J = 9.9 Hz, 1H, 11-H), 4.09-4.06 (m, 2H, 4-H_2), 3.76 (d, J = 9.9 Hz, 1H, 2-H), 3.25 (s, 3H, OMe), 3.15 (s, 3H, OMe), 1.75 (s, 3H), 1.68 (s, 3H), 1.64-1.60 (m, 2H, 5-H_2), 1.46 (s, 3H, 10-H_3), 1.34-1.28 (m, 6H, 6-H_2, 7-H_2 and 8-H_2), 0.90-0.87 (m, 3H, 9-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 171.8 (s, C-1), 136.5 (s, C-12), 118.5 (d, C-11), 102.3 (s, C-3), 64.6 (t, C-4), 50.9 (d, C-2), 48.5 (q, OMe), 48.1 (q, OMe), 31.4 (t, C-7), 28.5 (t, C-5), 26.1 (t, C-6), 25.5 (q), 22.5 (t, C-8), 18.3 (q, C-10), 13.9 (q, C-9); IR: (neat) 1737 (C=O) cm^{-1}; HRMS: (FAB+) Calculated ($C_{16}H_{30}NaO_4$) 309.2042 ($[M+Na]^+$) Found: 309.2040

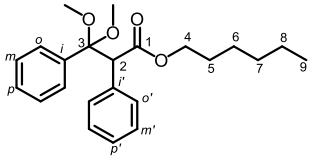
Hexyl 3,3-dimethoxy-2-(phenylethyn-1-yl)butanoate (9cb)



Modified general procedure D2 with 3,3-dimethoxy-1-phenyl-1-butyne **8c** (0.531 mmol, 0.101 g), *n*-hexyl diazoacetate **2b** (1.140 mmol, 0.194 g), and $InBr_3$ (0.062 mmol, 0.022 g). The yield in the crude product was determined by ^1H NMR using 1,1,2,2-tetrachloroethene as an internal standard (77%). The title compound was obtained after silica gel column chromatography (hexane/ethyl acetate/Et_3N = 94.5:5:0.5, column length 11 cm) as a colorless oil (0.1246 g, 71%).

^1H NMR: (400 MHz, $CDCl_3$) 7.45 (m, 2H, Ar), 7.31-7.25 (m, 3H, Ar), 4.21-4.13 (m, 2H, 4-H_2), 4.06 (s, 1H, 2-H), 3.30 (s, 3H, OMe), 3.27 (s, 3H, OMe), 1.69-1.67 (m, 2H, 5-H_2), 1.63 (s, 3H, 10-H_3), 1.41-1.29 (m, 6H, 6-H_2, 7-H_2 and 8-H_2), 0.90-0.86 (m, 3H, 9-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 168.2 (s, C-1), 131.8 (d, C-*o*), 128.2 (d, C-*m*), 128.1 (d, C-*p*), 122.9 (s, C-*i*), 102.2 (s, C-3), 84.1 (s, C-11), 83.3 (s, C-12), 65.6 (t, C-4), 49.0 (q, OMe), 48.5 (q, OMe), 45.9 (d, C-2), 31.3 (t, C-7), 28.4 (t, C-5), 25.5 (t, C-6), 22.5 (t, C-8), 19.1 (q, C-10), 13.9 (q, C-9); IR: (neat) 1743 (C=O) cm^{-1}; HRMS: (FAB+) Calculated ($C_{20}H_{28}NaO_4$) 355.1885 ($[M+Na]^+$) Found: 355.1883

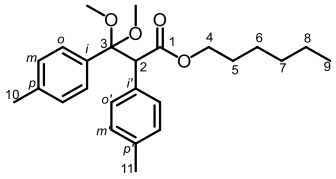
Hexyl 3,3-dimethoxy-2,3-diphenylpropanoate (9db)



General procedure D1 with benzophenone dimethyl ketal **8d** (0.518 mmol, 0.146 g), *n*-hexyl diazoacetate **2b** (1.174 mmol, 0.201 g), InI_3 (0.154 mmol, 0.076 g), and Me_3SiBr (0.150 mmol, 22 μL). The yield in the crude product was determined by ^1H NMR using 1,1,2,2-tetrachloroethene as an internal standard (65%). The title compound was obtained after silica gel column chromatography (hexane/ethyl acetate/Et_3N = 94.5:5:0.5, column length 11 cm) as a colorless oil (0.1283 g, 58%).

^1H NMR: (400 MHz, $CDCl_3$) 7.26-7.00 (m, 10H, Ar), 4.45 (s, 1H, 2-H), 4.15-3.96 (m, 2H, 4-H_2), 3.44 (s, 3H, OMe), 3.15 (s, 3H, OMe), 1.61-1.55 (m, 2H, 5-H_2), 1.26-1.23 (m, 6H, 6-H_2, 7-H_2 and 8-H_2), 0.94-0.79 (m, 3H, 9-H_3).; ^{13}C NMR: (100 MHz, $CDCl_3$) 170.0 (s, C-1), 136.5, 134.0, 130.4, 129.1, 127.8, 127.3, 126.5, 103.9 (s, C-3), 64.8 (t, C-4), 58.1 (d, C-2), 49.4 (q, OMe), 49.2 (q, OMe), 31.3 (t, C-7), 28.4 (t, C-5), 25.5 (t, C-6), 22.5 (t, C-8), 14.0 (q, C-9); IR: (neat) 1742 (C=O) cm^{-1}; HRMS: (FAB+) Calculated ($C_{23}H_{30}NaO_4$) 393.2042 ($[M+Na]^+$) Found: 393.2047

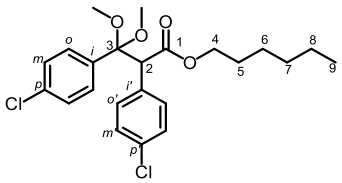
Hexyl 3,3-dimethoxy-2,3-di-*p*-tolylpropanoate (9eb)



General procedure D1 with 4,4'-dimethylbenzophenone dimethyl ketal **8e** (0.504 mmol, 0.129 g), *n*-hexyl diazoacetate **2b** (1.148 mmol, 0.195 g), InI_3 (0.155 mmol, 0.077 g), and Me_3SiBr (0.150 mmol, 22 μL). The yield in the crude product was determined by ^1H NMR using 1,1,2,2-tetrachloroethene as an internal standard (63%). The title compound was obtained after silica gel column chromatography (hexane/ethyl acetate/Et_3N = 94.5:5:0.5, column length 11 cm) as a colorless oil (0.1098 g, 55%).

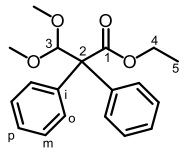
^1H NMR: (400 MHz, $CDCl_3$) 7.03-6.89 (m, 8H, Ar), 4.40 (s, 1H, 2-H), 4.16-3.94 (m, 2H, 4-H_2), 3.41 (s, 3H, OMe), 3.13 (s, 3H, OMe), 2.33 (s, 3H, Ar-Me), 2.30 (s, 3H, Ar-Me), 1.58-1.55 (m, 2H, 5-H_2), 1.28-1.24 (m, 6H, 6-H_2, 7-H_2 and 8-H_2), 0.88-0.85 (m, 3H, 9-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.1 (s, C-1), 137.4, 136.8, 133.6, 131.0, 130.4, 129.1, 127.9, 127.2, 103.8 (s, C-3), 64.7 (t, C-4), 57.7 (d, C-2), 49.2 (q, OMe), 49.1 (q, OMe), 31.3 (t, C-7), 28.4 (t, C-5), 25.5 (t, C-6), 22.5 (t, C-8), 21.1 (q, Ar-Me), 21.0 (q, Ar-Me), 13.9 (q, C-9); IR: (neat) 1742 (C=O) cm^{-1}; HRMS: (FAB+) Calculated ($C_{25}H_{34}NaO_4$) 421.2355 ($[M+Na]^+$) Found: 421.2363

Hexyl 2,3-bis(4-chlorophenyl)-3,3-dimethoxypropanoate (9fb)



General procedure D1 using 4,4'-dichlorobenzophenone dimethyl ketal **8c** (0.490 mmol, 0.146 g) and *n*-hexyl diazoacetate **2b** (1.077 mmol, 0.183 g) with InI_3 (0.155 mmol, 0.077 g) and Me_3SiBr (0.150 mmol, 22 μL). The yield in the crude product was determined by ^1H NMR using 1,1,2,2-tetrachloroethene as an internal standard (14%). Compound **9cb** could not be isolated because **9cb** underwent hydrolysis and transformed to the corresponding ketone through a silica gel column chromatography.

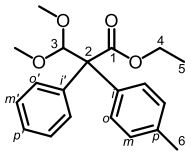
Ethyl 3,3-dimethoxy-2,2-(diphenyl)propanoate (7ac)



General procedure C with benzaldehyde dimethyl acetal **6a** (0.524 mmol, 0.079 g), ethyl 2-phenyl-2-diazoacetate **2c** (1.042 mmol, 0.198 g), and $InBr_3$ (0.050 mmol, 0.018 g). The yield in the crude product was determined by ^1H NMR using 1,1,2,2-tetrachloroethene as an internal standard (92%). The title compound was obtained after silica gel column chromatography (hexane/ethyl acetate/Et_3N = 94.5:5:0.5, column length 11 cm) and further purified by distillation with glass tube oven (140 °C, 0.36 Torr) as a colorless oil (0.1370 g, 84%).

^1H NMR: (400 MHz, $CDCl_3$) 7.28 (m, 10H, Ar), 5.34 (s, 1H, 3-H), 4.21 (q, J = 7.1 Hz, 2H, 4-H_2), 3.57 (s, 6H, OMe x 2), 1.19 (t, J = 7.1 Hz, 3H, 5-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 172.3 (s, C-1), 139.6 (s), 130.2 (d), 127.3 (d), 126.9 (d), 108.8 (d, C-3), 66.3 (s, C-2), 61.1 (t, C-4), 58.9 (q, OMe), 13.9 (q, C-5); IR: (neat) 1731 (C=O) cm^{-1}; HRMS: (FAB+) Calculated ($C_{19}H_{22}NaO_4$) 337.1416 ($[M+Na]^+$) Found: 337.1422

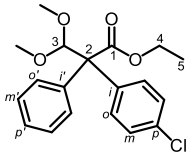
Ethyl 3,3-dimethoxy-2-(*p*-methylphenyl)-2-phenylpropanoate (7ad)



General procedure C using benzaldehyde dimethyl acetal **6a** (0.524 mmol, 0.080 g) and ethyl 2-(4-methylphenyl)-2-diazoacetate **2d** (0.987 mmol, 0.201 g) with $InBr_3$ (0.056 mmol, 0.020 g). The yield in the crude product was determined by ^1H NMR using 1,1,2,2-tetrachloroethene as an internal standard (68%). The title compound was obtained after silica gel column chromatography (hexane/ethyl acetate/Et_3N = 94.5:5:0.5, column length 11 cm) as a colorless oil (0.0910 g, 53%).

^1H NMR: (400 MHz, $CDCl_3$) 7.29-7.25 (m, 5H, Ar), 7.16 (d, J = 8.4 Hz, 2H, *o*), 7.09 (d, J = 8.4 Hz, 2H, *m*), 5.33 (s, 1H, 3-H), 4.19 (q, J = 7.1 Hz, 2H, 4-H_2), 3.57 (s, 6H, OMe), 2.33 (s, 3H, 6-H_3) 1.19 (t, J = 7.1 Hz, 3H, 5-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 172.5 (s, C-1), 139.6, 136.5, 130.1, 130.0, 128.1, 127.3, 126.9, 108.8 (d, C-3), 65.9 (s, C-2), 61.0 (t, C-4), 59.04 (q, OMe), 58.95 (q, OMe), 21.0 (q, C-6), 14.0 (q, C-5); IR: (neat) 1731 (C=O) cm^{-1}; HRMS: (EI, 70 eV) Calculated ($C_{20}H_{24}O_4$) 328.1675 (M^+) Found: 328.1672

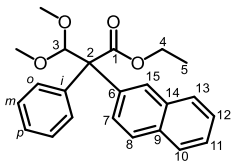
Ethyl 3,3-dimethoxy-2-(*p*-chlorophenyl)-2-phenylpropanoate (7ae)



General procedure C with benzaldehyde dimethyl acetal **6a** (0.521 mmol, 0.079 g), ethyl 2-(4-chlorophenyl)-2-diazoacetate **2e** (1.001 mmol, 0.224 g), $InBr_3$ (0.058 mmol, 0.022 g). The yield in the crude product was determined by ^1H NMR using 1,1,2,2-tetrachloroethene as an internal standard (94%). The title compound was obtained after silica gel column chromatography (hexane/ethyl acetate/Et_3N = 94.5:5:0.5, column length 11 cm) and further purified by distillation with glass tube oven (140 ℃, 0.36 Torr) as a colorless oil (0.1541 g, 85%).

^1H NMR: (400 MHz, $CDCl_3$) 7.31-7.18 (m, 9H, Ar), 5.31 (s, 1H, 3-H), 4.20 (q, J = 7.1 Hz, 2H, 4-H_2), 3.61 (s, 3H, OMe), 3.55 (s, 3H, OMe), 1.19 (t, J = 7.1 Hz, 3H, 5-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 172.0 (s, C-1), 139.5, 137.7, 132.9, 132.2, 129.6, 127.7, 127.3, 108.5 (d, C-3), 65.9 (s, C-2), 61.3 (t, C-4), 59.6 (q, OMe), 58.5 (q, OMe), 14.0 (q, C-5); IR: (neat) 1731 (C=O) cm^{-1}; HRMS: (EI, 70 eV) Calculated ($C_{19}H_{21}ClO_4$) 348.1128 (M^+) Found: 348.1125

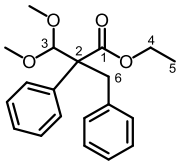
Ethyl 3,3-dimethoxy-2-(naphthalen-2-yl)-2-phenylpropanoate (7af)



General procedure C with benzaldehyde dimethyl acetal **6a** (0.500 mmol, 0.076 g), ethyl 2-diazo-2-(naphthalen-2-yl)acetate **2f** (1.000 mmol, 0.240 g), and $InBr_3$ (0.055 mmol, 0.020 g). The yield in the crude product was determined by ^1H NMR using 1,1,2,2-tetrachloroethene as an internal standard (47%). The title compound was obtained after silica gel column chromatography (hexane/ethyl acetate/Et_3N = 94.5:5:0.5, column length 11 cm) as a colorless oil (0.0840 g, 46%).

^1H NMR: (400 MHz, $CDCl_3$) 7.79-7.73 (m, 4H, Ar), 7.45-7.43 (m, 3H, Ar), 7.31-7.28 (m, 5H, Ar), 5.44 (s, 1H, 3-H), 4.22 (q, J = 7.0 Hz, 2H, 4-H_2), 3.60 (s, 3H, OMe), 3.58 (s, 3H, OMe), 1.20 (t, J = 7.0 Hz, 3H, 5-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 172.3 (s, C-1), 139.5, 137.1, 132.7, 132.3, 130.3, 129.1, 128.5, 128.4, 127.4, 127.3, 127.1, 126.6, 125.9, 125.6, 109.0 (d, C-3), 66.5 (s, C-2), 61.2 (t, C-4), 59.0 (q, OMe), 58.9 (q, OMe), 14.0 (q, C-5); IR: (neat) 1727 (C=O) cm^{-1}; HRMS: (ESI+) Calculated ($C_{23}H_{24}O_4Na$) 387.1567 ([M+Na]$^+$) Found: 387.1571

Ethyl 2-benzyl-3,3-dimethoxy-2-phenylpropanoate (7ag)

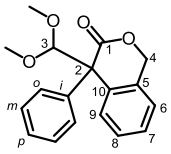


General procedure C with benzaldehyde dimethyl acetal **6a** (0.500 mmol, 0.076 g), ethyl 2-diazo-3-

phenylpropanoate **2g** (1.029 mmol, 0.210 g), and $InBr_3$ (0.064 mmol, 0.022 g). The yield in the crude product was determined by ^1H NMR using 1,1,2,2-tetrachloroethene as an internal standard (40%). The title compound was obtained after silica gel column chromatography (hexane/ethyl acetate/Et_3N = 94.5:5:0.5, column length 11 cm) as a colorless oil (0.0591 g, 36%).

^1H NMR: (400 MHz, $CDCl_3$) 7.31-7.21 (m, 8H, Ar), 7.10 (d, J = 10.7 Hz, Ar), 4.60 (s, 1H, 3-H), 4.18-4.14 (m, 2H, 4-H_2), 3.73 (d, J = 13.2 Hz, 1H, 6-H^a), 3.57 (s, 3H, OMe), 3.55 (s, 3H, OMe), 3.27 (d, J = 13.2 Hz, 1H, 6-H^b), 1.20 (t, J = 7.2 Hz, 3H, 5-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 173.2 (s, C-1), 138.2 (s), 137.1 (s), 130.3, 129.1, 127.9, 127.3, 127.0, 126.6, 107.0 (d, C-3), 61.5 (s, C-2), 60.6 (t, C-4), 60.2 (q, OMe), 56.8 (q, OMe), 39.9 (t, C-6), 14.0 (q, C-5); IR: (neat) 1732 (C=O) cm^{-1}; HRMS: (ESI+) Calculated ($C_{20}H_{24}O_4Na$) 351.1567 ($[M+Na]^+$) Found: 351.1558

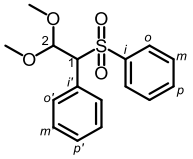
4-(Dimethoxymethyl)-4-phenylisochroman-3-one (7ah)



To a solution of $InBr_3$ (0.05 mmol, 0.0180 g) and 4-diazoisochroman-3-one **2h** (0.977 mmol, 0.170 g) in 1,2-dichloroethane (1.0 mL) was added benzaldehyde dimethyl acetal **6a** (0.500 mmol, 0.076 g) at 0 °C. The resultant solution was stirred at 0 °C for 5 min and then heated to 40 °C for 12 h. Then, the reaction was quenched by Et_3N (0.2 mL) and sat. $NaHCO_3$ (5 mL) and the mixture was extracted with chloroform (10 mL x 3). The collected organic layers were dried ($MgSO_4$) and the solvent was evaporated. The yield in the crude product was determined by ^1H NMR using 1,1,2,2-tetrachloroethene as an internal standard (69%). The title compound was obtained after silica gel column chromatography (hexane/ethyl acetate/Et_3N = 94.5:5:0.5, column length 11 cm) to give the product as a colorless oil (0.1029 g, 69%).

^1H NMR: (400 MHz, $CDCl_3$) 8.12 (d, J = 8.0 Hz, 1H, 9-H), 7.43 (t, J = 8.0 Hz, 1H, 8-H), 7.34 (t, J = 8.0 Hz, 1H, 7-H), 7.28-7.26 (m, 3H, Ar), 7.15 (d, J = 8.0 Hz, 1H, 6-H), 7.11-7.09 (m, 2H, Ar), 5.22 (s, 1H, 3-H), 4.98 (d, J = 14.0 Hz, 1H, 4-H^a), 4.72 (d, J = 14.0 Hz, 1H, 4-H^b), 3.63 (s, 3H, OMe), 3.15 (s, 3H, OMe); ^{13}C NMR: (100 MHz, $CDCl_3$) 171.4 (s, C-1), 135.4 (s, C-5), 133.3 (s, C-*i*), 132.9 (s, C-10), 130.4 (d, C-9), 128.5, 128.1, 128.0, 127.9, 127.4, 124.6 (d, C-6), 111.2 (d, C-3), 69.0 (t, C-4), 60.9 (s, C-2), 59.6 (q, OMe), 58.9 (q, OMe); IR: (neat) 1737 (C=O) cm^{-1}; HRMS: (ESI+) Calculated ($C_{18}H_{18}O_4Na$) 321.1097 ($[M+Na]^+$) Found: 321.1105

(2,2-Dimethoxy-1-(phenylsulfonyl)ethyl)benzene (7ai)

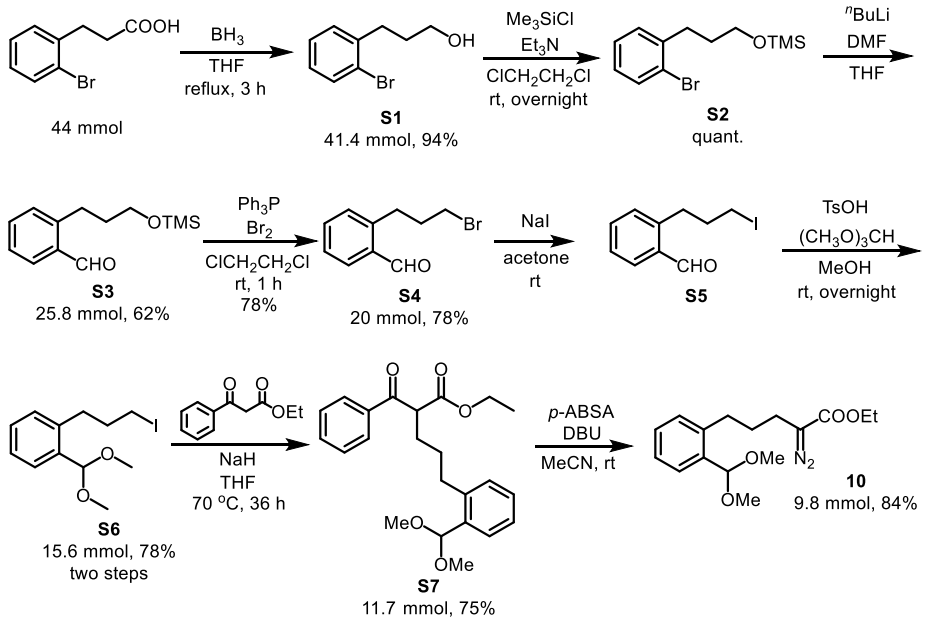


To a solution of $InBr_3$ (0.051 mmol, 0.018 g) and α-diazomethyl phenyl sulfone **2i** (1.001 mmol, 0.182 g) in 1,2-dichloroethane (1.0 mL) was added benzaldehyde dimethyl acetal **6a** (0.493 mmol, 0.075 g) at 0 °C. The resultant solution was stirred at 0 °C overnight. Then, the reaction was quenched by Et_3N (0.2 mL) and sat.

$NaHCO_3$ (5 mL) and extracted with chloroform (10 mL x 3). The collected organic layer was dried ($MgSO_4$) and the solvent was evaporated. The yield in the crude product was determined by ^1H NMR using 1,1,2,2-tetrachloroethene as an internal standard (53%). The title compound was obtained after silica gel column chromatography (hexane/ethyl acetate/Et_3N = 89.5:10:0.5, column length 11 cm) as a white solid (0.0790 g, 52%).

^1H NMR: (400 MHz, $CDCl_3$) 7.63 (d, *J* = 7.7 Hz, 2H, *o*), 7.54 (t, *J* = 7.7 Hz, 1H, *p*), 7.39 (t, *J* = 7.7 Hz, 2H, *m*), 7.28-7.26 (m, 5H, Ar), 5.29 (d, *J* = 7.0 Hz, 1H, 2-H), 4.42 (d, *J* = 7.0 Hz, 1H, 1-H), 3.37 (s, 3H, OMe), 3.23 (s, 3H, OMe); ^{13}C NMR: (100 MHz, $CDCl_3$) 139.3 (s, C-*i*), 133.2 (d, C-*p*), 130.7, 129.9, 130.4 (d, C-*m*), 128.8, 128.4, 102.4 (d, C-2), 73.2 (d, C-1), 55.1 (q, OMe), 53.7 (q, OMe); mp. 116–118 °C; IR: (KBr) 1295, 1141, 1118, 1078, 1066 cm^{-1}; HRMS: (EI, 70 eV) Calculated ($C_{16}H_{18}O_4S$) 306.0926 (M^+) Found: 306.0920

Preparation and characterization data of diazoester (10)



To a stirred solution of 3-(2-bromophenyl)propanoic acid (10 g, 44 mmol) in THF (100 mL) at 0 ºC, was added a solution of BH_3·THF (60 mL, 60 mmol, 1M in THF) over 20 min. At this point the reaction was warmed to room temperature and stirred for 20 min. Then the reaction was refluxed for additional 3 h, quenched slowly by addition of H_2O (30 mL), concentrated under vacuum and diluted in Et_2O (60 mL). The solution was transferred to a separatory funnel and washed twice with an aqueous saturated solution of Na_2CO_3, dried over $MgSO_4$ and concentrated under vacuum. The crude product **S1** was obtained with enough purity in 94% yield (8.9 g, 41.4 mmol) and used in the next step without further purification. To a stirred solution of crude **S1** (8.9 g, 41.4 mmol) in 1,2-dichloroethene (50 mL) at 0 °C, was added Et_3N (5.4 g, 53.8 mmol) and trimethylsilyl chloride (5.4 g, 49.7 mmol). At this point the reaction was warmed to room temperature and stirred overnight. The reaction mixture was filtrated on celite, and the filtrate was concentrated under vacuum to give the protected silyl ether **S2** as a colorless oil (11.9 g, quant.) and used in the next step without further purification. To a stirred solution of **S2** (11.9 g, 41.4 mmol) in THF (80 mL) at

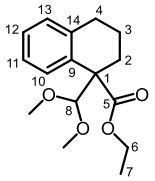
-78 ℃, was added ^{n}BuLi (39 mL, 62.1 mmol, 1.6 M in hexane) over 30 min. At this point the reaction was stirred for additional 30 min at -78 ℃ and DMF (6.1 g, 82.8 mmol) was added. The resultant mixture was stirred at -78 ℃ for 30 min and warmed to room temperature for additional 1 h. Then the reaction was slowly quenched by addition of saturated $NaHCO_3$ (50 mL) and extracted by EtOAc (50 mL x 3). The combined organic layer was washed by brine (50 mL) and water (50 mL), dried over $MgSO_4$ and concentrated under vacuum. The target product **S3** was obtained after purification by flash column (hexane/EtOAc = 80:20) as a colorless oil (6.1 g, 25.8 mmol, 62%). To a stirred mixture of **S3** (6.1 g, 25.8 mmol) and triphenylphosphine (6.8 g, 25.8 mmol) in $ClCH_2CH_2Cl$ (50 mL) at 0 ℃, was slowly added Br_2 (4.1 g, 25.8 mmol) at which time the color of reaction mixture was maintained from white to yellow. If the color change to red, excess of triphenylphosphine should be added to quench the excess of Br_2 to give white or yellow suspension. Then the reaction was warmed to room temperature and stirred for 2 h until the suspension became clear solution. The reaction was quenched by addition of saturated $NaHCO_3$ (50 mL) and extracted by ether. The organic layer was washed with brine and water, dried over $MgSO_4$ and concentrated under vacuum. The target product **S4** was obtained after purification by flash column (hexane/EtOAc = 80:20) as a pale yellow oil (4.5 g, 20 mmol, 78%). To a stirred mixture of **S4** (4.5 g, 20 mmol) in acetone (50 mL) at room temperature, was added sodium iodide (14.9 g, 100 mmol). The reaction was stirred at room temperature overnight. The resultant mixture was filtrated through celite and the solvent was removed by vacuum. The crude product **S5** was used in the next step without further purification. The crude **S5** (5.5 g, 20 mmol) was dissolved in anhydride methanol (50 mL), and $TsOH{\cdot}H_2O$ (0.076 g, 0.4 mmol) and trimethyl orthoformate (4.2 g, 40 mmol) were added sequentially. The reaction was stirred at room temperature overnight and quenched by addition of Et_3N (0.5 mL). The solvent was removed and purified by flash column (hexane/EtOAc/Et_3N = 94.5/5/0.5) to give pure compound **S5** as a pale yellow oil (5.0 g, 15.6 mmol, 78%). To a stirred suspension of NaH (0.75 g, 18.7 mmol, 60w% in mineral oil) in THF (40 mL) at 0 ℃, was slowly added ethyl 3-oxo-3-phenylpropionate (2.99 g, 15.6 mmol). This mixture was warmed to room temperature and stirred for additional 30 min. Then acetal **S6** (5.0 g, 15.6 mmol) was added and the resultant mixture was heated to 70 ℃ and stirred for 36 h. After cooling to room temperature, the reaction mixture was quenched by addition of saturated $NaHCO_3$ (40 mL) and extracted with EtOAc, dried over $MgSO_4$. The solvent was evaporated and crude product was purified by flash column (hexane/EtOAc/Et_3N = 80/19.5/0.5) to give the pure compound **S7** as colorless oil (4.5 g, 11.7 mmol, 75%). To a stirred solution of **S7** (4.5 g, 11.7 mmol) in acetonitrile (30 mL) at 0 ℃, was added 4-acetamidobenzenesulfonyl azide (*p*-ABSA) (2.81 g, 11.7 mmol). Then, DBU (1.78 g, 11.7 mmol) was slowly added by dropwise over 5 min. The resultant mixture was stirred at 0 ℃ for 30 min and additional *p*-ABSA (1.41 g, 5.9 mmol) and DBU (0.89 g, 5.9 mmol) were added. The reaction was stirred at 0 ℃ for additional 30 min and warmed to room temperature overnight. The reaction was quenched by addition of saturated $NaHCO_3$ (50 mL) and extracted with EtOAc, dried over $MgSO_4$. The solvent was evaporated and crude product was purified by flash column (hexane/EtOAc/Et_3N = 94.5/5/0.5) to give the diazo compound **10** as a yellow oil (3.0 g, 9.8 mmol, 84%).

Spectra data of **10** are shown below.

^{1}H NMR (400 MHz, $CDCl_3$) 7.55-7.53 (m, 1H), 7.28-7.18 (m, 3H), 5.47 (s, 1H), 4.23 (q, J = 7.0 Hz, 2H),

3.32 (s, 6H), 2.76 (t, J = 8.0 Hz, 2H), 2.39 (t, J = 7.5 Hz, 2H), 1.86-1.80 (m, 2H), 1.28 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 167.6 (s), 139.6 (s), 135.1 (s), 129.4 (d), 128.5 (d), 126.8 (d), 125.6 (d), 101.6 (d), 60.6 (t), 53.0 (q), 31.0 (t), 29.0 (t), 23.0 (t), 14.4 (q) (1 Csp^2 not located); IR: (neat) 2077, 1686 cm^{-1}; HRMS: (ESI+) Calculated ($C_{16}H_{22}N_2O_4Na$) 329.1472 ($[M+Na]^+$) Found: 329.1463

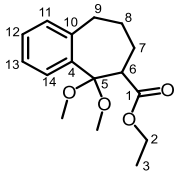
Ethyl 1-(dimethoxymethyl)-1,2,3,4-tetrahydronaphthalene-1-carboxylate (11)



To a solution of $InBr_3$ (0.02 mmol, 0.0072 g) in 1,2-dichloroethane (4.0 mL) was added ethyl 2-diazo-5-(2-(dimethoxymethyl)phenyl)pentanoate **10** (0.4 mmol, 0.123g) at -20 °C. The resultant solution was stirred at -20 °C for 4 h. The reaction was quenched by the addition of Et_3N (0.2 mL). The solvent was evaporated and the residue was purified by silica gel column chromatography (hexane/ethyl acetate/Et_3N = 94.5:5:0.5, column length 11 cm) to separate products **11** and **12**. Compound **11** was obtained as a colorless oil (0.0501 g, 44%).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.63-7.61 (m, 1H, 10-H), 7.26-7.11 (m, 3H, Ar), 4.97 (s, 1H, 8-H), 4.14 (q, J = 7.1 Hz, 2H, 6-H_2), 3.53 (s, 3H, OMe), 3.21 (s, 3H, OMe), 2.73-2.72 (m, 2H, 4-H_2), 2.34-2.29 (m, 1H, 2-H), 2.08-2.01 (m, 1H, 2-H), 1.95-1.88 (m, 2H, 3-H_2), 1.23 (t, J = 7.1 Hz, 3H, 7-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 173.9 (s, C-5), 139.2 (s, C-14), 133.6 (C-9), 129.5 (d, C-13), 128.1 (d, C-10), 126.6 (d), 125.4 (d), 111.8 (d, C-8), 60.7 (t, C-6), 59.2 (q, OMe), 58.1 (q, OMe), 54.4 (s, C-1), 30.2 (t, C-4), 25.8 (t, C-2), 20.3 (t, C-3), 14.0 (q, C-7); IR: (neat) 1729 (C=O) cm^{-1}; HRMS: (EI, 70 eV) Calculated ($C_{16}H_{22}O_4$) 278.1518 (M^+) Found: 278.1513

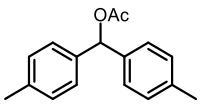
Ethyl 5,5-dimethoxy-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene-6-carboxylate (12)



Compound **12** was as a colorless oil (0.0279 g, 25%).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.70-7.67 (m, 1H, 14-H), 7.19-7.14 (m, 2H, Ar), 7.07-7.05 (m, 1H, 11-H), 3.93-3.88 (qd, J = 7.1, 1.0 Hz, 2H, 2-H_2), 3.42 (s, 3H, OMe), 3.37 (t, J = 4.6 Hz, 1H, 6-H), 3.19-3.13 (m, 1H, 9-H), 2.89 (s, 3H, OMe), 2.62-2.58 (m, 1H, 9-H), 2.27-2.19 (m, 1H, 7-H), 2.02-1.98 (m, 1H, 7-H), 1.85-1.78 (m, 2H, 8-H_2), 1.02 (t, J = 7.1 Hz, 3H, 3-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 171.6 (s, C-1), 140.9 (s), 137.8 (s), 129.7 (d), 128.8 (d, C-11), 128.1 (d, C-14), 125.4 (d), 101.8 (s, C-5), 59.9 (t, C-2), 48.6 (q, OMe), 47.7 (q, OMe), 46.5 (d, C-6), 35.5 (t, C-9), 28.2 (t, C-7), 23.8 (t, C-8), 13.9 (q, C-3); IR: (neat) 1721 (C=O) cm^{-1}; HRMS: (EI, 70 eV) Calculated ($C_{16}H_{22}O_4$) 278.1518 (M^+) Found: 278.1516

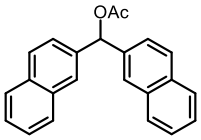
Di-*p*-tolylmethyl acetate (1b)



To a solution of di-*p*-tolylmethanol (10 mmol) in diethyl ether (10 mL) was added acetyl chloride (20 mmol) under 0 ℃. Then, triethylamine (20 mmol) was added dropwise over 5 min. The resultant solution was warmed to room temperature and stirred for additional 2 h. The precipitate was filtered on celite and washed with ether. The volatile was evaporated and the crude mixture was purified by silica gel column chromatography (hexane/ethyl acetate = 8:2) to give compound **1b** as a colorless oil (2.46 g, 97%).

^{1}H NMR (400 MHz, $CDCl_3$) 7.22 (d, *J* = 7.9 Hz, 4H), 7.12 (d, *J* = 7.9 Hz, 4H), 6.83 (s, 1H), 2.30 (s, 6H), 2.11 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 170.0, 137.4, 137.3, 129.0, 126.9, 76.9, 21.2, 21.0

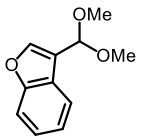
Di(naphthalen-2-yl)methyl acetate (1d)



To a solution of di-2-naphthylmethanol (2 mmol) in diethyl ether (10 mL) was added acetyl chloride (4 mmol) under 0 ℃. Then, triethylamine (4 mmol) was added dropwise over 5 min. The resultant solution was warmed to room temperature and stirred for additional 2 h. The precipitate was filtered on celite and washed with ether. The volatile was evaporated and the residue was purified by recrystallization in ether/hexane = 50:50 to give compound **1d** as a white solid (0.650 g, 99%).

^{1}H NMR (400 MHz, $CDCl_3$) 7.89 (s, 2H), 7.84-7.79 (m, 6H), 7.50-7.44 (m, 6H), 7.22 (s, 1H), 2.24 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 170.1, 137.3, 133.0, 132.9, 128.4, 128.1, 127.6, 126.3, 126.2, 126.1, 125.0, 77.0, 21.4; mp. 82–84 ℃

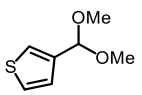
3-Dimethoxymethylbenzofuran (6g)



Into a 20 mL dry round bottom flask containing a magnetic stirring bar was weighed NH_4Cl (0.3 mmol) under nitrogen atmosphere. Anhydrous methanol (6 mL), benzofuran-3-carbaldehyde (6 mmol) and trimethyl orthoformate (3 mL) were added sequentially to the flask. The stirred mixture was heated to reflux (70 ℃). After 3.5 h, the reaction mixture was cooled to 0 ℃ and poured into saturated aqueous $NaHCO_3$ (10 mL). After extraction with $CHCl_3$ (10 mL x 3), the combined organic layer was washed with brine, dried over $MgSO_4$, and evaporated. Purification of the residual oil by distillation (110 ℃, 0.83 Torr) gave acetal **6g** as a colorless oil (0.77 g, 67%).

^{1}H NMR (400 MHz, $CDCl_3$) 7.59-7.57 (m, 1H), 7.52-7.50 (m, 1H), 7.32-7.28 (m, 1H), 7.26-7.22 (m, 1H), 6.82 (s, 1H), 5.58 (s, 1H), 3.42 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) 154.8, 153.0, 127.5, 124.5, 122.8, 121.2, 111.5, 105.4, 97.9, 52.9

3-Dimethoxymethylthiophene (6h)

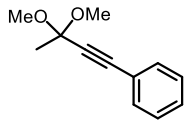


Modified procedure was used. Into a 50 mL dry round bottom flask containing a magnetic stirring bar was weighed the NH_4Cl (1 mmol, 0.05 eq.) under nitrogen. Anhydrous methanol (20 mL), thiophene-3-

carbaldehyde (20 mmol, 1 eq.) and trimethyl orthoformate (10 mL) were added sequentially to the flask. The stirred mixture was heated to reflux (70 ℃). After 3.5 h, the reaction mixture was cooled to 0 ℃ and poured into saturated aqueous $NaHCO_3$ (10 mL). After extraction with $CHCl_3$ (10 mL x 3), the combined organic layer was washed with brine, dried over $MgSO_4$, and evaporated. Purification of the residual oil by distillation (100 ℃, 10 Torr) gave the title acetal **6h** as yellow oil (2.11 g, 67%).

^{1}H NMR (400 MHz, $CDCl_3$) 7.35-7.34 (m, 1H), 7.31-7.29 (m, 1H), 7.10-7.09 (dd, J = 5.1, 1.2 Hz, 1H), 5.48 (s, 1H), 3.32 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.9, 126.0, 125.6, 123.2, 100.1, 52.2

(3,3-Dimethoxybut-1-yn-1-yl)benzene (8c)



To a stirred mixture of 4-phenylbut-3-yn-2-one (1.44 g, 10 mmol) and trimethyl orthoformate (3.18 g, 30 mmol, 3 eq.) in dehydrated methanol (15 mL) was added $Ce(OTf)_3$ (0.04 g, 0.07 mmol). The reaction mixture was stirred at room temperature for 24 h. The reaction mixture was cooling to room temperature and quenched by Et_3N (0.5 mL) and saturated $NaHCO_3$ (30 mL). This resulted mixture was extracted by diether ether (30 mL x 3). The combined organic layer was washed by brine (50 mL) and dried over $MgSO_4$, filtered and concentrated. The title compound was obtained by distillation (120 ℃, 10 Torr) as a pale yellow oil (1.33 g, 70%).

^{1}H NMR (400 MHz, $CDCl_3$) 7.49-7.47 (m, 2H), 7.33-7.32 (m, 3H), 3.39 (s, 6H), 1.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) 131.7, 128.6, 128.1, 121.7, 96.8, 86.5, 84.1, 50.0, 25.1

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[12] CCDC 2075523 (**3aa**) contains the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures

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Chapter 2: Lewis Acid-Catalyzed Diastereoselective C–C Bond Insertion of Diazoesters into Secondary Benzylic Halides for the Synthesis of *α*,*β*-Diaryl-*β*-haloesters

2-1. Introduction

α,*β*-Diaryl-*β*-halo compounds are important building blocks in organic chemistry. Among them, the compounds bearing another functional group at the *α*-position are well studied and applied in the medicinal and agrochemical industries (Figure 1a).[1] However, it is difficult to construct this type of structure while maintaining control of the stereochemistry in its vicinal chiral carbon centers because labile benzylic carbon–halogen (C–X) bonds often cause epimerization or decomposition. In addition, a high level of chemoselectivity is demanded for utilization in the later stages of the multi-step syntheses of pharmaceuticals.[2] The stereoselective synthesis of *α*,*β*-diaryl-*β*-haloalcohols by catalytic ring-opening halogenation of *meso*-epoxides was well developed (Figure 1b, **A**).[3] Gouverneur's group[4] established an enantioselective carbon–fluorine (C–F) bond formation with phase-transfer catalysts via halogen exchange from *β*-bromosulfides or *β*-bromoamines to *β*-fluorosulfides or *β*-fluoroamines, respectively (Figure 1b, **B** and **C**). In contrast to the methodologies mentioned above, the stereoselective synthesis of *α*,*β*-diaryl-*β*-halo carbonyl compounds has never been reported (Figure 1b, **D**)[5] due to a strong demand for the inhibition of spontaneous dehydrohalogenation.[6] In our previous studies,[7] 1-arylethyl halides underwent C–X insertion with *α*-aryl diazoesters in the presence of indium trihalides or $BF_3{\cdot}OEt_2$ to afford *α*,*β*-diaryl-*α*-haloesters (Figure 1c, **E**). This reaction involves the abstraction of X^- by a Lewis acid (LA), the addition of a carbocation to a diazoester, and the extrusion of N_2, followed by the re-formation of a C–X bond at the *α*-position of the carbonyl group (Figure 1d, path 1). In the current working hypothesis, the facilitation of an aryl-migration process would install a halogen atom at the *β*-position to yield an *α*,*β*-diaryl-*β*-halo carbonyl product (Figure 1d, path 2, **F**). Race's group[8] reported a carbon–carbon (C–C) bond insertion between primary benzylic bromides and *α*-diazoesters using a substoichiometric amount of $SnBr_4$ (Figure 1e, **G**), but the access to *α*,*β*-diaryl-*β*-halo carbonyls **F** is yet to have been achieved. Herein, we describe a novel C–C bond insertion between diarylmethyl halides and *α*-diazoesters toward a diastereoselective approach to *α*,*β*-diaryl-*β*-halo carbonyl structures (Figure 1f).[5]

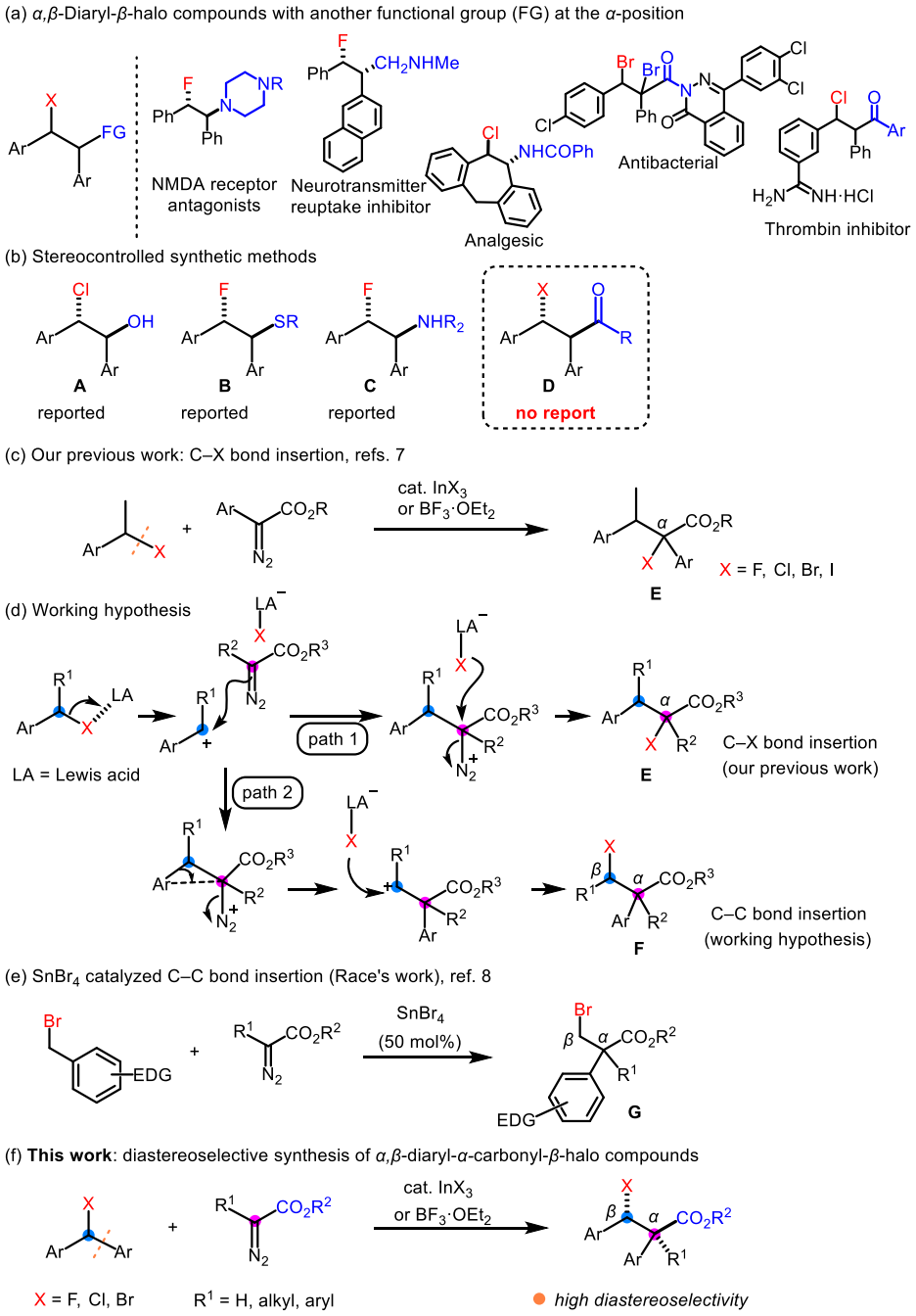


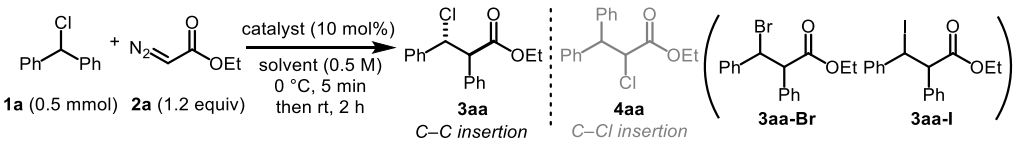
Figure 1. Stereoselective synthesis and representative bioactive targets containing *α,β*-diaryl-*β*-halo components.

2-2. Results and Discussion

Firstly, diphenylmethyl chloride **1a** and diazoester **2a** were selected as model substrates (Table 1). In a CH_2Cl_2 solution, $InCl_3$ afforded C–C bond insertion product **3aa** in 70% yield without the formation of carbon–chlorine (C–Cl) bond insertion product **4aa** (Table 1, Entry 1). The d.r. was moderate (75:25). $InBr_3$ and InI_3 also mediated the desired C–C bond insertion, but a halogen-exchange caused the by-production of **3aa-Br** and **3aa-I** (Entries 2 and 3). Strong Lewis acids $AlCl_3$ and $BF_3{\cdot}OEt_2$[7a] showed no products (Entries

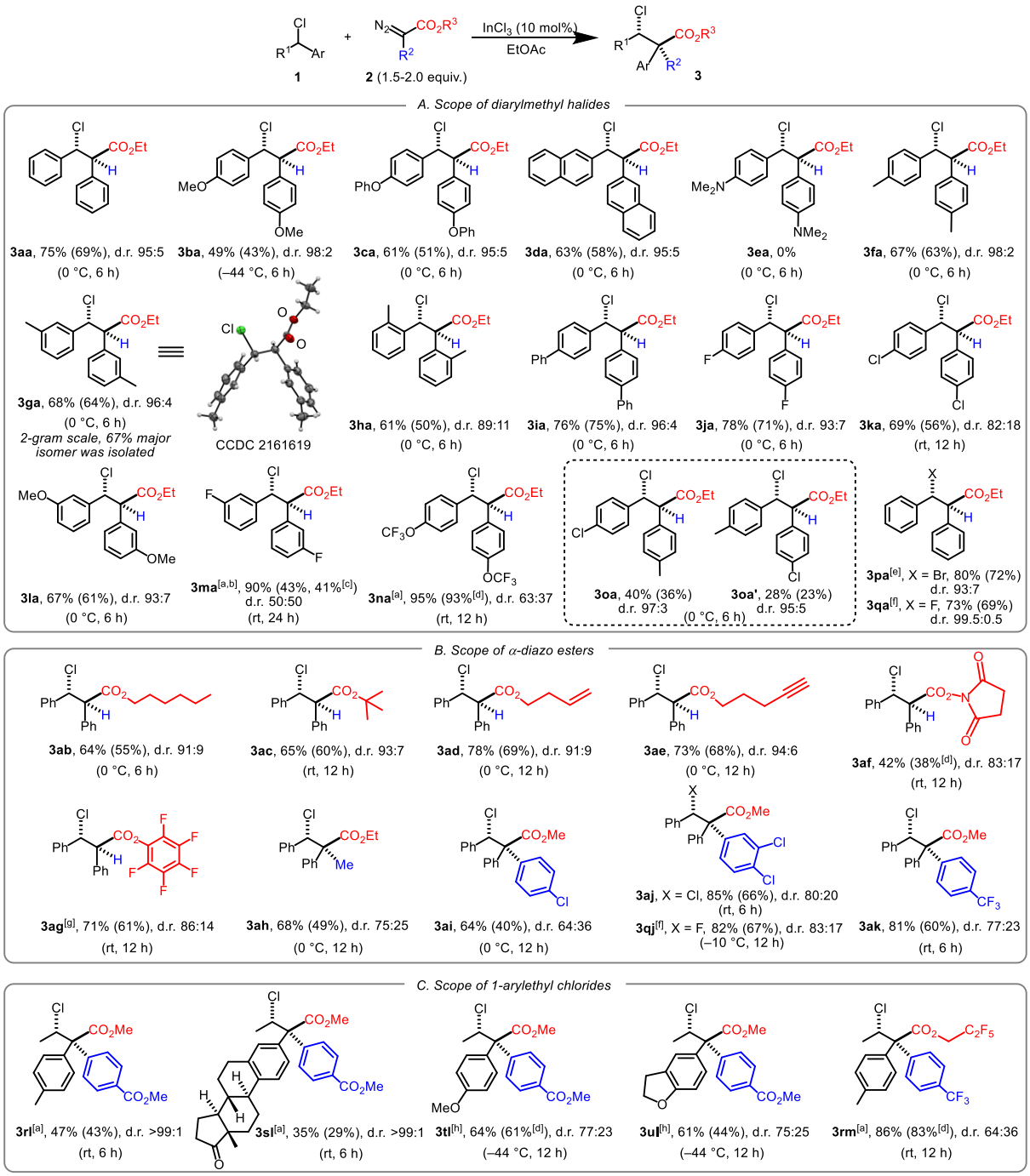
4 and 5). When using $ZnCl_2$ or $SnBr_4$,[8] **3aa** was obtained in 66 and 63% yields, respectively, but the diastereoselectivity was low (Entries 6 and 7). In an investigation into the effect of solvents (Entries 8-15), $CHCl_3$ afforded the highest yield, albeit with low diastereoselectivity (Entries 8-12). No elongation occurred when polar solvents such as THF and acetonitrile were used (Entries 13 and 14) due to the strong coordination between the solvent and InCl3. EtOAc afforded a high level of d.r. (87:13) in 52% yield (Entry 15). Finally, the low temperature, diluted conditions, and use of an excessive amount of **2a** (2.0 equiv) led to high d.r. (95:5) and high yield (75%) (Entry 18).

Table 1. Reaction optimization[a].



entry	catalyst	solvent	yield of **3aa** (%)	d.r.
1	$InCl_3$	CH_2Cl_2	70	75:25
2[b]	InI_3	CH_2Cl_2	53	62:38
3[c]	$InBr_3$	CH_2Cl_2	65	57:43
4	$AlCl_3$	CH_2Cl_2	0	-
5	$BF_3{\cdot}OEt_2$	CH_2Cl_2	0	-
6	$ZnCl_2$	CH_2Cl_2	66	65:35
7[c]	$SnBr_4$	CH_2Cl_2	63	58:42
8	$InCl_3$	toluene	68	69:31
9	$InCl_3$	Et_2O	61	73:27
10	$InCl_3$	$ClCH_2CH_2Cl$	66	82:18
11	$InCl_3$	$CHCl_3$	79	62:38
12	$InCl_3$	1,4-dioxane	20	62:38
13	$InCl_3$	THF	0	-
14	$InCl_3$	MeCN	0	-
15	$InCl_3$	EtOAc	52	87:13
16[d]	$InCl_3$	EtOAc	49	95:5
17[d,e]	$InCl_3$	EtOAc	66	95:5
18[d,e,f]	$InCl_3$	EtOAc	75	95:5

[a]**1a** (0.5 mmol), **2a** (0.6 mmol), catalyst (0.05 mmol), solvent (1 mL), 0 °C, 5 min and then rt, 2 h. Yields and diastereomeric ratios (d.r.) were determined by ^1H NMR using $CHCl_2CHCl_2$ as an internal standard. [b]**3aa-I** was obtained in 9% yield. [c]**3aa-Br** was obtained in 13% yield. [d]The reaction was carried out at 0 °C for 6 h. [e]**2a** (1.0 mmol). [f]EtOAc (2 mL).



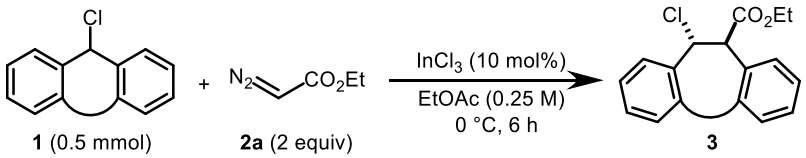
Scheme 1. Reactions of benzylic halides with α-diazoesters. **1** (0.5 mmol), **2** (1.5-2.0 equiv), $InCl_3$ (10 mol%), EtOAc (2 mL). Yields and diastereomeric ratios (d.r.) were determined by ^1H NMR using $CHCl_2CHCl_2$ as an internal standard. Isolated yields of major isomers are shown in parentheses. [a]$CHCl_3$ instead of EtOAc. [b]$InCl_3$ (20 mol%). [c]Isolated yields of minor isomers. [d]Isolated yields of diastereomeric mixtures. [e]$InBr_3$ instead of $InCl_3$, –30 °C for 20 h. [f]$BF_3{\cdot}OEt_2$ instead of $InCl_3$, 0 °C for 12 h. [g]0.2 mmol scale. [h]PhCl instead of EtOAc.

With the optimal conditions in hand, the scope of benzylic chlorides **1** was evaluated (Scheme 1A). Benzylic chlorides with electron-rich aryl groups **1b**, **1c**, **1d**, **1f**, **1g**, **1h**, and **1i** gave the corresponding C–Cinsertion products **3** in high yields with high diastereoselectivities. Use of a much more electron-rich substrate with NMe_2 group (**1e**) resulted in the rapid decomposition of **1e**. The diastereoselectivity was decreased by the steric effect of the *o*-Me group (**3ha**).[9] Fluoro and chloro groups at the *para*-position were

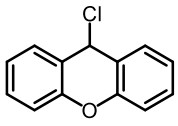
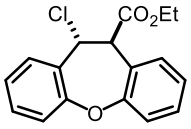
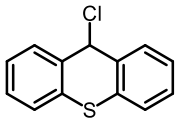
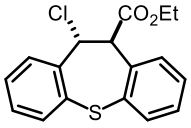
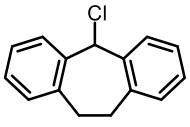
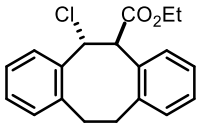
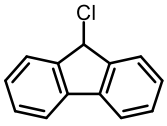
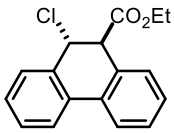
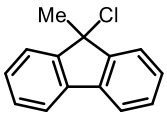
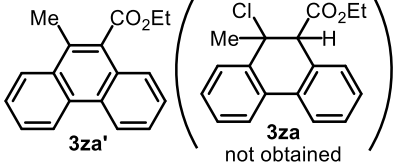
tolerated (**3ja** and **3ka**). Substrates bearing F or CF_3O group (**1m** or **1n**) afforded high yields in $CHCl_3$ rather than EtOAc. Diarylmethyl chloride **1o** with different aryl groups (4-MeC_6H_4 and 4-ClC_6H_4) was examined. The electron-rich aryl group (4-MeC_6H_4) showed higher migration ability than an electron-poor one (4-ClC_6H_4). That result indicated that an electron-donating group should have a positive effect on aryl migration.[9] The relative stereochemistry of a major diastereomer was confirmed by X-ray crystallographic analysis of **3ga**.[11] This elongation was extended to benzylic bromides and benzylic fluorides using $InBr_3$[7b] and $BF_3{\cdot}OEt_2$[7a], respectively, instead of $InCl_3$. *β*-Bromoester **3pa** and *β*-fluoroester **3qa** were obtained in high yields with excellent diastereoselectivity. Several diazoesters were examined (Scheme 1B). Hexyl and *tert*-butyl *α*-diazoesters (**2b** and **2c**) gave high yields and high diastereoselectivity. Diazoesters bearing terminal alkenyl and alkynyl groups exhibited good tolerance to elongation (**3ad** and **3ae**). Ester groups (**2f** and **2g**) that were more electron-deficient showed slightly lower levels of diastereoselectivity. *α*-Alkyl- or *α*-aryl-substituted diazoesters (**2h**, **2i**, **2j**, and **2k**) were used to diastereoselectively construct *α*-quaternary carbon esters. In our previous report,[7b] 1-arylethyl chlorides underwent C–Cl insertion with *α*-diazoesters. By contrast, the combination of 1-arylethyl chlorides with electron-donating groups and *α*-diazoesters with electron-deficient aryl groups afforded C–C insertion products in 35 to 86% yields with high d.r. (up to >99:1, Scheme 1C), although C–Cl insertion competitively occurred (See Scheme S1).

Ring expansion of fused polycyclic compounds via regioselective C–C bond insertion has worked wonders for the synthesis of more complex versions.[10] We examined ring expansion in cyclic benzylic chlorides (Table 2). The reaction of 9-chloro-9*H*-xanthene (**1v**) or 9-chloro-thioxanthene (**1w**) with **2a** produced dihydrodibenzo[*b*,*f*]oxepine **3va** or -dihydrodibenzo[*b*,*f*]thiepine **3wa** with high diastereoselectivity.[11] These fused cyclic frameworks are important to the pharmaceutical chemistry.[12] Tetrahydro-dibenzo[*a*,*e*]cyclooctene **3xa** was obtained in 83% yield from **1x**. However, 9-chloro-9*H*-fluorene **1y** failed to yield the desired product due to instability of the corresponding fluorenyl cation intermediate.[13] Owing to the stabilization of the cationic intermediate by a methyl group, ring expansion of **1z** smoothly occurred, and a subsequent dehydrochlorination gave phenanthrene **3za**' instead of the 9,10-dihydrophenanthrene **3za**.[14]

Table 2. Reaction optimization[a].



1 (0.5 mmol) **2a** (2 equiv) **3**

entry	benzylic chloride	product **3**	yield	d.r.
1	 **1v**	 **3va**[b]	84% (74%)	91:9
2	 **1w**	 **3wa**	80% (65%)	87:13
3	 **1x**	 **3xa**	83% (79%[c])	83:17
4	 **1y**	 **3ya**	no reaction	-
5	 **1z**	 **3za'** **3za** not obtained	80% (80%)	-

[a]**1** (0.5 mmol), **2a** (1.0 mmol), $InCl_3$ (0.05 mmol), EtOAc (2 mL), 0 °C, 6 h. Yields and diastereomeric ratios (d.r.) were determined by ^1H NMR using $CHCl_2CHCl_2$ as an internal standard. Isolated yields of major isomers are shown in parentheses. [b]0 °C for 1 h. [c]Isolated yields of diastereomeric mixture.

The high diastereoselectivity gained in the present reaction was charted via density functional theory (DFT) calculation (Figure 2). The abstraction of Cl^- by $InCl_3$ affords benzylic cation **6**, and then a nucleophilic addition of diazoester **2a** forms diazonium **7c**. Intermediates **7a** and **7b**, rotamers of **7c**, afford carbocation **Int-9a** and **Int-9b**, respectively, through three-membered ring transition states (**TS-8a** and **TS-8b**) where Ph-migration and N_2-extrusion occur in a concerted manner.[8,15] Spontaneous N_2 loss from **7a** or **7b** without Ph-migration leads to an unstable carbocation, which is contrast to recent studies.[8] Moreover, a local minimum phenonium intermediate **12** was not found in this step (Scheme S3).[8] The addition of Cl^- from $InCl_4^-$ to the cationic carbon centers in van der Waals complexes **Int-10a** and **Int-10b** occurs through **TS-11a** and **TS-11b** to give **3aa-major** and **3aa-minor**, respectively. Different Ph groups migrate in **TS-8a** and **TS-8b**, while **TS-8a** is more favored than **TS-8b**, because **TS-8a** contains the least amount of repulsion between a stationary phenyl group and an ester moiety (Figure 2 and Scheme S2).[15b] The solvent effect was investigated by DFT calculation and isomerization experiments (Figure S1 and Scheme S4), which

demonstrated the moderate donor solvent EtOAc inhibits the isomerization between elongation products and $InCl_3$.

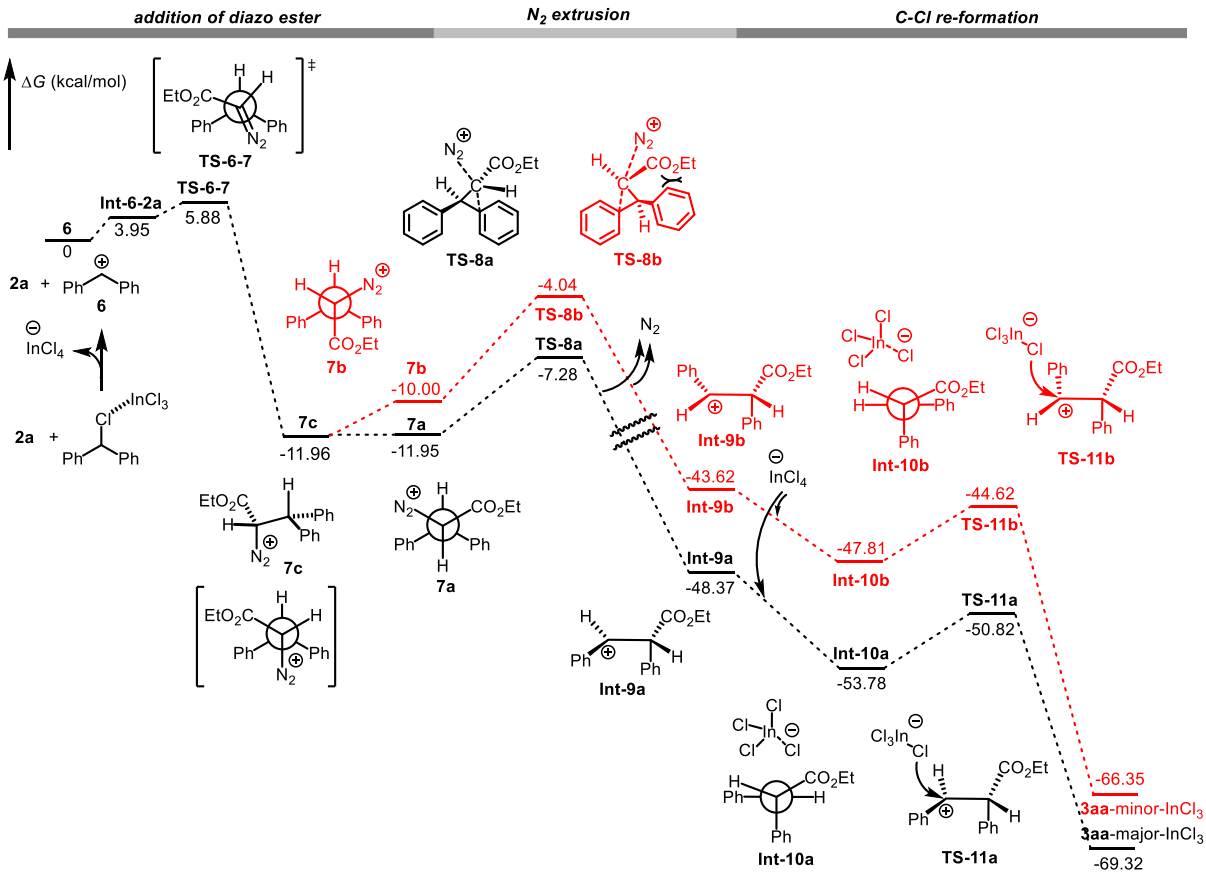


Figure 2. Rationale based on DFT calculations (SMD(EtOAc)/ωB97X-D/6-311+G(d,p) for H, C, N, O, Cl, and LANL2DZ for In, ΔG in kcal/mol at 273.15 K).

Figure 3 depicts the usefulness of the C–C bond insertion products. Product (2*R**,3*R**)-**3ga** was transformed to α,β-unsaturated carboxylic ester (*Z*)-**13** via E2 elimination.[6c] Reduction of the ester group in (2*R**,3*R**)-**3ga** by diisobutylaluminium hydride afforded γ-chloroalcohol **14**. Further treatment of **14** with chloromethyl methyl ether and $ZnCl_2$ catalyst gave isochromane **15** with no loss of stereochemistry.[3f,16] The substitution of a Cl group for other functional groups was examined. The use of $AgNO_2$[17] produced nitro compound **16** (60% yield, d.r. = >99:1) as a single diastereomer. Azide **17** (95% yield, d.r. = >99:1) was obtained with an inversion of the stereo configuration[18] from NaN_3.[3f] Both the two compounds have the potential to afford direct access to unnatural amino alcohol.[19] A one-pot procedure was performed to prepare dibenzo[*b*,*f*]oxepine derivative **18** from **3va**, which is an important motif in natural and medicinal compounds.[20]

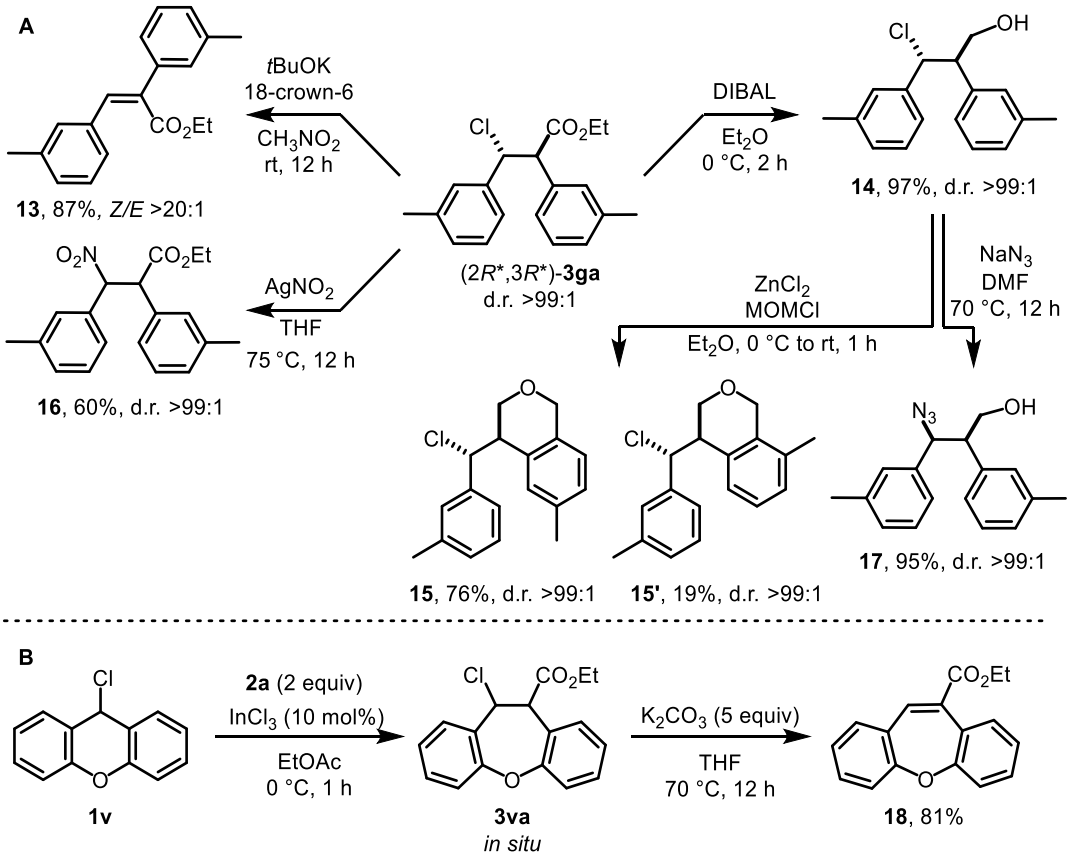


Figure 3. Diversification of *α,β*-diaryl-*β*-halo carbonyl compounds. Isolated yields are shown and diastereomeric ratios (d.r.) were determined by ^{1}H NMR in crude products.

2-3. Conclusion

In conclusion, we introduced a Lewis acid-catalyzed C–C bond insertion between secondary benzylic halides and α-diazoesters to afford *α,β*-diaryl-*β*-halo carbonyl compounds diastereoselectively. This reaction proceeds via chemoselective C–X bond cleavage and C–X bond re-formation at the benzylic position. The results of DFT study suggest that the diastereoselectivity is determined in three-membered ring-transition states where Ph-migration and N_2-extrusion occur in a concerted manner. The high level of the functional compatibility of the present elongation establishes its potential for use in the synthesis of pharmaceutical building blocks.

2-4. Experimental Section

General Information

NMR spectra were recorded on JEOL-AL400 and JNM-ECZL400S spectrometers (400 MHz for ^{1}H, 100 MHz for ^{13}C, and 376 MHz for ^{19}F NMR). Chemical shifts were reported in ppm on the δ scale relative to tetramethylsilane (δ = 0 for ^{1}H NMR) and $CDCl_3$ (δ = 77.0 for ^{13}C NMR) as internal references. Chemical shifts were reported in ppm on the δ scale relative to TFA (δ = -76.55 for ^{19}F NMR) as an external reference. Coupling constants were quoted in Hz (*J*). ^{1}H NMR spectroscopy splitting patterns were designated as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), and sextet (sext). Splitting patterns that could not be

interpreted or easily visualized were designated as multiplet (m) or broad (br). New compounds were characterized by ^{1}H NMR, ^{13}C NMR, H-H COSY, HMQC, and HMBC. HRMS measurements were obtained on a JMS-T100LP (TOF analyzer with ESI or DART ionization sources). Melting point was measured with MP-J3 (Yanaco) instrument. Infrared (IR) spectra were recorded on a JASCO FT/IR-6200 Fourier transform infrared spectrophotometer. Column chromatographies were performed with silica gel. Purification by preparative recycle HPLC was performed on SHIMADZU recycle HPLC system (SPD-20A, RID-10A, DGU-20A, LC-6AD, and FCV-20H2) and Japan Analytical Industry Co. (NEXT recycling preparative HPLC) with n-hexane/EtOAc as eluent (15 mL/min). Purification by recycle GPC was performed on Japan Analytical Industry Co. (NEXT recycling preparative HPLC) with $CHCl_3$ as eluent (7.5 mL/min). Reactions were carried out in dry solvents under nitrogen atmosphere, unless otherwise stated. Reagents were purchased from Aldrich or Tokyo Chemical Industry Co., Ltd. (TCI), FUJIFILM Wako Pure Co., Ltd., and used after purification by distillation or used without purification for solid substrates. X-ray diffraction analysis was carried out by Rigaku XtaLAB Synergy with Hypix-6000HE.

Materials

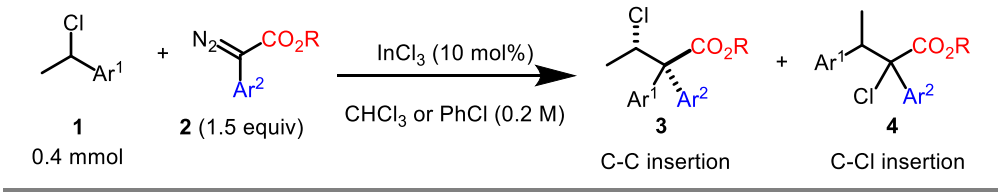
Dehydrated solvents were purchased from FUJIFILM Wako Pure Co., Ltd. and used as obtained. Benzylic chlorides (**1a** and **1j**) and benzylic bromide **1p** were purchased from Tokyo Chemical Industry Co., Ltd. (TCI) and used as obtained. Diazoester **2a** was purchased from Sigma Aldrich and used as obtained. The synthetic procedures for other benzylic halides and diazoesters were described below.

DFT calculation study

General

All calculations were performed with Gaussian 16, Revision C.01. Quantum chemical calculations were performed. The geometry optimizations and frequency calculations at 298.15 K and 1 bar were carried out at ωB97X-D level of theory with a mixed basis set; The effective core potential of Hay and Wadt with a double-ξ valence basis set (LANL2DZ) was chosen to describe In. The 6-311+G(d,p) basis set was used for other atoms. SMD (ethyl acetate) was used as a solvent effect. All molecular geometries were fully optimized and Gibbs free energies including contribution of vibrational entropy at an appropriate temperature were described in energy profiles. Stationary points, minima, and transition states on the potential energy surface were identified by vibrational analysis. It was confirmed that the transition state had only one imaginary frequency. Gibbs free energies were calculated as a sum of the single-point electronic energy and thermal correction to the Gibbs free energy. Gibbs free energies at 273.15 K were calculated by *GoodVibes* (Funes-Ardoiz, I.; Paton, R. S. *GoodVibes*, Version 2.0.1, **2018**.).

Competitive reaction between C–C and C–Cl insertions

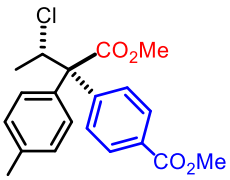


1
0.4 mmol

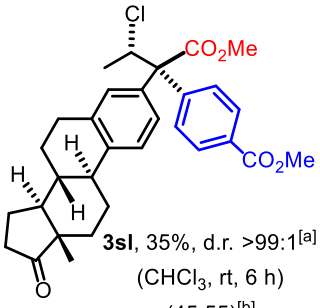
2 (1.5 equiv)

3
C-C insertion

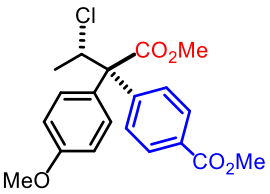
4
C-Cl insertion



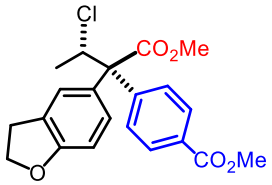
3rl, 47%, d.r. >99:1[a]
($CHCl_3$, rt, 6 h)
(47:53)[b]



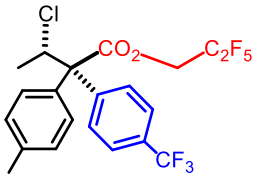
3sl, 35%, d.r. >99:1[a]
($CHCl_3$, rt, 6 h)
(45:55)[b]



3tl, 64%, d.r. 77:23[a]
(PhCl, -44 °C, 12 h)
(67:33)[b]



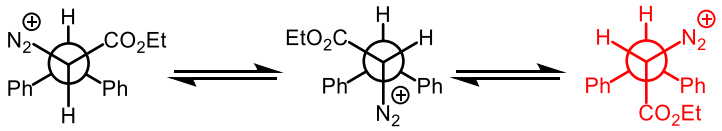
3ul, 61%, d.r. 75:25[a]
(PhCl, -44 °C, 12 h)
(75:25)[b]



3rm, 86%, d.r. 64:36[a]
($CHCl_3$, rt, 12 h)
(87:13)[b]

Scheme S1. Competitive reaction between C–C insertion and C–Cl insertion. [a]Sum of yields and diastereomeric ratios (d.r.) of C–C insertion **3**. [b]Ratio of C–C insertion **3** and C–Cl insertion **4**.

Rotamer exchange between 7a, 7b, and 7c

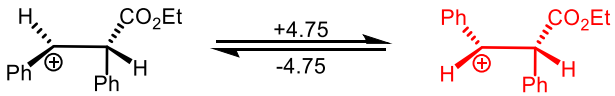


7a
0.01 kcal/mol

7c
0 kcal/mol

7b
1.96 kcal/mol

Rotamer exchange between Int-9a and Int-9b



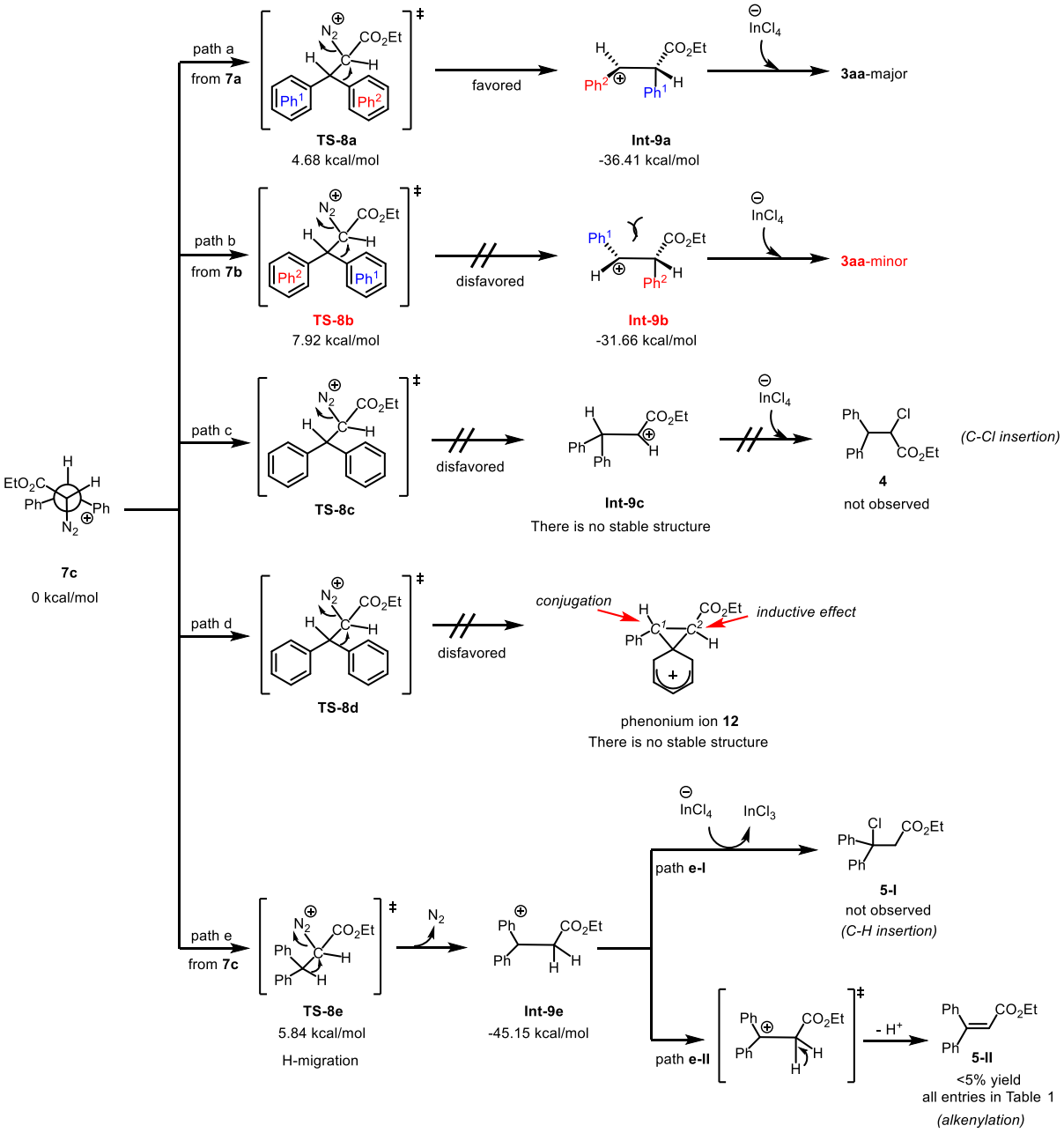
Int-9a
0 kcal/mol

Int-9b
4.75 kcal/mol

Scheme S2. Energy barriers of rotamers exchange for rotamers **7** and **Int-9**.

Consideration of phenonium intermediate 12 (Scheme S3)

The proposed structure of phenonium intermediate **12** has no local minimum structure, and the firstly-input structure **12** spontaneously gave intermediate **9a** or **9b** in DFT calculations. The adjacent ester group disfavors the formation of a carbocation like **Int-9c** in which a cationic center is at C^2 position due to electron-withdrawing effect of a carbonyl group and promotes the formation of phenonium intermediate as depicted by Race's work (N. J. Race et al. *J. Am. Chem. Soc.* **2022**, *144*, 86). However, in our work, a conjugation of stationary Ph group can well stabilize the formation of carbocation at C^1 position and further drive the aryl-migration. Therefore, the phenonium intermediate **12** does not have local minimum, and N_2 extrusion/Ph-migration concertedly occurs to generate intermediate **9a** or **9b**.



Scheme S3. Proposed pathways for the formation of cation **Int-9** and phenonium ion **12**.

Consideration of solvent effect on the enhancement of diastereoselectivity (Figure S1 and Scheme S4)

As shown in Figure S1, the energy barrier in diastereoselectivity determining step has the same level in a non-polar solvent ($CHCl_3$, by 3.54 kcal/mol) or a moderately polar solvent (EtOAc, by 3.24 kcal/mol). It demonstrates that the solvent has low effect on the selectivity. However, an isomerization of products was experimentally observed when non-polar $CHCl_3$ was used as solvent (Scheme S4). A single diastereomer of product (2*R**, 3*R**)-**3ga** was treated with 10 mol% of $InCl_3$ in $CHCl_3$ to give diastereomeric mixture of **3ga** (d.r. = 55:45). On the other hand, the examination using EtOAc as a solvent did not reduce the diastereomeric ratio. These results suggest that in $CHCl_3$ the retro reaction involving Cl^- abstraction from **3ga** by $InCl_3$ causes the isomerization. EtOAc moderately coordinates to $InCl_3$ and disturbs the Cl^- abstraction from **3ga**.

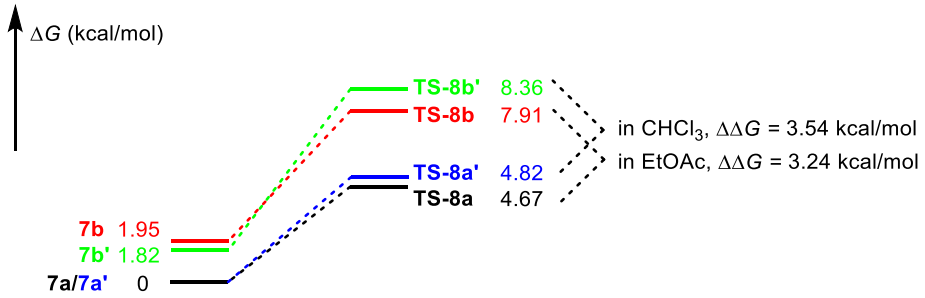
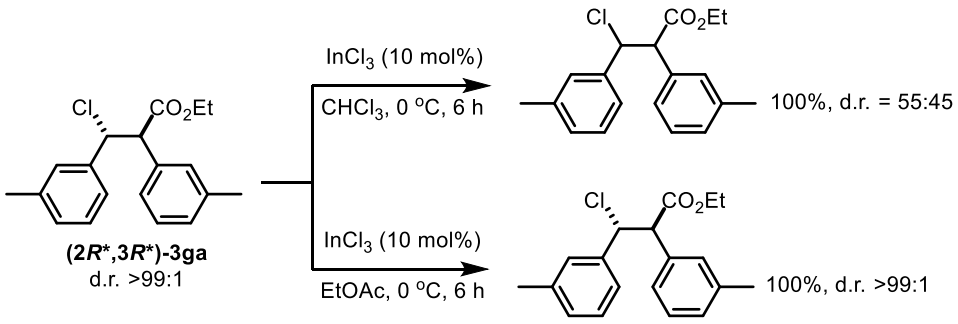


Figure S1. Solvent effect between EtOAc and $CHCl_3$ in intermediate **7** and **TS-8** based on DFT calculations (SMD/ωB97X-D/6-311+G(d,p) for H, C, N, O, ΔG in kcal/mol at 273.15 K). **7a**, **7b**, **TS-8a**, and **TS-8b** calculated by using EtOAc as solvent; **7a'**, **7b'**, **TS-8a'**, and **TS-8b'** calculated by using $CHCl_3$ as solvent.

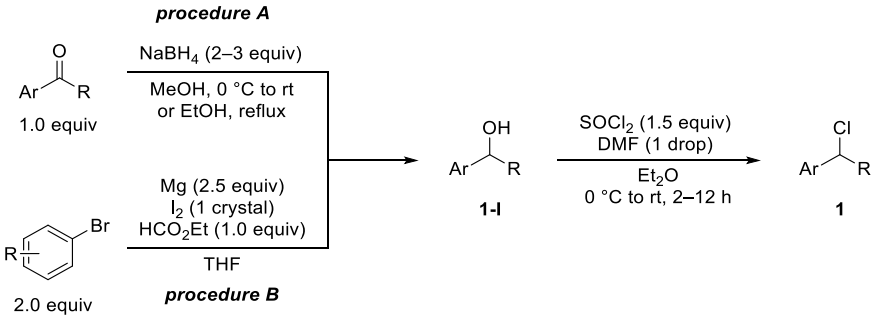
Isomerization experiments



Scheme S4. Isomerization Experiments

Procedure: to a reaction tube was charged with $InCl_3$ (0.01 mmol, 2.2 mg), solvent (0.4 mL), and single diastereomer (2*R**,3*R**)-**3ga** (0.1 mmol, 30.1 mg). The mixture was stirred at 0 °C for 6 h. The mixture was quenched by saturated $NaHCO_3$ aq and extracted with EtOAc (15 mL x 3). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The sum yield of diastereomers and diastereomeric ratio were determined by ^1H NMR in the crude product.

General procedures for preparation of benzylic chlorides 1

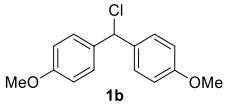


Procedure A: Under nitrogen atmosphere, the corresponding ketone (10 mmol, 1.0 equiv) and anhydrous MeOH or EtOH (30 mL) were added to a 50 mL three-necked round-bottomed flask at 0 °C. $NaBH_4$ (2-3 equiv) was slowly added to the resultant mixture. The reaction was then stirred for additional 30 min at this temperature, the ice bath was removed and the temperature was naturally warmed to room temperature and the reaction mixture was stirred for 2-6 h, or refluxed overnight. After completion of the reaction (checked by TLC), the reaction mixture was quenched by water and extracted by ethyl acetate (30 mL x 3). The combined organic layers were washed with brine and dried over $MgSO_4$. The solvent was then evaporated to afford the alcohol **1-I** which was used to the next step without further purification. The alcohol **1-I** (10 mmol, 1.0 equiv) was diluted with Et_2O (10 mL) and transferred to a 30 mL reaction tube. After cooling to 0 °C, one drop of DMF was added to the mixture and subsequently thionyl chloride (15 mmol, 1.5 equiv) was added dropwise over 5 min. The reaction mixture was stirred at room temperature for 2 h or overnight until the complete consumption of the starting material (checked by TLC). Upon completion of the reaction, the resulting mixture was poured into ice and washed with saturated $NaHCO_3$ aq (20 mL x 2), extracted with Et_2O (30 mL x 2), and dried over $MgSO_4$. The solvent was removed and the crude mixture was purified by silica gel flash column chromatography with *n*-hexane as eluent to give the benzylic chlorides **1**.

Procedure B: Under nitrogen atmosphere, THF (30 mL) was added to a flask with magnesium turnings (0.61 g, 25 mmol, 2.5 equiv). The reaction flask was heated at 70 °C and I_2 (1 crystal) was added to the mixture. After 5 minutes, aryl bromide (20 mmol, 2.0 equiv) in THF (20 mL) was added slowly to the reaction mixture over 30 min. The reaction mixture was then heated to reflux for 3 h. Upon cooling to 0 °C, ethyl formate (0.74 g, 10 mmol, 1.0 equiv) was added dropwise to the reaction mixture. After completion, the resultant solution was warmed to room temperature and stirred for additional 18 h. The reaction mixture was cooled by ice bath and carefully quenched by saturated NH_4Cl solution (30 mL). The resulted mixture was filtered and the filtrate was extracted by EtOAc (50 ml x 3). The organic layer was washed by brine (50 mL) and dried over $MgSO_4$, filtered and concentrated in vacuo to give the alcohol intermediate **1-I** which was used to the next step without further purification or purified by silica gel column chromatography (*n*-hexane/EtOAc = 80/20). The alcohol **1-I** (10 mmol, 1.0 equiv) was diluted with Et_2O (10 mL) and transferred to a 30 mL reaction tube. After cooling to 0 °C, DMF (1 drop) was added to the mixture subsequently thionyl chloride (15 mmol, 1.5 equiv) was added dropwise over 5 min. The reaction mixture was stirred at room temperature for 2 h or overnight until the complete consumption of starting material (checked by TLC). Upon completion of the reaction, the resulting mixture was poured into ice and washed with saturated

$NaHCO_3$ aq (20 mL x 2), extracted with Et_2O (30 mL x 2), and dried over $MgSO_4$. The solvent was removed and the crude mixture was purified by silica gel flash column with n-hexane as eluent to give benzylic chlorides **1**.

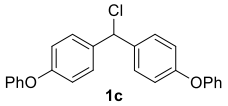
(1b) 4,4'-(Chloromethylene)bis(methoxybenzene)



1b

Compound **1b** was prepared from bis(4-methoxyphenyl)methanol (2.44 g, 10 mmol) according to the general procedure A. The reaction mixture was directly evaporated to give title compound as a white or red solid, 2.60 g, 99% yield. Which was used without purification. The characterization data were identical to those reported in the literature (Characterization data, M. A. Tandiary, Y. Masui, M. Onaka, *Synlett* **2014**, *25*, 2639.).

(1c) 4,4'-(Chloromethylene)bis(phenoxybenzene)

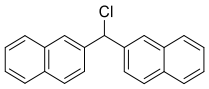


1c

Compound **1c** was prepared from 1-bromo-4-phenoxybenzene (4.98 g, 20 mmol) according to the general procedure B. White solid, 2.71 g, 70% yield, 2 steps. The product is enough pure and used to homologation reaction without further purification.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.37-7.32 (m, 8H, Ar-H), 7.12 (t, J = 7.0 Hz, 2H, Ar-H), 7.02 (d, J = 8.5 Hz, 4H, Ar-H), 6.96 (d, J = 8.5 Hz, 4H, Ar-H), 6.13 (s, 1H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 157.2, 156.6, 135.6, 129.8, 129.2, 123.6, 119.2, 118.4, 63.6; m.p. 82–83 °C; HRMS: (DART+) Calculated ($C_{25}H_{19}O_2$) 351.1380 $(M–Cl)^+$ Found: 351.1372

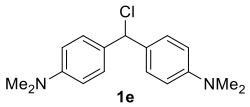
(1d) 2,2'-(Chloromethylene)dinaphthalene



1d

Compound **1d** was prepared from 2-bromonaphthalene (2.07 g, 10 mmol) according to the general procedure B. The reaction mixture was directly evaporated to give title compound as white solid, 2.87 g, 95% yield, two steps. Which was used without purification. The characterization data were identical to those reported in the literature (Characterization data, M. Holtz-Mulholland, S. K. Collins, *Synthesis* **2014**, *46*, 375.).

(1e) 4,4'-(Chloromethylene)bis(*N*,*N*-dimethylaniline)



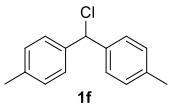
1e

Compound **1e** was prepared from bis(4-(dimethylamino)phenyl)methanone (2.68 g, 10 mmol) according to the general procedure A. The reduction was performed in EtOH and reflux for 6 h to give 4,4'-bis(dimethylamino)benzhydrol as a white solid, 2.70 g, 99%. The obtained crude alcohol was directly dissolved in Et_2O at 0 °C, then $SOCl_2$ (1.78 g, 15 mmol, 1.5 equiv) and DMF (1 drop) were added to the

mixture and stirred at this temperature for 1 h. The reaction mixture was evaporated to give title compound as a blue or grey solid without any purification, 2.87 g, 95% yield, two steps. Compound **1e** is unstable on silica gel and directly used to homologation reaction including a minor impurity (purity is over 90%).

^{1}H NMR: (400 MHz, DMSO-d_6) δ 7.76 (d, *J* = 8.3 Hz, 4H, Ar-H), 7.71 (s, 1H, Ar_2CH), 7.57 (d, *J* = 8.3 Hz, 4H, Ar-H), 3.06 (s, 12H, NMe_2); ^{13}C NMR: (100 MHz, DMSO-d_6) δ 142.1, 130.7, 127.6, 121.2, 72.8, 45.6; HRMS: (DART+) Calculated $(C_{17}H_{21}N_2)$ 253.1699 $(M–Cl)^+$ Found: 253.1695; m.p. 150–152 °C (decomposed)

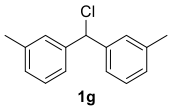
(1f) 4,4'-(Chloromethylene)bis(methylbenzene)



1f

Compound **1f** was prepared from di-*p*-tolylmethanone (3.15 g, 15 mmol) according to the general procedure A. The title compound was obtained as a white solid and used without any purification, 3.42 g, 99% yield, two steps. The characterization data were identical to those reported in the literature (Characterization data, B. Denegri, A.Streiter, S. Jurić, A. R. Ofial, O. Kronja,, H. Mayr, *Chem. Eur. J.* **2006**, *12*, 1648.).

(1g) 3,3'-(Chloromethylene)bis(methylbenzene)

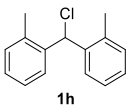


1g

Compound **1g** was prepared from 1-bromo-3-methylbenzene (7.18 g, 20 mmol) according to the general procedure B. The title compound was purified by silica gel column chromatography (n-hexane/EtOAc = 95/5) as a colorless oil, 2.08 g, 90% yield, two steps.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.25-7.21 (m, 6H, Ar-H), 7.10 (d, *J* = 7.0 Hz, 2H, Ar-H), 6.06 (s, 1H, Ar_2CH), 2.34 (s, 6H, $ArCH_3$); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 141.0, 138.1, 128.7, 128.34, 128.29, 124.7, 64.4, 21.4; HRMS: (DART+) Calculated $(C_{15}H_{15})$ 195.1168 $(M–Cl)^+$ Found: 195.1163

(1h) 2,2'-(Chloromethylene)bis(methylbenzene)

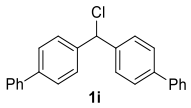


1h

Compound **1h** was prepared from 1-bromo-2-methylbenzene (3.42 g, 20 mmol) according to the general procedure B. The title compound was obtained as a pink solid and used without purification, 2.08 g, 90% yield, two steps.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.42-7.41 (m, 2H, Ar-H), 7.20-7.14 (m, 6H, Ar-H), 6.45 (s, 1H, Ar_2CH), 2.29 (s, 6H, $ArCH_3$); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 138.3, 135.4, 130.4, 128.0, 126.3, 58.8, 19.0; m.p. 64–65 °C; HRMS: (DART+) Calculated $(C_{15}H_{15})$ 195.1168 $(M–Cl)^+$ Found: 195.1167

(1i) 4,4''-(Chloromethylene)di-1,1'-biphenyl

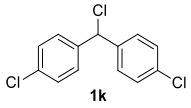


1i

Compound **1i** was prepared from 4-bromo-1,1'-biphenyl (3.49 g, 15 mmol) according to the general procedure B. The title compound was obtained as a white solid and used without any purification, 2.0 g, 75% yield, two steps.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.61-7.58 (m, 8H, Ar-H), 7.53 (d, *J* = 8.7 Hz, 4H, Ar-H), 7.44 (t, *J* = 7.6 Hz, 4H, Ar-H), 7.36 (d, *J* = 7.6 Hz, 2H, Ar-H), 6.24 (s, 1H, Ar_2CH); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 141.0, 140.4, 139.9, 128.8, 128.2, 127.5, 127.3, 127.1, 63.9; m.p. 120–121 °C; HRMS: (DART+) Calculated ($C_{25}H_{19}$) 319.1481 $(M–Cl)^+$ Found: 319.1478

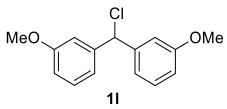
(1k) 4,4'-(Chloromethylene)bis(chlorobenzene)



1k

Compound **1k** was prepared from bis(4-chlorophenyl)methanone (3.77 g, 15 mmol) according to the general procedure A. The title compound was obtained as a white solid and used without any purification, 4.03 g, 99% yield, two steps. The characterization data were identical to those reported in the literature (Characterization data, M. A. Tandiary, Y. Masui, M. Onaka, *Synlett* **2014**, *25*, 2639.).

(1l) 3,3'-(Chloromethylene)bis(methoxybenzene)

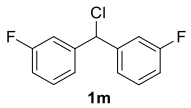


1l

Compound **1l** was prepared from bis(3-methoxyphenyl)methanone (2.42 g, 10 mmol) according to the general procedure A. The title compound was purified by silica gel column chromatography (n-hexane/EtOAc = 95/5) as a pale yellow oil, 2.23 g, 85% yield, two steps.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.22 (t, *J* = 8.3 Hz, 2H, Ar-H), 6.98 (br s, 4H, Ar-H), 6.80 (d, *J* = 8.3 Hz, 2H, Ar-H), 6.04 (s, 1H, Ar_2CH), 3.74 (s, 6H, OCH_3); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 159.5, 142.3, 129.5, 119.9, 113.5, 113.2, 63.9, 55.1; HRMS: (DART+) Calculated ($C_{15}H_{15}O_2$) 227.1067 $(M–Cl)^+$ Found: 227.1069

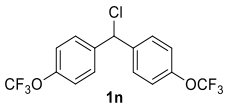
(1m) 3,3'-(Chloromethylene)bis(fluorobenzene)



1m

Compound **1m** was prepared from 1-bromo-3-fluorobenzene (5.25 g, 30 mmol) according to the general procedure B. The title compound was obtained as a colorless oil, 2.39 g, 67% yield, two steps. The characterization data were identical to those reported in the literature (Characterization data, C. Nolte, H. Mayr, *Eur. J. Org. Chem.* **2010**, *2010*, 1435.).

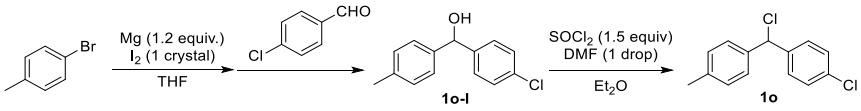
(1n) 4,4'-(Chloromethylene)bis((trifluoromethoxy)benzene)



Compound **1n** was prepared from 1-bromo-4-(trifluoromethoxy)benzene (2.65 g, 11 mmol) according to the general procedure B. Pale yellow oil, 1.85 g, 91% yield, two steps.

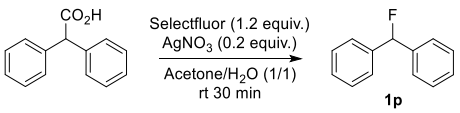
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.43 (d, J = 8.7 Hz, 4H, Ar-H), 7.21 (d, J = 8.7 Hz, 4H, Ar-H), 6.12 (s, 1H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 149.0 (q, J = 1.9 Hz), 139.2, 129.2, 121.1, 120.4 (q, J = 257.5 Hz), 62.2; ^{19}F NMR: (376 MHz, $CDCl_3$) δ -57.91 (s, 6F); HRMS: (DART+) Calculated ($C_{15}H_9O_2F_6$) 335.0501 $(M–Cl)^+$ Found: 335.0489

(1o) 1-Chloro-4-(chloro(*p*-tolyl)methyl)benzene



Under nitrogen atmosphere, THF (30 mL) was added to a flask with magnesium turnings (0.58 g, 24 mmol, 1.2 equiv). The reaction flask was heated at 70 °C and I_2 (1 crystal) was added to the mixture. After 5 minutes, 1-bromo-4-methylbenzene (3.42 g, 20 mmol, 1.0 equiv) in THF (20 mL) was added slowly to the reaction mixture over 30 min. The reaction mixture was then heated to reflux for 3 h. Upon cooling to 0 °C, 4-chlorobenzaldehyde (2.11 g, 15 mmol, 0.75 equiv) was added dropwise to the reaction mixture. After completion, the resultant solution was warmed to room temperature and stirred for 2 h. The reaction mixture was cooled by ice bath and carefully quenched by saturated NH_4Cl solution (30 mL). This resulted mixture was filtered and the filtrate was extracted by EtOAc (50 mL x 3). The organic layer was washed by brine (50 mL) and dried over $MgSO_4$, filtered and concentrated in vacuo to give alcohol intermediate **1o-I** (white solid, 3.5 g, 99% yield) which was used to the next step without further purification. Intermediate **1o-I** (1.0 g, 4.3 mmol, 1.0 equiv) was diluted in Et_2O (5 mL) and transferred to a 20 mL reaction tube. After cooling to 0 °C, thionyl chloride (0.79 g, 6.3 mmol, 1.5 equiv) was added dropwise over 2 min. The reaction mixture was stirred at room temperature for 2 h. Upon completion of the reaction, the resulting mixture was poured into ice and washed with saturated $NaHCO_3$ aq (20 mL x 2), extracted with Et_2O (30 mL x 2), and dried over $MgSO_4$. The solvent was removed to give title compound **1o** as a yellow solid, 1.08 g, 99% yield. The characterization data were identical to those reported in the literature (Characterization data, B. Peng, X. Feng, X. Zhang, S. Zhang, M. Bao, *J. Org. Chem.* **2010***, 75,* 2619.).

(1p) (Fluoromethylene)dibenzene

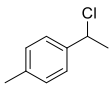


According to a modified procedure (F. Yin, Z. Wang, Z. Li, C. Li, *J. Am. Chem. Soc.* **2012**, *134*, 10401.). Selectfluor® (12 mmol) was placed to a reaction tube (30 mL) which was evacuated and filled with nitrogen. 2,2-Diphenylacetic acid (2.12 g, 10 mmol, 1.0 equiv), acetone (8 mL), dilute water (8 mL), and $AgNO_3$ (0.34

g, 2 mmol, 0.2 equiv) were then sequentially added. The reaction mixture was stirred at 0 °C for 5 min and rt for 30 min. Upon completion of the reaction, 5 mL aqueous HCl (1 M) was added to the resulting mixture to quench this reaction. The mixture was extracted with n-hexane (30 mL x 3) and combined organic layers were washed with saturated aqueous $NaHCO_3$ (30 mL x 2), dried over $MgSO_4$, filtration, and evaporation. The title compound was obtained as a colorless oil, 1.71 g, 92% yield. This compound is enough pure and used without further purification.

CAUTION: The evaporation must be operated with a Teflon bottle, because this benzylic fluoride is sensitive to glass container especially under high temperature and high concentration. If this compound is evaporated with a glass bottle, it is decomposed. The obtained product can be stored in a Teflon vial in freezer for a long time. The characterization data were identical to those reported in the literature (Characterization data, A. Vasilopoulos, D. L. Golden, J. A. Buss, S. S. Stahl, *Org. Lett.* **2010**, *22,* 5753.).

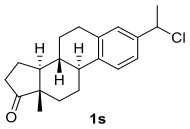
(1r) 1-(1-Chloroethyl)-4-methylbenzene



1r

Compound **1r** was prepared from 1-(*p*-tolyl)ethan-1-ol (1.63 g, 12 mmol) according to the general procedure A. Colorless oil, 1.34 g, 72% yield. (Characterization data, K. Kiyokawa, M. Yasuda, A. Baba, *Org. Lett*. **2010**, *12*, 1570.).

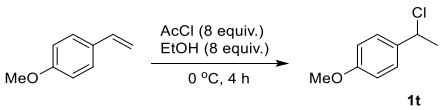
(1s) (8*R*,9*S*,13*S*,14*S*)-3-(1-chloroethyl)-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*-cyclopenta[*a*]phenanthren-17-one



1s

Compound **1s** was prepared from (+)-Estrone according to a reported literature (Preparation and characterization data, F. Wang, Y. Nishimoto, M. Yasuda, *Org. Lett*. **2022**, *24*, 1706.).

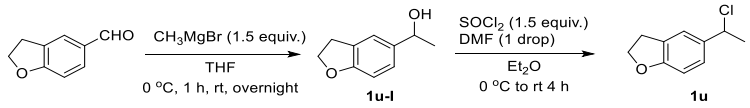
(1t) 1-(1-Chloroethyl)-4-methoxybenzene



1t

According to a reported literature (V. K. Yadav, K. G. Babu, *Eur. J. Org. Chem.* **2005**, 452). To a dried reaction tube was charged with 1-methoxy-4-vinylbenzene (0.67 g, 5 mmol, 1.0 equiv) and EtOH (1.84 g, 40 mmol, 8.0 equiv). Acetyl chloride (3.14 g, 40 mmol, 8.0 equiv) was added dropwise over 5 min at 0 °C. The resultant mixture was stirred at 0 °C for 4 h. Upon completion of the reaction (checked by TLC), the resulting mixture was poured into ice and diluted by Et_2O. The organic layer was separated and washed with brine (30 mL x 2), dried over $MgSO_4$. The solvent was removed to give the title compound **1t** as a colorless oil, 1.62 g, 95% yield. This compound is enough pure and used without further purification. The characterization data were identical to those reported in the literature (V. K. Yadav, K. G. Babu, *Eur. J. Org. Chem.* **2005**, 452.).

(1u) 5-(1-Chloroethyl)-2,3-dihydrobenzofuran

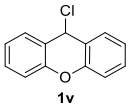


To a dried reaction tube was charged with 2,3-dihydrobenzofuran-5-carbaldehyde (1.48 g, 10 mmol, 1.0 equiv) and THF (20 mL). Methylmagnesium bromide (3 M in THF, 5 mL, 15 mmol, 1.5 equiv) was added dropwise over 5 min at 0 °C. The resultant mixture was stirred at 0 °C for 1 h and rt overnight. Upon completion of the reaction (checked by TLC), the resulting mixture was quenched by saturated NH_4Cl aq and diluted by Et_2O (50 mL). The organic layer was separated and washed with brine (30 mL x 2), dried over $MgSO_4$. The solvent was removed to give the intermediate **1u-I** as a yellow oil, 1.64 g, 99% yield. It was used to the next step without purification.

Alcohol **1u-I** (10 mmol, 1.0 equiv) was diluted by Et_2O (10 mL) and transferred to a 30 mL reaction tube. After cooling to 0 °C, DMF (1 drop) was added to the mixture subsequently thionyl chloride (15 mmol, 1.5 equiv) was added dropwise over 5 min. The reaction mixture was stirred at 0 °C for 4 h. Upon completion of the reaction, the resulting mixture concentrated and additional ether (2 mL) was added to co-evaporate the residue volatile. The title compound **1u** was obtained as a brown oil 1.92 g, 90% yield. Compound **1u** is unstable on silica gel and directly used to homologation reaction including a minor impurity (purity is over 90%).

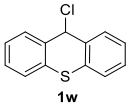
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.29 (s, 1H, Ar-H), 7.15 (d, *J* = 8.4 Hz, 1H, Ar-H), 6.74 (d, *J* = 8.4 Hz, 1H, Ar-H), 5.10 (q, *J* = 6.8 Hz, 1H, ArC*H*Cl), 4.58 (t, *J* = 8.8 Hz, 2H, CH_2), 3.21 (t, *J* = 8.8 Hz, 2H, CH_2), 1.84 (d, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 159.9, 134.7, 127.4, 126.4, 123.1, 108.8, 71.3, 59.2, 29.3, 26.3; HRMS: (DART+) Calculated ($C_{10}H_{11}O$) 147.0804 $(M–Cl)^+$ Found: 147.0808

(1v) 9-Chloro-9*H*-xanthene



Compound **1v** was prepared from 9*H*-xanthen-9-one (3.92 g, 20 mmol) according to the general procedure A. White solid, 3.68 g, 85% yield, two steps. The characterization data were identical to those reported in the literature (A. Gilbert, G. Bucher, R. S. Haines, J. B. Harper, *Org. Biomol. Chem.,* **2019***, 17,* 9336.).

(1w) 9-Chloro-9*H*-thioxanthene

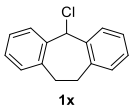


Compound **1w** is a commercially available reagent (Chemieliva Pharmaceutical Co., Ltd.) and was prepared from 9*H*-thioxanthen-9-one according to a reported procedure (T. Fujiwaraa, K. Ohiraa, K. Urushibarab, A. Itocd, M. Yoshidacde, M. Kanaib, A. Tanatanib, H. Kagechikaa, T. Hirano, *Bio. Med. Chem.* **2016**, *24*, 4318.). It was directly used to the homologation reaction after checking by ^{1}H NMR.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.57-7.55 (m, 2H, Ar-H), 7.53-7.50 (m, 2H, Ar-H), 7.35-7.30 (m, 4H. Ar-H),

6.43 (s, 1H, Ar_2CHCl)

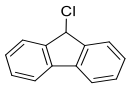
(1x) 5-Chloro-10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulene



1x

Compound **1x** was prepared from 10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulen-5-one (2.08 g, 10 mmol) according to the general procedure A. White to gray solid, 2.22 g, 97% yield, two steps. The characterization data were identical to those reported in the literature (J. E. Fritz, S. W. Kaldor, J. A. Kyle, J. E. Munroe, US6060484, A, **2000**).

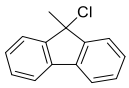
(1y) 9-Chloro-9*H*-fluorene



1y

Compound **1y** was prepared from 9*H*-fluoren-9-ol (1.82 g, 10 mmol) according to the general procedure A. White solid, 2.01 g, 100% yield. The characterization data were identical to those reported in the literature (R. Savela, J. Wärnå, D. Yu. Murzin, R. Leino, *Catal. Sci. Technol.* **2015***, 5,* 2406.).

(1z) 9-Chloro-9-methyl-9*H*-fluorene

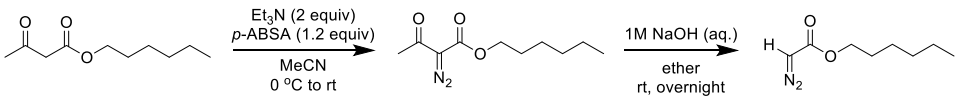


1z

Compound **1z** was prepared from 9-methyl-9*H*-fluoren-9-ol (1.96 g, 10 mmol) according to a reported procedure. Yellow oil, 1.63 g, 76% yield. The characterization data were identical to those reported in the literature (Preparation and characterization: P. Strazzolini, A. G. Giumanini, G. Verardo, *Tetrahedron* **1994***, 50,* 217.).

Preparation of diazoesters 2

(2b) *n*-Hexyl 2-diazoacetate



2b-I 2b-II 2b

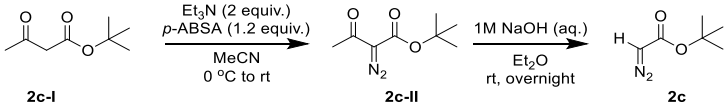
This compound was prepared according to a slightly modified reported procedure (J. Kim, E. J. Yoo, *Org. Lett.* **2021**, *23*, 4256.).

Step 1. To a solution of hexyl 3-oxobutanoate **2b-I** (5.56 g, 30 mmol, 1.0 equiv) and *p*-ABSA (8.65 g, 36 mmol, 1.2 equiv) in 75 mL of anhydrous MeCN was added Et_3N (6.07 g, 60 mmol, 2 equiv) at 0 °C, and the reaction mixture was stirred at room temperature for 6 h. The corresponding sulfonamide precipitated as a white solid. The white precipitate was filtered and washed with ether. The resulting solution was concentrated under reduced pressure to give crude product **2b-II**.

Step 2. The crude **2b-II** was dissolved in diethyl ether (30 mL) and followed addition of 1M NaOH (150 mL, 150 mmol, 5 equiv). The resultant mixture was stirred at room temperature overnight. After **2b-II** was

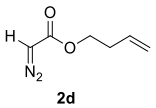
completely consumed, the reaction mixture was extracted by diethyl ether. Organic layer was washed with brine and dried over $MgSO_4$. The mixture was then filtered and evaporated in vacuo. The crude product was purified by silica gel column chromatography (n-hexane/EtOAc = 90:10) to afford **2b** as a yellow oil, 4.34 g, 85% yield, two steps. The characterization data were identical to those reported in the literature (J.-H. Chu, X.-H. Xu, S.-M. Kang, N. Liu, Z.-Q. Wu, *J. Am. Chem. Soc.* **2018**, *140*, 17773.).

(2c) *n*-Hexyl 2-diazoacetate



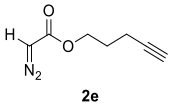
Compound **2c** was prepared from tert-butyl 3-oxobutanoate **2c-I** (3.16 g, 20 mmol, 1.0 equiv) following the same procedure as to **2b**. The title compound was obtained as a yellow oil, 2.22 g, 78% yield, two steps. The characterization data were identical to those reported in the literature (Characterization data: E. Nag, S. M. N. V. T. Gorantla, S. Arumugam, A. Kulkarni, K. C. Mondal, S. Roy, *Org. Lett.* **2020**, *22*, 6313.).

(2d) But-3-en-1-yl 2-diazoacetate



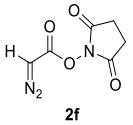
Compound **2d** was prepared according to a reported procedure (Preparation: D. M. Hodgson, D. Angrish, *Chem. Eur. J.* **2007**, *13*, 3470.) as a yellow oil, 1.45 g, 54% yield. The characterization data were identical to those reported in the literature (Characterization data: M. Bolsønes, H. T. Bonge-Hansen, T. Bonge-Hansen, *Synlett* **2014**, *25*, 221.).

(2e) Pent-4-yn-1-yl 2-diazoacetate



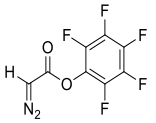
Compound **2e** was prepared according to a reported procedure as a yellow oil, 1.25 g, 43% yield. The characterization data were identical to those reported in the literature (Preparation and Characterization data: X. Huang, R. D. Webster, K. Harms, E. Meggers, *J. Am. Chem. Soc.* **2016**, *138*, 12636.).

(2f) 2,5-Dioxopyrrolidin-1-yl 2-diazoacetate



Compound **2f** was prepared according to a reported procedure as a pale yellow solid, 1.34 g, 46% yield. The characterization data were identical to those reported in the literature (Preparation and Characterization data: J. V. Jun, R. T. Raines, *Org. Lett.* **2021**, *23*, 3110.).

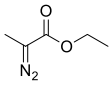
(2g) Perfluorophenyl 2-diazoacetate



2g

Compound **2g** was prepared according to a reported procedure as a yellow oil, 0.32 g, 13% yield. The characterization data were identical to those reported in the literature (Preparation and Characterization data: A. Modak, J. V. Alegre-Requena, L. D. Lescure, K. J. Rynders1, R. S. Paton, N. J. Race, *J. Am. Chem. Soc.* **2022**, *144*, 86.).

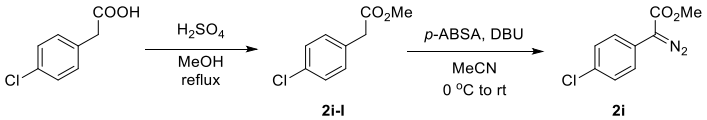
(2h) Ethyl 2-diazopropanoate



2h

Compound **2h** was prepared from ethyl 2-methyl-3-oxobutanoate (2.88 g, 20 mmol) according to a reported procedure. Yellow oil, 2.32 g, 44.5% in n-hexane, 60% yield. The characterization data were identical to those reported in the literature (Preparation and Characterization data: V. Arredondo, S. C. Hiew, E. S. Gutman, I. D. U. A. Premachandra, D. L. V. Vranken, *Angew. Chem. Int. Ed.* **2017**, *56*, 4156.).

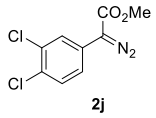
Representative procedure for preparation of α-aryl diazoesters (2i, 2j, 2k, and 2l)



Step 1: A mixture of 2-(4-chlorophenyl)acetic acid (1.71 g, 10 mmol) and 95 wt% sulfonic acid (0.28 mL) in methanol (20 mL) was refluxed for 6 h. The resulting mixture was cooled to room temperature and diluted with saturated $NaHCO_3$ aq. The mixture was extracted with ethyl acetate and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated to give methyl 2-(4-chlorophenyl)acetate (**2i-I**) (1.84 g, 99% yield) as a colorless oil. The crude product was used without purification.

Step 2: Diazoester **2i** was prepared according to a reported procedure. (Preparation, S. Thurow, A. A. G. Fernandes, Y. Quevedo-Acosta, M. F. de Oliveira, M. G. de Oliveira, I. D. Jurberg, *Org. Lett*. **2019**, *21*, 6909.). 1,8-Diazabicyclo[5.4.0]-7-undecene (DBU) (2.26 g, 14.84 mmol, 1.5 equiv) was added dropwise to a solution of **2i-I** (1.84 g, 9.89 mmol, 1.0 equiv) and *p*-ABSA (2.85 g, 11.87 mmol, 1.2 equiv) in acetonitrile (20 mL) at 0 °C over 5 min. The mixture was stirred at 0 °C for additional 30 min and warmed to room temperature for 20 h. The resulting mixture was quenched with saturated aqueous ammonium chloride and extracted with ethyl acetate (30 mL x 3). The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography (n-hexane/EtOAc = 90/10) to afford **2i** (1.98 g, 94% yield) as an orange solid. The characterization data were identical to those reported in the literature (Characterization data, E. Tayama, K. Horikawa, H. Iwamoto, E. Hasegawa, *Tetrahedron Lett*. **2014**, *55*, 3041.).

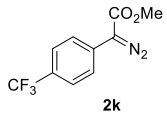
(**2j**) **Methyl 2-diazo-2-(3,4-dichlorophenyl)acetate**



2j

Compound **2j** was prepared from 2-(3,4-dichlorophenyl)acetic acid (2.05 g, 10 mmol) according to the general procedure. Yellow solid, 2.30 g, 94% yield. The characterization data were identical to those reported in the literature (Characterization data, D. Dar'in, G. Kantin, M. Krasavin, *Synthesis* **2019**, *51*, 4284.).

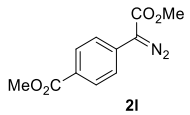
(**2k**) **Methyl 2-diazo-2-(4-(trifluoromethyl)phenyl)acetate**



2k

Compound **2k** was prepared from 2-(4-(trifluoromethyl)phenyl)acetic acid (2.04 g, 10 mmol) according to the general procedure. Yellow solid, 2.15 g, 88% yield. The characterization data were identical to those reported in the literature (Characterization data, M. Santi, D. M. C. Ould, J. Wenz, Y. Soltani, R. L. Melen, T. Wirth, *Angew. Chem. Int. Ed.* **2019**, *58*, 7861.).

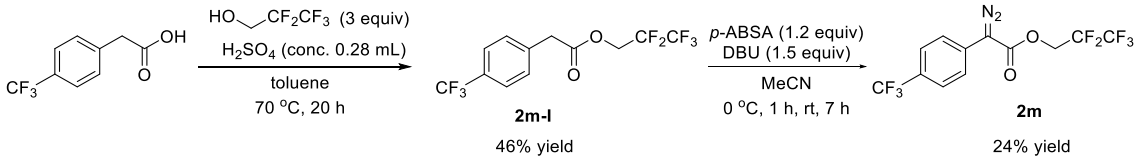
(**2l**) **Methyl 4-(1-diazo-2-methoxy-2-oxoethyl)benzoate**



2l

Compound **2l** was prepared from homoterephthalic acid dimethyl ester (2.08 g, 10 mmol) according to the general procedure. Yellow solid, 2.11 g, 90% yield. The characterization data were identical to those reported in the literature (Characterization data, F. Ye, C. Wang, Y, Zhang, J. Wang, *Angew. Chem. Int. Ed.* **2014**, *53*, 11625.).

(2m) 2,2,3,3,3-Pentafluoropropyl 2-diazo-2-(4-(trifluoromethyl)phenyl)acetate



Step 1: A mixture of 2-(4-(trifluoromethyl)phenyl)acetic acid (2.04 g, 10 mmol, 1.0 equiv), 2,2,3,3,3-pentafluoropropan-1-ol (4.50 g, 30 mmol, 3.0 equiv), and concentrated sulfonic acid (0.28 mL) in toluene (20 mL) was stirred at 70 °C for 20 h. The resulting mixture was cooled to room temperature and diluted with saturated $NaHCO_3$ aq. The mixture was extracted with ethyl acetate (30 mL x 2) and the combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to obtain 2,2,3,3,3-pentafluoropropyl 2-(4-(trifluoromethyl)phenyl)acetate (**2m-I**) (1.55 g, 46% yield) as a colorless oil. The crude product was used without purification.

Step 2: DBU (1.05 g, 6.90 mmol, 1.5 equiv) was added dropwise to a solution of **2m-I** (1.55 g, 4.60 mmol, 1.0 equiv) and *p*-ABSA (1.33 g, 5.52 mmol, 1.2 equiv) in acetonitrile (20 mL) at 0 °C over 5 min. The mixture was stirred at 0 °C for additional 1 h and warmed to room temperature for 7 h. The resulting mixture

was quenched with saturated aqueous ammonium chloride and extracted with ethyl acetate. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography (*n*-hexane/EtOAc = 90/10) to afford the title compound **2m** as a yellow solid (0.40 g, 24% yield).

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.65 (d, J = 8.6 Hz, 2H, Ar-H), 7.59 (d, J = 8.6 Hz, 2H, Ar-H), 4.74 (t, $^3J_{H\text{-}F}$ = 12.4 Hz, 2H, CH_2); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 162.4, 128.9, 128.2 (q, $J_{C\text{-}F}$ = 32.8 Hz), 126.0 (d, $J_{C\text{-}F}$ = 4.1 Hz), 123.4, 122.6 (t, $J_{C\text{-}F}$ = 271.6 Hz, CF$_2$), 120.2-108.7 (m, Ar-CF$_3$ and CH$_2$CF$_2$$CF_3$), 59.4 (t, $J_{C\text{-}F}$ = 28.7 Hz, CH$_2$CF$_2$CF$_3$); ^{19}F NMR: (376 MHz, $CDCl_3$) δ -62.74 (s, 3F), -83.87 (s, 3F), -123.69 (t, J = 12.2 Hz, 2F); IR: (KBr) 2101 (C=N$_2$), 1712 (C=O) cm^{-1}; m.p. 34–35 °C; HRMS: (DART+) Calculated ($C_{12}H_7O_2F_8$) 335.0313 (M–N$_2$+H)$^+$ Found: 335.0324

General procedure C for $InCl_3$ catalyzed C–C bond insertion and ring expansion

Under nitrogen atmosphere, a reaction tube was charged with $InCl_3$ (0.011 g, 0.05 mmol, 10 mol%) and dried by heating to about 200 °C with *heat gun* under vacuo. After cooling to 0 °C with ice bath, the reaction tube was sequentially charged with EtOAc (2 mL), benzylic chlorides **1** (0.5 mmol, 1 equiv), and diazoester **2** (1.0 mmol, 2.0 equiv) at 0 °C. The reaction mixture was stirred at 0 °C for 6 h. After completion of reaction, the mixture was quenched by saturated $NaHCO_3$ aq and extracted with EtOAc (15 mL x 3). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The sum yield of diastereomers and the diastereomeric ratio were determined by ^{1}H NMR in the crude product. 1,1,2,2-Tetrachloroethane was used as an internal standard. The major diastereomer was obtained by silica gel column chromatography (*n*-hexane/EtOAc) and/or recycle HPLC (*n*-hexane/EtOAc).

General procedure D for $InBr_3$ catalyzed C–C bond insertion

Under nitrogen atmosphere, a reaction tube was charged with $InBr_3$ (0.018 g, 0.05 mmol, 10 mol%) and dried by heating to about 200 °C with *heat gun* under vacuo. After cooling to –30 °C, the reaction tube was sequentially charged with EtOAc (2 mL), benzylic bromide **1** (0.5 mmol, 1.0 equiv), and diazoester **2** (1.0 mmol, 2.0 equiv). The reaction mixture was stirred at –30 °C for 20 h. After completion of reaction, the mixture was quenched by saturated $NaHCO_3$ aq and extracted with EtOAc (15 mL x 3). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The sum yield of diastereomers and the diastereomeric ratio were determined by ^{1}H NMR in the crude product. 1,1,2,2-Tetrachloroethane was used as an internal standard. The major diastereomer was obtained by silica gel column chromatography (*n*-hexane/EtOAc) and recycle HPLC (*n*-hexane/EtOAc).

General procedure E for $BF_3{\cdot}OEt_2$ catalyzed C–C bond insertion

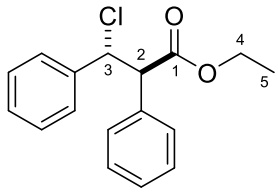
Under nitrogen atmosphere, a reaction tube was charged with EtOAc (2 mL), benzylic fluoride **1** (0.5 mmol, 1.0 equiv), and diazoester **2** (1.0 mmol, 2.0 equiv). After cooling to 0 °C, $BF_3{\cdot}OEt_2$ (0.0071 g, 0.05 mmol, 10 mol%) was added to the mixture. The reaction mixture was stirred at 0 °C for 20 h. After completion of reaction, the mixture was quenched by saturated $NaHCO_3$ aq and extracted with EtOAc (10 mL x 3). The

combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The sum yield of diastereomers and the diastereomeric ratio were determined by ^1H NMR and ^{19}F NMR in the crude product. 1,1,2,2-Tetrachloroethane and hexafluorobenzene were used as internal standards, respectively. The major diastereomer was obtained by silica gel column chromatography (*n*-hexane/EtOAc) and recycle HPLC (*n*-hexane/EtOAc).

Gram-scale synthesis of ethyl (2R*,3R*)-3-chloro-2,3-di-*m*-tolylpropanoate (3ga)

Under nitrogen atmosphere, a 100 mL three-necked round-bottomed flask equipped with a magnetic stir bar was charged with $InCl_3$ (0.095 g, 0.864 mmol, 10 mol%) and dried by heating to about 200 °C with *heat gun* under vacuo. After cooling to 0 °C with ice bath, the reaction tube was sequentially charged with EtOAc (40 mL) and bis(3-methylphenyl)methyl chloride (8.58 mmol, 1.0 equiv). The ethyl 2-diazoacetate (1.96 g, 17.16 mmol, 2.0 equiv) (dissolved in 5 mL EtOAc) was added dropwise to the reaction mixture over 30 min. The reaction mixture was stirred at 0 °C for additional 12 h. After completion of reaction (checked by TLC), the reaction was quenched by saturated $NaHCO_3$ aq and extracted with EtOAc (50 mL x 3). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (*n*-hexane/EtOAc = 95/5) and further recrystallization in pentane to give single diastereomer (2*R**, 3*R**)-**3ga** as a white solid, 1.62 g, 60% yield.

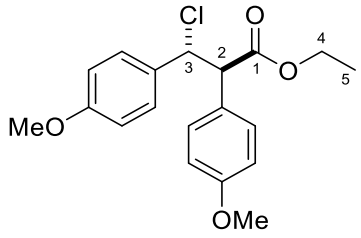
(2*R,3*R**)-3aa Ethyl (2*R**,3*R**)-3-chloro-2,3-diphenylpropanoate**



Following the general procedure C using diphenylmethyl chloride (0.500 mmol, 0.101 g) and ethyl 2-diazoacetate (1.017 mmol, 0.116 g) with $InCl_3$ (0.0497 mmol, 0.0110 g). The yield (sum of diastereomers) and diastereomeric ratio were determined by ^1H NMR in crude products (75%, 95:5). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by silica gel flash column chromatography (*n*-hexane/EtOAc = 95/5) and recycle HPLC (*n*-hexane/EtOAc = 90/10) to give the title compound as a colorless oil (0.0996 g, 69%).

^1H NMR: (400 MHz, $CDCl_3$) 7.15-7.09 (m, 10H, Ar-H), 5.45 (d, J = 11.3 Hz, 1H, 3-H), 4.33-4.12 (m, 3H, 2-H and 4-H_2), 1.26 (t, J = 7.0 Hz, 3H, 5-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 171.4 (C-1), 138.2, 134.7, 128.4, 128.34, 128.26, 128.21, 127.8, 127.6, 63.4 (C-3), 61.4 (C-4), 61.0 (C-2), 14.0 (C-5); IR: (neat) 1732 (C=O) $cm^{-1;}$ HRMS: (ESI+) Calculated ($C_{17}H_{17}O_2NaCl$) 311.0809 $(M+Na)^+$ Found: 311.0810

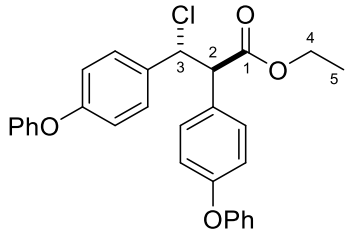
(2*R,3*R**)-3ba Ethyl (2*R**,3*R**)-3-chloro-2,3-bis(4-methoxyphenyl)propanoate**



Following a modified procedure C using 4,4'-dimethoxydiphenylmethyl chloride (1.001 mmol, 0.274 g), ethyl 2-diazoacetate (2.000 mmol, 0.228 g), $InCl_3$ (0.1002 mmol, 0.0221 g) and EtOAc (4 mL). The reaction was stirred at –44 °C for 6 h and warm to 0 °C for 30 min. The yield (sum of diastereomers) and diastereomeric ratio were determined by ^1H NMR in crude products (49%, 98:2). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by silica gel flash column chromatography (*n*-hexane/EtOAc = 90/10) and recycle HPLC (*n*-hexane/EtOAc = 85/15) to give the title compound as a colorless oil (0.150 g, 43%). *Note: this compound should be stabilized by trace amount of EtOAc to avoid the isomerization due to its instability.*

^1H NMR: (400 MHz, $CDCl_3$) 7.11-7.05 (m, 4H, Ar-H), 6.71-6.65 (m, 4H, Ar-H), 5.40 (d, J = 11.6 Hz, 1H, 3-H), 4.33-4.13 (m, 3H, 2-H and 4-H_2), 3.71 (s, 3H, OCH_3), 3.69 (s, 3H, OCH_3), 1.28 (t, J = 7.1 Hz, 3H, 5-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 171.8 (C-1), 159.3, 158.9, 130.5, 129.5, 128.9, 127.0, 113.8, 113.6, 63.4 (C-3), 61.3 (C-4), 60.2 (C-2), 55.10, 55.06, 14.1(C-5); IR: (neat) 1730 (C=O) cm^{-1}; HRMS: (ESI+) Calculated ($C_{19}H_{21}O_4$) 313.1434 $(M–Cl)^+$ Found: 313.1434

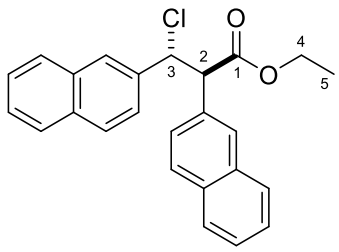
(2*R,3*R**)-3ca Ethyl (2*R**,3*R**)-3-chloro-2,3-bis(4-phenoxyphenyl)propanoate**



Following the general procedure C using bis(4-phenoxyphenyl)methyl chloride (0.495 mmol, 0.191 g) and ethyl 2-diazoacetate (1.000 mmol, 0.114 g) with $InCl_3$ (0.0497 mmol, 0.0110 g). The yield (sum of diastereomers) and diastereomeric ratio were determined by ^1H NMR in crude products (61%, 95:5). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by silica gel flash column chromatography (*n*-hexane/EtOAc = 90/10) and recycle HPLC (*n*-hexane/EtOAc = 85/15) to give the title compound as a colorless oil (0.119 g, 51%).

^1H NMR: (400 MHz, $CDCl_3$) 7.33-7.28 (m, 4H, Ar-H), 7.15-7.09 (m, 6H, Ar-H), 6.91 (t, J = 9.2 Hz, 4H, Ar-H), 6.81 (t, J = 8.9 Hz, 4H, Ar-H), 5.40 (d, J = 11.1 Hz, 1H, 3-H), 4.37-4.15 (m, 3H, 2-H and 4-H_2), 1.31 (t, J = 7.2 Hz, 3H, 5-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 171.5 (C-1), 157.2, 156.9, 156.71, 156.65, 133.0, 129.78, 129.76, 129.7, 129.6, 129.2, 123.54, 123.46, 119.0, 118.9, 118.7, 118.4, 63.1 (C-3), 61.5 (C-4), 60.5 (C-2). 14.1 (C-5); IR: (neat) 1739, 1589, 1484, 1220 cm^{-1}; HRMS: (ESI+) Calculated ($C_{29}H_{25}O_4NaCl$) 495.1334 $(M+Na)^+$ Found: 495.1334

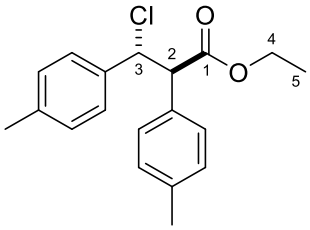
(2*R,3*R**)-3da Ethyl (2*R**,3*R**)-3-chloro-2,3-di(naphthalen-2-yl)propanoate**



Following the general procedure C using bis(2-naphthyl)methyl chloride (0.505 mmol, 0.153 g) and ethyl 2-diazoacetate (1.000 mmol, 0.114 g), $InCl_3$ (0.0501 mmol, 0.0111 g) and EtOAc (4 mL). The yield (sum of diastereomers) and diastereomeric ratio were determined by ^1H NMR in crude products (63%, 95:5). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by silica gel flash column chromatography (*n*-hexane/EtOAc = 95/5) and recycle HPLC (*n*-hexane/EtOAc = 90/10) to give the title compound as a white solid (0.114 g, 58%).

^1H NMR: (400 MHz, $CDCl_3$) 7.71-7.60 (m, 7H, Ar-H), 5.56 (d, J = 8.7 Hz, 1H, Ar-H), 7.44 (dd, J = 8.7, 1.9 Hz, 1H, Ar-H), 7.38-7.33 (m, 4H, Ar-H), 7.29 (dd, J = 8.5, 1.7 Hz, 1H, Ar-H), 5.80 (d, J = 11.1 Hz, 1H, 3-H), 4.57 (d, J = 11.1 Hz, 1H, 2-H), 4.38-4.15 (m, 2H, 4-H_2), 1.29 (t, J = 7.0 Hz, 3H, 5-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 171.5 (C-1), 135.4, 133.02, 132.98, 132.68, 132.66, 132.2, 128.5, 128.3, 128.0, 127.8, 127.7, 127.50, 127.47, 127.46, 126.4, 126.2, 126.14, 126.11, 125.8, 124.6, 63.7 (C-3), 61.6 (C-4), 60.7 (C-2), 14.1 (C-5); IR: (KBr) 1732 (C=O) cm^{-1}; m.p. 92–93 °C; HRMS: (ESI+) Calculated ($C_{25}H_{21}O_2NaCl$) 411.1122 $(M+Na)^+$ Found: 411.1128

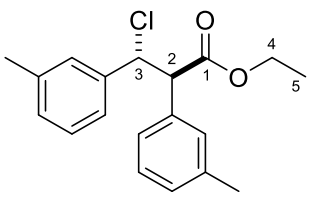
(2*R,3*R**)-3fa Ethyl (2*R**,3*R**)-3-chloro-2,3-di-*p*-tolylpropanoate**



Following the general procedure C using bis(4-methylphenyl)methyl chloride (0.514 mmol, 0.119 g) and ethyl 2-diazoacetate (1.000 mmol, 0.114 g) with $InCl_3$ (0.0522 mmol, 0.0120 g). The yield (sum of diastereomers) and diastereomeric ratio were determined by ^1H NMR in crude products (67%, 98:2). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by silica gel flash column chromatography (*n*-hexane/EtOAc = 95/5) and recycle HPLC (*n*-hexane/EtOAc = 90/10) to give the title compound as a white solid (0.103 g, 63%).

^1H NMR: (400 MHz, $CDCl_3$) 7.07 (d, J = 8.2 Hz, 2H, Ar-H), 7.04 (d, J = 8.2 Hz, 2H, Ar-H), 6.96 (d, J = 8.2 Hz, 2H, Ar-H), 6.93 (d, J = 8.2 Hz, 2H, Ar-H), 5.43 (d, J = 11.1 Hz, 1H, 3-H), 4.32-4.11 (m, 3H, 2-H and 4-H_2), 2.22 (s, 3H, Ar-CH_3), 2.19 (s, 3H, Ar-CH_3), 1.27 (t, J = 7.0 Hz, 3H, 5-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 171.7 (C-1), 138.0, 137.5, 135.3, 131.9, 129.2, 129.0, 128.2, 127.6, 63.4 (C-3), 61.3 (C-4), 60.4 (C-2), 21.1, 21.0, 14.0 (C-5); IR: (KBr) 1727 (C=O) cm^{-1}; m.p. 54–55 °C; HRMS: (ESI+) Calculated ($C_{19}H_{21}O_2NaCl$) 339.1122 $(M+Na)^+$ Found: 339.1125

(2*R,3*R**)-3ga Ethyl (2*R**,3*R**)-3-chloro-2,3-di-*m*-tolylpropanoate**

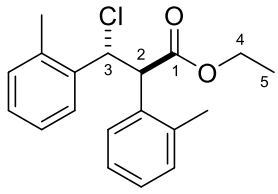


Following the general procedure C using bis(3-methylphenyl)methyl chloride (0.526 mmol, 0.121 g) and

ethyl 2-diazoacetate (1.000 mmol, 0.114 g) with $InCl_3$ (0.0535 mmol, 0.0123 g). The yield (sum of diastereomers) and diastereomeric ratio were determined by ^1H NMR in crude products (68%, 96:4). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by silica gel flash column chromatography (*n*-hexane/EtOAc = 95/5) and recycle HPLC (*n*-hexane/EtOAc = 90/10) to give the title compound as a white solid (0.107 g, 64%).

^1H NMR: (400 MHz, $CDCl_3$) 7.06-6.91 (m, 8H, Ar-H), 5.42 (d, J = 11.1 Hz, 1H, 3-H), 4.34-4.12 (m, 3H, 2-H and 4-H_2), 2.23 (s, 3H, Ar-CH_3), 2.20 (s, 3H, Ar-CH_3), 1.28 (t, J = 7.2 Hz, 3H, 5-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 171.6 (C-1), 138.13, 138.05, 137.9, 134.7, 129.1, 129.0, 128.6, 128.4, 128.3, 128.1, 125.5, 124.8, 63.5 (C-3), 61.3 (C-4), 60.8 (C-2), 21.25, 21.23, 14.1 (C-5); IR: (KBr) 1726 (C=O) cm^{-1}; m.p. 71–72 °C; HRMS: (ESI+) Calculated ($C_{19}H_{21}O_2NaCl$) 339.1122 $(M+Na)^+$ Found: 339.1122

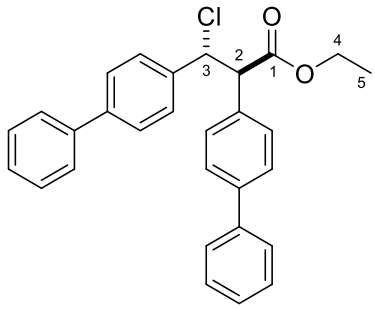
(2*R,3*R**)-3ha Ethyl (2*R**,3*R**)-3-chloro-2,3-di-*o*-tolylpropanoate**



Following the general procedure C using bis(2-methylphenyl)methyl chloride (0.502 mmol, 0.116 g) and ethyl 2-diazoacetate (1.000 mmol, 0.114 g) with $InCl_3$ (0.0495 mmol, 0.0110 g). The yield (sum of diastereomers) and diastereomeric ratio were determined by ^1H NMR in crude products (61%, 89:11). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by silica gel flash column chromatography (*n*-hexane/EtOAc = 95/5) and recycle HPLC (*n*-hexane/EtOAc = 90/10) to give the title compound as a white solid (0.0793 g, 50%).

^1H NMR: (400 MHz, $CDCl_3$) 7.46-7.43 (m, 2H, Ar-H), 7.11-6.92 (m, 6H, Ar-H), 5.93 (d, J = 11.6 Hz, 1H, 3-H), 4.73 (d, J = 11.6 Hz, 1H, 2-H), 4.32-4.09 (m, 2H, 4-H_2), 2.28 (s, 3H, Ar-CH_3), 2.26 (s, 3H, Ar-CH_3), 1.26 (t, J = 7.0 Hz, 3H, 5-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 171.9 (C-1), 136.6, 136.4, 135.7, 133.5, 130.6, 130.3, 128.2, 127.7, 127.2, 126.9, 126.1, 126.0, 61.3 (C-4), 59.0 (C-3), 54.7 (C-2), 19.8, 19.3, 14.1 (C-5); IR: (KBr) 1735 (C=O) cm^{-1}; m.p. 42–43 °C; HRMS: (ESI+) Calculated ($C_{19}H_{21}O_2NaCl$) 339.1122 $(M+Na)^+$ Found: 339.1122

(2*R,3*R**)-3ia Ethyl (2*R**,3*R**)-2,3-di([1,1'-biphenyl]-4-yl)-3-chloropropanoate**

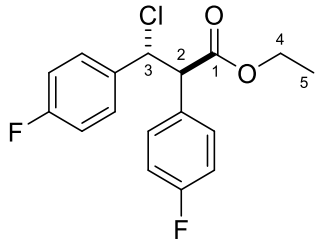


Following the general procedure C using bis(2-methylphenyl)methyl chloride (0.531 mmol, 0.188 g) and ethyl 2-diazoacetate (1.000 mmol, 0.114 g) with $InCl_3$ (0.0565 mmol, 0.0130 g). The yield (sum of

diastereomers) and diastereomeric ratio were determined by ^{1}H NMR in crude products (78%, 96:4). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by silica gel flash column chromatography (*n*-hexane/EtOAc = 95/5) and recycle HPLC (*n*-hexane/EtOAc = 90/10) to give the title compound as a colorless oil (0.176 g, 75%).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.50-7.24 (m, 18H, Ar-H), 5.55 (d, J = 11.3 Hz, 1H, 3-H), 4.38-4.17 (m, 3H, 2-H and 4-H_2), 1.32 (t, J = 7.1 Hz, 3H, 5-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 171.4 (C-1), 141.1, 140.6, 140.1, 137.2, 133.7, 128.8, 128.7, 128.2, 127.44, 127.39, 127.2, 127.0, 126.92, 126.86, 63.2 (C-3), 61.5 (C-4), 60.6 (C-2), 14.1 (C-5) *Two aromatic carbon resonances not located*; IR: (neat) 1730 (C=O) cm^{-1}; HRMS: (ESI+) Calculated ($C_{29}H_{25}O_2NaCl$) 463.1435 $(M+Na)^+$ Found: 463.1439

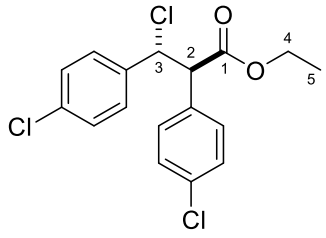
(2*R,3*R**)-3ja Ethyl (2*R**,3*R**)-3-chloro-2,3-bis(4-fluorophenyl)propanoate**



Following the general procedure C using 4,4'-difluorobenzhydryl chloride (0.523 mmol, 0.125 g) and ethyl 2-diazoacetate (1.000 mmol, 0.114 g) with $InCl_3$ (0.0497 mmol, 0.0110 g). The yield (sum of diastereomers) and diastereomeric ratio were determined by ^{1}H NMR in crude products (78%, 93:7). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by silica gel flash column chromatography (*n*-hexane/EtOAc = 95/5) and recycle HPLC (*n*-hexane/EtOAc = 90/10) to give the title compound as a colorless oil (0.121 g, 71%).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.15-7.09 (m, 4H, Ar-H), 6.89-6.82 (m, 4H, Ar-H), 5.39 (d, J = 11.3 Hz, 1H, 3-H), 4.33-4.13 (m, 3H, 2-H and 4-H_2), 1.28 (t, J = 7.1 Hz, 3H, 5-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 171.2 (C-1), 162.3 (d, $J_{C\text{-}F}$ = 248.2 Hz), 162.2 (d, $J_{C\text{-}F}$ = 247.4 Hz), 134.0 (d, $J_{C\text{-}F}$ = 3.3 Hz), 130.5 (d, $J_{C\text{-}F}$ = 3.3 Hz), 130.0 (d, $J_{C\text{-}F}$ = 8.2 Hz), 129.4 (d, $J_{C\text{-}F}$ = 8.2 Hz), 115.5 (d, $J_{C\text{-}F}$ = 22.1 Hz), 115.4 (d, $J_{C\text{-}F}$ = 22.1 Hz), 62.5 (C-3), 61.6 (C-4), 60.4 (C-2), 14.0 (C-5); ^{19}F NMR: (376 MHz, $CDCl_3$) -112.68 – -112.73 (m, 1F), -113.46 – -113.53 (m, 1F); IR: (neat) 1730, 1605, 1513, 1220, 1160 cm^{-1}; HRMS: (ESI+) Calculated ($C_{17}H_{15}O_2F_2NaCl$) 347.0621 $(M+Na)^+$ Found: 347.0613

(2*R,3*R**)-3ka Ethyl (2*R**,3*R**)-3-chloro-2,3-bis(4-chlorophenyl)propanoate**



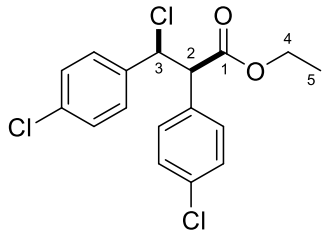
Following a modified procedure using 4,4'-dichlorobenzhydryl chloride (0.508 mmol, 0.138 g), ethyl 2-diazoacetate (1.000 mmol, 0.114 g), $InCl_3$ (0.0500 mmol, 0.0115 g), and EtOAc (2 mL) at room temperature for 12 h. The yield (sum of diastereomers) and diastereomeric ratio were determined by ^{1}H NMR in crude

products (69%, 82:18). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by silica gel flash column chromatography (*n*-hexane/EtOAc = 95/5) and recycle HPLC (*n*-hexane/EtOAc = 90/10). The major and minor diastereomers were separately obtained.

The title compound was obtained as a white solid, 0.102 g, 56% yield.

^{1}H NMR: (400 MHz, $CDCl_3$) 7.17-7.13 (m, 4H, Ar-H), 7.10-7.06 (m, 4H, Ar-H), 5.37 (d, *J* = 11.0 Hz, 1H, 3-H), 4.34-4.12 (m, 3H, 2-H and 4-H_2), 1.28 (t, *J* = 7.0 Hz, 3H, 5-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.9 (C-1), 136.5, 134.3, 134.1, 132.9, 129.6, 129.0, 128.9, 128.7, 62.2 (C-3), 61.7 (C-4), 60.3 (C-2), 14.0 (C-5); IR: (KBr) 1731 (C=O) cm^{-1}; m.p. 96–97 °C; HRMS: (ESI+) Calculated ($C_{17}H_{15}O_2NaCl_3$) 379.0030 $(M+Na)^+$ Found: 379.0033

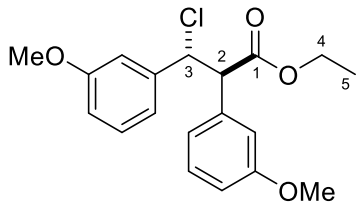
(2*R,3*S**)-3ka Ethyl (2*R**,3*S**)-3-chloro-2,3-bis(4-chlorophenyl)propanoate**



The title compound was obtained as a white solid, 0.0139 g, 8% yield.

^{1}H NMR: (400 MHz, $CDCl_3$) 7.43-7.34 (m, 8H, Ar-H), 5.31 (d, *J* = 10.8 Hz, 1H, 3-H), 4.11 (d, *J* = 10.8 Hz, 1H, 2-H), 3.97-3.83 (m, 2H, 4-H_2), 0.98 (t, *J* = 7.0 Hz, 3H, 5-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.0 (C-1), 137.8, 134.7, 134.3, 134.0, 130.0, 129.0, 128.91, 128.86, 62.7 (C-3), 61.4 (C-4), 59.7 (C-2), 13.7 (C-5); IR: (KBr) 1731 (C=O) cm^{-1}; m.p. 105–107 °C; HRMS: (ESI+) Calculated ($C_{17}H_{15}O_2NaCl_3$) 379.0030 $(M+Na)^+$ Found: 379.0033

(2*R,3*R**)-3la Ethyl (2*R**,3*R**)-3-chloro-2,3-bis(3-methoxyphenyl)propanoate**

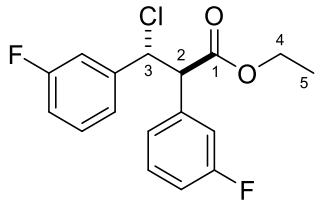


Following the general procedure C using 3,3'-dimethoxydiphenylmethyl chloride (0.482 mmol, 0.126 g) and ethyl 2-diazoacetate (1.000 mmol, 0.114 g) with $InCl_3$ (0.0497 mmol, 0.0110 g). The yield (sum of diastereomers) and diastereomeric ratio were determined by ^{1}H NMR in crude products (67%, 93:7). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by silica gel flash column chromatography (*n*-hexane/EtOAc = 90/10) and recycle HPLC (*n*-hexane/EtOAc = 85/15) to give the title compound as a colorless oil (0.103 g, 61%).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.10-7.03 (m, 2H, Ar-H), 6.78-6.66 (m, 6H, Ar-H), 5.40 (d, *J* = 11.6 Hz, 1H, 3-H), 4.35-4.14 (m, 3H, 2-H and 4-H_2), 3.69 (s, 3H, OCH_3), 3.67 (s, 3H, OCH_3), 1.29 (t, *J* = 7.2 Hz, 3H, 5-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 171.3 (C-1), 159.4, 159.3, 139.6, 136.1, 129.4, 129.3, 120.8, 120.1, 114.0, 113.9, 113.4, 113.2, 63.3 (C-3), 61.5 (C-4), 60.9 (C-2), 55.2, 55.1, 14.1 (C-5); IR: (neat) 1738, 1604, 1493, 1455, 1438, 1268, 1156, 1049 cm^{-1}; HRMS: (ESI+) Calculated ($C_{19}H_{21}O_4NaCl$) 371.1021 $(M+Na)^+$ Found:

371.1024

(2*R,3*R**)-3ma Ethyl (2*R**,3*R**)-3-chloro-2,3-bis(3-fluorophenyl)propanoate**

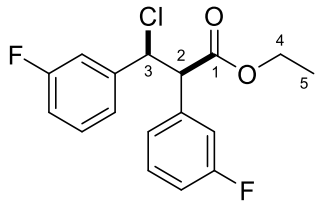


Following a modified procedure C. Under nitrogen atmosphere, a reaction tube was subsequently charged with $InCl_3$ (0.0957 mmol, 0.0220 g, 20 mol%), $CHCl_3$ (2 mL), and 3,3'-difluorobenzhydryl chloride (0.490 mmol, 0.117 g). The ethyl 2-diazoacetate (1.000 mmol, 0.114 g) was added to the resultant mixture by dropwise over 10 min at room temperature. The reaction was stirred at rt for 24 h. After completion of reaction, the mixture was quenched by saturated $NaHCO_3$ aq and extracted with $CHCl_3$ (10 mL x 3). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The sum yield of diastereomers and the diastereomeric ratio were determined by ^1H NMR in the crude product (90%, 50:50). 1,1,2,2-Tetrachloroethane was used as an internal standard. The two diastereomers were separately obtained by silica gel column chromatography (*n*-hexane/EtOAc = 95/5) and recycle HPLC (*n*-hexane/EtOAc = 90/10). The major and minor diastereomers were separately obtained.

The title compound was obtained as a colorless oil (0.0684 g, 43%).

^1H NMR: (400 MHz, $CDCl_3$) 7.15-7.08 (m, 2H, Ar-H), 6.95-6.82 (m, 6H, Ar-H), 5.38 (d, J = 11.0 Hz, 1H, 3-H), 4.35-4.14 (m, 3H, 2-H and 4-H_2), 1.29 (t, J = 7.3 Hz, 3H, 5-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.6 (C-1), 162.5 (d, $J_{C\text{-}F}$ = 247.2 Hz), 162.4 (d, $J_{C\text{-}F}$ = 247.2 Hz), 140.3 (d, $J_{C\text{-}F}$ = 7.7 Hz), 136.7 (d, $J_{C\text{-}F}$ = 7.7 Hz), 130.2-129.9 (m), 124.2 (d, $J_{C\text{-}F}$ = 2.9 Hz), 123.4 (d, $J_{C\text{-}F}$ = 2.9 Hz), 115.7-114.5 (m), 62.2 (C-3), 61.8 (C-4), 60.6 (C-2), 14.0 (C-5); ^{19}F NMR: (376 MHz, $CDCl_3$) -111.94 – -112.01 (m, 1F), -112.24 – -112.28 (m, 1F); IR: (neat) 1729 (C=O) cm^{-1}; HRMS: (ESI+) Calculated ($C_{17}H_{15}O_2F_2NaCl$) 347.0621 $(M+Na)^+$ Found: 347.0625

(2*R,3*S**)-3ma Ethyl (2*R**,3*S**)-3-chloro-2,3-bis(3-fluorophenyl)propanoate**

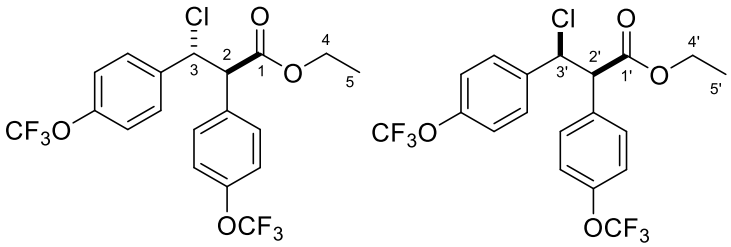


The title compound was obtained as a white solid (0.0652 g, 41%).

^1H NMR: (400 MHz, $CDCl_3$) 7.38-7.31 (m, 2H, Ar-H), 7.27-7.19 (m, 4H, Ar-H), 7.08-7.01 (m, 2H, Ar-H), 5.33 (d, J = 11.0 Hz, 1H, 3-H), 4.14 (d, J = 11.0 Hz, 1H, 2-H), 3.99-3.84 (m, 2H, 4-H_2), 0.96 (t, J = 7.1 Hz, 3H, 5-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 169.8 (C-1), 162.8 (d, $J_{C\text{-}F}$ = 246.3 Hz), 162.6 (d, $J_{C\text{-}F}$ = 247.3 Hz), 141.6 (d, $J_{C\text{-}F}$ = 6.7 Hz), 137.8 (d, $J_{C\text{-}F}$ = 7.7 Hz), 130.2 (d, $J_{C\text{-}F}$ = 7.7 Hz), 130.1 (d, $J_{C\text{-}F}$ = 8.6 Hz), 124.5 (d, $J_{C\text{-}F}$ = 2.9 Hz), 123.4 (d, $J_{C\text{-}F}$ = 2.9 Hz), 116.0-114.6 (m), 62.6 (d, $J_{C\text{-}F}$ = 1.9 Hz, C-3), 61.4 (C-4), 60.0 (d, $J_{C\text{-}F}$ = 1.9 Hz, C-2), 13.7 (C-5); ^{19}F NMR: (376 MHz, $CDCl_3$) -111.98 – -112.05 (m, 1F), -112.23 – -112.29 (m,

1F); IR: (KBr) 1733 (C=O) cm^{-1}; m.p. 74–75 °C; HRMS: (ESI+) Calculated ($C_{17}H_{15}O_2F_2NaCl$) 347.0621 $(M+Na)^+$ Found: 347.0623

3na Ethyl 3-chloro-2,3-bis(4-(trifluoromethoxy)phenyl)propanoate

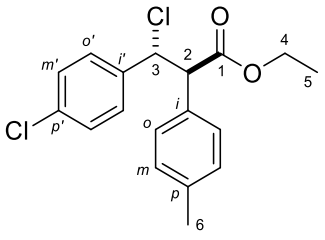


Following a modified procedure C. Under nitrogen atmosphere, a reaction tube was subsequently charged with $InCl_3$ (0.0497 mmol, 0.0110 g, 10 mol%), $CHCl_3$ (2 mL), and 4,4'-bis(trifluoromethoxy)diphenylmethyl chloride (0.532 mmol, 0.197 g) at 0 °C. The ethyl 2-diazoacetate (1.017 mmol, 0.116 g) was added to the resultant mixture in one portion. The reaction was stirred at rt for 12 h. After completion of reaction, the mixture was quenched by saturated $NaHCO_3$ aq and extracted with $CHCl_3$ (10 mL x 3). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The sum yield of diastereomers and the diastereomeric ratio were determined by ^1H NMR in the crude product (95%, 63:37). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by silica gel flash column chromatography (*n*-hexane/EtOAc = 90/10) and recycle HPLC (*n*-hexane/EtOAc = 90/10) to give the title compound as a diastereomeric mixture (colorless oil, 0.226 g, 93%, dr = 61:39).

*The below spectrum data are for a mixture of diastereomers **3na** because these diastereomers could not be separated by column chromatography.*

^1H NMR: (400 MHz, $CDCl_3$) 7.55-7.52 (m, 2.52H, Ar'-H), 7.25-7.21 (m, 2.52H, Ar'-H), 7.18-7.14 (m, 4H, Ar-H), 7.03-6.98 (m, 4H, Ar-H), 5.41 (d, J = 11.0 Hz, 1H, 3-H), 5.37 (d, J = 11.0 Hz, 0.63H, 3'-H), 4.36-4.15 (m, 3.63H, 2-H 2'-H, and 4-H_2), 3.99-3.81 (m, 1.26H, 4'-H_2), 1.29 (t, J = 7.1 Hz, 3H, 5-H_3), 0.92 (t, J = 7.1 Hz, 1.89H, 5'-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.8 (C-1), 170.0 (C-1'), 149.37-149.35 (m), 149.21-149.19 (m), 149.04-148.99 (m), 148.95-148.89 (m), 137.9, 136.7, 134.1, 133.2, 130.1, 129.8, 129.3, 129.1, 121.03, 121.00, 120.44 (q, J_{C-F} = 257.5 Hz), 120.40 (q, J_{C-F} = 257.8 Hz), 120.3 (q, J_{C-F} = 257.5 Hz), 120.7, 62.7, 62.2, 61.8, 61.4, 60.5, 59.9, 14.0, 13.5 *Some signals were overlapped so numbers of observed signals were less than expected ones;* ^{19}F NMR: (376 MHz, $CDCl_3$) -57.94 (s), -58.04 (s), -58.15 (s); IR: (neat) 1735, 1510, 1264, 1217, 1159 cm^{-1}; HRMS: (ESI+) Calculated ($C_{19}H_{15}O_4F_6NaCl$) 479.0455 $(M+Na)^+$ Found: 479.0462

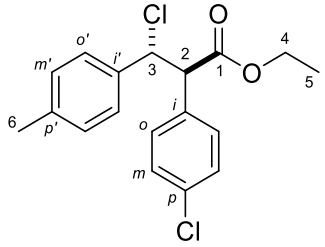
(2*R,3*R**)-3oa Ethyl (2*R**,3*R**)-3-chloro-3-(4-chlorophenyl)-2-(*p*-tolyl)propanoate**



Following the general procedure C using 4-chloro-4'-methylbenzhydrylchloride (0.500 mmol, 0.126 g) and ethyl 2-diazoacetate (1.001 mmol, 0.114 g) with $InCl_3$ (0.0497 mmol, 0.0110 g). The yield (sum of diastereomers) and diastereomeric ratio were determined by ^1H NMR in crude products (40%, 97:3). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by silica gel flash column chromatography (*n*-hexane/EtOAc = 95/5) and recycle HPLC (*n*-hexane/EtOAc = 90/10) to give the title compound as a white solid (0.0605 g, 36%).

^1H NMR: (400 MHz, $CDCl_3$) 7.14 (d, J = 8.7 Hz, 2H, *m'*-H), 7.10 (d, J = 8.7 Hz, 2H, *o'*-H), 7.00 (d, J = 8.1 Hz, 2H, *o*-H), 6.95 (d, J = 8.1 Hz, 2H, *m*-H), 5.40 (d, J = 11.3 Hz, 1H, 3-H), 4.33-4.11 (m, 3H, 2-H and 4-H_2), 2.22 (s, 3H, 6-H_3), 1.28 (t, J = 7.1 Hz, 3H, 5-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 171.4 (C-1), 137.8, 137.0 (C-*p*), 134.0, 131.5, 129.4, 129.1, 128.5, 128.2, 62.5 (C-3), 61.5 (C-4), 60.5 (C-2), 21.0 (C-6), 14.1 (C-5); IR: (KBr) 1727 (C=O) cm^{-1}; m.p. 78–79 °C; HRMS: (ESI+) Calculated ($C_{18}H_{18}O_2NaCl_2$) 359.0576 $(M+Na)^+$ Found: 359.0576

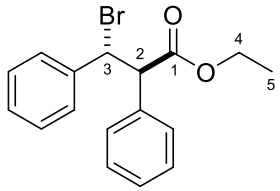
(2*R,3*R**)-3oa' Ethyl (2*R**,3*R**)-3-chloro-2-(4-chlorophenyl)-3-(*p*-tolyl)propanoate**



Following the general procedure C using 4-chloro-4'-methylbenzhydrylchloride (0.500 mmol, 0.126 g) and ethyl 2-diazoacetate (1.001 mmol, 0.114 g) with $InCl_3$ (0.0497 mmol, 0.0110 g). The yield (sum of diastereomers) and diastereomeric ratio were determined by ^1H NMR in crude products (28%, 95:5). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by silica gel flash column chromatography (*n*-hexane/EtOAc = 95/5) and recycle HPLC (*n*-hexane/EtOAc = 90/10) to give the title compound as a white solid (0.0388 g, 23%).

^1H NMR: (400 MHz, $CDCl_3$) 7.13-7.04 (m, 6H, Ar-H), 6.99 (d, J = 8.2 Hz, 2H, *m'*-H), 5.38 (d, J = 11.1 Hz, 1H, 3-H), 4.34-4.14 (m, 3H, 2-H and 4-H_2), 2.25 (s, 3H, 6-H_3), 1.29 (t, J = 7.2 Hz, 3H, 5-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 171.2 (C-1), 138.4 (C-*p'*), 134.9, 133.8, 133.5, 129.7, 129.2, 128.7, 127.5, 63.1 (C-3), 61.6 (C-4), 60.3 (C-2), 21.1 (C-6), 14.1 (C-5); IR: (KBr) 1740 (C=O) cm^{-1}; m.p. 98–99 °C; HRMS: (ESI+) Calculated ($C_{18}H_{18}O_2NaCl_2$) 359.0576 $(M+Na)^+$ Found: 359.0587

(2*R,3*R**)-3pa Ethyl (2*R**,3*R**)-3-bromo-2,3-diphenylpropanoate**

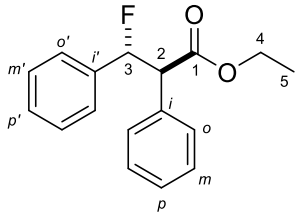


Following the general procedure D using diphenylmethyl bromide (0.524 mmol, 0.130 g) and ethyl 2-diazoacetate (1.000 mmol, 0.114 g) with $InBr_3$ (0.0514 mmol, 0.0180 g). The reaction was performed at –

30 °C for 20 h. The yield (sum of diastereomers) and diastereomeric ratio were determined by ^{1}H NMR in crude products (80%, 93:7). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by silica gel flash column chromatography (*n*-hexane/EtOAc = 95/5) and recycle HPLC (*n*-hexane/EtOAc = 90/10) to give the title compound as a white solid (0.124 g, 72%).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.21-7.06 (m, 10H, Ar-H), 5.55 (d, J = 11.8 Hz, 1H, 3-H), 4.42 (d, J = 11.8 Hz, 1H, 2-H), 4.33-4.11 (m, 2H, 4-H_2), 1.26 (t, J = 7.2 Hz, 3H, 5-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 171.5 (C-1), 138.6, 135.2, 128.5, 128.3, 128.2, 127.9, 127.8, 61.4 (C-4), 60.8 (C-2), 53.9 (C-3), 14.0 (C-5) *One aromatic carbon resonance not located*; IR: (KBr) 1733 (C=O) cm^{-1}; m.p. 64–65 °C; HRMS: (ESI+) Calculated ($C_{17}H_{17}O_2NaBr$) 355.0304 $(M+Na)^+$ Found: 355.0302

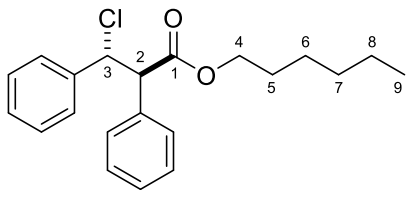
(2*R,3*R**)-3qa Ethyl (2*R**,3*R**)-3-fluoro-2,3-diphenylpropanoate**



Following the general procedure E. To a reaction tube was subsequently charged with EtOAc (2 mL), ethyl 2-diazoacetate (1.000 mmol, 0.114 g), and diphenylmethyl fluoride (0.495 mmol, 0.0922 g) at 0 °C. $BF_3{\cdot}OEt_2$ (0.0514 mmol, 0.0073 g) was added to the resultant mixture at same temperature. The reaction was stirred at 0 °C for 12 h. After completion of reaction, the mixture was quenched by saturated $NaHCO_3$ aq and extracted with EtOAc (10 mL x 3). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The yield (sum of diastereomers) and diastereomeric ratio were determined by ^{1}H NMR and ^{19}F NMR in crude products (73%, 99.5:0.5). 1,1,2,2-Tetrachloroethane and hexafluorobenzene were used as internal standards. The crude product was purified by silica gel column chromatography (*n*-hexane/EtOAc = 95/5) and recycle HPLC (*n*-hexane/EtOAc = 90/10) to give the title compound as a colorless oil (0.0930 g, 69%).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.19-7.10 (m, 8H, Ar-H), 7.07-7.05 (m, 2H, *o'*-H), 5.94 (d, $^2J_{H\text{-}F}$ = 45.5 Hz, d, J = 10.2 Hz, 1H, 3-H), 4.32-4.13 (m, 2H, 4-H_2), 4.03 (d, J = 10.2 Hz, $^3J_{H\text{-}F}$ = 9.3 Hz, 1H, 2-H), 1.25 (t, J = 7.0 Hz, 3H, 5-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 171.2 (C-1), 136.6 (d, $J_{C\text{-}F}$ = 20.0 Hz, C-*i'*), 133.3 (d, $J_{C\text{-}F}$ = 10.5 Hz, C-*i*), 128.68, 128.65, 128.5, 128.1, 127.9, 126.7 (d, $J_{C\text{-}F}$ = 5.7 Hz, C-*o'*), 95.2 (d, $J_{C\text{-}F}$ = 176.4 Hz, C-3), 61.3 (C-4), 58.7 (d, $J_{C\text{-}F}$ = 26.7 Hz, C-2), 14.0 (C-5); ^{19}F NMR: (376 MHz, $CDCl_3$) -171.52 (dd, J = 45.5, 11.4 Hz, 1F); IR: (neat) 1735 (C=O) cm^{-1}; HRMS: (ESI+) Calculated ($C_{17}H_{17}O_2FNa$) 295.1105 $(M+Na)^+$ Found: 295.1102

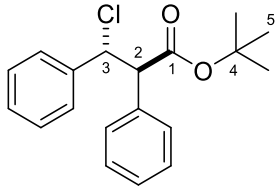
(2*R,3*R**)-3ab *n*-Hexyl (2*R**,3*R**)-3-chloro-2,3-diphenylpropanoate**



Following the general procedure C using diphenylmethyl chloride (0.500 mmol, 0.101 g) and *n*-hexyl diazoacetate (1.000 mmol, 0.170 g) with $InCl_3$ (0.0502 mmol, 0.0111 g). The yield (sum of diastereomers) and diastereomeric ratio were determined by ^1H NMR in crude products (64%, 91:9). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by silica gel flash column chromatography (*n*-hexane/EtOAc = 95/5) and recycle HPLC (*n*-hexane/EtOAc = 90/10) to give the title compound as a colorless oil (0.0948 g, 55%).

^1H NMR: (400 MHz, $CDCl_3$) 7.17-7.10 (m, 10H, Ar-H), 5.45 (d, J = 11.3 Hz, 1H, 3-H), 4.27-4.09 (m, 3H, 2-H and 4-H_2), 1.64 (quint, J = 7.1 Hz, 2H, 5-H_2), 1.33-1.27 (m, 6H, 6-H_2, 7-H_2, and 8-H_2), 0.86 (t, J = 7.1 Hz, 3H, 9-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 171.5 (C-1), 138.2, 134.8, 128.44, 128.35, 128.3, 128.2, 127.8, 127.7, 65.5 (C-4), 63.3 (C-3), 61.1 (C-2), 31.3 (C-7), 28.4 (C-5), 25.4 (C-6), 22.4 (C-8), 13.9 (C-9); IR: (neat) 1737 (C=O) cm^{-1}; HRMS: (ESI+) Calculated ($C_{21}H_{25}O_2NaCl$) 367.1435 $(M+Na)^+$ Found: 367.1436

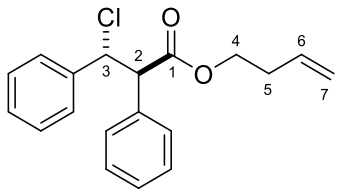
(2*R,3*R**)-3ac *tert*-Butyl (2*R**,3*R**)-3-chloro-2,3-diphenylpropanoate**



Following the general procedure C using diphenylmethyl chloride (0.550 mmol, 0.111 g) and *tert*-butyl 2-diazoacetate (1.070 mmol, 0.152 g) with $InCl_3$ (0.0520 mmol, 0.0115 g). The resultant mixture was stirred at 0 °C for 5 min and rt for 12 h. The yield (sum of diastereomers) and diastereomeric ratio were determined by ^1H NMR in crude products (65%, 93:7). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by silica gel flash column chromatography (*n*-hexane/EtOAc = 95/5) and recycle HPLC (*n*-hexane/EtOAc = 90/10) to give the title compound as a white solid (0.105 g, 60%).

^1H NMR: (400 MHz, $CDCl_3$) 7.14-7.11 (m, 10H, Ar-H), 5.38 (d, J = 11.3 Hz, 1H, 3-H), 4.10 (d, J = 11.3 Hz, 1H, 2-H), 1.48 (s, 9H, 5-H_3 x 3); ^{13}C NMR: (100 MHz, $CDCl_3$) 171.4 (C-1), 138.4, 135.2, 128.4, 128.3, 128.2, 127.7, 127.6, 81.8 (C-4), 63.8 (C-3), 61.9 (C-2), 27.9 (C-5); IR: (KBr) 1727 (C=O) cm^{-1}; m.p. 99–100 °C; HRMS: (ESI+) Calculated ($C_{19}H_{21}O_2NaCl$) 339.1122 $(M+Na)^+$ Found: 339.1120

(2*R,3*R**)-3ad But-3-en-1-yl (2*R**,3*R**)-3-chloro-2,3-diphenylpropanoate**

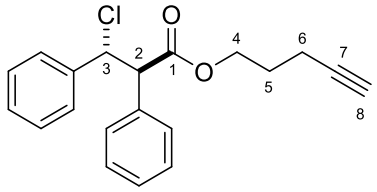


Following the general procedure C using diphenylmethyl chloride (0.510 mmol, 0.103 g) and but-3-enyl 2-diazoacetate (1.002 mmol, 0.140 g) with $InCl_3$ (0.0497 mmol, 0.0110 g). The resultant mixture was stirred at 0 °C for 12 h. The yield (sum of diastereomers) and diastereomeric ratio were determined by ^1H NMR in crude products (78%, 91:9). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by silica gel flash column chromatography (*n*-hexane/EtOAc = 95/5) and recycle HPLC (*n*-

hexane/EtOAc = 90/10) to give the title compound as a colorless oil (0.111 g, 69%).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.17-7.10 (m, 10H, Ar-H), 5.80-5.70 (m, 1H, 6-H), 5.45 (d, *J* = 11.4 Hz, 1H, 3-H), 5.08-5.01 (m, 2H, 7-H_2), 4.32-4.15 (m, 3H, 2-H and 4-H_2), 2.43-2.38 (m, 2H, 5-H_2); ^{13}C NMR: (100 MHz, $CDCl_3$) 171.3 (C-1), 138.2, 134.7, 133.6 (C-6), 128.5, 128.4, 128.3, 128.2, 127.9, 127.7, 117.3 (C-7), 63.4 (C-4), 63.3 (C-3), 61.1 (C-2), 32.9 (C-5); IR: (neat) 1737 (C=O) cm^{-1}; HRMS: (ESI+) Calculated ($C_{19}H_{19}O_2NaCl$) 337.0966 $(M+Na)^+$ Found: 337.0965

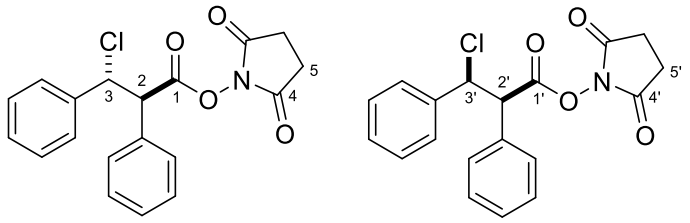
(2*R,3*R**)-3ae Pent-4-yn-1-yl (2*R**,3*R**)-3-chloro-2,3-diphenylpropanoate**



Following the general procedure C using diphenylmethyl chloride (0.528 mmol, 0.107 g) and pent-4-yn-1-yl 2-diazoacetate (1.006 mmol, 0.153 g) with $InCl_3$ (0.0542 mmol, 0.0120 g). The resultant mixture was stirred at 0 °C for 12 h. The yield (sum of diastereomers) and diastereomeric ratio were determined by ^{1}H NMR in crude products (73%, 94:6). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by silica gel flash column chromatography (*n*-hexane/EtOAc = 95/5) and recycle HPLC (*n*-hexane/EtOAc = 90/10) to give the title compound as a colorless oil (0.118 g, 68%).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.16-7.09 (m, 10H, Ar-H), 5.45 (d, *J* = 11.4 Hz, 1H, 3-H), 4.37-4.20 (m, 3H, 2-H and 4-H_2), 2.24 (dt, *J* = 2.7, 7.0 Hz, 2H, 6-H_2), 1.94 (t, *J* = 2.7 Hz, 1H, 8-H), 1.87 (quint, *J* = 7.0 Hz, 2H, 5-H_2); ^{13}C NMR: (100 MHz, $CDCl_3$) 171.3 (C-1), 138.1, 134.6, 128.5, 128.3, 128.2, 127.9, 127.6, 127.0, 82.9 (C-7), 69.0 (C-8), 63.8 (C-4), 63.3 (C-3), 61.0 (C-2), 27.4 (C-5), 15.0 (C-6); IR: (neat) 3301, 1737 (C=O) cm^{-1}; HRMS: (ESI+) Calculated ($C_{20}H_{19}O_2NaCl$) 349.0966 $(M+Na)^+$ Found: 349.0965

3af 2,5-Dioxopyrrolidin-1-yl 3-chloro-2,3-diphenylpropanoate



major minor

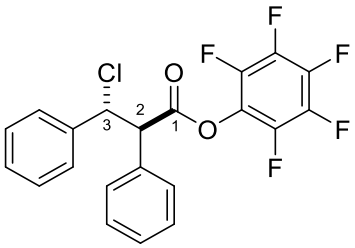
Following the general procedure using diphenylmethyl chloride (0.504 mmol, 0.102 g) and 2,5-dioxopyrrolidin-1-yl 2-diazoacetate (1.002 mmol, 0.183 g) with $InCl_3$ (0.0498 mmol, 0.0110 g). The resultant mixture was stirred at 0 °C for 1 h and rt 12 h. The yield (sum of diastereomers) and diastereomeric ratio were determined by ^{1}H NMR in crude products (42%, 83:17). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by silica gel flash column chromatography (*n*-hexane/EtOAc = 60/40) and recycle GPC ($CHCl_3$ as eluent) to give the title compound as a diastereomeric mixture (white solid, 0.0680 g, 38%, dr = 83:17).

*The below spectrum data are for a mixture of diastereomers **3af** because these diastereomers could not be*

separated by column chromatography.

^{1}H NMR: (400 MHz, $CDCl_3$) 7.47-7.08 (m, 12.5H, Ar-H and Ar'-H), 5.45 (d, *J* = 10.0 Hz, 0.25H, 3'-H), 5.40 (d, *J* = 10.9 Hz, 1H, 3-H), 4.54 (d, *J* = 10.0 Hz, 0.25H, 2'-H), 4.53 (d, *J* = 10.9 Hz, 1H, 2-H), 2.75 (br s, 4H, 5-H_2 x 2), 2.61 (br s, 1H, 5'-H_2 x 2); ^{13}C NMR: (100 MHz, $CDCl_3$) 168.6, 168.2, 167.0, 166.2, 138.2, 137.2, 133.3, 132.6, 129.04, 129.00, 128.83, 128.76, 128.74, 128.72, 128.62, 128.56, 128.4, 128.3, 127.7, 127.5, 62.8 (C-3'), 62.1 (C-3), 58.3 (C-2), 56.9 (C-2'), 25.5 (C-5), 25.3 (C-5'); IR: (KBr) 1809, 1781, 1738, 1200, 1072 cm^{-1}; HRMS: (ESI+) Calculated ($C_{19}H_{16}NO_4NaCl$) 380.0660 $(M+Na)^+$ Found: 380.0660

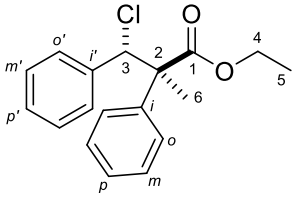
(2*R,3*R**)-3ma Perfluorophenyl (2*R**,3*R**)-3-chloro-2,3-diphenylpropanoate**



Following a modified procedure C. A reaction tube was subsequently charged with $InCl_3$ (0.0199 mmol, 0.0044 g, 10 mol%), EtOAc (0.8 mL), diphenylmethyl chloride (0.195 mmol, 0.0395 g), and perfluorophenyl 2-diazoacetate (0.397 mmol, 0.100 g) at 0 °C. The resultant mixture was stirred at 0 °C for 1 h and rt for 24 h. After completion of reaction, the mixture was quenched by saturated $NaHCO_3$ aq and extracted with EtOAc (10 mL x 3). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The sum yield of diastereomers and the diastereomeric ratio were determined by ^{1}H NMR in the crude product (71%, 86:14). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by silica gel flash column chromatography (*n*-hexane/EtOAc = 95/5) and recycle HPLC (*n*-hexane/EtOAc = 90/10) to give the title compound as a colorless oil (0.0508 g, 61%).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.19-7.15 (m, 10H, Ar-H), 5.48 (d, *J* = 11.4 Hz, 1H, 3-H), 4.57 (d, *J* = 11.4 Hz, 1H, 2-H); ^{13}C NMR: (100 MHz, $CDCl_3$) 167.6 (C-1), 142.5-142.3 (m), 141.0-140.7 (m), 140.0-139.8 (m), 139.2-139.0 (m), 138.5-138.3 (m), 137.4, 136.8-136.4 (m), 133.1, 128.9, 128.7, 128.6, 128.5, 128.4, 127.7, 62.3 (C-3), 60.7 (C-2); ^{19}F NMR: (376 MHz, $CDCl_3$) -151.75 (d, *J* = 18.3 Hz, 2F), -157.42 (t, *J* = 21.4 Hz, 1F), -162.09 (d, *J* = 19.8 Hz, 2F); IR: (neat) 1787, 1527, 1104, 1008 cm^{-1}; HRMS: (ESI+) Calculated ($C_{21}H_{12}O_2F_5NaCl$) 449.0338 $(M+Na)^+$ Found: 449.0344

(2*R,3*S**)-3ah Ethyl (2*R**,3*S**)-3-chloro-2-methyl-2,3-diphenylpropanoate**

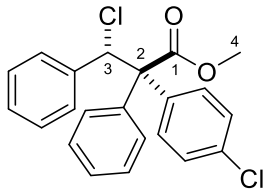


Following the general procedure C using diphenylmethyl chloride (0.493 mmol, 0.100 g) and ethyl 2-diazopropanoate (1.005 mmol, 0.128 g) with $InCl_3$ (0.0497 mmol, 0.0110 g). The reaction was stirred at 0 °C for 12 h and rt for 6 h. The yield (sum of diastereomers) and diastereomeric ratio were determined by ^{1}H

NMR in crude products (68%, 75:25). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by silica gel flash column chromatography (*n*-hexane/EtOAc = 95/5) and recycle HPLC (*n*-hexane/EtOAc = 90/10) to give the title compound as a colorless oil (0.0731 g, 49%).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.21-7.18 (m, 5H, Ar-H), 7.11 (t, *J* = 7.2 Hz, 1H, Ar-H), 7.04 (t, *J* = 7.2 Hz, 2H, Ar-H), 6.90 (d, *J* = 7.2 Hz, 2H, Ar-H), 5.83 (s, 1H, 3-H), 4.33-4.18 (m, 2H, 4-H_2), 1.76 (s, 3H, 6-H_3), 1.28 (t, *J* = 7.0 Hz, 3H, 5-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 173.3 (C-1), 138.7 (C-*i*), 136.6 (C-*i'*), 129.0 (C-*o*'), 128.2, 127.8, 127.7, 127.1, 126.8, 68.2 (C-3), 61.6 (C-4), 56.9 (C-2), 14.8 (C-6), 14.0 (C-5); IR: (neat) 1726 (C=O) cm^{-1}; HRMS: (ESI+) Calculated ($C_{18}H_{19}O_2NaCl$) 325.0966 $(M+Na)^+$ Found: 325.0965

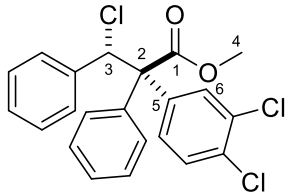
(2*R,3*R**)-3ai Methyl (2*R**,3*R**)-3-chloro-2-(4-chlorophenyl)-2,3-diphenylpropanoate**



Following the general procedure C using diphenylmethyl chloride (0.474 mmol, 0.0960 g) and methyl 2-(4-chlorophenyl)-2-diazoacetate (0.755 mmol, 0.159 g) with $InCl_3$ (0.0506 mmol, 0.0112 g). The reaction was stirred at 0 °C for 12 h. The yield (sum of diastereomers) and diastereomeric ratio were determined by ^{1}H NMR in crude products (64%, 64:36). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by silica gel flash column chromatography (*n*-hexane/EtOAc = 90/10) and recycle HPLC (*n*-hexane/EtOAc = 90/10) to give the title compound as a colorless oil (0.0730 g, 40%).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.47 (d, *J* = 8.7 Hz, 2H, Ar-H), 7.31 (d, *J* = 8.7 Hz, 3H, Ar-H), 7.24-7.17 (m, 3H, Ar-H), 7.10-7.03 (m, 4H, Ar-H), 6.82 (d, *J* = 7.5 Hz, 2H, Ar-H), 6.49 (s, 1H, 3-H), 3.60 (s, 3H, 4-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 171.9 (C-1), 138.3, 137.3, 136.1, 133.6, 132.2, 131.7, 130.3, 128.2, 127.8, 127.7, 127.0, 126.6, 67.5 (C-2), 64.2 (C-3), 52.6 (C-4); IR: (neat) 1731 (C=O) cm^{-1}; HRMS: (ESI+) Calculated ($C_{22}H_{18}O_2NaCl_2$) 407.0576 $(M+Na)^+$ Found: 407.0579

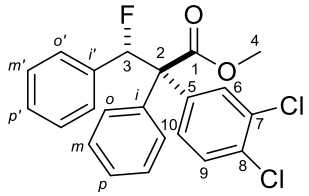
(2*R,3*R**)-3aj Methyl (2*R**,3*R**)-3-chloro-2-(3,4-dichlorophenyl)-2,3-diphenylpropanoate**



Following the general procedure C using diphenylmethyl chloride (0.505 mmol, 0.102 g) and methyl 2-diazo-2-(3,4-dichlorophenyl)acetate (0.748 mmol, 0.184 g) with $InCl_3$ (0.0520 mmol, 0.0115 g). The reaction was stirred at 0 °C for 5 min and warm to rt for 6 h. The yield (sum of diastereomers) and diastereomeric ratio were determined by ^{1}H NMR in crude products (85%, 80:20). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by silica gel flash column chromatography (*n*-hexane/EtOAc = 90/10) and recycle HPLC (*n*-hexane/EtOAc = 90/10) to give the title compound as a colorless oil (0.140 g, 66%).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.62 (s, 1H, 6-H), 7.41-7.31 (m, 3H, Ar-H), 7.25-7.16 (m, 3H, Ar-H), 7.10-7.04 (m, 3H, Ar-H), 6.81 (d, J = 7.2 Hz, 2H, Ar-H), 6.81 (d, J = 7.5 Hz, 2H, Ar-H), 6.45 (s, 1H, 3-H), 3.61 (s, 3H, 4-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 171.5 (C-1), 139.9, 136.9, 135.7, 132.4, 132.0, 131.9, 131.8, 130.3, 129.8, 129.4, 128.4, 127.9, 127.1, 126.8, 67.4 (C-2), 64.1 (C-3), 52.8 (C-4); IR: (neat) 1730 (C=O) cm^{-1}; HRMS: (ESI+) Calculated ($C_{22}H_{17}O_2NaCl_3$) 441.0186 $(M+Na)^+$ Found: 441.0189

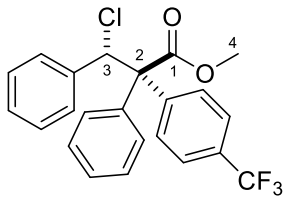
(2*R,3*R**)-3qj Methyl (2*R**,3*R**)-2-(3,4-dichlorophenyl)-3-fluoro-2,3-diphenylpropanoate**



Following the general procedure E. To a reaction tube was subsequently charged with 2-diazo-2-(3,4-dichlorophenyl)acetate (0.748 mmol, 0.184 g, 1.5 equiv), EtOAc (2 mL), and diphenylmethyl fluoride (0.522 mmol, 0.0970 g, 1.0 equiv) at –44 °C. $BF_3{\cdot}OEt_2$ (0.0514 mmol, 0.0073 g, 10 mol%) was added to the resultant mixture at same temperature. The reaction was stirred at –10 °C for 12 h. After completion of reaction, the mixture was quenched by saturated $NaHCO_3$ aq and extracted with EtOAc (15 mL x 3). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The yield (sum of diastereomers) and diastereomeric ratio were determined by ^{1}H NMR and ^{19}F NMR in crude products (82%, 83:17). 1,1,2,2-Tetrachloroethane and hexafluorobenzene were used as internal standards. The crude product was purified by silica gel column chromatography (*n*-hexane/EtOAc = 95/5) and recycle HPLC (*n*-hexane/EtOAc = 90/10) to give the title compound as a white solid (0.141 g, 67%).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.62 (s, 1H, 6-H), 7.41 (d, J = 8.5 Hz, 1H, 9-H), 7.34-7.17 (m, 5H, Ar-H), 7.12 (t, J = 7.5 Hz, 2H, Ar-H), 6.90 (d, J = 7.5 Hz, 2H, *o*-H), 6.89 (d, $^2J_{H\text{-}F}$ = 44.5 Hz, 1H, 3-H), 6.75 (d, J = 7.5 Hz, 2H, *o*'-H), 3.70 (s, 3H, 4-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 171.3 (d, $J_{C\text{-}F}$ = 9.1 Hz, C-1), 140.0, 136.1, 135.7 (d, $J_{C\text{-}F}$ = 21.1 Hz), 132.2, 131.8 (d, $J_{C\text{-}F}$ = 9.1 Hz), 131.7, 131.3, 129.8, 129.2, 128.5, 127.9-127.7 (m), 127.3, 127.1, 92.7 (d, $J_{C\text{-}F}$ = 181.3 Hz, C-3), 66.0 (d, $J_{C\text{-}F}$ = 24.2 Hz, C-2), 52.7 (C-4); ^{19}F NMR: (376 MHz, $CDCl_3$) -185.84 (d, J = 42.1 Hz, 1F); IR: (KBr) 1732 (C=O) cm^{-1}; m.p. 103–104 °C; HRMS: (ESI+) Calculated ($C_{22}H_{17}O_2FNaCl_2$) 425.0482 $(M+Na)^+$ Found: 425.0482

(2*R,3*R**)-3ak Methyl (2*R**,3*R**)-3-chloro-2,3-diphenyl-2-(4-(trifluoromethyl)phenyl)propanoate**

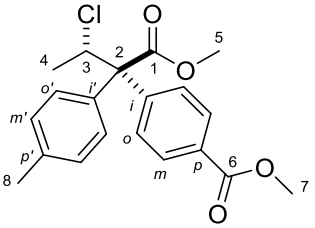


Following the general procedure C using diphenylmethyl chloride (0.514 mmol, 0.104 g) and methyl 2-diazo-2-(4-(trifluoromethyl)phenyl)acetate (0.761 mmol, 0.186 g) with $InCl_3$ (0.0498 mmol, 0.0110 g). The reaction was stirred at 0 °C for 5 min and warm to rt for 6 h. The yield (sum of diastereomers) and diastereomeric ratio were determined by ^{1}H NMR in crude products (81%, 77:23). 1,1,2,2-Tetrachloroethane

was used as an internal standard. The crude product was purified by silica gel flash column chromatography (*n*-hexane/EtOAc = 90/10) and recycle HPLC (*n*-hexane/EtOAc = 90/10) to give the title compound as a colorless oil (0.129 g, 60%).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.68 (d, J = 8.5 Hz, 2H, Ar-H), 7.60 (d, J = 8.7 Hz, 2H, Ar-H), 7.34 (t, J = 7.2 Hz, 1H, Ar-H), 7.26-7.18 (m, 3H, Ar-H), 7.09 (t, J = 7.7 Hz, 2H, Ar-H), 7.04 (d, J = 7.5 Hz, 2H, Ar-H), 6.82 (d, J = 7.2 Hz, 2H, Ar-H), 6.54 (s, 1H, 3-H), 3.61 (s, 3H, 4-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 171.7 (C-1), 143.8, 137.1, 135.9, 132.2, 130.7, 130.3, 129.6 (q, $J_{C\text{-}F}$ = 32.5 Hz), 128.4, 127.9, 127.1, 126.7, 124.6 (q, $J_{C\text{-}F}$ = 3.8 Hz), 124.0 (q, $J_{C\text{-}F}$ = 272.3 Hz), 67.9 (C-2), 64.1 (C-3), 52.8 (C-4); IR: (neat) 1730, 1331, 1220, 1168, 1127 cm^{-1}; HRMS: (ESI+) Calculated ($C_{23}H_{18}O_2F_3NaCl$) 441.0840 $(M+Na)^+$ Found: 441.0844

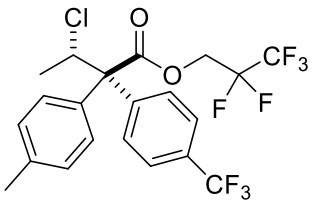
(2*R,3*R**)-3rl Methyl 4-((2*R**,3*R**)-3-chloro-1-methoxy-1-oxo-2-(*p*-tolyl)butan-2-yl)benzoate**



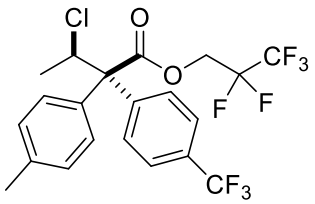
Following a modified procedure C using 1-(1-chloroethyl)-4-methylbenzene (0.415 mmol, 0.0642 g)**,** methyl 4-(1-diazo-2-methoxy-2-oxoethyl)benzoate (0.611 mmol, 0.143 g), and $InCl_3$ (0.0414 mmol, 0.0091 g) in $CHCl_3$ (1 mL). The resultant mixture was stirred at 0 °C for 5 min and rt for 6 h. The yield (sum of diastereomers) and diastereomeric ratio were determined by ^{1}H NMR in crude products (47%, >99:1). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by silica gel flash column chromatography (*n*-hexane/EtOAc = 90/10) and recycle HPLC (*n*-hexane/EtOAc = 90/10) to give the title compound as a colorless oil (0.0644 g, 43%).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.98 (d, J = 8.7 Hz, 2H, *m*-H), 7.48 (d, J = 8.7 Hz, 2H, *o*-H), 7.16 (s, 4H, *o'*-H and *m'*-H), 5.54 (q, J = 6.8 Hz, 1H, 3-H), 3.91 (s, 3H, 7-H_3), 3.66 (s, 3H, 5-H_3), 2.36 (s, 3H, 8-H_3), 1.35 (d, J = 6.8 Hz, 3H, 4-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 172.3 (C-1), 166.8 (C-6), 143.6 (br s, C-*i*), 137.6 (C-*p'*), 134.8 (br s, C-*i'*), 131.0 (br s, C-*o*), 129.8 (br s), 129.1, 128.5, 128.3, 66.0 (C-2), 58.8 (C-3), 52.7 (C-5), 52.1 (C-7), 21.6 (C-4), 21.0 (C-8); IR: (neat) 1724 (C=O) cm^{-1}; HRMS: (ESI+) Calculated ($C_{20}H_{21}O_4NaCl$) 383.1021 $(M+Na)^+$ Found: 383.1028

3rm 2,2,3,3,3-Pentafluoropropyl 3-chloro-2-(*p*-tolyl)-2-(4-(trifluoromethyl)phenyl)butanoate



major



minor

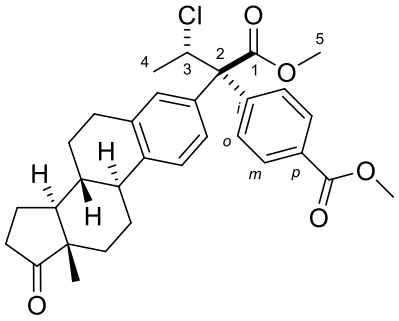
Following a modified procedure C using 1-(1-chloroethyl)-4-methylbenzene (0.409 mmol, 0.0633 g)**,** 2,2,3,3,3-pentafluoropropyl 2-diazo-2-(4-(trifluoromethyl)phenyl)acetate (0.583 mmol, 0.211 g), and $InCl_3$ (0.0400 mmol, 0.0088 g) in $CHCl_3$ (1 mL). The resultant mixture was stirred at 0 °C for 5 min and rt for 12

h. The yield (sum of diastereomers) and diastereomeric ratio were determined by ^{1}H NMR in crude products (86%, 64:36). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by silica gel flash column chromatography (*n*-hexane/EtOAc = 90/10) and recycle HPLC (*n*-hexane/EtOAc = 90/10) to give the title compound as a mixture of diastereomers (colorless oil, 0.166 g, 83%, *dr* = 63:37).

The below spectrum data are for a mixture of diastereomers ***3rm*** *because these diastereomers could not be separated by column chromatography.*

^{1}H NMR: (400 MHz, $CDCl_3$) 7.61-7.58 (m, 2H, Ar-H), 7.51 (d, *J* = 8.2 Hz, 1.25H, Ar-H), 7.44 (d, *J* = 8.2 Hz, 0.75H, Ar-H), 7.25 (d, *J* = 7.7 Hz, 0.75H, Ar-H), 7.16-7.14 (m, 3.25H, Ar-H), 5.57-5.48 (m, 1H, C*H*), 4.57-4.40 (m, 2H, CH_2), 2.363-2.355 (m, 3H, Ar-CH_3), 1.38 (d, *J* = 6.3 Hz, 1.12H, CH_3), 1.35 (d, *J* = 6.3 Hz, 1.88H, CH_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.3, 141.2 (br s), 138.3, 138.1, 134.2 (br s), 131.6 (br s), 131.1 (br s), 130.4-128.2 (m), 125.4, 125.3, 124.3 (br s), 124.6 (br s), 122.7, 122.6, 120.0-108.7 (m, Ar-*C*F_3, *C*F_2, and *C*F_3), 66.0, 60.3-59.7 (m, *C*$H_2CF_2CF_3$), 58.1, 57.6, 21.6, 21.2, 21.0; ^{19}F NMR: (376 MHz, $CDCl_3$) -62.68 (s), -62.71 (s), -83.97 (s), -123.32 (m) IR: (neat) 1755 (C=O) cm^{-1}; HRMS: (ESI+) Calculated ($C_{21}H_{17}O_2F_8NaCl$) 511.0682 $(M+Na)^+$ Found: 511.0689

(2*R,3*S**)-3sl Methyl 4-((2*R**,3*S**)-3-chloro-1-methoxy-2-((8*R*,9*S*,13*S*,14*S*)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-3-yl)-1-oxobutan-2-yl)benzoate**



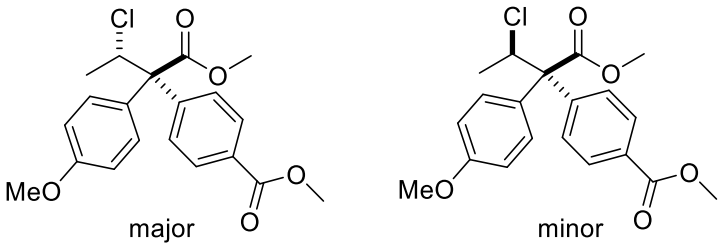
Following a modified procedure C using (8*R*,9*S*,13*S*,14*S*)-3-(1-chloroethyl)-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*-cyclopenta[*a*]phenanthren-17-one (0.400 mmol, 0.127 g)**,** methyl 4-(1-diazo-2-methoxy-2-oxoethyl)benzoate (0.578 mmol, 0.140 g), and $InCl_3$ (0.0405 mmol, 0.0089 g) in $CHCl_3$ (1 mL). The reaction was stirred at 0 °C for 5 min and rt for 6 h. The yield (sum of diastereomers) and diastereomeric ratio were determined by ^{1}H NMR in crude products (35%, >99:1, *this ratio means that (2R*,3S*)-isomer was exclusively obtained*). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by silica gel flash column chromatography (*n*-hexane/EtOAc = 85/15) and recycle HPLC (*n*-hexane/EtOAc = 85/15) to give the title compound as a mixture of diastereomers (colorless oil, 0.0607 g, 29%, *dr* = 50:50, *this means that (2R,3S):(2S,3R) = 50:50*).

The below spectrum data are for a mixture of diastereomers ***3sl*** *because these diastereomers could not be separated.*

^{1}H NMR: (400 MHz, $CDCl_3$) 7.98 (d, *J* = 8.5 Hz, 2H, *m*-H), 7.48 (d, *J* = 8.5 Hz, 2H, *o*-H), 7.25 (d, *J* = 8.2 Hz, 1H, Ar-H), 7.04 (d, *J* = 8.2 Hz, 1H, Ar-H), 6.98 (s, 1H, Ar-H), 5.54 (q, *J* = 6.4 Hz, 1H, 3-H), 3.92 (s, 3H, OCH_3), 3.68 (s, 3H, 5-H_3), 2.89-2.86 (m, 2H), 2.55-2.29 (m, 3H), 2.21-1.97 (m, 4H), 1.69-1.47 (m, 6H), 1.35 (d, *J* = 6.4 Hz, 3H, 4-H_3), 0.94 (s, 3H, CH_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 220.7, 172.2 (C-1), 166.8,

143.4 (br s), 139.3, 135.9, 135.3 (br s), 131.1, 130.3, 128.9, 128.2, 127.2, 124.7, 65.8 (C-2), 58.8 (C-3), 52.7 (C-5), 52.0, 50.4, 47.9, 44.2, 37.8, 35.7, 31.5, 29.4, 26.4, 25.43, 25.40, 21.5, 13.8 *Some signals were overlapped so numbers of observed signals were less than expected ones;* IR: (neat) 1738, 1727 cm^{-1}; HRMS: (ESI+) Calculated ($C_{31}H_{35}O_5NaCl$) 545.2065 $(M+Na)^+$ Found: 545.2061

3tl Methyl 4-(3-chloro-1-methoxy-2-(4-methoxyphenyl)-1-oxobutan-2-yl)benzoate

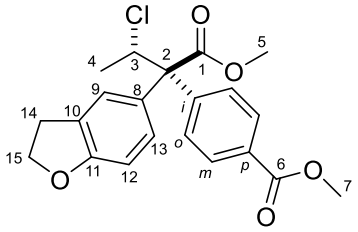


Following a modified procedure C using 1-(1-chloroethyl)-4-methoxybenzene (0.407 mmol, 0.0695 g)**,** methyl 4-(1-diazo-2-methoxy-2-oxoethyl)benzoate (0.600 mmol, 0.141 g), and $InCl_3$ (0.0400 mmol, 0.0088 g) in PhCl (2 mL). The reaction was stirred at –44 °C for 12 h. The yield (sum of diastereomers) and diastereomeric ratio were determined by ^1H NMR in crude products (64%, 77:23). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by silica gel flash column chromatography (*n*-hexane/EtOAc = 85/15) and recycle HPLC (*n*-hexane/EtOAc = 85/15) to give the title compound as a mixture of diastereomers (colorless oil, 0.0936 g, 61%, *dr* = 77:23).

The below spectrum data are for a mixture of diastereomers ***3tl*** *because these diastereomers could not be separated by column chromatography.*

^1H NMR: (400 MHz, $CDCl_3$) 8.01-7.98 (m, 2H, Ar-H), 7.49 (d, *J* = 8.7 Hz, 1.55H, Ar-H), 7.39 (d, *J* = 8.7 Hz, 0.45H, Ar-H), 7.29 (d, *J* = 8.7 Hz, 0.45H, Ar-H), 7.20 (d, *J* = 8.7 Hz, 1.55H, Ar-H), 6.88-6.84 (m, 2H, Ar-H), 5.55-5.48 (m, 1H), 3.92-3.91 (m, 3H, OCH_3), 3.82-3.81 (m, 3H, OCH_3), 3.66 (s, 3H, OCH_3), 1.37-1.34 (m, 3H, CH_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 172.32, 172.29, 166.7, 166.6, 158.9, 158.8, 143.6 (br s), 131.1-130.8 (m), 129.7 (br s), 129.2, 129.0, 128.4-128.3 (m), 113.1, 112.9, 65.63, 65.57, 58.8, 58.6, 55.2, 55.1, 52.7, 52.1, 52.0, 21.8, 21.5 *Some signals were overlapped so numbers of observed signals were less than expected ones*; IR: (neat) 1725 (C=O) cm^{-1}; HRMS: (ESI+) Calculated ($C_{20}H_{21}O_5NaCl$) 399.0970 $(M+Na)^+$ Found: 399.0973

(2*R,3*S**)-3ul Methyl 4-((2*R**,3*S**)-3-chloro-2-(2,3-dihydrobenzofuran-5-yl)-1-methoxy-1-oxobutan-2-yl)benzoate**

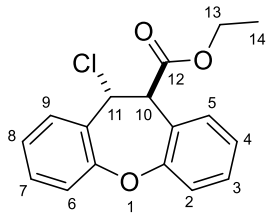


Following a modified procedure C using 5-(1-chloroethyl)-2,3-dihydrobenzofuran (0.400 mmol, 0.0731 g)**,** methyl 4-(1-diazo-2-methoxy-2-oxoethyl)benzoate (0.600 mmol, 0.141 g), and $InCl_3$ (0.0400 mmol, 0.0088 g) in PhCl (2 mL). The reaction was stirred at –44 °C for 12 h. The yield (sum of diastereomers) and

diastereomeric ratio were determined by ^{1}H NMR in crude products (61%, 75:25). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by silica gel flash column chromatography (*n*-hexane/EtOAc = 85/15) and recycle HPLC (*n*-hexane/EtOAc = 85/15) to give the title compound as a colorless oil (0.0684 g, 44%).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.99 (d, *J* = 8.5 Hz, 2H, *m*-H), 7.49 (d, *J* = 8.5 Hz, 2H, *o*-H), 7.08 (s, 1H, 9-H), 7.02 (d, *J* = 8.5 Hz, 1H, 13-H), 6.74 (d, *J* = 8.5 Hz, 1H, 12-H), 5.52 (q, *J* = 6.5 Hz, 1H, 3-H), 4.60 (t, *J* = 8.7 Hz, 2H, 15-H_2), 3.92 (s, 3H, 7-H_3), 3.67 (s, 3H, 5-H_3), 3.20 (t, *J* = 8.7 Hz, 2H, 14-H_2), 1.35 (d, *J* = 6.5 Hz, 3H, 4-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 172.4 (C-1), 166.7 (C-6), 159.5 (C-11), 143.7 (br s, C-*i*), 130.9 (br s, C-*p*), 129.7 (br s, C-10), 129.0 (C-*o*), 128.2 (C-*m*), 126.7 (br s, C-9), 108.3 (C-12), 71.4 (C-15), 65.8 (C-2), 58.9 (C-3), 52.7 (C-5), 52.0 (C-7), 29.6 (C-14), 21.5 (C-4) *Some signals were overlapped so numbers of observed signals were less than expected ones;* IR: (neat) 1726 (C=O) cm^{-1}; HRMS: (ESI+) Calculated ($C_{21}H_{21}O_5NaCl$) 411.0970 $(M+Na)^+$ Found: 411.0978

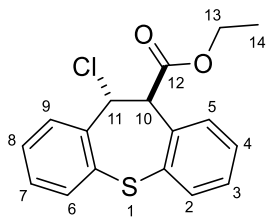
(10*R,11*R**)-3va Ethyl (10*R**,11*R**)-11-chloro-10,11-dihydrodibenzo[*b*,*f*]oxepine-10-carboxylate**



Following the general procedure C using 9-chloro-9*H*-xanthene (0.494 mmol, 0.107 g) and ethyl 2-diazoacetate (1.000 mmol, 0.114 g) with $InCl_3$ (0.0497 mmol, 0.0110 g). The yield (sum of diastereomers) and diastereomeric ratio were determined by ^{1}H NMR in crude products (84%, 91:9). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by silica gel flash column chromatography (*n*-hexane/EtOAc = 95/5) and recycle HPLC (*n*-hexane/EtOAc = 90/10) to give the title compound as a colorless oil (0.111 g, 74%).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.44 (d, *J* = 7.7 Hz, 1H, 9-H), 7.30-7.07 (m, 7H, Ar-H), 5.92 (d, *J* = 6.9 Hz, 1H, 11-H), 4.41 (d, *J* = 6.9 Hz, 1H, 10-H), 4.17 (q, *J* = 7.1 Hz, 2H, 13-H_2), 1.14 (t, *J* = 7.1 Hz, 3H, 14-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.0 (C-12), 157.1, 154.8, 132.4, 131.0, 129.9, 129.4, 128.0, 127.4, 124.8, 124.3, 121.4, 121.1, 61.5 (C-13), 58.6 (C-11), 54.9 (C-10), 13.9 (C-14); IR: (neat) 1738, 1484, 1450 cm^{-1}; HRMS: (ESI+) Calculated ($C_{17}H_{15}O_3NaCl$) 325.0602 $(M+Na)^+$ Found: 325.0602

(10*R,11*R**)-3wa Ethyl (10*R**,11*R**)-11-chloro-10,11-dihydrodibenzo[*b*,*f*]thiepine-10-carboxylate**

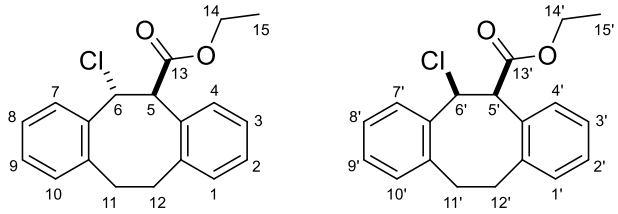


Following the general procedure C using 9-chloro-9*H*-thioxanthene (0.514 mmol, 0.119 g) and ethyl 2-diazoacetate (1.000 mmol, 0.114 g) with $InCl_3$ (0.0497 mmol, 0.0110 g). The yield (sum of diastereomers) and diastereomeric ratio were determined by ^{1}H NMR in crude products (80%, 87:13). 1,1,2,2-

Tetrachloroethane was used as an internal standard. The crude product was purified by silica gel flash column chromatography (*n*-hexane/EtOAc = 95/5) and recycle HPLC (*n*-hexane/EtOAc = 90/10) to give the title compound as a white solid (0.107 g, 65%).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.59 (d, *J* = 7.7 Hz, 1H, Ar-H), 7.54 (d, *J* = 7.7 Hz, 1H, Ar-H), 7.49 (d, *J* = 7.7 Hz, 1H, Ar-H), 7.33-7.13 (m, 5H, Ar-H), 6.21 (d, *J* = 10.4 Hz, 1H, 11-H), 5.00 (d, *J* = 10.4 Hz, 1H, 10-H), 4.34-4.26 (m, 2H, 13-H_2), 1.28 (t, *J* = 7.0 Hz, 3H, 14-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 171.1 (C-12), 138.5, 137.2, 137.1, 134.8, 133.1, 132.6, 132.5, 129.5, 128.8, 128.6, 128.3, 127.9, 61.7 (C-13), 60.8 (C-11), 57.7 (C-10), 14.0 (C-14); IR: (KBr) 1731, 1468, 1308, 1240, 1211, 1163 cm^{-1}; m.p. 115–116 °C; HRMS: (ESI+) Calculated ($C_{17}H_{15}O_2NaSCl$) 341.0374 $(M+Na)^+$ Found: 341.0375

3xa Ethyl 6-chloro-5,6,11,12-tetrahydrodibenzo[*a*,*e*][8]annulene-5-carboxylate



major minor

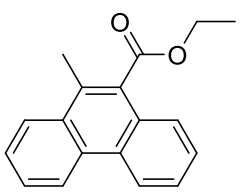
Following the general procedure C using 5-chloro-10,11-dihydro-5*H*-dibenzo[*a*,*d*][7]annulene (0.515 mmol, 0.118 g) and ethyl 2-diazoacetate (1.003 mmol, 0.114 g) with $InCl_3$ (0.0497 mmol, 0.0110 g). The yield (sum of diastereomers) and diastereomeric ratio were determined by ^{1}H NMR in crude products (83%, 83:17). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by silica gel flash column chromatography (*n*-hexane/EtOAc = 95/5) and recycle HPLC (*n*-hexane/EtOAc = 90/10) to give the title compound as a diastereomeric mixture (white solid, 0.128 g, 79%, dr = 81:19).

*The below spectrum data are for a mixture of diastereomers **3xa** because these diastereomers could not be separated by column chromatography.*

^{1}H NMR: (400 MHz, $CDCl_3$)

7.58 (d, *J* = 10.1 Hz, 0.23H, Ar'-H), 7.10-6.76 (m, 8.61H, Ar-H and Ar'-H), 6.35 (d, *J* = 10.6 Hz, 0.23H, 6'-H), 5.58 (d, *J* = 10.6 Hz, 1H, 6-H), 4.85 (d, *J* = 10.6 Hz, 1H, 5-H), 4.39-4.03 (m, 2.69H, 14-H_2, 14'-H_2, and 5'-H), 3.84-3.53 (m, 2.46H), 3.11-2.89 (m, 2.46H), 1.30-1.23 (m, 3.69H, 15-H_3 and 15'-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 171.8 (C-13), 171.4 (C-13'), 139.0, 138.6, 138.4, 137.4, 137.1, 136.9, 135.2, 134.6, 131.6, 131.3, 130.7, 130.5, 130.0, 129.1, 128.0, 127.9, 126.8, 126.6, 126.4, 126.3, 125.2, 65.1, 64.9 (C-6), 61.6 (C-14), 61.4, 59.6, 56.4 (C-5), 35.2, 34.8, 32.0, 31.8, 14.1 (C-15) *Some signals were overlapped so numbers of observed signals were less than expected ones;* IR: (KBr) 1734, 1718, 1473, 1210 cm^{-1}; HRMS: (ESI+) Calculated ($C_{19}H_{19}O_2NaCl$) 337.0966 $(M+Na)^+$ Found: 337.0964

3za' Ethyl 10-methylphenanthrene-9-carboxylate

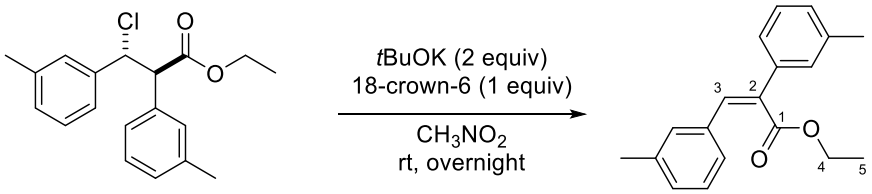


Following the general procedure C using 9-chloro-9-methyl-9*H*-fluorene (0.554 mmol, 0.119 g) and ethyl 2-diazoacetate (1.051 mmol, 0.120 g) with $InCl_3$ (0.0506 mmol, 0.0112 g). The title compound was purified by silica gel flash column chromatography (*n*-hexane/EtOAc = 95/5) and recycle HPLC (*n*-hexane/EtOAc = 90/10) as a white solid (0.117 g, 80%). The spectral data were identical with literature (Y. H. Kim, H. Lee, Y. J. Kim, B. T. Kim, J. Heo, *J. Org. Chem*. **2008**, *73*, 495).

^{1}H NMR: (400 MHz, $CDCl_3$) 8.71-8.66 (m, 2H, Ar-H), 8.11 (d, J = 7.7 Hz, 1H, Ar-H), 7.76-7.57 (m, 5H, Ar-H), 4.58 (q, J = 7.2 Hz, 2H, OCH_2CH$_3$), 2.70 (s, 3H, Ar-CH_3), 1.48 (t, J = 7.2 Hz, 3H, OCH$_2$CH_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.4, 130.9, 130.35, 130.33, 129.5, 129.4, 128.1, 127.2, 127.1, 127.0, 126.4, 125.15, 125.06, 122.9, 122.7, 61.5, 17.1, 14.4; IR: (neat) 1717 (C=O) cm^{-1}; m.p. 62–63 °C; HRMS: (ESI+) Calculated ($C_{18}H_{16}O_2Na$) 287.1043 $(M+Na)^+$ Found: 287.1043

Synthetic Applications

(*Z*)-13 Ethyl (*Z*)-2,3-di-*m*-tolylacrylate



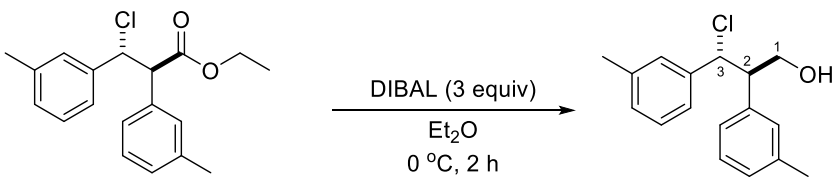
(2*R**,3*R**)-**3ga**
dr >99:1

(*Z*)-**13**

To a reaction tube was subsequently charged with (2*R**,3*R**)-**3ga** (0.0317 g, 0.100 mmol, 1 equiv), 18-crown-6 (0.0264 g, 0.100 mmol, 1 equiv), *t*BuOK (0.0224 g, 0.200 mmol, 2 equiv), and nitromethane (0.5 mL). The resultant mixture was stirred at room temperature overnight. The reaction was quenched by water and the organic layer was washed with brine and extracted by ether, dried over $MgSO_4$. The solvent was evaporated. The yield was determined by ^{1}H NMR in crude products (>95% yield, *Z/E* >95:5). 1,1,2,2-Tetrachloroethane was used as an internal standard. The title compound was purified by recycle HPLC (*n*-hexane/EtOAc = 90/10) as a colorless oil, 0.0245 g, 87% yield. The configuration was identified by a similar compound in reported literature (C. H. Oh, H. H. Jung, K. S. Kim, N. Kim, *Angew. Chem. Int. Ed.* **2003**, *42*, 805.).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.28-6.99 (m, 9H, 3-H and Ar-H), 4.28 (q, J = 7.2 Hz, 2H, 4-H_2), 2.38 (s, 3H, Ar-CH_3), 2.35 (s, 3H, Ar-CH_3), 1.21 (t, J = 7.2 Hz, 3H, 5-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 169.8 (C-1), 138.3, 137.9, 136.9, 135.6, 135.1, 131.0, 129.01, 128.96, 128.9, 128.5, 128.3, 127.0, 125.3, 123.5, 61.2 (C-4), 21.5, 21.4, 13.9 (C-5); IR: (neat) 1723 (C=O) cm^{-1}; HRMS: (ESI+) Calculated ($C_{19}H_{20}O_2Na$) 303.1356 $(M+Na)^+$ Found: 303.1359

14 (2*R,3*R**)-3-Chloro-2,3-di-*m*-tolylpropan-1-ol**



(2*R**,3*R**)-**3ga**
dr >99:1

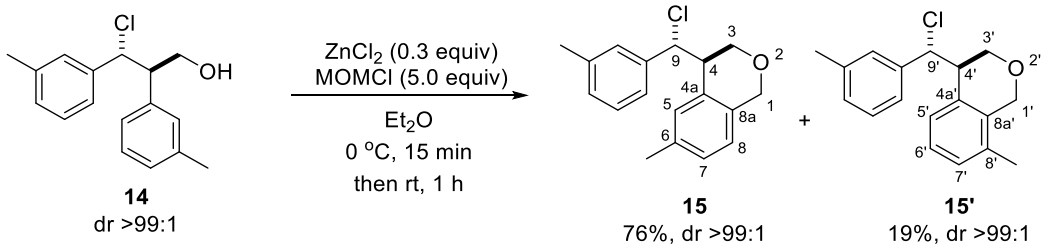
14
97%, dr >99:1

(2*R**,3*R**)-**3ga** (0.158 g, 0.500 mmol, 1 equiv) was diluted in Et_2O (2 mL) and transferred to a reaction tube. Diisobutylaluminium hydride (DIBAL) (1 M in THF, 1.5 mL, 1.5 mmol, 3 equiv) was added dropwise over 3 min to the resultant solution at 0 °C. The reaction was stirred at this temperature for 2 h. The reaction was carefully quenched by addition of methanol (0.15 mL) followed by water (0.15 mL). The crude mixture was diluted in ether (20 mL) and dried over $MgSO_4$, and evaporate the solvent. The diastereomeric ratio was determined by ^{1}H NMR in crude products (dr >99:1). The title compound was purified by silica gel flash column (*n*-hexane/EtOAc = 80/20) as a colorless oil, 0.133 g, 97% yield.

^{1}H NMR: (400 MHz, $CDCl_3$) 7.09-7.05 (m, 2H, Ar-H), 7.01-6.94 (m, 4H, Ar-H), 6.86-6.84 (m, 2H, Ar-H), 5.18 (d, *J* = 9.9 Hz, 1H, 3-H), 4.21-4.14 (m, 2H, 1-H_2), 3.46-3.41 (m, 1H, 2-H), 2.25 (s, 3H, Ar-CH_3), 2.24 (s, 3H, Ar-CH_3), 1.56 (br s, 1H, OH); ^{13}C NMR: (100 MHz, $CDCl_3$) 139.7, 138.4, 137.9, 137.7, 129.5, 128.7, 128.3, 128.2, 128.0, 127.9, 125.7, 124.7, 64.7, 64.4, 55.4, 21.3, 21.2; IR: (neat) 3451 cm^{-1}; HRMS: (ESI+) Calculated ($C_{17}H_{19}ONaCl$) 297.1017 $(M+Na)^+$ Found: 297.1019

15 (*R)-4-((*R**)-Chloro(*m*-tolyl)methyl)-6-methylisochromane**

15' (*R)-4-((*R**)-Chloro(*m*-tolyl)methyl)-8-methylisochromane**



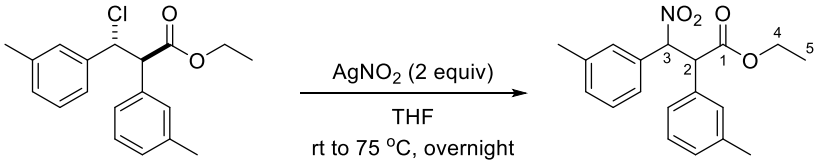
To a reaction tube was subsequently charged with **14** (0.0550 g, 0.200 mmol, 1.0 equiv), chloromethyl methyl ether (MOMCl) (0.0810 g, 1.006 mmol, 5.0 equiv), and Et_2O (2 mL). $ZnCl_2$ (1 M in ether, 60 μL, 0.06 mmol, 0.3 equiv) was added dropwise over 3 min to the mixture at 0 °C. The resultant mixture was stirred at 0 °C for 15 min and warmed to rt for 1 h. The reaction was quenched by saturated $NaHCO_3$ aq and extracted with ether. The organic layer was washed by brine and dried over $MgSO_4$ and concentrated *in vacuo*. The yield and diastereomeric ratio were determined by ^{1}H NMR in crude products (95%, **15**:**15'** = 80:20, dr >99:1). 1,1,2,2-Tetrachloroethane was used as an internal standard. The title compounds were purified by recycle HPLC (*n*-hexane/EtOAc = 90/10) as a regio mixture, colorless oil, 0.0545 g, 95% yield, **15**:**15'** = 80:20, dr >99:1.

*The below spectrum data are for a mixture of regioisomers **15/15'** because these isomers could not be separated by column chromatography.*

^{1}H NMR: (400 MHz, $CDCl_3$) 7.18-6.90 (m, 6.30H, Ar-H and Ar'-H), 6.83 (d, *J* = 7.7 Hz, 1H, Ar-H), 6.70 (t, *J* = 7.6 Hz, 0.26H, Ar'-H), 6.02 (d, *J* = 7.7 Hz, 0.26H, 5'-H), 5.91 (s, 1H, 5-H), 5.17-5.13 (m, 1.26H, 9-H and 9'-H), 4.90-4.86 (m, 1.26H), 4.78-4.66 (m, 2.52H), 3.82-3.76 (m, 1.26H), 3.13 (m, 0.26H, 4'-H), 3.04 (m, 1H, 4-H), 2.30 (s, 3.78H), 2.11 (s, 0.78H), 1.96 (s, 3H); ^{13}C NMR: (100 MHz, $CDCl_3$) 140.1, 137.7, 137.6, 134.7, 133.0, 132.9, 132.2, 132.0, 131.7, 131.2, 128.8, 128.5, 128.4, 127.9, 127.7, 125.2, 125.1, 123.7, 68.2, 67.1, 66.8, 66.4, 65.1, 46.5, 21.3, 20.7, 17.9 *Some signals were overlapped so numbers of observed signals were less than expected ones;* IR: (neat) 1462, 1101 cm^{-1}; HRMS: (ESI+) Calculated ($C_{18}H_{19}ONaCl$)

309.1017 $(M+Na)^+$ Found: 309.1018

16 Ethyl 3-nitro-2,3-di-*m*-tolylpropanoate



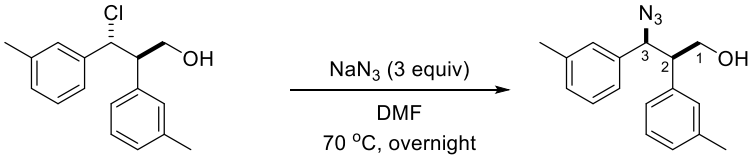
(2*R**,3*R**)-**3ga**
dr >99:1

16
60%, dr >99:1

To a reaction tube was subsequently charged with (2*R**,3*R**)-**3ga** (0.0634 g, 0.200 mmol, 1 equiv), $AgNO_2$ (0.0615 g, 0.400 mmol, 2 equiv), and THF (1 mL). The resultant mixture was stirred at room temperature for 1 h and heated to 75 °C overnight. The reaction was quenched by path through a plug of celite and washed with ether. The solvent was evaporated. The diastereomeric ratio was determined by ^{1}H NMR in crude products (dr >99:1). The title compound was purified by recycle HPLC (*n*-hexane/EtOAc = 90/10) as a single diastereomer (colorless solid, 0.0245 g, 60% yield). The stereochemistry of **16** was not confirmed.

^{1}H NMR: (400 MHz, $CDCl_3$) 7.08-6.87 (m, 8H, Ar-H), 6.32 (d, J = 11.2 Hz, 1H, 3-H), 4.31-4.11 (m, 2H, 4-H_2), 3.94 (d, J = 11.2 Hz, 1H, 2-H), 2.23 (s, 3H, Ar-CH_3), 2.22 (s, 3H, Ar-CH_3), 1.25 (t, J = 7.1 Hz, 3H, 5-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.8 (C-1), 138.4, 138.0, 134.7, 132.7, 129.7, 129.2, 128.9, 128.5, 128.1, 127.8, 125.7, 124.5, 85.7 (C-3), 61.6 (C-4), 55.2 (C-2), 21.2, 14.0 (C-5); IR: (KBr) 1734, 1645 cm^{-1}; m.p. 48–49 °C; HRMS: (ESI+) Calculated ($C_{19}H_{21}NO_4K$) 366.1102 $(M+K)^+$ Found: 366.1111

17 (2*R,3*S**)-3-Azido-2,3-di-*m*-tolylpropan-1-ol**



14
dr >99:1

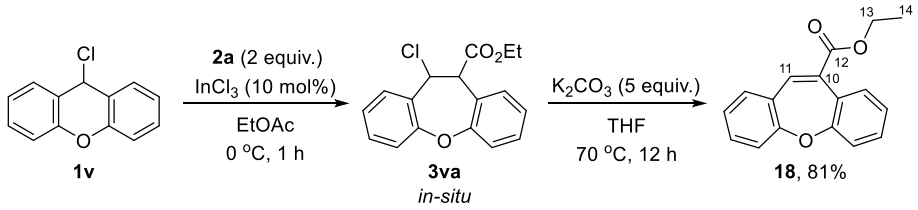
17
>95%, dr >99:1

To a reaction tube was subsequently charged with **14** (0.0275 g, 0.100 mmol, 1 equiv), NaN_3 (0.0195 g, 0.300 mmol, 3 equiv), and DMF (2 mL). The resultant mixture was stirred at 70 °C overnight. After cooling to rt, the crude mixture was diluted by ether (30 mL). The organic layer was washed with brine (10 mL x 3) and extracted by ether. The combined organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The diastereomeric ratio was determined by ^{1}H NMR in crude products (dr >99:1). The title compound was purified by silica gel flash column (*n*-hexane/EtOAc = 80/20) as a colorless oil, 0.0245 g, 95% yield. We estimated that the transformation of **3ga** with NaN_3 proceeded via S_N2 mechanism with the inversion of the stereochemistry. Generally, the substitution reaction of alkyl chlorides with NaN_3 in DMF proceeds via S_N2 mechanism. See selected papers: a) D. A. Evans, J. A. Ellman, R. L. Dorow, *Tetrahedron Lett.* **1987**, *28*, 1123–1126; b) D. A. Evans, E. B. Sjogren, A. E. Weber, R. E. Conn, *Tetrahedron Lett*. **1987**, *28*, 39–42; c) D. A. Evans, T. C. Britton, J. A. Ellman, R. L. Dorow, *J. Am. Chem. Soc.* **1990**, *112*, 4011–4030; d) S. Xu, H. M. Holst, S. B. McGuire, N. J. Race, *J. Am. Chem. Soc.* **2020**, *142*, 8090–8096.

^{1}H NMR: (400 MHz, $CDCl_3$) 7.27-7.09 (m, 8H, Ar-H), 4.80 (d, J = 8.9 Hz, 1H, 3-H), 3.59 (br s, 2H, 1-H_2), 3.12-3.07 (m, 1H, 2-H), 2.37 (s, 6H, Ar-CH_3), 1.27 (br s, 1H, OH); ^{13}C NMR: (100 MHz, $CDCl_3$) 138.59,

138.57, 138.3, 137.8, 129.5, 129.4, 128.7, 128.6, 128.4, 128.1, 125.7, 124.5, 67.5 (C-3), 64.0 (C-1), 53.8 (C-2), 21.51, 21.46; IR: (neat) 3416, 2098, 1710 cm^{-1}; HRMS: (ESI+) Calculated ($C_{17}H_{19}N_3ONa$) 304.1420 $(M+Na)^+$ Found: 304.1424

One-pot synthesis of ethyl dibenzo[*b*,*f*]oxepine-10-carboxylate (18)



To a reaction tube was subsequently charged with $InCl_3$ (0.100 mmol, 0.0221 g), EtOAc (4 mL), 9-chloro-9*H*-xanthene (0.217 g, 1.003 mmol), and ethyl 2-diazoacetate (2.004 mmol, 0.231 g) at 0 °C. The reaction was stirred at 0 °C for 1 h. K_2CO_3 (5.003 mmol, 0.693 g) and THF (5 mL) were added to the resultant reaction mixture. Then this reaction was heated to 70 °C and stirred overnight. The reaction was quenched by water and extracted with EtOAc (20 mL x 3). The organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography (*n*-hexane/EtOAc = 90/10) and recycle HPLC (*n*-hexane/EtOAc = 90/10) as a colorless oil (0.216 g, 81% yield). The characterization data were identical to those reported in the literature. (Characterization data, L. A. Arnold, W. Luo, R. K. Guy, *Org. Lett.* **2004**, *6*, 3005.).

^1H NMR: (400 MHz, $CDCl_3$) 7.91 (s, 1H, 11-H), 7.52 (d, J = 6.3 Hz, 1H, Ar-H), 7.38-7.31 (m, 3H, Ar-H), 7.23 (d, J = 8.2 Hz, 2H, Ar-H), 7.18-7.13 (m, 2H, Ar-H), 4.38 (q, J = 7.1 Hz, 2H, 13-H_2), 1.38 (t, J = 7.1 Hz, 3H, 14-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 166.9 (C-12), 158.9, 158.8, 137.7 (C-11), 131.5, 131.4, 130.6, 130.25, 130.21, 128.7, 127.7, 125.0, 124.6, 121.3, 121.0, 61.3 (C-13), 14.2 (C-14); IR: (neat) 1712 (C=O) cm^{-1}; HRMS: (ESI+) Calculated ($C_{17}H_{14}O_3Na$) 289.0835 $(M+Na)^+$ Found: 289.0839

2-5. Reference

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A. E. Weber, R. E. Conn, *Tetrahedron Lett*. **1987**, *28*, 39. (c) D. A. Evans, T. C. Britton, J. A. Ellman, R. L. Dorow, *J. Am. Chem. Soc.* **1990**, *112*, 4011; and [3f]. Therefore, we estimated that the transformation of **3ga** with NaN_3 proceeded via S_N2 mechanism with the inversion of the stereochemistry.

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Chapter 3: Insertion of Diazoesters into C−F Bonds toward Diastereoselective One-Carbon Elongation of Benzylic Fluorides: Unprecedented BF_3 Catalysis with C−F Bond Cleavage and Re-formation

3-1. Introduction

C−F bonds are among the most robust examples of chemical bonds, and the development of a method for their sophisticated selective transformation is a significant goal in organic chemistry.[1] Substitution reactions of fluoro groups[2] are representative of the various methodologies that have been established. The insertion of a carbon unit into a C−F bond, however, remains underdeveloped despite the production of organofluorine compounds with extended carbon skeletons that have demonstrated special chemical and biological properties in pharmaceutical chemistry and agrochemistry (Figure 1A).[3] Generally, the stability of an eliminated F^- and/or the formation of stable metal−F bonds thermodynamically drives the cleavage of strong C−F bonds,[1] but these factors also inhibit the re-formation of C−F bonds and complicate the C−F insertion process. In fact, only two reports could be found in the literature for the C−F insertion of a C−N unit with transient reactive N-heterocyclic carbenes derived from diazonium salts,[4] and two studies reported the insertion of alkynes or benzofuran into the C−F bonds of acyl fluorides[5] Thus, one-carbon insertion into C−F bonds to accomplish elongation of organofluorines has never been developed (Figure 1B). The establishment of a novel strategy that could accomplish this reaction is an urgent and challenging issue. In this context, herein we report the BF_3-catalyzed elongation of benzylic fluorides via the formal insertion of diazoesters into C−F bonds to give homobenzylic fluorides with a high level of diastereoselectivity (Figure 1C). This is the first report of C−F insertion of a one-carbon-atom unit. It is noteworthy that simple BF_3/BF_4^- catalysis successfully mediates C−F bond cleavage and re-formation to complete the formal C−F insertion.

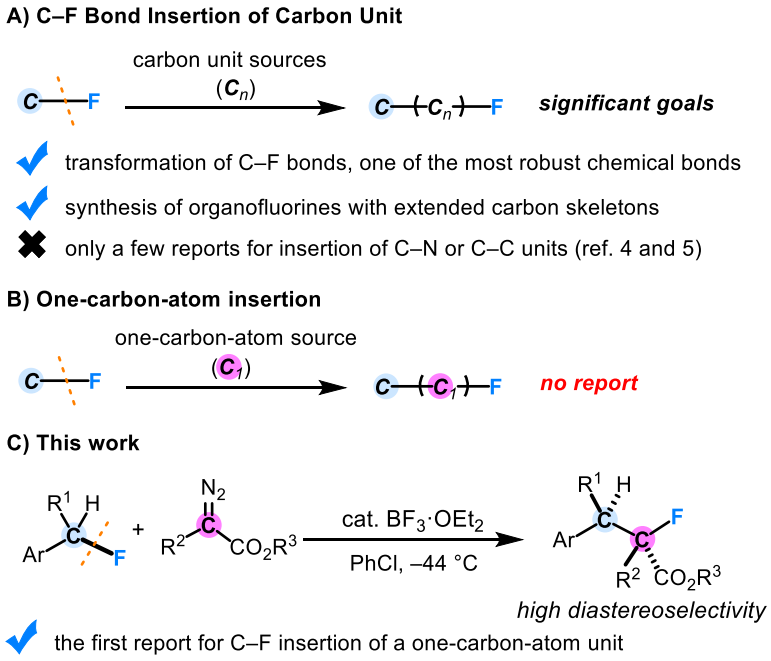
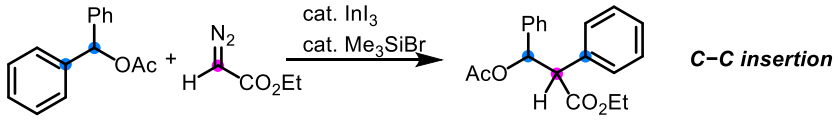


Figure 1. (A) C−F bond insertion of carbon units. (B) One-carbon insertion into C−F bonds. (C) This work: insertion of diazoesters into C−F bonds of benzylic fluorides catalyzed by BF_3

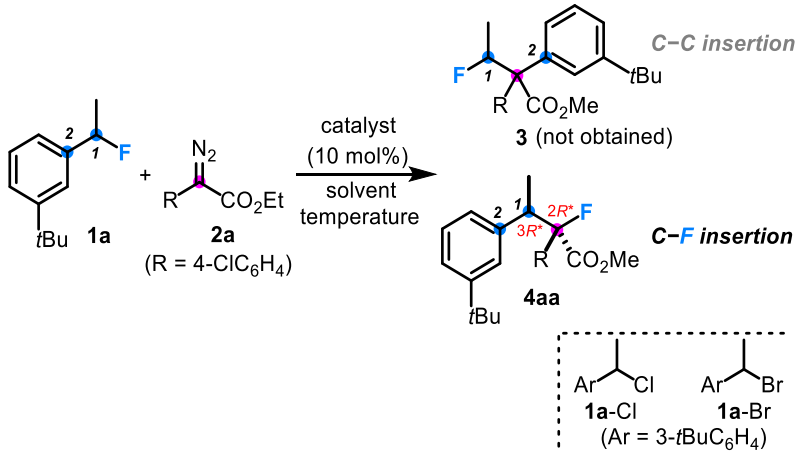
3-2. Results and Discussion

We reported InI_3/Me_3SiBr-catalyzed elongation of benzylic acetates with diazoesters via C−C formal insertion (Scheme 1).[6] This elongation mechanism involves the abstraction of the AcO group by the InI_3/Me_3SiBr Lewis acid,[7] addition of the carbocation to the diazoester, rearrangement of the Ar group, and C−OAc bond re-formation. This study turned our attention to benzylic fluorides to synthesize complex organofluorine compounds. We began an investigation of the catalysts in the reaction of benzylic fluoride **1a** with diazoester **2a** (Table 1). The reaction using InI_3 and Me_3SiBr resulted in no products (entry 1). Unexpectedly, $BF_3{\cdot}OEt_2$[8] did not yield the C^1−C^2 insertion product **3** but instead produced C^1−F insertion product **4aa** in 33% yield with moderate diastereoselectivity (entry 2).[9] BCl_3,[8a,10] BBr_3,[11] $B(C_6F_5)_3$,[12] $AlCl_3$,[13] $AlBr_3$,[13b] and Me_3Al[14] were examined because they are known as Lewis acids that have the ability to abstract F^- from alkyl fluorides (entries 3−8).[15] BCl_3 and BBr_3 yielded a lessened amount of **4aa** compared with that from $BF_3{\cdot}OEt_2$ (entries 3 and 4). Furthermore, halogen-exchanged benzylic halides **1a-Cl** and **1a-Br** were obtained in 6% and 13% yield, respectively. The use of $B(C_6F_5)_3$ and $AlCl_3$ afforded complicated products with complete consumption of **1a** (entries 5 and 6). $AlBr_3$ and Me_3Al resulted in no reaction (entries 7 and 8). Heavier group 13 metal catalysts gave poor results (entries 9 and 10). Transition metal catalysts such as $Rh_2(OAc)_4$,[16] AgOTf,[17] and $Cu(OTf)_2$[18] that mediated reactions through metal carbenoids derived from diazoesters were ineffective in this elongation (entries 11−13). After the investigation of solvents and temperature using $BF_3{\cdot}OEt_2$ (entries 14−18), the conditions with PhCl as a solvent at −44 °C gave a better result (entry 18). Finally, the dilution conditions afforded the best result (entry 21).



Scheme 1. Our previous work: insertion of a diazoester into a C−C bond of benzylic acetate

Table 1. Optimization of C−F bond insertion between benzylic fluoride **1a** and diazoester **2a**[a].



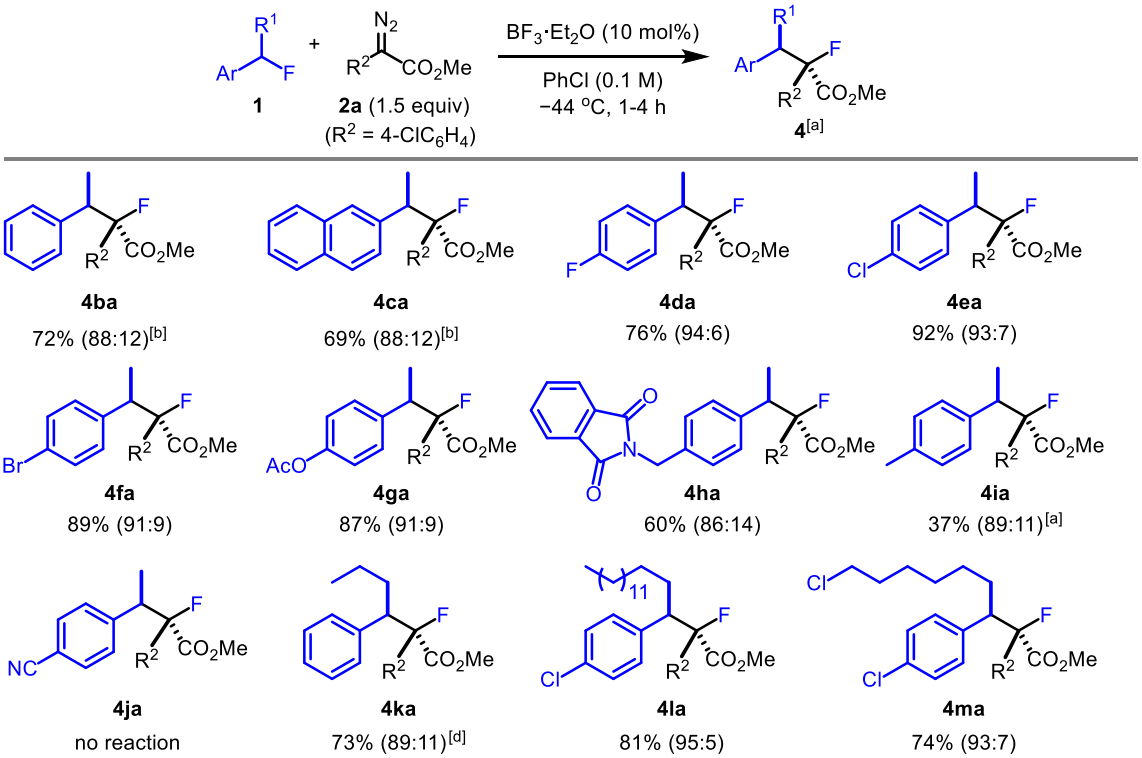
entry	catalyst	solvent	temp. (°C)	% yield (*d.r.* of **4aa**)
1	InI_3/Me_3SiBr	$CHCl_3$	0 °C to rt	0
2	$BF_3{\cdot}OEt_2$	$CHCl_3$	0 °C to rt	33 (68:32)
3[b]	BCl_3	$CHCl_3$	0 °C to rt	32 (64:36)
4[c]	BBr_3	$CHCl_3$	0 °C to rt	26 (69:31)
5	$B(C_6F_5)_3$	$CHCl_3$	0 °C to rt	0
6	$AlCl_3$	$CHCl_3$	0 °C to rt	0
7	$AlBr_3$	$CHCl_3$	0 °C to rt	0
8	Me_3Al	$CHCl_3$	0 °C to rt	0
9	$GaCl_3$	$CHCl_3$	0 °C to rt	25 (83:17)
10	$InCl_3$	$CHCl_3$	0 °C to rt	0
11	$Rh_2(OAc)_4$	$CHCl_3$	0 °C to rt	0
12	AgOTf	$CHCl_3$	0 °C to rt	0
13	$Cu(OTf)_2$	$CHCl_3$	0 °C to rt	0
14	$BF_3{\cdot}OEt_2$	Et_2O	0 °C to rt	29 (66:34)
15	$BF_3{\cdot}OEt_2$	EtOAc	0 °C to rt	42 (61:39)
16	$BF_3{\cdot}OEt_2$	MeCN	0 °C to rt	0
17	$BF_3{\cdot}OEt_2$	PhCl	0 °C to rt	44 (63:37)
18	$BF_3{\cdot}OEt_2$	PhCl	−44	58 (88:12)
19[d]	BCl_3	PhCl	−44	48 (88:12)
20[e]	BBr_3	PhCl	−44	43 (88:12)
21[f]	$BF_3{\cdot}OEt_2$	PhCl	−44	60 (91:9)

[a]**1a** (0.2 mmol), **2a** (0.3 mol), catalyst (0.02 mmol), solvent (1 mL), 4 h. Shown yields (sum of diastereomers) and diastereomeric ratios were determined by ^{1}H NMR and ^{19}F NMR in crude products. 1,1,2,2-Tetrachloroethane and hexafluorobenzene were used as internal standards, respectively. [b]**1a-Cl** (6% yield) was obtained. [c]**1a-Br** (13%) was obtained. [d]**1a-Cl** (12% yield) was obtained. [e]**1a-Br** (29%) was obtained. [f]Solvent (2 mL) was used.

The scope of benzylic fluorides is illustrated in Scheme 2. The reaction of 1-phenyl- and 1-naphthyl-substituted ethyl fluorides gave **4ba** and **4ca** in 72% and 69% yield, respectively. C(sp^2)−halogen bonds were tolerated and showed high yields and high levels of diastereoselectivity (**4da**−**4fa**). The relative

stereochemistry of the major isomer of **4ea** was determined via X-ray diffraction analysis. Valuable functional groups such as AcO and phthaloylamino groups were available (**4ga** and **4ha**). Electron-rich benzylic fluoride **1i** gave **4ia** in 51% yield. Strong electron-withdrawing groups such as a CN group disturbed this elongation (**4ja**). Different alkyl groups (R^1) were explored.[19] The presence of longer alkyl groups (R^1 = *n*-C_3H_7 and *n*-$C_{15}H_{31}$) did not decrease the efficiency of this elongation (**4ka** and **4la**). The examination of **4ma** showed good compatibility with an alkyl chloride moiety.

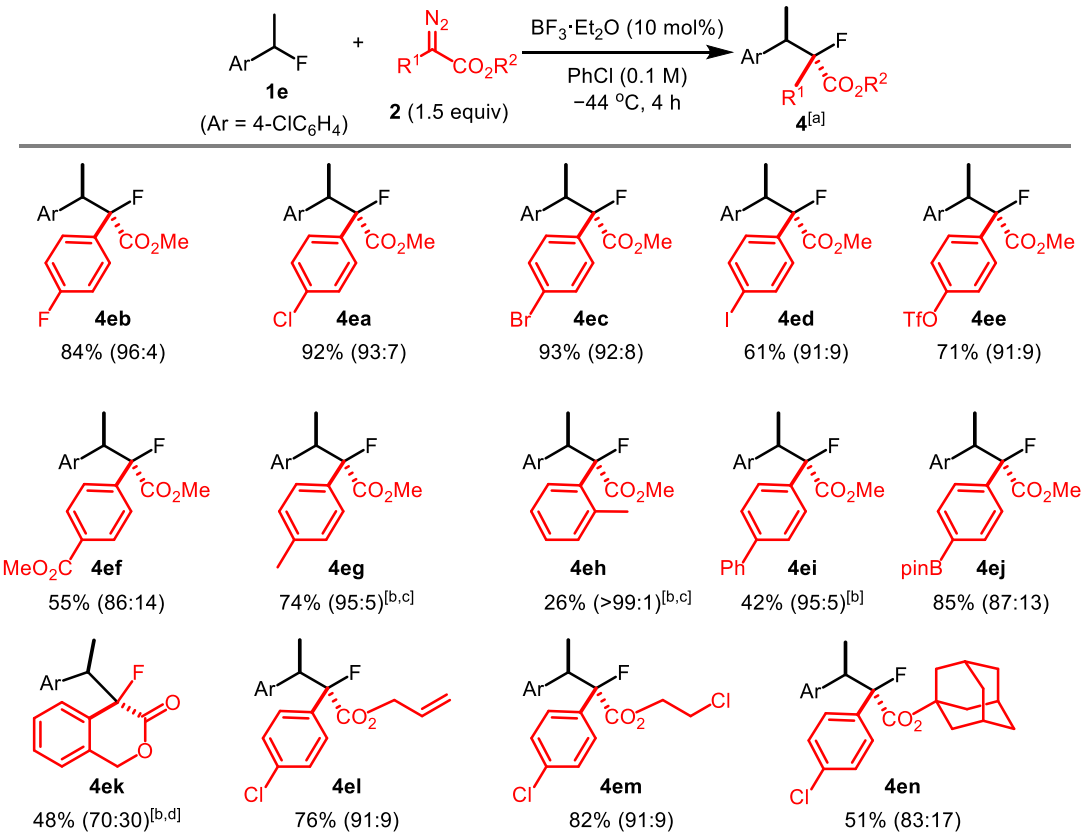
Various *α*-aryl diazoesters **2** were examined (Scheme 3). Substrates with electron-withdrawing groups gave high yields with high levels of diastereoselectivity (**4ea**, **4eb**, **4ec**, **4ed**, **4ee**, and **4ef**). In cases involving electron-donating groups, a larger amount of **2** was necessary for the efficient progress of the elongation because of rapid dimerization of **2** (**4eg**, **4eh**, and **4ei**).[20] Compatibility with the (pinacolato)boryl group is significant in organic synthesis (**4ej**). The reaction using cyclic **2k** afforded a fluorinated 3-isochromanone scaffold (**4ek**), although the yield and selectivity were moderate because of its low nucleophilicity and higher reaction temperature. Allyl and chloroalkyl groups attached to the ester moiety were tolerated (**4el** and **4em**). The steric demand of the 1-adamantyl ester moiety decreased the efficiency of elongation (**4en**).



Scheme 2. Scope of benzylic fluorides **1** in elongation using diazoester **2a**. [a]**1** (0.2 mmol), **2a** (0.3 mmol), $BF_3{\cdot}OEt_2$ (0.02 mmol), PhCl (2 mL), −44 °C, 4 h. Yields (sum of diastereomers) and diastereomeric ratios were determined by ^1H and ^{19}F NMR analyses of the crude products. 1,1,2,2-Tetrachloroethane and hexafluorobenzene were used as internal standards, respectively. [b]**1** (0.3 mmol), **2a** (0.2 mmol). [c]**1i** (1 mmol), **2a** (1.5 mmol), $BF_3{\cdot}OEt_2$ (0.05 mmol), PhCl (10 mL), −44 °C. [d]−30 °C, 4 h.

The competitive elongation between benzylic fluorides **1b** and **1f**, the more electron-deficient **1f** exhibited lower reactivity than **1b** (Scheme S2). This reactivity order is related to the stability of the corresponding benzylic cations generated by abstraction of F^- with BF_3.[8] The outline of the proposed mechanism is illustrated in Figure 2A. BF_3 abstracts F^- from benzylic fluoride **1** to produce the corresponding benzylic cation (step **i**). Electrophilic addition of the cation to diazoester **2** (step **ii**) and N_2

extrusion (step **iii**) are followed by reformation of a C−F bond mediated by BF_4^- (step **iv**)[21] to afford product **4**. DFT calculations allowed us to reveal details that include the origin of the high diastereoselectivity. The energy profile of the reaction between benzylic fluoride **1e** and diazoester **2a** is shown in Figure 2B. BF_3 undergoes coordination of the F atom in **1e** and then abstracts F^- to generate cation **7** with BF_4^-.[8] Carbocation **7** leaves BF_4^- to form van der Waals complex **8** with **2a**. Then the C−C bond formation in complex **8** occurs through TS **9** with the π−π interaction between Ar^1 and Ar^2 groups to give diazonium **10**, and highly exergonic N_2 extrusion from **10** affords carbocation **11**. There is not an unreasonably high activation barrier in the route from the starting materials to **11**. The activation energy in the cleavage of the C−F bond is only 5.92 kcal/mol because of the thermodynamic stability of BF_4^-. The diastereoselectivity is determined in the course of C−F bond re-formation.[21] Cation **11** forms the thermodynamically favorable contact ion pair **12** with BF_4^-, and the optimized structure of the most stable form **12a** is shown. Through TS **13a**, **12a** gives diastereomer **4ea-major** via nucleophilic attack of the F atom in BF_4^- to the carbocation. On the other hand, diastereomer **4ea-minor** is produced from metastable conformer **12b** through TS **13b**.[22] TS **13b** is less stable than **13a** by 1.0 kcal/mol because of the steric repulsion between the Ar^1 and Ar^2 groups (Figure 2C), and **4ea-major** is provided as the major diastereomer according to the Curtin−Hammett principle.[23] Therefore, the formation of contact ion pair **12** works in favor of the re-formation of a C−F bond rather than undesired paths, such as migration of the Ar^1 group,[24] and the achievement of a high level of diastereoselectivity. The activation barrier in the C−F re-formation is not high, and the elongation and regeneration of BF_3 catalyst are smoothly completed because the fluoride ion affinity (FIA) of BF_3 (346 kJ/mol) is comparatively lower than that with other Lewis acids to abstract F^- from alkyl fluorides.[25] In fact, $B(C_6F_5)_3$ (FIA = 448 kJ/mol) and $AlCl_3$ (FIA = 505 kJ/mol) could abstract F^- but could not release it to afford complicated products (Table 1, entries 5 and 6). The DFT calculation study revealed that the specific catalysis of BF_3 is due to the abstraction of F^- and to the C−F bond re-formation via the capture of carbocation intermediates with BF_4^-.



Scheme 3. [a]**1e** (0.2 mmol), **2** (0.3 mmol), $BF_3{\cdot}OEt_2$ (0.02 mmol), PhCl (2 mL), −44 °C, 4 h. Yields (sum of diastereomers) and diastereomeric ratios were determined by ^1H and ^{19}F NMR analyses of the crude products. 1,1,2,2-Tetrachloroethane and hexafluorobenzene were used as internal standards, respectively. [b]**2** (0.4 mmol). [c]12 h. [d]0 °C to rt, 4 h.

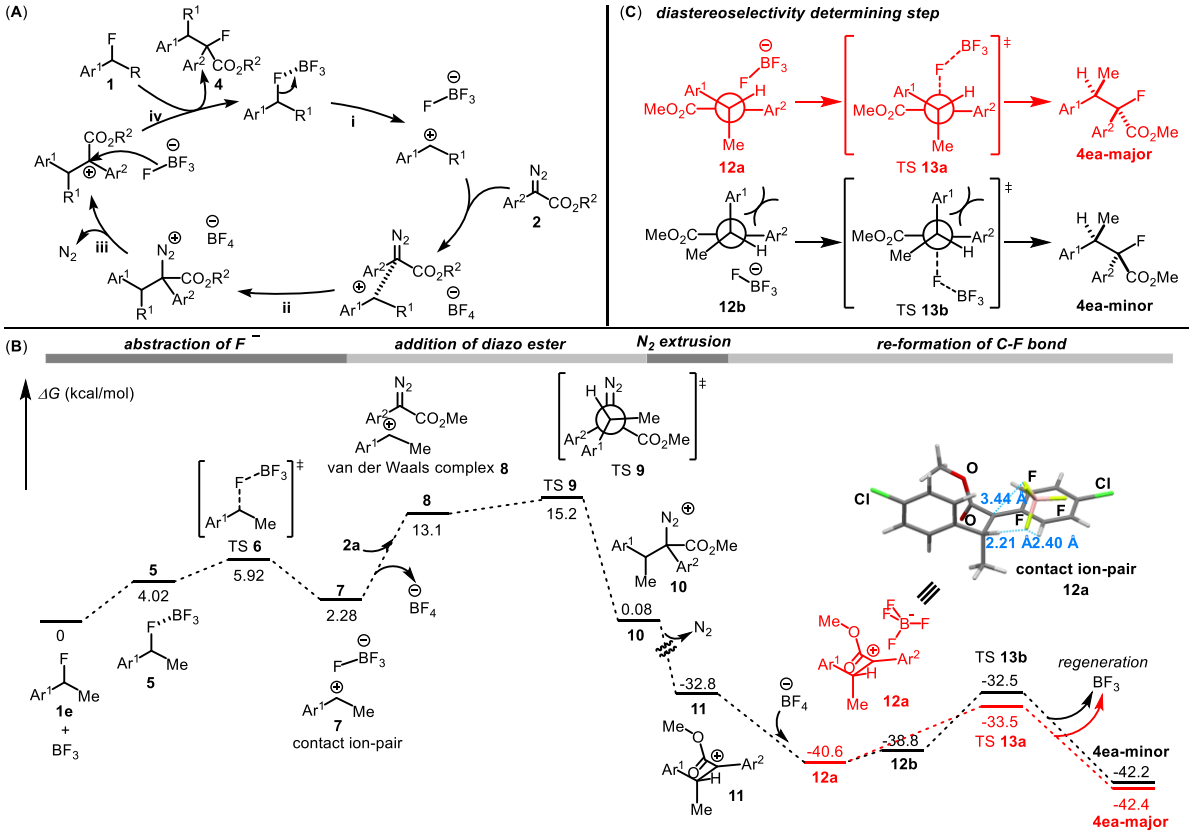
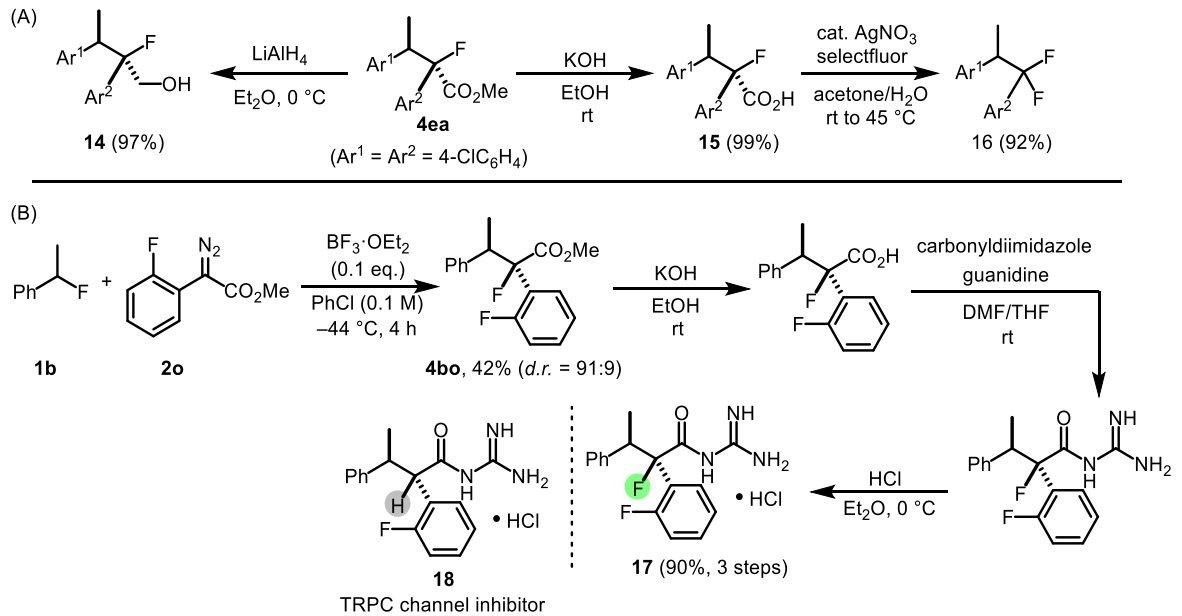


Figure 2. (A) Outline of the proposed reaction mechanism. (B) Rationale based on DFT calculations (ωB97XD/6-31+G(d)/SMD(chlorobenzene), Δ*G* in kcal/mol at 229.15 K). (C) Explanation of the origin of the diastereoselectivity.



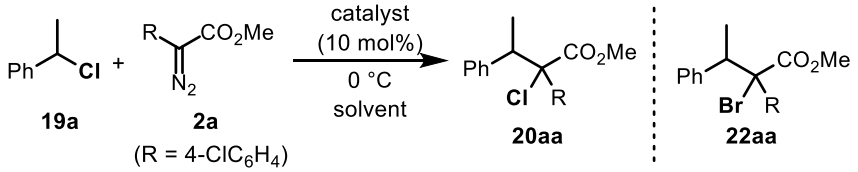
Scheme 4. (A) Synthetic diversity of α-fluoro esters provided by BF_3-catalyzed elongation. (B) Synthesis of a fluoro analogue of a compound acting as a TRPC channel inhibitor.

This elongation provides α-fluoro esters that can be transformed into valuable compounds with F groups. Compound **4ea** was converted to fluoro alcohol **14** by $LiAlH_4$ with no loss of stereochemistry (Scheme 4A).

After hydrolysis of the ester moiety in **4ea**, decarboxylative fluorination[26] afforded difluoro compound **16** with a CF_2 unit that could be utilized as a bioisostere of either oxygen atoms or carbonyl groups (Scheme 4A).[27] We focused on the synthesis of compound **17**, a fluoro analogue of compound **18**, with the intention of using it as a transient receptor potential canonical (TRPC) channel inhibitor (Scheme 4B).[28] α-Fluoro ester **4bo** was obtained by BF_3-catalyzed diastereoselective elongation of **1b** with **2o**. Then hydrolysis of **4bo** and amidation with guanidine followed by treatment with HCl gave **17**. This demonstration confers great significance in pharmaceutical chemistry.[3]

The current C−F bond insertion was further extended to the insertion of diazo compounds into C−Cl, C−Br, or C−I bonds. In the insertion of diazoesters into C−F bonds, BF_3 worked well as a catalyst. However, the BF_3-catalyzed reaction of benzylic chloride **19a** with diazoester **2a** in 1,2-dichloroethane did not proceed at all, and unreacted **19a** was recovered in 41% yield (Table 2, entry 1). Our group reported that InX_3 possesses an affinity to halogen sufficient to abstract X^- from alkyl halides and generate carbocation intermediates.[29−31] Thus, InI_3, $InBr_3$, and $InCl_3$ were examined (entries 2−4). $InCl_3$ exhibited the best catalytic ability to give product **20aa** in 75% yield (entry 4). Although $InBr_3$ afforded 58% yield of **20aa**, the undesired halogen exchange product **22aa** was generated in 21% yield (entry 3). InI_3 was ineffective (entry 2). Among typical Lewis acids, $FeCl_3$, $ZnCl_2$, and $SnCl_4$ gave moderate yields that were less than that given by $InCl_3$ (entries 5−12). Other Lewis acid catalysts such as $AlCl_3$, $TiCl_4$, $GaCl_3$, $ZrCl_4$, $CeCl_3$, and $BiCl_3$ showed no catalytic activity. Transition-metal catalysts such as $Sc(OTf)_3$,[32] CuI,[33] and TfOH[34] failed to mediate this elongation (entries 13−15). After the solvents and temperature were optimized using $InCl_3$, the conditions with $CHCl_3$ at room temperature showed the best results (entries 16−20). Unfortunately, the conditions needed to achieve a high diastereomeric ratio could not be found.

Table 2. Optimization of C–Cl bond insertion between benzylic chloride **19a** and diazoester **2a**[a].

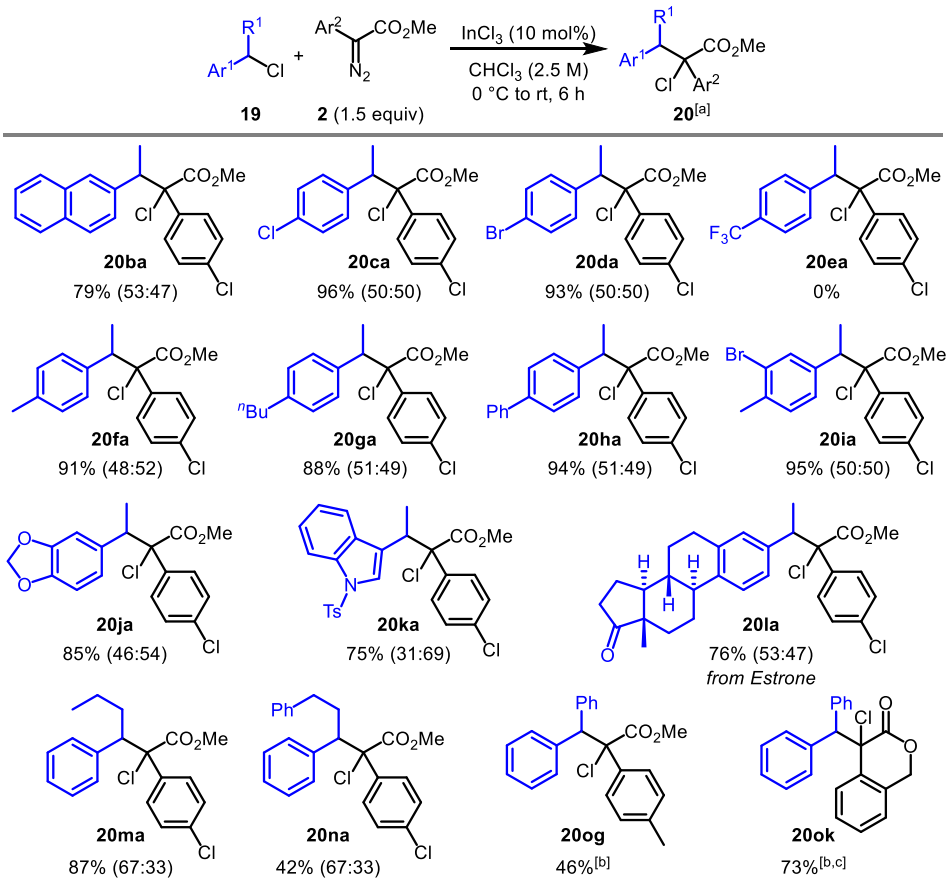


entry	catalyst	solvent	yield of **20aa** (%)	d.r.
1	$BF_3{\cdot}OEt_2$	$ClCH_2CH_2Cl$	0	-
2	InI_3	$ClCH_2CH_2Cl$	0	-
3	$InBr_3$	$ClCH_2CH_2Cl$	58[b]	52:48
4	$InCl_3$	$ClCH_2CH_2Cl$	75	55:45
5	$AlCl_3$	$ClCH_2CH_2Cl$	0	-
6	$ZnCl_2$	$ClCH_2CH_2Cl$	57	58:42
7	$FeCl_3$	$ClCH_2CH_2Cl$	70	56:44
8	$SnCl_4$	$ClCH_2CH_2Cl$	72	50:50
9	$TiCl_4$	$ClCH_2CH_2Cl$	0	-
10	$ZrCl_4$	$ClCH_2CH_2Cl$	0	-
11	$BiCl_3$	$ClCH_2CH_2Cl$	70	33:67
12	$GaCl_3$	$ClCH_2CH_2Cl$	0	-
13	$Sc(OTf)_3$	$ClCH_2CH_2Cl$	0	-
14[c]	CuI	$ClCH_2CH_2Cl$	0	-
15[d]	TfOH	Toluene	0	-
16[e]	$InCl_3$	$ClCH_2CH_2Cl$	79	55:45
17[e]	$InCl_3$	$CHCl_3$	83	52:48
18[e]	$InCl_3$	EtOAc	0	-
19[e]	$InCl_3$	Et_2O	0	-
20[e,f]	$InCl_3$	$CHCl_3$	93	52:48

[a]**19a** (0.4 mmol), **2a** (0.5 mmol), catalyst (0.04 mmol), solvent (1 mL), 0 °C, 4 h. Shown yields (sum of diastereomers) and diastereomeric ratios were determined by ^{1}H NMR in crude products. 1,1,2,2-Tetrachloroethane was used as an internal standard. [b]Other than **20aa**, **22aa** (21%) was also obtained. [c]Rt, 24 h. [d]–78 to 0 °C, 6 h. [e]0 °C to rt, 6 h. [f]**2a** (0.6 mmol) was used.

The scope of benzylic chlorides **19** is illustrated in Scheme 5. Naphthyl chloride gave *α*-chloro ester **20ba** in 79% yield. Benzylic chlorides with electron-withdrawing groups gave excellent yields (**20ca** and **20da**). A CF_3 group had strong electron-withdrawing ability and retarded the reaction (**20ea**) due to the instability of the corresponding benzylic cation. Electron-rich benzylic chlorides possessing Me, *n*Bu, or Ph groups were well tolerated and afforded high yields (**20fa**–**20ha**). Substrates with disubstituted benzene rings were also applicable to afford the corresponding products **20ia** and **20ja** in high yields. Notably, a substrate including an indole moiety was tolerated to give product **20ka** in 75% yield. Functionalization of a biorelevant molecule derived from estrone provided **20la** in 76% yield. Next, different types of R^1 groups were evaluated. The presence of longer alkyl groups (R^1 = *n*-C_3H_7) showed no variation in the progress of the desired reaction (**20ma**), but a bulkier group (R^1 = CH_2CH_2Ph) decreased the yield (**20na**). The use of a

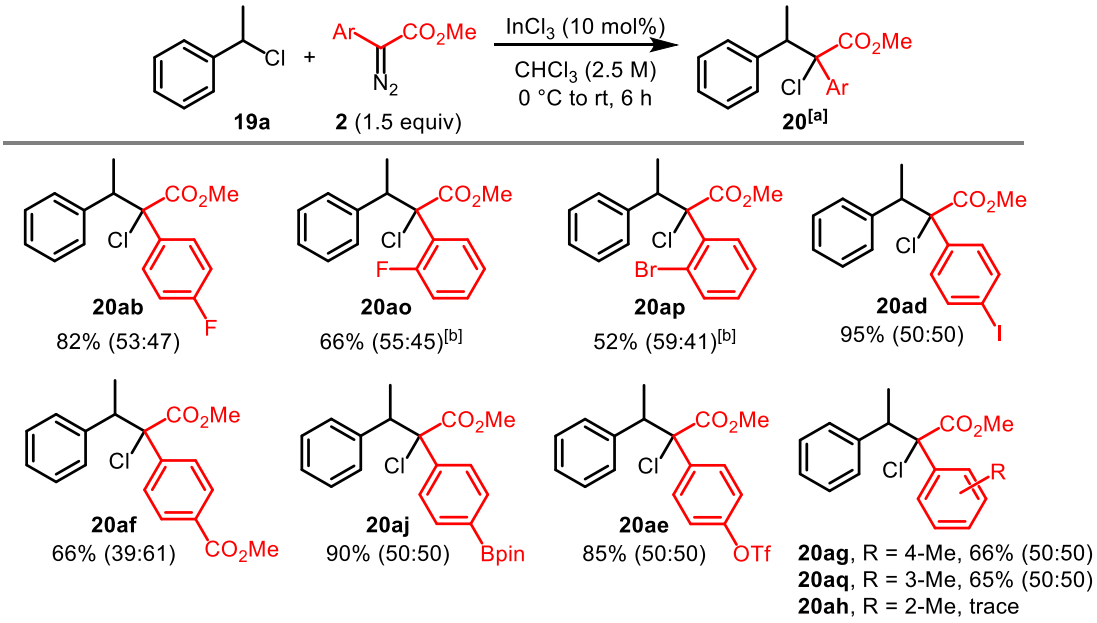
phenyl group (R^1 = Ph) instead of an alkyl group was well tolerated to produce **20oi** and **20ol** in 46 and 73% yields, respectively. In all entries, the diastereomeric ratios of products were low, but almost all diastereomers could be easily separated using conventional isolation procedures.



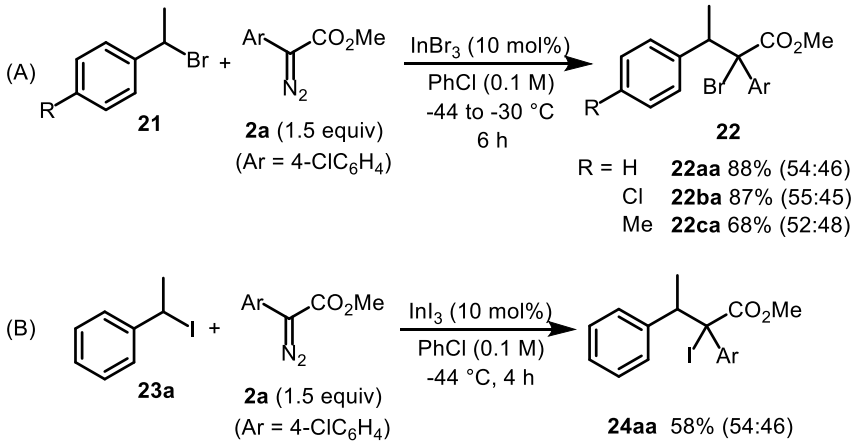
Scheme 5. Scope of benzylic chlorides **19**. [a]**19** (0.4 mmol), **2a** (0.6 mmol), $InCl_3$ (0.04 mmol), $CHCl_3$ (1 mL), 0 °C to rt, 6 h. Shown yields (sum of diastereomers) and diastereomeric ratios were determined by ^1H NMR in crude products. 1,1,2,2-Tetrachloroethane was used as an internal standard. [b]**19o** (0.5 mmol), **2** (0.75 mmol), $InCl_3$ (0.05 mmol), EtOAc (2 mL), 0 °C, 6 h. [c]**2k** (1.0 mmol).

Various α-aryl diazoesters performed well in this reaction system (Scheme 6). Functional groups were compatible with the present reaction conditions: fluoro (**20ab** and **20ao**), bromo (**20ap**), iodo (**20ad**), methoxycarbonyl (**20af**), Bpin (**20aj**), TfO (**20ae**), and methyl (**20ag** and **20aq**). Electronic perturbation by the substituents on benzene rings did not have much of an impact on the yields. The steric hindrance by an ortho-substituent disrupted this reaction (**20ah**). Other diazo compounds bearing electron-deficient groups (Figure S2, **2r**–**2x**) afforded no desired products.

We applied this method to the synthesis of α-bromo and α-iodo esters using benzylic bromides and benzylic iodides, respectively (Scheme 7). To avoid contamination from different halogeno groups in the products (Table 2, entry 3), $InBr_3$ and InI_3 were used for the corresponding halide substrates. $InBr_3$ successfully mediated the elongation of benzylic bromides **21** with **2a** under low temperature conditions to yield the corresponding α-bromo esters **22** in high yields (**22aa**, **22ba**, and **22ca**). The C–I bond insertion of **2a** catalyzed by InI_3 also proceeded, and α-iodo ester **24aa** was obtained in 58% yield. The lower yield of **24aa** was due to its low level of stability.



Scheme 6. Scope of diazoesters **2**. [a]**19a** (0.4 mmol), **2** (0.6 mmol), $InCl_3$ (0.04 mmol), $CHCl_3$ (1 mL), 0 °C to rt, 6 h. Shown yields (sum of diastereomers) and diastereomeric ratios were determined by ^1H NMR in crude products. 1,1,2,2-Tetrachloroethane was used as an internal standard. [b]Reaction run at rt for 12 h.



Scheme 7. Synthesis of α-bromo and α-iodo esters by C–Br and C–I bond insertions. (A) **21** (0.4 mmol), **2a** (0.6 mmol), $InBr_3$ (0.04 mmol), PhCl (4 mL), –44 to –30 °C for 6 h. (B) **23a** (0.4 mmol), **2a** (0.6 mmol), InI_3 (0.04 mmol), PhCl (4 mL), –44 °C for 4 h. Shown yields (sum of diastereomers) and diastereomeric ratios were determined by ^1H NMR in crude products. 1,1,2,2-Tetrachloroethane was used as an internal standard.

The proposed mechanism of the reaction of benzylic chloride **19** with diazoester **2** appears in Figure 3. $InCl_3$ abstracts Cl^- from **19** to generate benzylic cation **26** (step **i**). The electrophilic addition of **26** to **2** gives diazonium intermediate **27** (step **ii**). Extrusion of N_2 from **27** affords carbocation **28** (step **iii**). The nucleophilic attack of Cl^- in $InCl_4^-$ to **28** forms a C–Cl bond (step **iv**). Finally, product **20** dissociates from $InCl_3$ (step **v**). A low-level diastereomeric ratio of α-chloro ester **20** (up to 67:33) contrasts with that of α-fluoro ester (up to >99:1) in the BF_3-catalyzed C–F bond insertion. A single diastereomer of **20ca** was exposed to the standard conditions, and then the ratio was decreased (from >99:1 to 70:30) (Scheme S9 and Figure S3). This result suggests that C–Cl bond reformation (step **iv**) is an equilibrium process to degrade

the diastereomeric ratio, which was supported by a DFT study (Scheme S7 and S8). Notably, $BF_3{\cdot}OEt_2$ is ineffective for this C−Cl insertion in contrast to the previously reported C−F bond insertion. DFT studies revealed that the abstraction of Cl^- from benzylic chloride **19** by BF_3 is a much more uphill process compared with abstraction from $InCl_3$ (Scheme S7). Thus, the level of soft Lewis acidity in $InCl_3$ was appropriate to allow both the abstraction and release of Cl^-, which is an important factor for the completion of elongation.

C−Br insertion product **22aa** was successfully transformed to a variety of valuable compounds (Scheme 8). A reduction by Zn metal followed by protonation gave the debromination product **40**. Substitution reactions of **22aa** with NO_2^-,[35] N_3^-,[36] or PhS^-[37] afforded nitrite **41**, azide **42**, or sulfide **43**, respectively. *α*,*β*-Unsaturated carboxylic acid methyl esters (*E*)-**44** and (*Z*)-**44** were selectively obtained via E2 elimination when the single diastereomer **22aa** was treated with NaN_3 as a base in the presence of 18-crown-6.

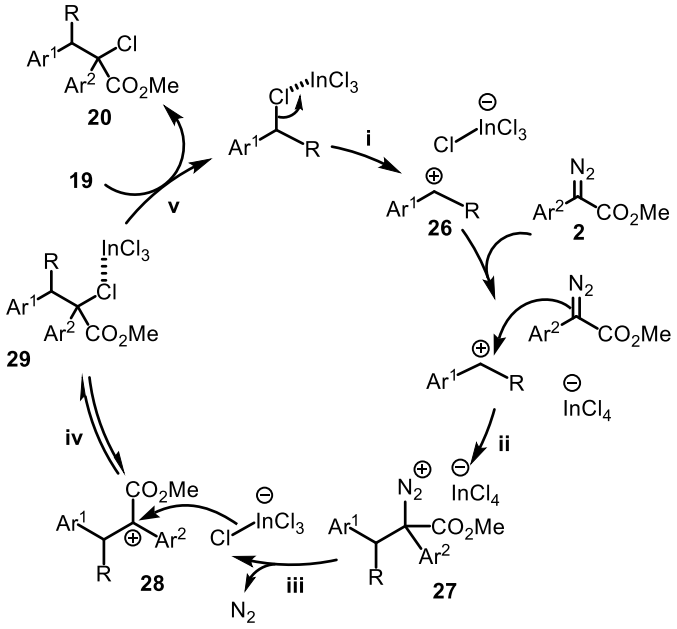
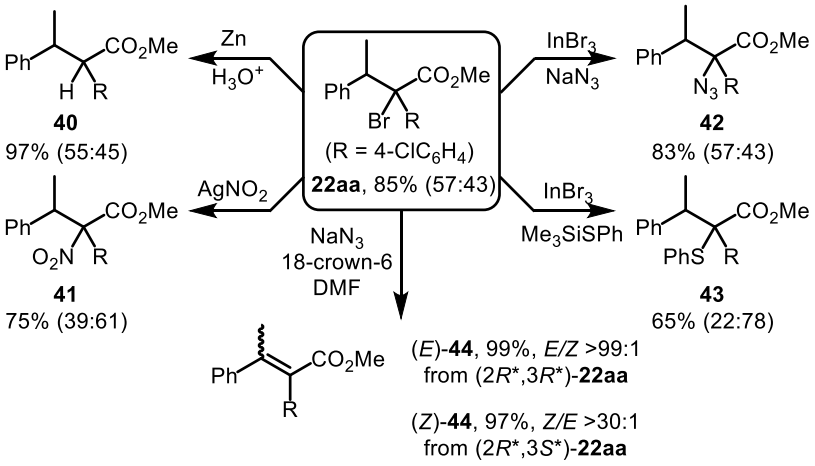


Figure 3. Proposed mechanism for C–Cl insertion.



Scheme 8. Synthetic applications of *α*-bromo ester **22aa**.

3-3. Conclusion

I have accomplished BF_3-catalyzed diastereoselective elongation of benzylic fluorides with diazoesters via formal insertion of a one-carbon atom into C−F bonds. This elongation exhibited high chemoselectivity, and various benzylic fluorides and diazoesters were applicable to afford *α*-fluoro-*α*,*β*-diaryl esters. DFT calculations suggested that the abstraction of F^- by BF_3 and the re-formation of a C−F bond mediated by BF_4^- led to the unique catalytic activity of BF_3. Similarly, I also developed a one-carbon-atom insertion into C−Cl, C−Br, or C−I bonds for the elongation of benzylic halides with *α*-diazoesters to produce *α*-halo esters. Indium trihalides performed extremely well in the cleavage and reformation of C−X bonds. This elongation is operationally convenient, exhibits a broad scope, and is highly compatible with various functional groups. These features combined with the accessibility of the starting materials introduce a potentially valuable methodology for the synthesis of complex *α*-halo carbonyl compounds in organic chemistry.

3-4. Experimental Section

General Information

NMR spectra were recorded on a JEOL-AL400 spectrometer (400 MHz for ^{1}H, 100 MHz for ^{13}C, and 372 MHz for ^{19}F NMR). Chemical shifts were reported in ppm on the δ scale relative to tetramethylsilane (δ = 0 for ^{1}H NMR) and residual $CDCl_3$ (δ = 77.0 for ^{13}C NMR) as an internal reference. Chemical shifts were reported in ppm on the δ scale relative to TFA (δ = -76.55 for ^{19}F NMR) as an external reference. Coupling constants were quoted in Hz (*J*). ^{1}H NMR spectroscopy splitting patterns were designated as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), and sextet (sext). Splitting patterns that could not be interpreted or easily visualized were designated as multiplet (m) or broad (br). New compounds were characterized by ^{1}H NMR, ^{13}C NMR, H-H COSY, HMQC, and HMBC. Infrared (IR) spectra were recorded on a JASCO FT/IR-6200 Fourier transform infrared spectrophotometer. Column chromatographies were performed with silica gel. Purification by recycle HPLC was performed on SHIMADZU recycle HPLC system (SPD-20A, RID-10A, DGU-20A, LC-6AD, and FCV-20H2). Purification by recycle GPC was performed on Japan Analytical Industry Co. (NEXT recycling preparative HPLC). Reactions were carried out in dry solvents under nitrogen atmosphere, unless otherwise stated. Reagents were purchased from Aldrich or Tokyo Chemical Industry Co., Ltd. (TCI), FUJIFILM Wako Pure Co., Ltd., and used after purification by distillation or used without purification for solid substrates. X-ray diffraction analysis was carried out by Rigaku XtaLAB Synergy with Hypix-6000HE.

Materials

Dehydrated solvents were purchased from FUJIFILM Wako Pure Co., Ltd. and used as obtained. Benzylic fluorides **1g**, **1h**, and **1j** were synthesized according to a reported literature, and the characterization data were reported. (**1g**, **1h**, and **1j**: Preparation and Characterization data, E. Emer, L. Pfeifer, J. M. Brown, V. Gouverneur, *Angew. Chem. Int. Ed.* **2014**, *53*, 4181.). Benzylic fluoride **1a** was synthesized according to a reported literature, and the characterization data were reported. (Preparation and Characterization data, J. Xia, C. Zhu, C. Chen, *J. Am. Chem. Soc.* **2013**, *135*, 17494.). The synthetic procedures for **1b**, **1c**, **1d**, **1e**, **1f**,

1i, **1k**, **1l**, and **1m** were described below. (**1b**, **1d**, and **1e**: Characterization data, J. Xia, C. Zhu, C. Chen, *J. Am. Chem. Soc.* **2013**, *135*, 17494. **1c**, **1f**: Characterization data, E. Emer, L. Pfeifer, J. M. Brown, V. Gouverneur, *Angew. Chem. Int. Ed.* **2014**, *53*, 4181. **1i**: Characterization data, D. E. Sood, S. Champion, D. M. Dawson, S. Chabbra, B, E. Bode, A. Sutherland, A. J. B. Watson, *Angew. Chem. Int. Ed*. **2020**, *59*, 8460.). Diazoesters, **2a**, **2b**, **2c**, **2d**, **2e**, **2f**, **2g**, **2h**, **2i**, **2j**, **2k**, **2l**, **2o**, **2p**, and **2q** were prepared according to reported procedures and the well characterization data were reported. The synthetic procedures and characterization data for new compound **2m** and **2n** were described below.

Benzylic chlorides **19a** and **19o** and benzylic bromide **21a** were purchased from Tokyo Chemical Industry Co., Ltd. (TCI) and used as obtained. The synthetic procedures for benzylic chlorides **19b**, **19c**, **19d**, **19e**, **19f**, **19g**, **19h**, **19i**, **19j**, **19k**, **19l**, **19m**, and **19n** were described below. **19b**, **19c**, and **19f**: Characterization data, K. Kiyokawa, M. Yasuda, A. Baba, *Org. Lett*. **2010**, *12*, 1570. **19d**: Characterization data, J. Ozawa, M. Kanai, *Org. Lett*. **2017**, *19*, 1430. **19e** and **19h**: Characterization data, B. Xing, X. Zhao, Y. Qin, P. Zhang, Z. Guo, *J. Chem. Res*. **2020**, *44*, 667. **19j**: Characterization data, S. A. Asceneuron, A. Quattropani, S. S. Kulkarni, A. G. Giri, WO 2019037861 A1 February 28, 2019. **19m**: Characterization data, T. O. Ronson, E. Renders, B. F. Van Steijvoort, X. Wang, C. C. D. Wybon, H. Prokopcov, L. Meerpoel, B. U. W. Maes *Angew. Chem. Int. Ed*. **2019**, *58*, 482. **19n**: Characterization data, C. M. Vanos, T. H. Lambert, *Angew. Chem. Int. Ed*. **2011**, *50*, 12222. The synthetic procedures and characterization data for new compounds **19g**, **19i**, **19k**, and **19l** were described below. The synthetic procedures for benzylic bromides **21b** and **21c**, and benzylic iodide **23a** were described below.

DFT calculation study

General for C–F bond insertion

All calculations were performed with Gaussian 16, Revision C.01. Quantum chemical calculations were performed under vacuum at 298.15 K and 1 bar. The geometry optimizations were carried out at ωB97X-D level of theory with a mixed basis set; 6-31+G(d) for all elements. SMD (chlorobenzene) was used as a solvent effect. All molecular geometries were fully optimized and Gibbs free energies including contribution of vibrational entropy at an appropriate temperature were described in energy profiles. Stationary points, minima, and transition states on the potential energy surface were identified by vibrational analysis. It was confirmed that the transition state had only one imaginary frequency. Gibbs free energies were calculated as a sum of the single-point electronic energy and thermal correction to the Gibbs free energy. Gibbs free energies at 229.15 K were calculated by *GoodVibes* (Funes-Ardoiz, I.; Paton, R. S. *GoodVibes*, Version 2.0.1, **2018**.). The estimation of a diastereomer ratio from an activation energy gap was carried out by *GoodVibes*.

General for C–Cl bond insertion

All calculations were performed with Gaussian 16, Revision C.01. Quantum chemical calculations were performed under vacuum at 298.15 K and 1 bar. The geometry optimizations were carried out at ωB97X-D level of theory with a mixed basis set; The effective core potential of Hay and Wadt with a double-ξ valence basis set (LANL2DZ) was chosen to describe In. The 6-31+G(d) basis set was used for other atoms. SMD

(chloroform) was used as a solvent effect. Frequency calculations were carried out at ωB97X-D level of theory with a mixed basis set; LANL2DZ was chosen to describe In. The 6-311+G(d,p) basis set was used for other atoms. SMD (chloroform) was used as a solvent effect. All molecular geometries were fully optimized and Gibbs free energies including contribution of vibrational entropy at an appropriate temperature were described in energy profiles. Stationary points, minima, and transition states on the potential energy surface were identified by vibrational analysis. It was confirmed that the transition state had only one imaginary frequency. Gibbs free energies were calculated as a sum of the single-point electronic energy and thermal correction to the Gibbs free energy.

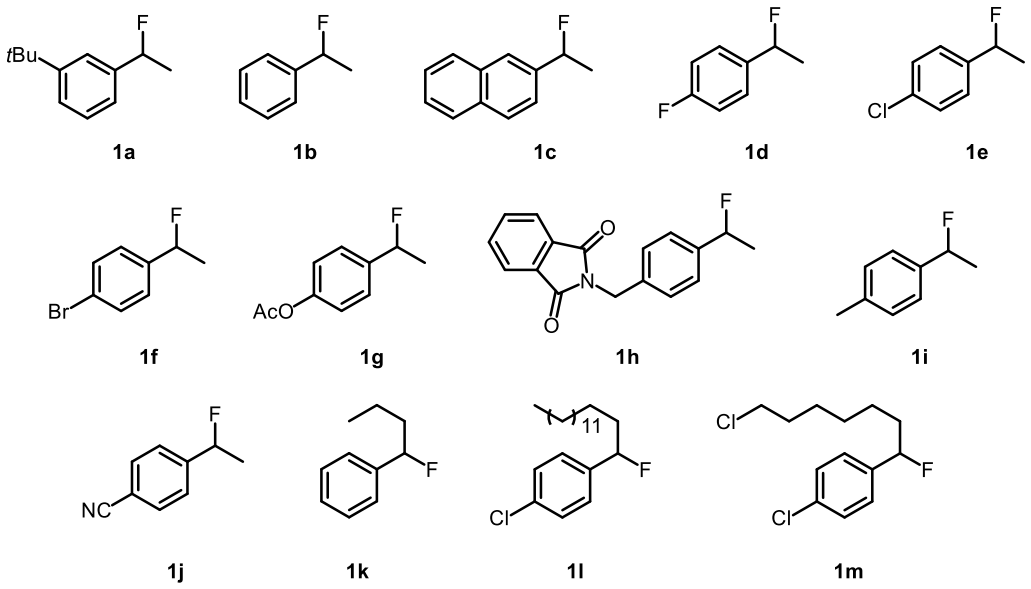
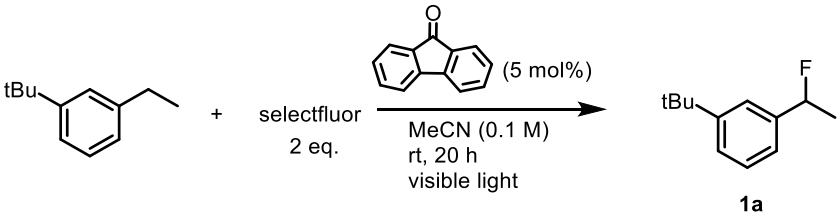


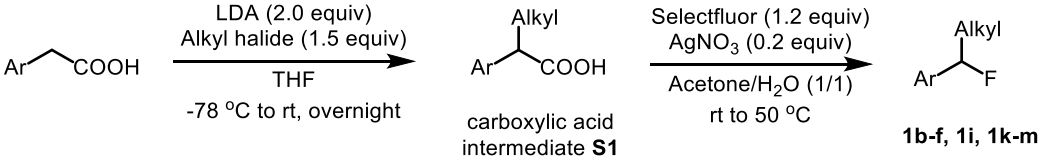
Figure S1. Selected benzylic fluorides for substrates scope.

(1a) 1-(*tert*-Butyl)-3-(1-fluoroethyl)benzene



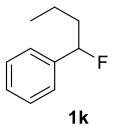
To a 100 mL round-bottom flask charged with Selectfluor® (3.54 g, 10 mmol) was added anhydrous acetonitrile (50 mL), 9-fluorenone (2.5 mmol, 0.45 g), and 1-(*tert*-butyl)-3-ethylbenzene (5 mmol) under nitrogen atmosphere. The reaction mixture was degassed three times by freeze-pump-thaw cycles and irradiated with a 19 W CFL at room temperature for 20 h. Diethyl ether (20 mL) was then added to crush out the remaining Selectfluor® and its byproduct. After filtration, the solvent was removed by distillation in a Teflon flask (avoid the decomposition). The residue was purified by silica gel column chromatography using hexane as the eluent and concentrated by rotary evaporator in a Teflon flask as colorless oil, 0.77 g, 85% yield. The characterization data were identical to those reported in the literature. (Preparation and Characterization data, J. Xia, C. Zhu, C. Chen, *J. Am. Chem. Soc.* **2013**, *135*, 17494.)

General procedure for preparation of benzylic fluorides 1b-f, 1i, 1k-m



Step 1: Under nitrogen atmosphere, diisopropylamine (2.20 g, 20 mmol, 2.0 equiv) and anhydrous THF (30 mL) were added to a 50 mL round-bottom flask at -78 °C. *n*BuLi (11.7 mL, 21 mmol, 1.05 equiv, 1.8 M in hexane) was added dropwise to the resultant mixture over 10 min. After stirred for additional 20 min at this temperature, corresponding carboxylic acid (10 mmol) dissolved in 10 mL THF was added dropwise over 10 min. The temperature was warmed to 0 °C and stirred for 1 h. After cooling to -78 °C again, corresponding alkyl bromide or alkyl iodide (15 mmol) was added dropwise over 5 min. This mixture was naturally warmed to room temperature and stirred for overnight. Then the reaction was quenched by 10 mL aqueous HCl (1 M) and further adjust the pH = 2. The desired product was extracted by ethyl acetate (30 mL x 3) and washed with brine, dried over $MgSO_4$. The solvent was removed by rotary evaporator to give carboxylic acid intermediate (**S1**) which was usually enough pure and used to the next step without further purification. If necessary, **S1** can be purified by silica gel column chromatography using EtOAc/hexane (3:7) as the eluent.
Step 2: Selectfluor® (12 mmol) was placed to a Schlenk-tube (30 mL) which was evacuated and filled with nitrogen. **S1** (10 mmol), acetone (8 mL), dilute water (8 mL), and $AgNO_3$ (2 mmol) were then sequentially added. The reaction mixture was stirred at room temperature for 5 min and heated to 50 °C for 25 min. Upon completion of the reaction, the resulting mixture was cooled down to room temperature and 5 mL aqueous HCl (1 M) was added to quench this reaction. The mixture was extracted with pentene (30 mL x 3) and combined organic layers were washed with saturated aqueous $NaHCO_3$ (30 mL x 2), dried over $MgSO_4$, filtration, and evaporation. The obtained crude mixture was usually enough pure and can be used without further purification. If necessary, this crude can be further purified by silica gel flash column with pentane or hexane as eluent.
CAUTION: The evaporation should be operated with a Teflon bottle, because these benzylic fluorides are usually sensitive to glass container especially under high temperature and high concentration. If these compounds are evaporated with a glass bottle, they are decomposed. The obtained product can be stored in a Teflon vial in freezer for a long time.

(1k) (1-Fluorobutyl)benzene

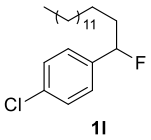


1k

Compound **1k** was prepared from phenylacetic acid (1.36 g, 10 mmol) and 1-iodopropane (2.55 g, 15 mmol) according to the general procedure. Colorless oil, 1.09 g, 72% yield, 2 steps.
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.38-7.16 (m, 5H), 5.42 (d, $^2J_{H\text{-}F}$ = 47.8 Hz, dd, J = 8.2, 4.8 Hz, 1H), 2.04-1.69 (m, 2H), 1.63-1.30 (m, 2H), 0.95 (t, J = 7.4 Hz, 3H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 140.6 (d, $J_{C\text{-}F}$ = 19.7 Hz), 128.4, 128.1 (d, $J_{C\text{-}F}$ = 2.5 Hz), 125.5 (d, $J_{C\text{-}F}$ = 6.6 Hz), 94.4 (d, $J_{C\text{-}F}$ = 169.6 Hz), 39.3 (d, $J_{C\text{-}F}$ =

23.8 Hz), 18.4 (d, $J_{C\text{-}F}$ = 4.9 Hz), 13.8; ^{19}F NMR: (376 MHz, $CDCl_3$) δ -174.51 (ddd, J = 45.8, 30.5, 15.3 Hz, 1F); HRMS: (DART+) Calculated ($C_{10}H_{13}$) 133.1012 $(M–F)^+$ Found: 133.1014

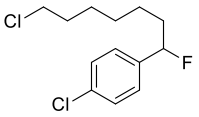
(1l) 1-Chloro-4-(1-fluoropentadecyl)benzene



1l

Compound **1l** was prepared from 2-(4-chlorophenyl)acetic acid (1.70 g, 10 mmol) and 1-iodotetradecane (4.86 g, 15 mmol) according to the general procedure. White solid, 1.23 g, 36% yield, 2 steps.
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.34 (d, J = 8.1 Hz, 2H), 7.25 (d, J = 8.1 Hz, 2H), 5.39 (d, $^2J_{H\text{-}F}$ = 47.6 Hz, dd, J = 7.9, 5.0 Hz, 1H), 2.00-1.69 (m, 2H), 1.46-1.16 (m, 24H), 0.88 (t, J = 6.5 Hz, 3H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 139.1 (d, $J_{C\text{-}F}$ = 19.7 Hz), 133.9 (d, $J_{C\text{-}F}$ = 2.5 Hz), 128.6, 126.9 (d, $J_{C\text{-}F}$ = 6.6 Hz), 94.0 (d, $J_{C\text{-}F}$ = 171.2 Hz), 37.2 (d, $J_{C\text{-}F}$ = 22.9 Hz), 31.9 (d, $J_{C\text{-}F}$ = 2.5 Hz), 29.69, 29.67, 29.64, 29.60, 29.52, 29.45, 29.36, 29.31, 25.0 (d, $J_{C\text{-}F}$ = 4.1 Hz), 22.7, 14.1; ^{19}F NMR: (376 MHz, $CDCl_3$) δ -174.52 (ddd, J = 45.8, 29.0, 16.8 Hz, 1F); m.p. 27-28 °C; HRMS: (EI) Calculated ($C_{21}H_{34}ClF$) 340.2333 (M^+) Found: 340.2330

(**1m**) **1-Chloro-4-(7-chloro-1-fluoroheptyl)benzene**

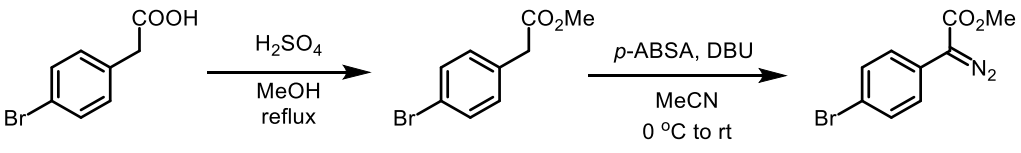


1m

Compound **1m** was prepared from 2-(4-chlorophenyl)acetic acid (1.70 g, 10 mmol) and 1-bromo-6-chlorohexane (2.99 g, 15 mmol) according to the general procedure. Colorless oil, 2.21 g, 84% yield, 2 steps.
^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.34 (d, J = 8.4 Hz, 2H), 7.25 (d, J = 8.4 Hz, 2H), 5.40 (d, $^2J_{H\text{-}F}$ = 47.7 Hz, dd, J = 8.0, 5.0 Hz, 1H), 3.52 (t, J = 6.8 Hz, 2H), 1.97-1.66 (m, 4H), 1.46-1.25 (m, 6H); ^{13}C NMR: (100 MHz, $CDCl_3$); δ 138.9 (d, $J_{C\text{-}F}$ = 19.7 Hz), 133.9 (d, $J_{C\text{-}F}$ = 2.5 Hz), 128.6, 126.9 (d, $J_{C\text{-}F}$ = 6.6 Hz), 93.8 (d, $J_{C\text{-}F}$ = 171.2 Hz), 45.0, 37.0 (d, $J_{C\text{-}F}$ = 23.8 Hz), 32.4, 28.5, 26.6, 24.7 (d, $J_{C\text{-}F}$ = 4.1 Hz); ^{19}F NMR: (376 MHz, $CDCl_3$) δ -174.92 (ddd, J = 45.8, 29.0, 16.8 Hz, 1F); HRMS: (EI) Calculated ($C_{13}H_{17}Cl_2F$) 262.0691 (M^+) Found: 262.0687

Preparation of diazoesters 2

Representative procedure for preparation of methyl 2-(4-bromophenyl)-2-diazoacetate (2c)



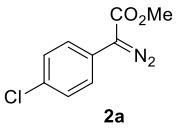
S2 **2c**

Step 1: A mixture of 4-bromophenylacetic acid (2.16 g, 10 mmol) and 95 wt% sulfonic acid (0.28 mL) in methanol (20 mL) was refluxed for 6 h. The resulting mixture was cooled to room temperature and diluted with saturated $NaHCO_3$ aq. The mixture was extracted with ethyl acetate and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated to give methyl (4-bromophenyl)acetate (**S2**)

(2.26 g, 99% yield) as a colorless oil. The crude product was used without purification.

Step 2: The diazo transfer was prepared according to a reported procedure. (Preparation, S. Thurow, A. A. G. Fernandes, Y. Quevedo-Acosta, M. F. de Oliveira, M. G. de Oliveira, I. D. Jurberg, *Org. Lett*. **2019**, *21*, 6909.). DBU (2.26 g, 14.84 mmol) was added dropwise to a solution of **S2** (2.26 g, 9.89 mmol) and *p*-acetamidobenzenesulfonyl azide (2.85 g, 11.87 mmol) in acetonitrile (20 mL) at 0 °C over 5 min. The mixture was stirred at 0 °C for additional 30 min and warmed to room temperature for 20 h. The resulting mixture was quenched with saturated aqueous ammonium chloride and extracted with ethyl acetate. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc = 9/1 as the eluent) to afford **2c** (2.44 g, 97% yield) as orange solid. The characterization data were identical to those reported in the literature. (Characterization data, E. Tayama, K. Horikawa, H. Iwamoto, E. Hasegawa, *Tetrahedron Lett*. **2014**, *55*, 3041.).

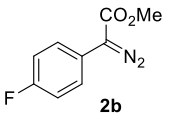
(**2a**) **Methyl 2-(4-chlorophenyl)-2-diazoacetate**



2a

Compound **2a** was prepared from 2-(4-chlorophenyl)acetic acid (1.71 g, 10 mmol) according to the general procedure. Yellow solid, 1.98 g, 94% yield. The characterization data were identical to those reported in the literature. (Characterization data, E. Tayama, K. Horikawa, H. Iwamoto, E. Hasegawa, *Tetrahedron Lett*. **2014**, *55*, 3041.).

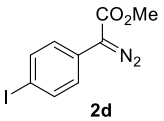
(**2b**) **Methyl 2-diazo-2-(4-fluorophenyl)acetate**



2b

Compound **2b** was prepared from 2-(4-fluorophenyl)acetic acid (1.54 g, 10 mmol) according to the general procedure. Red oil, 1.80 g, 93% yield. The characterization data were identical to those reported in the literature. (Characterization data, K. Stefkova, M. J. Heard, A. Dasgupta, R. L. Melen, *Chem. Commun*. **2021**, *57*, 6736.).

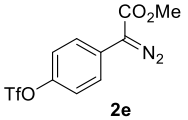
(**2d**) **Methyl 2-diazo-2-(4-iodophenyl)acetate**



2d

Compound **2d** was prepared from 2-(4-iodophenyl)acetic acid (2.62 g, 10 mmol) according to the general procedure. Yellow solid, 2.84 g, 94% yield. The characterization data were identical to those reported in the literature. (Characterization data, A. Ni, J. E. France, H. M. L. Davies, *J. Org. Chem*. **2006**, *71*, 5594.).

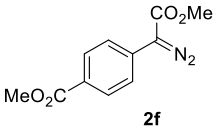
(**2e**) **Methyl 2-diazo-2-(4-(((trifluoromethyl)sulfonyl)oxy)phenyl)acetate**



2e

Compound **2e** was prepared from 2-(4-hydroxyphenyl)acetic acid (1.52 g, 10 mmol) according to the reported procedure. Yellow solid, 2.63 g, 81% yield. The characterization data were identical to those reported in the literature. (Preparation and Characterization data, A. Ni, J. E. France, H. M. L. Davies, *J. Org. Chem*. **2006**, *71*, 5594.).

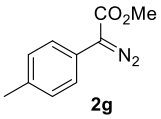
(2f) Methyl 4-(1-diazo-2-methoxy-2-oxoethyl)benzoate



2f

Compound **2f** was prepared from homoterephthalic acid dimethyl ester (2.08 g, 10 mmol) according to the general procedure. Yellow solid, 2.11 g, 90% yield. The characterization data were identical to those reported in the literature. (Characterization data, F. Ye, C. Wang, Y, Zhang, J. Wang, *Angew. Chem. Int. Ed.* **2014**, *53*, 11625.).

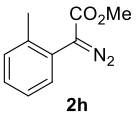
(2g) Methyl 2-diazo-2-(*p*-tolyl)acetate



2g

Compound **2g** was prepared from 2-(*p*-tolyl)acetic acid (1.50 g, 10 mmol) according to the general procedure. Yellow solid, 1.24 g, 65% yield. The characterization data were identical to those reported in the literature. (Characterization data, E. Tayama, K. Horikawa, H. Iwamoto, E. Hasegawa, *Tetrahedron Lett*. **2014**, *55*, 3041.).

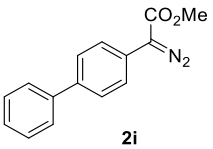
(2h) Methyl 2-diazo-2-(*o*-tolyl)acetate



2h

Compound **2h** was prepared from 2-(*o*-tolyl)acetic acid (1.50 g, 10 mmol) according to the general procedure. Yellow oil, 1.20 g, 63% yield. The characterization data were identical to those reported in the literature. (Characterization data, E. Tayama, K. Horikawa, H. Iwamoto, E. Hasegawa, *Tetrahedron Lett*. **2014**, *55*, 3041.).

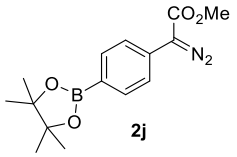
(2i) Methyl 2-([1,1'-biphenyl]-4-yl)-2-diazoacetate



2i

Compound **2i** was prepared from 2-([1,1'-biphenyl]-4-yl)acetic acid (2.12 g, 10 mmol) according to the general procedure. Red solid, 2.14 g, 85% yield. The characterization data were identical to those reported in the literature. (I. D. Jurberg, H. M. L. Davies, *Org. Lett*. **2017**, *19*, 5158.).

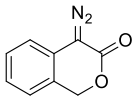
(**2j**) **Methyl 2-diazo-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate**



2j

Compound **2j** was prepared from methyl (4-bromophenyl)acetate (2.75 g, 12 mmol) according to the reported procedure. Yellow solid, 2.94 g, 81% yield (2 steps). The characterization data were identical to those reported in the literature. (Preparation and Characterization data, A. Ni, J. E. France, H. M. L. Davies, *J. Org. Chem*. **2006**, *71*, 5594.).

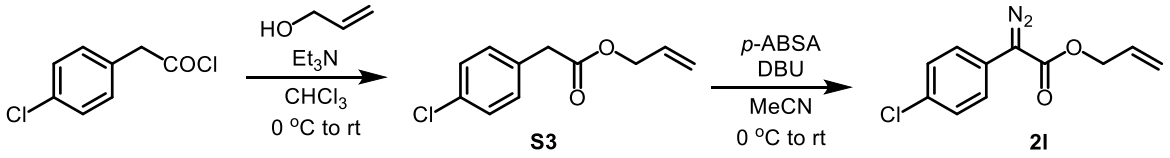
(**2k**) **4-Diazoisochroman-3-one**



2k

Compound **2k** was prepared from isochroman-3-one (1.48 g, 10 mmol) according to the general procedure. Yellow solid, 1.23 g, 71% yield. The characterization data were identical to those reported in the literature. (Characterization data, S. Zhu, X. Song, Y. Li, Y. Cai, Q. Zhou, *J. Am. Chem. Soc*. **2010**, *132*, 16374.).

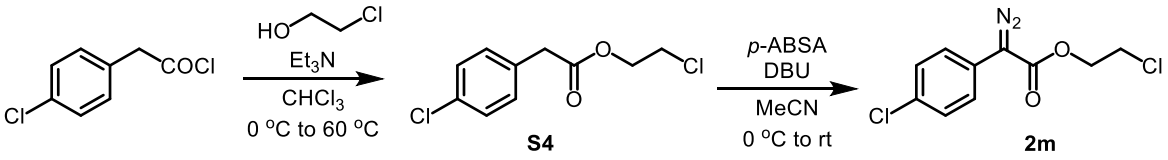
(**2l**) **Allyl 2-(4-chlorophenyl)-2-diazoacetate**



Step 1: Et_3N was added dropwise to a solution of 2-(4-chlorophenyl)acetyl chloride (1.89 g, 10 mmol) and allyl alcohol (0.87 g, 15 mmol) in $CHCl_3$ (20 mL) at 0 °C. The mixture was warmed to room temperature and stirred for overnight. The reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with ethyl acetate. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to obtain allyl 2-(4-chlorophenyl)acetate (**S3**) as colorless oil. This crude product was used without purification.

Step 2: The obtained **S3** was dissolved in acetonitrile (20 mL) and transferred to a 30 mL reaction tube. Subsequentially *p*-acetamidobenzenesulfonyl azide (2.88 g, 12 mmol) and DBU (2.28 g, 15 mmol) were added at 0 °C. The mixture was stirred at 0 °C for additional 30 min and warmed to room temperature for 20 h. The resulting mixture was quenched with saturated aqueous ammonium chloride and extracted with ethyl acetate. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc = 9/1 as the eluent) to afford **2l** (1.40 g, 59% yield, 2 steps) as red oil. The characterization data were identical to those reported in the literature. (Characterization data, J. R. Combs, Y. Lai, D. L. V. Vranken, *Org. Lett*. **2021**, *23*, 2841.).

(**2m**) **2-Chloroethyl 2-(4-chlorophenyl)-2-diazoacetate**

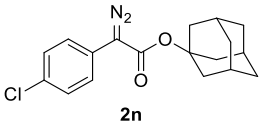


Step 1: Et_3N was added dropwise to a solution of 2-(4-chlorophenyl)acetyl chloride (1.89 g, 10 mmol) and 2-chloroethan-1-ol (1.21 g, 15 mmol) in $CHCl_3$ (20 mL) at 0 °C. The mixture was warmed to room temperature and stirred for 1 h. The mixture was then heated to 60 °C and stirred for overnight. The reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with ethyl acetate. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated to obtain 2-chloroethyl 2-(4-chlorophenyl)acetate (**S4**) as colorless oil. This crude product was used without purification.

Step 2: The obtained **S4** was dissolved in acetonitrile (20 mL) and transferred to a 30 mL reaction tube. Subsequentially *p*-acetamidobenzenesulfonyl azide (2.88 g, 12 mmol) and DBU (2.28 g, 15 mmol) were added at 0 °C. The mixture was stirred at 0 °C for additional 30 min and warmed to room temperature for 20 h. The resulting mixture was quenched with saturated aqueous ammonium chloride and extracted with ethyl acetate. The combined extracts were washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography (hexane/EtOAc = 9/1 as the eluent) to afford **2l** (1.61 g, 62% yield, 2 steps) as yellow solid.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.42 (d, J = 8.9 Hz, 2H), 7.36 (d, J = 8.9 Hz, 2H), 4.52 (t, J = 5.7 Hz, 2H), 3.76 (t, J = 5.7 Hz, 2H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 164.3, 131.7, 129.1, 125.1, 123.7, 64.4, 41.6, CN_2 was not observed; IR: (KBr) 2098, 1697 cm^{-1}; m.p. 54-55 °C; HRMS: (DART+) Calculated ($C_{10}H_9O_2Cl_2$) 230.9974 $(M–N_2+H)^+$ Found: 230.9980

(**2n**) **Adamantan-1-yl 2-(4-chlorophenyl)-2-diazoacetate**

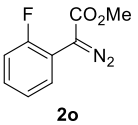


2n

Compound **2n** was prepared from 2-(4-chlorophenyl)acetic acid (1.71 g, 10 mmol) and adamantan-1-ol (1.52 g, 10 mmol) in toluene according to the general procedure. Yellow solid, 1.39 g, 42% yield.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.40 (d, J = 8.9 Hz, 2H), 7.32 (d, J = 8.9 Hz, 2H), 2.19 (s, 9H), 1.69 (s, 6H); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 163.8, 131.0, 128.9, 125.0, 124.8, 82.4, 41.6, 36.1, 30.9, CN_2 was not observed; IR: (KBr) 2097, 1694 cm^{-1}; m.p. 131-132 °C; HRMS: (DART+) Calculated ($C_{18}H_{20}O_2Cl$) 303.1146 $(M–N_2+H)^+$ Found: 303.1158

(**2o**) **Methyl 2-diazo-2-(2-fluorophenyl)acetate**

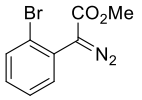


2o

Compound **2o** was prepared from 2-(2-fluorophenyl)acetic acid (1.54 g, 10 mmol) according to the general procedure. Yellow oil, 1.65 g, 85% yield. The characterization data were identical to those reported in the

literature. (Characterization data, T. C. Maier, G. C. Fu, *J. Am. Chem. Soc.* **2006**, *128*, 4594.).

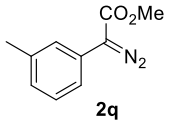
(**2p**) **Methyl 2-diazo-2-(2-bromophenyl)acetate**



2p

Compound **2d** was prepared from 2-(2-bromophenyl)acetic acid (2.15 g, 10 mmol) according to the general procedure. Yellow oil, 2.37 g, 93% yield, two steps. The characterization data were identical to those reported in the literature. (Characterization data, P. Zhou, Z. Zhou, Z. Chen, Y. Ye, L. Zhao, Y. Yang, X. Xia, J. Luo, Y. Liang, *Chem. Commun*. **2013**, *49*, 561.).

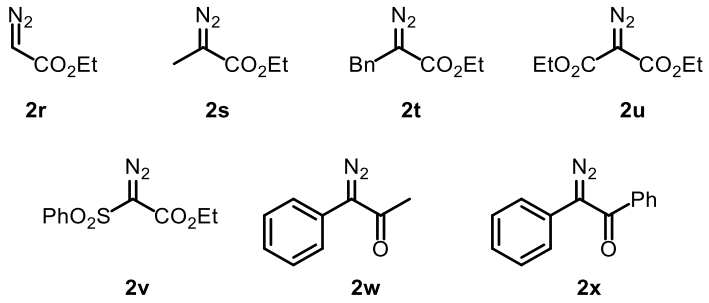
(**2q**) **Methyl 2-diazo-2-(*m*-tolyl)acetate**



2q

Compound **2j** was prepared from 2-(*m*-tolyl)acetic acid (1.50 g, 10 mmol) according to the general procedure. Yellow oil, 1.20 g, 63% yield. The characterization data were identical to those reported in the literature. (Characterization data, P. Zhou, Z. Zhou, Z. Chen, Y. Ye, L. Zhao, Y. Yang, X. Xia, J. Luo, Y. Liang, *Chem. Commun*. **2013**, *49*, 561.).

Figure S2. Ineffective diazo compounds.

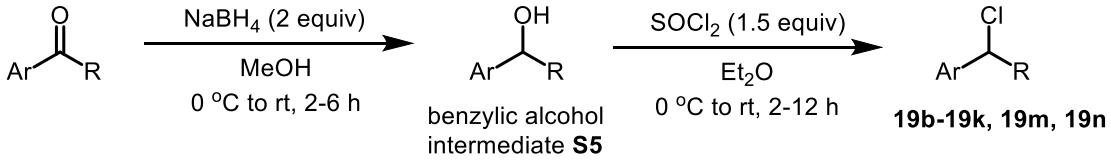


2r **2s** **2t** **2u**

2v **2w** **2x**

Those diazo compounds **2r-2x** are known compounds and synthesized by reported procedures.

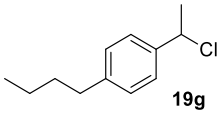
General procedure for preparation of benzylic chlorides 19b-19k, 19m, and 19n



Step 1: Under nitrogen atmosphere, acetophenone (10 mmol, 1.0 equiv) and anhydrous MeOH (30 mL) were added to a 50 mL three-necked round-bottomed flask at 0 °C. $NaBH_4$ (20 mmol, 0.75 g, 2.0 equiv) was slowly added to the resultant mixture. The reaction was then stirred for additional 30 min at this temperature, the ice bath was removed and the temperature was naturally warmed to room temperature and stirred for 2-6 h. After rection complete (checked by TLC), the reaction was quenched by water and extracted by ethyl acetate (30 mL x 3) and washed with brine, dried over $MgSO_4$. The solvent was then evaporated to afford intermediate **S5** which was enough pure and used to the next step without further purification.

Step 2: Intermediate **S5** (10 mmol, 1.0 equiv) was diluted with Et_2O (10 mL) and transferred to a 30 mL reaction tube. After cooling to 0 °C, thionyl chloride (15 mmol, 1.5 equiv) was added dropwise over 5 min. The reaction mixture was stirred at room temperature for 2 h to overnight until the complete consumption of **S1** (checked by TLC). Upon completion of the reaction, the resulting mixture was poured into ice and washed with saturated $NaHCO_3$ aq (20 mL x 2), extracted with Et_2O (30 mL x 2), and dried over $MgSO_4$. The solvent was removed and the crude mixture was purified by silica gel flash column with n-hexane as eluent to give benzylic chlorides **19b**-**19k**, **19m**, and **19n**.

(19g) 1-Butyl-4-(1-chloroethyl)benzene

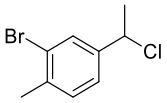


19g

Compound **19g** was prepared from 1-(4-butylphenyl)ethan-1-one (1.76 g, 10 mmol) according to the general procedure. Colorless oil, 1.77 g, 90% yield, 2 steps.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.16 (d, *J* = 8.1 Hz, 2H, Ar-H), 5.09 (q, *J* = 6.8 Hz, 1H), 2.60 (t, *J* = 7.5 Hz, 2H), 1.85 (d, *J* = 6.8 Hz, 3H), 1.59 (quint, *J* = 7.5 Hz, 2H), 1.35 (sextet, *J* = 7.5 Hz, 2H), 0.92 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR: (100 MHz, CDCl3) δ 143.0, 140.0, 128.5, 126.3, 58.7, 35.2, 33.5, 26.4, 22.3, 13.9; HRMS (ESI+, TOF) m/z: $[M+H]^+$ Calculated for $C_{12}H_{18}Cl$ 197.1092; Found 197.1090

(19i) 2-Bromo-4-(1-chloroethyl)-1-methylbenzene

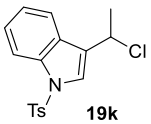


19i

Compound **19i** was prepared from 1-(3-bromo-4-methylphenyl)ethan-1-one (3.19 g, 15 mmol) according to the general procedure. Colorless oil, 2.26 g, 71% yield, 2 steps.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 1.2 Hz, 1H, Ar-H), 7.25 (dd, *J* = 7.7, 1.2 Hz, 1H, Ar-H), 7.21 (d, *J* = 7.7 Hz, 1H, Ar-H), 5.01 (q, *J* = 6.9 Hz, 1H), 2.39 (s, 3H, Ar-CH_3), 1.82 (d, *J* = 6.9 Hz, 3H, CH_3); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 142.1, 137.8, 130.8, 130.3, 125.4, 124.8, 57.4, 26.3, 22.5; HRMS (DART+, TOF) m/z: $[M–Cl]^+$ Calculated for $C_9H_{10}Br$ 196.9960; Found 196.9965

(19k) 3-(1-Chloroethyl)-1-tosyl-1*H*-indole



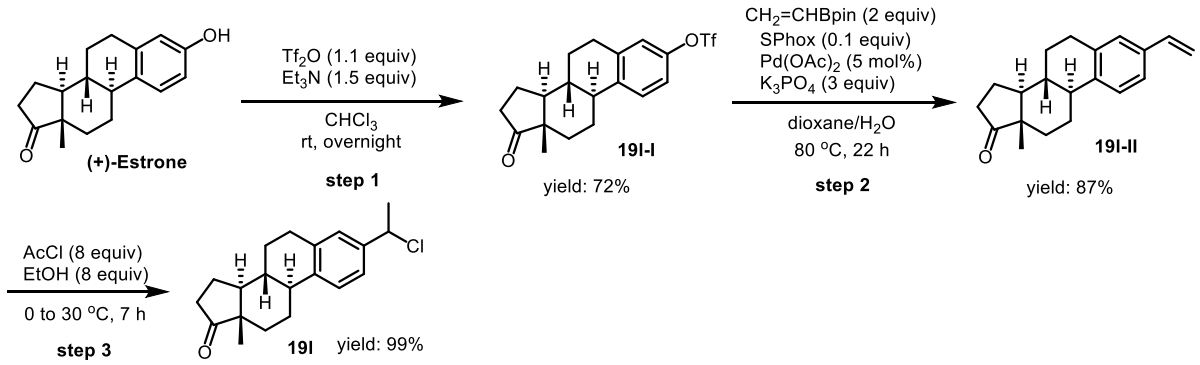
19k

Compound **19k** was prepared from 1-(1-tosyl-1*H*-indol-3-yl)ethan-1-ol (1.26 g, 4 mmol) according to the general procedure. Brown solid, 1.29 g, 97% yield.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.9 Hz, 1H, Ar-H), 7.78 (d, *J* = 8.2 Hz, 2H, Ar-H), 7.70 (d, *J* = 7.9 Hz, 1H, Ar-H), 7.58 (s, 1H), 7.34 (t, *J* = 7.9 Hz, 1H, Ar-H), 7.27 (t, *J* = 7.9 Hz, 1H, Ar-H), 7.24 (d, *J* = 8.2 Hz, 2H, Ar-H), 5.29 (q, *J* = 6.8 Hz, 1H), 2.26 (s, 3H, Ar-CH_3), 1.94 (d, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR: (100 MHz, $CDCl_3$) δ 145.1, 135.2, 134.9, 129.9, 128.4, 126.7, 125.0, 124.2, 123.2, 122.9, 120.3, 113.5, 50.7, 24.4, 21.4; IR: (KBr) 1595 1562 cm^{-1}; m.p. 77–78 °C; HRMS (ESI+, TOF) m/z: $[M+H_3O]^+$ Calculated for

$C_{17}H_{19}NO_3SCl$ 352.0769; Found 352.0760

(19l) (8*R*,9*S*,13*S*,14*S*)-3-(1-chloroethyl)-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*-cyclopenta[*a*]phenanthren-17-one



Step 1: To a dried Schlenk flask was charged with (+)-Estrone (5.02 g, 18.5 mmol, 1.0 equiv), $CHCl_3$ (20 mL), and triethylamine (2.81 g, 27.75 mmol, 1.5 equiv) at 0 °C. Trifluoromethanesulfonic anhydride (5.75 g, 20.4 mmol, 1.1 equiv) was added dropwise over 2 min and stirred at 0 °C for 10 min under N_2. Then the reaction mixture was naturally warmed to room temperature and stirred overnight. The reaction was quenched by saturated $NaHCO_3$ aq and extracted by $CHCl_3$ (30 mL x 3), dried over $MgSO_4$. The **19l-I** was obtained after purification on silica gel flash column with n-hexane/EtOAc (4/1) as eluent. White solid, 5.36 g, 72% yield.

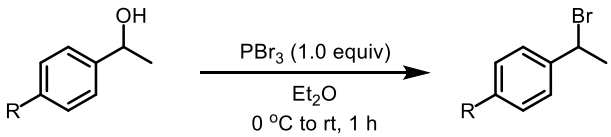
Step 2: **19l-II** was prepared according to a reported procedure (F. Scheidt, J. Neufeld, M. Schäfer, C. Thiehoff, R. Gilmour, *Org. Lett*. **2018**, *20*, 8073). A Schlenk flask was charged with **19l-I** (2.00 g, 5 mmol, 1.0 equiv)**,** SPhos (0.21 g, 0.5 mmol, 0.1 equiv), K_3PO_4 (2.60 g, 15 mmol, 3.0 equiv), 4,4,5,5-tetramethyl-2-vinyl-1,3,2-dioxaborolane (1.54 g, 10 mmol, 2.0 equiv), 1,4-dioxane (30 mL), and water (4.8 mL). The reaction vessel was sealed with a septum, evacuated and refilled with N_2 (cycle 3 times). $Pd(OAc)_2$ (0.056 g, 0.25 mmol, 5 mol%) was added under a flow of N_2 and the reaction mixture was heated to 80 °C (oil bath) and stirred for 22 h. After cooling to room temperature, the reaction mixture was diluted with EtOAc (30 mL). The mixture was filtered through a plug of silica. The organic layer was washed with brine, dried over $MgSO_4$ and the solvent was evaporated. The residue was purified by silica gel flash column (n-hexane/EtOAc = 9/1). The **19l-II** was obtained as white solid, 1.22 g, 87% yield. The characterization data for **19l-II** was identical to those reported in the literature (F. Scheidt, J. Neufeld, M. Schäfer, C. Thiehoff, R. Gilmour, *Org. Lett*. **2018**, *20*, 8073).

Step 3: To a dried reaction tube was charged with **19l-II** (0.28 g, 1.0 mmol, 1.0 equiv) and EtOH (0.37 g, 8.0 mmol, 8.0 equiv). Acetyl chloride (0.63 g, 8.0 mmol, 8.0 equiv) was added dropwise over 2 min at 0 °C. The resultant mixture was heated to 30 °C (oil bath) and stirred for 7 h. The volatile was evaporated *in vacuo* and the crude product was purified by path through a plug of silica gel (n-hexane/EtOAc = 5/1) to give the title compound **19l** as a colorless solid (0.31 g, 99% yield). This is a mixture of diastereomers.

^{1}H NMR: (400 MHz, $CDCl_3$) δ 7.28 (d, J = 8.2 Hz, 1H, Ar-H), 7.20 (d, J = 8.2 Hz, 1H, Ar-H), 7.15 (s, 1H, Ar-H), 5.05 (q, J = 6.3 Hz, 1H), 2.94-2.91 (m, 2H), 2.54-2.40 (m, 2H), 2.29 (t, J = 10.6 Hz, 1H), 2.19-1.95 (m, 4H), 1.84 (m, J = 6.3 Hz, 3H, CH_3), 1.68-1.39 (m, 6H), 0.90 (s, 3H, CH_3); ^{13}C NMR: (100 MHz, $CDCl_3$)

δ 220.7, 140.1, 139.8, 136.7, 127.0, 125.6, 123.8, 58.64, 58.59, 50.3, 47.8, 44.2, 37.9, 35.7, 31.4, 29.29, 29.27, 26.30, 26.26, 26.2, 25.5, 21.5, 13.7; IR: (KBr) 1738 (C=O) cm^{-1}; m.p. 122–123 °C; HRMS (DART+, TOF) m/z: $[M+NH_4]^+$ Calculated for $C_{20}H_{29}NOCl$ 334.1932; Found 334.1946

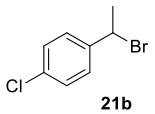
General procedure for preparation of benzylic bromides 21b and 21c



21b, R = Cl
21c, R = Me

Benzylic alcohol (10 mmol, 1.0 equiv) was diluted with Et_2O (20 mL) and transferred to a reaction tube. After cooling to 0 °C, PBr_3 (10 mmol, 1.0 equiv) was added dropwise. The reaction mixture was stirred at room temperature for 1 h at which time the complete consumption of alcohol (checked by TLC). Upon completion of the reaction, the resulting mixture was poured into ice and washed with saturated $NaHCO_3$ aq (30 mL x 2), extracted with Et_2O (30 mL x 2), and dried over $MgSO_4$. The solvent was then evaporated *in vacuo*, the crude mixture was purified by silica gel flash column with n-hexane as eluent.

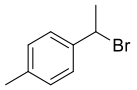
(21b) 1-(1-Bromoethyl)-4-chlorobenzene



21b

Compound **21b** was prepared from 1-(4-chlorophenyl)ethan-1-ol (1.57 g, 10 mmol) according to the general procedure. Colorless oil, 2.05 g, 93% yield. (Characterization data, A. Nielsena, S. Raez-Villanuevab, D. J. Crankshawb, A. C. Hollowayb, J. McNulty, *Bioorg. Med. Chem. Lett*. **2019**, *29*, 1395.)

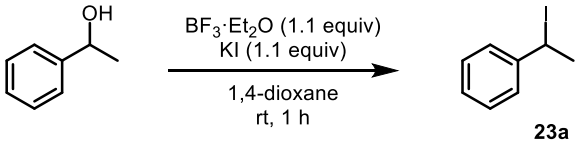
(21c) 1-(1-Bromoethyl)-4-methylbenzene



21c

Compound **21c** was prepared from 1-(*p*-tolyl)ethan-1-ol (2.04 g, 15 mmol) according to the general procedure. Colorless oil, 2.72 g, 91% yield. (Characterization data, J. Holz, C. Pfeffer, H. Zuo, D. Beierlein, G. Richter, E. Klemm, Ren. Peters, *Angew. Chem. Int. Ed.* **2019**, *58*, 10330.)

General procedure for preparation of benzylic iodide 23a



23a

Compound **23a** was prepared according to a reported procedure (B. P. Bandgar, V. S. Sadavarte, L. S. Uppalla, *Tetrahedron Lett*. **2001**, *42*, 951). A reaction tube was sequentially charged with potassium iodide (1.83 g, 11 mmol, 1.1 equiv), benzylic alcohol (10 mmol, 1 equiv), and 1,4-dioxane (10 mL). Then $BF_3·Et_2O$ (1.56 g, 11 mmol, 1.1 equiv) was added in one portion. The resultant mixture was stirred at room temperature for

1 h. At which time the alcohol was complete consumption (checked by TLC), the reaction was quenched by water and washed with saturated $NaHCO_3$ aq, $Na_2S_2O_3$ aq, and brine, extracted with Et_2O (30 mL x 2), and dried over $MgSO_4$. The solvent was then removed and the crude mixture was purified by silica gel flash column with n-hexane as eluent to give pure product **6a** as colorless oil, 1.74 g, 75% yield. (Characterization data, B. P. Bandgar, V. S. Sadavarte, L. S. Uppalla, *Tetrahedron Lett*. **2001**, *42*, 951).

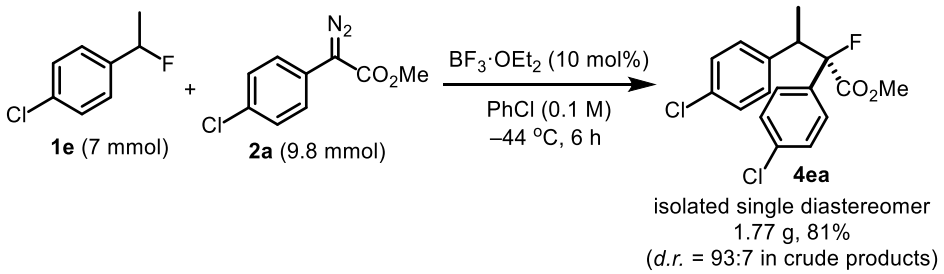
General Procedure

BF_3 catalyzed C–F bond insertion between alkyl fluoride 1 with diazoester 2 (Entry 21, Table 1)

Under nitrogen atmosphere, a reaction tube was sequentially charged with diazoester **2** (0.3 mmol, 1.5 equiv), chlorobenzene (2 mL), and alkyl fluoride **1** (0.2 mmol, 1 equiv) at –44 °C. Then boron trifluoride diethyl etherate (0.02 mmol, 2.5 μL, 0.1 equiv) was added to this mixture by microsyringe at the same temperature. The resulting mixture was stirred at –44 °C for 4 h. The reaction was quenched by saturated $NaHCO_3$ aq and extracted with $CHCl_3$ (10 mL x 3). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The sum yield of diastereomers and the diastereo ratio were determined by ^1H NMR and ^{19}F NMR in the crude product, in which 1,1,2,2-tetrachloroethane and hexafluorobenzene were used as internal standards, respectively. The crude was purified by recycle HPLC using hexane/EtOAc as the eluent to obtain a major diastereomer. The isolated yield of a major diastereomer was calculated based on the obtained weight.

Gram-scale Synthesis of 4ea

A gram-scale reaction using benzylic fluoride **1e** and diazoester **2a** exhibited a high level of diastereoselectivity for **4ea**. A 100 mL three-necked round-bottomed flask equipped with a magnetic stir bar was charged with methyl 2-(4-chlorophenyl)-2-diazoacetate (9.80 mmol, 2.06 g). Chlorobenzene (70 mL) followed by 1-chloro-4-(1-fluoroethyl)benzene (7.00 mmol, 1.11 g, 1.0 equiv) was added into the flask. After cooling to –44 °C, boron trifluoride diethyl etherate (0.70 mmol, 86 μL) was added to the mixture and stirred at –44 °C for 6 h. The reaction was quenched by saturated $NaHCO_3$ aq (100 mL) and extracted with $CHCl_3$ (50 mL x 3). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The sum yield of diastereomers and the diastereo ratio were determined by ^1H NMR and ^{19}F NMR in the crude product, in which 1,1,2,2-tetrachloroethane and hexafluorobenzene were used as internal standards, respectively. The crude was purified by silica gel column chromatography (hexane/EtOAc = 95/5) and further purified by recycle HPLC using hexane/EtOAc (hexane/EtOAc = 95/5) as the eluent. The major and minor diastereomers were separately obtained. The pure major isomer of **4ea** was isolated in 81% (1.77 g).



Scheme S1. Competitive elongation between benzylic fluorides **1b** and **1f**

$InCl_3$ catalyzed C–Cl bond insertion between benzylic chlorides 19 with diazoesters 2

Under nitrogen atmosphere, a reaction tube was charged with $InCl_3$ (0.0088 g, 0.04 mmol, 10 mol%) and dried by heating to 200 °C with *heat gun* under vacuo. After cooling to 0 °C with ice bath, the reaction tube was sequentially charged with $CHCl_3$ (1 mL), benzylic chloride **19** (0.4 mmol, 1 equiv), and diazoester **2** (0.6 mmol, 1.5 equiv) at 0 °C. The reaction mixture was stirred at 0 °C for 5 min. Then the ice bath was removed and naturally warmed to room temperature and stirred for additional 6 h. After completion of reaction, the mixture was quenched by saturated $NaHCO_3$ aq and extracted with $CHCl_3$ (10 mL x 3). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The sum yield of diastereomers and the diastereomeric ratio were determined by ^1H NMR in the crude product, in which 1,1,2,2-tetrachloroethane was used as an internal standard. The two diastereomers were separately obtained by silica gel column chromatography and recycle HPLC. The isolated yields of two diastereomers were calculated based on the obtained weight.

$InBr_3$ catalyzed C–Br bond insertion between benzylic bromides 21 with diazoester 2a

Under nitrogen atmosphere, a reaction tube was charged with $InBr_3$ (0.0142 g, 0.04 mmol, 10 mol%) and dried by heating to 200 °C with *heat gun* under vacuo. After cooling to –44 °C, the reaction tube was sequentially charged with chlorobenzene (4 mL), benzylic bromide **21** (0.4 mmol, 1 equiv), and diazoester **2a** (0.6 mmol, 1.5 equiv). The reaction mixture was stirred for 5 min at –44 °C and then 6 h at –30 °C. After completion of reaction, the mixture was quenched by saturated $NaHCO_3$ aq and extracted with $CHCl_3$ (10 mL x 3). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The sum yield of diastereomers and the diastereomeric ratio were determined by ^1H NMR in the crude product, in which 1,1,2,2-tetrachloroethane was used as an internal standard. The two diastereomers were separately obtained by silica gel column chromatography and recycle HPLC. The isolated yields of two diastereomers were calculated based on the obtained weight.

InI_3 catalyzed C–I bond insertion between benzylic iodide 23 with diazoester 2a

Under nitrogen atmosphere, a reaction tube was charged with InI_3 (0.0198 g, 0.04 mmol, 10 mol%). After cooling to –44 °C, the reaction tube was sequentially charged with chlorobenzene (4 mL), benzylic iodide **23** (0.4 mmol, 1 equiv), and diazoester **2a** (0.6 mmol, 1.5 equiv). The reaction mixture was stirred at –44 °C for 4 h. After completion of reaction, the mixture was quenched by saturated $NaHCO_3$ aq and extracted with $CHCl_3$ (10 mL x 3). The combined organic layers were washed with $Na_2S_2O_3$ aq and dried over $MgSO_4$ and concentrated under reduced pressure. The sum yield of diastereomers and the diastereomeric ratio were determined by ^1H NMR in the crude product, in which 1,1,2,2-tetrachloroethane was used as an internal standard. The two diastereomers were separately obtained by silica gel column chromatography and recycle HPLC. The isolated yields of two diastereomers were calculated based on the obtained weight.

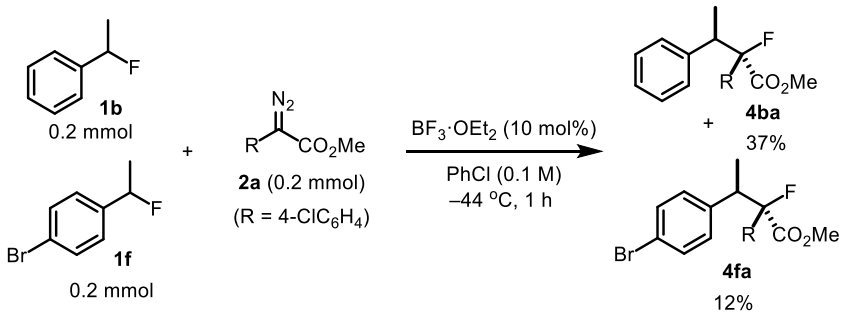
Gram-scale synthesis of methyl 2-bromo-2-(4-chlorophenyl)-3-phenylbutanoate (22aa)

Under nitrogen atmosphere, a 100 mL three-necked round-bottomed flask equipped with a magnetic stir bar was charged with $InBr_3$ (0.150 g, 0.424 mmol, 10 mol%) and dried by heating to 200 °C with *heat gun* under vacuo. After cooling to –44 °C, to the flask was sequentially charged with chlorobenzene (20 mL), benzylic bromide **21** (0.784 g, 4.24 mmol, 1 equiv), and diazoester **2a** (1.12 g, 5.30 mmol, 1.25 equiv). The reaction

mixture was stirred for 5 min at –44 °C and then 6 h at –30 °C. After completion of reaction, the mixture was quenched by saturated $NaHCO_3$ aq and extracted with $CHCl_3$ (50 mL x 3). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The **22aa** was obtained by silica gel column chromatography (n-hexane/EtOAc = 90/10) and recycle GPC ($CHCl_3$) as a diastereomeric mixture, 1.32 g, dr = 57:43, 85% yield.

Competitive elongation between benzylic fluorides 1b and 1f (Scheme S2)

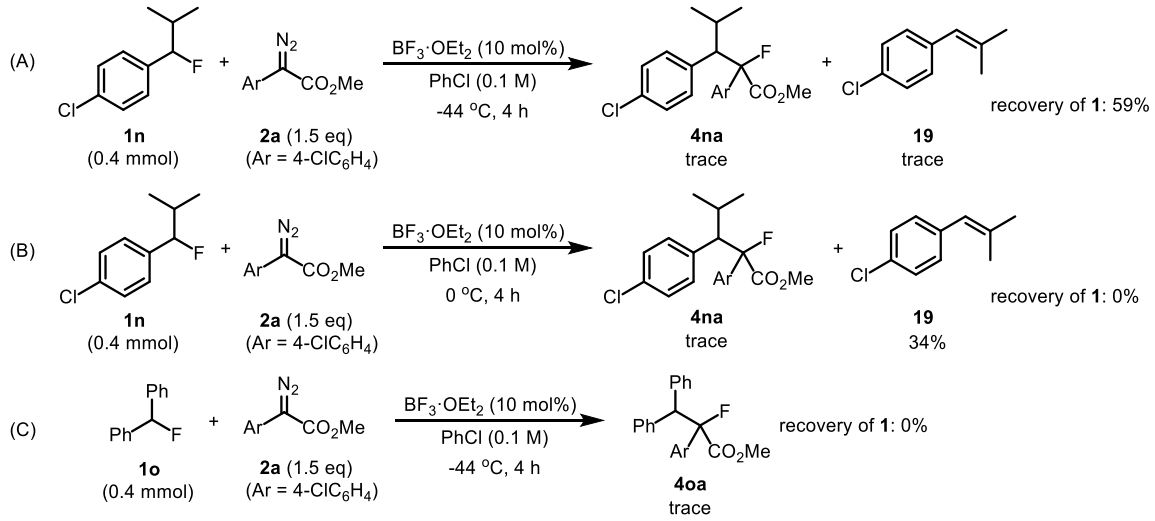
Under nitrogen atmosphere, a reaction tube was sequentially charged with methyl 2-(4-chlorophenyl)-2-diazoacetate (0.0432 g, 0.206 mmol, 1.0 equiv), chlorobenzene (2 mL), (1-fluoroethyl)benzene **1b** (0.0253 g, 0.204 mmol, 1.0 equiv), and 1-bromo-4-(1-fluoroethyl)benzene **1f** (0.0410 g, 0.202 mmol, 1.0 equiv) at –44 °C. Then boron trifluoride diethyl etherate (0.02 mmol, 2.5 μL, 0.1 equiv) was added to this mixture by microsyringe at the same temperature. The resulting mixture was stirred at –44 °C for 1 h. The reaction was quenched by saturated $NaHCO_3$ aq and extracted with $CHCl_3$ (10 mL x 3). The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The sum yield of diastereomers and the diastereo ratio were determined by ^1H NMR and ^{19}F NMR in the crude product, in which 1,1,2,2-tetrachloroethane and hexafluorobenzene were used as internal standards, respectively. Because of the competitive elongation between benzylic fluorides **1b** and **1f**, the more electron-deficient **1f** exhibited less reactivity than **1b**. This reactivity order is consistent with the order of the stability of the corresponding benzylic cations.



Scheme S2. Competitive elongation between benzylic fluorides **1b** and **1f**

Limitation of benzylic fluorides (Scheme S3)

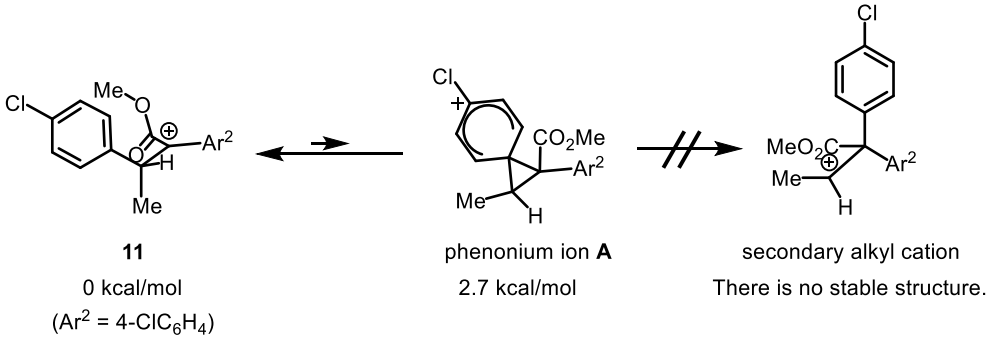
The desired elongation of benzylic fluoride **1n** and **1o** did not give the desired products (eqs A, B, and C). The steric hindrance of isopropyl or Ph group would disturb the addition of diazoester **2a**.



Scheme S3. Unsuccessful benzylic fluorides for C–F bond insertion

Consideration of Ar-migration path (Scheme S4)

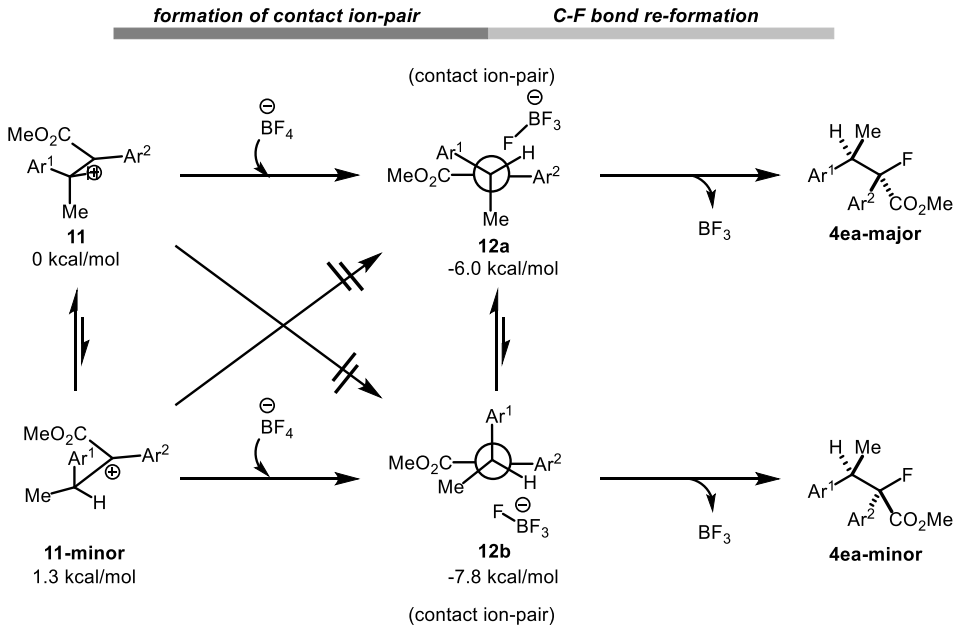
The phenonium ion intermediate **A** toward Ar-migration is less stable than **11** by 2.7 kcal/mol. In addition, a secondary alkyl cation produced after the completion of the migration is unstable and then no stable structures could be found. Therefore, the migration path from **11** is disfavored.



Scheme S4. Consideration of Ar-migration path.

Routes of generation of contact ion-pairs 12 (Scheme S5)

Cation **11** is the most stable conformer among the corresponding cation intermediates. Cation **11** has the similar conformation of the carbon scaffold to contact ion-pair **12a**. Therefore, **12a** is directly generated from **11**, and then **12a** gives product **4ea-major**. Metastable conformer **12b** of contact ion-pair is generated from **12a**. This conformation change from **12a** to **12b** proceeds through carbon-carbon single bond rotation, and the activation energy would be low because the energy gap between **12a** and **12b** is small. On the other hand, minor conformer **12b** of contact ion-pair can be directly generated from **11-minor**, but **11-minor** is a metastable conformer of cation **11**, so this path would be a minor route to generate **12b**.

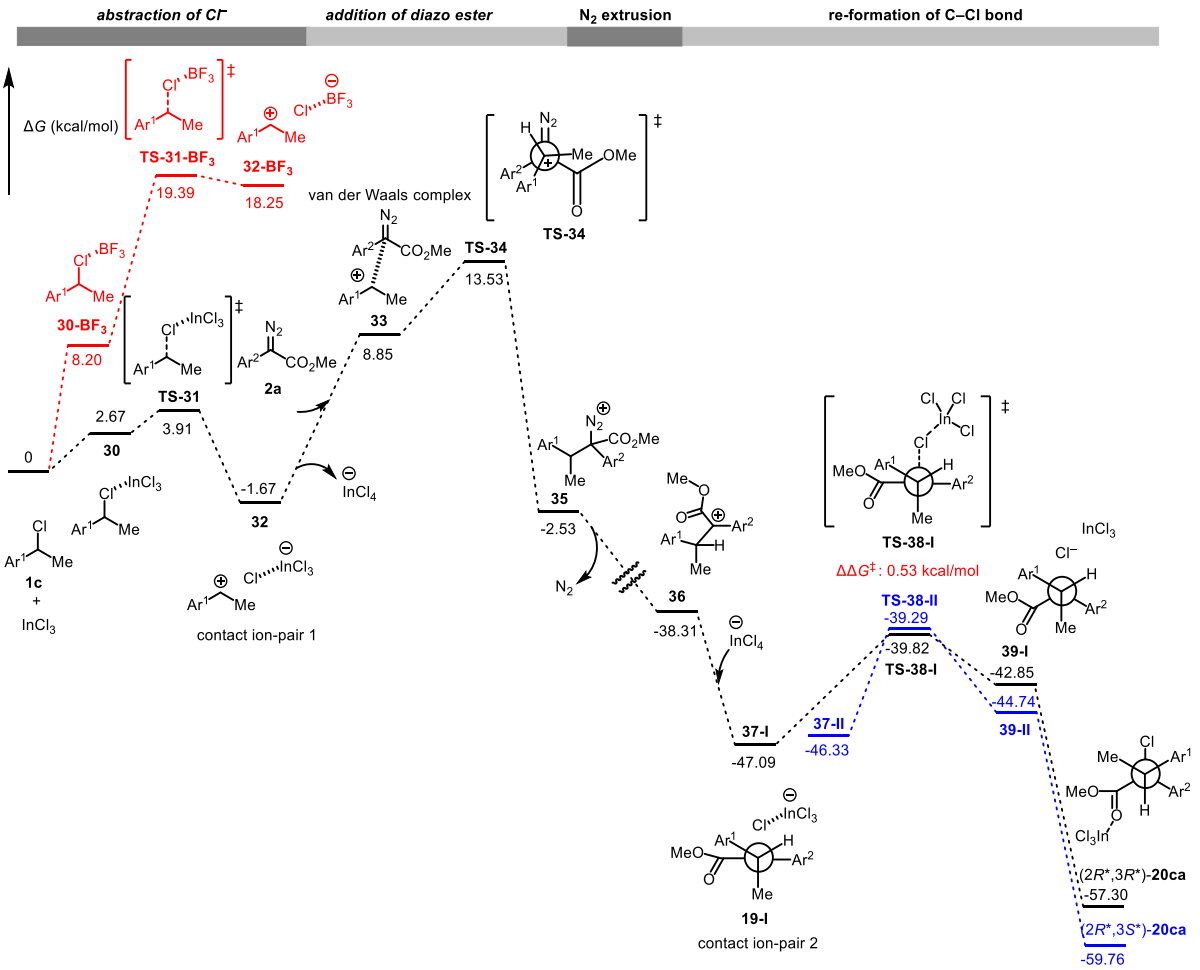


Scheme S5. Routes of generation of contact ion-pairs **12**.

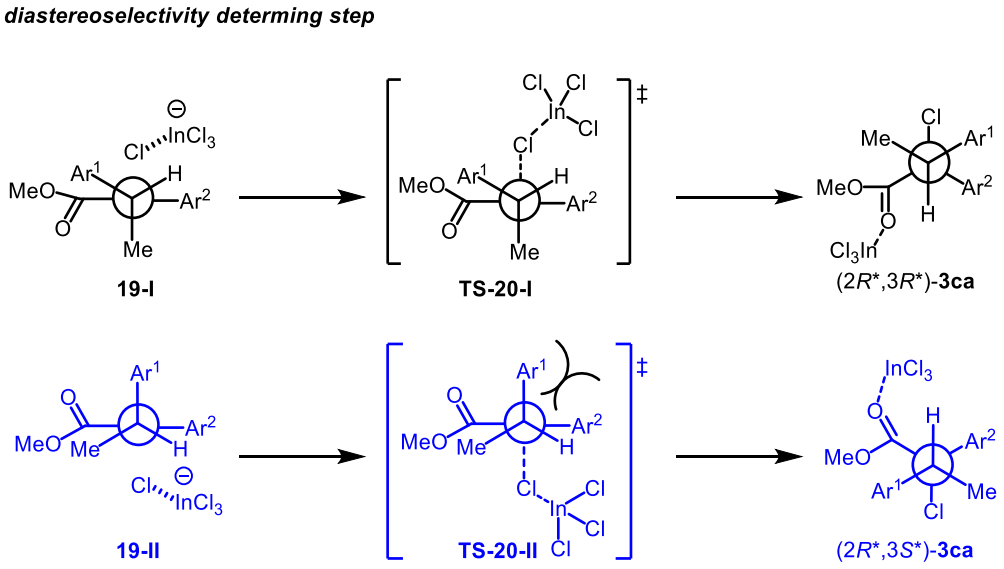
Consideration of transition states for the addition of diazoester to benzylic cation (Scheme S6)

Ar^1 and Ar^2 groups in TS **9** are stacked by face-to-face, and a π-π interaction between Ar^1 and Ar^2 would lead to the stability of TS **9**. In fact, we confirmed by DFT calculation that another transition state (TS **9** another) with an *anti*-configuration between Ar^1 and Ar^2 was unstable than TS **9** by 0.46 kcal/mol.

Scheme S6. Consideration of transition states for the addition of diazoester to benzylic cation.

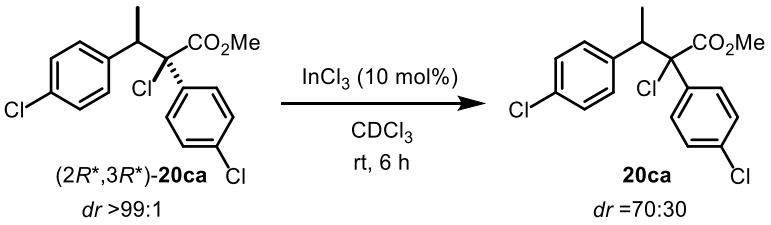


Scheme S7. Rationale based on DFT calculations (SMD($CHCl_3$)/ωB97X-D/6-311+G(d,p)[LANL2DZ for In]//SMD($CHCl_3$)/ωB97X-D/6-31+G(d)[LANL2DZ for In], ΔG in kcal/mol at 298.15 K). $Ar^1 = Ar^2$ = 4-ClC_6H_4.



Scheme S8. Explanation of the origin of the diastereoselectivity.

Isomerization Experiment



Scheme S9. Isomerization experiment.

Procedure: To a reaction vial was charged with diastereomer (2*R**,3*R**)-**20ca** (0.2 mmol, 71.5 mg), $InCl_3$ (0.02 mmol, 4.4 mg), and $CDCl_3$ (1 mL). The mixture was stirred at room temperature for 6 h. The solution was directly transferred to an NMR tube.

^1H NMR (400 MHz, $CDCl_3$)

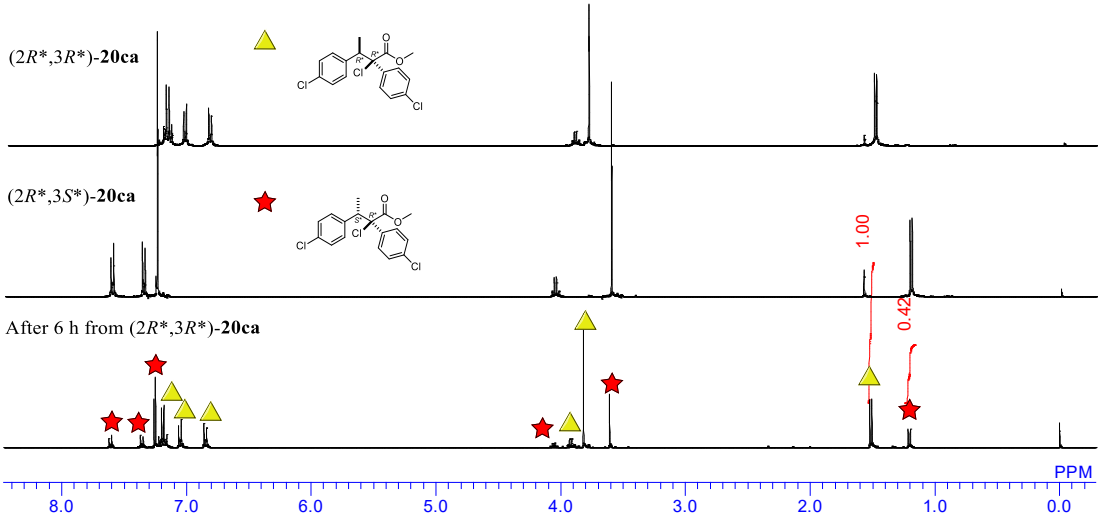
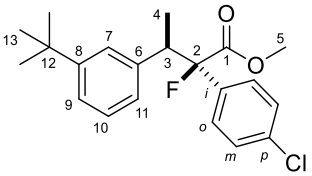


Figure S3. ^1H NMR chart for **20ca** in isomerization experiments.

(4aa) Methyl (2*R,3*R**)-3-(3-(*tert*-butyl)phenyl)-2-(4-chlorophenyl)-2-fluorobutanoate**

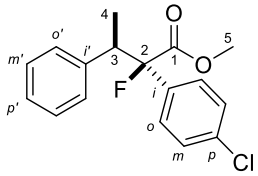


Following the general procedure using 1-(*tert*-butyl)-3-(1-fluoroethyl)benzene (0.200 mmol, 0.0361 g) and methyl 2-(4-chlorophenyl)-2-diazoacetate (0.300 mmol, 0.0632 g) with $BF_3{\cdot}OEt_2$ (0.020 mmol, 2.5 μL). The yield and diastereo ratio were determined by ^1H NMR and ^{19}F NMR in crude products (60%, 91:9). 1,1,2,2-Tetrachloroethane and hexafluorobenzene were used as internal standards. The crude product was purified by recycle HPLC to give the title compound as colorless oil (0.0341 g, 47%).

^1H NMR: (400 MHz, $CDCl_3$) 7.23 (d, J = 8.7 Hz, 2H, *o*-H), 7.14-7.08 (m, 4H, Ar-H), 6.96-6.94 (m, 1H, Ar-H), 6.80 (s, 1H, 7-H), 3.85 (s, 3H, 5-H_3), 3.69 (d, $^3J_{H\text{-}F}$ = 33.1 Hz, q, J = 7.3 Hz, 1H, 3-H), 1.48 (d, J = 7.3

Hz, 3H, 4-H_3), 1.12 (s, 9H, ^{t}Bu); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.7 (d, $J_{C\text{-}F}$ = 25.4 Hz, C-1), 150.3 (C-8), 138.4 (C-6), 135.8 (d, $J_{C\text{-}F}$ = 23.8 Hz, C-*i*), 134.0 (d, $J_{C\text{-}F}$ = 1.6 Hz, C-*p*), 128.0 (d, $J_{C\text{-}F}$ = 2.5 Hz), 127.5, 127.0 (d, $J_{C\text{-}F}$ = 1.6 Hz), 126.1 (d, $J_{C\text{-}F}$ = 10.7 Hz, C-*o*), 125.6 (d, $J_{C\text{-}F}$ = 2.5 Hz), 123.6, 99.2 (d, $J_{C\text{-}F}$ = 199.9 Hz, C-2), 53.0 (C-5), 48.2 (d, $J_{C\text{-}F}$ = 21.3 Hz, C-3), 34.3 (C-12), 31.1 (C-13), 15.9 (d, $J_{C\text{-}F}$ = 5.7 Hz, C-4); ^{19}F NMR: (376 MHz, $CDCl_3$) -182.15 (d, J = 33.6 Hz, 1F); IR: (neat) 1739 (C=O) cm^{-1}; HRMS: (ESI+) Calculated ($C_{21}H_{24}O_2FNaCl$) 385.1341 $(M+Na)^+$ Found: 385.1341

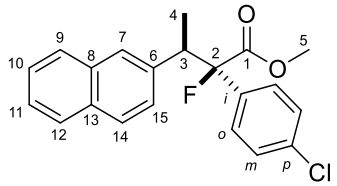
(4ba) Methyl (2*R,3*R**)-2-(4-chlorophenyl)-2-fluoro-3-phenylbutanoate**



Following the general procedure using (1-fluoroethyl)benzene (0.311 mmol, 0.0386 g) and methyl 2-(4-chlorophenyl)-2-diazoacetate (0.200 mmol, 0.0413 g) with $BF_3{\cdot}OEt_2$ (0.020 mmol, 2.5 μL). The yield and diastereo ratio were determined by ^{1}H NMR and ^{19}F NMR in crude products (72%, 88:12). 1,1,2,2-Tetrachloroethane and hexafluorobenzene were used as internal standards. The crude product was purified by recycle HPLC to give the title compound as colorless oil (0.0350 g, 57%).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.27 (d, J = 8.7 Hz, 2H, *o*-H), 7.12-7.05 (m, 7H, Ar-H), 3.83 (s, 3H, 5-H_3), 3.73 (d, $^3J_{H\text{-}F}$ = 32.8 Hz, q, J = 7.0 Hz, 1H, 3-H), 1.46 (d, J = 7.0 Hz, 3H, 4-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.7 (d, $J_{C\text{-}F}$ = 25.4 Hz, C-1), 139.3 (C-*i'*), 135.7 (d, $J_{C\text{-}F}$ = 22.9 Hz, C-*i*), 134.0 (d, $J_{C\text{-}F}$ = 1.6 Hz, C-*p*), 129.0 (d, $J_{C\text{-}F}$ = 2.5 Hz, C-*m'*), 128.1 (d, $J_{C\text{-}F}$ = 2.5 Hz, C-*m*), 127.9 (C-*o'*), 126.9 (C-*p'*), 126.2 (d, $J_{C\text{-}F}$ = 10.7 Hz, C-*o*), 99.2 (d, $J_{C\text{-}F}$ = 199.1 Hz, C-2), 53.0 (C-5), 47.7 (d, $J_{C\text{-}F}$ = 21.3 Hz, C-3), 16.5 (d, $J_{C\text{-}F}$ = 5.7 Hz, C-4); ^{19}F NMR: (376 MHz, $CDCl_3$) -181.54 (d, J = 30.5 Hz, 1F); IR: (neat) 1739 (C=O) cm^{-1}; HRMS: (ESI+) Calculated ($C_{17}H_{16}O_2FNaCl$) 329.0715 $(M+Na)^+$ Found: 329.0721

(4ca) Methyl (2*R,3*R**)-2-(4-chlorophenyl)-2-fluoro-3-(naphthalen-2-yl)butanoate**

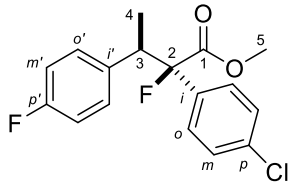


Following the general procedure using 2-(1-fluoroethyl)naphthalene (0.298 mmol, 0.0523 g) and methyl 2-(4-chlorophenyl)-2-diazoacetate (0.200 mmol, 0.0413 g) with $BF_3{\cdot}OEt_2$ (0.020 mmol, 2.5 μL). The yield and diastereo ratio were determined by ^{1}H NMR and ^{19}F NMR in crude products (69%, 88:12). 1,1,2,2-Tetrachloroethane and hexafluorobenzene were used as internal standards. The crude product was purified by recycle HPLC to give the title compound as colorless oil (0.0393 g, 55%).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.70-7.67 (m, 2H, Ar-H), 7.58 (d, J = 8.7 Hz, 2H, Ar-H), 7.51 (s, 1H, 7-H), 7.39-7.36 (m, 2H, Ar-H), 7.31 (d, J = 8.7 Hz, 2H, *o*-H), 7.18 (d, J = 8.7 Hz, 1H, 15-H), 7.10 (d, J = 8.7 Hz, 2H, *m*-H), 3.92 (d, $^3J_{H\text{-}F}$ = 32.5 Hz, q, J = 7.2 Hz, 1H, 3-H), 3.84 (s, 3H, 5-H_3), 1.54 (d, J = 7.2 Hz, 3H, 4-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.7 (d, $J_{C\text{-}F}$ = 24.9 Hz, C-1), 136.9, 135.6 (d, $J_{C\text{-}F}$ = 23.0 Hz, C-*i*), 134.0 (d, $J_{C\text{-}F}$ = 1.9 Hz), 133.0, 132.3, 128.2 (d, $J_{C\text{-}F}$ = 1.9 Hz, C-*m*), 128.0 (C-7), 127.7, 127.5, 127.4, 127.0 (d, $J_{C\text{-}$

$_F$ = 2.9 Hz, C-15), 126.2 (d, J_{C-F} = 10.5 Hz, C-*o*), 125.8, 125.6, 99.3 (d, J_{C-F} = 198.4 Hz, C-2), 53.1 (C-5), 47.6 (d, J_{C-F} = 21.1 Hz, C-3), 16.8 (d, J_{C-F} = 5.8 Hz, C-4); ^{19}F NMR: (376 MHz, $CDCl_3$) -180.92 (d, J = 33.6 Hz, 1F); IR: (neat) 1739 (C=O) cm^{-1}; HRMS: (ESI+) Calculated ($C_{21}H_{18}O_2FNaCl$) 379.0872 $(M+Na)^+$ Found: 379.0869

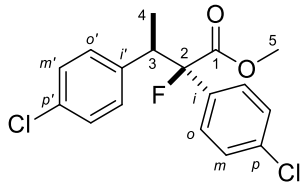
(4da) Methyl (2*R,3*R**)-2-(4-chlorophenyl)-2-fluoro-3-(4-fluorophenyl)butanoate**



Following the general procedure using 1-fluoro-4-(1-fluoroethyl)benzene (0.222 mmol, 0.0316 g) and methyl 2-(4-chlorophenyl)-2-diazoacetate (0.300 mmol, 0.0632 g) with $BF_3{\cdot}OEt_2$ (0.020 mmol, 2.5 μL). The yield and diastereo ratio were determined by ^{1}H NMR and ^{19}F NMR in crude products (76%, 94:6). 1,1,2,2-Tetrachloroethane and hexafluorobenzene were used as internal standards. The crude product was purified by recycle HPLC to give the title compound as colorless oil (0.0469 g, 65%).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.26 (d, J = 8.5 Hz, 2H, *m*-H), 7.17 (d, J = 8.5 Hz, 2H, *o*-H), 6.99-6.97 (m, 2H, Ar-H), 6.80-6.78 (m, 2H, Ar-H), 3.83 (d, J = 1.0 Hz, 3H, 5-H_3), 3.72 (d, $^3J_{H-F}$ = 32.7 Hz, q, J = 7.0 Hz, 1H, 3-H), 1.44 (d, J = 7.0 Hz, 3H, 4-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.5 (d, J_{C-F} = 25.4 Hz, C-1), 161.7 (d, J_{C-F} = 245.0 Hz, C-*p'*), 135.6 (d, J_{C-F} = 22.9 Hz, C-*i*), 135.0 (d, J_{C-F} = 3.3 Hz, C-*i'*), 134.2 (d, J_{C-F} = 1.6 Hz, C-*p*), 130.4 (dd, J_{C-F} = 8.2, 2.5 Hz, C-*o'*), 128.2 (d, J_{C-F} = 1.6 Hz, C-*m*), 126.1 (d, J_{C-F} = 9.8 Hz, C-*o*), 114.8 (d, J_{C-F} = 21.3 Hz, C-*m'*), 99.0 (d, J_{C-F} = 199.1 Hz, C-2), 53.1 (C-5), 47.0 (d, J_{C-F} = 20.5 Hz, C-3), 16.6 (d, J_{C-F} = 4.9 Hz, C-4); ^{19}F NMR: (376 MHz, $CDCl_3$) -118.85 – -118.90 (m, 1F), -182.18 (d, J = 33.6 Hz, 1F); IR: (neat) 1739 (C=O) cm^{-1}; HRMS: (ESI+) Calculated ($C_{17}H_{15}O_2F_2NaCl$) 347.0621 $(M+Na)^+$ Found: 347.0622

(4ea major isomer) Methyl (2*R,3*R**)-2,3-bis(4-chlorophenyl)-2-fluorobutanoate**

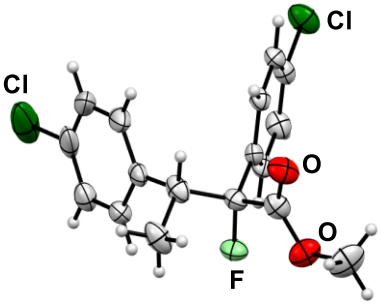


Following the general procedure using 1-chloro-4-(1-fluoroethyl)benzene (0.205 mmol, 0.0325 g) and methyl 2-(4-chlorophenyl)-2-diazoacetate (0.300 mmol, 0.0632 g) with $BF_3{\cdot}OEt_2$ (0.020 mmol, 2.5 μL). The yield and diastereo ratio were determined by ^{1}H NMR and ^{19}F NMR in crude products (92%, 93:7). 1,1,2,2-Tetrachloroethane and hexafluorobenzene were used as internal standards. The crude product was purified by recycle HPLC to give the title compound as white solid (0.0567 g, 81%). The structure of **4ea major isomer** was determined by X-ray diffraction analysis (CCDC: 2111191).

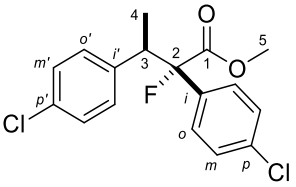
^{1}H NMR: (400 MHz, $CDCl_3$) 7.26 (d, J = 9.0 Hz, 2H, *m*-H), 7.18 (d, J = 9.0 Hz, 2H, *o*-H), 7.08 (d, J = 8.2 Hz, 2H, *m'*-H), 6.96 (d, J = 8.2 Hz, 2H, *o'*-H), 3.84 (s, 3H, 5-H_3), 3.71 (d, $^3J_{H-F}$ = 32.5 Hz, q, J = 7.2 Hz, 1H, 3-H), 1.44 (d, J = 7.2 Hz, 3H, 4-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.4 (d, J_{C-F} = 25.4 Hz, C-1), 137.8 (C-*i'*), 135.4 (d, J_{C-F} = 22.9 Hz, C-*i*), 134.3 (d, J_{C-F} = 1.6 Hz, C-*p*), 132.7 (C-*p'*), 130.3 (d, J_{C-F} = 1.6 Hz, C-*m'*),

128.3 (d, $J_{C\text{-}F}$ = 1.6 Hz, C-*m*), 128.1 (C- *o'*), 126.1 (d, $J_{C\text{-}F}$ = 10.7 Hz, C-*o*), 98.9 (d, $J_{C\text{-}F}$ = 199.1 Hz, C-2), 53.2 (C-5), 47.1 (d, $J_{C\text{-}F}$ = 21.3 Hz, C-3), 16.5 (d, $J_{C\text{-}F}$ = 4.9 Hz, C-4); ^{19}F NMR: (376 MHz, $CDCl_3$) -179.09 (d, *J* = 30.5 Hz, 1F); IR: (KBr) 1732 (C=O) cm^{-1}; m.p. 48–49 °C; HRMS: (ESI+) Calculated ($C_{17}H_{15}O_2FNaCl_2$) 363.0325 $(M+Na)^+$ Found: 363.0326

X-ray structure (CCDC: 2111191)



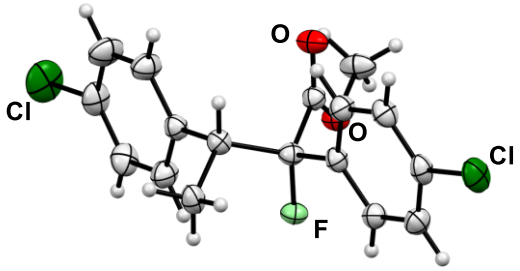
(4ea minor isomer) Methyl (2*R,3*S**)-2,3-bis(4-chlorophenyl)-2-fluorobutanoate**



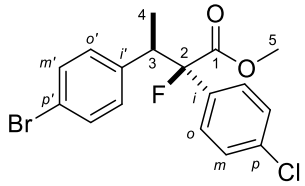
This minor isomer was isolated from the gram-scale crude with recycle HPLC as white solid (0.119 g, 5%). Recrystallization in ethyl acetate to give colorless crystal. The structure of **4ea minor isomer** was determined by X-ray diffraction analysis (CCDC: 2111192).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.59 (d, *J* = 7.7 Hz, 2H, Ar-H), 7.41 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.33-7.28 (m, 4H, Ar-H), 3.67 (d, $^3J_{H\text{-}F}$ = 32.6 Hz, q, *J* = 7.3 Hz, 1H, 3-H), 3.50 (s, 3H, 5-H_3), 1.11 (d, *J* = 7.3 Hz, 3H, 4-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 169.8 (d, $J_{C\text{-}F}$ = 26.7 Hz, C-1), 138.7 (C-*i'*), 135.4 (d, $J_{C\text{-}F}$ = 22.9 Hz, C-*i*), 134.7, 133.2, 130.2 (d, $J_{C\text{-}F}$ = 1.6 Hz), 128.7 (d, $J_{C\text{-}F}$ = 1.6 Hz), 128.5, 126.4 (d, $J_{C\text{-}F}$ = 10.5 Hz, C-*o*), 98.8 (d, $J_{C\text{-}F}$ = 199.3 Hz, C-2), 53.7 (C-5), 47.8 (d, $J_{C\text{-}F}$ = 20.0 Hz, C-3), 14.9 (d, $J_{C\text{-}F}$ = 4.8 Hz, C-4); ^{19}F NMR: (376 MHz, $CDCl_3$) -179.25 (d, *J* = 33.6 Hz, 1F); IR: (KBr) 1749 (C=O) cm^{-1}; m.p. 130–131 °C; HRMS: (ESI+) Calculated ($C_{17}H_{15}O_2FNaCl_2$) 363.0325 $(M+Na)^+$ Found: 363.0331

X-ray structure (CCDC: 2111192)



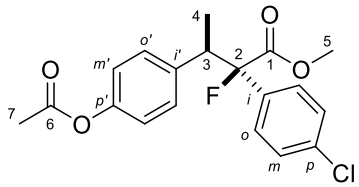
(4fa) Methyl (2*R,3*R**)-3-(4-bromophenyl)-2-(4-chlorophenyl)-2-fluorobutanoate**



Following the general procedure using 1-bromo-4-(1-fluoroethyl)benzene (0.201 mmol, 0.0408 g) and methyl 2-(4-chlorophenyl)-2-diazoacetate (0.300 mmol, 0.0632 g) with $BF_3 \cdot OEt_2$ (0.020 mmol, 2.5 μL). The yield and diastereo ratio were determined by ^{1}H NMR and ^{19}F NMR in crude products (89%, 91:9). 1,1,2,2-Tetrachloroethane and hexafluorobenzene were used as internal standards. The crude product was purified by recycle HPLC to give the title compound as colorless oil (0.0589 g, 76%).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.26-7.24 (m, 4H, Ar-H), 7.18 (d, J = 8.7 Hz, 2H, *m*-H), 6.90 (d, J = 7.2 Hz, 2H, *o'*-H), 3.83 (s, 3H, 5-H_3), 3.70 (d, $^3J_{H\text{-}F}$ = 32.5 Hz, q, J = 7.2 Hz, 1H, 3-H), 1.44 (d, J = 7.2 Hz, 3H, 4-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.4 (d, $J_{C\text{-}F}$ = 25.4 Hz, C-1), 138.4 (C-*i'*), 135.4 (d, $J_{C\text{-}F}$ = 22.9 Hz, C-*i*), 134.3 (C-*p*), 131.1 (C-*o'*), 130.7 (d, $J_{C\text{-}F}$ = 2.5 Hz, C-*m'*), 128.3 (d, $J_{C\text{-}F}$ = 2.5 Hz, C-*m*), 126.1 (d, $J_{C\text{-}F}$ = 10.7 Hz, C-*o*), 120.9 (C-*p'*), 98.9 (d, $J_{C\text{-}F}$ = 199.9 Hz, C-2), 53.1 (C-5), 47.2 (d, $J_{C\text{-}F}$ = 20.5 Hz, C-3), 16.5 (d, $J_{C\text{-}F}$ = 5.7 Hz, C-4); ^{19}F NMR: (376 MHz, $CDCl_3$) -182.11 (d, J = 30.5 Hz, 1F); IR: (neat) 1739 (C=O) cm^{-1}; HRMS: (ESI+) Calculated ($C_{17}H_{15}O_2FNaClBr$) 406.9820 $(M+Na)^+$ Found: 406.9817

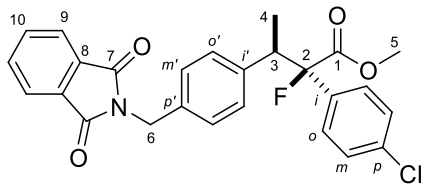
(4ga) Methyl (2*R,3*R**)-3-(4-acetoxyphenyl)-2-(4-chlorophenyl)-2-fluorobutanoate**



Following the general procedure using 4-(1-fluoroethyl)phenyl acetate (0.193 mmol, 0.0351 g) and methyl 2-(4-chlorophenyl)-2-diazoacetate (0.300 mmol, 0.0633 g) with $BF_3 \cdot OEt_2$ (0.020 mmol, 2.5 μL). The yield and diastereo ratio were determined by ^{1}H NMR and ^{19}F NMR in crude products (87%, 91:9). 1,1,2,2-Tetrachloroethane and hexafluorobenzene were used as internal standards. The crude product was purified by recycle HPLC to give the title compound as colorless oil (0.0506 g, 72%).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.26 (d, J = 9.0 Hz, 2H, *o*-H), 7.17 (d, J = 9.0 Hz, 2H, *m*-H), 7.02 (d, J = 8.7 Hz, 2H, *o'*-H), 6.84 (d, J = 8.7 Hz, 2H, *m'*-H), 3.83 (s, 3H, 5-H_3), 3.73 (d, $^3J_{H\text{-}F}$ = 32.5 Hz, q, J = 7.0 Hz, 1H, 3-H), 2.23 (s, 3H, 7-H_3), 1.45 (d, J = 7.0 Hz, 3H, 4-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.5 (d, $J_{C\text{-}F}$ = 24.9 Hz, C-1), 169.2 (C-6), 149.4 (C-*p'*), 136.7 (C-*i'*), 135.5 (d, $J_{C\text{-}F}$ = 24.0 Hz, C-*i*), 134.1 (C-*p*), 129.9 (d, $J_{C\text{-}F}$ = 1.9 Hz, C-*o'*), 128.2 (d, $J_{C\text{-}F}$ = 1.9 Hz, C-*m*), 126.1 (d, $J_{C\text{-}F}$ = 10.5 Hz, C-*o*), 120.9 (C-*p'*), 99.0 (d, $J_{C\text{-}F}$ = 198.4 Hz, C-2), 53.1 (d, $J_{C\text{-}F}$ = 6.7 Hz, C-5), 47.1 (d, $J_{C\text{-}F}$ = 21.1 Hz, C-3), 21.0 (C-7), 16.4 (d, $J_{C\text{-}F}$ = 4.8 Hz, C-4); ^{19}F NMR: (376 MHz, $CDCl_3$) -181.85 (d, J = 33.6 Hz, 1F); IR: (neat) 1759 (C=O) cm^{-1}; HRMS: (ESI+) Calculated ($C_{19}H_{18}O_4FNaCl$) 387.0770 $(M+Na)^+$ Found: 387.0770

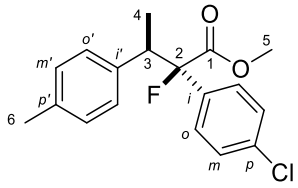
(4ha) Methyl (2*R,3*R**)-2-(4-chlorophenyl)-3-(4-((1,3-dioxoisoindolin-2-yl)methyl)phenyl)-2-fluorobutanoate**



Following the general procedure using 2-(4-(1-fluoroethyl)benzyl)isoindoline-1,3-dione (0.201 mmol, 0.0570 g) and methyl 2-(4-chlorophenyl)-2-diazoacetate (0.300 mmol, 0.0632 g) with $BF_3{\cdot}OEt_2$ (0.020 mmol, 2.5 μL). The yield and diastereo ratio were determined by ^{1}H NMR and ^{19}F NMR in crude products (60%, 86:14). 1,1,2,2-Tetrachloroethane and hexafluorobenzene were used as internal standards. The crude product was purified by recycle HPLC to give the title compound as white solid (0.0466 g, 50%).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.82-7.81 (m, 2H, 9-H), 7.68-7.67 (m, 2H, 10-H), 7.25 (d, J = 8.5 Hz, 2H, *o*-H), 7.17 (d, J = 7.6 Hz, 2H, *m'*-H), 7.13 (d, J = 8.5 Hz, 2H, *m*-H), 6.98 (d, J = 7.6 Hz, 2H, *o'*-H), 4.72 (s, 1H, 6-H^a), 4.71 (s, 1H, 6-H^b), 3.82 (s, 3H, 5-H_3), 3.70 (d, $^3J_{H\text{-}F}$ = 32.6 Hz, q, J = 7.0 Hz, 1H, 3-H), 1.41 (d, J = 7.0 Hz, 3H, 4-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.6 (d, $J_{C\text{-}F}$ = 25.9 Hz, C-1), 167.9 (C-7), 138.9 (C-*i'*), 135.5 (d, $J_{C\text{-}F}$ = 23.0 Hz, C-*i*), 134.9 (C-*p'*), 134.0 (C-*p*), 133.9 (C-10), 132.0 (C-8), 129.3 (d, $J_{C\text{-}F}$ = 1.9 Hz, C-*o'*), 128.2 (d, $J_{C\text{-}F}$ = 2.5 Hz, C-*m*), 128.2 (C-*m'*), 126.2 (d, $J_{C\text{-}F}$ = 10.5 Hz, C-*o*), 123.3 (C-9), 99.0 (d, $J_{C\text{-}F}$ = 199.4 Hz, C-2), 53.1 (C-5), 47.2 (d, $J_{C\text{-}F}$ = 21.1 Hz, C-3), 41.1 (C-6), 16.6 (d, $J_{C\text{-}F}$ = 4.8 Hz, C-4); ^{19}F NMR: (376 MHz, $CDCl_3$) -181.27 (d, J = 33.6 Hz, 1F); IR: (KBr) 1754 (C=O), 1715 (C=O) cm^{-1}; m.p.: 96–98 °C; HRMS: (ESI+) Calculated ($C_{26}H_{21}NO_4FNaCl$) 488.1035 $(M+Na)^+$ Found: 488.1031

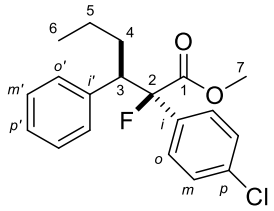
(4ia) Methyl (2*R,3*R**)-2-(4-chlorophenyl)-2-fluoro-3-(*p*-tolyl)butanoate**



Following the general procedure using 1-(1-fluoroethyl)-4-methylbenzene **1i** (1.023 mmol, 0.141 g) and methyl 2-(4-chlorophenyl)-2-diazoacetate **2a** (1.500 mmol, 0.316 g) with $BF_3{\cdot}OEt_2$ (0.050 mmol, 12.5 μL). The yield and diastereo ratio were determined by ^{1}H NMR and ^{19}F NMR in crude products (51%, 89:11). 1,1,2,2-Tetrachloroethane and hexafluorobenzene were used as internal standards. The crude product was purified by recycle HPLC to give the title compound as colorless oil (0.137 g, 42%).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.28 (d, J = 8.9 Hz, 2H, *o*-H), 7.15 (d, J = 8.9 Hz, 2H, *m*-H), 6.91 (s, 4H, Ar-H), 3.82 (s, 3H, 5-H_3), 3.70 (d, $^4J_{H\text{-}F}$ = 32.7 Hz, q, J = 7.0 Hz, 1H, 3-H), 2.20 (s, 3H, 6-H_3), 1.44 (d, J = 7.0 Hz, 3H, 4-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.7 (d, $J_{C\text{-}F}$ = 25.7 Hz, C-1), 138.3, 136.1, 135.8 (d, $J_{C\text{-}F}$ = 22.9 Hz, C-*i*), 133.9 (C-*p*), 128.8 (d, $J_{C\text{-}F}$ = 1.9 Hz), 128.6, 128.1 (d, $J_{C\text{-}F}$ = 1.9 Hz, C-*m*), 126.2 (d, $J_{C\text{-}F}$ = 9.5 Hz, C-*o*), 99.2 (d, $J_{C\text{-}F}$ = 198.4 Hz, C-2), 53.0 (C-5), 47.1 (d, $J_{C\text{-}F}$ = 21.0 Hz, C-3), 20.9 (C-6), 16.6 (d, $J_{C\text{-}F}$ = 5.7 Hz, C-4); ^{19}F NMR: (372 MHz, $CDCl_3$) -178.49 (d, J = 33.6 Hz, 1F); IR: (neat) 1739 (C=O) cm^{-1}; HRMS: (ESI+) Calculated ($C_{18}H_{18}O_2FNaCl$) 343.0872 $(M+Na)^+$ Found: 343.0875

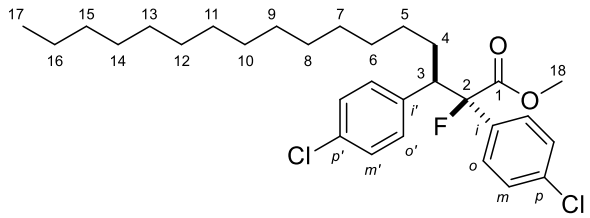
(4ka) Methyl (2*R,3*R**)-2-(4-chlorophenyl)-2-fluoro-3-phenylhexanoate**



Following the general procedure using (1-fluorobutyl)benzene (0.199 mmol, 0.0720 g) and methyl 2-(4-chlorophenyl)-2-diazoacetate (0.300 mmol, 0.0632 g) with $BF_3{\cdot}OEt_2$ (0.020 mmol, 2.5 μL) at -30 °C for 4 h. The yield and diastereo ratio were determined by ^{1}H NMR and ^{19}F NMR in crude products (73%, 89:11). 1,1,2,2-Tetrachloroethane and hexafluorobenzene were used as internal standards. The crude product was purified by recycle HPLC to give the title compound as colorless oil (0.0386 g, 58%).

^{1}H NMR: (400 MHz, $CDCl_3$); 7.25 (d, J = 9.2 Hz, 2H, *o*-H), 7.10-7.05 (m, 7H, Ar-H), 3.84 (s, 3H, 7-H_3), 3.55 (d, $^3J_{H\text{-}F}$ = 33.8 Hz, dd, J = 11.8, 3.1 Hz, 1H, 3-H), 2.10-2.00 (m, 1H, 4-H^a), 1.63-1.60 (m, 1H, 4-H^b), 1.15-1.11 (sextet, J = 7.5 Hz, 2H, 5-H_2), 0.85 (t, J = 7.5 Hz, 3H, 6-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.9 (d, $J_{C\text{-}F}$ = 25.9 Hz, C-1), 137.4 (C-*i'*), 135.7 (d, $J_{C\text{-}F}$ = 24.0 Hz, C-*i*), 133.9 (C-*p*), 129.6 (d, $J_{C\text{-}F}$ = 1.9 Hz), 128.1 (d, $J_{C\text{-}F}$ = 1.9 Hz), 127.9, 126.8 (C-*p'*), 126.2 (d, $J_{C\text{-}F}$ = 10.5 Hz, C-*o*), 99.6 (d, $J_{C\text{-}F}$ = 197.4 Hz, C-2), 53.2 (d, $J_{C\text{-}F}$ = 20.1 Hz, C-3), 53.1 (C-7), 32.8 (d, $J_{C\text{-}F}$ = 3.8 Hz, C-4), 20.6 (C-5), 13.8 (C-6); ^{19}F NMR: (376 MHz, $CDCl_3$) -180.05 (d, J = 33.6 Hz, 1F); IR: (neat) 1737 (C=O) cm^{-1}; HRMS: (ESI+) Calculated ($C_{19}H_{20}O_2FNaCl$) 357.1028 $(M+Na)^+$ Found: 357.1027

(4la) Methyl (2*R,3*R**)-2,3-bis(4-chlorophenyl)-2-fluoroheptadecanoate**

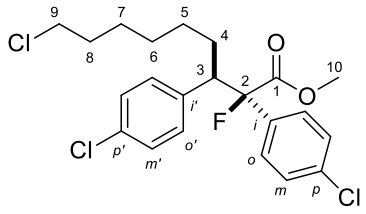


Following the general procedure using 1-chloro-4-(1-fluoropentadecyl)benzene (0.191 mmol, 0.0653 g) and methyl 2-(4-chlorophenyl)-2-diazoacetate (0.300 mmol, 0.0633 g) with $BF_3{\cdot}OEt_2$ (0.020 mmol, 2.5 μL). The yield and diastereo ratio were determined by ^{1}H NMR and ^{19}F NMR in crude products (81%, 95:5). 1,1,2,2-Tetrachloroethane and hexafluorobenzene were used as internal standards. The crude product was purified by recycle HPLC to give the title compound as colorless oil (0.0750 g, 75%).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.24 (d, J = 8.5 Hz, 2H, *o*-H), 7.15 (d, J = 8.5 Hz, 2H, *m*-H), 7.07 (d, J = 8.0 Hz, 2H, *m'*-H), 6.95 (d, J = 8.0 Hz, 2H, *o'*-H), 3.83 (s, 3H, 18-H_3), 3.51 (d, $^3J_{H\text{-}F}$ = 33.3 Hz, dd, J = 11.6, 2.9 Hz, 1H, 3-H), 2.04-1.94 (m, 1H, 4-H^a), 1.68-1.60 (m, 1H, 4-H^b), 1.25-1.07 (m, 24H), 0.88 (t, J = 6.8 Hz, 3H, 17-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.6 (d, $J_{C\text{-}F}$ = 25.4 Hz, C-1), 136.1 (C-*i'*), 135.5 (d, $J_{C\text{-}F}$ = 22.9 Hz, C-*i*), 134.1 (C-*p*), 132.7 (C-*p'*), 130.9 (d, $J_{C\text{-}F}$ = 2.5 Hz, C-*m'*), 128.3 (d, $J_{C\text{-}F}$ = 2.5 Hz, C-*m*), 128.1 (C-*o'*), 126.1 (d, $J_{C\text{-}F}$ = 9.8 Hz, C-*o*), 99.4 (d, $J_{C\text{-}F}$ = 199.1 Hz, C-2), 53.1 (C-18), 52.9 (d, $J_{C\text{-}F}$ = 20.5 Hz, C-3), 31.9, 30.6 (d, $J_{C\text{-}F}$ = 4.1 Hz, C-4), 29.67, 29.65, 29.62, 29.57, 29.5, 29.34, 29.28, 29.2, 27.4, 22.7, 14.1; ^{19}F NMR: (376 MHz, $CDCl_3$) -180.65 (d, J = 33.6 Hz, 1F); IR: (neat) 1740 (C=O) cm^{-1}; HRMS: (ESI+) Calculated

($C_{30}H_{41}O_2FNaCl_2$) 545.2360 $(M+Na)^+$ Found: 545.2348

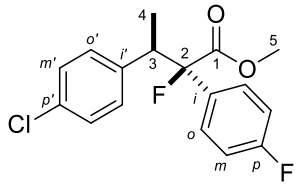
(4ma) Methyl (2*R,3*R**)-9-chloro-2,3-bis(4-chlorophenyl)-2-fluorononanoate**



Following the general procedure using 1-chloro-4-(7-chloro-1-fluoroheptyl)benzene (0.201 mmol, 0.0530 g) and methyl 2-(4-chlorophenyl)-2-diazoacetate (0.304 mmol, 0.0640 g) with $BF_3{\cdot}OEt_2$ (0.020 mmol, 2.5 μL). The yield and diastereo ratio were determined by ^{1}H NMR and ^{19}F NMR in crude products (74%, 93:7). 1,1,2,2-Tetrachloroethane and hexafluorobenzene were used as internal standards. The crude product was purified by recycle HPLC to give the title compound as colorless oil (0.0600 g, 67%).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.23 (d, J = 8.7 Hz, 2H, *o*-H), 7.15 (d, J = 8.7 Hz, 2H, *m*-H), 7.08 (d, J = 8.5 Hz, 2H, *m'*-H), 6.95 (d, J = 8.5 Hz, 2H, *o'*-H), 3.84 (s, 3H, 10-H_3), 3.54-3.49 (m, 3H, 3-H and 9-H_2), 2.05-1.95 (m, 1H, 4-H^a), 1.73-1.61 (m, 3H, 4-H^b and 8-H_2), 1.32-1.10 (m, 6H); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.6 (d, $J_{C\text{-}F}$ = 24.6 Hz, C-1), 135.9 (C-*i'*), 135.4 (d, $J_{C\text{-}F}$ = 23.8 Hz, C-*i*), 134.2 (C-*p*), 132.8 (C-*p'*), 130.8 (d, $J_{C\text{-}F}$ = 2.5 Hz, C-*m'*), 128.3 (d, $J_{C\text{-}F}$ = 1.6 Hz, C-*m*), 128.2 (C-*o'*), 126.0 (d, $J_{C\text{-}F}$ = 10.7 Hz, C-*o*), 99.3 (d, $J_{C\text{-}F}$ = 199.1 Hz, C-2), 53.2 (C-10), 52.9 (d, $J_{C\text{-}F}$ = 20.5 Hz, C-3), 45.0 (C-9), 32.4 (C-8), 30.4 (d, $J_{C\text{-}F}$ = 4.1 Hz, C-4), 28.5 (C-5), 27.2 (C-7), 26.5 (C-6); ^{19}F NMR: (376 MHz, $CDCl_3$) -180.74 (d, J = 30.5 Hz, 1F); IR: (neat) 1740 (C=O) cm^{-1}; HRMS: (ESI+) Calculated ($C_{22}H_{24}O_2FNaCl_3$) 467.0718 $(M+Na)^+$ Found: 467.0716

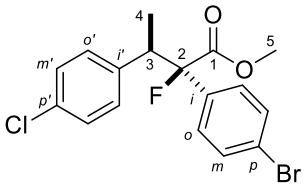
(4eb) Methyl (2*R,3*R**)-3-(4-chlorophenyl)-2-fluoro-2-(4-fluorophenyl)butanoate**



Following the general procedure using 1-chloro-4-(1-fluoroethyl)benzene (0.213 mmol, 0.0337 g) and methyl 2-diazo-2-(4-fluorophenyl)acetate (0.302 mmol, 0.0586 g) with $BF_3{\cdot}OEt_2$ (0.020 mmol, 2.5 μL). The yield and diastereo ratio were determined by ^{1}H NMR and ^{19}F NMR in crude products (84%, 96:4). 1,1,2,2-Tetrachloroethane and hexafluorobenzene were used as internal standards. The crude product was purified by recycle HPLC to give the title compound as colorless oil (0.0533 g, 81%).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.31-7.26 (m, 2H, *o*-H), 7.07 (d, J = 8.7 Hz, 2H, *m'*-H), 6.95 (d, J = 7.7 Hz, 2H, *o'*-H), 6.89 (d, J = 8.5 Hz, d, $^3J_{H\text{-}F}$ = 8.5 Hz, 2H, *m*-H), 3.84 (s, 3H, 5-H_3), 3.71 (d, $^3J_{H\text{-}F}$ = 32.0 Hz, q, J = 7.1 Hz, 1H, 3-H), 1.44 (d, J = 7.1 Hz, 3H, 4-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.6 (d, $J_{C\text{-}F}$ = 25.4 Hz, C-1), 162.4 (d, $J_{C\text{-}F}$ = 248.2 Hz, C-*p*), 137.9 (C-*i'*), 132.71 (dd, $J_{C\text{-}F}$ = 23.8, 3.3 Hz, C-*i*), 132.67 (C-*p'*), 130.3 (d, $J_{C\text{-}F}$ = 2.5 Hz, C-*m'*), 128.1 (C- *o'*), 126.5 (dd, $J_{C\text{-}F}$ = 10.2, 8.6 Hz, C-*o*), 115.1 (dd, $J_{C\text{-}F}$ = 22.1, 1.6 Hz, C-*m*), 99.0 (d, $J_{C\text{-}F}$ = 198.3 Hz, C-2), 53.1 (C-5), 47.3 (d, $J_{C\text{-}F}$ = 20.5 Hz, C-3), 16.4 (d, $J_{C\text{-}F}$ = 5.7 Hz, C-4); ^{19}F NMR: (376 MHz, $CDCl_3$) -117.04 – -117.11 (m, 1F), -181.66 (d, J = 30.5 Hz, 1F); IR: (neat) 1740 (C=O) cm^{-1}; HRMS: (ESI+) Calculated ($C_{17}H_{15}O_2F_2NaCl$) 347.0621 $(M+Na)^+$ Found: 347.0623

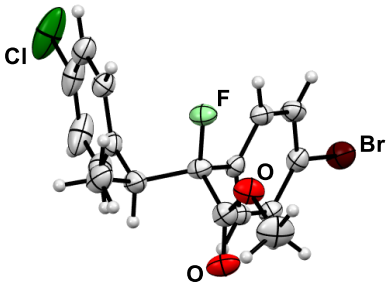
(4ec) Methyl (2*R,3*R**)-2-(4-bromophenyl)-3-(4-chlorophenyl)-2-fluorobutanoate**



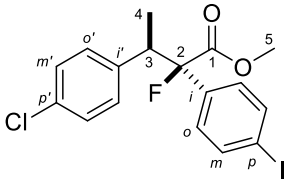
Following the general procedure using 1-chloro-4-(1-fluoroethyl)benzene (0.237 mmol, 0.0377 g) and methyl 2-(4-bromophenyl)-2-diazoacetate (0.314 mmol, 0.0801 g) with $BF_3{\cdot}OEt_2$ (0.020 mmol, 2.5 μL). The yield and diastereo ratio were determined by ^{1}H NMR and ^{19}F NMR in crude products (93%, 92:8). 1,1,2,2-Tetrachloroethane and hexafluorobenzene were used as internal standards. The crude product was purified by recycle HPLC to give the title compound as a white solid (0.0751 g, 82%). The structure of **4ec** was determined by X-ray diffraction analysis (CCDC: 2111200).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.33 (d, J = 9.2 Hz, 2H, *m*-H), 7.20 (d, J = 9.2 Hz, 2H, *o*-H), 7.08 (d, J = 8.5 Hz, 2H, *m'*-H), 6.96 (d, J = 8.5 Hz, 2H, *o'*-H), 3.83 (s, 3H, 5-H_3), 3.71 (d, $^3J_{H\text{-}F}$ = 32.5 Hz, q, J = 7.5 Hz, 1H, 3-H), 1.44 (d, J = 7.5 Hz, 3H, 4-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.3 (d, $J_{C\text{-}F}$ = 25.4 Hz, C-1), 137.8 (C-*i'*), 136.0 (d, $J_{C\text{-}F}$ = 23.8 Hz, C-*i*), 132.7 (C-*p'*), 131.3 (d, $J_{C\text{-}F}$ = 1.6 Hz), 130.3 (d, $J_{C\text{-}F}$ = 1.6 Hz), 128.1, 126.4 (d, $J_{C\text{-}F}$ = 10.7 Hz, C-*o*), 122.5 (C-*p*), 98.9 (d, $J_{C\text{-}F}$ = 199.1 Hz, C-2), 53.1 (C-5), 47.0 (d, $J_{C\text{-}F}$ = 21.3 Hz, C-3), 16.5 (d, $J_{C\text{-}F}$ = 4.9 Hz, C-4); ^{19}F NMR: (376 MHz, $CDCl_3$) -185.36 (d, J = 30.5 Hz, 1F); IR: (KBr) 1732 (C=O) cm^{-1}; m.p. 68–69 °C; HRMS: (ESI+) Calculated ($C_{17}H_{15}O_2FNaClBr$) 406.9820 $(M+Na)^+$ Found: 406.9822

X-ray structure (CCDC: 2111200)



(4ed) Methyl (2*R,3*R**)-3-(4-chlorophenyl)-2-fluoro-2-(4-iodophenyl)butanoate**

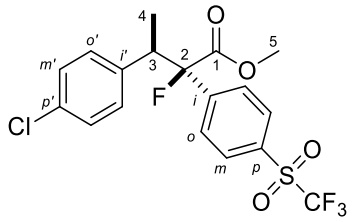


Following the general procedure using 1-chloro-4-(1-fluoroethyl)benzene (0.201 mmol, 0.0318 g) and methyl 2-diazo-2-(4-iodophenyl)acetate (0.300 mmol, 0.0907 g) with $BF_3{\cdot}OEt_2$ (0.020 mmol, 2.5 μL). The yield and diastereo ratio were determined by ^{1}H NMR and ^{19}F NMR in crude products (61%, 91:9). 1,1,2,2-Tetrachloroethane and hexafluorobenzene were used as internal standards. The crude product was purified by recycle HPLC to give the title compound as colorless oil (0.0461 g, 53%).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.54 (d, J = 8.5 Hz, 2H, *m*-H), 7.10-7.06 (m, 4H, Ar-H), 6.96 (d, J = 8.2 Hz,

2H, *o'*-H), 3.83 (s, 3H, 5-H_3), 3.71 (d, $^3J_{H\text{-}F}$ = 32.5 Hz, q, *J* = 7.0 Hz, 1H, 3-H), 1.43 (d, *J* = 7.0 Hz, 3H, 4-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.3 (d, $J_{C\text{-}F}$ = 25.4 Hz, C-1), 137.8 (C-*i'*), 137.2 (d, $J_{C\text{-}F}$ = 1.6 Hz, C-*m*), 136.6 (d, $J_{C\text{-}F}$ = 22.9 Hz, C-*i*), 132.7 (C-*p'*), 130.3 (d, $J_{C\text{-}F}$ = 1.6 Hz, C-*m'*), 128.1 (C-*o'*), 126.5 (d, $J_{C\text{-}F}$ = 10.7 Hz, C-*o*), 99.0 (d, $J_{C\text{-}F}$ = 199.1 Hz, C-2), 94.3 (C-*p*), 53.2 (C-5), 46.9 (d, $J_{C\text{-}F}$ = 20.5 Hz, C-3), 16.5 (d, $J_{C\text{-}F}$ = 5.7 Hz, C-4); ^{19}F NMR: (376 MHz, $CDCl_3$) -182.45 (d, *J* = 33.6 Hz, 1F); IR: (neat) 1739 (C=O) cm^{-1}; HRMS: (ESI+) Calculated ($C_{17}H_{15}O_2FNaClI$) 454.9682 $(M+Na)^+$ Found: 454.9678

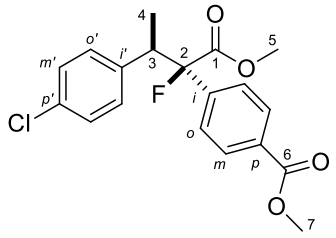
(4ee) Methyl (2*R,3*R**)-3-(4-chlorophenyl)-2-fluoro-2-(4-((trifluoromethyl)sulfonyl)phenyl)butanoate**



Following the general procedure using 1-chloro-4-(1-fluoroethyl)benzene (0.218 mmol, 0.0346 g) and methyl 2-diazo-2-(4-(((trifluoromethyl)sulfonyl)oxy)phenyl)acetate (0.302 mmol, 0.0980 g) with $BF_3{\cdot}OEt_2$ (0.020 mmol, 2.5 μL). The yield and diastereo ratio were determined by ^{1}H NMR and ^{19}F NMR in crude products (71%, 91:9). 1,1,2,2-Tetrachloroethane and hexafluorobenzene were used as internal standards. The crude product was purified by recycle HPLC to give the title compound as colorless oil (0.0526 g, 55%).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.41 (d, *J* = 9.0 Hz, 2H, *o*-H), 7.12 (d, *J* = 9.0 Hz, 2H, *m*-H), 7.07 (d, *J* = 8.2 Hz, 2H, *m'*-H), 6.91 (d, *J* = 8.2 Hz, 2H, *o'*-H), 3.87 (s, 3H, 5-H_3), 3.69 (d, $^3J_{H\text{-}F}$ = 32.2 Hz, q, *J* = 7.0 Hz, 1H, 3-H), 1.46 (d, *J* = 7.3 Hz, 3H, 4-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.1 (d, $J_{C\text{-}F}$ = 24.9 Hz, C-1), 149.1 (C-*p*), 137.4 (d, $J_{C\text{-}F}$ = 22.0 Hz, C-*i*), 137.3 (C-*i'*), 132.9 (C-*p'*), 130.2 (d, $J_{C\text{-}F}$ = 1.9 Hz, C-*o'*), 128.1 (C-*m'*), 126.7 (d, $J_{C\text{-}F}$ = 10.5 Hz, C-*o*), 121.0 (C-*m*), 118.6 (q, $J_{C\text{-}F}$ = 320.6 Hz, CF_3), 98.7 (d, $J_{C\text{-}F}$ = 200.3 Hz, C-2), 53.3 (C-5), 47.6 (d, $J_{C\text{-}F}$ = 21.1 Hz, C-3), 16.2 (d, $J_{C\text{-}F}$ = 4.8 Hz, C-4); ^{19}F NMR: (376 MHz, $CDCl_3$) -75.64 – -75.66 (m, 3F), -181.95 (d, *J* = 33.6 Hz, 1F); IR: (neat) 1741 (C=O) cm^{-1}; HRMS: (ESI+) Calculated ($C_{18}H_{15}O_5F_4NaSCl$) 477.0157 $(M+Na)^+$ Found: 477.0154

(4ef) Methyl 4-((2*R,3*R**)-3-(4-chlorophenyl)-2-fluoro-1-methoxy-1-oxobutan-2-yl)benzoate**

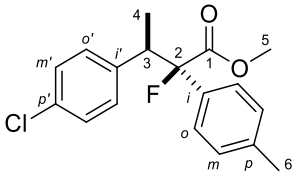


Following the general procedure using 1-chloro-4-(1-fluoroethyl)benzene (0.233 mmol, 0.0370 g) and methyl 4-(1-diazo-2-methoxy-2-oxoethyl)benzoate (0.303 mmol, 0.0710 g) with $BF_3{\cdot}OEt_2$ (0.020 mmol, 2.5 μL). The yield and diastereo ratio were determined by ^{1}H NMR and ^{19}F NMR in crude products (55%, 86:14). 1,1,2,2-Tetrachloroethane and hexafluorobenzene were used as internal standards. The crude product was purified by recycle HPLC to give the title compound as white solid (0.0365 g, 43%).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.88 (d, *J* = 8.4 Hz, 2H, *m*-H), 7.41 (d, *J* = 8.4 Hz, 2H, *o*-H), 7.05 (d, *J* = 8.6

Hz, 2H, *m'*-H), 6.95 (d, *J* = 8.6 Hz, 2H, *o'*-H), 3.87 (s, 3H, 7-H_3), 3.85 (s, 3H, 5-H_3), 3.77 (d, $^3J_{H\text{-}F}$ = 32.4 Hz, q, *J* = 7.2 Hz, 1H, 3-H), 1.46 (d, *J* = 7.2 Hz, 3H, 4-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.2 (d, $J_{C\text{-}F}$ = 25.7 Hz, C-1), 166.5 (C-6), 141.6 (d, $J_{C\text{-}F}$ = 22.9 Hz, C-*i*), 137.6 (C-*i'*), 132.7 (C-*p'*), 130.2 (d, $J_{C\text{-}F}$ = 1.9 Hz, C-*o'*), 129.9 (C-*p*), 129.3 (d, $J_{C\text{-}F}$ = 2.9 Hz, C-*m*), 128.1 (C-*o'*), 124.7 (d, $J_{C\text{-}F}$ = 10.5 Hz, C-*o*), 99.2 (d, $J_{C\text{-}F}$ = 200.3 Hz, C-2), 53.2 (C-5), 52.2 (C-7), 47.2 (d, $J_{C\text{-}F}$ = 21.0 Hz, C-3), 16.5 (d, $J_{C\text{-}F}$ = 5.7 Hz, C-4); ^{19}F NMR: (376 MHz, $CDCl_3$) -179.55 (d, *J* = 30.5 Hz, 1F); IR: (KBr) 1756 (C=O), 1732 (C=O) cm^{-1}; m.p.: 75–77 °C; HRMS: (ESI+) Calculated ($C_{19}H_{18}O_4FNaCl$) 387.0770 $(M+Na)^+$ Found: 387.0773

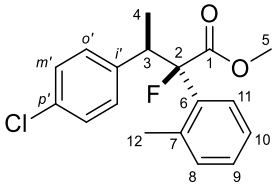
(4eg) Methyl (2*R,3*R**)-3-(4-chlorophenyl)-2-fluoro-2-(*p*-tolyl)butanoate**



Following the general procedure using 1-chloro-4-(1-fluoroethyl)benzene (0.216 mmol, 0.0342 g) and methyl 2-diazo-2-(*p*-tolyl)acetate (0.415 mmol, 0.0790 g) with $BF_3{\cdot}OEt_2$ (0.020 mmol, 2.5 μL) at -44 °C for 12 h. The yield and diastereo ratio were determined by ^{1}H NMR and ^{19}F NMR in crude products (74%, 95:5). 1,1,2,2-Tetrachloroethane and hexafluorobenzene were used as internal standards. The crude product was purified by recycle HPLC to give the title compound as colorless oil (0.0450 g, 65%).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.20 (d, *J* = 8.2 Hz, 2H, *o*-H), 7.06 (d, *J* = 8.7 Hz, 2H, *m'*-H), 7.01-6.97 (m, 4H, Ar-H), 3.78-3.70 (m, 4H, 5-H_3 and 3-H), 2.24 (s, 3H, 6-H_3), 1.43 (d, *J* = 6.8 Hz, 3H, 4-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.9 (d, $J_{C\text{-}F}$ = 26.2 Hz, C-1), 138.4 (C-*i'*), 137.9 (d, $J_{C\text{-}F}$ = 1.6 Hz, C-*p*), 133.9 (d, $J_{C\text{-}F}$ = 22.9 Hz, C-*i*), 132.4 (C-*p'*), 130.4 (d, $J_{C\text{-}F}$ = 2.5 Hz, C-*m'*), 128.8 (d, $J_{C\text{-}F}$ = 1.6 Hz, C-*m*), 127.9 (C-*o'*), 124.5 (d, $J_{C\text{-}F}$ = 9.8 Hz, C-*o*), 99.3 (d, $J_{C\text{-}F}$ = 198.3 Hz, C-2), 52.9 (C-5), 46.9 (d, $J_{C\text{-}F}$ = 20.5 Hz, C-3), 21.0 (C-6), 16.6 (d, $J_{C\text{-}F}$ = 5.7 Hz, C-4); ^{19}F NMR: (376 MHz, $CDCl_3$) -181.95 (d, *J* = 33.6 Hz, 1F); IR: (neat) 1739 (C=O) cm^{-1}; HRMS: (ESI+) Calculated ($C_{18}H_{18}O_2FNaCl$) 343.0872 $(M+Na)^+$ Found: 343.0874

(4eh) Methyl (2*R,3*R**)-3-(4-chlorophenyl)-2-fluoro-2-(*o*-tolyl)butanoate**

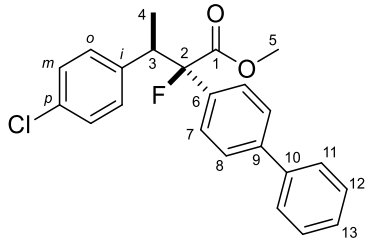


Following the general procedure using 1-chloro-4-(1-fluoroethyl)benzene (0.204 mmol, 0.0323 g) and methyl 2-diazo-2-(*o*-tolyl)acetate (0.400 mmol, 0.0761 g) with $BF_3{\cdot}OEt_2$ (0.020 mmol, 2.5 μL) at -44 °C for 12 h. The yield and diastereo ratio were determined by ^{1}H NMR and ^{19}F NMR in crude products (26%, >99:1). 1,1,2,2-Tetrachloroethane and hexafluorobenzene were used as internal standards. The crude product was purified by recycle HPLC to give the title compound as colorless oil (0.0151 g, 23%).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.37 (m, 1H, 11-H), 7.11-7.05 (m, 6H, Ar-H), 6.98-6.96 (m, 1H, 8-H), 3.93 (d, $^3J_{H\text{-}F}$ = 31.8 Hz, q, *J* = 6.9 Hz, 1H, 3-H), 3.79 (s, 3H, 5-H_3), 2.28 (s, 3H, 12-H_3), 1.44 (d, *J* = 6.9 Hz, 3H, 4-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.5 (d, $J_{C\text{-}F}$ = 26.2 Hz, C-1), 139.1 (C-*i'*), 136.2 (C-7), 134.5 (d, $J_{C\text{-}F}$ =

21.3 Hz, C-6), 132.5 (C-8), 132.4 (C-*p*), 130.3 (d, $J_{C\text{-}F}$ = 2.5 Hz, C-*o*), 128.2 (C-9), 128.1 (C-*m*), 126.6 (d, $J_{C\text{-}F}$ = 9.8 Hz, C-11), 125.5 (d, $J_{C\text{-}F}$ = 2.5 Hz, C-10), 101.1 (d, $J_{C\text{-}F}$ = 198.3 Hz, C-2), 52.9 (C-5), 45.8 (d, $J_{C\text{-}F}$ = 21.3 Hz, C-3), 21.5 (C-12), 17.1 (d, $J_{C\text{-}F}$ = 6.6 Hz, C-4); ^{19}F NMR: (376 MHz, $CDCl_3$) -174.55 (d, J = 30.5 Hz, 1F); IR: (neat) 1741 (C=O) cm^{-1}; HRMS: (ESI+) Calculated ($C_{18}H_{18}O_2FNaCl$) 343.0872 $(M+Na)^+$ Found: 343.0873

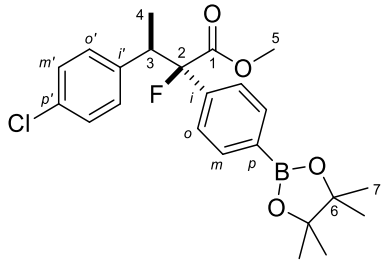
(4ei) Methyl (2*R,3*R**)-2-([1,1'-biphenyl]-4-yl)-3-(4-chlorophenyl)-2-fluorobutanoate**



Following the general procedure using 1-chloro-4-(1-fluoroethyl)benzene (0.252 mmol, 0.0400 g) and methyl 2-([1,1'-biphenyl]-4-yl)-2-diazoacetate (0.504 mmol, 0.127 g) with $BF_3{\cdot}OEt_2$ (0.025 mmol, 3.1 μL). The yield and diastereo ratio were determined by ^{1}H NMR and ^{19}F NMR in crude products (42%, 95:5). 1,1,2,2-Tetrachloroethane and hexafluorobenzene were used as internal standards. The crude product was purified by recycle HPLC to give the title compound as colorless oil (0.0357 g, 37%).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.51 (d, J = 8.2 Hz, 2H, Ar-H), 7.45-7.30 (m, 7H, Ar-H), 7.07 (d, J = 8.7 Hz, 2H, Ar-H), 7.01 (d, J = 7.7 Hz, 2H, *o*-H), 3.85-3.73 (m, 4H, 5-H_3 and 3-H), 1.47 (d, J = 7.2 Hz, 3H, 4-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.7 (d, $J_{C\text{-}F}$ = 25.4 Hz, C-1), 140.9, 140.1, 138.2, 135.8 (d, $J_{C\text{-}F}$ = 22.9 Hz, C-6), 132.6, 130.4 (d, $J_{C\text{-}F}$ = 2.5 Hz), 128.7, 128.0, 127.5, 127.0, 126.7 (d, $J_{C\text{-}F}$ = 2.5 Hz), 125.1 (d, $J_{C\text{-}F}$ = 10.7 Hz, C-7), 99.3 (d, $J_{C\text{-}F}$ = 198.3 Hz, C-2), 53.0 (C-5), 47.0 (d, $J_{C\text{-}F}$ = 21.3 Hz, C-3), 16.6 (d, $J_{C\text{-}F}$ = 4.9 Hz, C-4); ^{19}F NMR: (376 MHz, $CDCl_3$) -181.95 (d, J = 33.6 Hz, 1F); IR: (neat) 1739 (C=O) cm^{-1}; HRMS: (ESI+) Calculated ($C_{23}H_{20}O_2FNaCl$) 405.1028 $(M+Na)^+$ Found: 405.1024

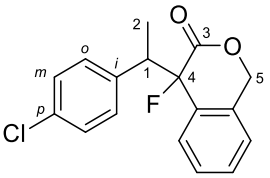
(4ej) Methyl (2*R,3*R**)-3-(4-chlorophenyl)-2-fluoro-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)butanoate**



Following the general procedure using 1-chloro-4-(1-fluoroethyl)benzene (0.255 mmol, 0.0404 g) and methyl 2-diazo-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate (0.382 mmol, 0.116 g) with $BF_3{\cdot}OEt_2$ (0.025 mmol, 3.0 μL). The yield and diastereo ratio were determined by ^{1}H NMR and ^{19}F NMR in crude products (85%, 87:13). 1,1,2,2-Tetrachloroethane and hexafluorobenzene were used as internal standards. The crude product was purified by recycle HPLC to give the title compound as colorless oil (0.0772 g, 70%).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.65 (d, J = 8.3 Hz, 2H, *m*-H), 7.34 (d, J = 8.3 Hz, 2H, *o*-H), 7.05 (d, J = 8.7 Hz, 2H, *m'*-H), 6.98 (d, J = 8.7 Hz, 2H, *o'*-H), 3.86-3.73 (4H, 3-H and 5-H_3), 1.45 (d, J = 7.3 Hz, 3H, 4-H_3), 1.31 (s, 12H, Bpin); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.5 (d, $J_{C\text{-}F}$ = 25.9 Hz, C-1), 139.6 (d, $J_{C\text{-}F}$ = 23.0 Hz, C-*i*), 138.0 (C-*i'*), 134.5 (d, $J_{C\text{-}F}$ = 1.9 Hz, C-*m*), 132.4 (C-*p'*), 130.3 (d, $J_{C\text{-}F}$ = 1.9 Hz, C-*o'*), 128.0 (C-*m'*), 123.8 (d, $J_{C\text{-}F}$ = 9.6 Hz, C-*o*), 99.3 (d, $J_{C\text{-}F}$ = 198.4 Hz, C-2), 83.8 (C-6), 53.0 (C-5), 46.8 (d, $J_{C\text{-}F}$ = 21.1 Hz, C-3), 24.83, 24.76, 16.6 (d, $J_{C\text{-}F}$ = 4.8 Hz, C-4) The signal of α-carbon of the boron atom was not observed; ^{19}F NMR: (376 MHz, $CDCl_3$) -182.59 (d, J = 30.5 Hz, 1F); IR: (neat) 1741 (C=O) cm^{-1}; HRMS: (ESI+) Calculated ($C_{23}H_{27}BO_4FNaCl$) 455.1567 $(M+Na)^+$ Found: 455.1561

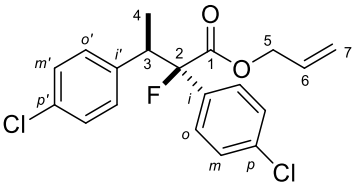
(4ek) 4-(1-(4-Chlorophenyl)ethyl)-4-fluoroisochroman-3-one



Following the general procedure using 1-chloro-4-(1-fluoroethyl)benzene (0.218 mmol, 0.0346 g) and 4-diazoisochroman-3-one (0.343 mmol, 0.0598 g) with $BF_3{\cdot}OEt_2$ (0.020 mmol, 2.5 μL) at 0 °C for 5 min and rt for 4 h. The yield and diastereo ratio were determined by ^{1}H NMR and ^{19}F NMR in crude products (48%, 70:30). 1,1,2,2-Tetrachloroethane and hexafluorobenzene were used as internal standards. The crude product was purified by recycle GPC to give the diastereo mixture of the title compound as white solid (0.0319 g, 48%, dr = 65:35).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.53 (d, J = 7.8 Hz, 0.65H, Ar-H), 7.46 (t, J = 7.8 Hz, 0.65H, Ar-H), 7.41 (t, J = 7.8 Hz, 0.65H, Ar-H), 7.34 (t, J = 7.3 Hz, 0.35H, Ar-H), 7.26 (t, J = 7.3 Hz, 0.35H, Ar-H), 7.22 (d, J = 8.5 Hz, 1.30H, Ar-H), 7.15-7.05 (m, 2.1H, Ar-H), 7.01 (d, J = 8.5 Hz, 1.30H, Ar-H), 6.79 (d, J = 7.8 Hz, 0.65H, Ar-H), 4.92 (d, J = 173.1 Hz, 1.3H, 5-H_2), 4.88 (d, J = 173.1 Hz, 0.65H, 5-H_2), 3.47-3.28 (m, 1H, 1-H), 1.53 (d, J = 7.1 Hz, 1.05H, 2-H_3), 1.47 (d, J = 7.1 Hz, 1.95H, 2-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 168.5 (d, $J_{C\text{-}F}$ = 21.1 Hz, C-3), 167.0 (d, $J_{C\text{-}F}$ = 22.0 Hz, C-3), 136.4 (d, $J_{C\text{-}F}$ = 3.8 Hz), 135.8 (d, $J_{C\text{-}F}$ = 3.8 Hz), 133.8, 133.7, 132.8, 132.6, 130.3, 130.0, 129.9 (d, $J_{C\text{-}F}$ = 4.8 Hz), 129.6 (d, $J_{C\text{-}F}$ = 4.8 Hz), 129.1, 128.9, 128.7, 128.5, 128.3, 128.2, 126.0 (d, $J_{C\text{-}F}$ = 7.7 Hz), 125.4 (d, $J_{C\text{-}F}$ = 7.7 Hz), 123.8, 123.7, 92.3 ($J_{C\text{-}F}$ = 195.5 Hz, C-4), 92.1 ($J_{C\text{-}F}$ = 197.4 Hz, C-4), 69.8 (C-5), 47.3 (d, $J_{C\text{-}F}$ = 26.8 Hz, C-1), 45.0 (d, $J_{C\text{-}F}$ = 25.9 Hz, C-1), 14.4 (d, $J_{C\text{-}F}$ = 32.6 Hz, C-2), 14.3 (d, $J_{C\text{-}F}$ = 33.5 Hz, C-2); ^{19}F NMR: (376 MHz, $CDCl_3$) -160.68 (d, J = 18.3 Hz), -163.60 (d, J = 18.3 Hz); IR: (KBr) 1771 (C=O) cm^{-1}; HRMS: (ESI+) Calculated ($C_{17}H_{14}O_2FNaCl$) 327.0559 $(M+Na)^+$ Found: 327.0563

(4el) Allyl (2*R,3*R**)-2,3-bis(4-chlorophenyl)-2-fluorobutanoate**

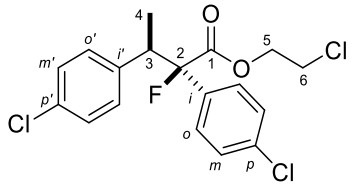


Following the general procedure using 1-chloro-4-(1-fluoroethyl)benzene (0.226 mmol, 0.0359 g) and allyl 2-(4-chlorophenyl)-2-diazoacetate (0.300 mmol, 0.0710 g) with $BF_3{\cdot}OEt_2$ (0.020 mmol, 2.5 μL). The yield

and diastereo ratio were determined by ^{1}H NMR and ^{19}F NMR in crude products (76%, 91:9). 1,1,2,2-Tetrachloroethane and hexafluorobenzene were used as internal standards. The crude product was purified by recycle HPLC to give the title compound as colorless oil (0.0565 g, 68%).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.27 (d, J = 9.0 Hz, 2H, *o*-H), 7.18 (d, J = 9.0 Hz, 2H, *m*-H), 7.08 (d, J = 8.5 Hz, 2H, *m'*-H), 6.96 (d, J = 8.5 Hz, 2H, *o'*-H), 5.96-5.86 (m, 1H, 6-H), 5.32 (dq, J = 13.7, 1.3 Hz, 1H, 7-H^{a}), 5.27 (dq, J = 13.7, 1.3 Hz, 1H, 7-H^{b}), 4.77-4.66 (m, 2H, 5-H_2), 3.72 (d, $^{3}J_{H\text{-}F}$ = 32.5 Hz, q, J = 7.2 Hz, 1H, 3-H), 1.45 (d, J = 7.2 Hz, 3H, 4-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 169.6 (d, $J_{C\text{-}F}$ = 26.2 Hz, C-1), 137.9 (C-*i'*), 135.5 (d, $J_{C\text{-}F}$ = 22.9 Hz, C-*i*), 134.3 (d, $J_{C\text{-}F}$ = 1.6 Hz, C-*p*), 132.7 (C-*p'*), 131.0 (C-6), 130.3 (d, $J_{C\text{-}F}$ = 2.5 Hz, C-*m'*), 128.3 (d, $J_{C\text{-}F}$ = 1.6 Hz, C-*m*), 128.1 (C-*o'*), 126.1 (d, $J_{C\text{-}F}$ = 9.8 Hz, C-*o*), 119.6 (C-7), 98.8 (d, $J_{C\text{-}F}$ = 199.1 Hz, C-2), 66.7 (C-5), 47.1 (d, $J_{C\text{-}F}$ = 21.3 Hz, C-3), 16.5 (d, $J_{C\text{-}F}$ = 5.7 Hz, C-4); ^{19}F NMR: (376 MHz, $CDCl_3$) -181.95 (d, J = 33.6 Hz, 1F); IR: (neat) 1738 (C=O) cm^{-1}; HRMS: (ESI+) Calculated ($C_{19}H_{17}O_2FNaCl_2$) 389.0482 $(M+Na)^+$ Found: 389.0483

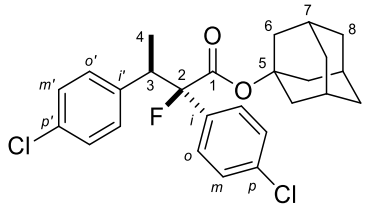
(4em) 2-Chloroethyl (2*R,3*R**)-2,3-bis(4-chlorophenyl)-2-fluorobutanoate**



Following the general procedure using 1-chloro-4-(1-fluoroethyl)benzene (0.209 mmol, 0.0332 g) and chloromethyl 2-(4-chlorophenyl)-2-diazoacetate (0.301 mmol, 0.0780 g) with $BF_3{\cdot}OEt_2$ (0.020 mmol, 2.5 μL). The yield and diastereo ratio were determined by ^{1}H NMR and ^{19}F NMR in crude products (82%, 91:9). 1,1,2,2-Tetrachloroethane and hexafluorobenzene were used as internal standards. The crude product was purified by recycle HPLC to give the title compound as colorless oil (0.0571 g, 70%).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.28 (d, J = 8.7 Hz, 2H, *o*-H), 7.19 (d, J = 8.7 Hz, 2H, *m*-H), 7.09 (d, J = 8.0 Hz, 2H, *m'*-H), 6.97 (d, J = 8.0 Hz, 2H, *o'*-H), 4.54-4.42 (m, 2H, 6-H_2), 3.80-3.67 (m, 3H, 3-H and 5-H_2), 1.47 (d, J = 7.2 Hz, 3H, 4-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 169.5 (d, $J_{C\text{-}F}$ = 26.2 Hz, C-1), 137.7 (C-*i'*), 135.2 (d, $J_{C\text{-}F}$ = 23.8 Hz, C-*i*), 134.4 (C-*p*), 132.8 (C-*p'*), 130.3 (d, $J_{C\text{-}F}$ = 2.5 Hz, C-*m'*), 128.4 (d, $J_{C\text{-}F}$ = 1.6 Hz, C-*m*), 128.2 (C-*o'*), 126.2 (d, $J_{C\text{-}F}$ = 9.8 Hz, C-*o*), 98.7 (d, $J_{C\text{-}F}$ = 199.1 Hz, C-2), 65.5 (C-5), 46.9 (d, $J_{C\text{-}F}$ = 21.3 Hz, C-3), 41.1 (C-6), 16.5 (d, $J_{C\text{-}F}$ = 5.7 Hz, C-4); ^{19}F NMR: (376 MHz, $CDCl_3$) -181.74 (d, J = 30.5 Hz, 1F); IR: (neat) 1742 (C=O) cm^{-1}; HRMS: (ESI+) Calculated ($C_{18}H_{16}O_2FNaCl_3$) 411.0092 $(M+Na)^+$ Found: 411.0092

(4en) Adamantan-1-yl (2*R,3*R**)-2,3-bis(4-chlorophenyl)-2-fluorobutanoate**

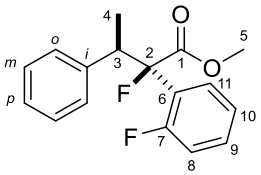


Following the general procedure using 1-chloro-4-(1-fluoroethyl)benzene (0.217 mmol, 0.0344 g) and adamantan-1-yl 2-(4-chlorophenyl)-2-diazoacetate (0.326 mmol, 0.0986 g) with $BF_3{\cdot}OEt_2$ (0.020 mmol, 2.5

μL). The yield and diastereo ratio were determined by ^{1}H NMR and ^{19}F NMR in crude products (51%, 83:17). 1,1,2,2-Tetrachloroethane and hexafluorobenzene were used as internal standards. The crude product was purified by recycle HPLC to give the title compound as white solid (0.0350 g, 35%).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.26 (d, J = 8.7 Hz, 2H, *o*-H), 7.16 (d, J = 8.7 Hz, 2H, *m*-H), 7.07 (d, J = 8.5 Hz, 2H, *m'*-H), 6.95 (d, J = 8.5 Hz, 2H, *o'*-H), 3.64 (d, $^{3}J_{H\text{-}F}$ = 32.2 Hz, q, J = 7.1 Hz, 1H, 3-H), 2.19-2.14 (m, 9H, 6-H_2 x 3 and 7-H x 3), 1.67 (br s, 6H, 8-H_2 x 3), 1.46 (d, J = 7.1 Hz, 3H, 4-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 168.2 (d, $J_{C\text{-}F}$ = 25.9 Hz, C-1), 138.2 (C-*i'*), 136.1 (d, $J_{C\text{-}F}$ = 24.0 Hz, C-*i*), 133.9 (C-*p*), 132.5 (C-*p'*), 130.3 (d, $J_{C\text{-}F}$ = 2.9 Hz, C-*m'*), 128.1 (d, $J_{C\text{-}F}$ = 1.9 Hz, C-*m*), 128.0 (C-*o'*), 126.2 (d, $J_{C\text{-}F}$ = 10.5 Hz, C-*o*), 98.2 (d, $J_{C\text{-}F}$ = 199.4 Hz, C-2), 83.7 (C-5), 46.9 (d, $J_{C\text{-}F}$ = 21.1 Hz, C-3), 41.1 (C-6), 36.0 (C-8), 30.9 (C-7), 16.4 (d, $J_{C\text{-}F}$ = 4.8 Hz, C-4); ^{19}F NMR: (376 MHz, $CDCl_3$) -180.56 (d, J = 30.5 Hz, 1F); IR: (KBr) 1742 (C=O) cm^{-1}; m.p.: 130–132 °C; HRMS: (ESI+) Calculated ($C_{26}H_{27}O_2FNaCl_2$) 483.1264 $(M+Na)^+$ Found: 483.1259

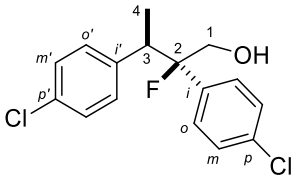
(4bo) Methyl (2*R,3*R**)-2-fluoro-2-(2-fluorophenyl)-3-phenylbutanoate**



Following the general procedure using (1-fluoroethyl)benzene (1.097 mmol, 0.136 g) and methyl 2-diazo-2-(2-fluorophenyl)acetate (1.526 mmol, 0.296 g) with $BF_3{\cdot}OEt_2$ (0.100 mmol, 12.5 μL). The yield and diastereo ratio were determined by ^{1}H NMR and ^{19}F NMR in crude products (44%, 91:9). 1,1,2,2-Tetrachloroethane and hexafluorobenzene were used as internal standards. The crude product was purified by recycle HPLC to give the title compound as colorless oil (0.127 g, 40%).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.33-7.29 (m, 1H, 11-H), 7.20 (d, J = 7.8 Hz, 2H, *o*-H), 7.16-7.05 (m, 4H, Ar-H), 6.95-6.91 (m, 1H, 9-H), 6.90-6.88 (m, 1H, 8-H), 4.16 (d, $^{3}J_{H\text{-}F}$ = 33.9 Hz, q, J = 7.2 Hz, 1H, 3-H), 3.80 (s, 3H, 5-H_3), 1.48 (d, J = 7.2 Hz, 3H, 4-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 169.5 (d, $J_{C\text{-}F}$ = 25.9 Hz, C-1), 158.2 (dd, $J_{C\text{-}F}$ = 249.2, 5.8 Hz, C-7), 140.4 (C-*i*), 130.2 (d, $J_{C\text{-}F}$ = 8.6 Hz, C-10), 128.5 (d, $J_{C\text{-}F}$ = 1.9 Hz, C-*o*), 127.9 (C-*m*), 127.7 (d, $J_{C\text{-}F}$ = 21.1 Hz, C-6), 127.1 (dd, $J_{C\text{-}F}$ = 15.8, 3.4 Hz, C-11), 126.9 (C-*p*), 123.9 (t, $J_{C\text{-}F}$ = 3.4 Hz, C-9), 116.1 (dd, $J_{C\text{-}F}$ = 24.0, 1.9 Hz, C-8), 97.9 (dd, $J_{C\text{-}F}$ = 196.5, 4.8 Hz, C-2), 53.0 (C-5), 44.2 (dd, $J_{C\text{-}F}$ = 20.6, 5.3 Hz, C-3), 16.6 (d, $J_{C\text{-}F}$ = 7.7 Hz, C-4); ^{19}F NMR: (376 MHz, $CDCl_3$) -113.19 (s, 1F), -175.47 (dd, J = 33.6, 15.3 Hz, 1F); IR: (neat) 1753 (C=O) cm^{-1}; HRMS: (ESI+) Calculated ($C_{17}H_{16}O_2F_2Na$) 313.1011 $(M+Na)^+$ Found: 313.1020

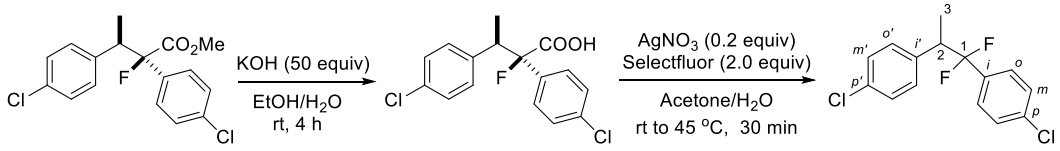
(14) (2*R,3*R**)-2,3-Bis(4-chlorophenyl)-2-fluorobutan-1-ol**



Under nitrogen atmosphere, $LiAlH_4$ (0.819 mmol, 0.0311 g) was added to a stirred solution of single isomer **4ba** (0.200 mmol, 0.0681 g) and diethyl ether (4 mL) in one portion at 0 °C. The resultant mixture was

further stirred at 0 °C for 3 h and quenched by addition of MeOH (0.2 mL). Aqueous KOH (0.5 mL, 1 M) and $MgSO_4$ (5 g) were subsequently added. The mixture was filtrated and the obtained filtrate was concentrated and purified by silica gel flash column to give title compound as colorless oil. (0.0608 g, 97%). ^{1}H NMR: (400 MHz, $CDCl_3$) 7.23 (d, J = 8.5 Hz, 2H, *m*-H), 7.16 (d, J = 8.5 Hz, 2H, *m'*-H), 6.92 (d, J = 8.5 Hz, 4H, Ar-H), 4.02-3.83 (m, 2H, 1-H_2), 3.52 (d, $^3J_{H\text{-}F}$ = 19.3 Hz, q, J = 6.5 Hz, 1H, 3-H), 1.91 (br s, 1H, OH), 1.29 (d, J = 6.5 Hz, 3H, 4-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 138.8 (d, $J_{C\text{-}F}$ = 6.6 Hz, C-*i'*), 136.3 (d, $J_{C\text{-}F}$ = 22.1 Hz, C-*i*), 133.7 (d, $J_{C\text{-}F}$ = 1.6 Hz, C-*p*), 132.7 (C-*p'*), 130.5 (d, $J_{C\text{-}F}$ = 1.6 Hz, C-*o'*), 128.02 (C-*m'*), 127.95 (d, $J_{C\text{-}F}$ = 1.6 Hz, C-*m*), 127.14 (d, $J_{C\text{-}F}$ = 10.7 Hz, C-*o*), 100.9 (d, $J_{C\text{-}F}$ = 181.1 Hz, C-2), 65.9 (d, $J_{C\text{-}F}$ = 23.8 Hz, C-1), 43.9 (d, $J_{C\text{-}F}$ = 24.6 Hz, C-3), 14.6 (d, $J_{C\text{-}F}$ = 4.9 Hz, C-4); ^{19}F NMR: (376 MHz, $CDCl_3$) -168.53 (q, J = 19.3 Hz, 1F); IR: (neat) 3393 cm^{-1}; HRMS: (ESI+) Calculated ($C_{16}H_{15}OFNaCl_2$) 335.0376 $(M+Na)^+$ Found: 335.0389

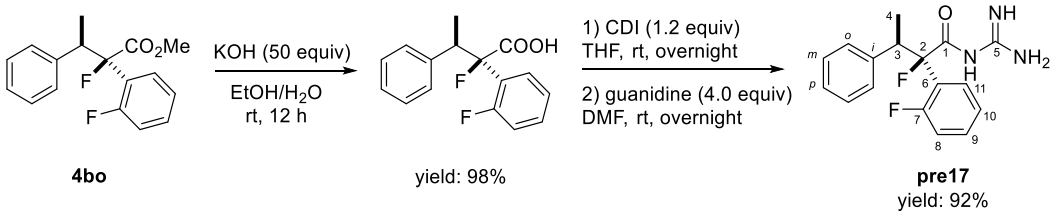
(16) 4,4'-(1,1-Difluoropropane-1,2-diyl)bis(chlorobenzene)



To a solution of single isomer **4ea-major** (0.200 mmol, 0.0681 g) in EtOH (2 mL) was added aqueous KOH (1 M, 50 equiv) at room temperature. The reaction mixture was then stirred at this temperature for 4 hour and monitored by TLC analysis. After the reaction was complete, it was acidified by aqueous HCl (1 M) to pH = about 2 and extracted by EtOAc (3 x 20 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to give crude product **15** as white solid (65.3 mg, >99%) which was used to the next step without further purification. To a reaction tube was charged with **15** (32.7 mg, 0.1 mmol) and Selectfluor® (70.9 mg, 0.2 mmol). Subsequently were added acetone (1 mL), dilute water (1 mL) and $AgNO_3$ (3.4 mg, 0.02 mmol). The reaction mixture was stirred at room temperature for 10 min and heated to 45 °C for 20 min. After cooling to room temperature, it was quenched by aqueous HCl (1 M) and extracted with hexane, and the organic layer was washed with saturated $NaHCO_3$, dried over $MgSO_4$ and concentrated in a Teflon® round-bottom flask. The product **16** was obtained after purification on silica gel column (hexane 100%) as a white solid (27.7 mg, 92%).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.28 (d, J = 8.2 Hz, 2H, *m*-H), 7.21 (d, J = 8.5 Hz, 2H, *m'*-H), 7.12 (d, J = 8.2 Hz, 2H, *o*-H), 7.02 (d, J = 8.5 Hz, 2H, *o'*-H), 3.44-3.32 (m, 1H, 2-H), 1.40 (d, J = 7.2 Hz, 3H, 3-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 136.7 (t, $J_{C\text{-}F}$ = 3.3 Hz, C-*i'*), 135.7 (t, $J_{C\text{-}F}$ = 2.0 Hz, C-*p*), 134.4 (d, $J_{C\text{-}F}$ = 27.4 Hz, C-*i*), 133.3 (C-*p'*), 130.4 (d, $J_{C\text{-}F}$ = 1.6 Hz, C-*o'*), 128.3, 128.2, 127.1 (t, $J_{C\text{-}F}$ = 6.1 Hz, C-*o*), 122.7 (t, $J_{C\text{-}F}$ = 247.8 Hz, C-1), 47.8 (t, $J_{C\text{-}F}$ = 27.0 Hz, C-2), 14.5 (t, $J_{C\text{-}F}$ = 4.5 Hz, C-3); ^{19}F NMR: (376 MHz, $CDCl_3$) -102.28 (dd, J = 243.4, 14.5 Hz, 1F), -106.0 (dd, J = 243.4, 14.5 Hz, 1F),; IR: (KBr) 1494 cm^{-1}; m.p. 45–46 °C; HRMS: (EI) Calculated ($C_{15}H_{12}F_2Cl_2$) 300.0284 $(M)^+$ Found: 300.0281

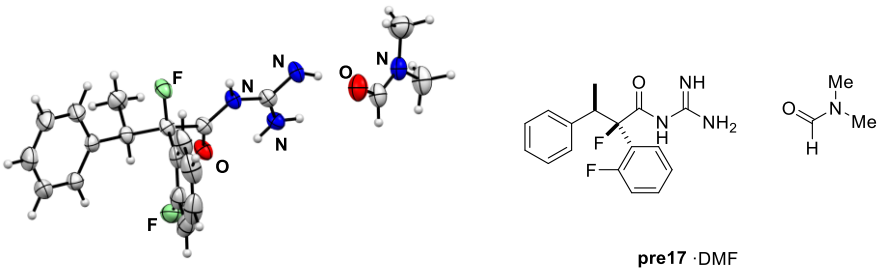
(pre17) (2*R,3*R**)-N-Carbamimidoyl-2-fluoro-2-(2-fluorophenyl)-3-phenylbutanamide**



To a solution of single isomer **4bo** (0.200 mmol, 58.1 mg) in EtOH (2 mL) was added aqueous KOH (5 M, 50 equiv) at room temperature. The reaction mixture was then stirred at this temperature for 12 h and monitored by TLC analysis. After the reaction was complete, it was acidified by aqueous HCl (1 M) to pH = 2 and extracted by EtOAc (3 x 20 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to give crude carboxylic acid as a white solid (54.1 mg, 98%) which was used to the next step without further purification. To a reaction tube was charged with the carboxylic acid (0.135 mmol, 37.2 mg), carbonyldiimidazole (CDI) (0.162 mmol, 26.2 mg). Subsequently was added THF (2 mL). The resultant solution was stirred at room temperature for 12 h. To another reaction tube was charged with guanidinium chloride (0.538 mmol, 51.4 mg), NaOEt (0.538 mmol, 36.6 mg), DMF (2 mL) and stirred at room temperature for 2 h to get the free guanidine. After the TLC analysis showed a complete disappearance of the starting carboxylic acid, the resultant mixture was directly added dropwise to the freshly prepared guanidine solution and stirred for additional 2 h at this temperature. Then the mixture was diluted by water (30 mL) and extracted by EtOAc (4 x 20 mL). Combined organic phase was sequentially washed with brine (2 x 20 mL), saturated aqueous ammonium chloride solution (2 x 20 mL) and brine (20 mL) again, dried over $MgSO_4$ and concentrated *in vacuo* to give colorless crystal, which was suitable to the X-ray crystal analysis. The crude product was purified by washing with ether/pentane (50/50) to give title compound **pre17** as viscous and colorless liquid. (39.3 mg, 92%). The structure of **pre17** was determined by X-ray diffraction analysis (CCDC: 2111205).

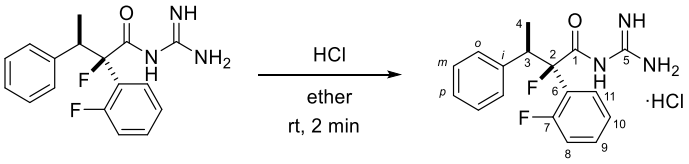
^{1}H NMR: (400 MHz, $CDCl_3$) 7.36 (d, J = 7.3 Hz, d, $^4J_{H\text{-}F}$ = 7.3 Hz, 1H, 11-H), 7.23 (d, J = 7.3 Hz, 2H, *o*-H), 7.11-7.02 (m, 4H, Ar-H), 6.91-6.83 (m, 2H, Ar-H), 4.24 (d, $^3J_{H\text{-}F}$ = 34.7 Hz, q, J = 6.8 Hz, 1H, 3-H), 1.44 (d, J = 6.8 Hz, 3H, 4-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$); 180.0 (d, $J_{C\text{-}F}$ = 22.9 Hz, C-1), 162.2 (C-5), 158.7 (dd, $J_{C\text{-}F}$ = 249.4, 5.2 Hz, C-7), 141.6 (C-*i*), 129.6 (d, $J_{C\text{-}F}$ = 8.6 Hz, C-10), 128.7 (d, $J_{C\text{-}F}$ = 1.9 Hz, C-*o*), 127.8 (C-*m*), 127.5 (dd, $J_{C\text{-}F}$ = 14.3, 3.8 Hz, C-6), 126.4 (C-*p*), 126.4 (dd, $J_{C\text{-}F}$ = 24.3, 11.9 Hz, C-11), 123.7 (C-9), 116.2 (d, $J_{C\text{-}F}$ = 23.8 Hz, C-8), 100.4 (dd, $J_{C\text{-}F}$ = 196.0, 5.2 Hz, C-2), 44.4 (dd, $J_{C\text{-}F}$ = 20.0, 4.8 Hz, C-3), 17.0 (d, $J_{C\text{-}F}$ = 7.6 Hz, C-4); ^{19}F NMR: (376 MHz, $CDCl_3$) -109.86 (s, 1F), -169.57 (d, J = 24.4 Hz, 1F); IR: (neat) 3443, 1732, 1615 cm^{-1}; HRMS: (ESI+) Calculated ($C_{17}H_{18}N_3OF_2$) 318.1413 $(M+H)^+$ Found: 318.1416

X-ray structure (CCDC: 2111205): DMF is included as a solvent molecule.



pre17 ·DMF

(17) (2*R,3*R**)-N-Carbamimidoyl-2-fluoro-2-(2-fluorophenyl)-3-phenylbutanamide hydrochloride**



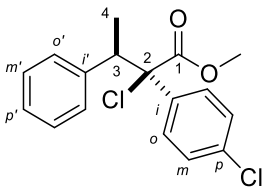
pre17 → (HCl, ether, rt, 2 min) → 17 ·HCl

yield: 100%

Compound **pre17** (0.105 mmol, 33.2 mg) was dissolved in diethyl ether (3 mL). Then, hydrochloride (2 mL, 1 M in diethyl ether) was added to the solution at room temperature. White precipitate was generated and the solvent was removed *in vacuo*. Hydrochloride salt **17** was obtained as white solid. (37.0 mg, 100%).

^{1}H NMR: (400 MHz, DMSO-d_6) 11.67 (s, HCl), 8.68 (br s, 2H, NH), 8.55 (br s, 2H, NH), 7.47-7.43 (m, 1H, 11-H), 7.36-7.30 (m, 1H, Ar-H), 7.22-7.08 (m, 7H, Ar-H), 4.19 (d, $^{3}J_{H\text{-}F}$ = 34.7 Hz, q, J = 6.9 Hz, 1H, 3-H), 1.39 (d, J = 6.9 Hz, 3H, 4-H$_3$); ^{13}C NMR: (100 MHz, DMSO-d_6) 170.3 (d, $J_{C\text{-}F}$ = 26.7 Hz, C-1), 158.1 (dd, $J_{C\text{-}F}$ = 250.3, 5.2 Hz, C-7), 154.6 (C-5), 139.7 (C-*i*), 131.6 (d, $J_{C\text{-}F}$ = 8.6 Hz, C-10), 128.4 (C-*o*), 128.2 (C-*m*), 127.4 (dd, $J_{C\text{-}F}$ = 13.8, 2.4 Hz, C-6), 127.1 (C-*p*), 124.6 (C-9), 123.0 (dd, $J_{C\text{-}F}$ = 23.8, 11.4 Hz, C-11), 116.6 (d, $J_{C\text{-}F}$ = 21.9 Hz, C-8), 99.4 (d, $J_{C\text{-}F}$ = 201.2 Hz, C-2), 43.1 (d, $J_{C\text{-}F}$ = 15.3 Hz, C-3), 16.7 (d, $J_{C\text{-}F}$ = 7.6 Hz, C-4); ^{19}F NMR: (376 MHz, DMSO-d_6) -110.14 (s, 1F), -169.60 (s, 1F); IR: (KBr) 3388, 3184, 3105, 1732, 1694 cm^{-1}; m.p. 154–156 °C; HRMS: (ESI–) Calculated ($C_{17}H_{17}N_3OF_2Cl$) 352.1034 $(M\text{-}H)^-$ Found: 352.1028; HRMS: (ESI+) Calculated ($C_{17}H_{18}N_3OF_2$) 318.1413 $(M\text{-}Cl)^+$ Found: 318.1403

(2*R,3*R**)-20aa Methyl (2*R**,3*R**)-2-chloro-2-(4-chlorophenyl)-3-phenylbutanoate**

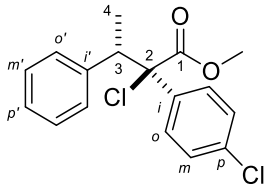


Following the general procedure using (1-chloroethyl)benzene (0.413 mmol, 0.0580 g) and methyl 2-(4-chlorophenyl)-2-diazoacetate (0.605 mmol, 0.127 g) with $InCl_3$ (0.0400 mmol, 0.0088 g). The yield and diastereomeric ratio were determined by ^{1}H NMR in crude products (93%, 52:48). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by recycle HPLC (n-hexane/EtOAc = 90/10) to give the title compound as a colorless oil (0.0608 g, 46%).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.20 (d, J = 9.2 Hz, 2H, *o*-H), 7.13 (d, J = 9.2 Hz, 2H, *m*-H), 7.09-7.06 (m, 3H, Ar-H), 6.92 (d, J = 7.7 Hz, 2H, *o'*-H), 3.94 (q, J = 6.8 Hz, 1H, 3-H), 3.81 (s, 3H, OCH_3), 1.54 (d, J = 6.8 Hz, 3H, 4-H$_3$); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.5 (C-1), 139.3 (C-*i'*), 136.6 (C-*i*), 134.0 (C-*p*), 129.6 (C-*o'*),

127.9, 127.8, 127.4, 126.9, 79.5 (C-2), 53.7 (OCH_3), 49.4 (C-3), 18.0 (C-4); IR: (neat) 1733 (C=O) cm^{-1}; HRMS (ESI+, TOF) m/z: $[M+Na]^+$ Calculated for $C_{17}H_{16}O_2NaCl_2$ 345.0420; Found 345.0419

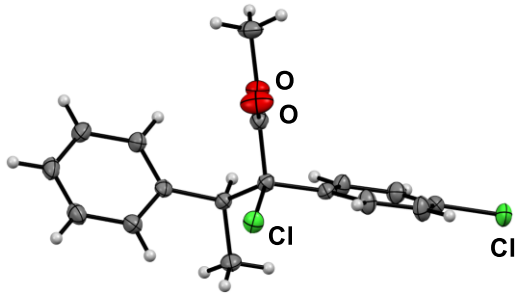
(2*R,3*S**)-20aa Methyl (2*R**,3*S**)-2-chloro-2-(4-chlorophenyl)-3-phenylbutanoate**



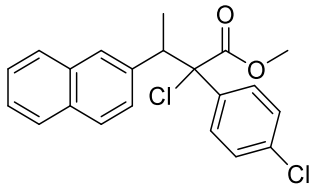
Following the general procedure using (1-chloroethyl)benzene (0.413 mmol, 0.0580 g) and methyl 2-(4-chlorophenyl)-2-diazoacetate (0.605 mmol, 0.127 g) with $InCl_3$ (0.0400 mmol, 0.0088 g). The yield and diastereomeric ratio were determined by ^1H NMR in crude products (93%, 52:48). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by recycle HPLC (n-hexane/EtOAc = 90/10) to give the title compound as a white solid (0.0555 g, 42%).

^1H NMR: (400 MHz, $CDCl_3$) 7.64 (d, *J* = 9.2 Hz, 2H, *o*-H), 7.36-7.26 (m, 7H, Ar-H), 4.08 (q, *J* = 6.9 Hz, 1H, 3-H), 3.58 (s, 3H, OCH_3), 1.25 (d, *J* = 6.9 Hz, 3H, 4-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 169.9 (C-1), 140.0 (C-*i'*), 136.4 (C-*i*), 134.4 (C-*p*), 129.9, 128.9, 128.2, 127.7, 127.4, 79.8 (C-2), 53.4 (OCH_3), 48.1 (C-3), 16.5 (C-4); IR: (KBr) 1747 (C=O) cm^{-1} m.p. 92–93 °C; HRMS (ESI+, TOF) m/z: $[M+Na]^+$ Calculated for $C_{17}H_{16}O_2NaCl_2$ 345.0420; Found 345.0422

X-ray structure (CCDC: 2144290)



20ba Methyl 2-chloro-2-(4-chlorophenyl)-3-(naphthalen-2-yl)butanoate

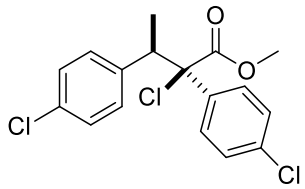


Following the general procedure using 2-(1-chloroethyl)naphthalene (0.403 mmol, 0.0769 g) and methyl 2-(4-chlorophenyl)-2-diazoacetate (0.600 mmol, 0.124 g) with $InCl_3$ (0.0400 mmol, 0.0088 g). The yield and diastereomeric ratio were determined by ^1H NMR in crude products (79%, 53:47). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by recycle HPLC (n-hexane/EtOAc = 90/10) to give a diastereomeric mixture of the title compound as a colorless oil (0.116 g, 77%, *dr* = 50:50).

*The below spectrum data are for a mixture of diastereomers **20ba** because these diastereomers could not be separated by column chromatography.*

^{1}H NMR: (400 MHz, $CDCl_3$) 7.81-7.65 (m, 8H, Ar-H), 7.52 (d, *J* = 10.0 Hz, 1H, Ar-H), 7.46-7.35 (m, 8H, Ar-H), 7.22 (d, *J* = 8.9 Hz, 2H, Ar-H), 7.10 (d, *J* = 8.9 Hz, 2H, Ar-H), 6.99 (d, *J* = 8.7 Hz, 1H, Ar-H), 4.26 (q, *J* = 7.0 Hz, 1H), 4.13 (q, *J* = 6.8 Hz, 1H), 3.83 (s, 3H, OMe), 3.56 (s, 3H, OMe), 1.63 (d, *J* = 6.8 Hz, 3H, CH_3), 1.33 (d, *J* = 7.0 Hz, 3H, CH_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.5, 169.9, 137.6, 136.9, 136.4, 136.3, 134.4, 134.1, 132.9, 132.71, 132.67, 132.3, 129.1, 129.0, 128.7, 128.2, 128.1, 128.0, 127.9, 127.84, 127.77, 127.4, 127.3, 127.0, 126.7, 125.87, 125.85, 125.74, 125.71, 79.8, 79.5, 53.7, 53.4, 49.4, 48.3, 18.2, 16.6 *Two signals were overlapped so numbers of observed signals were less than expected ones;* IR: (neat) 1732 (C=O) cm^{-1}; HRMS (ESI+, TOF) m/z: $[M+Na]^+$ Calculated for $C_{21}H_{18}O_2NaCl_2$ 395.0576; Found 395.0577

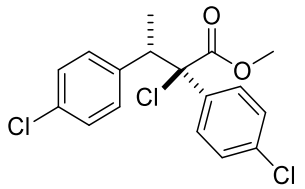
(2*R,3*R**)-20ca Methyl (2*R**,3*R**)-2-chloro-2,3-bis(4-chlorophenyl)butanoate**



Following the general procedure using 1-chloro-4-(1-chloroethyl)benzene (0.400 mmol, 0.0700 g) and methyl 2-(4-chlorophenyl)-2-diazoacetate (0.600 mmol, 0.126 g) with $InCl_3$ (0.0418 mmol, 0.0092 g). The yield and diastereomeric ratio were determined by ^{1}H NMR in crude products (96%, 50:50). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by recycle HPLC (n-hexane/EtOAc = 90/10) to give the title compound as a colorless oil (0.0687 g, 48%).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.21 (d, *J* = 9.1 Hz, 2H, Ar-H), 7.17 (d, *J* = 9.1 Hz, 2H, Ar-H), 7.05 (d, *J* = 8.5 Hz, 2H, Ar-H), 6.85 (d, *J* = 8.5 Hz, 2H, Ar-H), 3.92 (q, *J* = 6.8 Hz, 1H), 3.81 (s, 3H, OMe), 1.51 (d, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.3, 137.8, 136.3, 134.2, 132.8, 130.9, 128.1, 127.8, 127.6, 79.2, 53.8, 48.8, 18.0; IR: (neat) 1733 (C=O) cm^{-1}; HRMS (ESI+, TOF) m/z: $[M+Na]^+$ Calculated for $C_{17}H_{15}O_2NaCl_3$ 379.0030; Found 379.0020

(2*R,3*S**)-20ca Methyl (2*R**,3*S**)-2-chloro-2,3-bis(4-chlorophenyl)butanoate**

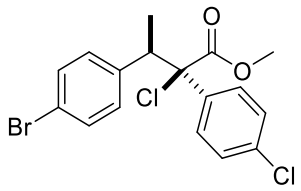


Following the general procedure using 1-chloro-4-(1-chloroethyl)benzene (0.400 mmol, 0.0700 g) and methyl 2-(4-chlorophenyl)-2-diazoacetate (0.600 mmol, 0.126 g) with $InCl_3$ (0.0418 mmol, 0.0092 g). The yield and diastereomeric ratio were determined by ^{1}H NMR in crude products (96%, 50:50). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by recycle HPLC (n-hexane/EtOAc = 90/10) to give the title compound as a colorless oil (0.0681 g, 48%).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.61 (d, *J* = 8.9 Hz, 2H, Ar-H), 7.36 (d, *J* = 8.9 Hz, 2H, Ar-H), 7.25 (s, 4H, Ar-H), 4.06 (q, *J* = 7.0 Hz, 1H), 3.61 (s, 3H, OMe), 1.21 (d, *J* = 7.0 Hz, 3H, CH_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 169.8, 138.5, 136.0, 134.5, 133.3, 131.3, 128.8, 128.3, 127.8, 79.4, 53.5, 47.6, 16.4; IR: (neat) 1759 (C=O)

cm^{-1}; HRMS (ESI+, TOF) m/z: $[M+Na]^+$ Calculated for $C_{17}H_{15}O_2NaCl_3$ 379.0030; Found 379.0029

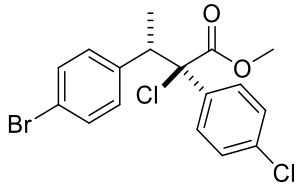
(2*R,3*R**)-20da Methyl (2*R**,3*R**)-3-(4-bromophenyl)-2-chloro-2-(4-chlorophenyl)butanoate**



Following the general procedure using 1-bromo-4-(1-chloroethyl)benzene (0.410 mmol, 0.0900 g) and methyl 2-(4-chlorophenyl)-2-diazoacetate (0.600 mmol, 0.126 g) with $InCl_3$ (0.0409 mmol, 0.0090 g). The yield and diastereomeric ratio were determined by ^1H NMR in crude products (93%, 50:50). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by recycle HPLC (n-hexane/EtOAc = 90/10) to give the title compound as a colorless oil (0.0725 g, 44%).

^1H NMR: (400 MHz, $CDCl_3$) 7.23-7.16 (m, 6H, Ar-H), 6.79 (d, J = 8.5 Hz, 2H, Ar-H), 3.91 (q, J = 6.8 Hz, 1H), 3.81 (s, 3H, OMe), 1.51 (d, J = 6.8 Hz, 3H, CH_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.3, 138.3, 136.2, 134.2, 131.2, 130.5, 128.1, 127.8, 121.0, 79.1, 53.8, 48.9, 17.9; IR: (neat) 1733 (C=O) cm^{-1}; HRMS (ESI+, TOF) m/z: $[M+Na]^+$ Calculated for $C_{17}H_{15}O_2NaCl_2Br$ 422.9525; Found 422.9520

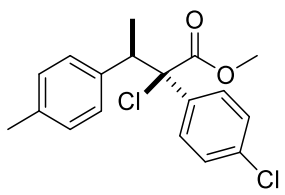
(2*R,3*S**)-20da Methyl (2*R**,3*S**)-3-(4-bromophenyl)-2-chloro-2-(4-chlorophenyl)butanoate**



Following the general procedure using 1-bromo-4-(1-chloroethyl)benzene (0.410 mmol, 0.0900 g) and methyl 2-(4-chlorophenyl)-2-diazoacetate (0.600 mmol, 0.126 g) with $InCl_3$ (0.0409 mmol, 0.0090 g). The yield and diastereomeric ratio were determined by ^1H NMR in crude products (93%, 50:50). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by recycle HPLC (n-hexane/EtOAc = 90/10) to give the title compound as a colorless oil (0.0709 g, 43%).

^1H NMR: (400 MHz, $CDCl_3$) 7.61 (d, J = 8.9 Hz, 2H, Ar-H), 7.40 (d, J = 8.6 Hz, 2H, Ar-H), 7.35 (d, J = 8.9 Hz, 2H, Ar-H), 7.19 (d, J = 8.6 Hz, 2H, Ar-H), 4.05 (q, J = 7.1 Hz, 1H), 3.61 (s, 3H, OMe), 1.20 (d, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 169.8, 139.0, 136.0, 134.5, 131.7, 130.8, 128.8, 128.3, 121.5, 79.3, 53.5, 47.7, 16.4; IR: (neat) 1733 (C=O) cm^{-1}; HRMS (ESI+, TOF) m/z: $[M+Na]^+$ Calculated for $C_{17}H_{15}O_2NaCl_2Br$ 422.9525; Found 422.9516

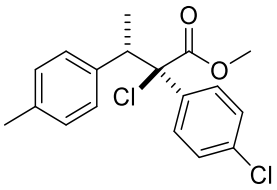
(2*R,3*R**)-20fa Methyl (2*R**,3*R**)-2-chloro-2-(4-chlorophenyl)-3-(*p*-tolyl)butanoate**



Following the general procedure using 1-(1-chloroethyl)-4-methylbenzene (0.398 mmol, 0.0616 g) and methyl 2-(4-chlorophenyl)-2-diazoacetate (0.600 mmol, 0.126 g) with $InCl_3$ (0.0400 mmol, 0.0088 g). The yield and diastereomeric ratio were determined by ^1H NMR in crude products (91%, 48:52). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by recycle HPLC (n-hexane/EtOAc = 90/10) to give the title compound as a colorless oil (0.0564 g, 42%).

^1H NMR: (400 MHz, $CDCl_3$) 7.22 (d, J = 9.1 Hz, 2H, Ar-H), 7.15 (d, J = 9.1 Hz, 2H, Ar-H), 6.89 (d, J = 8.1 Hz, 2H, Ar-H), 6.81 (d, J = 8.1 Hz, 2H, Ar-H), 3.92 (q, J = 6.8 Hz, 1H), 3.81 (s, 3H, OMe), 2.23 (s, 3H, Ar-CH_3), 1.51 (d, J = 6.8 Hz, 3H, CH_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.6, 136.6, 136.5, 136.2, 133.9, 129.5, 128.14, 128.06, 127.8, 79.6, 53.7, 48.9, 20.9, 18.0; IR: (neat) 1732 (C=O) cm^{-1}; HRMS (ESI+, TOF) m/z: $[M+Na]^+$ Calculated for $C_{18}H_{18}O_2NaCl_2$ 359.0576; Found 359.0579

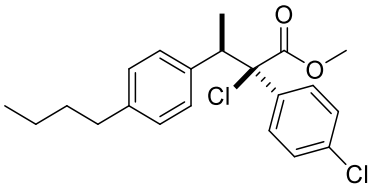
(2*R,3*S**)-20fa Methyl (2*R**,3*S**)-2-chloro-2-(4-chlorophenyl)-3-(*p*-tolyl)butanoate**



Following the general procedure using 1-(1-chloroethyl)-4-methylbenzene (0.398 mmol, 0.0616 g) and methyl 2-(4-chlorophenyl)-2-diazoacetate (0.600 mmol, 0.126 g) with $InCl_3$ (0.0400 mmol, 0.0088 g). The yield and diastereomeric ratio were determined by ^1H NMR in crude products (91%, 48:52). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by recycle HPLC (n-hexane/EtOAc = 90/10) to give the title compound as a colorless oil (0.0604 g, 45%).

^1H NMR: (400 MHz, $CDCl_3$) 7.64 (d, J = 8.9 Hz, 2H, Ar-H), 7.35 (d, J = 8.9 Hz, 2H, Ar-H), 7.20 (d, J = 8.1 Hz, 2H, Ar-H), 7.08 (d, J = 8.1 Hz, 2H, Ar-H), 4.06 (q, J = 7.0 Hz, 1H), 3.59 (s, 3H, OMe), 2.32 (s, 3H, Ar-CH_3), 1.22 (d, J = 7.0 Hz, 3H, CH_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 169.9, 137.0, 136.9, 136.5, 134.3, 129.7, 128.9, 128.4, 128.2, 80.0, 53.4, 47.7, 21.0, 16.5; IR: (neat) 1733 (C=O) cm^{-1}; HRMS (ESI+, TOF) m/z: $[M+Na]^+$ Calculated for $C_{18}H_{18}O_2NaCl_2$ 359.0576; Found 359.0581

(2*R,3*R**)-20ga Methyl (2*R**,3*R**)-3-(4-butylphenyl)-2-chloro-2-(4-chlorophenyl)butanoate**

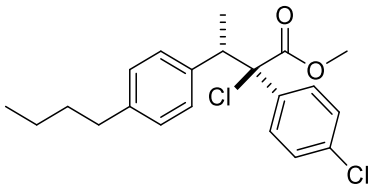


Following the general procedure using 1-butyl-4-(1-chloroethyl)benzene (0.407 mmol, 0.0800 g) and methyl 2-(4-chlorophenyl)-2-diazoacetate (0.600 mmol, 0.126 g) with $InCl_3$ (0.0405 mmol, 0.0089 g). The yield and diastereomeric ratio were determined by ^1H NMR in crude products (88%, 51:49). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by recycle HPLC (n-hexane/EtOAc = 90/10) to give the title compound as a colorless oil (0.0648 g, 42%).

^1H NMR: (400 MHz, $CDCl_3$) 7.18 (d, J = 8.8 Hz, 2H, Ar-H), 7.12 (d, J = 8.8 Hz, 2H, Ar-H), 6.88 (d, J = 8.2

Hz, 2H, Ar-H), 6.81 (d, *J* = 8.2 Hz, 2H, Ar-H), 3.90 (q, *J* = 6.8 Hz, 1H), 3.81 (s, 3H, OMe), 2.49 (t, *J* = 7.5 Hz, 2H, C*H*$_2$CH$_2$CH$_2$CH$_3$), 1.55-1.47 (m, 5H), 1.28 (sextet, *J* = 7.5 Hz, 2H, CH$_2$CH$_2$C*H*$_2$CH$_3$), 0.89 (t, *J* = 7.5 Hz, 3H, CH$_2$CH$_2$CH$_2$C*H*$_3$); ^{13}C NMR: (100 MHz, CDCl$_3$) 170.6, 141.6, 136.7, 136.3, 133.9, 129.4, 128.0, 127.8, 127.5, 79.9, 53.7, 49.0, 35.1, 33.4, 22.2, 18.0, 13.9; IR: (neat) 1733 (C=O) cm^{-1}; HRMS (ESI+, TOF) m/z: [M+Na]$^+$ Calculated for $C_{21}H_{24}O_2NaCl_2$ 401.1046; Found 401.1055

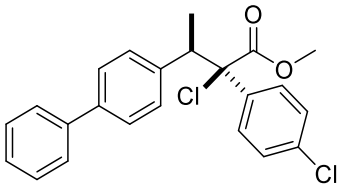
(2*R,3*S**)-20ga Methyl (2*R**,3*S**)-3-(4-butylphenyl)-2-chloro-2-(4-chlorophenyl)butanoate**



Following the general procedure using 1-butyl-4-(1-chloroethyl)benzene (0.407 mmol, 0.0800 g) and methyl 2-(4-chlorophenyl)-2-diazoacetate (0.600 mmol, 0.126 g) with InCl$_3$ (0.0405 mmol, 0.0089 g). The yield and diastereomeric ratio were determined by ^{1}H NMR in crude products (88%, 51:49). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by recycle HPLC (n-hexane/EtOAc = 90/10) to give the title compound as a colorless oil (0.0633 g, 41%).

^{1}H NMR: (400 MHz, CDCl$_3$) 7.64 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.35 (d, *J* = 8.6 Hz, 2H, Ar-H), 7.21 (d, *J* = 8.1 Hz, 2H, Ar-H), 7.09 (d, *J* = 8.1 Hz, 2H, Ar-H), 4.06 (q, *J* = 7.0 Hz, 1H), 3.58 (s, 3H, OMe), 2.58 (t, *J* = 7.5 Hz, 2H, C*H*$_2$CH$_2$CH$_2$CH$_3$), 1.59 (quint, *J* = 7.5 Hz, 2H, CH$_2$C*H*$_2$CH$_2$CH$_3$), 1.35 (sextet, *J* = 7.5 Hz, 2H, CH$_2$CH$_2$C*H*$_2$CH$_3$), 1.23 (d, *J* = 7.0 Hz, 3H, CH$_3$), 0.92 (t, *J* = 7.5 Hz, 3H, CH$_2$CH$_2$CH$_2$C*H*$_3$); ^{13}C NMR: (100 MHz, CDCl$_3$) 169.9, 142.0, 137.1, 136.5, 134.3, 129.7, 129.0, 128.2, 127.7, 80.0, 53.3, 47.8, 35.2, 33.5, 22.4, 16.5, 13.9; IR: (neat) 1732 (C=O) cm^{-1}; HRMS (ESI+, TOF) m/z: [M+Na]$^+$ Calculated for $C_{21}H_{24}O_2NaCl_2$ 401.1046; Found 401.1056

(2*R,3*R**)-20ha Methyl (2*R**,3*R**)-3-([1,1'-biphenyl]-4-yl)-2-chloro-2-(4-chlorophenyl)butanoate**

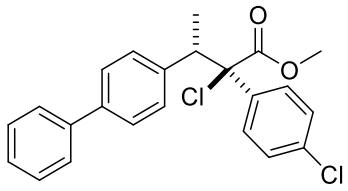


Following the general procedure using 4-(1-chloroethyl)-1,1'-biphenyl (0.418 mmol, 0.0905 g) and methyl 2-(4-chlorophenyl)-2-diazoacetate (0.597 mmol, 0.126 g) with InCl$_3$ (0.0400 mmol, 0.0088 g). The yield and diastereomeric ratio were determined by ^{1}H NMR in crude products (92%, 51:49). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by recycle HPLC (n-hexane/EtOAc = 90/10). The title compound was recrystallized by ether/pentane (1/1) to afford a colorless oil (0.0768 g, 46%).

^{1}H NMR: (400 MHz, CDCl$_3$) 7.52 (d, *J* = 7.2 Hz, 2H, Ar-H), 7.39 (t, *J* = 7.6 Hz, 2H, Ar-H), 7.32-7.29 (m, 3H, Ar-H), 7.25 (d, *J* = 8.7 Hz, 2H, Ar-H), 7.15 (d, *J* = 8.7 Hz, 2H, Ar-H), 6.99 (d, *J* = 8.5 Hz, 2H, Ar-H), 3.99 (q, *J* = 6.8 Hz, 1H), 3.82 (s, 3H, OMe), 1.57 (d, *J* = 6.8 Hz, 3H, CH$_3$); ^{13}C NMR: (100 MHz, CDCl$_3$)

170.5, 140.5, 139.6, 138.3, 136.5, 134.1, 130.0, 128.7, 128.0, 127.9, 127.2, 126.9, 126.0, 79.5, 53.7, 49.1, 18.0; IR: (neat) 1733 (C=O) cm^{-1}; HRMS (ESI+, TOF) m/z: $[M+Na]^+$ Calculated for $C_{23}H_{20}O_2NaCl_2$ 421.0733; Found 421.0726

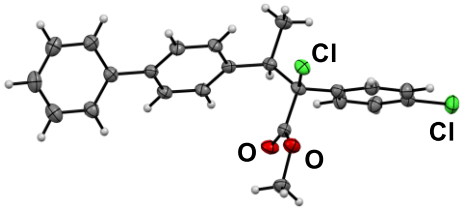
(2*R,3*S**)-20ha Methyl (2*R**,3*S**)-3-([1,1'-biphenyl]-4-yl)-2-chloro-2-(4-chlorophenyl)butanoate**



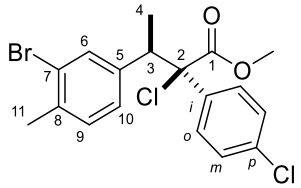
Following the general procedure using 4-(1-chloroethyl)-1,1'-biphenyl (0.418 mmol, 0.0905 g) and methyl 2-(4-chlorophenyl)-2-diazoacetate (0.597 mmol, 0.126 g) with $InCl_3$ (0.0400 mmol, 0.0088 g). The yield and diastereomeric ratio were determined by ^1H NMR in crude products (92%, 51:49). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by recycle HPLC (n-hexane/EtOAc = 90/10).The title compound was recrystallized by ether/pentane (1/1) to afford a white solid (0.0684 g, 41%).

^1H NMR: (400 MHz, $CDCl_3$) 7.66 (d, *J* = 8.5 Hz, 2H, Ar-H), 7.59 (d, *J* = 7.7 Hz, 2H, Ar-H), 7.51 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.45-7.31 (m, 7H, Ar-H), 4.13 (q, *J* = 7.1 Hz, 1H), 3.61 (s, 3H, OMe), 1.27 (d, *J* = 7.1 Hz, 3H, CH_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 169.9, 140.6, 140.1, 139.1, 136.3, 134.4, 130.3, 128.9, 128.7, 128.2, 127.2, 127.0, 126.3, 79.8, 53.5, 47.8, 16.5; IR: (KBr) 1731 (C=O) cm^{-1}; m.p. 164–165 °C; HRMS (ESI+, TOF) m/z: $[M+Na]^+$ Calculated for $C_{23}H_{20}O_2NaCl_2$ 421.0733; Found 421.0728

X-ray structure (CCDC: 2144291)



(2*R,3*R**)-20ia Methyl (2*R**,3*R**)-3-(3-bromo-4-methylphenyl)-2-chloro-2-(4-chlorophenyl)butanoate**

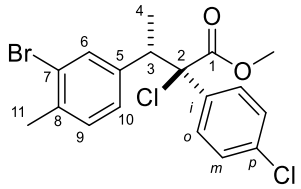


Following the general procedure using 2-bromo-4-(1-chloroethyl)-1-methylbenzene (0.400 mmol, 0.0933 g) and methyl 2-(4-chlorophenyl)-2-diazoacetate (0.600 mmol, 0.126 g) with $InCl_3$ (0.0405 mmol, 0.0089 g). The yield and diastereomeric ratio were determined by ^1H NMR in crude products (95%, 50:50). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by recycle HPLC (n-hexane/EtOAc = 90/10) to give the title compound as a colorless oil (0.0766 g, 46%).

^1H NMR: (400 MHz, $CDCl_3$) 7.23 (d, *J* = 8.9 Hz, 2H, *o*-H), 7.18 (d, *J* = 8.9 Hz, 2H, *m*-H), 7.13 (d, *J* = 1.8 Hz, 1H, 6-H), 6.90 (d, *J* = 7.7 Hz, 1H, 9-H), 6.68 (dd, *J* = 7.7, 1.8 Hz, 1H, 10-H), 3.88 (q, *J* = 6.8 Hz, 1H, 3-

H), 3.81 (s, 3H, OCH_3), 2.27 (s, 3H, 11-H_3), 1.49 (d, J = 6.8 Hz, 3H, 4-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.3 (C-1), 138.7 (C-5), 136.4, 136.3, 134.2, 133.2 (C-6), 129.7 (C-9), 128.6 (C-10), 128.0, 127.9, 123.9 (C-8), 79.1 (C-2), 53.7 (O*C*H_3), 48.7 (C-3), 22.4 (C-10), 17.9 (C-4); IR: (neat) 1732 (C=O) cm^{-1}; HRMS (ESI+, TOF) m/z: $[M+Na]^+$ Calculated for $C_{18}H_{17}O_2NaCl_2Br$ 436.9681; Found 436.9688

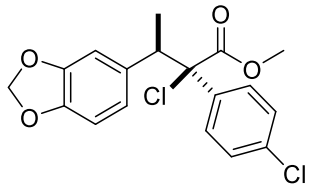
(2*R,3*S**)-20ia Methyl (2*R**,3*S**)-3-(3-bromo-4-methylphenyl)-2-chloro-2-(4-chlorophenyl)butanoate**



Following the general procedure using 2-bromo-4-(1-chloroethyl)-1-methylbenzene (0.400 mmol, 0.0933 g) and methyl 2-(4-chlorophenyl)-2-diazoacetate (0.600 mmol, 0.126 g) with $InCl_3$ (0.0405 mmol, 0.0089 g). The yield and diastereomeric ratio were determined by ^{1}H NMR in crude products (95%, 50:50). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by recycle HPLC (n-hexane/EtOAc = 90/10) to give the title compound as a colorless oil (0.0782 g, 47%).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.62 (d, J = 8.8 Hz, 2H, *o*-H), 7.47 (s, 1H, 6-H), 7.35 (d, J = 8.8 Hz, 2H, *m*-H), 7.16-7.13 (m, 2H, Ar-H), 4.03 (q, J = 7.1 Hz, 1H, 3-H), 3.62 (s, 3H, OCH_3), 2.36 (s, 3H, 11-H_3), 1.20 (d, J = 7.1 Hz, 3H, 4-H_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 169.7 (C-1), 139.4 (C-5), 136.9, 136.1, 134.5, 133.6, 130.0, 128.8, 128.7, 128.3, 124.1 (C-8), 79.6 (C-2), 53.5 (O*C*H_3), 47.3 (C-3), 22.5 (C-11), 16.3 (C-4); IR: (neat) 1733 (C=O) cm^{-1}; HRMS (ESI+, TOF) m/z: $[M+Na]^+$ Calculated for $C_{18}H_{17}O_2NaCl_2Br$ 436.9681; Found 436.9685

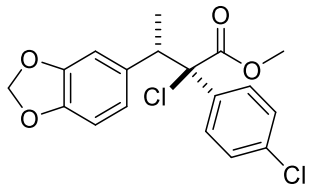
(2*R,3*R**)-20ja Methyl (2*R**,3*R**)-3-(benzo[*d*][1,3]dioxol-5-yl)-2-chloro-2-(4-chlorophenyl)butanoate**



Following the general procedure using 5-(1-chloroethyl)benzo[*d*][1,3]dioxole (0.400 mmol, 0.0738 g) and methyl 2-(4-chlorophenyl)-2-diazoacetate (0.600 mmol, 0.127 g) with $InCl_3$ (0.0391 mmol, 0.0086 g). The yield and diastereomeric ratio were determined by ^{1}H NMR in crude products (85%, 46:54). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by recycle HPLC (n-hexane/EtOAc = 85/15) to give the title compound as a colorless oil (0.0543 g, 37%).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.23 (d, J = 8.8 Hz, 2H, Ar-H), 7.17 (d, J = 8.8 Hz, 2H, Ar-H), 6.61 (d, J = 1.7 Hz, 1H, Ar-H), 6.48 (d, J = 8.1 Hz, 1H, Ar-H), 6.25 (dd, J = 8.1, 1.7 Hz, 1H, Ar-H), 5.87-5.86 (m, 2H, OCH_2O), 3.87 (q, J = 6.9 Hz, 1H), 3.81 (s, 3H, OCH_3), 1.48 (d, J = 6.9 Hz, 3H, CH_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.5, 146.8, 146.3, 136.6, 134.0, 133.1, 127.91, 127.90, 123.2, 109.5, 107.2, 100.8, 79.6, 53.7, 49.1, 18.4; IR: (neat) 1731 (C=O) cm^{-1}; HRMS (ESI+, TOF) m/z: $[M+Na]^+$ Calculated for $C_{18}H_{16}O_4NaCl_2$ 389.0318; Found 389.0315

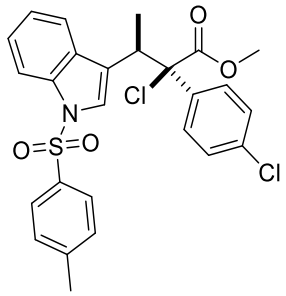
(2*R,3*S**)-20ja Methyl (2*R**,3*S**)-3-(benzo[*d*][1,3]dioxol-5-yl)-2-chloro-2-(4-chlorophenyl)butanoate**



Following the general procedure using 5-(1-chloroethyl)benzo[*d*][1,3]dioxole (0.400 mmol, 0.0738 g) and methyl 2-(4-chlorophenyl)-2-diazoacetate (0.600 mmol, 0.127 g) with $InCl_3$ (0.0391 mmol, 0.0086 g). The yield and diastereomeric ratio were determined by ^1H NMR in crude products (85%, 46:54). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by recycle HPLC (n-hexane/EtOAc = 85/15) to give the title compound as a colorless oil (0.0602 g, 41%).

^1H NMR: (400 MHz, $CDCl_3$) 7.64 (d, J = 8.7 Hz, 2H, Ar-H), 7.35 (d, J = 8.7 Hz, 2H, Ar-H), 6.87 (d, J = 1.7 Hz, 1H, Ar-H), 6.75 (dd, J = 8.1, 1.7 Hz, 1H, Ar-H), 6.71 (d, J = 8.1 Hz, 1H, Ar-H), 5.93 (s, 2H, OCH_2O), 4.03 (q, J = 7.0 Hz, 1H), 3.61 (s, 3H, OCH_3), 1.19 (d, J = 7.0 Hz, 3H, CH_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 169.8, 147.0, 146.7, 136.4, 134.4, 133.7, 128.9, 128.2, 123.3, 110.1, 107.4, 100.9, 80.1, 53.4, 47.8, 16.6; IR: (neat) 1732 (C=O) cm^{-1}; HRMS (ESI+, TOF) m/z: $[M+Na]^+$ Calculated for $C_{18}H_{16}O_4NaCl_2$ 389.0318; Found 389.0318

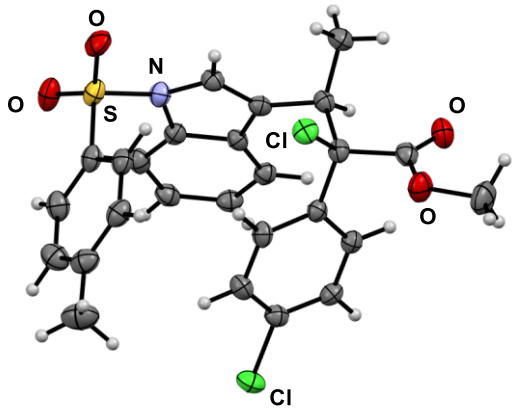
(2*R,3*R**)-20ka Methyl (2*R**,3*R**)-2-chloro-2-(4-chlorophenyl)-3-(1-tosyl-1*H*-indol-3-yl)butanoate**



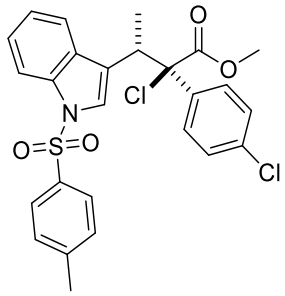
Following the general procedure using 3-(1-chloroethyl)-1-tosyl-1*H*-indole (0.406 mmol, 0.135 g) and methyl 2-(4-chlorophenyl)-2-diazoacetate (0.601 mmol, 0.127 g) with $InCl_3$ (0.0400 mmol, 0.0088 g). The yield and diastereomeric ratio were determined by ^1H NMR in crude products (75%, 31:69). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by recycle HPLC (n-hexane/EtOAc = 80/20), followed by recrystallization in methanol to give the title compound as a colorless solid (0.0481 g, 23%).

^1H NMR: (400 MHz, $CDCl_3$) 7.88 (d, J = 8.5 Hz, 1H, Ar-H), 7.56 (d, J = 8.5 Hz, 2H, Ar-H), 7.45 (s, 1H, Ar-H), 7.21-7.19 (m, 3H, Ar-H), 7.10-7.06 (m, 4H, Ar-H), 6.87 (d, J = 8.9 Hz, 2H, Ar-H), 4.26 (q, J = 6.7 Hz, 1H), 3.82 (s, 3H, OCH_3), 2.35 (s, 3H, Ar-CH_3), 1.55 (d, J = 6.7 Hz, 3H, CH_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.2, 144.8, 136.6, 135.0, 134.2, 134.0, 130.7, 129.7, 129.2, 127.9, 127.8, 126.6, 125.0, 124.5, 122.9, 121.8, 118.9, 113.5, 79.2, 53.9, 40.3, 21.5, 19.0; IR: (KBr) 1734 (C=O), 1596 cm^{-1}; m.p. 149–150 °C; HRMS (ESI+, TOF) m/z: $[M+Na]^+$ Calculated for $C_{26}H_{23}NO_4NaSCl_2$ 538.0617; Found 538.0638

X-ray structure (CCDC: 2144292)



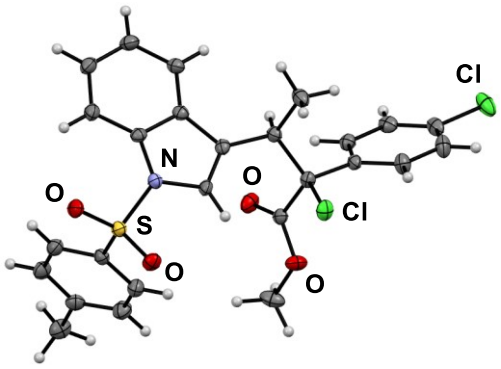
(2*R,3*S**)-20ka Methyl (2*R**,3*S**)-2-chloro-2-(4-chlorophenyl)-3-(1-tosyl-1*H*-indol-3-yl)butanoate**



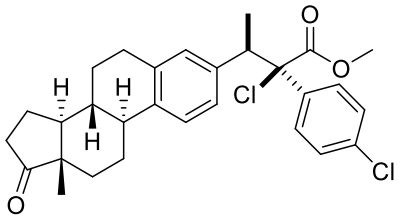
Following the general procedure using 3-(1-chloroethyl)-1-tosyl-1*H*-indole (0.406 mmol, 0.135 g) and methyl 2-(4-chlorophenyl)-2-diazoacetate (0.601 mmol, 0.127 g) with $InCl_3$ (0.0400 mmol, 0.0088 g). The yield and diastereomeric ratio were determined by ^1H NMR in crude products (75%, 31:69). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by recycle HPLC (n-hexane/EtOAc = 80/20), followed by recrystallization in methanol to give the title compound as a colorless solid (0.107 g, 51%).

^1H NMR: (400 MHz, $CDCl_3$) 7.96 (d, J = 7.5 Hz, 1H, Ar-H), 7.72 (d, J = 8.5 Hz, 2H, Ar-H), 7.65-7.63 (m, 3H, Ar-H), 7.59 (d, J = 7.5 Hz, 1H, Ar-H), 7.32-7.24 (m, 6H, Ar-H), 4.30 (q, J = 7.0 Hz, 1H), 3.31 (s, 3H, OCH_3), 2.33 (s, 3H, Ar-CH_3), 1.27 (d, J = 7.0 Hz, 3H, CH_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 169.6, 144.7, 136.1, 135.0, 134.6, 134.4, 130.7, 129.7, 128.6, 128.4, 126.7, 125.4, 124.6, 123.0, 122.6, 119.9, 113.6, 79.6, 53.3, 39.9, 21.5, 17.5; IR: (KBr) 1740 (C=O), 1597 cm^{-1}; m.p. 137–138 °C; HRMS (ESI+, TOF) m/z: $[M+Na]^+$ Calculated for $C_{26}H_{23}NO_4NaSCl_2$ 538.0617; Found 538.0640

X-ray structure (CCDC: 2144294)



(2*R,3*R**)-20la Methyl (2*R**,3*R**)-2-chloro-2-(4-chlorophenyl)-3-((8*R*,9*S*,13*S*,14*S*)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-3-yl)butanoate**

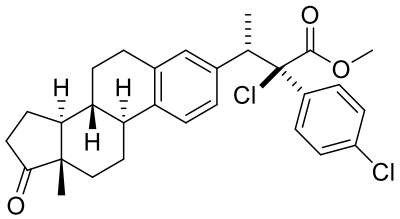


Following the general procedure using (8*R*,9*S*,13*S*,14*S*)-3-(1-chloroethyl)-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*-cyclopenta[*a*]phenanthren-17-one (0.401 mmol, 0.127 g) and methyl 2-(4-chlorophenyl)-2-diazoacetate (0.601 mmol, 0.127 g) with $InCl_3$ (0.0409 mmol, 0.0090 g). The yield and diastereomeric ratio were determined by ^1H NMR in crude products (76%, 53:47). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by recycle HPLC (n-hexane/EtOAc = 85/15) to give the title compound as a colorless oil (0.0775 g, 39%, *dr* = 50:50).

*The below spectrum data are for a mixture of diastereomers **20la** because these diastereomers could not be separated by column chromatography.*

^1H NMR: (400 MHz, $CDCl_3$) 7.25 (d, *J* = 8.9 Hz, 1H, Ar-H), 7.24 (d, *J* = 8.9 Hz, 1H, Ar-H), 7.17 (d, *J* = 8.9 Hz, 2H, Ar-H), 7.03 (d, *J* = 8.2 Hz, 0.5H, Ar-H), 6.97 (d, *J* = 8.2 Hz, 0.5H, Ar-H), 6.80 (d, *J* = 8.2 Hz, 0.5H, Ar-H), 6.66 (s, 0.5H, Ar-H), 6.63 (d, *J* = 8.2 Hz, 0.5H, Ar-H), 6.51 (s, 0.5H, Ar-H), 3.89 (q, *J* = 7.0 Hz, 1H), 3.82 (s, 3H, OCH_3), 2.75-2.63 (m, 2H), 2.52-2.47 (m, 1H), 2.35-2.32 (m, 1H), 2.12-2.00 (m, 5H), 1.65-1.33 (m, 9H), 0.893 (s, 1.5H, CH_3), 0.889 (s, 1.5H, CH_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 220.9, 170.5, 138.3, 136.6, 136.5, 135.33, 135.29, 133.96, 133.94, 130.6, 130.1, 128.3, 128.2, 127.73, 127.70, 127.2, 126.7, 124.4, 124.2, 79.6, 79.5, 53.6, 50.5, 50.4, 48.9, 48.8, 47.9, 44.2, 44.1, 37.97, 37.96, 35.8, 31.6, 31.5, 29.3, 29.2, 26.5, 26.4, 25.5, 25.4, 22.6, 21.5, 17.84, 17.83, 14.1, 13.8 *Some signals were overlapped so numbers of observed signals were less than expected ones*; IR: (neat) 1739 (C=O) cm^{-1}; HRMS (DART+, TOF) m/z: $[M+H]^+$ Calculated for $C_{29}H_{33}O_3Cl_2$ 499.1801; Found 499.1823

(2*R,3*S**)-20la Methyl (2*R**,3*S**)-2-chloro-2-(4-chlorophenyl)-3-((8*R*,9*S*,13*S*,14*S*)-13-methyl-17-oxo-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[*a*]phenanthren-3-yl)butanoate**

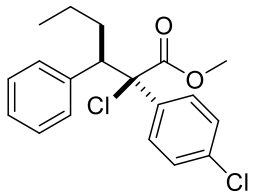


Following the general procedure using (8*R*,9*S*,13*S*,14*S*)-3-(1-chloroethyl)-13-methyl-6,7,8,9,11,12,13,14,15,16-decahydro-17*H*-cyclopenta[*a*]phenanthren-17-one (0.401 mmol, 0.127 g) and methyl 2-(4-chlorophenyl)-2-diazoacetate (0.601 mmol, 0.127 g) with $InCl_3$ (0.0409 mmol, 0.0090 g). The yield and diastereomeric ratio were determined by ^1H NMR in crude products (76%, 53:47). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by recycle HPLC (n-hexane/EtOAc = 85/15) to give the title compound as a colorless oil (0.0672 g, 34%, *dr* = 50:50)

The below spectrum data are for a mixture of diastereomers ***20la*** *because these diastereomers could not be separated by column chromatography.*

^{1}H NMR: (400 MHz, $CDCl_3$) 7.65 (d, J = 8.6 Hz, 1H, Ar-H), 7.64 (d, J = 8.6 Hz, 1H, Ar-H), 7.35 (d, J = 8.6 Hz, 2H, Ar-H), 7.19 (d, J = 8.4 Hz, 1H, Ar-H), 7.08-7.01 (m, 2H, Ar-H), 4.05 (q, J = 7.1 Hz, 1H), 3.62 (s, 1.5H, OCH_3), 3.61 (s, 1.5H, OCH_3), 2.91-2.88 (m, 2H), 2.55-2.48 (m, 1H), 2.42-2.40 (m, 1H), 2.32-2.26 (m, 1H), 2.20-1.93 (m, 4H), 1.65-1.41 (m, 6H), 1.22 (d, J = 7.1 Hz, 3H, CH_3), 0.92 (s, 3H, CH_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 220.90, 220.89, 169.89, 169.87, 138.8, 138.7, 137.3, 135.62, 135.60, 134.3, 130.6, 130.3, 129.0, 128.2, 128.1, 127.3, 127.1, 124.63, 124.59, 80.02, 79.96, 53.3, 50.5, 47.9, 47.49, 47.47, 44.3, 44.2, 38.0, 35.8, 31.5, 29.45, 29.43, 26.5, 25.6, 25.5, 22.6, 21.5, 16.44, 16.40, 14.1, 13.8 *Some signals were overlapped so numbers of observed signals were less than expected ones*; IR: (neat) 1736 (C=O) cm^{-1}; HRMS (DART+, TOF) m/z: $[M+H]^+$ Calculated for $C_{29}H_{33}O_3Cl_2$ 499.1801; Found 499.1816

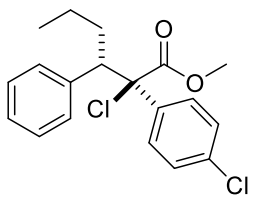
(2*R,3*R**)-20ma Methyl (2*R**,3*R**)-2-chloro-2-(4-chlorophenyl)-3-phenylhexanoate**



Following the general procedure using (1-chlorobutyl)benzene (0.404 mmol, 0.0682 g) and methyl 2-(4-chlorophenyl)-2-diazoacetate (0.600 mmol, 0.126 g) with $InCl_3$ (0.0405 mmol, 0.0089 g). The yield and diastereomeric ratio were determined by ^{1}H NMR in crude products (87%, 67:33). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by recycle HPLC (n-hexane/EtOAc = 90/10) to give the title compound as a colorless oil (0.0780 g, 55%).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.18 (d, J = 8.7 Hz, 2H, Ar-H), 7.10-7.05 (m, 5H, Ar-H), 6.96 (d, J = 6.8 Hz, 2H, Ar-H), 3.81 (s, 3H, OCH_3), 3.73 (d, J = 11.1 Hz, 1H), 2.08-2.04 (m, 1H, CH_2CH$_2$CH$_3$), 1.82-1.75 (m, 1H, CH_2CH$_2$CH$_3$), 1.20-1.09 (m, 2H, CH$_2$CH_2CH$_3$), 0.86 (t, J = 7.4 Hz, 3H, CH$_2$CH$_2$CH_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.7, 137.4, 136.6, 133.8, 130.0, 127.8, 127.7, 127.5, 126.9, 79.5, 55.1, 53.7, 34.5, 20.7, 13.9; IR: (neat) 1732 (C=O) cm^{-1}; HRMS (ESI+, TOF) m/z: $[M+Na]^+$ Calculated for $C_{19}H_{20}O_2NaCl_2$ 373.0733; Found 373.0721

(2*R,3*S**)-20ma Methyl (2*R**,3*S**)-2-chloro-2-(4-chlorophenyl)-3-phenylhexanoate**

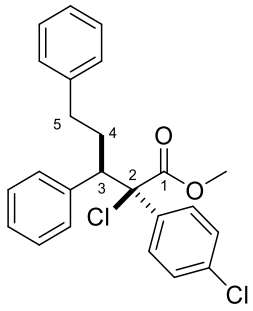


Following the general procedure using (1-chlorobutyl)benzene (0.404 mmol, 0.0682 g) and methyl 2-(4-chlorophenyl)-2-diazoacetate (0.600 mmol, 0.126 g) with $InCl_3$ (0.0405 mmol, 0.0089 g). The yield and diastereomeric ratio were determined by ^{1}H NMR in crude products (87%, 67:33). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by recycle HPLC (n-hexane/EtOAc = 90/10)

to give the title compound as a colorless oil (0.0380 g, 27%).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.62 (d, J = 8.9 Hz, 2H, Ar-H), 7.35 (d, J = 8.9 Hz, 2H, Ar-H), 7.29-7.26 (m, 5H, Ar-H), 3.85 (dd, J = 11.7, 2.5 Hz, 1H), 3.54 (s, 3H, OCH_3), 1.87-1.77 (m, 1H, CH_2CH$_2$CH$_3$), 1.52-1.44 (m, 1H, CH_2CH$_2$CH$_3$), 1.12-1.00 (m, 2H, CH$_2$CH_2CH$_3$), 0.76 (t, J = 7.4 Hz, 3H, CH$_2$CH$_2$CH_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 169.8, 137.9, 136.6, 134.3, 130.5, 129.1, 128.2, 127.7, 127.5, 79.6, 53.7, 53.3, 32.4, 20.4, 13.8; IR: (neat) 1732 (C=O) cm^{-1}; HRMS (ESI+, TOF) m/z: $[M+Na]^+$ Calculated for $C_{19}H_{20}O_2NaCl_2$ 373.0733; Found 373.0724

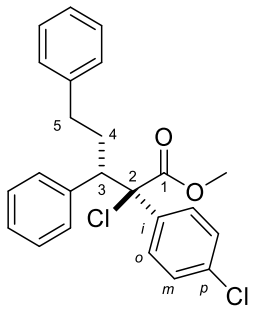
(2*R,3*R**)-20na Methyl (2*R**,3*R**)-2-chloro-2-(4-chlorophenyl)-3,5-diphenylpentanoate**



Following the general procedure using (1-chloropropane-1,3-diyl)dibenzene (0.403 mmol, 0.0930 g) and methyl 2-(4-chlorophenyl)-2-diazoacetate (0.600 mmol, 0.126 g) with $InCl_3$ (0.0401 mmol, 0.0088 g). The yield and diastereomeric ratio were determined by ^{1}H NMR in crude products (42%, 67:33). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by recycle HPLC (n-hexane/EtOAc = 90/10) to give the title compound as a colorless oil (0.0401 g, 24%).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.25-7.07 (m, 10H, Ar-H), 6.84-6.80 (m, 4H, Ar-H), 3.58 (s, 3H, OCH_3), 3.11-3.93 (m, 4H, 3-H, 4-H^a, and 5-H$_2$), 2.08-2.02 (m, 1H, 4-H^b); ^{13}C NMR: (100 MHz, $CDCl_3$) 172.8 (C-1), 143.8, 141.1, 138.2, 138.0, 132.2, 131.6, 131.5, 129.8, 129.2, 127.4, 127.18, 127.16, 126.7, 125.8, 61.0 (C-2), 54.5 (C-5), 51.8 (O*C*H$_3$), 30.3 (C-3), 26.2 (C-4); IR: (neat) 1731 (C=O) cm^{-1}; HRMS (ESI+, TOF) m/z: $[M+Na]^+$ Calculated for $C_{24}H_{22}O_2NaCl_2$ 435.0889; Found 435.0888

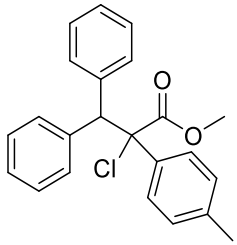
(2*R,3*S**)-20na Methyl (2*R**,3*S**)-2-chloro-2-(4-chlorophenyl)-3,5-diphenylpentanoate**



Following the general procedure using (1-chloropropane-1,3-diyl)dibenzene (0.403 mmol, 0.0930 g) and methyl 2-(4-chlorophenyl)-2-diazoacetate (0.600 mmol, 0.126 g) with $InCl_3$ (0.0401 mmol, 0.0088 g). The yield and diastereomeric ratio were determined by ^{1}H NMR in crude products (42%, 67:33). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by recycle HPLC (n-hexane/EtOAc = 90/10) to give the title compound as a colorless oil (0.0225 g, 14%).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.27 (t, J = 7.4 Hz, 2H, Ar-H), 7.20-7.08 (m, 10H, Ar-H), 6.99 (d, J = 6.0 Hz, 2H, Ar-H), 3.78 (s, 3H, OCH_3), 3.73 (dd, J = 10.6, 2.9 Hz, 1H, 3-H), 2.48-2.34 (m, 3H, 4-H^a and 5-H_2), 2.22-2.14 (m, 1H, 4-H^b); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.5 (C-1), 141.6, 136.9, 136.6, 133.9, 130.2, 128.4, 128.3, 127.9, 127.71, 127.70, 127.2, 125.9, 79.3 (C-2), 54.8 (C-5), 53.7 (O*C*H_3), 34.1 (C-4), 33.6 (C-3); IR: (neat) 1756, 1726 (C=O) cm^{-1}; HRMS (ESI+, TOF) m/z: $[M+Na]^+$ Calculated for $C_{24}H_{22}O_2NaCl_2$ 435.0889; Found 435.0891

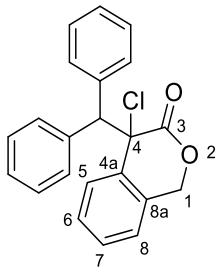
20og Methyl 2-chloro-3,3-diphenyl-2-(*p*-tolyl)propanoate



Following a modified procedure using (chloromethylene)dibenzene (0.526 mmol, 0.106 g) and methyl 2-diazo-2-(*p*-tolyl)acetate (0.773 mmol, 0.147 g) with $InCl_3$ (0.0522 mmol, 0.0115 g) in EtOAc (2 mL). The reaction was stirred at 0 °C for 6 h. The yield was determined by ^{1}H NMR in crude product (46%). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by recycle GPC ($CHCl_3$ as eluent) to give the title compound as a colorless oil (0.0825 g, 43%).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.46 (t, J = 8.1 Hz, 4H, Ar-H), 7.29-7.21 (m, 3H, Ar-H), 7.06-7.04 (m, 7H, Ar-H), 5.44 (s, 1H), 3.62 (s, 3H, Ome), 2.29 (s, 3H, Ar-C*H*$_3$); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.4, 140.8, 139.0, 138.1, 135.3, 130.7, 129.9, 128.7, 127.9, 127.4, 127.2, 126.8, 126.5, 78.8, 59.3, 53.6, 20.9; IR: (neat) 1739 (C=O) cm^{-1}; HRMS (ESI+, TOF) m/z: $[M+Na]^+$ Calculated for $C_{23}H_{21}O_2NaCl$ 387.1122; Found 387.1132

20ok 4-Benzhydryl-4-chloroisochroman-3-one

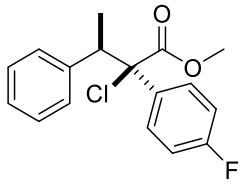


Following a modified procedure using (chloromethylene)dibenzene (0.505 mmol, 0.102 g) and 4-diazoisochroman-3-one (1.001 mmol, 0.174 g) with $InCl_3$ (0.0502 mmol, 0.0112 g) in EtOAc (2 Ml). The reaction was stirred at 0 °C for 6 h. The yield was determined by ^{1}H NMR in crude product (73%). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by recycle HPLC (n-hexane/EtOAc = 80/20) to give the title compound as a colorless solid (0.119 g, 68%).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.44-7.14 (m, 13H, Ar-H), 7.07 (d, J = 7.7 Hz, 1H, 8-H), 5.16 (d, J = 15.3 Hz, 1H, 1-H^a), 4.77 (s, 1H, C*H*Ph_2), 4.71 (d, J = 15.3 Hz, 1H, 1-H^b); ^{13}C NMR: (100 MHz, $CDCl_3$) 167.9 (C-3), 137.3, 137.1, 133.8, 130.4, 130.3, 130.0, 129.9, 128.9, 128.2, 128.1, 128.0, 127.9, 127.8, 123.2 (C-8), 71.9 (C-4), 69.9 (C-1), 62.0 (4-*C*Ph_2); IR: (KBr) 1771 (C=O) cm^{-1}; m.p. 160–161 °C; HRMS (ESI+, TOF) m/z:

[M+Na]$^+$Calculated for $C_{22}H_{17}O_2NaCl$ 371.0809; Found 371.0807

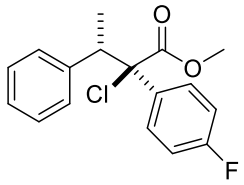
(2*R,3*R**)-20ab Methyl (2*R**,3*R**)-2-chloro-2-(4-fluorophenyl)-3-phenylbutanoate**



Following the general procedure using (1-chloroethyl)benzene (0.412 mmol, 0.0579 g) and methyl 2-diazo-2-(4-fluorophenyl)acetate (0.610 mmol, 0.119 g) with $InCl_3$ (0.0432 mmol, 0.0095 g). The yield and diastereomeric ratio were determined by ^{1}H NMR in crude products (82%, 53:47). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by recycle HPLC (n-hexane/EtOAc = 90/10) to give the title compound as a colorless oil (0.0529 g, 42%).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.23 (d, J = 9.1 Hz, d, $^3J_{H\text{-}F}$ = 5.2 Hz, 2H, Ar-H), 7.12-7.04 (m, 3H, Ar-H), 6.91 (d, J = 8.2 Hz, 2H, Ar-H), 6.85 (t, J = 8.2 Hz, 2H, Ar-H), 3.94 (q, J = 6.8 Hz, 1H), 3.82 (s, 3H, OCH_3), 1.54 (d, J = 6.8 Hz, 3H, CH_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.7, 162.2 (d, $J_{C\text{-}F}$ = 247.4 Hz), 139.4, 133.8 (d, $J_{C\text{-}F}$ = 3.3 Hz), 129.6, 128.3 (d, $J_{C\text{-}F}$ = 8.2 Hz), 127.4, 126.9, 114.6 (d, $J_{C\text{-}F}$ = 22.1 Hz), 79.5, 53.7, 49.5, 18.0; IR: (neat) 1732 (C=O) cm^{-1}; HRMS (ESI+, TOF) m/z: [M+Na]$^+$ Calculated for $C_{17}H_{16}O_2FNaCl$ 329.0715; Found 329.0701

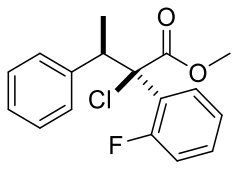
(2*R,3*S**)-20ab Methyl (2*R**,3*S**)-2-chloro-2-(4-fluorophenyl)-3-phenylbutanoate**



Following the general procedure using (1-chloroethyl)benzene (0.412 mmol, 0.0579 g) and methyl 2-diazo-2-(4-fluorophenyl)acetate (0.610 mmol, 0.119 g) with $InCl_3$ (0.0432 mmol, 0.0095 g). The yield and diastereomeric ratio were determined by ^{1}H NMR in crude products (82%, 53:47). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by recycle HPLC (n-hexane/EtOAc = 90/10) to give the title compound as a colorless oil (0.0469 g, 37%).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.67 (d, J = 8.9 Hz, d, $^3J_{H\text{-}F}$ = 5.1 Hz, 2H, Ar-H), 7.32-7.25 (m, 5H, Ar-H), 7.06 (t, J = 8.6 Hz, 2H, Ar-H), 4.09 (q, J = 7.0 Hz, 1H), 3.59 (s, 3H, OCH_3), 1.25 (d, J = 7.0 Hz, 3H, CH_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.1, 162.5 (d, $J_{C\text{-}F}$ = 249.1 Hz), 140.1, 133.6 (d, $J_{C\text{-}F}$ = 3.3 Hz), 129.9, 129.4 (d, $J_{C\text{-}F}$ = 8.2 Hz), 127.7, 127.4, 114.9 (d, $J_{C\text{-}F}$ = 22.1 Hz), 79.8, 53.3, 48.2, 16.5; IR: (neat) 1732 (C=O) cm^{-1}; HRMS (ESI+, TOF) m/z: [M+Na]$^+$ Calculated for $C_{17}H_{16}O_2FNaCl$ 329.0715; Found 329.0699

(2*R,3*R**)-20ao Methyl (2*R**,3*R**)-2-chloro-2-(2-fluorophenyl)-3-phenylbutanoate**

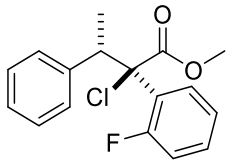


Following the general procedure using (1-chloroethyl)benzene (0.406 mmol, 0.0571 g) and methyl 2-diazo-

2-(2-fluorophenyl)acetate (0.610 mmol, 0.119 g) with $InCl_3$ (0.0368 mmol, 0.0081 g). The yield and diastereomeric ratio were determined by ^1H NMR in crude products (66%, 55:45). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by recycle HPLC (n-hexane/EtOAc = 90/10) to give the title compound as a colorless oil (0.0423 g, 34%).

^1H NMR: (400 MHz, $CDCl_3$) 7.26 (t, J = 8.2 Hz, d, $^4J_{H\text{-}F}$ = 1.5 Hz, 1H, Ar-H), 7.18-7.12 (m, 1H, Ar-H), 7.08-7.01 (m, 3H, Ar-H), 6.98-6.96 (m, 2H, Ar-H), 6.92-6.84 (m, 2H, Ar-H), 3.99 (q, J = 6.8 Hz, 1H), 3.76 (s, 3H, OCH_3), 1.69 (d, J = 6.8 Hz, 3H, CH_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.7, 158.6 (d, $J_{C\text{-}F}$ = 245.8 Hz), 140.9, 129.8 (d, $J_{C\text{-}F}$ = 8.2 Hz), 129.6 (d, $J_{C\text{-}F}$ = 8.2 Hz), 128.8, 127.5, 126.8, 126.6 (d, $J_{C\text{-}F}$ = 12.3 Hz), 123.6 (d, $J_{C\text{-}F}$ = 3.3 Hz), 115.0 (d, $J_{C\text{-}F}$ = 22.1 Hz), 74.7, 53.2, 46.4 (d, $J_{C\text{-}F}$ = 1.6 Hz), 18.2; IR: (neat) 1749 (C=O) cm^{-1}; HRMS (ESI+, TOF) m/z: $[M+Na]^+$ Calculated for $C_{17}H_{16}O_2FNaCl$ 329.0715; Found 329.0708

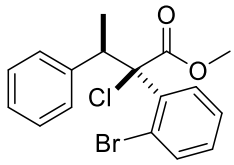
(2*R,3*S**)-20ao Methyl (2*R**,3*S**)-2-chloro-2-(2-fluorophenyl)-3-phenylbutanoate**



Following the general procedure using (1-chloroethyl)benzene (0.406 mmol, 0.0571 g) and methyl 2-diazo-2-(2-fluorophenyl)acetate (0.610 mmol, 0.119 g) with $InCl_3$ (0.0368 mmol, 0.0081 g). The yield and diastereomeric ratio were determined by ^1H NMR in crude products (66%, 55:45). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by recycle HPLC (n-hexane/EtOAc = 90/10) to give the title compound as a colorless oil (0.0349 g, 28%).

^1H NMR: (400 MHz, $CDCl_3$) 7.37-7.33 (m, 1H, Ar-H), 7.25-7.16 (m, 4H, Ar-H), 7.09-7.05 (m, 2H, Ar-H), 6.94 (d, J = 7.7 Hz, 2H, Ar-H), 3.98 (q, J = 7.1 Hz, 1H), 3.75 (s, 3H, OCH_3), 1.41 (d, J = 7.1 Hz, d, $^6J_{H\text{-}F}$ = 3.9 Hz, 3H, CH_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 169.9, 159.3 (d, $J_{C\text{-}F}$ = 247.4 Hz), 139.8, 131.6 (d, $J_{C\text{-}F}$ = 2.5 Hz), 130.5 (d, $J_{C\text{-}F}$ = 9.0 Hz), 130.4, 127.23, 127.20, 124.3 (d, $J_{C\text{-}F}$ = 11.5 Hz), 123.5 (d, $J_{C\text{-}F}$ = 3.3 Hz), 115.4 (d, $J_{C\text{-}F}$ = 23.8 Hz), 73.4, 53.2, 48.6, 17.6 (d, $J_{C\text{-}F}$ = 4.9 Hz); IR: (neat) 1748 (C=O) cm^{-1}; HRMS (ESI+, TOF) m/z: $[M+Na]^+$ Calculated for $C_{17}H_{16}O_2FNaCl$ 329.0715; Found 329.0706

(2*R,3*R**)-20ap Methyl (2*R**,3*R**)-2-(2-bromophenyl)-2-chloro-3-phenylbutanoate**

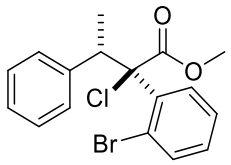


Following the general procedure using (1-chloroethyl)benzene (0.418 mmol, 0.0587 g) and methyl 2-(2-bromophenyl)-2-diazoacetate (0.605 mmol, 0.154 g) with $InCl_3$ (0.0400 mmol, 0.0088 g). The yield and diastereomeric ratio were determined by ^1H NMR in crude products (52%, 59:41). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by recycle HPLC (n-hexane/EtOAc = 90/10) to give the title compound as a colorless oil (0.0423 g, 28%).

^1H NMR: (400 MHz, $CDCl_3$) 7.42-7.41 (m, 1H, Ar-H), 7.33-7.31 (m, 1H, Ar-H), 7.00 (br s, 5H, Ar-H), 6.96-6.90 (m, 2H, Ar-H), 4.32 (q, J = 6.6 Hz, 1H), 3.78 (s, 3H, OCH_3), 1.83 (d, J = 6.6 Hz, 3H, CH_3); ^{13}C NMR:

(100 MHz, $CDCl_3$) 170.2, 141.5, 138.3, 133.4, 130.7, 129.0, 128.3, 127.5, 126.71, 126.67, 120.6, 78.3, 53.4, 44.5, 18.6; IR: (neat) 1747 (C=O) cm^{-1}; HRMS (ESI+, TOF) m/z: $[M+Na]^+$ Calculated for $C_{17}H_{16}O_2NaClBr$ 388.9914; Found 388.9912

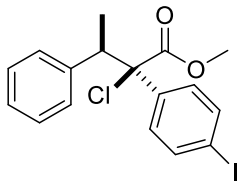
(2*R,3*S**)-20ap Methyl (2*R**,3*S**)-2-(2-bromophenyl)-2-chloro-3-phenylbutanoate**



Following the general procedure using (1-chloroethyl)benzene (0.418 mmol, 0.0587 g) and methyl 2-(2-bromophenyl)-2-diazoacetate (0.605 mmol, 0.154 g) with $InCl_3$ (0.0400 mmol, 0.0088 g). The yield and diastereomeric ratio were determined by ^1H NMR in crude products (52%, 59:41). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by recycle HPLC (n-hexane/EtOAc = 90/10) to give the title compound as a colorless oil (0.0308 g, 20%).

^1H NMR: (400 MHz, $CDCl_3$) 7.71 (d, J = 7.6 Hz, 1H, Ar-H), 7.62 (d, J = 7.6 Hz, 1H, Ar-H), 7.31-7.24 (m, 7H, Ar-H), 4.11 (q, J = 6.9 Hz, 1H), 3.57 (s, 3H, OCH_3), 1.42 (d, J = 6.9 Hz, 3H, CH_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 169.5, 140.9, 138.0, 134.7, 131.1, 130.2, 129.7, 127.4, 127.2, 126.9, 122.5, 77.6, 53.1, 46.9, 19.1; IR: (neat) 1747 (C=O) cm^{-1}; HRMS (ESI+, TOF) m/z: $[M+Na]^+$ Calculated for $C_{17}H_{16}O_2NaClBr$ 388.9914; Found 388.9916

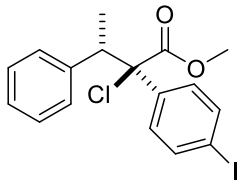
(2*R,3*R**)-20ad Methyl (2*R**,3*R**)-2-chloro-2-(4-iodophenyl)-3-phenylbutanoate**



Following the general procedure using (1-chloroethyl)benzene (0.420 mmol, 0.0590 g) and methyl 2-diazo-2-(4-iodophenyl)acetate (0.603 mmol, 0.182 g) with $InCl_3$ (0.0391 mmol, 0.0086 g). The yield and diastereomeric ratio were determined by ^1H NMR in crude products (95%, 50:50). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by recycle HPLC (n-hexane/EtOAc = 90/10) to give the title compound as a colorless oil (0.0801 g, 46%).

^1H NMR: (400 MHz, $CDCl_3$) 7.49 (d, J = 8.5 Hz, 2H, Ar-H), 7.13-7.06 (m, 3H, Ar-H), 7.00 (d, J = 7.0 Hz, 2H, Ar-H), 6.93 (d, J = 7.0 Hz, 2H, Ar-H), 3.93 (q, J = 6.8 Hz, 1H), 3.81 (s, 3H, OCH_3), 1.54 (d, J = 6.8 Hz, 3H, CH_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.4, 139.2, 137.8, 136.8, 129.6, 128.4, 127.4, 127.0, 94.0, 79.6, 53.7, 49.2, 18.0; IR: (neat) 1732 (C=O) cm^{-1}; HRMS (ESI+, TOF) m/z: $[M+Na]^+$ Calculated for $C_{17}H_{16}O_2NaClI$ 436.9776; Found 436.9777

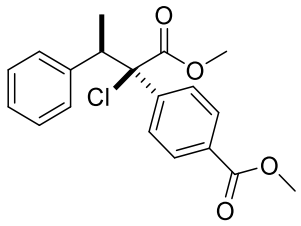
(2*R,3*S**)-20ad Methyl (2*R**,3*S**)-2-chloro-2-(4-iodophenyl)-3-phenylbutanoate**



Following the general procedure using (1-chloroethyl)benzene (0.420 mmol, 0.0590 g) and methyl 2-diazo-2-(4-iodophenyl)acetate (0.603 mmol, 0.182 g) with $InCl_3$ (0.0391 mmol, 0.0086 g). The yield and diastereomeric ratio were determined by ^1H NMR in crude products (95%, 50:50). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by recycle HPLC (n-hexane/EtOAc = 90/10) to give the title compound as a colorless oil (0.0818 g, 47%).

^1H NMR: (400 MHz, $CDCl_3$) 7.71 (d, J = 8.7 Hz, 2H, Ar-H), 7.44 (d, J = 8.2 Hz, 2H, Ar-H), 7.31-7.26 (m, 5H, Ar-H), 4.08 (q, J = 7.1 Hz, 1H), 3.57 (s, 3H, OCH_3), 1.25 (d, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 169.8, 139.9, 137.7, 137.1, 129.8, 129.4, 127.7, 127.4, 94.5, 79.9, 53.4, 48.0, 16.5; IR: (neat) 1732 (C=O) cm^{-1}; HRMS (ESI+, TOF) m/z: $[M+Na]^+$ Calculated for $C_{17}H_{16}O_2NaClI$ 436.9776; Found 436.9778

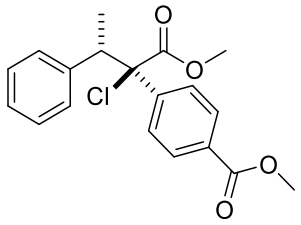
(2*R,3*R**)-20af Methyl 4-((2*R**,3*R**)-2-chloro-1-methoxy-1-oxo-3-phenylbutan-2-yl)benzoate**



Following the general procedure using (1-chloroethyl)benzene (0.419 mmol, 0.0589 g) and methyl 4-(1-diazo-2-methoxy-2-oxoethyl)benzoate (0.600 mmol, 0.141 g) with $InCl_3$ (0.0409 mmol, 0.0090 g). The yield and diastereomeric ratio were determined by ^1H NMR in crude products (66%, 39:61). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by recycle HPLC (n-hexane/EtOAc = 80/20) to give the title compound as a colorless oil (0.0349 g, 24%).

^1H NMR: (400 MHz, $CDCl_3$) 7.83 (d, J = 8.7 Hz, 2H, Ar-H), 7.35 (d, J = 8.7 Hz, 2H, Ar-H), 7.08-7.04 (m, 3H, Ar-H), 6.91 (d, J = 7.8 Hz, 2H, Ar-H), 3.98 (q, J = 6.8 Hz, 1H), 3.88 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 1.57 (d, J = 6.8 Hz, 3H, CH_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.4, 166.4, 142.8, 139.1, 129.7, 129.5, 129.0, 127.4, 127.0, 126.5, 79.8, 53.7, 52.1, 49.4, 18.0; IR: (neat) 1731 (C=O) cm^{-1}; HRMS (ESI+, TOF) m/z: $[M+Na]^+$ Calculated for $C_{19}H_{19}O_4NaCl$ 369.0864; Found 369.0851

(2*R,3*S**)-20af Methyl 4-((2*R**,3*S**)-2-chloro-1-methoxy-1-oxo-3-phenylbutan-2-yl)benzoate**

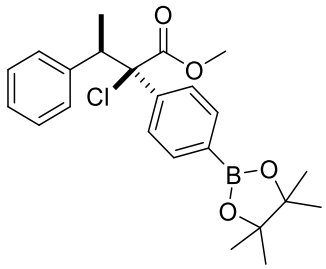


Following the general procedure using (1-chloroethyl)benzene (0.419 mmol, 0.0589 g) and methyl 4-(1-diazo-2-methoxy-2-oxoethyl)benzoate (0.600 mmol, 0.141 g) with $InCl_3$ (0.0409 mmol, 0.0090 g). The yield and diastereomeric ratio were determined by ^1H NMR in crude products (66%, 39:61). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by recycle HPLC (n-hexane/EtOAc = 80/20) to give the title compound as a colorless oil (0.0546 g, 38%).

^1H NMR: (400 MHz, $CDCl_3$) 8.05 (d, J = 8.9 Hz, 2H, Ar-H), 7.78 (d, J = 8.9 Hz, 2H, Ar-H), 7.32-7.24 (m,

5H, Ar-H), 4.14 (q, *J* = 7.1 Hz, 1H), 3.92 (s, 3H, OCH_3), 3.58 (s, 3H, OCH_3), 1.25 (d, *J* = 7.1 Hz, 3H, CH_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 169.6, 166.4, 142.5, 139.8, 130.0, 129.8, 129.2, 127.62, 127.57, 127.4, 79.9, 53.3, 52.2, 48.1, 16.5; IR: (neat) 1725 (C=O) cm^{-1}; HRMS (ESI+, TOF) m/z: $[M+Na]^+$ Calculated for $C_{19}H_{19}O_4NaCl$ 369.0864; Found 369.0849

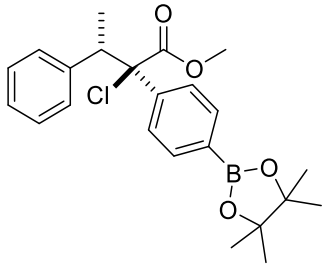
(2*R,3*R**)-20aj Methyl (2*R**,3*R**)-2-chloro-3-phenyl-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)butanoate**



Following the general procedure using (1-chloroethyl)benzene (0.423 mmol, 0.0594 g) and methyl 2-diazo-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate (0.601 mmol, 0.181 g) with $InCl_3$ (0.0405 mmol, 0.0089 g). The yield and diastereomeric ratio were determined by ^1H NMR in crude products (90%, 50:50). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by recycle HPLC (n-hexane/EtOAc = 90/10) to give the title compound as a white solid (0.0754 g, 43%).

^1H NMR: (400 MHz, $CDCl_3$) 7.61 (d, *J* = 8.5 Hz, 2H, Ar-H), 7.28 (d, *J* = 8.5 Hz, 2H, Ar-H), 7.09-7.01 (m, 3H, Ar-H), 6.94 (d, *J* = 8.0 Hz, 2H, Ar-H), 4.00 (q, *J* = 6.8 Hz, 1H), 3.78 (s, 3H, OCH_3), 1.56 (d, *J* = 6.8 Hz, 3H, CH_3), 1.32 (s, 12H, Bpin); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.7, 140.8, 139.5, 134.2, 129.6, 127.3, 126.8, 125.7, 83.8, 80.1, 53.5, 49.2, 24.85, 24.81, 18.1, C-B signal was not observed; IR: (KBr) 1734 (C=O) cm^{-1}; m.p. 96–97 °C; HRMS (ESI+, TOF) m/z: $[M+Na]^+$ Calculated for $C_{23}H_{28}BO_4NaCl$ 437.1661; Found 437.1663

(2*R,3*S**)-20aj Methyl (2*R**,3*S**)-2-chloro-3-phenyl-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)butanoate**

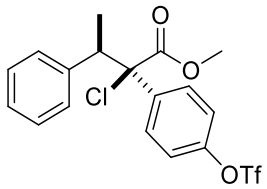


Following the general procedure using (1-chloroethyl)benzene (0.423 mmol, 0.0594 g) and methyl 2-diazo-2-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)acetate (0.601 mmol, 0.181 g) with $InCl_3$ (0.0405 mmol, 0.0089 g). The yield and diastereomeric ratio were determined by ^1H NMR in crude products (90%, 50:50). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by recycle HPLC (n-hexane/EtOAc = 90/10) to give the title compound as a white solid (0.0789 g, 45%).

^1H NMR: (400 MHz, $CDCl_3$) 7.83 (d, *J* = 8.5 Hz, 2H, Ar-H), 7.70 (d, *J* = 8.5 Hz, 2H, Ar-H), 7.35 (d, *J* = 7.5 Hz, 2H, Ar-H), 7.27-7.26 (m, 3H, Ar-H), 4.15 (q, *J* = 7.1 Hz, 1H), 3.56 (s, 3H, OCH_3), 1.35 (s, 12H, Bpin),

1.24 (d, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.0, 140.8, 140.4, 134.5, 130.0, 127.6, 127.3, 126.7, 83.9, 80.4, 53.2, 47.9, 24.85, 24.82, 16.6, C-B signal was not observed; IR: (KBr) 1734 (C=O) cm^{-1}; m.p. 74–75 °C; HRMS (ESI+, TOF) m/z: $[M+Na]^+$ Calculated for $C_{23}H_{28}BO_4NaCl$ 437.1661; Found 437.1671

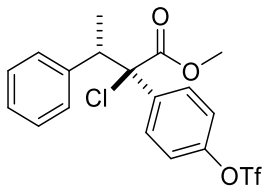
(2*R,3*R**)-20ae Methyl (2*R**,3*R**)-2-chloro-3-phenyl-2-(4-(trifluoromethanesulfonyloxy)phenyl)butanoate**



Following the general procedure using (1-chloroethyl)benzene (0.422 mmol, 0.0593 g) and methyl 2-diazo-2-(4-(trifluoromethanesulfonyloxy)phenyl)acetate (0.596 mmol, 0.193 g) with $InCl_3$ (0.0409 mmol, 0.0090 g). The yield and diastereomeric ratio were determined by ^1H NMR in crude products (85%, 50:50). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by recycle HPLC (n-hexane/EtOAc = 90/10) to give the title compound as a colorless oil (0.0774 g, 42%).

^1H NMR: (400 MHz, $CDCl_3$) 7.33 (d, J = 9.2 Hz, 2H, Ar-H), 7.09-7.05 (m, 5H, Ar-H), 6.86 (d, J = 7.0 Hz, 2H, Ar-H), 3.91 (q, J = 6.8 Hz, 1H), 3.85 (s, 3H, OCH_3), 1.55 (d, J = 6.8 Hz, 3H, CH_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.3, 149.0, 138.9, 138.6, 129.5, 128.5, 127.5, 127.1, 120.5, 118.6 (q, $J_{C\text{-}F}$ = 320.6 Hz), 79.2, 53.8, 49.7, 17.8; IR: (neat) 1735 (C=O) cm^{-1}; HRMS (ESI+, TOF) m/z: $[M+Na]^+$ Calculated for $C_{18}H_{16}O_5F_3NaSCl$ 459.0251; Found 459.0271

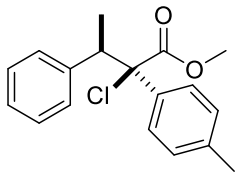
(2*R,3*S**)-20ae Methyl (2*R**,3*S**)-2-chloro-3-phenyl-2-(4-(trifluoromethanesulfonyloxy)phenyl)butanoate**



Following the general procedure using (1-chloroethyl)benzene (0.422 mmol, 0.0593 g) and methyl 2-diazo-2-(4-(trifluoromethanesulfonyloxy)phenyl)acetate (0.596 mmol, 0.193 g) with $InCl_3$ (0.0409 mmol, 0.0090 g). The yield and diastereomeric ratio were determined by ^1H NMR in crude products (85%, 50:50). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by recycle HPLC (n-hexane/EtOAc = 90/10) to give the title compound as a colorless oil (0.0737 g, 40%).

^1H NMR: (400 MHz, $CDCl_3$) 7.80 (d, J = 9.2 Hz, 2H, Ar-H), 7.30-7.27 (m, 7H, Ar-H), 4.08 (q, J = 7.1 Hz, 1H), 3.61 (s, 3H, OCH_3), 1.25 (d, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 169.6, 149.2, 139.6, 138.2, 129.8, 129.7, 127.7, 127.5, 120.8, 118.7 (q, $J_{C\text{-}F}$ = 321.2 Hz), 79.4, 53.5, 48.6, 16.4; IR: (neat) 1742 (C=O) cm^{-1}; HRMS (ESI+, TOF) m/z: $[M+Na]^+$ Calculated for $C_{18}H_{16}O_5F_3NaSCl$ 459.0251; Found 459.0268

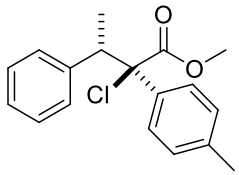
(2*R,3*R**)-20ag Methyl (2*R**,3*R**)-2-chloro-3-phenyl-2-(*p*-tolyl)butanoate**



Following the general procedure using (1-chloroethyl)benzene (0.426 mmol, 0.0599 g) and methyl 2-diazo-2-(*p*-tolyl)acetate (0.600 mmol, 0.114 g) with $InCl_3$ (0.0400 mmol, 0.0088 g). The yield and diastereomeric ratio were determined by ^1H NMR in crude products (66%, 50:50). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by recycle HPLC (n-hexane/EtOAc = 90/10) to give the title compound as a colorless oil (0.0413 g, 32%).

^1H NMR: (400 MHz, $CDCl_3$) 7.14 (d, J = 8.5 Hz, 2H, Ar-H), 7.08-7.04 (m, 3H, Ar-H), 6.97-6.94 (m, 4H, Ar-H), 3.96 (q, J = 6.8 Hz, 1H), 3.80 (s, 3H, OCH_3), 2.26 (s, 3H, Ar-CH_3), 1.54 (d, J = 6.8 Hz, 3H, CH_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 171.0, 139.8, 137.7, 135.0, 129.7, 128.4, 127.2, 126.7, 126.3, 80.1, 53.5, 49.3, 20.9, 18.1; IR: (neat) 1732 (C=O) cm^{-1}; HRMS (ESI+, TOF) m/z: $[M+Na]^+$ Calculated for $C_{18}H_{19}O_2NaCl$ 325.0966; Found 325.0956

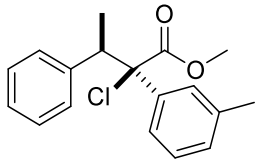
(2*R,3*S**)-20ag Methyl (2*R**,3*S**)-2-chloro-3-phenyl-2-(*p*-tolyl)butanoate**



Following the general procedure using (1-chloroethyl)benzene (0.426 mmol, 0.0599 g) and methyl 2-diazo-2-(*p*-tolyl)acetate (0.600 mmol, 0.114 g) with $InCl_3$ (0.0400 mmol, 0.0088 g). The yield and diastereomeric ratio were determined by ^1H NMR in crude products (66%, 50:50). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by recycle HPLC (n-hexane/EtOAc = 90/10) to give the title compound as a colorless oil (0.0374 g, 29%).

^1H NMR: (400 MHz, $CDCl_3$) 7.58 (d, J = 8.2 Hz, 2H, Ar-H), 7.35 (d, J = 8.2 Hz, 2H, Ar-H), 7.29-7.24 (m, 3H, Ar-H), 7.18 (d, J = 8.2 Hz, 2H, Ar-H), 4.12 (q, J = 7.0 Hz, 1H), 3.56 (s, 3H, OCH_3), 2.37 (s, 3H, Ar-CH_3), 1.26 (d, J = 7.0 Hz, 3H, CH_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.3, 140.6, 138.1, 135.0, 130.0, 128.8, 127.6, 127.23, 127.21, 80.4, 53.2, 47.9, 20.9, 16.7; IR: (neat) 1732 (C=O) cm^{-1}; HRMS (ESI+, TOF) m/z: $[M+Na]^+$ Calculated for $C_{18}H_{19}O_2NaCl$ 325.0966; Found 325.0954

(2*R,3*R**)-20aq Methyl (2*R**,3*R**)-2-chloro-3-phenyl-2-(*m*-tolyl)butanoate**

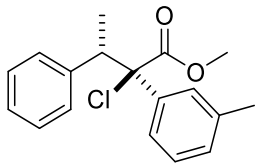


Following the general procedure using (1-chloroethyl)benzene (0.438 mmol, 0.0615 g) and methyl 2-diazo-2-(*m*-tolyl)acetate (0.647 mmol, 0.123 g) with $InCl_3$ (0.0423 mmol, 0.0093 g). The yield and diastereomeric ratio were determined by ^1H NMR in crude products (65%, 50:50). 1,1,2,2-Tetrachloroethane was used as

an internal standard. The crude product was purified by recycle HPLC (n-hexane/EtOAc = 90/10) to give the title compound as a colorless oil (0.0398 g, 30%).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.08-6.99 (m, 7H, Ar-H), 6.92 (d, *J* = 7.7 Hz, 2H, Ar-H), 3.95 (q, *J* = 6.8 Hz, 1H), 3.81 (s, 3H, OCH_3), 2.20 (s, 3H, Ar-CH_3), 1.55 (d, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.9, 139.7, 137.8, 137.4, 129.6, 128.7, 127.6, 127.2, 127.1, 126.7, 123.3, 80.0, 53.5, 49.3, 21.4, 18.0; IR: (neat) 1733 (C=O) cm^{-1}; HRMS (ESI+, TOF) m/z: $[M+Na]^+$Calculated for $C_{18}H_{19}O_2NaCl$ 325.0966; Found 325.0955

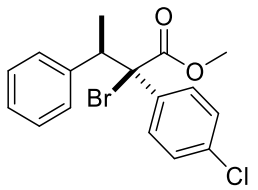
(2*R,3*S**)-20aq Methyl (2*R**,3*S**)-2-chloro-3-phenyl-2-(*m*-tolyl)butanoate**



Following the general procedure using (1-chloroethyl)benzene (0.438 mmol, 0.0615 g) and methyl 2-diazo-2-(*m*-tolyl)acetate (0.647 mmol, 0.123 g) with $InCl_3$ (0.0423 mmol, 0.0093 g). The yield and diastereomeric ratio were determined by ^{1}H NMR in crude products (65%, 50:50). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by recycle HPLC (n-hexane/EtOAc = 90/10) to give the title compound as a colorless oil (0.0437 g, 33%).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.51-7.49 (m, 2H, Ar-H), 7.37 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.28-7.25 (m, 4H, Ar-H), 7.16 (d, *J* = 7.7 Hz, 1H, Ar-H), 4.13 (q, *J* = 7.0 Hz, 1H), 3.56 (s, 3H, OCH_3), 2.39 (s, 3H, Ar-CH_3), 1.26 (d, *J* = 7.0 Hz, 3H, CH_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.2, 140.6, 137.85, 137.83, 130.0, 129.0, 127.99, 127.97, 127.6, 127.2, 124.3, 80.5, 53.2, 47.8, 21.6, 16.7; IR: (neat) 1732 (C=O) cm^{-1}; HRMS (ESI+, TOF) m/z: $[M+Na]^+$ Calculated for $C_{18}H_{19}O_2NaCl$ 325.0966; Found 325.0952

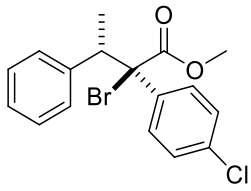
(2*R,3*R**)-22aa Methyl (2*R**,3*R**)-2-bromo-2-(4-chlorophenyl)-3-phenylbutanoate**



Following the general procedure using (1-bromoethyl)benzene (0.413 mmol, 0.0750 g) and methyl 2-(4-chlorophenyl)-2-diazoacetate (0.601 mmol, 0.126 g) with $InBr_3$ (0.0399 mmol, 0.0141 g). The yield and diastereomeric ratio were determined by ^{1}H NMR in crude products (88%, 54:46). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by recycle HPLC (n-hexane/EtOAc = 90/10) to give the title compound as a colorless oil (0.0670 g, 45%).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.12-7.09 (m, 7H, Ar-H), 6.89 (d, *J* = 7.5 Hz, 2H, Ar-H), 3.82-3.79 (m, 4H), 1.56 (d, *J* = 6.8 Hz, 3H, CH_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.7, 139.5, 136.1, 134.0, 129.7, 129.6, 127.5, 127.4, 127.1, 74.6, 53.5, 49.3, 19.5; IR: (neat) 1734 (C=O) cm^{-1}; HRMS (ESI+, TOF) m/z: $[M+Na]^+$ Calculated for $C_{17}H_{16}O_2NaClBr$ 388.9914; Found 388.9911

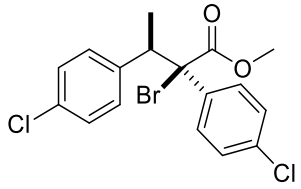
(2*R,3*S**)-22aa Methyl (2*R**,3*S**)-2-bromo-2-(4-chlorophenyl)-3-phenylbutanoate**



Following the general procedure using (1-bromoethyl)benzene (0.413 mmol, 0.0750 g) and methyl 2-(4-chlorophenyl)-2-diazoacetate (0.601 mmol, 0.126 g) with $InBr_3$ (0.0399 mmol, 0.0141 g). The yield and diastereomeric ratio were determined by ^1H NMR in crude products (88%, 54:46). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by recycle HPLC (n-hexane/EtOAc = 90/10) to give the title compound as a colorless oil (0.0541 g, 36%).

^1H NMR: (400 MHz, $CDCl_3$) 7.35 (d, J = 8.9 Hz, 2H, Ar-H), 7.27 (d, J = 8.9 Hz, 2H, Ar-H), 7.24-7.20 (m, 3H, Ar-H), 7.03 (d, J = 7.7 Hz, 2H, Ar-H), 3.99 (q, J = 7.1 Hz, 1H), 3.72 (s, 3H, OCH_3), 1.34 (d, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.5, 140.0, 135.1, 134.3, 130.8, 130.2, 127.5, 127.4, 127.3, 73.8, 53.5, 48.6, 18.2; IR: (neat) 1737 (C=O) cm^{-1}; HRMS (ESI+, TOF) m/z: $[M+Na]^+$ Calculated for $C_{17}H_{16}O_2NaClBr$ 388.9914; Found 388.9913

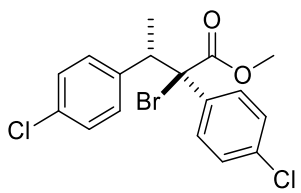
(2*R,3*R**)-22ba Methyl (2*R**,3*R**)-2-bromo-2,3-bis(4-chlorophenyl)butanoate**



Following the general procedure using 1-(1-bromoethyl)-4-chlorobenzene (0.405 mmol, 0.0890 g) and methyl 2-(4-chlorophenyl)-2-diazoacetate (0.604 mmol, 0.127 g) with $InBr_3$ (0.0400 mmol, 0.0142 g). The yield and diastereomeric ratio were determined by ^1H NMR in crude products (87%, 55:45). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by recycle HPLC (n-hexane/EtOAc = 90/10) to give the title compound as a colorless oil (0.0762 g, 47%).

^1H NMR: (400 MHz, $CDCl_3$) 7.15 (d, J = 8.9 Hz, 2H, Ar-H), 7.10 (d, J = 8.9 Hz, 2H, Ar-H), 7.06 (d, J = 8.5 Hz, 2H, Ar-H), 6.81 (d, J = 8.5 Hz, 2H, Ar-H), 3.79-3.78 (m, 4H), 1.52 (d, J = 7.0 Hz, 3H, CH_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.5, 138.1, 135.8, 134.2, 132.9, 131.1, 129.5, 127.7, 127.5, 74.2, 53.6, 48.8, 19.4; IR: (neat) 1734 (C=O) cm^{-1}; HRMS (ESI+, TOF) m/z: $[M+Na]^+$ Calculated for $C_{17}H_{15}O_2NaCl_2Br$ 422.9525; Found 422.9516

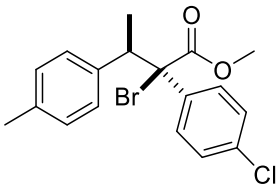
(2*R,3*S**)-22ba Methyl (2*R**,3*S**)-2-bromo-2,3-bis(4-chlorophenyl)butanoate**



Following the general procedure using 1-(1-bromoethyl)-4-chlorobenzene (0.405 mmol, 0.0890 g) and methyl 2-(4-chlorophenyl)-2-diazoacetate (0.604 mmol, 0.127 g) with $InBr_3$ (0.0400 mmol, 0.0142 g). The yield and diastereomeric ratio were determined by ^1H NMR in crude products (87%, 55:45). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by recycle HPLC (n-hexane/EtOAc = 90/10) to give the title compound as a colorless oil (0.0610 g, 37%).

^1H NMR: (400 MHz, $CDCl_3$) 7.34 (d, J = 8.8 Hz, 2H, Ar-H), 7.28 (d, J = 8.8 Hz, 2H, Ar-H), 7.18 (d, J = 8.7 Hz, 2H, Ar-H), 6.97 (d, J = 8.7 Hz, 2H, Ar-H), 3.96 (q, J = 7.1 Hz, 1H), 3.73 (s, 3H, OCH_3), 1.30 (d, J = 7.1 Hz, 3H, CH_3); ^{13}C NMR: (100 MHz, $CDCl_3$); 170.3, 138.5, 134.8, 134.5, 133.2, 131.6, 130.7, 127.7, 127.5, 73.3, 53.5, 48.2, 18.1; IR: (neat) 1737 (C=O) cm^{-1}; HRMS (ESI+, TOF) m/z: $[M+Na]^+$ Calculated for $C_{17}H_{15}O_2NaCl_2Br$ 422.9525; Found 422.9516

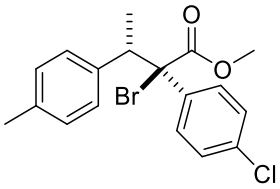
(2*R,3*R**)-22ca Methyl (2*R**,3*R**)-2-bromo-2-(4-chlorophenyl)-3-(*p*-tolyl)butanoate**



Following the general procedure using 1-(1-bromoethyl)-4-methylbenzene (0.439 mmol, 0.0873 g) and methyl 2-(4-chlorophenyl)-2-diazoacetate (0.635 mmol, 0.134 g) with $InBr_3$ (0.0425 mmol, 0.0151 g). The yield and diastereomeric ratio were determined by ^1H NMR in crude products (68%, 52:48). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by recycle HPLC (n-hexane/EtOAc = 90/10) to give the title compound as a colorless oil (0.0549 g, 33%).

^1H NMR: (400 MHz, $CDCl_3$) 7.13-7.12 (m, 4H, Ar-H), 6.90 (d, J = 7.9 Hz, 2H, Ar-H), 6.77 (d, J = 7.9 Hz, 2H, Ar-H), 3.81-3.80 (m, 4H), 2.25 (s, 3H, Ar-CH_3), 1.52 (d, J = 6.8 Hz, 3H, CH_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.7, 136.7, 136.4, 136.1, 133.9, 129.8, 129.7, 128.1, 127.5, 74.7, 53.5, 48.9, 21.0, 19.4; IR: (neat) 1734 (C=O) cm^{-1}; HRMS (ESI+, TOF) m/z: $[M+Na]^+$ Calculated for $C_{18}H_{18}O_2NaClBr$ 403.0071; Found 403.0079

(2*R,3*S**)-22ca Methyl (2*R**,3*S**)-2-bromo-2-(4-chlorophenyl)-3-(*p*-tolyl)butanoate**

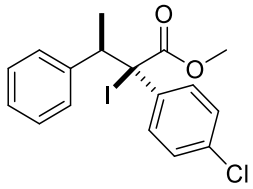


Following the general procedure using 1-(1-bromoethyl)-4-methylbenzene (0.439 mmol, 0.0873 g) and methyl 2-(4-chlorophenyl)-2-diazoacetate (0.635 mmol, 0.134 g) with $InBr_3$ (0.0425 mmol, 0.0151 g). The yield and diastereomeric ratio were determined by ^1H NMR in crude products (68%, 52:48). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by recycle HPLC (n-hexane/EtOAc = 90/10) to give the title compound as a colorless oil (0.0527 g, 32%).

^1H NMR: (400 MHz, $CDCl_3$) 7.36 (d, J = 8.9 Hz, 2H, Ar-H), 7.27 (d, J = 8.9 Hz, 2H, Ar-H), 7.02 (d, J = 8.0

Hz, 2H, Ar-H), 6.93 (d, *J* = 8.0 Hz, 2H, Ar-H), 3.95 (q, *J* = 7.0 Hz, 1H), 3.72 (s, 3H, OCH_3), 2.31 (s, 3H, Ar-CH_3), 1.32 (d, *J* = 7.0 Hz, 3H, CH_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.5, 136.97, 136.96, 135.3, 134.2, 130.8, 130.1, 128.1, 127.5, 74.2, 53.5, 48.2, 21.1, 18.3; IR: (neat) 1737 (C=O) cm^{-1}; HRMS (ESI+, TOF) m/z: $[M+Na]^+$ Calculated for $C_{18}H_{18}O_2NaClBr$ 403.0071; Found 403.0077

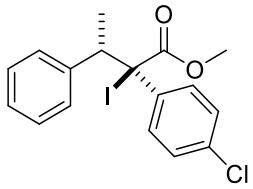
(2*R,3*R**)-24aa Methyl (2*R**,3*R**)-2-(4-chlorophenyl)-2-iodo-3-phenylbutanoate**



Following the general procedure using (1-iodoethyl)benzene (0.454 mmol, 0.105 g) and methyl 2-(4-chlorophenyl)-2-diazoacetate (0.601 mmol, 0.126 g) with InI_3 (0.0424 mmol, 0.0210 g). The yield and diastereomeric ratio were determined by ^1H NMR in crude products (58%, 54:46). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by recycle HPLC (n-hexane/EtOAc = 90/10) to give the title compound as a colorless oil (0.0458 g, 24%).

^1H NMR: (400 MHz, $CDCl_3$) 7.15-7.04 (m, 7H, Ar-H), 6.82 (d, *J* = 7.0 Hz, 2H, Ar-H), 3.78 (s, 3H, OCH_3), 3.58 (q, *J* = 7.0 Hz, 1H), 1.57 (d, *J* = 7.0 Hz, 3H, CH_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 172.4, 139.3, 136.5, 133.9, 131.9, 129.9, 127.4, 127.1, 60.0, 53.3, 49.9, 22.3; IR: (neat) 1724 (C=O) cm^{-1}; HRMS (DART+, TOF) m/z: $[M–I]^+$ Calculated for $C_{17}H_{16}O_2Cl$ 287.0833; Found 287.0835; HRMS (DART–, TOF) m/z: $[I]^–$ Calculated for I 126.9050; Found 126.9046

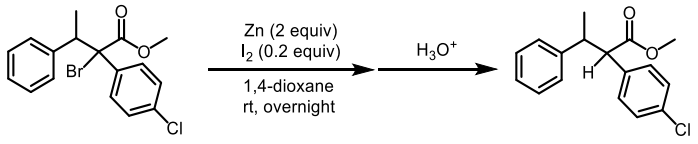
(2*R,3*S**)-24aa Methyl (2*R**,3*S**)-2-(4-chlorophenyl)-2-iodo-3-phenylbutanoate**



Following the general procedure using (1-iodoethyl)benzene (0.454 mmol, 0.105 g) and methyl 2-(4-chlorophenyl)-2-diazoacetate (0.601 mmol, 0.126 g) with InI_3 (0.0424 mmol, 0.0210 g). The yield and diastereomeric ratio were determined by ^1H NMR in crude products (58%, 54:46). 1,1,2,2-Tetrachloroethane was used as an internal standard. The crude product was purified by recycle HPLC (n-hexane/EtOAc = 90/10) to give the title compound as a colorless oil (0.0381 g, 20%).

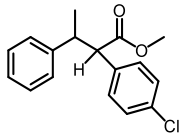
^1H NMR: (400 MHz, $CDCl_3$) 7.21-7.18 (m, 7H, Ar-H), 6.82 (d, *J* = 7.0 Hz, 2H, Ar-H), 3.94 (q, *J* = 7.0 Hz, 1H), 3.81 (s, 3H, OCH_3), 1.35 (d, *J* = 7.0 Hz, 3H, CH_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 172.8, 140.8, 135.1, 134.0, 132.9, 130.4, 127.3, 127.2, 127.0, 58.6, 53.4, 50.7, 18.4; IR: (neat) 1724 (C=O) cm^{-1}; HRMS (DART+, TOF) m/z: $[M–I]^+$ Calculated for $C_{17}H_{16}O_2Cl$ 287.0833; Found 287.0836; HRMS (DART–, TOF) m/z: $[I]^–$ Calculated for I 126.9050; Found 126.9048

Debromination and protonation of 22aa



Zn powder (0.015 g, 0.231 mmol, 2 equiv) and I_2 (0.0072 g, 0.028 mmol, 0.2 equiv) were added to a reaction tube, which was then evacuated and backfilled with N_2. Subsequently, **22aa** (0.0373 g, 0.101 mmol, 1 equiv) in 1,4-dioxane (1 mL) was added in one portion to the reaction tube. The resultant mixture was stirred at room temperature overnight under N_2. The reaction was quenched by addition of H_2O, followed by HCl aq (1 M). The organic compound was extracted by ether and washed with saturated $NaHCO_3$ aq. The solvent was evaporated. The yield and diastereomeric ratio were determined by ^1H NMR in crude products (97%, dr = 55:45). 1,1,2,2-Tetrachloroethane was used as an internal standard.

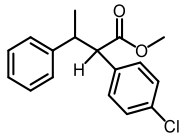
(major-40) Methyl 2-(4-chlorophenyl)-3-phenylbutanoate



The title compound was separated by recycle HPLC (n-hexane/EtOAc = 90/10) as a white solid. (0.0134 g, 46% yield).

^1H NMR: (400 MHz, $CDCl_3$) 7.40 (d, J = 8.5 Hz, 2H, Ar-H), 7.31-7.24 (m, 7H, Ar-H), 3.69 (d, J = 11.1 Hz, 1H), 3.43-3.25 (m, 4H), 1.02 (d, J = 7.0 Hz, 3H, CH_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 173.1, 144.3, 136.0, 133.4, 129.9, 128.8, 128.4, 127.2, 126.7, 58.8, 51.7, 43.4, 19.8; IR: (KBr) 1734 (C=O) cm^{-1}; m.p. 85–86 °C; HRMS (ESI+, TOF) m/z: $[M+Na]^+$ Calculated for $C_{17}H_{17}O_2NaCl$ 311.0809; Found 311.0805

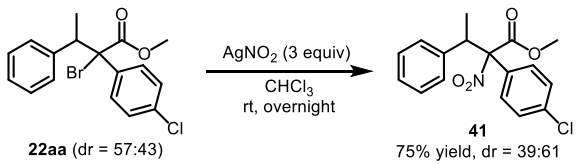
(minor-40) Methyl 2-(4-chlorophenyl)-3-phenylbutanoate



The title compound was separated by recycle HPLC (n-hexane/EtOAc = 90/10) as a white solid. (0.0140 g, 48% yield).

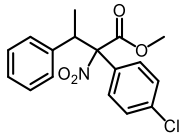
^1H NMR: (400 MHz, $CDCl_3$) 7.12-7.08 (m, 7H, Ar-H), 6.96 (d, J = 7.0 Hz, 2H, Ar-H), 3.70-3.68 (m, 4H), 3.41 (sextet, J = 6.8 Hz, 1H), 1.38 (d, J = 6.8 Hz, 3H, CH_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 173.8, 143.1, 136.0, 132.9, 129.8, 128.3, 128.2, 127.5, 126.3, 58.5, 52.1, 43.9, 21.0; IR: (KBr) 1734 (C=O) cm^{-1}; m.p. 82–83 °C; HRMS (ESI+, TOF) m/z: $[M+Na]^+$ Calculated for $C_{17}H_{17}O_2NaCl$ 311.0809; Found 311.0805

Bromo–nitro substitution of 22aa



$AgNO_2$ (0.0556 g, 0.348 mmol, 3 equiv) and **22aa** (0.0426 g, 0.116 mmol, 1 equiv) in $CHCl_3$ (1 mL) were subsequently added to a reaction tube. The resultant mixture was stirred at room temperature overnight under N_2. The reaction was quenched by path through a plug of silica gel and washed with ether. The yield and diastereomeric ratio were determined by ^1H NMR in crude products (75%, dr = 39:61). 1,1,2,2-Tetrachloroethane was used as an internal standard.

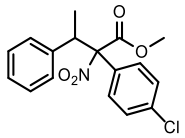
(major-41) Methyl 2-(4-chlorophenyl)-2-nitro-3-phenylbutanoate



The title compound was separated by recycle HPLC (n-hexane/EtOAc = 90/10) as a colorless oil (0.0164 g, 42% yield).

^1H NMR: (400 MHz, $CDCl_3$) 7.57 (d, J = 8.8 Hz, 2H, Ar-H), 7.32 (d, J = 8.8 Hz, 2H, Ar-H), 7.26-7.24 (m, 3H, Ar-H), 7.04 (dd, J = 6.5, 2.9 Hz, 2H, Ar-H), 3.54 (s, 3H, OMe), 3.45 (q, J = 7.3 Hz, 1H), 1.26 (d, J = 7.3 Hz, 3H, CH_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 168.8, 138.4, 134.4, 133.7, 129.1, 128.2, 128.0, 127.8, 127.5, 91.2, 52.8, 49.7, 15.3; IR: (neat) 1747, 1653 cm^{-1}; HRMS (ESI+, TOF) m/z: $[M+K]^+$ Calculated for $C_{17}H_{16}NO_4ClK$ 372.0399; Found 372.0391

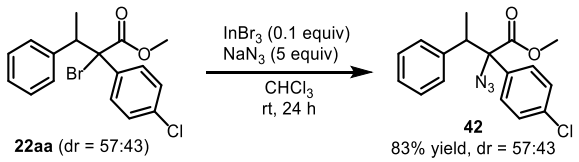
(minor-41) Methyl 2-(4-chlorophenyl)-2-nitro-3-phenylbutanoate



The title compound was separated by recycle HPLC (n-hexane/EtOAc = 90/10) as a white solid (0.0109 g, 28% yield).

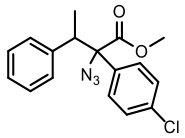
^1H NMR: (400 MHz, $CDCl_3$) 7.45 (d, J = 8.7 Hz, 2H, Ar-H), 7.27-7.22 (m, 5H, Ar-H), 7.00 (dd, J = 6.5, 3.1 Hz, 2H, Ar-H), 3.72 (s, 3H, OMe), 3.48 (q, J = 7.2 Hz, 1H), 1.29 (d, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 168.1, 138.0, 134.3, 134.2, 129.1, 128.2, 128.0, 127.8, 127.4, 91.6, 52.7, 49.3, 15.6; IR: (KBr) 1748, 1653 cm^{-1}; m.p. 108–109 °C; HRMS (ESI+, TOF) m/z: $[M+K]^+$ Calculated for $C_{17}H_{16}NO_4ClK$ 372.0399; Found 372.0403

Bromo–azide substitution of 42aa



$InBr_3$ (0.0071 g, 0.02 mmol, 0.1 equiv), NaN_3 (0.065 g, 1.00 mmol, 5 equiv), **22aa** (0.0736 g, 0.200 mmol, 1 equiv) in $CHCl_3$ (1 mL) were subsequently added to a reaction tube. The resultant mixture was stirred at room temperature for 24 h under N_2. The reaction was quenched by path through a plug of silica gel and washed with ether. The yield and diastereomeric ratio were determined by ^1H NMR in crude products (83%, dr = 57:43). 1,1,2,2-Tetrachloroethane was used as an internal standard.

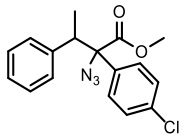
(major-42) Methyl 2-azido-2-(4-chlorophenyl)-3-phenylbutanoate



The title compound was separated by recycle HPLC (n-hexane/EtOAc = 90/10) as a colorless oil (0.0286 g, 43% yield).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.16-7.10 (m, 5H, Ar-H), 7.00 (dd, *J* = 6.8, 2.2 Hz, 2H, Ar-H), 6.92 (dd, *J* = 7.7, 1.7 Hz, 2H, Ar-H), 3.92 (s, 3H, OMe), 3.52 (q, *J* = 6.9 Hz, 1H), 1.41 (d, *J* = 6.9 Hz, 3H, CH_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 171.4, 139.6, 135.5, 134.1, 129.4, 128.4, 127.6, 127.4, 126.9, 76.9, 53.3, 48.6, 17.0; IR: (neat) 2116, 1737 (C=O) cm^{-1}; HRMS (ESI+, TOF) m/z: $[M+Na]^+$ Calculated for $C_{17}H_{16}N_3O_2NaCl$ 352.0823; Found 352.0819

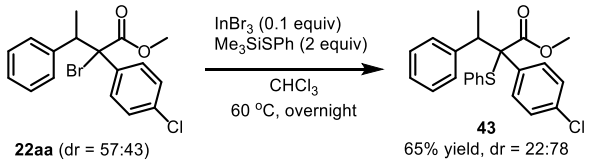
(minor-42) Methyl 2-azido-2-(4-chlorophenyl)-3-phenylbutanoate



The title was separated by recycle HPLC (n-hexane/EtOAc = 90/10) as a colorless oil (0.0212 g, 32% yield).

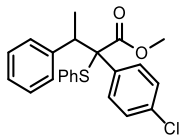
^{1}H NMR: (400 MHz, $CDCl_3$) 7.58 (d, *J* = 8.9 Hz, 2H, Ar-H), 7.40 (d, *J* = 8.9 Hz, 2H, Ar-H), 7.37-7.26 (m, 5H, Ar-H), 3.69 (q, *J* = 6.9 Hz, 1H), 3.64 (s, 3H, OMe), 1.10 (d, *J* = 6.9 Hz, 3H, CH_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.5, 140.5, 135.8, 134.4, 129.3, 128.8, 128.0, 127.4, 76.5, 52.9, 47.6, 15.7; IR: (neat) 2116, 1741 cm^{-1}; HRMS (ESI+, TOF) m/z: $[M+Na]^+$ Calculated for $C_{17}H_{16}N_3O_2NaCl$ 352.0823; Found 352.0822

Direct coupling between alkyl bromide 22aa and thiosilane



$InBr_3$ (0.0056 g, 0.016 mmol, 0.1 equiv), phenylthiotrimethylsilane (0.0583 g, 0.320 mmol, 2 equiv), **22aa** (0.0602 g, 0.164 mmol, 1 equiv) in $CHCl_3$ (1 mL) were subsequently added to a reaction tube. The resultant mixture was stirred at room temperature for 1 h and then heated to 60 °C for 12 h. After cooling to room temperature, the reaction was quenched sat $NaHCO_3$ aq and extracted with ether, dried over $MgSO_4$. The solvent was evaporated. The yield and diastereomeric ratio were determined by ^{1}H NMR in crude products (65%, dr = 22:78). 1,1,2,2-Tetrachloroethane was used as an internal standard.

(major-43) Methyl 2-(4-chlorophenyl)-3-phenyl-2-(phenylthio)butanoate

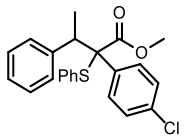


The title compound was separated by recycle HPLC (n-hexane/EtOAc = 90/10) as a white solid (0.0313 g, 48% yield).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.35 (d, *J* = 8.9 Hz, 2H, Ar-H), 7.27-7.12 (m, 10H, Ar-H), 6.76 (d, *J* = 7.0 Hz,

2H, Ar-H), 4.11 (q, J = 7.0 Hz, 1H), 3.45 (s, 3H, OMe), 1.25 (d, J = 7.0 Hz, 3H, CH_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.9, 139.2, 134.9, 133.43, 133.36, 133.1, 132.0, 130.3, 128.9, 128.5, 127.3, 127.2, 126.8, 69.9, 52.1, 47.3, 18.7; IR: (KBr) 1724 (C=O) cm^{-1}; m.p. 165–166 °C; HRMS (ESI+, TOF) m/z: $[M+Na]^+$ Calculated for $C_{23}H_{21}O_2NaSCl$ 419.0843; Found 419.0844

(minor-43) Methyl 2-(4-chlorophenyl)-3-phenyl-2-(phenylthio)butanoate

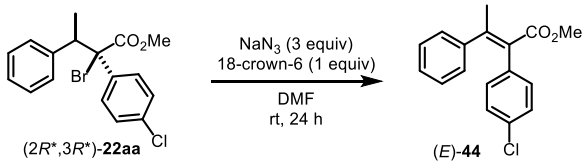


The title compound was separated by recycle HPLC (n-hexane/EtOAc = 90/10) as a colorless oil (0.0088 g, 14% yield).

^{1}H NMR: (400 MHz, $CDCl_3$) 7.30 (t, J = 8.0 Hz, 3H, Ar-H), 7.20-7.14 (m, 9H, Ar-H), 6.79 (d, J = 8.0 Hz, 2H, Ar-H), 4.02 (q, J = 7.2 Hz, 1H), 3.48 (s, 3H, OMe), 1.41 (d, J = 7.2 Hz, 3H, CH_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 170.5, 140.8, 135.5, 133.8, 133.4, 132.5, 131.6, 130.1, 129.2, 128.6, 127.4, 127.0, 126.7, 70.4, 51.8, 45.6, 16.6; IR: (neat) 1730 (C=O) cm^{-1}; HRMS (ESI+, TOF) m/z: $[M+Na]^+$ Calculated for $C_{23}H_{21}O_2NaSCl$ 419.0843; Found 419.0844

Synthesis of α,β-unsaturated carboxylic acid methyl ester (E)-44

Methyl (E)-2-(4-chlorophenyl)-3-phenylbut-2-enoate

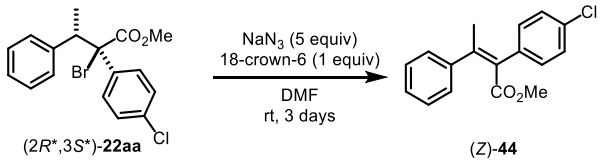


The isolated single diastereomer (2*R**,3*R**)-**22aa** (0.055 g, 0.15 mmol, 1 equiv), NaN_3 (0.0301 g, 0.46 mmol, 3 equiv), 18-crown-6 (0.0396 g, 0.15 mmol, 1 equiv), and DMF (1 mL) were added to a reaction tube. The resultant mixture was stirred at room temperature for 24 h under N_2 (monitored by TLC). The reaction was quenched by water and the organic layer was washed with brine and extracted by ether, dried over $MgSO_4$. The solvent was evaporated. The yield was determined by ^{1}H NMR in crude products (99%, *E/Z* >99:1). 1,1,2,2-Tetrachloroethane was used as an internal standard. The title compound was purified by silica gel chromatography (n-hexane as eluent) as a colorless oil, 0.0413 g, 96% yield. The characterization data matched those reported in the literature. (Y. Ashida, Y. Sato, T. Suzuki, K. Ueno, K. Kai, H. Nakatsuji, Y. Tanabe, *Chem. Eur. J.* **2015**, *21*, 5934–5945.)

^{1}H NMR: (400 MHz, $CDCl_3$) 7.16-7.14 (m, 3H, Ar-H), 7.08 (d, J = 8.6 Hz, 2H, Ar-H), 7.01-6.99 (m, 2H, Ar-H), 6.92 (d, J = 8.6 Hz, 2H, Ar-H), 3.78 (s, 3H, OMe), 2.37 (s, 3H, CH_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 169.4, 146.0, 141.6, 135.7, 132.7, 131.3, 130.4, 128.3, 128.1, 128.0, 127.3, 52.1, 23.3; IR: (neat) 1718 (C=O) cm^{-1}; HRMS (ESI+, TOF) m/z: $[M+Na]^+$ Calculated for $C_{17}H_{15}O_2NaCl$ 309.0653; Found 309.0652

Synthesis of α,β-unsaturated carboxylic acid methyl ester (Z)-44

Methyl (Z)-2-(4-chlorophenyl)-3-phenylbut-2-enoate



The isolated single diastereomer (2*R**,3*S**)-**22aa** (0.0367 g, 0.100 mmol, 1 equiv), NaN_3 (0.0325 g, 0.501 mmol, 5 equiv), 18-crown-6 (0.0264 g, 0.100 mmol, 1 equiv), and DMF (0.7 mL) were added to a reaction tube. The resultant mixture was stirred at room temperature for 3 days under N_2 (monitored by TLC). The reaction was quenched by water and the organic layer was washed with brine and extracted by ether, dried over $MgSO_4$. The solvent was evaporated. The yield was determined by ^1H NMR in crude products (97%, *E/Z* = 3:97). 1,1,2,2-Tetrachloroethane was used as an internal standard. The title compound was purified by recycle HPLC (n-hexane/EtOAc = 90/10) as a colorless oil, 0.0264 g, 92% yield. The characterization data matched those reported in the literature. (Y. Ashida, Y. Sato, T. Suzuki, K. Ueno, K. Kai, H. Nakatsuji, Y. Tanabe, *Chem. Eur. J.* **2015**, *21*, 5934–5945.)

^1H NMR: (400 MHz, $CDCl_3$) 7.39-7.29 (m, 9H, Ar-H), 3.43 (s, 3H, OMe), 2.04 (s, 3H, CH_3); ^{13}C NMR: (100 MHz, $CDCl_3$) 169.3, 145.1, 142.6, 135.6, 133.5, 131.3, 130.7, 128.6, 128.3, 127.7, 126.8, 51.8, 22.5; IR: (neat) 1718 (C=O) cm^{-1}; HRMS (ESI+, TOF) m/z: $[M+Na]^+$ Calculated for $C_{17}H_{15}O_2NaCl$ 309.0653; Found 309.0652

3-5. Reference

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[9] The X-ray crystal structure of **4ea** (shown in Table 2) was used to estimate the relative stereochemistry (2*R**,3*R**) of the major isomer of **4aa**.

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Conclusion

In this study, the methodology for carbon chain elongation via insertion of C_1 unit into a chemical bond such as C–C, C–F, C–Cl, C–Br, or C–I bond have been established. The abstraction of a leaving group by Lewis acids and the re-formation of a chemical bond by release of the leaving group from Lewis acids play an important role in these elongations.

In chapter 1, the elongation of benzylic ethers, acetates, and acetals via an insertion of diazo compounds into C–C σ-bonds was established. The key point of the mechanism is that the indium catalysts have appropriate Lewis acidity to achieve both abstraction and release of alkoxy or acetoxy groups. Its scope of substrates was much wider than existing methods. Various types of benzylic ethers, acetates, acetals, and diazo compounds were applicable.

In chapter 2, the insertion of C_1 unit into C–C σ-bond via the reaction of benzylic halides (fluorides, chlorides, and bromides) with *α*-diazoesters catalyzed by InX_3 (X = Cl or Br) or BF_3 was achieved. Secondary benzylic halides underwent elongation to afford *α*,*β*-diaryl-*β*-haloesters with excellent diastereoselectivity. DFT calculation revealed that the present C–C bond insertion was completed by Lewis acid-promoted cleavage and the re-formation of a carbon–halogen (C–X) bond and that the aryl-migration step determined the diastereoselectivity. A control experiment exhibited that the use of a basic solvent EtOAc effectively prevented the retro reaction in C–Cl bond re-formation step. Various diarylmethyl halides and *α*-diazoesters were applicable to this reaction system. In addition, ring expansion in cyclic benzylic chlorides was accomplished.

In chapter 3, the development of a new methodology for the synthesis of *α*,*β*-diaryl-*α*-fluoroesters with high level of diastereoselectivity was accomplished by the BF_3-catalyzed insertion of diazoesters into C−F bonds. A DFT calculation study suggested that the BF_3 catalyst contributed to both C−F bond cleavage and re-formation. The inhibited aryl-migration enabled the re-formation of C–F bond at *α*-position of a carbonyl group. The synthetic utility of this method was demonstrated by the synthesis of a fluoro analogue of a compound that is used as a transient receptor and potential canonical channel inhibitor. Moreover, the present strategy was applied to insertion of diazoesters into C–Cl, C–Br, and C–I bonds catalyzed by indium trihalides.

A knowledge obtained from chapters 1 and 2 is that the combination of aryl migration with capture of a leaving group at *β*-position of a carbonyl group furnishes a C–C bond insertion product. Chapter 3 gives us an important knowledge that a C–X bond insertion is realized by an inhibition of aryl-migration and capture of a halide ion at *α*-position of a carbonyl group.

In conclusion, the insertion of diazo compounds into C–C or C–X bond catalyzed by a Lewis acid have been established in this doctoral dissertation. The insights obtained from the present study have a great contribution to the methodology for the construction of highly-functionalized organic compounds.

List of Publications

1) **Homologation of Alkyl Acetates, Alkyl Ethers, Acetals, and Ketals by Formal Insertion of Diazo Compounds into a Carbon–Carbon Bond**
F. Wang, J. Yi, Y. Nishimoto, M. Yasuda
Synthesis **2021**, *53*, 4004–4019.

2) **Insertion of Diazo Esters into C−F Bonds toward Diastereoselective One-Carbon Elongation of Benzylic Fluorides: Unprecedented BF_3 Catalysis with C−F Bond Cleavage and Re-formation**
F. Wang, Y. Nishimoto, M. Yasuda
J. Am. Chem. Soc. **2021**, *143*, 20616–20621.

3) **Indium-Catalyzed Formal Carbon−Halogen Bond Insertion: Synthesis of *α*-Halo-*α*,*α*-disubstituted Esters from Benzylic Halides and Diazo Esters**
F. Wang, Y. Nishimoto, M. Yasuda
Org. Lett. **2022**, *24*, 1706–1710.

4) **Lewis Acid-Catalyzed Diastereoselective C–C Bond Insertion of Diazo Esters into Secondary Benzylic Halides for the Synthesis of *α*,*β*-Diaryl-*β*-haloesters**
F. Wang, Y. Nishimoto, M. Yasuda
Angew. Chem. Int. Ed. DOI: 10.1002/anie.202204462