Doctoral Dissertation

Transition Metal-Catalyzed Unimolecular Fragment Coupling of Amides and Esters

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Preface and Acknowledgement

The research presented in this thesis was carried out under the direction of Professor Mamoru Tobisu of the Department of Applied Chemistry, Graduate School of Engineering, Osaka University. I joined the Tobisu laboratory in April 2018 and progressed to the role of a Ph.D. student from April 2021 to March 2024. This thesis focuses on the transition metal-catalyzed unimolecular fragment coupling (UFC) of amides and esters. This thesis could not have been completed without the support of numerous people. Here, I wish to express my sincerest appreciation to all of these people.

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Contents

General Introduction

Transition metal-catalyzed cross-coupling stands as a powerful method for forming C–C and C–heteroatom bonds that enable extensive applications in the synthesis of natural products, pharmaceuticals, and organic materials.[1] However, the use of organic halides as electrophiles and organometallic reagents as nucleophiles raises issues concerning the need for their pre preparation as well as for the generation of stoichiometric metal waste (**Fig 1a**). Although a partial solution to these issues has been provided by the emergence of C–H[2] and C–O[3] bond functionalization, the scope of such sophisticated methods remains substantially limited compared with classical cross-coupling reactions.

Unimolecular fragment coupling (UFC) is a conceptually distinct approach wherein the formation of new chemical bonds occur through the elimination of atom(s) from the middle of the substrate, followed by recombination of the remaining fragments (**Fig 1b**). Typical starting materials for UFC are common carbonyl compounds, which can be synthesized by well-established methods such as condensation. The key feature of UFC is that the target chemical bond is formed intramolecularly without the addition of external reagents, with the noted exception of catalysts, thereby facilitating high levels of chemoselectivity and stereoselectivity.y.

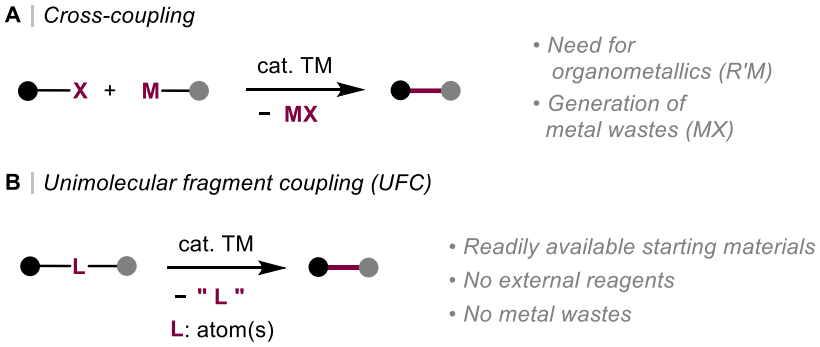


Fig 1. Cross-coupling and unimolecular fragment coupling

As generalized in **Fig 2**, transition metal-catalyzed UFC requires two bond activation processes through metal-mediated oxidative addition and β-elimination reactions. Because these elementary reactions are applicable to a limited class of relatively reactive chemical bonds, the scope of UFC reactions remains limited primarily to substrates that contain such reactive bonds, which includes allylic and benzylic substrates.

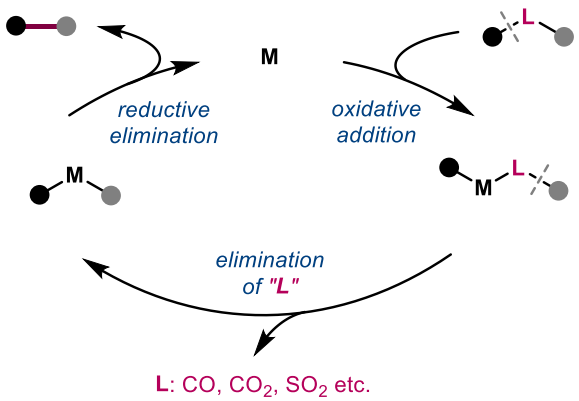


Fig 2. Generalized mechanism for TM-catalyzed UFC

In terms of the eliminated molecules, several types of catalytic UFC have been reported to date: decarbonylation (the removal of CO),[4-11] decarboxylation (the removal of CO_2),[12-13] desulfonylation (the removal of SO_2),[14] and deletion of single atoms.[15] Regarding catalytic decarbonylative UFC, acid chlorides,[5] thioesters,[6] acylsilanes,[7] and acylphosphonates[8] have been reported to be successful substrates for the formation of C–Cl, C–S, C–Si, and C–P bonds, respectively, whereas other carbonyl compounds such as ketones (C–C bond formation),[9] esters (C–O bond formation),[10] and amides (C–N bond formation)[1] have met with only limited success in terms of the generality of substrates. Decarboxylative UFC is primarily restricted to activated esters, which includes allylic or benzylic systems,[12a–e] with the noted exception of two examples of C–N bond formation: UFC of aryl carbamates and aroyloxycarbamates.[12f–i] Desulfonylative UFC has been reported for only two substrate classes (i.e., divinylsulfones[14a] and pyridylsulfonamides[14b-e]). In addition, UFC with the deletion of single atoms that include the release of an oxygen atom[15] from dibenzyl substrates has also been reported.

In recent years, Levin and co-workers developed a novel method for directly removing the nitrogen atoms from secondary amines, although stoichiometric amounts of reagents are required.[16] This approach is now recognized as a part of 'skeletal editing'.[17] Therefore, further expanding the scope of UFC is anticipated to contribute to future progress in methods for 'skeletal editing'.

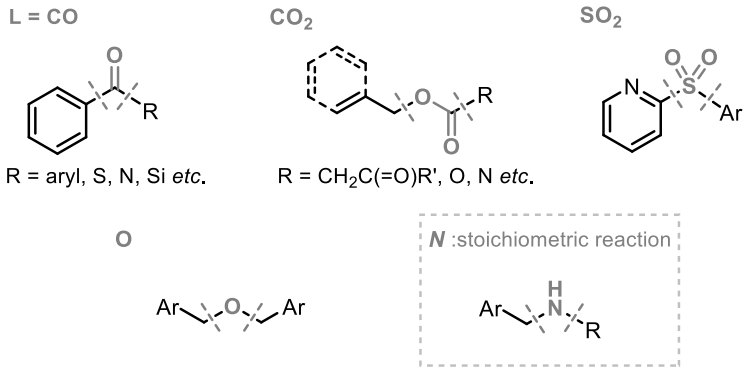


Fig 3. Examples of catalytic and non-catalytic UFC

"Skeletal editing" is a new research format with applications in various fields such as medicinal chemistry. This is because it serves as a novel and attractive form of retrosynthetic analysis. Retrosynthetic analysis is crucial for organic synthesis and for evaluating chemical transformations in terms of retrosynthetic disconnections. Assessing the progress of synthesis involves identifying synthetically attractive transformations. Molecular editing and late-stage functionalization are strategies for finding 'missing' transformations with a current focus on ‘peripheral editing’ such as in C–H functionalization (Fig 4. left).[2] ‘Skeletal editing’, despite growing interest, lacks refinement compared with ‘peripheral editing’. Utilizing UFC as a skeletal-editing strategy would make it possible to directly transform robust molecular skeletons by removing various versatile functional groups and forming new chemical bonds to create entirely different skeletons (Fig 4. right). However, the UFC reactions reported to date continue to be limited by substrate scope and reaction formats compared with that of cross-coupling, which highlights the need for further development.

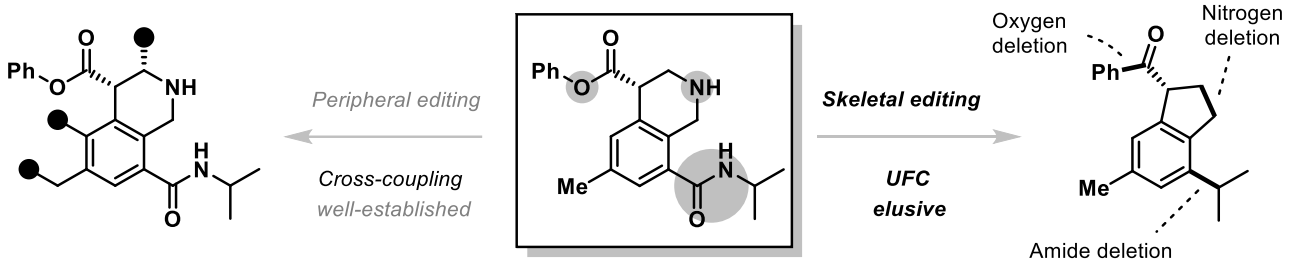


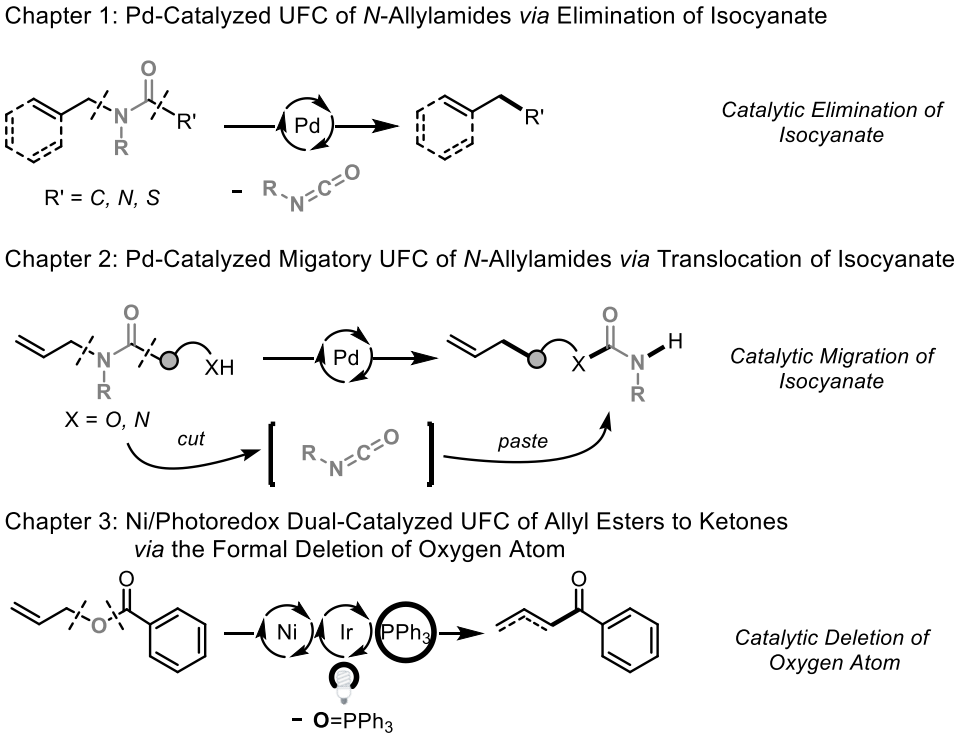
Fig 4. UFC as skeletal editing strategy

In the present study, a novel type of catalytic UFC was developed using amides and esters. This thesis consists of the following three chapters.

In chapter 1, a new UFC reaction that involves the palladium-catalyzed elimination of an isocyanate fragment from a *N*-allylamide is discussed. This UFC forms carbon–carbon and carbon–heteroatom bonds through the loss of isocyanates.

In chapter 2, the palladium-catalyzed migratory UFC reaction of *N*-allylamides bearing a tethered nucleophile is discussed. This reaction results in the extrusion of an amide moiety in the form of an isocyanate with its subsequent capture by the pendant nucleophile. This reaction also involves the net catalytic transposition of an amide group.

In chapter 3, a new UFC reaction of allylic esters into the corresponding ketones via the formal deletion of an oxygen atom is discussed. The key to the success of the reaction is the dual use of nickel and photoredox catalysts; the former mediates C–O bond activation and C–C bond formation, and the latter is responsible for deoxygenation of the acyloxy group using PPh_3 as a stoichiometric reductant.



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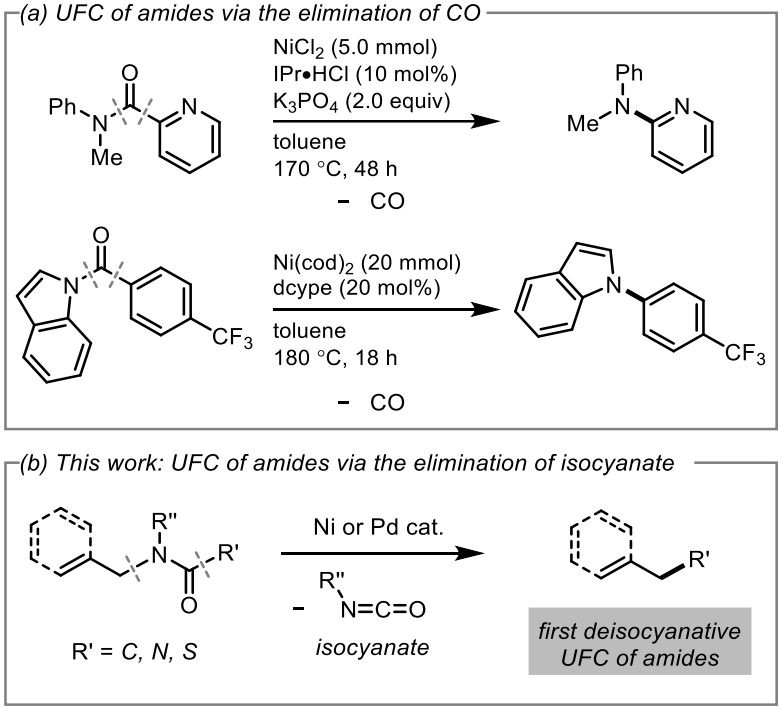
Chapter 1

Palladium-Catalyzed Unimolecular Fragment Coupling of *N*-Allylamides via Elimination of Isocyanate

1.1. Introduction

Amide is a common functionality found in both natural and non-natural compounds, and a variety of derivatives can be readily prepared by reliable condensation protocols using amine and carboxylic acid feedstocks.[1] Therefore, amides would be one of the most attractive substrtaes for UFC. Nevertheless, only two examples of UFC[2] involving amide compounds had been reproted. Both involve the eimination of CO (i.e., decarbonyltive UFC) to form C–N bonds (Scheme 1a). In view of great success of catalytic decarboxylation of etsers[3], one can envision that another mode for UFC of amides would be the elimination of isocyanate, in which an entire amide group is deleted. However, the process requires the activation of unactivated C–N bonds, rendering such UFC of amides a daunting challenge.[4] Herein, the author reported on the proof-of-concept study on the first UFC of amides, which established that C–C, C–N and C–S bonds can be catalytically created via elimination of isocyanate (Scheme 1b).

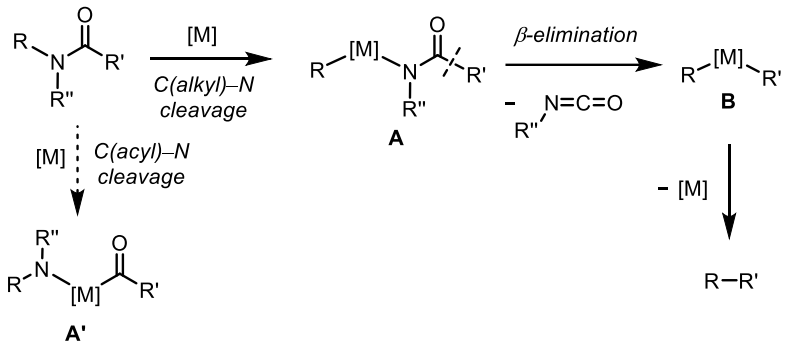


Scheme 1. Unimolecular Fragment Coupling (UFC) of Amides

1.2. Results and Discussion

C–N bond-forming unimolecular fragment coupling of amides via elimination of isocyanate. To realize the UFC of amides via the elimination of isocyanate, the author needs to develop a catalyst that can activate a C–N bond derived from an amine (*i.e.*, formation of intermediate **A**), in preference to an apparently weaker C(acyl)–N bond (*i.e.*, formation of intermediate **A'**)[5] (Scheme 2). In view of great success of palladium-catalyzed decarboxylative UFC of allylic esters,[3a] the author initiated our study using *N*-allylamide derivatives. The C(allyl)–N bond is known to undergo oxidative addition relatively easily because a stable π-allylmetal species is generated.[4] Therefore the author anticipated that a C(allyl)–N bond would be activated preferentially over amide bonds. Once oxidative addition of a C(allyl)–N bond occurs to form complex **A**, *β*-elimination of acyl substituent R' needs to

follow. Although a stoichiometric reaction of an amide-metal complex similar to **A** was reproted to undego *β*-aryl elimination to generate arylmetal species and isocyanate,[6] applicable substituents are limited (**A** in Scheme 2; R' = C_6F_5, R" = 2,6-^{i}Pr$_2$C$_6$H$_3$). On the other hand, our group previsouly reported a decarboxylative UFC of aromatic carbamates,[7] in which *β*-elimination of an amino group occurs to promote the decarboxylation. Prompted by this finding, the author envisioned that the elminaiton of isocyanate could also be facilitated by using an amino group as the acyl substituent (*i.e.*, R' in the substrate). Based on this hypothesis, *N*-allylurea derivatives were chosen as our initial model substrate for the development of UFC involing the elimination of isocyanate.



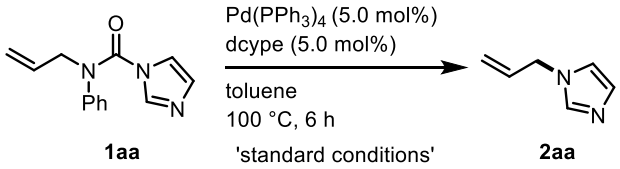
Scheme 2. Working Mechanism

As a result of extensive optimization, the desired UFC reaction of urea **1** proceeded in the presence of Pd(PPh$_3$)$_4$ (5.0 mol%) and 1,2-bis(dicyclohexylphosphino)ethane (dcype) (5.0 mol%) in toluene at 100 °C to form *N*-allylimidazole (**2aa**) in 87% yield (Table 1a, entry 1). The nature of the ligand did not excert profound impact on the efficiency of the reaction of **1**. For example, the use of less basic 1,2-bis(diphenylphosphino)ethane (dppe) or the analogous lignad with a larger bite angle (*i.e.*, dcypb) also afforded **2aa** in 75% and 65% yields, respectively (entries 2 and 3). Monodentate ligands, including PCy$_3$ (63%), ICy (56%) and IPr (68%), can also be used for this reaction (entries 4-6), and, moreover, Pd(PPh$_3$)$_4$ alone is catalytically active (64%, entry 7). Pd(dba)$_2$ can be used as a catalyst precursor that is comparably effective to Pd(PPh$_3$)$_4$ (86%, entry 8), whereas Pd(OAc)$_2$ was less effective (45%, entry 9). While no reaction was observed in the absence of a palladium catalyst with complete recovery of **1aa** (entry 10), palladium is not the only metal center that can catalyze UFC of **1aa**. When Ni(cod)$_2$ was used as a catalyst, **2aa** was also obtained in 88% yield, although higher loadings of catalyst and ligand (10 mol% each) were required (entry 11).

The author next investigated UFC of urea, in which an aliphatic amine moiety is to be eliminated. The Pd/dcype-catalyzed reaction of **1ab** afforded the corresponding aminated product **2ab** in only 57% yield even at higher reaction temperature of 140 °C (Table 1b). Unlike CO, CO$_2$ or SO$_2$, which are released from the reported UFCs, isocyanate has one organic substituent, which can serve as a traceless handle for the reactivity tuning. Taking advantage of this aspect of the reaction, the author examined the effect of the nitrogen substituent that is to be eliminated. While cyclohexyl (**1ab-Cy**) and electron-rich aryl (**1ab-OMe**) groups were less effective (10% and 39% yield, respectively), the electron-deficient group (*i.e.*, **1ab-CF$_3$**), improved the yield of **2ab** to 66%. Finally, the yield of **2ab** increased to 86% by using 10 mol% catalyst and shortening the reaction time to 6 h.

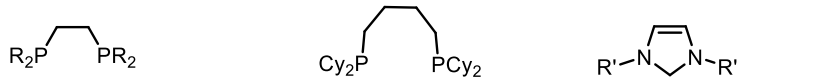
Table 1. Pd-Catalyzed Unimolecular Fragment Coupling of *N*-Allylureas

(a) Optimization



1aa 'standard conditions' **2aa**

entry	deviation from standard conditions[a]	NMR yield [%]
1	none	87
2	dppe instead of dcype	75
3	dcypb instead of dcype	65
4	PCy_3 (10 mol%) instead of dcype	63
5[b]	$ICy{\bullet}HBF_4$ (10 mol%) instead of dcype	56
6[b]	IPr•HCl (10 mol%) instead of dcype	68
7	without dcype	64
8	$Pd(dba)_2$ instead of $Pd(PPh_3)_4$	86
9	$Pd(OAc)_2$ instead of $Pd(PPh_3)_4$	45
10	without $Pd(PPh_3)_4$	0
11	$Ni(cod)_2$ (10 mol%)/dcype (10 mol%) instead of $Pd(PPh_3)_4$/dcype	88

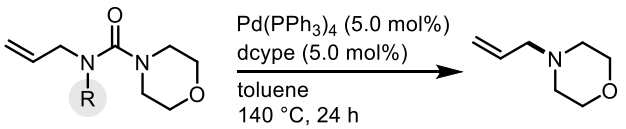


dcype (R = cyclohexyl)
dppe (R = C_6H_5)

dcypb

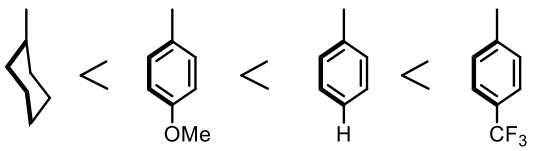
IPr (R' = 2,6-^{i}Pr$_2$C$_6$H$_3$)
ICy (R' = cyclohexyl))

(b) reactivity tuning by a substituent to be eliminated



1ab **2ab** GC yield

R =



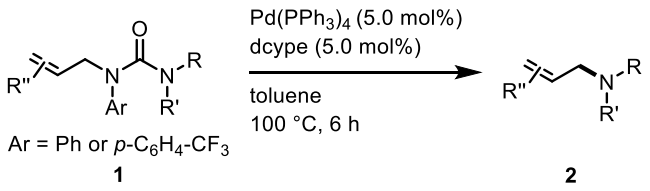
1ab-Cy	**1ab-OMe**	**1ab**	**1ab-CF$_3$**
10%	39%	57% (66%)[c]	66% (86%)[c]

[a]Reaction conditions: **1** (0.20 mmol), $Pd(PPh_3)_4$ (0.010 mmol), dcype (0.010 mmol), in toluene (1.0 mL) for 6 h at 100 °C. [b]With NaO^{t}Bu 12 mol%. [c]$Pd(PPh_3)_4$/dcype (10 mol% each), 6 h

With the optimized reaction conditions in hand, the author subsequently examined the scope of substrates (Scheme 1). Regarding the allylic fragment, several substituted derivatives were applicable. For example, 2-methylallyl derivative **1ba** underwent the UFC to form the corresponding *N*-allylimidazole **2ba** in 74% yield. A terminally substituted **1ca** readily participated in this reaction to produce the linear product **2ca** regioselectively. In the case of urea bearing a 3-cyclohexenyl group (**1dc**), the product was not efficiently obtained since the competing b-hydrogen elimination from the π-allylpalladium intermediate occurred to form 1,3-cyclohexadiene as a side product. This problem was overcome by using the substrate bearing a *p*-$CF_3C_6H_4$ group as the substituent on the nitrogen, leading to the formation of product **2dc** in 56% isolated yield. With regard to the amine fragment, various *N*-heteroarenes, including benzimidazoles (**2ac**, **2bc** and **2ad**), triazoles (**2ce**), and indoles (**2af**), can be allylated through the catalytic UFC. A substrate derived from L-histidine (**1ag**) also underwent this UFC successfully. It should be noted that this reaction can be performed on a gram scale by simply applying the standard protocol (**2ad**: 1.42 g, 96% isolated yield). Aliphatic amine and aniline derivatives can also be coupled under these palladium-catalyzed conditions. For example, cyclic amine fragments, including morpholine (**2ab** and **2cb**), Boc-piperazine (**2cg**), 1,2,3,4-tetrahydroisoquinoline (**2ah**) and indoline (**2ai**), served as viable substrates for this C–N bond formation reaction. Acyclic amine fragments (*i.e.*, **2cj**, **2ck** and **2cl**) can also be coupled, although the yields were lower due to the formation of deallylation side products (ca. 30-50%). A substrate bearing a primary alcohol moiety, *i.e.*, **2cr**, also successfully underwent this UFC to form a deisocyanated product with the OH moiety being intercepted with an eliminated isocyanate. This example represents a unique transposition reaction of an amide moiety.

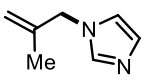
In addition to allylic ureas, substrates bearing an arylmethyl fragment can also participate in this UFC, likely via the formation of a π-benzylpalladium type intermediate.[3c] For example, palladium-catalyed UFC of 2-naphtylmethyl and 3-indolylmethylamides successfully provided the desired produtcts **2ea** and **2fc**, respectively. Futhermore, the UFC via extruction of isocyanate is not limited to C–N bond formation, but other heteroatom nucleophiles such as thiols and alcohols can also be used. Carbamothioate **1am** underwent C–S bond formation via extrusion of isocyanate to afford allylthiol **2am**. Under the identical conditions, carbamate **1an** resulted in the formation of 1-allylated 2-naphthol **2an**, possibly via elimination of isocyanate, followed by [3,3] sigmatropic rearrangement.[8]

Table 2. Scope of Pd-Catalyzed Unimolecular Fragment Coupling of *N*-Allyureas[a]

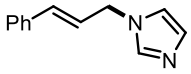


N-Allylureas

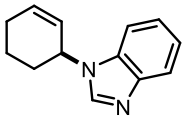
N-Heteroarenes (Ar = Ph)



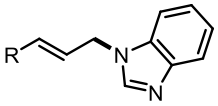
2ba 74%



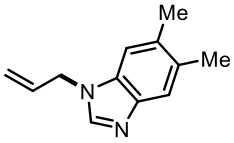
2ca 86%



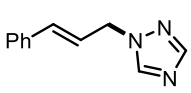
2dc 56%[b] (Ar = *p*-$CF_3C_6H_4$)



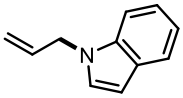
2ac (R = H) 88%
2cc (R = Ph) 87%



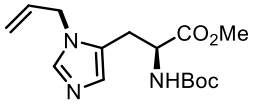
2ad 94%
gram scale
1.42 g, 96%



2ce 84%

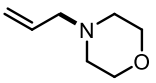


2af 68%[d,e,j] (Ar = *p*-$CF_3C_6H_4$)

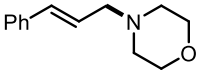


2ag 63% (2:1)[f]

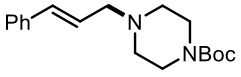
Aliphatic and aromatic amines (Ar = *p*-$CF_3C_6H_4$)



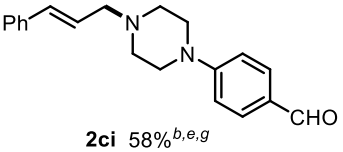
2ab 86%[b,e,k]



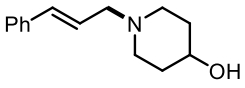
2cb 62%[d,e,g]



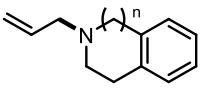
2ch 65%[b,e,g]



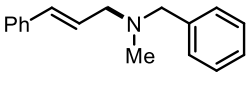
2ci 58%[b,e,g]



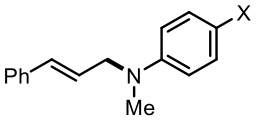
2cj 66%[d,e,g]



2ak (n = 1) 62%[b,g,j]
2al (n = 0) 65%[b,j]

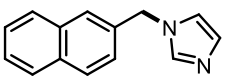


2cm 50%[d,e,h]

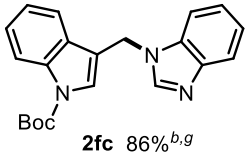


2cn (X = H) 41%[b,e,g]
2co (X = OMe) 42%[b,e,g]

Non-allylic substrates (Ar = Ph)

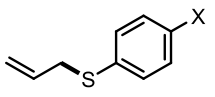


2ea 89%[b,e,h]

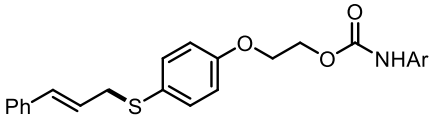


2fc 86%[b,g]

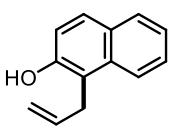
S- and O-nucleophiles (Ar = p-$CF_3C_6H_4$)



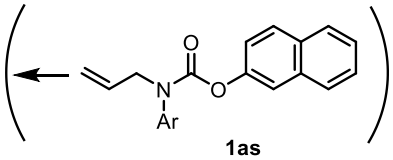
2ap (X = ^{t}Bu) 69%[c,h] (87%[b,h,j])
2cq (X = OH) 89%[b,h]



2cr 68%[b,h]



2as 55%[i]



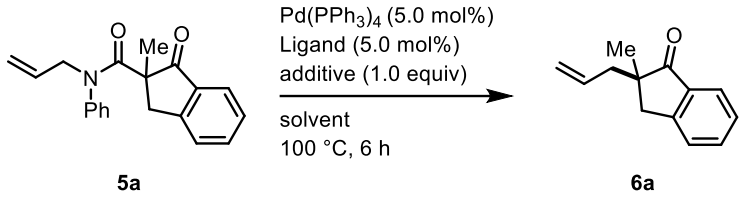
1as

[a]Reaction conditions: **1** (0.20 mmol), $Pd(PPh_3)_4$ (0.010 mmol), dcype (0.010 mmol), in toluene (1.0 mL) for 6 h at 100 °C. [b]Using 10 mol% of $Pd(PPh_3)_4$. [c]Using $Pd(dba)_2$ (5.0 mol%). [d]Using $Pd(dba)_2$ (10 mol%). [e]Run at 140 °C. [f]Run for 12 h. [g]Run for 18 h. [h]Run for 1 h. [i]Yield was determined by NMR due to the unstability of the product. [j]Yield was determined by GC due to the volatility of the product.

C–C bond-forming unimolecular fragment coupling of amides via elimination of isocyanate.

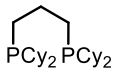
The author next investigated whether this catalytic UFC could be applied not only to the C–heteroatom bond formation with urea derivatives but also to the C–C bond formation with amides. In transition metal-catalyzed decarboxylative UFC, a *β*-ketoester moiety has been exploited as among the most successful fragment since the pioneering discoveries by Saegusa[3a] and Tsuji.[3b] In these reactions, the π-allylmetal species is captured by the ketone enolate generated by decarboxylation of a *β*-ketoester fragment. The author hypothesized that *β*-ketoamides would be susceptible to our UFC and form a new C–C bond if isocyanate is similarly extruded to form ketone enolate. To verify the feasibility of our hypothesis, the author examined the reaction of *N*-allyl-*β*-ketoamide **5a** using the Pd/dcype catalytic system. The author initially investigated the $Pd(PPh_3)_4$/dcype catalytic system, which is effective for *N*-allylurea derivatives, for its ability to promote the UFC of *β*-ketoamide **5a** via elimination of isocyanates. However, the desired C–C bond form ation did not occur (Table 3, entry 1). Changing the solvent from toluene to THF was effective, with **6a** being formed in 42% yield (entry 2). The addition of Cs_2CO_3 as a base markedly improved the yield of **6a** to 80% isolated yield (entry 3). Regarding the effect of the ligand, only 1,2-bis(dicyclohexylphosphino)propane (dcypp, entry 4) and ICy (entry 7) afforded the UFC products in comparable yields, which is in sharp contrast to the C–N bond-forming UFC of ureas, in which a wide range of lignads can be used in the reaction (see Table 1). The author next investigated the effect of bases. Although the use of KO^{t}Bu lowered the yield (31%, entry 9), the desired UFC reaction proceeded quantitatively when K_3PO_4 was used (entry 10).

Table 3. Pd-Catalyzed Unimolecular Fragment Coupling of *β*-Ketoamide **5a**[a]



5a **6a**

entry	Ligand	solvent	additive	NMR yield [%]
1	dcype	toluene	none	trace
2	dcype	THF	none	42
3	dcype	THF	Cs_2CO_3	87 (80)[b]
4	dcypp	THF	Cs_2CO_3	82
5	dppe	THF	Cs_2CO_3	0
6	PCy_3	THF	Cs_2CO_3	trace
7	ICy•HBF_4	THF	Cs_2CO_3	70
8	IPr•HCl	THF	Cs_2CO_3	0
9	dcype	THF	KO^{t}Bu	31
10	dcype	THF	K_3PO_4	>99 (>99)[b]

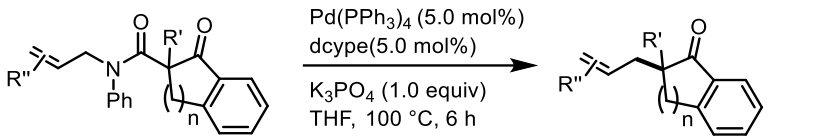


dcypp

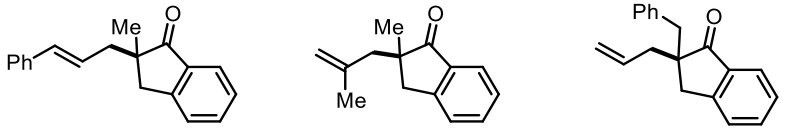
[a]Reaction conditions: **5a** (0.20 mmol), $Pd(PPh_3)_4$ (0.010 mmol), ligand (0.010 mmol) and additive (0.20 mmol) in solvent (1.0 mL) for 6 h at 100 °C. [b]Isolated yield.

Using the optimized conditions, the substrate scope for this palladium-catalyzed C–C bond-forming UFC of *N*-allyl-*β*-ketoamides were explored (Table 4). Several substituted allyl derivatives, such as **5b** and **5c**, also participated in the UFC to form the corresponding allylated indenones **6b** and **6c**. Regarding the substituent at the a position of the carbonyl group, in addition to a methyl group, benzyl derivatives **5d** and **5e** and allyl derivative **5f** successfully participated in the UFC, allowing access to a sterically congested all-carbon quaternary stereocenter. Electron-rich (**5g**) and electron-deficient (**5h**) indenones were both applicable to this UFC reaction. This UFC can also be applied to substrates containing six-membered rings (i.e., **5i**). In addition to allylic amides, amides bearing a 2-naphtylmethyl group successfully underwent the elimination of isocyanide to provide the corresponding produtct **6j**.

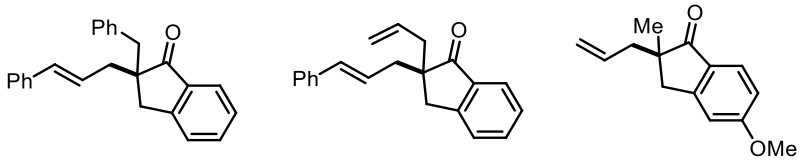
Table 4. Scope of Pd-Catalyzed Unimolecular Fragment Coupling of *β*-Ketoamides[a]



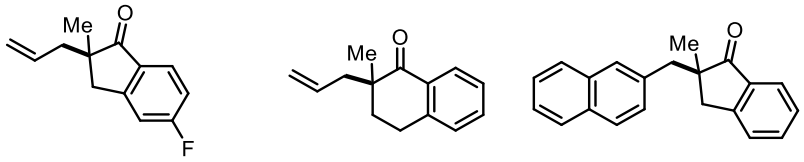
5a-j **6a-j**



6b[b] 57% **6c** 49% **6d** 93%



6e 98% **6f** 82% **6g** 43%

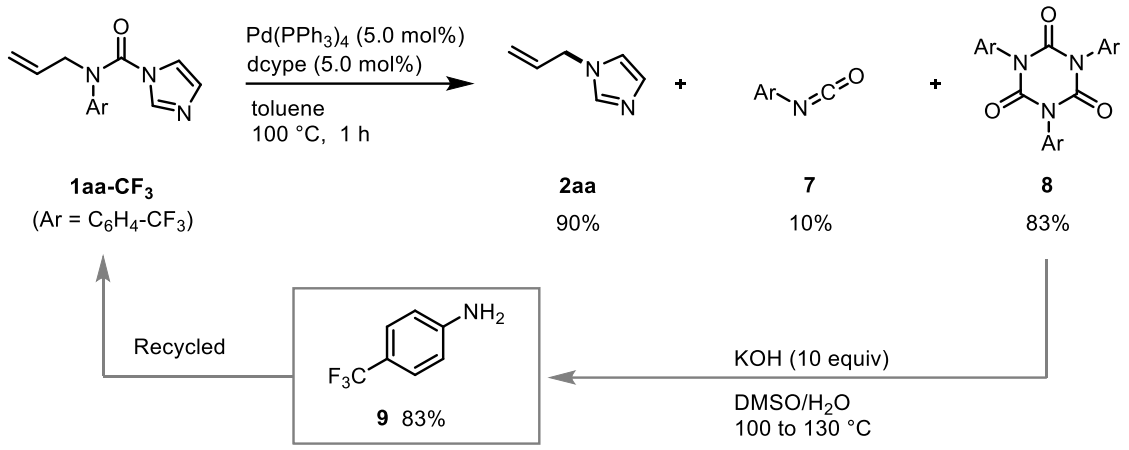


6h 60% **6i** 67% **6j** 53%[c]

[a]Reaction conditions: **5** (0.20 mmol), $Pd(PPh_3)_4$ (0.010 mmol), dcype (0.010 mmol) and K_3PO_4 (0.20 mmol) in THF (1.0 mL) for 6 h at 100 °C. [b]0.15 mmol scale. [c]At 140 °C for 24 h

Mechanistic Studies.

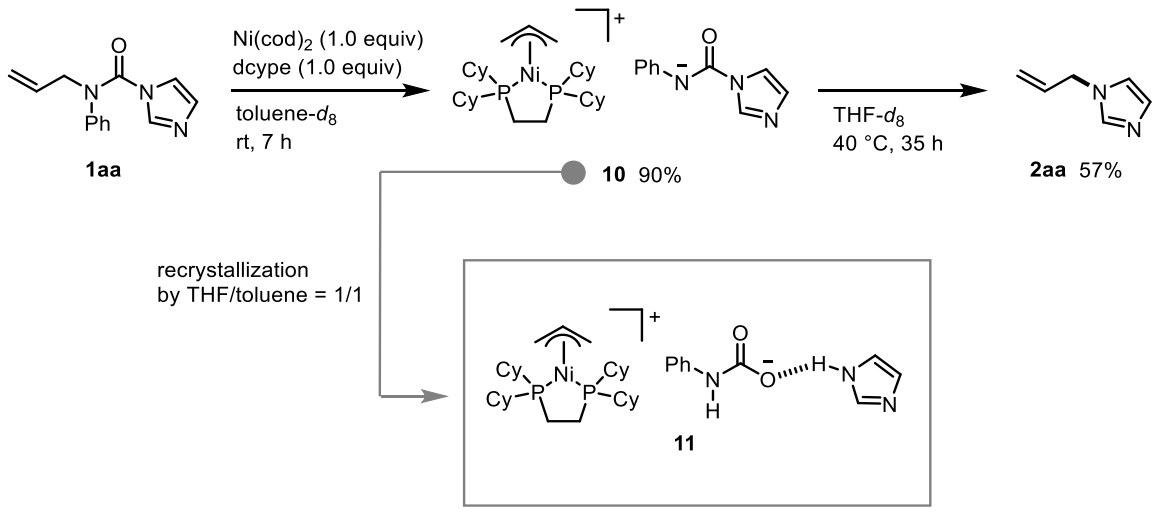
To verify his mechanistic hypothesis, the author examined the fate of the eliminated fragment of this UFC by monitoring the palladium-catalyzed reaction of **1aa-CF$_3$** by ^{19}F-NMR. This monitoring revealed that the reaction proceeded readily at 100°C for 1 h to form **2aa** in 90% yield and that isocyanate **7** and its cyclic trimer **8** were produced in 10% and 83% yields, respectively (Scheme 3). Control experiments revealed that the trimerization of **7** is promoted by $Pd(PPh_3)_4$/dcype and does not occur without either Pd catalyst or dcype.[9] The trimerization of **7** is an exergonic process of 7.4 kcal/mol,[10] which serves as one of the driving forces for this UFC reaction. The trimer **8** can be hydrolyzed to the corresponding aniline **9**, which can be recycled for use in the preparation of the starting **1aa-CF$_3$**.



Scheme 3. Fate of the Eliminated Fragment Generated in Pd-Catalyzed Reaction of **1aa-CF$_3$**

Next, the author attempted to isolate an organometallic intermediate by conducting the reaction of **1aa** with a stoichiometric amount of a Pd/dcype, but this attempt was unsuccessful. The author also conducted a similar stoichiometric reaction using Ni(cod)$_2$/dcype, since this complex can also catalyze the UFC of **1aa** (Table 1, entry 11). Thus, in the reaction of **1aa** with 1 equiv of Ni(cod)$_2$/dcype in toluene at room temperature, the author was able to successfully isolate cationic π-allyl nickel complex **10** in 90% yield (Scheme 4). X-ray crystallography unambiguously confirmed the structure of the cationic π-allylnickel framework in **10**, with the counter anion being hydrolyzed by a small amount of water upon recrystallization (*i.e.*, **11**). When the cationic π-allylnickel complex **10** was stirred in THF at 40 °C for 35 h, *N*–allylimidazole (**2aa**) was formed in 57% yield via the elimination of phenyl isocyanate. These results indicate that the UFC using a nickel catalyst proceeds through an ion-paired π-allyl complex.

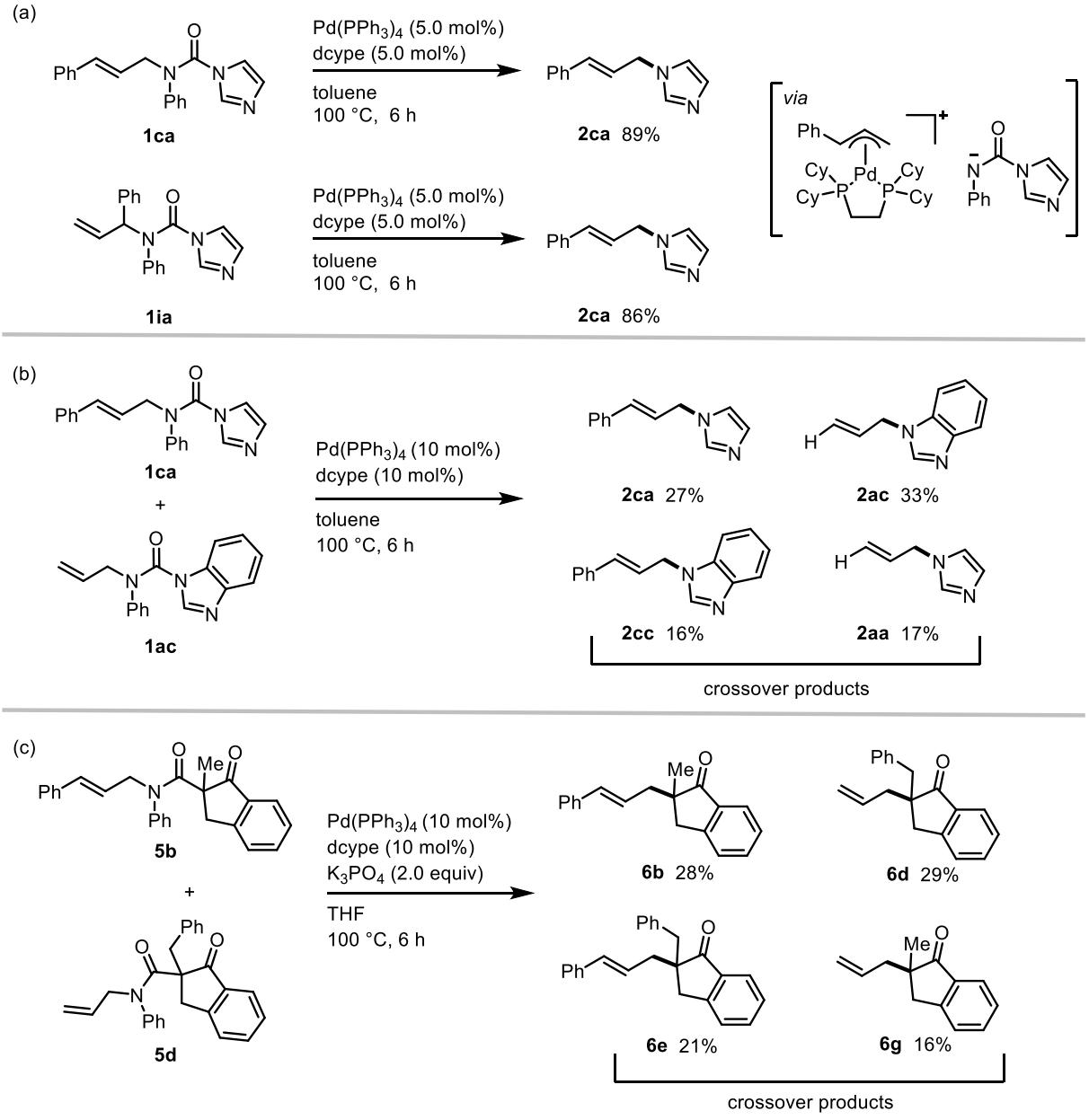
Scheme 4. Isolation of Reaction Intermediate



Although the author was unable to isolate a π-allyl intermediate complex in the case of palladium, some supporting evidence for the intermediacy of a π-allylpalladium complex was obtained. For example, amides bearing linear (**1ca**) and branched (**1ia**) allyl groups both afforded linear allylated product **2ca** under the Pd/dcype-catalyzed conditions,

which suggests that both reactions proceed via a common π-allylpalladium intermediate (Scheme 5a).[11] In addition, crossover experiments provided support that the π-allylpalladium intermediate in this study exists in an ion-paired form, rather than as an electronically neutral form. A palladium-catalyzed UFC of two different *N*-allylureas **1ca** and **1ac** led to the formation of crossover products **2ca** and **2ac**, in addition to intramolecular amination products **2cc** and **2aa** (Scheme 5b). Similarly, in the case of the C–C bond formation reaction using *N*-allyl *β*-ketoamide **5b** and **5d**, crossover products **6e** and **6g** were formed, along with the intermolecular coupling products **6b** and **6d** (Scheme 5c). These observations suggest that the palladium-catalyzed UFC reaction of amides and ureas proceeds via an ion-paired π-allyl complex, the counter anion of which can exchange under the reaction conditions.

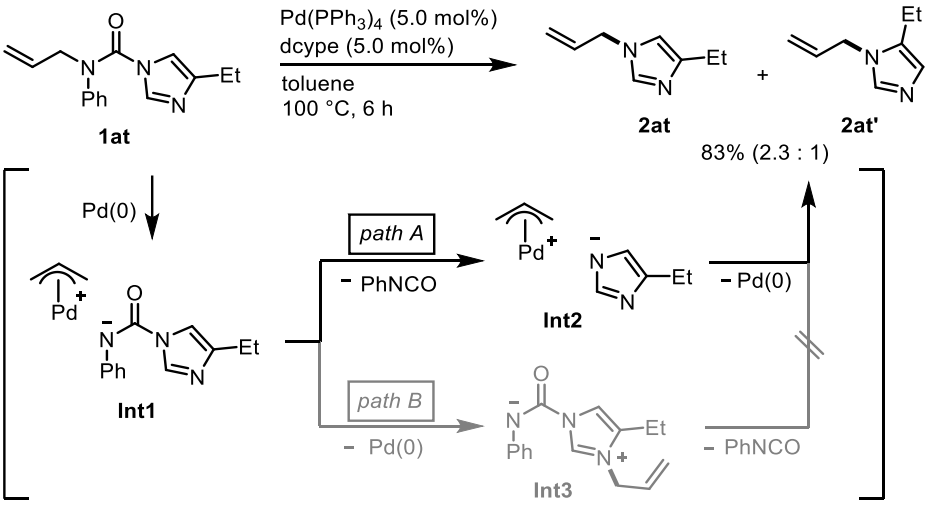
Scheme 5. Experimental Support for the Intermediacy of an Ion-Paired π-Allyl Palladium Complex



Tunge pointed out that, in the Pd-catalyzed decarboxylative amination of an allylic carbamate bearing an imidazole

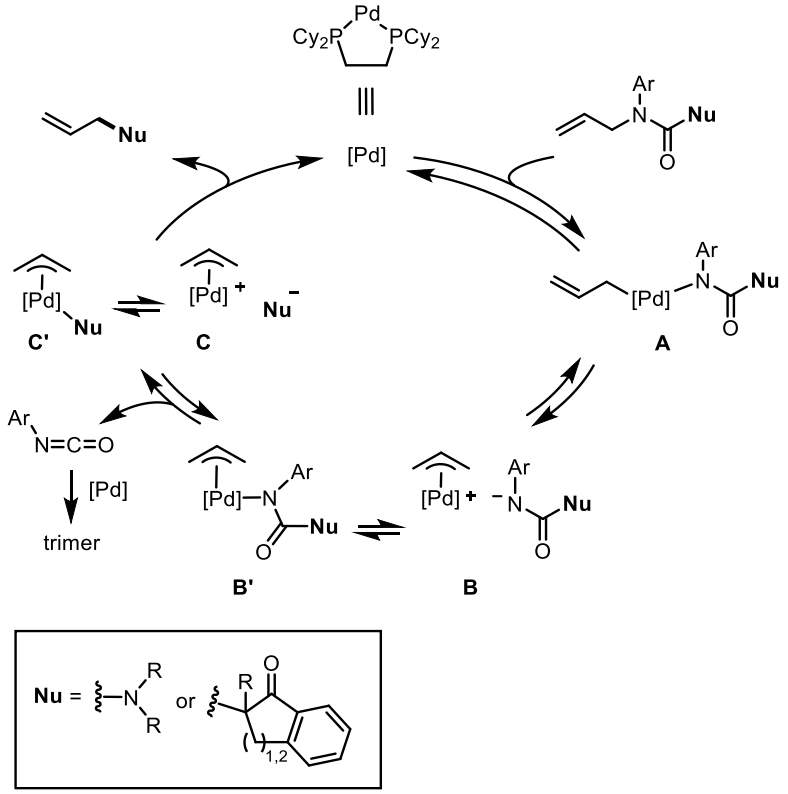
ring, there are two potential reaction pathways that a π-allylpalladium could follow to produce an aminated product, depending on which of the decarboxylation and C–N bond formation occurs first.[3e] These pathways can also be considered for the deisocyanative UFC of urea substrates bearing an imidazole moiety, such as **1at** (Scheme 6). One possible pathway involves the initial elimination of isocyanate from π-allylpalladium intermediate **Int1** to form **Int2**, which subsequently undergoes *N*-allylation (path A). An alternative pathway involves an initial *N*-allylation of the imidazole moiety with the generation of the zwitterionic imidazolium intermediate **Int3**, followed by the elimination of isocyanate (path B). These two pathways could be differentiated by examining the reaction of a substrate bearing an unsymmetrical imidazole moiety, because *N*-allylation would occur at the both of the nitrogen atoms in **Int2** whereas a new C–N bond would be formed regioselectively at the other nitrogen when **Int3** is involved. Therefore, the author examined the reaction of **1at** under the standard palladium-catalyzed conditions and found that positional isomers **2at** and **2at'** were obtained in a ratio of 2.3:1 (83% combined yield). This result suggests that this deisocyanative UFC likely involves path A.

Scheme 6. Two possible pathways for UFC of **1at** via the elimination of isocyanate.



On the basis of the mechanistic studies described above as well as related studies on decarboxylative UFC,[12] a plausible mechanism for the deisocyanative UFC reaction is depicted in Scheme 7. A palladium(0) coordinated with a phosphine ligand undergoes oxidative addition of the C(allyl)–N bond to give the σ-allylpalladium intermediate **A**, which subsequently isomerized to a more stable π-allylpalladium complex that is in equilibrium between the neutral (**B**) or the ion-paired (**B'**) forms. Isocyanate is eliminated from **B** or **B'** to form π-allylpalladium species **C** and **C'**, which lead to the final UFC product by reductive elimination via an inner- or outer-sphere mechanism.[12] Based on the results of crossover experiments (Scheme 5), ion-paired **B'** and **C'** are the likely predominant species under the catalytic conditions used in this study. The elimination of isocyanate is presumably a reversible process, and the trimerization of the eliminated isocyanate by a Pd/dcype catalyst drives the reaction forward.

Scheme 7. A Plausible Mechanism

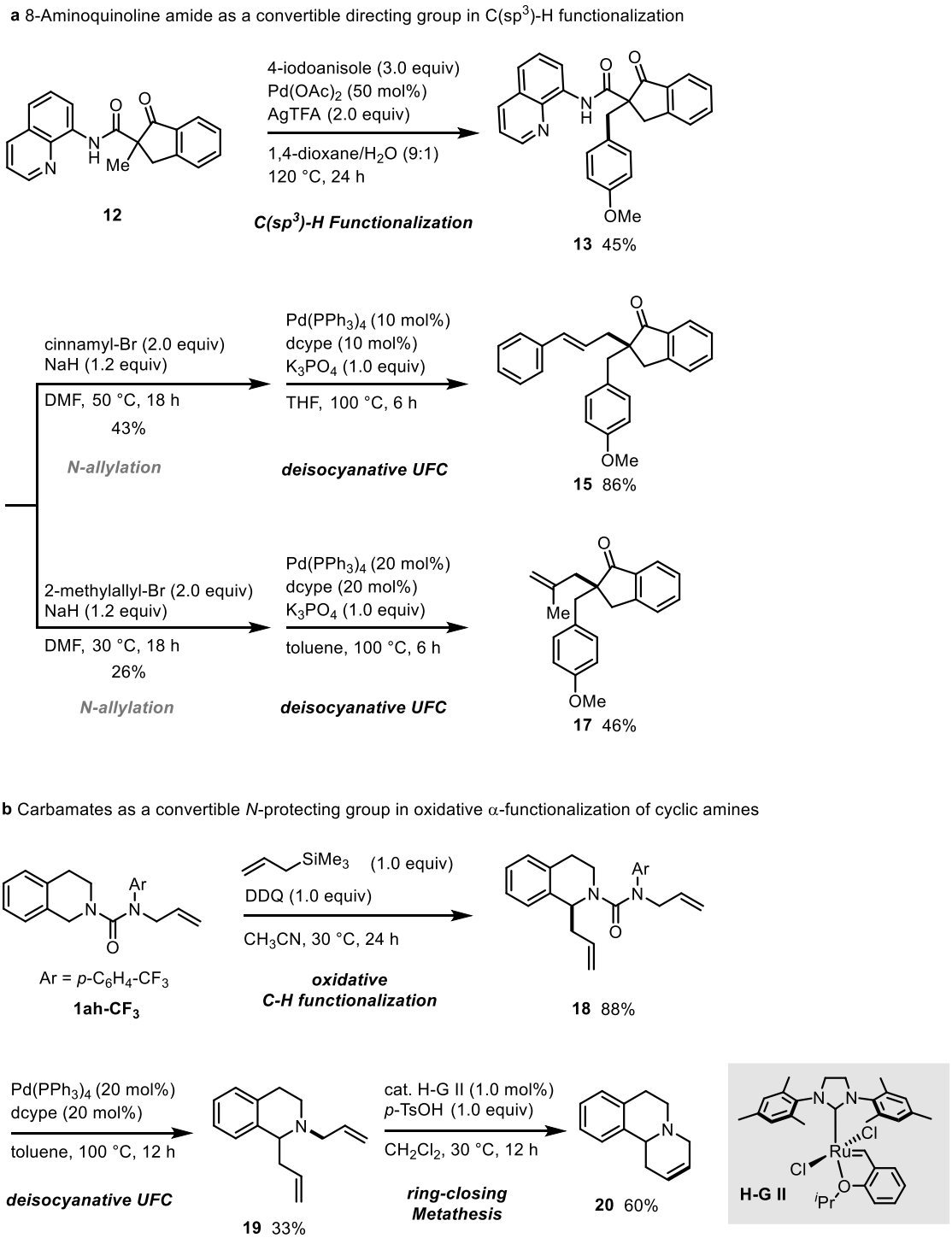


Synthetic Applications

An amide group is a common structural motif in organic chemistry and has various functions. From a synthetic perspective, one of the most important functions of an amide group involve serving as a protecting group for amines[13] and a directing group for metal-catalyzed transformation reactions of strong chemical bonds, such as C–H,[14] C–O,[15] and C–F[16] bonds. The deisocyanative UFC allows an amide group to be used as a protecting or a directing group that can be converted into allyl or arylmethyl groups. For example, an amide group containing an aminoquinoline moiety in **12** can serve as a directing group, which allowed for the arylation of a C(sp^3)–H bond in the presence of a palladium catalyst to generate **13**.[17] The aminoquinolinyl amide moiety in **13** can be converted into a cinnamyl group by *N*-alkylation, followed by the palladium-catalyzed UFC reaction to provide **15** in 86% yield (Scheme 8a). Similarly, an aminoquinoline-based directing group can be substituted by a 2-methylallyl group based on this UFC strategy. Although the synthetic elaboration of the aminoquinoline-based directing groups is limited to hydrolysis to the corresponding carboxylic acids, the UFC strategy described in this study broadens the scope of derivatization of the products obtained in C–H functionalization reactions.

Another example involves the use of the UFC in the conversion of amide-based protecting group. An *N*-allylcarboxyamide group is used as a protecting group for the α-oxidative functionalization of cyclic amides.[18] For example, the reaction of *N*-protected cyclic amine **1ah-CF$_3$** with allyltrimethylsilane in the presence of DDQ afforded α-allylated product **18** in 88% yield. The deisocyanative UFC of **18** can eliminate the amide moiety to form diallylated tetrahydroisoquinoline **19**, which can be further transformed into benzohydro[*a*]quinolozine **20**[19] by ring-closing metathesis.[20]

Scheme 8. Synthetic Applications



1.3. Conclusion

In summary, the author reports on the development of the first unimolecular fragment coupling of amides through the elimination of isocyanate, which is catalyzed by a palladium complex. The palladium-catalyzed UFC reaction can be used for the formation of carbon–carbon, carbon–nitrogen and carbon–sulfur bonds from readily

available amides. Several mechanistic experiments, including the isolation of a relevant π-allyl complex and the formation of crossover products indicated that this UFC reaction proceeds through a sequence that involves the activation of the C–N bond, the formation of a π-allyl complex, the extrusion of isocyanate, and reductive elimination. The author has also demonstrated that the UFC allows for the late-stage conversion of amide moieties into allyl groups in a one-step process, which should be useful in the synthetic elaboration of products that are synthesized by C–H functionalization reactions.

1.4. Experimental Section

I. General Information

^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a JEOL ECS-400 spectrometer in $CDCl_3$ or CD_2Cl_2. The chemical shifts in ^{1}H NMR spectra were recorded relative to $CHCl_3$ (δ 7.26) or CH_2Cl_2 (δ 5.32). The chemical shifts in ^{13}C NMR spectra were recorded relative to $CDCl_3$ (δ 77.16). The chemical shifts in ^{19}F NMR spectra were recorded relative to perfluorobenzene (-163.0 ppm). The chemical shifts in ^{31}P NMR spectra were recorded relative to H_3PO_4 (δ 0.0). The data is reported as follows: chemical shift (δ) in ppm, coupling constant (Hz), and integration. Infrared spectra (IR) were obtained using a JASCO FT/IR-4200 spectrometer. Absorption is reported in reciprocal centimeters (cm^{-1}) with the following relative intensities: s (strong), m (medium), or w (weak). High resolution mass spectra (HRMS) were obtained using a JEOL JMS-T100LP spectrometer. Melting points were determined using a Yamato melting point apparatus. Column chromatography was performed with Biotage Isolera® equipped with Biotage SNAP Ultra or SNAP Isolute NH_2 Cartridge.

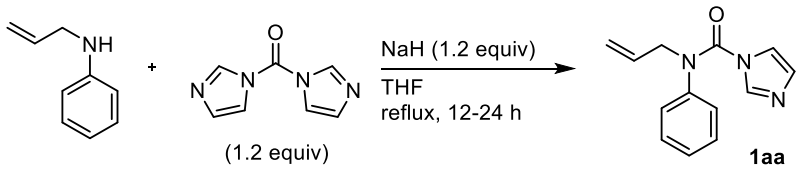
II. Materials

All commercially available reagents and solvents were supplied from TCI, WAKO and Aldrich. These corresponding *N*-allylamine including *N*-allyl-4-(trifluoromethyl)aniline [CAS:949535-52-8],[1] *N*-allyl-4-methoxyaniline [CAS:71954-46-6],[1] *N*-cinnamylaniline [CAS:1142-24-1],[1] *N*-(cyclohex-2-en-1-yl)aniline [CAS:52304-22-7],[1] *N*-(2-methylallyl)aniline [CAS:22774-81-8],[1] *N*-allylcyclohexanamine [CAS:6628-00-8],[2] *N*-cinnamyl-4-(trifluoromethyl)aniline [CAS:1191260-11-3],[3] *N*-(naphthalen-2-ylmethyl)aniline [CAS:181825-27-4][4], *N*-(1-phenylallyl)aniline [CAS:35755-81-8][5], methyl (tert-butoxycarbonyl)histidinate [CAS:2488-14-4][6] were prepared according to literature procedures.

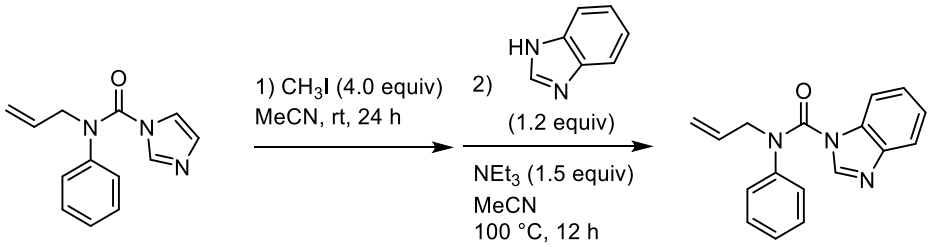
III. Preparation of Starting Materials for C–N Bond Formation Reactions

N-Allylurea derivatives were prepared based on General Procedure A[7] or General Procedure B.[8]

General Procedure A.



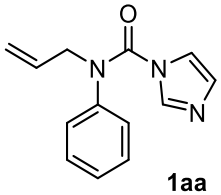
Synthesis of *N*-carbamoylimidazole. A 100 mL two-necked flask with a magnetic stirring bar was evacuated and backfilled with nitrogen three times. To the flask, NaH (60% in mineral oil, 481.7 mg, 12.0 mmol) was suspended in THF (20 mL), and *N*-allylaniline (1.40 mL, 10.2 mmol) was added portionwise. The resulting mixture was then stirred at 50 °C for 1 h. The solution was cooled to rt and CDI (1.78 g, 11.0 mmol) was added. The mixture was refluxed for 20 h. The solution was then cooled to rt and extracted with EtOAc. The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography on silica gel (hexane/EtOAc = 1/1) to afford **1aa** as a yellow oil (1.8 g, 78%).



1aa **1ac**

Synthesis of *N*-allylurea derivatives. To a solution of *N*-allylamide **1aa** (4.0 g, 17.6 mmol) in MeCN (40 mL), MeI (4.92 mL, 70.5 mmol) was added, and the mixture was stirred at rt for 12 h. The solvent was removed *in vacuo* to obtain the corresponding *N*-methylimidazolium salt, which was used in the next step without further purification. To a solution of the imidazolium salt (5.0 mmol) in MeCN (24 mL), benzimidazole (590 mg, 5.0 mmol) and Et_3N (0.35 mL, 5.0 mmol) were added. The mixture was refluxed for 12 h, and then partitioned between EtOAc and HCl (1 M). The organic layer was washed with brine, dried over Na_2SO_4 and filtered. The filtrate was concentrated. The crude product was purified by column chromatography on silica gel (hexane/EtOAc = 1/1) to afford **1ac** as a yellow solid (1.1 g, 89%).

***N*-Allyl-*N*-phenyl-1*H*-imidazole-1-carboxamide (1aa).**



1aa

Yellow oil (1.8 g, 78%). R_f 0.40 (SiO_2, hexane/EtOAc = 1/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.57 (s, 1H), 7.39–7.29 (m, 3H), 7.12–7.109 (m, 2H), 6.85 (t, *J* = 1.6 Hz, 1H), 6.80 (d, *J* = 2.4 Hz, 1H), 6.02–5.92 (m, 1H), 5.24–5.18 (m, 2H), 4.46–4.44 (m, 2H).

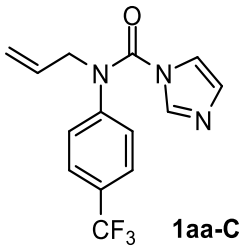
^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 150.0, 141.6, 137.9, 131.8, 130.3, 129.1, 128.3, 126.8, 119.3, 118.6, 55.37.

IR (ATR, cm^{-1}): 2982 w, 1701 m, 1394 m, 1373 m, 1296 m, 1280 m, 1240 s, 1043 m, 754 w, 702 m.

MS, m/z (relative intensity, %): 227 (M^+, 27), 161 (14), 160 (96), 132 (50), 119 (26), 104 (11), 91 (25), 77 (42), 68 (16), 64 (16), 51 (27), 42 (79), 41 (100), 40 (42)

HRMS (DART) *m/z* [M+H^+] calcd for $C_{13}H_{14}N_3O$: 228.1131, found: 228.1134.

***N*-Allyl-*N*-(4-(trifluoromethyl)phenyl)-1*H*-imidazole-1-carboxamide (1aa-CF_3).**



1aa-CF_3

General Procedure A was followed using *N*-allyl-4-(trifluoromethyl)aniline (8.1 g, 50 mmol).

Colorless solid (3.0 g, 63%). Mp 78.1°C. R_f0.24 (SiO_2, hexane/EtOAc = 1/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.63 (d, *J* = 9.2 Hz, 3H), 7.22 (d, *J* = 8.8 Hz, 2H), 6.88–6.87 (m, 4H), 6.02–5.92 (m, 1H), 5.27–5.20 (m, 1H), 4.48 (d, *J* = 6.4 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 149.9, 145.0, 137.7, 131.4, 130.1(q, J_{CF} = 33.2 Hz), 129.7, 127.4 (q, J_{CF} = 3.5 Hz), 126.7, 123.5(q, J_{CF} = 272.2 Hz), 119.8, 118.3, 55.2.

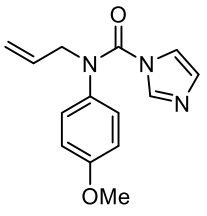
^{19}F NMR ($CDCl_3$, 376 MHz) δ: -63.9.

IR (ATR, cm^{-1}): 3069 m, 3031 m, 2963 m, 2838 m, 2807 m, 1934 w, 1859 w, 1804 w, 1747 w, 1734 w, 1681 s, 1620 m, 1601 s, 1576 m, 1514 m, 1496 m, 1477 s, 1451 s, 1439 s, 1389 s, 1325 s, 1265 s, 1227 s, 1209 s, 1173 s, 1117 s, 1065 s, 1029 s, 980 s, 930 s, 901 s, 849 s, 819 s, 778 s, 770 s, 747 s, 728 s, 698 s, 660 m.

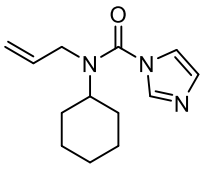
MS, m/z (relative intensity, %): 295 (41, M+), 229 (19), 228 (95), 187 (13), 168 (11), 107 (10), 95 (13), 68 (17), 42 (49), 41 (100).

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{14}H_{13}F_3N_3O$: 296.1005, found: 296.1006.

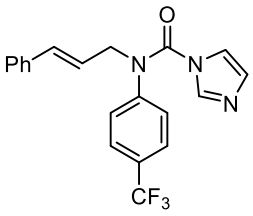
N-Carbamoylimidazole **1aa-OMe**, **1aa-Cy** and **1ca-CF_3**(see below) were also prepared through the same method. However, these compounds could not be purified completely. Therefore, **1aa-OMe**, **1aa-Cy** and **1ca-CF_3** were used in the next step without further purification.



1aa-OMe

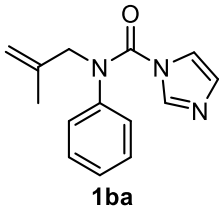


1aa-Cy



1ca-CF_3

***N*-(2-Methylallyl)-*N*-phenyl-1*H*-imidazole-1-carboxamide (1ba).**



1ba

General Procedure A was followed using *N*-(2-methylallyl)aniline (1.1 g, 5.4 mmol).

Run on a 5.4 mmol scale.

Colorless oil (0.17 g, 13%). R_f 0.16 (SiO_2, EtOAc).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.55 (s, 1H), 7.32–7.24 (m, 3H), 7.08–7.05 (m, 2H), 6.82 (d, *J* = 1.60 Hz, 1H), 6.77 (d, *J* = 1.60 Hz, 1H), 4.89 (s, 1H), 4.84 (s, 1H), 4.40 (s, 2H), 1.78 (s, 3H).

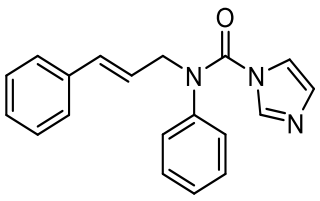
^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 150.0, 141.7, 139.8, 137.7, 130.1, 129.0, 127.9, 126.0, 118.4, 113.7, 57.7, 20.4.

IR (KBr, cm^{-1}): 1698 s, 1654 w, 1595 m, 1494 m, 1456 w, 1393 s, 1298 m, 1279 m, 1249 m, 1213 w, 1195 w, 1100 w, 1073 w, 1037 m, 1020 w, 945 w, 898 m, 820 w, 749 m, 699 m, 652 m, 602.

MS, m/z (relative intensity, %): 241 (M^+, 27), 174 (57), 132 (925), 77 (11), 55 (100).

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{14}H_{16}N_3O$: 242.1288, found: 242.1290.

_N_-Cinnamyl-_N_-phenyl-1_H_-imidazole-1-carboxamide (1ca).



1ca

General Procedure A was followed using *N*-cinnamylaniline (0.30 g, 2.5 mmol).

Run on a 4.2 mmol scale.

Colorless solid (1.3 g, 99%). Mp 83 °C. R_f 0.10 (SiO_2, hexane/EtOAc = 1/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.59 (s, 1H), 7.38–7.23 (m, 9H), 7.15–7.13 (m, 1H), 6.87 (dd, *J* = 1.2, 1.2 Hz, 1H), 6.81–6.80 (m, 1H), 6.50 (d, *J* = 16.0 Hz, 1H), 6.39–6.32 (m, 1H), 4.60 (dd, *J* = 6.8, 6.4 Hz, 2H).

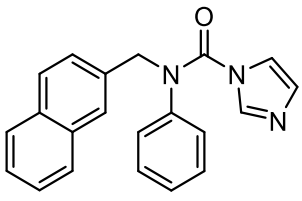
^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 150.1, 141.6, 137.9, 136.3, 134.9, 130.4, 129.1, 128.8, 128.5, 128.2, 127.0, 126.7, 122.6, 118.6, 55.1.

IR (ATR, cm^{-1}): 1694 s, 1493 m, 1394 s, 1293 s, 1250 s, 1219 m, 773 s, 746 s, 695 s.

MS, m/z (relative intensity, %): 303 (M^+, 0.85), 118 (10), 117 (100), 115 (32), 91 (20).

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{19}H_{18}N_3O$:304.1444, found: 304.1448.

_N_-(Naphthalen-2-ylmethyl)-_N_-phenyl-1_H_-imidazole-1-carboxamide (1ea).



1ea

General Procedure A was followed using *N*-(naphthalen-2-ylmethyl)aniline (1.5 g, 6.4 mmol).

Run on a 6.4 mmol scale.

Colorless solid (1.4 g, 65%). M.p. 133 °C. R_f 0.20 (SiO_2, hexane/EtOAc = 1/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.83–7.75 (m, 3H), 7.67 (s, 1H), 7.61 (s, 1H), 7.50–7.43 (m, 3H), 7.31–7.27 (m, 3H), 7.02–6.99 (m, 2H), 6.89 (t, *J* = 1.6 Hz, 1H), 6.81 (t, *J* = 1.2 Hz, 1H), 5.21 (s, 2H).

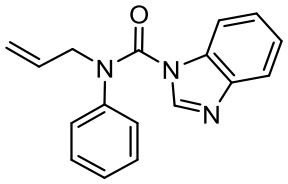
^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 150.5, 141.4, 138.0, 133.5, 133.3, 133.1, 130.3, 129.2, 128.7, 128.5, 128.1, 128.1, 127.8, 127.1, 126.6, 126.4, 126.4, 118.7, 56.3.

IR (KBr, cm^{-1}): 3154 w, 3117 m, 3046 m, 2951 w, 2360 w, 1694 s, 1594 m, 1586 m, 1507 m, 1493 s, 1470 m, 1455 m, 1382 s, 1366 s, 1215 w, 1176 m, 1126 w, 1103 m, 947 w, 916 w, 900 m, 845 s, 765 s, 592 m, 551 m.

MS, m/z (relative intensity, %): 327 (M^+, 2.0), 208 (12), 142 (13), 141 (100), 115 (28).

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{21}H_{18}N_3O$: 328.1444, found: 328.1448.

_N_-Allyl-_N_-phenyl-1_H_-benzo[d]imidazole-1-carboxamide (1ac).



1ac

Yellow solid (1.1 g, 89%, 5.0 mmol scale). Mp 83 °C. R_f 0.36 (SiO_2, EtOAc).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.96 (d, *J* = 8.0 Hz, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.54 (s, 1H), 7.39–7.29 (m, 4H), 7.24–7.22 (m, 1H), 7.13–7.09 (m, 2H), 6.09–6.00 (m, 1H), 5.29–5.24 (m, 2H), 4.54 (dt, *J* = 5.9, 1.2 Hz, 2H).

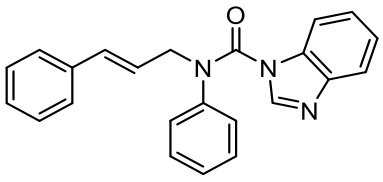
^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 150.7, 142.8, 142.2, 141.6, 132.7, 132.1, 130.3, 127.9, 126.2, 125.0, 124.1, 120.4, 119.2, 114.3, 55.0.

IR (KBr, cm^{-1}): 1698 s, 1608 m, 1594 m, 1493 m, 1476 m, 1450 m, 1388 m, 1283 m, 1257 m, 1202 s, 1182 m, 1144 m, 953 m, 926 w, 788 w, 768 s, 755 s, 744 s, 700 s, 669 m.

MS, m/z (relative intensity, %): 277 (M^+, 16), 160 (36), 133 (13), 132 (31), 119 (13), 91 (15), 90(23), 77 (18), 64 (12), 63 (10), 41 (100).

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{17}H_{16}N_3O$: 278.1288, found: 278.1298.

_N_-Cinnamyl-_N_-phenyl-1_H_-benzo[d]imidazole-1-carboxamide (1cc).



1cc

General Procedure A was followed using **1ca** (0.28 mg, 2.3 mmol).

Run on a 2.2 mmol scale.

Colorless oil (0.69 g, 88%). R_f 0.31 (SiO_2, hexane/EtOAc = 1/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 8.02 (d, *J* = 8.0 Hz, 1H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.57 (s, 1H), 7.41–7.21 (m, 10H), 7.14–7.12 (m, 2H), 6.57 (d, *J* = 8.0 Hz, 1H), 6.43 (dt, *J* = 16, 6.8 Hz, 1H), 4.69 (d, *J* = 6.8 Hz, 2H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 150.7, 142.7, 142.0, 141.5, 136.3, 134.6, 132.6, 130.3, 128.7, 128.1, 127.9, 126.6,

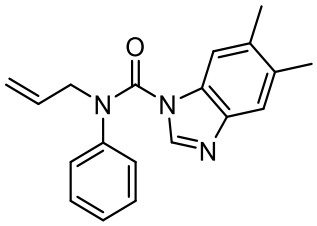
126.3, 124.9, 124.0, 122.9, 120.3, 114.3, 54.6.

IR (KBr, cm^{-1}): 2360 w, 1697 s, 1594 w, 1496 m, 1478 w, 1450 m, 1431 w, 1389 s, 1351 m, 1339 w, 1285 s, 1253 m, 1201 m, 966 w, 888 w, 787 w, 749 s, 697 w, 668 w, 637 w, 614 w, 604 w, 506 w.

MS, m/z (relative intensity, %): 353 (M^+, 1.1), 235 (13), 234 (20), 119 (13), 118 (13), 117 (1100), 115 (30), 91 (16).

HRMS (DART) *m/z* [M+H^+] calcd for $C_{23}H_{20}N_3O$: 354.1601, found: 354.1595.

_N_-Allyl-5,6-dimethyl-_N_-phenyl-1_H_-benzo[_d_]imidazole-1-carboxamide (1ad).



1ad

General Procedure A was followed using 5,6-dimethylbenzimidazole (0.95g, 6.4 mmol).

Run on a 6.2 mml scale.

Yellow solid (1.8 g, 93%). Mp 135 °C. R_f 0.20 (SiO_2, hexane/EtOAc = 1/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.76 (s, 1H), 7.45 (s, 2H), 7.32–7.21 (m, 3H), 7.08 (d, *J* = 8.0 Hz, 2H), 6.07–6.00 (m, 1H), 5.28-5.24 (m, 2H), 4.53 (d, *J* = 6.4 Hz, 2H), 2.39 (s, 3H), 2.35 (s, 3H).

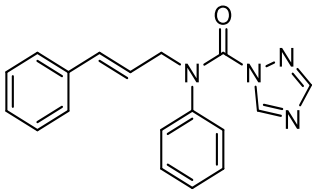
^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 150.9, 142.4, 141.3, 140.9, 134.3, 133.0, 132.2, 131.0, 130.3, 127.8, 126.1, 120.3, 119.1, 114.5, 54.9, 20.6, 20.3.

IR (KBr, cm^{-1}): 3106 m, 2965 m, 1686 s, 1597 m, 1586 m, 1499 m, 1470 m, 1456 m, 1444 m, 1393 s, 1307 m, 1268 m, 1194 s, 1177 m, 1167 m, 1120 m, 962 w, 915 w, 845 s, 751 s, 697 s, 680 m, 591 m, 559 m.

MS, m/z (relative intensity, %): 305 (M^+, 79), 171 (12), 162 (11), 160 (76), 145 (16), 133 (19), 132 (70), 131 (13), 118 (16), 117 (11), 116 (17), 91 (724), 77 (14), 41 (100).

HRMS (DART) *m/z* [M+H^+] calcd for $C_{19}H_{20}N_3O$: 306.1601, found: 306.1606.

_N_-Cinnamyl-_N_-phenyl-4_H_-1,2,4-triazole-1-carboxamide (1ce).



1ce

General Procedure A was followed using **1ca** (1.0 g, 2.0 mmol) and 1,2,4-triazole (0.17 g, 2.5 mmol).

Run on a 2.0 mmol scale.

Colorless oil (0.39 g, 65%). R_f 0.32 (SiO_2, hexane/EtOAc = 1/2).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 8.66 (s, 1H), 7.70 (s, 1H), 7.33–7.19 (m, 8H), 7.10 (d, *J* = 7.2 Hz, 2H), 6.50 (d, *J* = 16.0 Hz, 1H), 6.40–6.32 (m, 1H), 4.62 (d, *J* = 6.4 Hz, 2H).

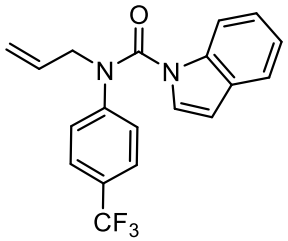
^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 151.6, 148.7, 145.7, 141.4, 136.0, 134.6, 129.3, 128.4, 127.9, 127.6, 126.7, 126.4, 122.3, 54.9.

IR (KBr, cm^{-1}): 3125 m, 3061 w, 3041 w, 1804 w, 1700 s, 1660 m, 1597 s, 1589 m, 1505 s, 1495 s, 1457 w, 1433 m, 1417 m, 1386 m, 1358 m, 1320 m, 1301 m, 1286 s, 1275 s, 1224 m, 1206 m, 1180 s, 1122 s, 1097 s, 1031 m, 993 w, 951 m, 834 m, 750 s, 674 s, 612 w, 542 w.

MS, m/z (relative intensity, %): 304 (M^+, 0.61), 235 (36), 207 (35), 206 (61), 119 (14), 118 (11), 117 (100), 116 (16), 115 (60), 91 (30), 77 (15).

HRMS (DART) Calcd for $C_{18}H_{17}N_4O$ ([M+H$^+$]): 305.1397, found: 305.1390.

_N_-Allyl-_N_-(4-(trifluoromethyl)phenyl)-1_H_-indole-1-carboxamide (1af).



1af

General Procedure A was followed using **1aa** (1.0g, 2.3 mmol) and indole (0.27 mg, 2.3 mmol).

Run on a 2.3 mmol scale.

Colorless oil (0.32 g, 41%). R_f 0.29 (SiO_2, hexane/EtOAc = 5/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 8.08 (d, 7.8 Hz, 1H), 7.50 (d, J = 8.4 Hz, 3H), 7.32 (t, J = 7.2 Hz, 1H), 7.21 (t, J = 7.6 Hz, 1H), 7.12 (d, J = 4.4 Hz, 2H), 6.77 (d, J = 4.0 Hz, 1H), 6.32 (d, J = 4.0 Hz, 1H), 6.04 (m, 1H), 5.26 (m, 2H), 4.56 (d, J = 6.0 Hz, 2H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 153.1, 146.8, 136.0, 132.7, 129.5, 128.1 (q, J_{CF} = 32.6 Hz), 126.9 (q, J_{CF} = 3.8 Hz), 126.1, 125.0, 124.6, 123.8 (q, J_{CF} = 272.0 Hz), 122.9, 121.0, 118.6, 114.8, 107.1, 54.4.

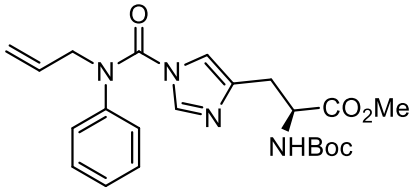
^{19}F NMR ($CDCl_3$, 376 MHz) δ: -63.5.

IR (ATR, cm^{-1}): 2119 (w), 2130 w, 1685 m, 1614 m, 1453 w, 1434 w, 1383 m, 1365 m, 1321 s, 1297 m, 1256 w, 1222 w, 1207 w, 1166 w, 1120 m, 1111 m, 1068 m, 1015 w, 948 w, 932 w, 844 w, 827 w, 771 s, 752 m, 631 w.

MS, m/z (relative intensity, %): 344 (M^+, 34), 228 (16), 157 (13), 156 (13), 130 (11), 116 (27), 89 (19), 41 (100.

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{19}H_{16}N_2OF_3$: 345.1209, found: 345.1206.

Methyl _N^t_-(allyl(phenyl)carbamoyl)-_N^a_-(*tert*-butoxycarbonyl)histidinate (1ag).



1ag

General Procedure A was followed using **1aa** (3.0 g, 7.0 mmol) and methyl (*tert*-butoxycarbonyl)histidinate (1.7 g,

6.4 mmol) [6].

Run on a 6.4 mmol scale.

Yellow oil (2.6 g, 94%). R_f 0.12 (SiO_2, hexane/EtOAc = 1/1).

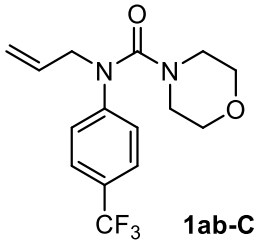
^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.46 (d, *J* = 1.4 Hz, 1H), 7.38–7.28 (m, 3H), 7.08–7.05 (m, 2H), 6.58 (s, 1H), 5.98–5.88 (m, 1H), 5.54 (d, *J* = 8.5 Hz, 1H), 5.21–5.15 (m, 2H), 4.45–4.39 (m, 2H), 3.62 (s, 3H), 2.91–2.78 (m, 2H), 1.40 (s, 9H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 172.2, 155.5, 149.7, 141.5, 137.7, 137.3, 131.7, 130.3, 128.3, 126.7, 119.3, 116.0, 79.8, 55.3, 53.1, 52.3, 30.0, 28.4.

IR (ATR, cm^{-1}): 3370 w, 2978 w, 1751 m, 1700 s, 1596 w, 1495 m, 1455 w, 1435 m, 1396 s, 1365 w, 1295 w, 1261 w, 1225 w, 1165 s, 1025 m, 991 w, 925 w, 857 w, 754 m, 701 m, 565 w.

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{22}H_{29}N_4O$: 429.2133, found: 429.2131.

_N_-Allyl-_N_-(4-(trifluoromethyl)phenyl)morpholine-4-carboxamide (1ab-CF$_3$).



1ab-CF$_3$

General Procedure A was followed using **1aa-CF$_3$** (2.0 mg, 6.7 mmol) and morpholine (63 mg, 7.5 mmol).

Run on a 2.1 mmol scale.

Yellow oil (0.55 g, 85%). R_f 0.52 (SiO_2, hexane/EtOAc = 1/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.57 (d, *J* = 8.7 Hz, 2H), 7.16 (d, *J* = 8.2 Hz, 2H), 5.97–5.88 (m, 1H), 5.16–5.12 (m, 2H), 4.32 (d, *J* = 5.5 Hz, 2H), 3.53 (dd, *J* = 5.0, 4.6 Hz, 4H), 3.25 (dd, *J* = 5.0, 4.6 Hz, 4H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 159.6, 148.5, 134.5, 126.7 (q, J_{CF} = 3.8 Hz), 125.9 (q, J_{CF} = 32.9 Hz), 125.4(q, J_{CF} = 271.6 Hz), 122.8, 117.0, 66.4, 53.9, 46.2.

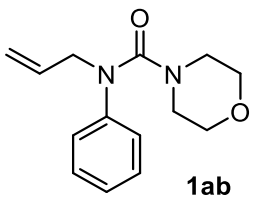
^{19}F NMR ($CDCl_3$, 376 MHz) δ: -63.4.

IR (ATR, cm^{-1}): 1654 m, 1613 m, 1323 s, 1255 m, 1220 s, 1163 m, 1111 s, 1068 m, 913 m, 844 m, 780 s, 740 m, 731 m.

MS, m/z (relative intensity, %): 314 (M$^+$, 4.4), 270 (10), 257 (14), 145 (10), 115 (12), 114 (100), 70 (100), 56 (19), 45 (12), 42 (48), 41 (94).

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{15}H_{18}F_3N_2O_2$: 315.1315, found: 315.1315.

_N_-Allyl-_N_-phenylmorpholine-4-carboxamide (1ab).



1ab

General Procedure A was followed using **1aa** (0.46 mg, 2.0 mmol) and morpholine (21 mg, 2.5 mmol)

Run on a 2.0 mmol scale.

Colorless oil (1.6 g, 65%). R_f 0.48 (SiO_2, hexane/EtOAc = 1/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.34–7.29 (m, 2H), 7.13–7.07 (m, 3H), 5.98-5.90 (m, 1H), 5.13–5.07 (m, 2H), 4.27 (dd, *J* = 5.5, 1.4 Hz, 2H), 3.49–3.46 (m, 4H), 3.21–3.19 (m, 4H).

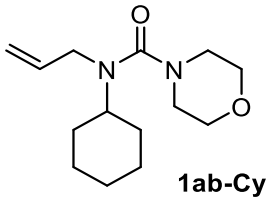
^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 160.4, 145.4, 135.0, 129.5, 125.0, 124.3, 116.6, 66.5, 54.5, 46.2.

IR (KBr, cm^{-1}): 2362 m, 1661 s, 1654 s, 1614 s, 1580 w, 1519 m, 1434 m, 1407 m, 1373 w, 1324 s, 1295 m, 1243 m, 1218 m, 1192 w, 1165 m, 1114 s, 1070 s, 1013 m, 997 w, 918 m, 842 s, 764 m, 747 m.

MS, m/z (relative intensity, %): 246 (M^+, 6), 132 (24), 114 (79), 77 (20), 70 (100), 42 (42), 41 (82).

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{14}H_{19}N_2O_2$: 247.1441, found: 247.1441.

***N*-Allyl-*N*-cyclohexylmorpholine-4-carboxamide (1ab-Cy).**



1ab-Cy

General Procedure A was followed using **1aa-Cy** (1.2 g, 4.1 mmol) and morpholine (27 mg, 3.2 mmol).

Run on a 3.1 mmol scale.

Yellow oil (0.65 g, 82%). R_f 0.44 (SiO_2, EtOAc).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 5.85–5.76 (m, 1H), 5.16–5.05 (m, 2H), 3.77–3.75 (m, 2H), 3.68 (t, *J* = 4.6 Hz, 4H), 3.39–3.31 (m, 1H), 3.22 (dd, *J* = 4.6, 5.0 Hz, 4H) 1.80 (d, *J* = 12.0 Hz, 2H), 1.74–1.71 (m, 2H), 1.62 (d, *J* = 12.8 Hz, 1H), 1.58–1.48 (m, 2H), 1.32–1.21 (m, 2H), 1.13–1.03 (m, 1H).

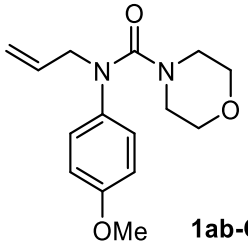
^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 164.7, 136,8, 115.6, 67.0, 59.3, 47.9, 46.8, 31.3, 26.6, 25.9.

IR (ATR, cm^{-1}): 2927 w, 1637 m, 1512 w, 1453 m, 1399 m, 1362 w, 1326 w, 1298 w, 1220 m, 1115 m, 993 w, 921 w, 792 s, 665 w, 421 m, 403 m.

MS, m/z (relative intensity, %): 252 (M^+, 4), 209 (11), 208 (11), 195 (36), 138 (21), 126 (13), 114 (100), 88 (16), 86 (21), 84 (20), 83 (78), 82 (14), 81 (11), 70 (91), 57 (14), 56 (26), 55 (68), 54 (10), 42 (43), 41 (67).

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{14}H_{25}N_2O_2$: 253.1911, found: 253.1909.

***N*-Allyl-*N*-(4-methoxyphenyl)morpholine-4-carboxamide (1ab-OMe).**



1ab-OMe

General Procedure A was followed using morpholine (21 mg, 2.5 mmol).

Run on a 2.0 mmol scale.

Yellow oil (0.31 g, 56%). R_f 0.22 (SiO_2, hexane/EtOAc = 1/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.04–7.01 (m, 2H), 6.85 (dd, *J* = 12.1, 3.4 Hz, 2H), 5.98–5.89 (m, 1H), 5.10–5.06 (m, 2H), 4.19 (d, *J* = 6.0 Hz, 2H), 3.80 (s, 3H), 3.46 (t, *J* = 4.8 Hz, 4H), 3.19 (t, *J* = 4.8 Hz, 4H).

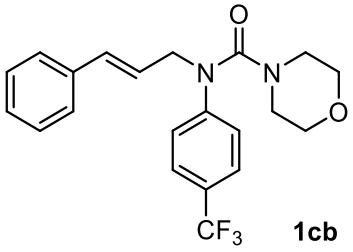
^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 160.8, 157.0, 138.2, 135.0, 126.2, 116.8, 114.7, 66.6, 55.6, 54.9, 46.3.

IR (ATR, cm^{-1}): 1654 m, 1613 m, 1323 s, 1255 m, 1220 s, 1163 m, 1111 s, 1068 m, 913 m, 844 m, 780 s, 740 m, 731 m.

MS, m/z (relative intensity, %): 276 (M^+, 21), 253 (11), 162 (15), 149 (25), 134 (20), 114 (68), 86 (11), 70 (100), 56 (12), 42 (43), 41 (41).

HRMS (DART) *m/z* [M+H^+] calcd for $C_{15}H_{21}N_2O_3$: 277.1547, found: 277.1549.

***N*-Cinnamyl-*N*-(4-(trifluoromethyl)phenyl)morpholine-4-carboxamide (1cb).**



1cb

General Procedure A was followed using **1ca-CF$_3$** (2.3 g, 8.3 mmol) and morpholine (0.84 g, 8.5 mmol).

Run on a 1.6 mmol scale.

Yellow oil (1.7 g, 44%). R_f 0.38 (SiO_2, hexane/EtOAc = 1/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.56 (d, *J* = 8.2, 2H), 7.30–7.18 (m, 7H), 6.44 (d, *J* = 16.0 Hz, 1H), 6.34–6.27 (m, 1H), 4.47 (d, *J* = 6.0, 2.0 H), 3.53 (dd, *J* = 4.6, 5.0, 4H), 3.25 (dd, *J* = 5.0, 4.6, 4H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 159.8, 148.4, 136.6, 132.6, 128.6, 127.9, 126.8 (q, J_{CF} = 2.8 Hz), 126.6, 126.4 (q, J_{CF} = 33.5 Hz), 125.8, 124.0 (q, J_{CF} = 272.2 Hz), 123.1, 66.5, 53.7, 46.3.

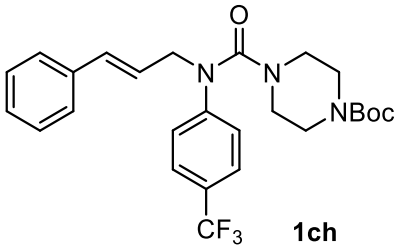
^{19}F NMR ($CDCl_3$, 376 MHz) δ: -62.0.

IR (KBr, cm^{-1}): 2854 w, 1661 s, 1653 s, 1613 s, 1579 w, 1519 m, 1455 w, 1411 w, 1325 s, 1300 w, 1272 m, 1254 m, 1165 m, 1113 m, 1070 w, 1026 m, 1014 w, 966 w, 950 w, 866 m, 845 m, 768 m, 732 m, 693 m.

MS, m/z (relative intensity, %): 390 (M^+, 26), 276 (27), 118 (12), 117 (100), 115 (39), 113 (29), 91 (19), 85 (18), 70 (14), 27 (69), 56 (30), 44 (15), 42 (12).

HRMS (DART) *m/z* [M+H^+] calcd for $C_{21}H_{22}F_3N_2O_2$: 391.1628, found: 391.1631.

***tert*-Butyl 4-(cinnamyl(4-(trifluoromethyl)phenyl)carbamoyl)piperazine-1-carboxylate (1ch).**



1ch

General Procedure A was followed using **1ca-CF$_3$** (1.5 g, 5.3 mmol) and 1-(*tert*-butoxycarbonyl)piperazine (1.1 g, 6.0 mmol).

Run on a 5.3 mmol scale.

Yellow oil (0.99 g, 38%). R_f 0.40 (SiO_2, hexane/EtOAc = 6/4).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.57 (d, J = 8.0 Hz, 2H), 7.33–7.18 (m, 7 H), 6.44 (d, J = 16.0 Hz, 1H), 6.35–6.28 (m, 1H), 4.46 (d, J = 6.0 Hz, 2H), 3.30–3.16 (m, 8H), 1.43 (s, 9H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 159.8, 154.6, 148.4, 136.5, 132.6, 128.6, 127.8, 126.8 (q, J_{CF} = 2.9 Hz), 126.5, 126.4 (q, J_{CF} = 34.5 Hz), 125.7, 124.0 (q, J_{CF} = 272.2 Hz), 123.3, 80.3, 53.7, 45.7 (two overlapping peaks), 28.4.

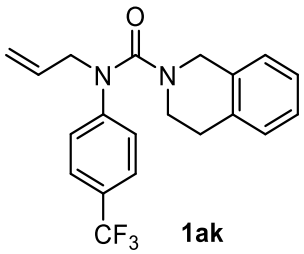
^{19}F NMR ($CDCl_3$, 376 MHz) δ: -63.5.

IR (KBr, cm^{-1}): 1700 m, 1685 s, 1646 s, 1612 m, 1462 w, 1457 w, 1438 w, 1418 m, 1365 m, 1327 s, 1281 w, 1257 m, 1177 w, 1159 w, 1111 m, 1069 s, 772 w, 739 w, 690 w, 545 w.

MS, m/z (relative intensity, %): 490 (M^+, 0), 389 (M^+–Boc, 25), 276 (26), 118 (11), 117 (100), 115 (39), 113 (29), 91 (19), 85 (18), 70 (14), 69 (27), 56 (30), 44 (16), 42 (12).

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{26}H_{31}F_3N_3O_3$: 490.2312, found: 490.2328.

_N_-Allyl-_N_-(4-(trifluoromethyl)phenyl)-3,4-dihydroisoquinoline-2(1_H_)-carboxamide (1ak).



1ak

General Procedure A was followed using **1aa-CF$_3$** (3.0 g, 10 mmol) and 1,2,3,4-tetrahydroisoquinoline (1.6 g, 12 mmol).

Run on a 10 mmol scale.

Colorless solid (0.76 g, 90%). M.p. 82 °C. R_f 0.50 (SiO_2, hexane/EtOAc = 1/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.55 (d, J = 8.7 Hz, 2H), 7.20–7.07 (m, 5H), 6.98–6.96 (m, 1H), 6.00–5.90 (m, 1H), 5.17–5.11 (m, 2H), 4.38–4.34 (m, 4H), 3.50 (t, J = 6.0 Hz, 2H), 2,70 (t, J = 6.0 Hz, 2H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 159.9, 148.6, 134.6, 134.5, 133.2, 128.8, 126.7, 126.4 (two overlapping peaks), 126.3, 125.9 (q, J_{CF} = 32.6 Hz), 124.1 (q, J_{CF} = 272.2 Hz), 123.0, 117.1, 54.0, 48.0, 43.9, 28.4.

^{19}F NMR ($CDCl_3$, 376 MHz) δ: -63.4.

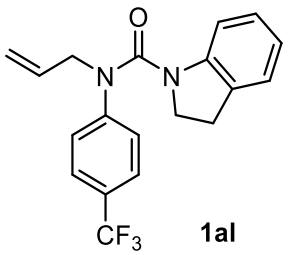
IR (ATR, cm^{-1}): 2555 s, 2197 s, 2028 s, 1651 m, 1613 s, 1582 m, 1322 s, 1218 m, 1164 m, 1111 s, 1068 m, 771 m,

747 m, 422 m, 412 s, 408 s.

MS, m/z (relative intensity, %): 360 (M^+, 13), 332 (11), 161 (13), 160 (100), 159 (19), 145 (20), 143 (11), 142 (93), 133 (12), 132 (91), 131 (47), 130 (32), 118 (17), 117 (63), 116 (14), 115 (39), 105 (24), 104 (29), 103 (25), 91 (22), 78 (21), 77 (21), 41 (75).

HRMS (DART) *m/z* [M+H^+] calcd for $C_{20}H_{20}N_2OF_3$: 361.1522, found: 361.1522.

***N*-Allyl-*N*-(4-(trifluoromethyl)phenyl)indoline-1-carboxamide (1al).**



1al

Procedure A was followed, except that *n*-BuLi was used instead of NaH. A 50 mL two-necked flask with a magnetic stirring bar was evacuated and backfilled with nitrogen three times. To a solution of indolin (0.25 mL, 2.7 mmol) in THF (12 mL), *n*-BuLi (1.33 mL, 3.3 mmol, 2.6 M in hexane) was added at –78 °C. The mixture was stirred at rt for 3 h. Imidazolium salt, which was prepared from **1aa-CF₃** and MeI, was added, and the mixture was stirred at rt for 12 h. The solution was then cooled to rt and extracted with EtOAc. The combined extracts were washed with brine, dried over Na_2SO_4 and concentrated. The crude product was purified by column chromatography on silica gel (hexane/EtOAc = 1/1) to afford **1ak** as a yellow oil.

Yellow oil (0.29 g, 37%). R_f 0.65 (SiO_2, hexane/EtOAc = 1/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.70 (d, *J* = 8.2 Hz, 1H), 7.56 (d, *J* = 8.7 Hz, 2H), 7.25–7.11 (m, 4H), 6.95 (t, *J* = 7.3 Hz, 1H), 6.06–5.96 (m, 1H), 5.22–5.09 (m, 2H), 4.40 (d, *J* = 5.5 Hz, 2H), 3.44 (dd, *J* = 8.7, 8.2 Hz, 2H), 2.97–2.93 (t, *J* = 8.7, 8.2 Hz, 2H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 157.1, 147.6, 143.5, 134.3, 131.2, 127.4, 126.8 (q, J_{CF} = 3.8 Hz), 126.7 (q, J_{CF} = 32.9 Hz), 124.8, 124.1, 124.0 (q, J_{CF} = 272.2 Hz), 123.1, 117.6, 116.4, 54.0, 50.0, 28.6.

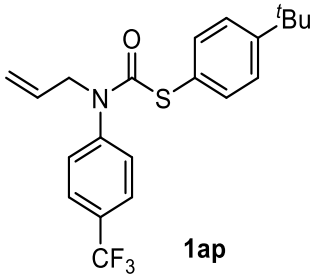
^{19}F NMR ($CDCl_3$, 376 MHz) δ: -63.5.

IR (ATR, cm^{-1}): 1656 m, 1385 s, 1323 s, 1295 m, 1221 m, 1114 s, 1067 m, 772 s, 753 m, 420 s.

MS, m/z (relative intensity, %): 346 (M^+, 13), 146 (25), 118 (18), 117 (10), 91 (24), 41 (100).

HRMS (DART) *m/z* [M+H^+] calcd for $C_{19}H_{18}F_3N_2O$: 347.1366, found: 347.1369.

***S*-(4-(*tert*-Butyl)phenyl) Allyl(4-(trifluoromethyl)phenyl)carbamothioate (1ap).**



1ap

General Procedure A was followed using **1aa-CF$_3$** (0.47 g, 1.6 mmol) and 4-*tert*-butylbenzenethiol (0.27 mL, 1.6 mmol).

Run on a 1.6 mmol scale.

Colorless solid (0.52 g, 83%). Mp 100 °C. R_f 0.40 (SiO_2, hexane/EtOAc = 9/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.71 (d, J = 8.0 Hz, 2H), 7.49 (d, J = 8.0 Hz, 2H), 7.41–7.36 (m, 4H), 5.92–5.85 (m, 1H), 5.19–5.11 (m, 2H), 4.34 (d, J = 6.4 Hz, 2H), 1.31 (s, 9H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 167.6, 152.6, 143.7, 135.3, 132.3, 130.7 (q, J_{CF} = 33.6 Hz), 129.8, 126.7 (q, J_{CF} = 3.8 Hz), 126.3, 125.3, 123.8 (q, J_{CF} = 273.1 Hz), 119.1, 53.9 34.8, 31.3

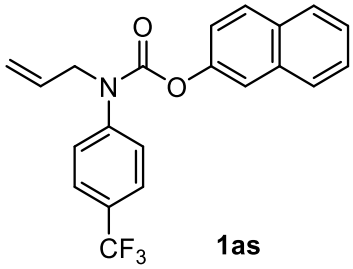
^{19}F NMR ($CDCl_3$, 376 MHz) δ: -63.9.

IR (KBr, cm^{-1}): 2965 m, 2927 m, 2905 w, 2868 m, 1668 s, 1613 s, 1516 s, 1494 m, 1478 w, 1461 m, 1369 s, 1323 s, 1267 w, 1254 m, 1241 m, 1223 s, 1180 m, 1165 s, 1125 m, 1120 m, 1104 s, 910 w, 776 w, 752 m, 700 m, 675 s, 651 s.

MS, m/z (relative intensity, %): 393 (M^+, 19), 228 (64), 191 (12), 41 (100).

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{21}H_{23}F_3NOS$: 394.1447, found: 394.1447.

Naphthalen-2-yl Allyl(4-(trifluoromethyl)phenyl)carbamate (1as).



1as

General Procedure A was followed using **1aa-CF$_3$** (0.47 g, 1.6 mmol) and 2-naphthol (0.25 g, 1.6 mmol).

Run on a 1.6 mmol scale.

Colorless solid (0.58 g, 97%). R_f 0.48 (SiO_2, hexane/EtOAc = 1/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.84 (d, J = 9.2 Hz, 2H), 7.79 (d, J = 7.2 Hz, 1H), 7.67 (d, J = 8.2 Hz, 2H), 7.59–7.44 (m, 5H), 7.28–7.26 (m, 2H), 6.07–6.00 (m, 1H), 5.29 (t, J = 8.8 Hz, 2H), 4.47. (d, J = 4.8 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 153.6, 148.7, 145.1, 133.8, 133.1 (two overlapping peaks), 131.4, 129.4, 127.8, 127.7, 126.7, 126.4 (q, J_{CF} = 27.8 Hz), 126.3 (q, J_{CF} = 2.9 Hz), 125.7, 124.0 (q, J_{CF} = 272.2 Hz), 121.2, 118.5, 118.1, 53.5.

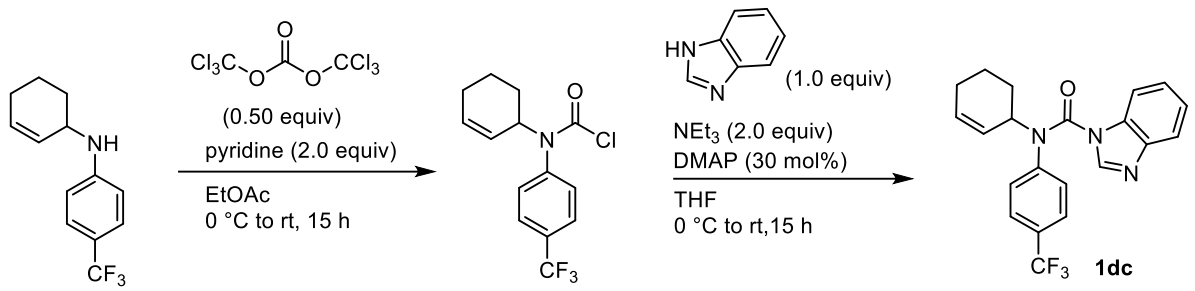
^{19}F NMR ($CDCl_3$, 376 MHz) δ: -63.7.

IR (KBr, cm^{-1}): 2360 m, 1724 s, 1627 m, 1612 s, 1601 m, 1519 s, 1508 s, 1419 m, 1387 m, 1324 s, 1246 s, 1237 s, 1214 m, 1017 m, 963 m, 862 m, 847 m, 727 m, 705 m, 564 m.

MS, m/z (relative intensity, %): 371 (M^+, 58), 229 (11), 228 (85), 169 (15), 144 (15), 143 (15), 127 (13), 116 (13), 115 (93), 41 (100).

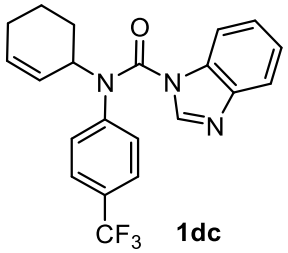
HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{21}H_{17}F_3NO_2$: 372.1206, found: 372.1209.

General Procedure B.



A 100 mL two-necked flask with a magnetic stirring bar was evacuated and backfilled with nitrogen three times. Triphosgene (0.74 g, 2.5 mmol) and dry EtOAc (15 mL) were added to the flask. The mixture was cooled at 0 °C and pyridine (0.80 mL, 10 mmol) was slowly added to the flask. After stirring for 15 min at 0 °C, *N*-(cyclohex-2-en-1-yl)-4-(trifluoromethyl)aniline (1.2 g, 5.0 mmol) was slowly added to the mixture. The mixture was warmed to rt and stirred for 6 h. The reaction mixture was carefully quenched with HCl (1 M) and was extracted with EtOAc. The organic layer was washed with water, and then dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to obtain the carbamoyl chloride as a dark oil. This material was used in the next step without further purification. Benzimidazole (730 mg, 5.0 mmol) in THF (10 mL) and Et_3N (1.7 mL, 10 mmol) were added to the solution. The mixture was stirred at rt for 15 min, after which the carbamoyl chloride and DMAP (0.20 g, 1.5 mmol) were added. The mixture was stirred for 12 h at rt. The reaction mixture was quenched with H_2O and was extracted with EtOAc. The organic layer was washed H_2O and dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/EtOAc = 1/1) to afford **1dc** as a yellow solid (1.5 g, 80%).

***N*-(Cyclohex-2-en-1-yl)-*N*-(4-(trifluoromethyl)phenyl)-1*H*-benzo[d]imidazole-1-carboxamide (1dc).**



Yellow oil (1.5 g, 80%). R_f 0.60 (SiO_2, hexane/EtOAc = 1/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.92 (d, *J* = 8.0 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.57 (s, 1H), 7.52 (d, *J* = 8.0 Hz, 2H), 7.38–7.28 (m, 2H), 7.23 (d, *J* = 8.0 Hz, 2H), 5.93–5.90 (m, 1H), 5.80 (d, *J* = 8.0 Hz, 1H), 5.34–5.32 (m. 1H), 2.09–1.95 (m, 3H), 1.70–1.60 (m, 3H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 150.9, 143.2, 142.7, 141.2, 132.5, 132.0, 130.2 (q, J_{CF} = 32.6 Hz), 128.42, 127.47, 127.0 (q, J_{CF} = 3.8 Hz), 125.2, 124.3, 123.5 (q, J_{CF} = 273.2 Hz), 120.5, 114.1, 56.8, 27.2, 24.3, 21.2.

^{19}F NMR ($CDCl_3$, 376 MHz) δ: -63.9.

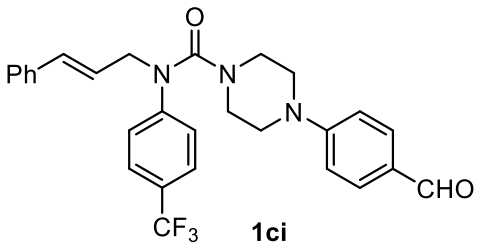
IR (KBr, cm^{-1}):2939 w, 1698 s, 1614 m, 1585 w, 1517 m, 1500 m, 1479 w, 1451 m, 1396 w, 1381 m, 1358 m, 1325 s, 1308 w, 1289 m, 1237 w, 1198 m, 1168 m, 1127 s, 1070 s, 888 w, 849 w, 798 w, 779 w, 763 m, 749 s, 716.

MS, m/z (relative intensity, %): 385 (M^+, 11), 198 (42), 119 (48), 118 (65), 90 (20), 81 (100), 80 (18), 79 (31), 653

(11), 41 (11).

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{21}H_{19}F_3N_3O$: 386.1475, found: 386.1487.

_N_-Cinnamyl-4-(4-formylphenyl)-_N_-(4-(trifluoromethyl)phenyl)piperazine-1-carboxamide (1ci).



1ci

General Procedure B was followed using *N*-cinnamyl-4-(trifluoromethyl)aniline (1.4 g, 5.0 mmol) and 4-(piperazin-1-yl)benzalfehyde [9] (1.1 g, 6.0 mmol).

Run on a 5.0 mmol scale.

Colorless solid (0.97 g, 39%). Mp 155 °C. R_f 0.20 (SiO_2, hexane/EtOAc = 1/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 9.78 (s, 1H), 7.74 (d, *J* = 8.7 Hz, 2H), 7.59 (d, *J* = 8.7 Hz, 2H), 7.22–7.33 (m, 7H), 6.83 (d, *J* = 9.2 Hz, 2H), 6.46 (d, *J* = 16.0 Hz, 1H), 6.36-6.30 (m, 1H), 4.48 (d, *J* = 6.0 Hz, 2H), 3.43 (dd, *J* = 6.2, 3.9 Hz, 4H), 3.29 (dd, *J* = 6.2, 3.9 Hz, 4H)

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 190.6, 159.8, 154.6, 148.3, 136.5, 132.8, 132.0, 128.7, 127.9, 127.7, 126.9 (q, J_{CF} = 3.8 Hz), 126.64 (q, J_{CF} = 32.6 Hz), 126.57, 125.6, 124.0 (q, J_{CF} = 271.3 Hz), 123.6, 113.8, 53.9, 46.7, 45.4.

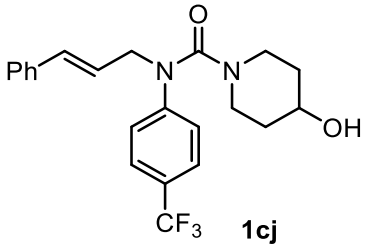
^{19}F NMR ($CDCl_3$, 376 MHz) δ: -63.4.

IR (KBr, cm^{-1}): 2829 w, 1650 s, 1559 w, 1461 s, 1421 m, 1367 w, 1286 m, 1257 s, 1212 w, 1164 s, 1074 m, 1001 w, 907 w, 828 m, 758 w, 690 w, 514 w.

MS, m/z (relative intensity, %): 493 (M$^+$, 28), 276 (14), 255 (12), 217 (13), 161 (12), 160 (13), 148 (20), 134 (10), 133 (14), 132 (22), 118 (15), 117 (100), 115 (32), 91 (23), 56 (29).

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{28}H_{27}F_3N_3O_2$: 494.2050, found: 494.2055.

_N_-Cinnamyl-4-hydroxy-_N_-(4-(trifluoromethyl)phenyl)piperidine-1-carboxamide (1cj).



1cj

General Procedure B was followed using *N*-cinnamyl-4-(trifluoromethyl)aniline (1.4 g, 5.0 mmol) and 4-hydroxypiperidine (0.60 g, 6.0 mmol).

Run on a 5.0 mmol scale.

Yellow oil (0.95 g, 47%). R_f 0.20 (SiO_2, hexane/EtOAc = 1/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.55 (d, *J* = 8.2 Hz, 2H), 7.33–7.15 (m, 7H), 6.45 (d, *J* = 16.0 Hz, 1H), 6.30 (dt, *J*

= 16.0, 6.0 Hz, 1H), 4.44 (dd, *J* = 6.0, 0.9 Hz, 2H), 3.79–3.75 (m, 1H), 3.62 (td, *J* = 9.2, 4.3 Hz, 2H), 2.97–2.90 (m, 2H), 2.22 (s, 1H), 1.76–1.72 (m, 2H), 1.39 (tt, *J* = 13.1, 4.3 Hz, 2H)

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 159.7, 148.7, 136.6, 132.2, 128.6, 127.8, 126.7 (q, J_{CF} = 3.8 Hz), 126.5, 126.0, 125.7 (q, J_{CF} = 32.6 Hz), 124.1 (q, J_{CF} = 271.3 Hz), 122.6, 67.2, 53.4, 43.3, 33.8.

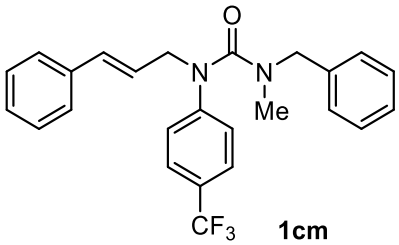
^{19}F NMR ($CDCl_3$, 376 MHz) δ: -63.3.

IR (KBr, cm^{-1}): 3444 s, 2945 w, 2854 w, 1651 m, 1614 m, 1582 w, 1520 w, 966 w, 927 m, 846 m, 769 w, 733 m, 693 m, 628 w, 607 w.

MS, m/z (relative intensity, %): 404 (M^+, 2), 277 (10), 276 (55), 128 (39), 118 (11), 117 (100), 115 (34), 91 (16), 84 (23), 57 (18), 56 (16), 55 (10).

HRMS (DART) *m/z* [M+H^+] calcd for $C_{22}H_{24}F_3N_2O_2$: 405.1784, found: 405.1791.

1-Benzyl-3-cinnamyl-1-methyl-3-(4-(trifluoromethyl)phenyl)urea (1cm).



1cm

General Procedure B was followed using *N*-cinnamyl-4-(trifluoromethyl)aniline (2.8 g, 10 mmol) and *N*-methylbenzylamine (1.5 mL, 12 mmol).

Run on a 10 mmol scale.

Yellow oil (1.9 g, 44%). R_f 0.60 (SiO_2, hexane/EtOAc = 1/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.52 (d, *J* = 8.0 Hz, 2H), 7.33–7.27 (m, 7H), 7.25–7.21 (m, 3H), 7.12 (d, *J* = 8.0 Hz, 2H), 6.48 (d, *J* = 16.0 Hz, 1H), 6.37–6.30 (m, 1H), 4.48 (d, *J* = 6.4 Hz, 2H), 4.41 (s, 2H), 2.59 (s, 3H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 160.6, 148.6, 137.1, 136.7, 132.6, 128.8, 128.6, 128.1, 127.8, 127.6, 126.7 (q, J_{CF} = 3.8 Hz), 126.6, 126.0, 125.7 (q, J_{CF} = 32.6 Hz), 124.1 (q, J_{CF} = 267.4 Hz), 122.8, 53.9, 53.7, 36.1.

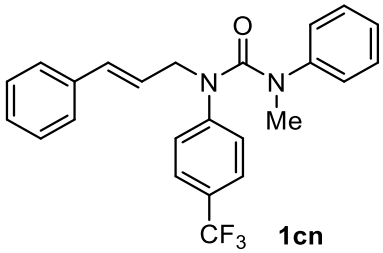
^{19}F NMR ($CDCl_3$, 376 MHz) δ: -63.4.

IR (KBr, cm^{-1}): 3065 w, 3036 m, 3006 m, 2976 w, 2949 m, 2932 m, 1581 s, 1517 s, 1495 w, 1472 s, 1455 s, 1434 s, 1418 s, 1391 s, 1348 s, 1299 m, 1212 m, 1188 m, 1167 m, 1127 s, 1086 m, 1014 m, 989 m, 954 m, 855 s, 773 m, 749 s, 714 m, 651 m, 515 m.

MS, m/z (relative intensity, %): 424 (M^+,0), 277 (21), 276 (92), 274 (17), 118 (21), 117 (100), 116 (16), 115 (69), 91 (30), 72 (98).

HRMS (DART) *m/z* [M+H^+] calcd for $C_{25}H_{24}F_3N_2O$: 425.1835, found: 425.1835.

1-Cinnamyl-3-methyl-3-phenyl-1-(4-(trifluoromethyl)phenyl)urea (1cn).



1cn

General Procedure B was followed using *N*-cinnamyl-4-(trifluoromethyl)aniline (1.5 g, 5.3 mmol) and *N*-methylaniline (0.7 mg, 5.5 mmol).

Run on a 5.3 mmol scale.

Yellow oil (1.3 g, 60%). R_f 0.44 (SiO_2, hexane/EtOAc = 1/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.35–7.22 (m, 7H), 7.05 (t, *J* = 8.0 Hz, 2H), 6.88 (t, *J* = 7.2 Hz, 1H), 6.86 (d, *J* = 8.4 Hz, 2H), 6.77 (d, *J* = 8.4 Hz, 2H), 6.40–6.34 (m, 2H), 4.38 (d, *J* = 6.0 Hz, 2H), 3.25 (s, 3H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 160.4, 142.3, 145.0, 136.6, 133.2, 128.8, 128.6, 127.8, 126.8 (q, J_{CF} = 32.6 Hz), 126.5, 126.4, 126.3, 125.7 (q, J_{CF} = 3.8 Hz), 125.5, 125.2 124.0 (q, J_{CF} = 272.2 Hz), 53.6, 39.5.

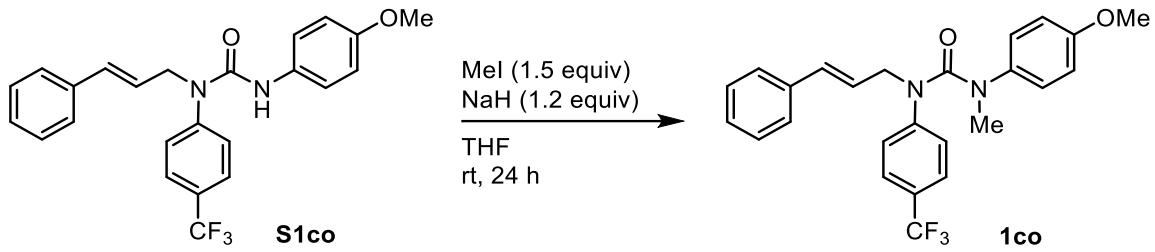
^{19}F NMR ($CDCl_3$, 376 MHz) δ: -63.6.

IR (KBr, cm^{-1}): 2360 m, 1661 m, 1654 s, 1613 m, 1595 w, 1495 m, 1374 w, 1324 s, 1164 m, 1118 m, 1068 m, 757 w, 695 m.

MS, m/z (relative intensity, %): 410 (M^+, 3.4), 276 (20), 134 (38), 118 (10), 117 (100), 115 (41), 107 (20), 106 (23), 91 (24), 77 (29).

HRMS (DART) *m/z* [M+H^+] calcd for $C_{24}H_{22}F_3N_2O$: 411.1679, found: 411.1681.

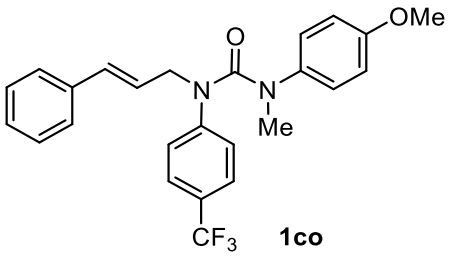
Procedure for the synthesis of *N*-allylurea 1co.



S1co **1co**

Amide **S1co** was synthesized by General Procedure B. Amide **S1co** (0.74 g, 1.7 mmol) was added sequentially to a suspension of NaH (96 mg, 2.0 mmol, 60% dispersion in mineral oil) in THF (17 mL), and MeI (0.17 mL, 2.5 mmol) was then added dropwise. The reaction was stirred at rt for 12 h, and H_2O was added. The mixture was extracted with EtOAc, and the combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The resulting crude product was purified by flash chromatography (Hexane/EtOAc = 9/1) toto give **1co** as colorless solid (0.51 g, 67%).

1-Cinnamyl-3-(4-methoxyphenyl)-3-methyl-1-(4-(trifluoromethyl)phenyl)urea (1co).



1co

Yellow oil (0.51 g, 67%). R_f 0.10 (SiO_2, hexane/EtOAc = 4/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.33–7.22 (m, 7H), 6.86 (d, *J* = 8.0 Hz, 2H), 6.67–6.64 (m, 2H), 6.57–6.54 (m, 2H), 6.38–6.29 (m, 2H), 4.33 (d, *J* = 5.6 Hz, 2H), 3.68 (s, 3H), 3.19 (s, 3H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 160.6, 157.4, 147.5, 138.0, 136.7, 133.1, 128.6, 127.8, 127.7, 126.8 (q, J_{CF} = 32.6 Hz), 126.5 (two overlapping peaks), 125.7 (q, J_{CF} = 3.8 Hz), 125.3, 124.1 (q, J_{CF} = 272.2 Hz), 114.09, 55.5, 53.7, 39.9.

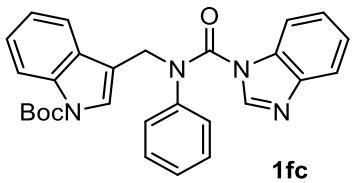
^{19}F NMR ($CDCl_3$, 376 MHz) δ: -63.7.

IR (KBr, cm^{-1}): 3008 m, 2955 m, 2934 m, 1647 s, 1612 s, 1583 m, 1512 s, 1444 m, 1431 m, 1421 m, 1375 m, 1323 m, 1248 m, 1171 m, 1108 m, 1065 m, 969 s, 822 m, 802 m, 695 s, 614 s, 559 s, 501 m.

MS, m/z (relative intensity, %): 440 (M^+, 16), 276 (29), 223 (20), 164 (23), 137 (39), 136 (78), 121 (28), 118 (14), 117 (100), 115 (52), 108 (13), 91 (23).

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{25}H_{24}F_3N_2O_2$: 441.1784, found: 441.1792.

***tert*-Butyl 3-((*N*-phenyl-1*H*-benzo[d]imidazole-1-carboxamido)methyl)-1*H*-indole-1-carboxylate (1fc).**



1fc

General Procedure B was followed using *tert*-butyl 3-((phenylamino)methyl)-1*H*-indole-1-carboxylate[3] (1.0g, 3.1 mmol).

Run on a 3.1 mmol scale.

Colorless solid (1.1 g, 78%). Mp 148 °C. R_f 0.20 (SiO_2, hexane/EtOAc = 1/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 8.10 (d, *J* = 8.4 Hz, 1H), 7.99 (d, *J* = 8.4 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.53–7.49 (m, 3H), 7.39–7.16 (m, 7H), 7.00–6.98 (m, 2H), 5.24 (s, 2H), 1.64 (s, 9H).

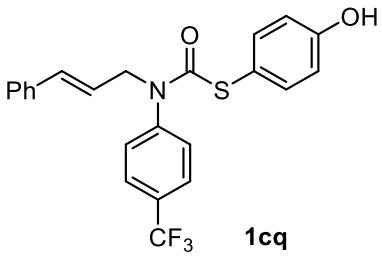
^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 151.0, 149.6, 142.7, 141.7, 141.5, 135.5, 132.7, 130.3, 129.5, 128.2, 126.7, 126.1, 125.0, 124.8, 124.0, 123.0, 120.3, 119.5, 115.6, 115.3, 114.3, 84.1, 46.8, 28.3.

IR (KBr, cm^{-1}): 2976 w, 2360 w, 1741 s, 1682 s, 1607 w, 1593 w, 1586 w, 1503 m, 1495 m, 1475 m, 1455 m, 1396 s, 1378 m, 1355 s, 1279 s, 1258 m, 1239 m, 1195 m, 1158 m, 1081 s, 958 m, 846 m, 787 m, 766 s, 749 s, 705 s.

MS, m/z (relative intensity, %): 466 (M^+, 0), 247 (21), 131 (11), 130 (100), 129 (14), 118 (24), 102 (10), 77 (12).

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{28}H_{27}N_4O_3$: 467.2078, found: 467.2079.

***S*-(4-Hydroxyphenyl) cinnamyl(4-(trifluoromethyl)phenyl)carbamothioate (1cq).**



1cq

General Procedure B was followed using *N*-cinnamyl-4-(trifluoromethyl)aniline (1.4 g, 5.0 mmol) and *p*-mercaptophenol (0.70 g, 6.0 mmol).

Run on a 5.0 mmol scale.

Colorless solid (0.84 g, 37%). Mp 199 °C. R_f 0.60 (SiO_2, hexane/EtOAc = 9/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.72 (d, *J* = 8.7 Hz, 2H), 7.51 (d, *J* = 8.2 Hz, 2H), 7.36–7.29 (m, 4H), 7.28–7.24 (m, 3H), 6.71–6.67 (m, 2H), 6.42 (d, *J* = 16.0 Hz, 1H), 6.26 (dt, *J* = 16.0, 6.8 Hz, 2H), 4.50 (d, *J* = 6.8 Hz, 2H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 169.6, 157.8, 143.5, 137.4, 136.3, 134.7, 131.1 (q, J_{CF} = 33.6 Hz), 130.0, 128.8, 128.2, 126.9 (q, J_{CF} = 2.8 Hz), 126.7, 123.8 (q, J_{CF} = 272.2 Hz), 123.0, 118.2, 116.8, 53.7.

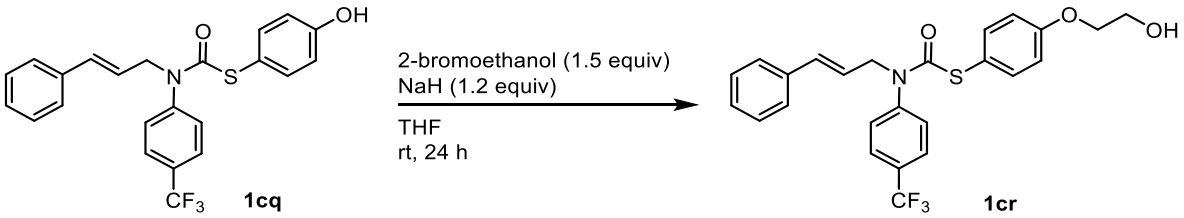
^{19}F NMR ($CDCl_3$, 376 MHz) δ: -63.9.

IR (KBr, cm^{-1}): 3345 s, 1644 s, 1609 s, 1515 s, 1437 m, 1321 m, 1173 m, 1103 m, 1018 m, 838 m, 689 m, 665 m, 616 m, 564 m.

MS, m/z (relative intensity, %): 429 (M^+, 2), 118 (14), 117 (100), 115 (27), 91 (10), 43 (11).

HRMS (DART) *m/z* [M+H^+] calcd for $C_{23}H_{19}F_3NO_2S$: 430.1083, found: 430.1086.

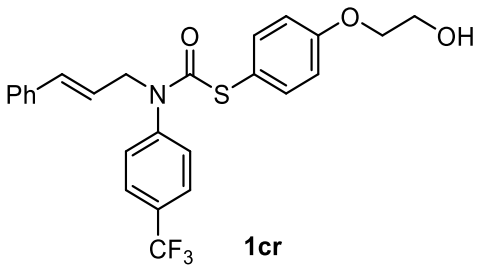
Procedure for the synthesis of *N*-allyl carbamothioate 1cr.



1cq **1cr**

Amide **1cq** (0.43 g, 1.0 mmol) was added portionwise to a suspension of NaH (48 mg, 1.2 mmol, 60% dispersion in mineral oil) in THF (17 mL), and 2-bromoethanol (0.1 mL, 1.5 mmol) was then added dropwise. The reaction was stirred at rt for 12 h, and H_2O was added. The mixture was extracted with EtOAc, and the combined extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The resulting crude product was purified by flash chromatography (Hexane/EtOAc = 1/1) to give **1cr** as colorless solid (0.24g, 50%).

***S*-(4-(2-Hydroxyethoxy)phenyl) cinnamyl(4-(trifluoromethyl)phenyl)carbamothioate (1cr).**



1cr

Colorless solid (0.24 g, 50%). Mp 107 °C. R_f 0.60 (SiO_2, hexane/EtOAc = 1/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.71 (d, *J* = 8.2 Hz, 2H), 7.50 (d, *J* = 8.2 Hz, 2H), 7.39–7.25 (m, 7H), 6.93 (d, *J* = 8.7 Hz, 2H), 6.42 (d, *J* = 16.0 Hz, 1H), 6.30–6.25 (m, 1H), 4.49 (d, *J* = 6.4 Hz, 2H), 4.09 (t, *J* = 4.6 Hz, 2H), 3.98–3.94 (m, 2H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 167.9, 159.8, 143.6, 137.3, 136.3, 134.4, 130.9 (q, J_{CF} = 32.6 Hz), 130.0, 128.7, 128.1, 126.7 (q, J_{CF} = 3.8 Hz), 126.6, 123.8 (q, J_{CF} = 268.4 Hz), 123.3, 120.0, 115.3, 69.4, 61.4, 53.5.

^{19}F NMR ($CDCl_3$, 376 MHz) δ: -63.8.

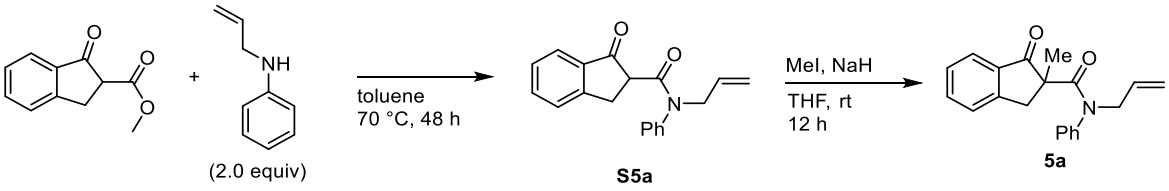
IR (KBr, cm^{-1}): 3494 s, 2933 m, 1775 m, 1592 s, 1515 s, 1451 m, 1324 m, 1170 m, 1018 w, 969 s, 866 w, 774 m, 694 s, 636 m.

MS, m/z (relative intensity, %): 473 (M^+, 1), 118 (11), 117 (100), 115 (17).

HRMS (DART) *m/z* [M+H^+] calcd for $C_{25}H_{23}F_3NO_3S$: 474.1345, found: 474.1346.

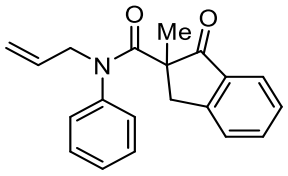
IV. Preparation of Starting Materials for C–C Bond Formation Reactions

General Procedure C.[10]



A 100 mL two-necked flask with a magnetic stirring bar was evacuated and backfilled with nitrogen three times. Methyl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate[11] (2.2 g, 12 mmol) and *N*-allylaniline (5.0 mL, 24 mmol) in toluene were added to the flask. The mixture was stirred at 70 °C for 48 h, and then cooled to rt. The residue was concentrated and purified by column chromatography on silica gel (hexane/EtOAc = 9/1) to afford **S5a** as a yellow solid (0.92 g, ca. 28%), which was used in the next step without further purification. Amide **S5a** (0.60 g, 2.0 mmol) was added to a suspension of NaH (0.16 g, 4 mmol, 60% dispersion in mineral oil) in THF, and MeI (10 mmol, 0.61 mL) was then added dropwise. The reaction was stirred at rt for 12 h, and then H_2O was added. The residue was extracted with EtOAc, the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The resulting crude product was purified by flash chromatography (Hexane/EtOAc, v/v = 8/2) to give **5a** as a yellow solid (0.44 g, 73%).

***N*-Allyl-2-methyl-1-oxo-*N*-phenyl-2,3-dihydro-1*H*-indene-2-carboxamide (5a).**



5a

Yellow solid (0.31 g, 80% in methylation step). Mp 99 °C. R_f 0.17 (SiO_2, hexane/EtOAc = 4/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.39 (dd, *J* = 7.3 Hz, 1H), 7.31 (d, *J* = 7.8 Hz, 1H), 7.18–7.10 (m, 2H), 6.93 (s, 3H), 6.80 (m, 2H), 5.89–5.82 (m, 1H), 5.09–5.00 (m, 2H), 4.23–4.17 (m, 2H), 3.52 (d, *J* = 17.9 Hz, 1H), 2.91 (d, *J* = 17.9 Hz, 1H), 1.41 (s, 3H).

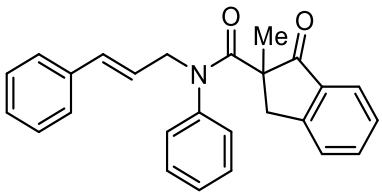
^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 205.7, 171.5, 151.0, 139.2, 135.5, 134.5, 132.9 (two overlapping peaks), 128.4 (two overlapping peaks), 127.1, 126.0, 124.5, 118.2, 56.3, 54.9, 41.5, 24.8.

IR (KBr, cm^{-1}): 3028 w, 2931 w, 2911 w, 1715 s, 1699 s, 1684 s, 1652 w, 1609 m, 1558 m, 1540 m, 1508 m, 1497 m, 1473 m, 1464 m, 1457 m, 1436 m, 1249 m, 1178 m, 1034 m, 968 w, 792 m, 736 m, 722 w, 693 m, 668 w.

MS, m/z (relative intensity, %): 305 (M^+, 1.2), 160 (15), 146 (22), 145 (50), 133 (140), 117 (44), 115 (34), 91 (16), 77 (10), 41 (14).

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{20}H_{20}NO_2$: 306.1489, found: 306.1490.

_N_-Cinnamyl-2-methyl-1-oxo-_N_-phenyl-2,3-dihydro-1_H_-indene-2-carboxamide (5b).



5b

General Procedure C was followed using *N*-cinnamylaniline (3.7 g, 19 mmol). The intermediate amide **S5b** was obtained in ca. 12% yield, which was used for the subsequent step without additional purification.

Yellow oil (0.55 g, 85% for a methylation step). R_f 0.66 (SiO_2, hexane/EtOAc = 1/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.40–7.25 (m, 5H), 7.25–7.19 (m, 1H), 7.13 (t, *J* = 7.3 Hz, 2H), 7.09–6.60 (m, 4H), 7.16 (d, *J* = 8.2 Hz, 2H), 6.35–6.26 (m, 2H), 4.50–4.42 (m, 1H), 4.36–4.26 (m, 1H), 3.55 (d, *J* = 17.9 Hz, 1H), 2.9(d, *J* = 17.9 Hz, 1H), 1.46 (s, 3H).

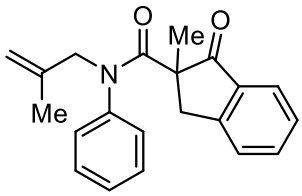
^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 205.7, 171.6, 151.0, 139.1, 136.8, 135.5, 134.5, 133.7, 128.6 (two overlapping peaks), 128.5, 127.8, 127.1, 126.6 (two overlapping peaks), 126.0, 124.5, 124.1, 56.3, 54.4, 41.6, 24.8.

IR (KBr, cm^{-1}): 2926 m, 1716 s, 1706 s, 1684 w, 1652 s, 1646 s, 1593 m, 1540 m, 1507 m, 1473 m, 1449 m, 1435 m, 1419 m, 1395 m, 1386 m, 1278 m, 969 m, 700 s.

MS, m/z (relative intensity, %): 381 (M^+, 0.66), 290 (18), 208 (100), 146 (19), 145 (15), 117 (83), 116 (10), 115 (50), 91 (25), 77 (10).

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{26}H_{24}NO_2$: 382.1802, found: 382.1801.

2-Methyl-*N*-(2-methylallyl)-1-oxo-*N*-phenyl-2,3-dihydro-1*H*-indene-2-carboxamide (5c).



5c

General Procedure C was followed using *N*-(2-methylallyl)aniline (1.0 g, 7.0 mmol). The intermediate amide **S5c** was obtained in ca. 15% yield, which was used for the subsequent step without additional purification.

Colorless solid (0.13 g, 40% for a methylation step). Mp 114 °C. R_f 0.14 (SiO_2, hexane/EtOAc = 4/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.37 (t, *J* = 7.3, 7.8 Hz, 1H), 7.32 (d, *J* = 7.8 Hz, 1H), 7.14 (t, *J* = 7.8 Hz, 2H), 7.05–6.88 (m, 3H), 6.87–6.60 (m, 2H), 4.74 (d, *J* = 47.6 Hz, 2H), 4.32 (d, *J* = 15.1 Hz, 1H), 4.15 (d, *J* = 15.1 Hz, 1H), 3.56 (d, *J* = 17.9 Hz, 1H), 2.92 (d, *J* = 17.9 Hz, 1H), 1.79 (s, 3H), 1.44 (s, 3H).

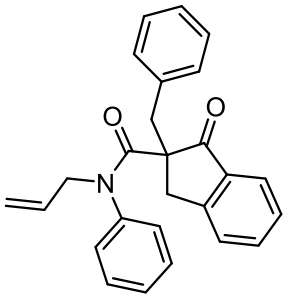
^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 205.7, 171.8, 151.0, 140.6, 139.3, 135.5, 134.4, 128.3 (two overlapping peaks), 127.1, 126.0, 124.5 (two overlapping peaks), 113.4, 57.8, 56.4, 41.5, 25.0, 20.5.

IR (KBr, cm^{-1}): 3032 w, 2926 w, 1732 w, 1716 s, 1706 s, 1684 w, 1652 s, 1646 s, 1636 s, 1607 m, 1593 w, 1576 m, 1540 m, 1507 m, 1473 w, 1456 m, 1435 m, 1395 m, 1386 m, 1278 m, 969 m, 700 s, 660 w.

MS, m/z (relative intensity, %): 319 (M^+, 2), 174 (15), 147 (13), 146 (100), 145 (64), 117 (51), 115 (43), 91 (20), 77 (15), 55 (17).

HRMS (DART) *m/z* [M+H^+] calcd for $C_{21}H_{22}NO_2$: 320.1645, found: 320.1644.

***N*-Allyl-2-benzyl-1-oxo-*N*-phenyl-2,3-dihydro-1*H*-indene-2-carboxamide (5d).**



5d

General Procedure C was followed using benzyl bromide (0.75 g, 6.3 mmol).

Yellow solid (0.81 g, 67% for a benzylation step). Mp 130 °C. R_f 0.40 (SiO_2, hexane/EtOAc = 4/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.20–7.10 (m, 2H), 7.09–6.60 (m, 12H), 5.97–5.85 (m, 1H), 5.15–5.02 (m, 2H), 4.33–4.18 (m, 2H), 3.52–3.36 (m, 3H), 3.19 (d, *J* = 18.3 Hz, 1H).

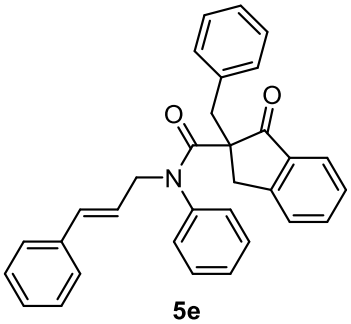
^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 205.5, 171.2, 151.4, 139.2, 137.3, 135.8, 134.1, 132.8, 130.7, 128.4 (two overlapping peaks), 127.7 (two overlapping peaks), 126.7, 126.5, 125.3, 123.6, 118.3, 60.6, 55.3, 42.5, 37.2.

IR (KBr, cm^{-1}): 3074 m, 3027 m, 1701 s, 1645 m, 1638 m, 1605 m, 1594 m, 1590 m, 1494 s, 1451 m, 1380 s, 1273 s, 1193 m, 1041 m, 971 m, 906 m, 770 m, 754 s, 718 w, 703 s.

MS, m/z (relative intensity, %): 381 (M^+, 3.4), 290 (11), 221 (16), 157 (10), 133 (14), 132 (56), 115 (15), 91 (100), 41 (11).

HRMS (DART) *m/z* [M+H^+] calcd for $C_{26}H_{24}NO_2$: 382.1802, found: 382.1793.

2-Benzyl-*N*-cinnamyl-1-oxo-*N*-phenyl-2,3-dihydro-1*H*-indene-2-carboxamide (5e).



5e

General Procedure C was followed using *N*-cinnamylaniline (0.86 g, 3.8 mmol) for the synthesis of amide **S5b** (ca. 19%) and benzyl bromide (0.25 g, 1.4 mmol).

Colorless solid (0.10 g, 36% for a benzylation step). Mp 156 °C. R_f 0.11 (SiO_2, hexane/EtOAc = 4/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.40–7.27 (m, 4H), 7.25–7.20 (m, 1H), 7.18–7.10 (m, 2H), 7.04–6.60 (m, 12H), 6.32 (s, 2H), 4.51–4.43 (m, 1H), 4.38–4.29 (m, 1H), 3.54–3.36 (m, 3H), 3.20 (d, *J* = 17.9 Hz, 1H).

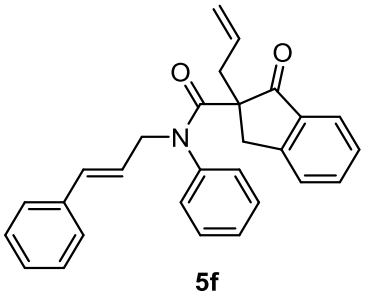
^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 205.5, 171.3, 151.4, 139.0, 137.2, 136.8, 135.8, 134.1, 133.7, 130.7 (two overlapping peaks), 128.6 (two overlapping peaks), 128.4, 127.8, 127.7, 126.7, 126.6, 126.5, 125.3, 124.0, 123.6, 60.6, 54.8, 42.5, 37.2.

IR (KBr, cm^{-1}): 3044 m, 2927 m, 1703 s, 1604 m, 1494 s, 1439 m, 1387 s, 1308 m, 1261 s, 1182 m, 1077 w, 1011 w, 965 m, 906 m, 767 m, 744 m, 705 s, 662 m, 584 w, 503 m.

MS, m/z (relative intensity, %): 457 (M+, 0.77), 209 (17), 208 (100), 131 (13), 117 (46), 115 (27), 91 (60).

HRMS (DART) *m/z* [M+H^+] calcd for $C_{32}H_{28}NO_2$: 458.2115, found: 458.2117.

2-Allyl-*N*-cinnamyl-1-oxo-*N*-phenyl-2,3-dihydro-1*H*-indene-2-carboxamide (5f).



5f

General Procedure C was followed using *N*-cinnamylaniline (3.7 g, 19 mmol) for the synthesis of amide **S5b** (ca. 12%) and allyl bromide (0.19 mL, 2.2 mmol).

Yellow solid (0.27 g, 35% for an allylation step). Mp 126 °C. R_f 0.29 (SiO_2, hexane/EtOAc = 4/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.36–7.27 (m, 6H), 7.25–7.20 (m, 2H), 7.10 (m, 2H), 7.00–6.80 (m, 4H), 6.29–6.27 (m, 2H), 5.52–5.41 (m, 1H), 5.02 (dd, *J* = 16.9, 1.8 Hz, 1H), 4.88 (dd, *J* = 10.1, 2.3 Hz, 1H), 4.46–4.41 (m, 1H),

4.33–4.28 (m, 1H), 3.40 (d, *J* = 18.3 Hz, 1H), 3.11 (d, *J* = 18.3 Hz, 1H), 2.88 (dd, *J* = 13.7, 8.2 Hz, 1H), 2.72 (dd, *J* = 13.7, 6.9 Hz, 1H).

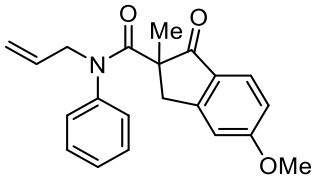
^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 204.9, 171.1, 151.4, 138.9, 136.8, 136.7, 134.4, 133.7, 133.2, 128.6 (two overlapping peaks), 128.5, 127.8, 127.0, 126.6 (two overlapping peaks), 125.7, 124.1, 124.0, 119.3, 59.5, 54.5, 42.2, 37.8.

IR (KBr, cm^{-1}): 3065 w, 3024 w, 2934 m, 1703 s, 1603 s, 1494 s, 1452 m, 1427 w, 1348 w, 1321 w, 1295 m, 1264 s, 1191 m, 1091 m, 994 m, 967 s, 926 s, 778 w, 753 m, 730 m, 641 w.

MS, m/z (relative intensity, %): 407 (M^+, 0.57), 208 (100), 117 (61), 115 (36), 128 (20), 91 (20), 209 (17), 131 (13), 77 (11).

HRMS (DART) *m/z* [M+H^+] calcd for $C_{28}H_{26}NO_2$: 408.1958, found: 408.1960.

***N*-Allyl-5-methoxy-2-methyl-1-oxo-*N*-phenyl-2,3-dihydro-1*H*-indene-2-carboxamide (5g).**



5g

General Procedure C was followed using methyl 5-methoxy-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate[10] (1.7 g, 7.9 mmol) for the synthesis of amide **S5g** (ca. 29%).

Yellow solid (0.34 g, 44% for a methylation step). Mp 104 °C. R_f 0.34 (SiO_2, hexane/EtOAc = 1/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.24 (d, *J* = 8.2 Hz, 1H), 6.98 (s, 3H), 6.88 (s, 2H), 6.69–6.64 (m, 1H), 6.57 (s, 1H), 5.93–5.83 (m, 1H), 5.11–5.01 (m, 2H), 4.30–4.15 (m, 2H), 3.81 (s, 3H), 3.48 (d, *J* = 17.9 Hz, 1H), 2.86 (d, *J* = 17.9 Hz, 1H), 1.42 (s, 3H).

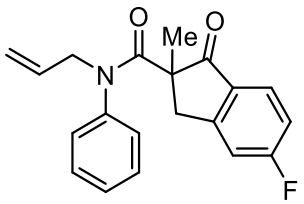
^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 203.9, 171.6, 165.1, 154.0, 139.4, 132.9, 128.9, 128.4 (two overlapping peaks), 126.1 (two overlapping peaks), 118.2, 115.2, 109.1, 56.6, 55.7, 54.9, 41.5, 24.9.

IR (KBr, cm^{-1}): 1697 s, 1653 s, 1636 s, 1600 s, 1493 m, 1450 m, 1437 m, 1382 m, 1303 m, 1293 w, 1276 m, 1259 m, 1142 w, 1088 m, 1024 w, 970 m, 701 m.

MS, m/z (relative intensity, %): 335 (M^+, 1.7), 176 (100), 132 (76), 175 (59), 147 (36), 91 (25), 41 (25), 115 (21), 77 (20), 133 (15), 177 (13), 104 (12), 103 (12), 160 (11), 131 (10).

HRMS (DART) *m/z* [M+H^+] calcd for $C_{21}H_{22}NO_3$: 336.1594, found: 336.1596.

***N*-Allyl-5-fluoro-2-methyl-1-oxo-*N*-phenyl-2,3-dihydro-1*H*-indene-2-carboxamide (5h).**



5h

General Procedure C was followed using methyl 5-fluoro-1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate[11] (1.9 g, 9.1 mmol) for the synthesis of amide **S5h** (ca. 20%).

Colorless (0.28 g, 47% for a methylation step). Mp 90 °C. R_f 0.52 (SiO_2, hexane/EtOAc = 1/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.37–7.34 (m, 2H), 7.13–7.10 (m, 2H), 6.93 (br, 3H), 6.84–6.77 (m, 1H), 5.91–5.80 (m, 1H), 5.11–4.96 (m, 2H), 4.28–4.10 (m, 2H), 3.52 (d, J = 17.9 Hz, 1H), 2.90 (d, J = 17.9 Hz, 1H), 1.44 (s, 3H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 203.7, 171.0, 166.8 (d, J_F = 256.9 Hz), 153.8 (d, J_F = 10.5 Hz), 139.1, 132.7 (two overlapping peaks), 131.8, 128.5 (two overlapping peaks), 126.7 (d, J_F = 10.5 Hz), 118.3, 115.4 (d, J_F = 24.0 Hz), 112.5 (d, J_F = 23.0 Hz), 56.6, 54.9, 41.3, 24.8.

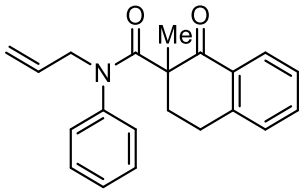
^{19}F NMR ($CDCl_3$, 376 MHz) δ: -105.8.

IR (KBr, cm^{-1}): 2360 w, 1713 s, 1652 s, 1637 m, 1617 m, 1593 m, 1495 m, 1434 w, 1384 m, 1293 m, 1281 m, 1265 w, 1247 s, 1083 w, 973 m, 707 m.

MS, m/z (relative intensity, %): 323 (M+, 0.68), 164 (16), 163 (38), 160 (11), 135 (33), 133 (28), 132 (100), 115 (16), 109 (11), 77 (11), 41 (19).

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{20}H_{19}FNO_2$: 324.1394, found: 324.1397.

***N*-Allyl-2-methyl-1-oxo-*N*-phenyl-1,2,3,4-tetrahydronaphthalene-2-carboxamide (5i).**



5i

General Procedure C was followed using methyl 1-oxo-1,2,3,4-tetrahydronaphthalene-2-carboxylate[11] (4.0 mg, 20 mmol) for the synthesis of amide **S5i** (ca. 40%).

Yellow oil (0.37 g, 42% for a methylation step). R_f 0.49 (SiO_2, EtOAc/hexane = 1/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.48 (d, J = 6.9 Hz, 1H), 7.42–7.34 (m, 1H), 7.32–7.21 (m, 3H), 7.20–7.10 (m, 3H), 7.09–6.58 (br, 1H), 5.87–5.74 (m, 1H), 5.08–5.02 (m, 1H), 4.98–4.91 (m, 1H), 4.21 (dd, J = 14.7, 6.0 Hz, 1H), 4.13–4.07(m, 1H), 3.15–3.03 (m, 1H), 2.81 (dt, J = 17.4, 5.0 Hz, 1H), 2.68–2.60 (m, 1H), 1.90–1.80 (m, 1H), 1.44 (s, 3H).

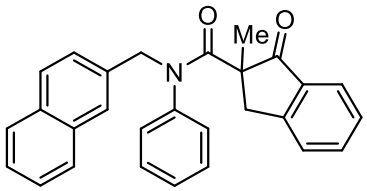
^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 197.6, 171.5, 142.8, 140.7, 133.0, 132.8, 130.4 (two overlapping peaks), 129.0, 128.7, 128.6, 128.4, 126.1, 118.1, 55.4, 55.3, 35.9, 26.2, 23.0.

IR (KBr, cm^{-1}): 3064 w, 2977 w, 2933 w, 1684 m, 1674 m, 1644 s, 1637 s, 1594 m, 1494 m, 1455 m, 1430 m, 1270 m, 1224 m, 1201 m, 1156 w, 1136 w, 997 w, 984 m, 961 w, 925 m, 910 w, 741 m, 702 m.

MS, m/z (relative intensity, %): 319 (M$^+$, 3.7), 132 (100), 131 (86), 159 (35), 91 (34), 41 (28), 160 (21), 133 (19), 158 (18), 77 (15), 115 (13), 129 (11), 116 (11).

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{21}H_{22}NO_2$: 320.1645, found: 320.1639.

2-Methyl-*N*-(naphthalen-2-ylmethyl)-1-oxo-*N*-phenyl-2,3-dihydro-1*H*-indene-2-carboxamide (5j).



5j

General Procedure C was followed using *N*-(naphthalen-2-ylmethyl)aniline (2.3 mg, 10 mmol) for the synthesis of amide **S5j** (ca. 13%).

Colorless solid (69 mg, 40% for a methylation step). Mp 140 °C. R_f 0.21 (SiO_2, hexane/EtOAc = 4/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.81–7.71 (m, 3H), 7.52 (s, 1H), 7.46–7.41 (m, 3H), 7.36–7.32 (m, 1H), 7.28 (s, 1H), 7.12–7.08 (m, 2H), 7.00–6.66 (m, 5H), 5.17 (d, *J* = 14.2 Hz, 1H), 4.89 (d, *J* = 14.2 Hz, 1H), 3.52 (d, *J* = 17.9 Hz, 1H), 2.94 (d, *J* = 17.9 Hz, 1H), 1.51 (s, 3H).

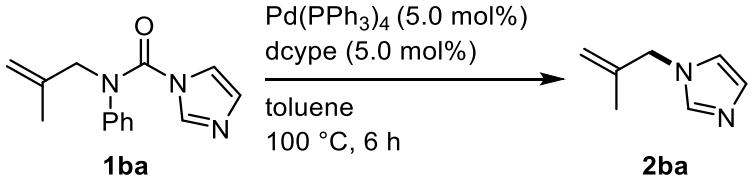
^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 205.6, 172.0, 150.9, 138.8, 135.4, 134.9, 134.4, 133.3, 132.9, 128.4, 128.3 (two overlapping peaks), 128.0 (two overlapping peaks), 127.9, 127.7, 127.1 (two overlapping peaks), 126.1, 125.9 (two overlapping peaks), 124.5, 56.3, 55.6, 41.5, 25.0.

IR (KBr, cm^{-1}): 2360 w, 1716 w, 1701 s, 1646 s, 1496 m, 1364 m, 1292 w, 1280 m, 1209 w, 1014 w, 812 m, 745 m, 710 m.

MS, m/z (relative intensity, %): 405 (M^+, 2.2),141 (79), 115 (43), 117 (21), 146 (20), 233 (20), 145 (16), 142 (12), 77 (11), 91 (10).

HRMS (DART) *m/z* [M+H^+] calcd for $C_{28}H_{24}NO_2$: 406.1802, found: 406.1802.

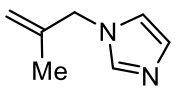
V. Palladium-Catalyzed Elimination of Isocyanate from *N*-Allylurea Derivatives



1ba **2ba**

In a glovebox filled with nitrogen, $Pd(PPh_3)_4$ 11.6 mg, 0.010 mmol), dcype (4.7 mg, 0.010 mmol) and toluene (1.0 mL) were added to a 10 mL vial with a Teflon-sealed screwcap, and stirred for 5 min at rt. Urea **1ba** (48.2 mg, 0.20 mmol) were then added, and the cap was applied to seal the vial. The vessel was heated at 100 °C for 6 h, then cooled at room temperature and the crude mixture was filtered through a pad of celite. The filtrate was then concentrated *in vacuo* to afford crude 1-allylimidazole **2ba** [75% yield by ^{1}H-NMR analysis using 1,3,5-trimethoxybenzene (6.9 mg) as an internal standard]. The crude product was purified by flash column chromatography over silica gel to give **2ba** as a yellow solid (40.0 mg, 74%).

1-(2-Methylallyl)-1*H*-imidazole (2ba). CAS [87266-35-1]



2ba

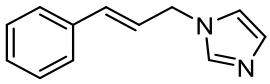
Colorless solid (40 mg, 74%). R_f 0.10 (SiO_2, EtOA).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.46 (s, 1H), 7.05 (s, 1H), 6.87 (s, 1H), 4.94 (s, 1H), 4.77 (s, 1H), 4.43 (s, 2H), 1.66 (s, 3H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 140.6, 137.56, 129.4, 119.4, 114.0, 53.2, 19.8.

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_7H_{11}N_2$: 123.0917, found: 123.0917.

1-Phenyl-3-(1*H*-imidazol-1yl)prop-1-ene (2ca). CAS [56643-93-7]



2ca

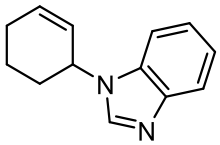
Colorless solid (31 mg, 86%). R_f 0.17 (SiO_2, hexane/EtOAc = 1/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.55 (s, 1H), 7.38–7.29 (m, 5H), 7.10 (s, 1H), 6.97 (s, 1H), 6.53 (d, *J* = 15.6 Hz, 1H), 6.32–6.25 (m, 1H), 4.71 (dd, *J* = 6.2, 1.2 Hz, 2H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 137.2, 135.8, 133.8, 129.8, 128.9, 128.4, 126.7, 123.8, 119.1, 49.1.

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{12}H_{13}N_2$: 185.1073, found: 185.1076.

1-(Cyclohex-2-en-1-yl)-1*H*-benzo[*d*]imidazole (2dc). CAS [95792-97-5]



2dc

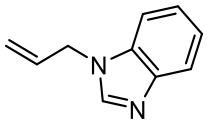
Colorless oil (22 mg, 56%). R_f 0.80 (NH silica, hexane/EtOAc = 1/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.98 (s, 1H), 7.83–7.79 (m, 1H), 7.46–7.42 (m, 1H), 7.30–7.25 (m, 2H), 6.23–6.18 (m, 1H), 5.87–5.83 (m, 1H), 5.03–4.98 (m, 1H), 2.28–1.96 (m, 4H), 1.76–1.68 (m, 2H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 144.4, 142.2, 133.8, 133.4, 124.8, 122.7, 122.2, 120.5, 110.2, 51.1, 29.6, 24.9, 19.3.

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{13}H_{15}N_2$: 199.1230, found: 199.1231.

1-Allyl-benzoimidazole (2ac). CAS [19018-22-5]

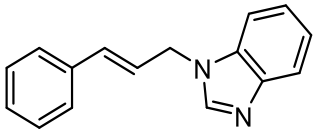


2ac

Yellow oil (27 mg, 88%). R_f 0.20 (SiO_2, hexane/EtOAc = 1/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.90 (s, 1H), 7.82 (t, *J* = 4.4 Hz, 1H), 7.38 (d, *J* = 4.4 Hz, 1H), 7.31–7.28 (m, 2H), 6.06–5.96 (m, 1H), 5.29 (d, *J* = 10.0 Hz, 1H), 5.19 (d, *J* = 16.8 Hz, 1H), 4.78 (dd, *J* = 5.6, 1.2 Hz, 2H).
^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 144.0, 143.1, 134.0, 132.0, 123.1, 122.3, 121.0, 118.8, 110.1, 48.0.
HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{10}H_{11}N_2$: 159.0917, found: 159.0918.

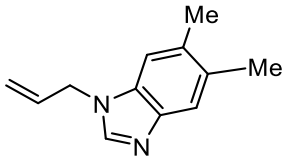
1-(3-Phenylallyl) -1*H*-benzoimidazole (2cc). CAS [565442-00-4]



2cc

Colorless solid (41 mg, 87%). R_f 0.10 (SiO_2, hexane/EtOAc = 1/1).
^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.96 (s, 1H), 7.85–7.83 (m, 1H), 7.45–7.42 (m, 1H), 7.36–7.24 (m, 6H), 6.57 (d, *J* = 16.0 Hz, 1H), 6.34 (dt, *J* = 16.0, 6.0 Hz, 2H), 4.95 (dd, *J* = 6.0, 1.6 Hz, 2H).
^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 144.1, 143.0, 135.8, 134.0, 133.8, 128.8, 128.4, 126.7, 123.2, 123.1, 122.4, 120.6, 110.1, 47.2.
HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{16}H_{15}N_2$: 235.1230, found: 235.1231.

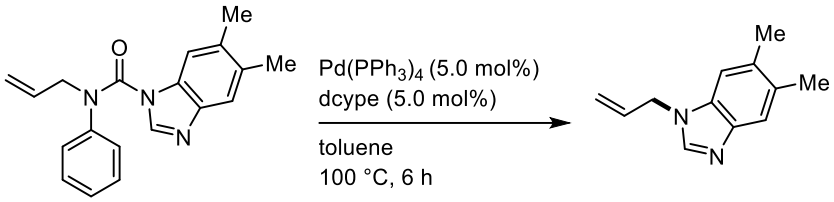
1-Allyl-5,6-dimethyl-1*H*-benzoimidazole (2ad). CAS [91649-62-6]



2ad

Yellow solid (35 mg, 94%). R_f 0.12 (SiO_2, hexane/EtOAc = 1/1).
^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.80 (s, 1H), 7.57 (s, 1H), 7.13 (s, 1H), 6.04–5.95 (m, 1H), 5.28 (d, *J* = 10.8 Hz, 1H), 5.16 (d, *J* = 17.6 Hz, 1H), 4.74 (d, *J* = 5.6 Hz, 2H). 2.38 (s, 3H), 2.37 (s, 3H).
^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 142.5, 142.3, 132.5, 132.3, 132.2, 131.2, 120.4, 118.5, 110.2, 47.5, 20.7, 20.4.
HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{12}H_{15}N_2$: 187.1230, found: 187.1231.

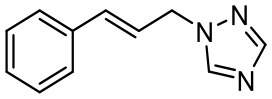
Procedure for a gram scale reaction. A 100 mL two-necked flask with a magnetic stirring bar was evacuated and backfilled with nitrogen three times. $Pd(PPh_3)_4$ (0.46g, 0.4 mmol), dcype (0.19 g, 0.4 mmol) and toluene (40 mL) were added, and stirred for 15 min at rt. Urea **1ad** (2.4 g, 8.0 mmol) was then added, and the vessel was heated at 100 °C for 6 h. After being cooled to rt, the crude mixture was filtered through a pad of celite, and the filtrate was concentrated *in vacuo.* The residue was purified by flash column chromatography over silica gel to give allylamine **1ad** as a yellow solid (1.4 g, 96%).



1ad **2ad**

1.4 g, 96%

4-Cinnamyl-1*H*-1,2,4-triazole (2ce). CAS [148528-01-2]



2ce

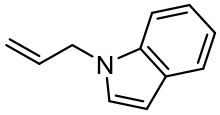
Colorless solid (39 mg, 84%). R_f 0.20 (SiO_2, hexane/EtOAc = 1/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 8.15 (s, 1H), 7.99 (s, 1H), 7.39–7.28 (m, 4H), 6.64 (d, *J* = 16.0 Hz, 1H), 6.34 (dt, *J* = 16.0, 6.4 Hz, 2H), 4.96 (dd, *J* = 6.4, 1.2 Hz, 2H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 152.2, 142.9, 135.6, 135.3, 128.8, 128.6, 126.8, 121.9, 51.9.

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{11}H_{12}N_3$: 186.1026, found: 186.1029.

1-Allylindole (2af). CAS [16886-08-1]



2af

The yield was determined by NMR analysis using 1,3,5-tri(methoxy) benzene as an internal standard due to the instability of the product. Spectroscopic dates were consistent with those reported in literature.[12]

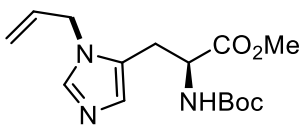
68% NMR yield. R_f 0.32 (SiO_2, hexane/EtOAc = 5/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.64 (d, *J* = 8.0 Hz, 1H), 7.33 (d, *J* = 8.0 Hz, 1H), 7.21 (t, *J* = 6.8 Hz, 1H), 7.13–7.10 (m, 2H), 6.53 (d, *J* = 3.2 Hz, 1H), 6.05–5.96 (m, 1H), 5.20 (dd, *J* = 10.4, 1.2 Hz, 1H), 5.09 (dd, *J* = 16.8, 1.2 Hz, 1H), 4.74 (dt, *J* = 6.0, 1.6 Hz, 2H).

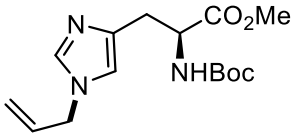
^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 136.2, 133.6, 128.6, 127.9, 121.6, 121.1, 119.5, 117.4, 109.7, 101.5, 49.0.

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{11}H_{12}N$: 158.0964, found: 158.0967.

Methyl *N*$^{\pi}$-allyl-*N*$^{\alpha}$-(*tert*-butoxycarbonyl)histidinate and methyl *N*$^{\tau}$-allyl-*N*$^{\alpha}$-(*tert*-butoxycarbonyl)histidinate (2ag and **2ag')**. CAS [196607-93-9]; CAS [196607-97-3]



2ag



2ag'

Colorless oil (78 mg, 63%, **2ag**:**2ag'** = 2:1). R_f 0.20, 0.30 (SiO_2, $CHCl_3$/MeOH = 9/1).

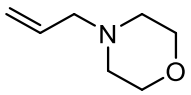
Run on a 0.40 mmol scale.

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.40 (s, 1H: **2ag**), 7.34 (s, 1H: **2ag'**), 6.78 (s, 1H: **2ag**), 6.64 (s, 1H: **2ag'**), 5.94–5.84 (m, 1H + 1H: **2ag** and **2ag'**), 5.22 (d, *J* = 10.1 Hz, 2H: **2ag**), 5.13–4.98 (m, 2H: **2ag'**), 4.52-4.43 (m, 3H + 3H: **2ag** and **2ag'**), 3.71 (s, 3H: **2ag**), 3.66 (s, 3H: **2ag'**), 3.09–2.95 (m, 2H + 2H: **2ag** and **2ag'**), 1.40 (s, 9H + 9H: **2ag** and **2ag'**).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 172.7, 171.9, 155.7, 155.1, 137.9, 137.8, 137.0, 132.9, 132.8, 128.4, 126.3, 118.6, 118.1, 116.8, 80.3, 79.6, 53.7, 53.1, 52.6, 52.2, 49.4, 47.2, 30.3, 28.4, 28.3, 26.9. (**2ag** and **2ag')**

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{15}H_{24}N_3O_4$: 310.1761, found: 310.1757.

***N*-Allylmorpholine (2ab).** CAS [696-57-1]



2ab

The yield was determined by GC analysis using undecane as an internal standard due to the volatility of the product. Spectroscopic dates were consistent with those reported in literature.[13]

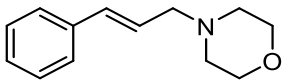
86% GC yield.

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 5.83–5.73 (m, 1H), 5.11 (t, *J* = 14.0 Hz, 2H), 3.65 (t, *J* = 4.4 Hz, 4H), 2.92 (dd, *J* = 6.8, 1.2 Hz, 2H), 2.37 (s, 4H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 134.6, 118.3, 67.0, 62.2, 53.6.

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_7H_{14}NO$: 128.1070, found: 128.1069.

(*E*)-4-Cinnamylmorpholine (2cb). CAS [85620-82-2]



2cb

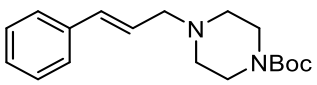
Colorless oil (27 mg, 62%). R_f 0.20 (SiO_2, hexane/EtOAc = 1/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.39–7.21 (m, 5H), 6.53 (d, *J* = 16.0 Hz, 1H), 6.26 (dt, *J* = 16.0, 6.8 Hz, 1H), 3.74 (t, *J* = 4.4 Hz, 4H), 3.16 (dd, *J* = 6.8, 1.2 Hz, 2H), 2.51 (s, 4H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 136.8, 133.4, 128.6, 127.6, 126.3, 126.0, 67.0, 61.5, 53.7.

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{13}H_{18}NO$: 204.1383, found: 204.1383.

4-Cinnamylpiperazine-1-carboxylic acid *tert*-butyl ester (2ch). CAS [778560-29-5]



2ch

Colorless solid (17 mg, 85%, 0.10 mmol scale). R_f 0.28 (SiO_2, hexane/EtOAc = 1/1).

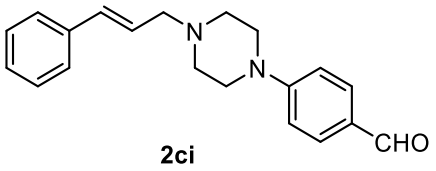
^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.39–7.21 (m, 5H), 6.52 (d, *J* = 16.0 Hz, 1H), 6.26 (dt, *J* = 16.0, 6.8 Hz, 1H), 3.47

(t, *J* = 5.2 Hz, 4H), 3.17 (dd, *J* = 6.8, 0.8 Hz, 2H), 2.46 (t, *J* = 4.8 Hz, 4H), 1.47 (s, 9H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 154.9, 136.9, 133.5, 129.0, 128.7, 127.7, 126.4, 126.3, 79.8, 61.2, 53.1, 28.5.

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{18}H_{27}N_2O_2$: 303.2067, found: 303.2070.

4-(4-Cinnamylpiperazin-1-yl)benzaldehyde (2ci).



2ci

Yellow oil (36 mg, 58%). R_f 0.22 (SiO_2, hexane/EtOAc = 2/3).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 9.78 (s, 1H), 7.76 (d, *J* = 8.7 Hz, 2H), 7.40 (d, *J* = 7.3 Hz, 2H), 7.33 (t, *J* = 7.3 Hz, 2H), 7.26 (t, *J* = 3.7 Hz, 1H), 6.92 (d, *J* = 8.7 Hz, 2H), 6.57 (d, *J* = 16.0 Hz, 1H), 6.33–6.27 (m, 1H), 3.43 (t, *J* = 5.0 Hz, 4H), 3.22 (d, *J* = 6.4 Hz, 2H), 2.65 (t, *J* = 5.0 Hz, 4H).

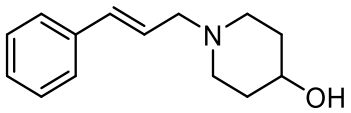
^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 190.6, 155.2, 136.8, 133.7, 132.0, 128.8, 127.8, 127.3, 126.5, 126.1, 113.7, 61.2, 52.9, 47.3.

IR (KBr, cm^{-1}): 1734 w, 1671 m, 1655 m, 1598 s, 1519 m, 1386 w, 1373 w, 1322 m, 1223 s, 1172 s, 1112 m, 1065 m, 1047 w, 1001 m, 921 w, 842 m, 818 m, 741 w, 693 w, 649 m, 509 m.

MS, m/z (relative intensity, %): 307 (22), 306 (M$^+$, 100), 215 (15), 201 (22), 189 (10), 172 (22), 160 (24), 145 (44), 144 (34), 134 (23), 133 (16), 132 (36), 118 (13), 117 (73), 116 (15), 115 (15), 104 (12), 91 (37), 77 (18), 68 (11), 56 (77), 42 (15).

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{20}H_{23}N_2O$: 307.1805, found: 307.1806.

1-Cinnamylpiperidin-4-ol (2cj).



2cj

White solid (29 mg, 66%). R_f 0.28 (NH silica, EtOAc).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.39–7.21 (m, 5H), 6.50 (d, *J* = 16.0 Hz, 1H), 6.28 (dt, *J* = 16.0, 6.9 Hz, 1H), 3.72 (s, 1H), 3.15 (dd, *J* = 6.6, 1.1 Hz, 2H), 2.83 (t, *J* = 5.7 Hz, 2H), 2.19 (t, *J* = 9.8 Hz, 2H), 1.92 (dq, *J* = 12.9, 3.7 Hz, 2H), 1.77 (s, 1H), 1.66–1.57 (m, 2H).

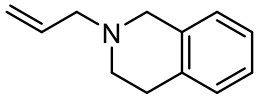
^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 137.0, 133.0, 128.7, 127.6, 127.0, 126.4, 68.1, 61.1, 51.23, 34.7.

IR (KBr, cm^{-1}): 3155 m, 2944 w, 2827 w, 1494 w, 1360 s, 1320 w, 1138 m, 1019 w, 965 m, 779 w, 744 s, 692 s, 420 w.

MS, m/z (relative intensity, %): 217 (M$^+$, 25), 216 (26), 158 (11), 127 (13), 126 (100), 118 (20), 117 (89), 116 (15), 115 (63), 114 (21), 108 (19), 100 (14), 91 (28), 82 (24), 44 (17), 42 (16).

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{14}H_{20}NO$: 218.1539, found: 218.1534.

***N*-Allyl 1,2,3,4-tetrahydroisoquinoline (2ak).** CAS [2079-11-0]



2ak

The yield was determined by NMR analysis using 1,3,5-tri(methoxy) benzene as an internal standard due to the instability of the product. Spectroscopic dates were consistent with those reported in literature. [14]

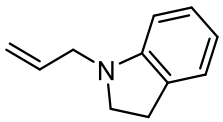
62% NMR yield. R_f 0.82 (NH silica, hexane/EtOAc = 1/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.12–7.09 (m, 3H), 7.02–7.01 (m, 1H), 5.99–5.93 (m, 1H), 5.26 (dd, *J* = 17.2, 1.6 Hz, 1H), 5.20 (d, *J* = 10.0 Hz, 1H), 3.63 (s, 2H), 3.18 (d, *J* = 6.4 Hz, 2H), 2.92 (t, *J* = 6.0 Hz, 2H), 2.74 (t, *J* = 6.0 Hz, 2H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 135.5, 134.9, 134.4, 128.8, 126.7, 126.2, 125.7, 118.0, 61.7, 56.2, 50.8, 29.2.

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{12}H_{16}N$: 174.1277, found: 174.1278.

***N*-Allylindoline (2al).** CAS [88876-27-1]



2al

The yield was determined by NMR analysis using 1,3,5-tri(methoxy) benzene as an internal standard due to the instability of the product. Spectroscopic dates were consistent with those reported in literature. [15]

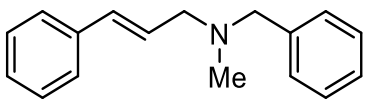
65% NMR yield. R_f 0.72 (NH silica, hexane/EtOAc = 1/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.13–7.08 (m, 2H), 6.70 (dt, *J* = 8.0, 0.8 Hz, 1H), 6.55 (d, *J* = 8.0 Hz, 1H), 6.00–5.90 (m, 1H), 5.33 (dd, *J* = 16.8, 1.6 Hz, 1H), 5.23 (dd, *J* = 10.0, 1.6 Hz, 1H), 3.75 (dt, *J* = 6.0, 1.6 Hz, 2H), 3.37 (t, *J* = 8.0 Hz, 2H), 3.00 (t, *J* = 8.0 Hz, 2H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 152.3, 134.3, 130.3, 127.4, 124.5, 117.8, 117.4, 107.4, 53.3, 52.3, 28.6.

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{11}H_{14}N$: 160.1121, found: 160.1123.

(*E*)-*N*-Benzyl-*N*-methyl-3-phenylprop-2-en-1-amine (2cm). CAS [98977-53-8]



2cm

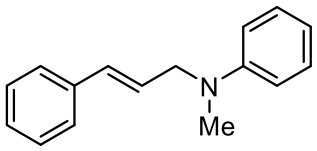
Yellow oil (27 mg, 50%). R_f 0.56 (SiO_2, hexane/EtOAc = 1/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.41–7.24 (m, 10H), 6.56 (d, *J* = 8.0 Hz, 1H), 6.33 (dt, *J* = 16.0, 6.4 Hz, 1H), 3.57 (s, 2H), 3.21 (d, *J* = 6.8 Hz, 2H), 2.26 (s, 3H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 139.0, 137.2, 132.8, 129.3, 128.7, 128.4, 127.6, 127.5, 127.2, 126.4, 62.0, 60.0, 42.3.

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{17}H_{20}N$: 238.1590, found: 238.1595.

(*E*)-*N*-Methyl-*N*-phenyl-3-phenyl-2-propenylamine (2cn). CAS [33603-47-3]



2cn

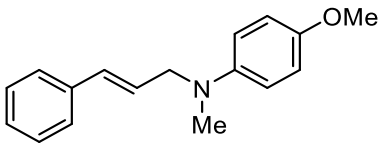
Yellow oil (21 mg, 41%). R_f 0.48 (SiO_2, hexane/EtOAc = 1/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.40–7.21 (m, 7H), 6.86–6.72 (m, 3H), 6.53 (d, *J* = 16.0 Hz, 1H), 6.26 (dt, *J* = 16.0, 1.2 Hz, 1H), 4.10 (dd, *J* = 5.6, 1.6 Hz, 2H), 2.99 (s, 3H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 149.7, 137.0, 131.4, 129.3, 128.7, 127.5, 126.4, 125.9, 116.7, 112.7, 55.0, 38.2.

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{16}H_{18}N$: 224.1434, found: 224.1438.

***N*-Cinnamyl-*N*-methyl-*p*-methoxy-aniline (2co).** CAS [86575-79-6]



2co

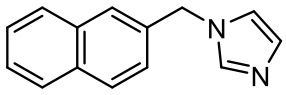
Colorless oil (24 mg, 42%). R_f 0.40 (SiO_2, hexane/EtOAc = 4/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.43–7.20 (m, 6H), 6.87–6.80 (m, 3H), 6.54 (d, *J* = 16.0 Hz, 1H), 6.27 (dt, *J* = 16.0, 2.0 Hz, 1H), 4.00 (dd, *J* = 5.2, 1.6 Hz, 2H), 3.78 (s, 3H), 2.91 (s, 3H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 152.0, 144.7, 137.1, 131.7, 128.7, 127.5, 126.4, 126.3, 115.1, 114.8, 56.4, 55.9, 38.9.

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{17}H_{20}NO$: 254.1539, found: 254.1536.

1-(Naphthalen-2-ylmethyl)imidazole (2ea). CAS [98318-77-5]



2ea

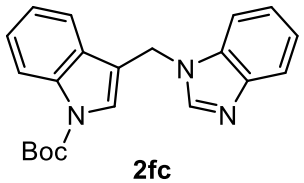
Colorless solid (33 mg, 89%). R_f 0.18 (SiO_2, hexane/EtOAc = 1/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.84–7.78 (m, 3H), 7.60 (d, *J* = 9.2 Hz, 2H), 7.52–7.50 (m, 2H), 7.27–7.25 (m, 1H), 7.12 (s, 1H), 6.94 (s, 1H), 5.27 (s, 2H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 137.7, 133.7, 133.4, 133.1, 130.1, 129.1, 128.0, 127.9, 126.8, 126.6, 126.4, 125.0, 119.5, 51.1.

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{14}H_{13}N_2$: 209.1073, found: 209.1073.

***tert*-Butyl 3-((1*H*-benzo[d]imidazol-1-yl)methyl)-1*H*-indole-1-carboxylate (2fc).** CAS [1632128-80-3]



2fc

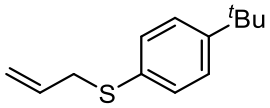
Colorless oil (33 mg, 86%, 0.10 mmol scale). R_f 0.40 (NH silica, hexane/EtOAc = 1/2).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 8.14 (d, *J* = 8.0 Hz, 1H), 7.96 (s, 1H), 7.83 (t, *J* = 4.0 Hz, 1H), 7.59 (s, 1H), 7.47 (d, *J* = 4.0 Hz, 1H), 7.36–7.29 (m, 4H), 7.20 (t, *J* = 8.0 Hz, 1H), 5.46 (s, 2H), 1.67 (s, 9H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 149.6, 144.1, 143.0, 135.7, 134.0, 128.7, 125.2, 125.0, 123.2 (two overlapping peaks), 122.5, 120.6, 118.7, 115.7, 114.7, 109.9, 84.5, 40.7, 28.3.

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{21}H_{22}N_3O_2$: 348.1707, found: 348.1712.

Allyl(4-(*tert*-butyl)phenyl)sulfane (2ap). CAS [157581-05-0]



2ap

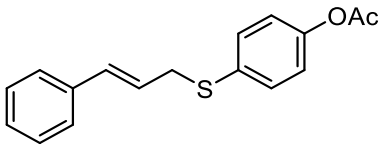
Colorless oil (28 mg, 69%). R_f 0.32 (SiO_2, hexane).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.32–7.28 (m, 4H), 5.93–5.84 (m, 1H), 5.15 (dd, *J* = 16.8, 1.6 Hz, 1H), 5.08 (d, *J* = 8.0 Hz, 1H), 3.53 (s, *J* = 6.9 Hz, 2H), 1.30 (s, 9H).

^{3}C NMR ($CDCl_3$, 100.53 MHz) δ: 149.6, 134.0, 132.5, 130.0, 126.0, 117.7, 37.6, 34.6, 31.4.

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{13}H_{19}S$: 207.1202, found: 207.1203.

4-(Cinnamylthio)phenyl acetate (2cq-Ac).



2cq-Ac

Run on a 0.10 mmol scale.

The product was isolated in an *O*-acetylated form, by treating the reaction mixture with Ac_2O (0.040 mL, 0.040 mmol) and pyridine (0.040 mL, 0.40 mmol) at 50 °C for 12 h. This is because unprotected phenol product was unstable and partially decomposed upon chromatographic purification.

Colorless oil (25 mg, 89%). R_f 0.24 (SiO_2, hexane/EtOAc = 9/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.40 (d, *J* = 8.2 Hz, 2H), 7.33–7.26 (m, 5H), 7.02 (d, *J* = 8.7 Hz, 2H), 6.39 (s, 1H), 6.26 (s, 1H), 3.68 (d, *J* = 6.9 Hz, 2H), 2.29 (s, 3H).

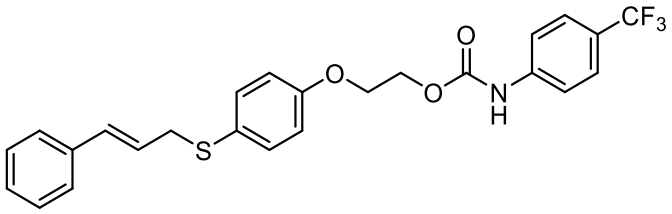
^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 169.5, 149.6, 136.8, 133.11, 133.05, 132.1, 128.7, 127.8, 126.5, 125.0, 122.2, 37.9, 21.3.

IR (KBr, cm^{-1}): 1748 s, 1577 w, 1449 w, 1397 w, 1237 s, 1197 m, 1106 w, 1012 m, 945 m, 841 s, 755 s, 713 m, 593 m, 504 s.

MS, m/z (relative intensity, %): 284 (M^+, 3), 117 (100), 115 (27), 91 (10), 43 (11).

HRMS (DART) *m/z* [M+H^+] calcd for $C_{17}H_{17}O_2S$: 285.0944, found: 285.0944.

4-(Cinnamylthio)phenyl (4-(trifluoromethyl)phenyl)carbamate (2cr).



2cr

Run on a 0.40 mmol scale.

Yellow solid (127.5 mg, 68%). Mp 161 °C. R_f 0.70 (SiO_2, hexane/EtOAc = 1/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.57 (d, *J* = 8.7 Hz, 2H), 7.49 (d, *J* = 8.7 Hz, 2H), 7.37 (dd, *J* = 6.6, 2.1 Hz, 2H), 7.29–7.28 (m, 3H), 7.23–7.21 (m, 1H), 6.84 (dd, *J* = 6.9, 1.8 Hz, 3H), 6.31–6.23 (m, 2H), 4.53 (t, *J* = 4.4 Hz, 2H), 4.19 (t, *J* = 4.6 Hz, 2H), 3.59 (d, *J* = 6.9 Hz, 2H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 158.0, 152.9, 140.9, 137.0, 134.4, 132.7, 128.7, 127.7, 126.60 (q, J_{CF} = 22.4 Hz), 126.56, 126.5 (q, J_{CF} = 3.8 Hz), 126.4, 125.6, 124.2 (q, J_{CF} = 273.2 Hz), 118.2, 115.2, 66.3, 63.9, 39.2.

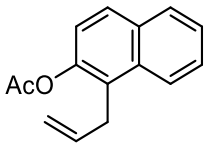
^{19}F NMR ($CDCl_3$, 376 MHz) δ: -63.3.

IR (KBr, cm^{-1}): 3362 s, 1618 m, 1537 s, 1492 s, 1415 m, 1271 m, 1182 w, 1071 m, 970 m, 834 s, 691 w..

MS, m/z (relative intensity, %): 473 (M^+, 4), 118 (11), 117 (100), 115 (16).

HRMS (DART) *m/z* [M+H^+] calcd for $C_{25}H_{22}F_3NO_3S$: 474.1345, found: 474.1350.

1-Allyl-2-acetoxy-naphthalene (2as-Ac). CAS [129589-53-3]



2as-Ac

The product was isolated in an *O*-acetylated form, by treating the reaction mixture with Ac_2O (0.060 mL, 0.060 mmol) and pyridine (0.050 mL, 0.60 mmol) at 50 °C for 12 h.

Colorless oil (25 mg, 55%). R_f 0.60 (SiO_2, hexane/EtOAc = 1/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 8.00 (d, *J* = 8.0 Hz, 1H), 7.84 (d, *J* = 8.0 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.54–7.44 (m, 2H), 7.21 (t, *J* = 8.0 Hz, 1H), 6.00–5.94 (m, 1H), 5.05–5.00 (m, 2H), 3.76 (d, *J* = 6.0 Hz, 2H), 2.37 (s, 3H).

^{13}C NMR (CD_2Cl_2, 100.53 MHz) δ: 169.9, 146.5, 135.7, 132.9, 132.2, 128.8, 128.2, 126.6, 125.6, 125.5, 124.4, 121.7, 116.1, 30.2, 21.2.

HRMS (DART) *m/z* [M+H^+] calcd for $C_{15}H_{15}O_2$: 227.1067, found: 227.1069.

VI. Robustness Screening[16]

In a glovebox filled with nitrogen, $Pd(PPh_3)_4$ (0.010 mmol), dcype (0.010 mmol) and toluene (1.0 mL) were added to a 10 mL vial with a Teflon-sealed screwcap, and stirred for 5 min at rt. **1ap** (0.20 mmol) and additives (0.20 mmol) were then added, and the cap was applied to seal the vial. The vessel was heated at 100 °C for 6 h. After being cooled to rt, the crude mixture was filtered through a pad of celite. The filtrate was concentrated *in vacuo* to give a residue, which was analyzed by ^{1}H-NMR using 1,3,5-trimethoxybenzene as an internal standard (Figure S2). These results revealed that polar functional groups such as OH, NH_2 and $CONH_2$ did not significantly inhibit the unimolecular fragment coupling reaction.

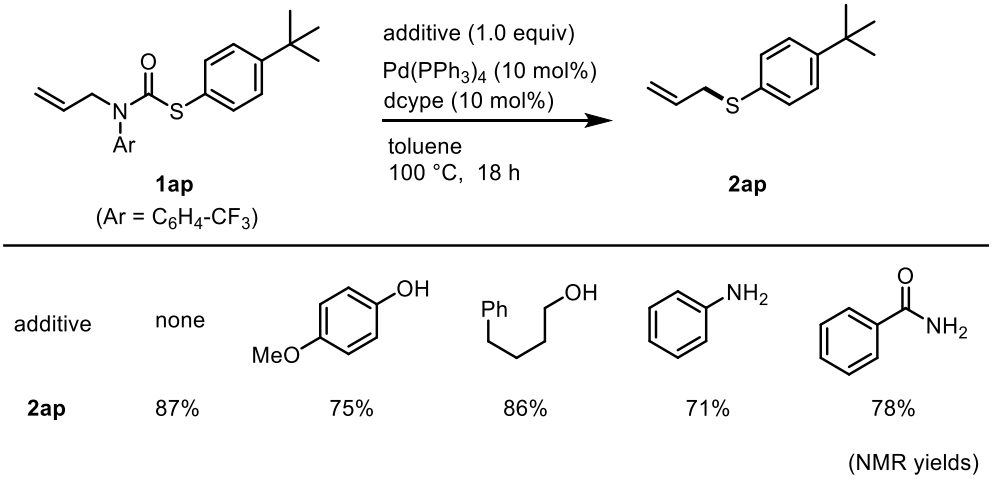
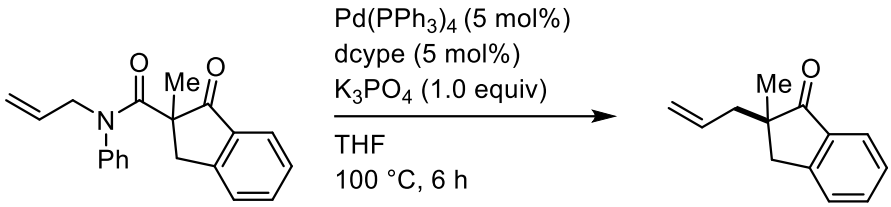


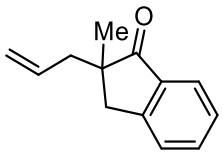
Figure S2. Robustness screening for unimolecular fragment coupling of **1ap**.

VII. Palladium-Catalyzed Elimination of Isocyanate from *N*-Allyl-β-ketoamide Derivatives



In a glovebox filled with nitrogen, $Pd(PPh_3)_4$ (11.6 mg, 0.010 mmol), dcype (4.2 mg, 0.010 mmol) and THF (1.0 mL) were added to a 10 mL vial with a Teflon-sealed screwcap, and stirred for 5 min at rt. Amide **5a** (61.1 mg, 0.20 mmol) and K_3PO_4 (27.6 mg, 0.20 mmol) were then added, and the cap was applied to seal the vial and the vessel was heated at 100 °C for 6 h. After being cooled to rt, the crude mixture was filtered through a pad of celite, and the filtrate was concentrated *in vacuo.* The residue was purified by flash column chromatography over silica gel to give indanone derivative **6a** as a yellow solid (42.7 mg, quant).

2-Allyl-2-methyl-2,3-dihydro-1*H*-inden-1-one (6a). CAS [836628-53-6]



6a

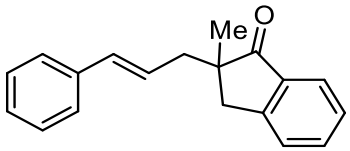
Yellow oil (42.7. mg, quant). R_f 0.31 (SiO_2, hexane/EtOAc = 1/4).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ 7.75 (d, *J* = 7.8 Hz, 1H), 7.58 (m, 1H), 7.42 (d, *J* = 7.3 Hz, 1H), 7.38–7.34 (m, 1H), 5.70–5.60 (m, 1H), 5.10–4.99 (m, 2H), 3.16 (d, *J* = 17.4 Hz, 1H), 2.83 (d, *J* = 17.4 Hz, 1H), 2.41–2.30 (m, 2H), 1.22 (s, 3H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 210.9, 152.7, 136.0, 135.0, 134.0, 127.5, 126.7, 124.3, 118.5, 48.9, 42.6, 39.5, 23.9.

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{13}H_{15}O$: 187.1117, found: 187.1118.

2-Cinnamyl-2-methyl-2,3-dihydro-1*H*-inden-1-one (6b).



6b

Run on a 0.15 mmol scale.

Yellow oil (22 mg, 57%). R_f 0.31 (SiO_2, hexane/EtOAc = 4/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.77 (d, *J* = 7.8 Hz, 1H), 7.59 (t, *J* = 7.3, 7.8 Hz, 1H), 7.45–7.34 (m, 2H), 7.30–7.23 (m, 4H), 7.22–7.11 (m, 1H), 6.44 (d, *J* = 15.6 Hz, 1H), 6.15–6.02 (m, 1H), 3.23 (d, *J* = 16.9 Hz, 1H), 2.88 (d, *J* = 16.9 Hz, 1H), 2.59–2.42 (m, 2H), 1.28 (s, 3H).

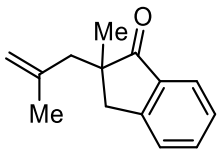
^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 210.9, 152.7, 137.4, 135.9, 135.1, 133.5, 128.6, 127.6, 127.3, 126.8, 126.2, 125.8, 124.4, 49.5, 41.8, 39.6, 24.0.

IR (KBr, cm^{-1}): 3026 w, 2960 w, 2925 w, 2866 w, 1709 s, 1607 m, 1588 w, 1493 w, 1464 w, 1449 w, 1431 w, 1326 w, 1293 w, 968 w, 793 w, 734 m, 693 w.

MS, m/z (relative intensity, %): 262 (M$^+$, 16), 247 (11), 118 (21), 116 (11), 91 (25).

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{19}H_{19}O$: 263.1430, found: 263.1429.

2-Methyl-2-(2-methylallyl)-2,3-dihydro-1*H*-inden-1-one (6c). CAS [157485-24-0]



6c

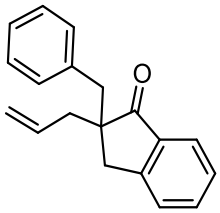
Yellow oil (24 mg, 49%). R_f 0.11 (SiO_2, hexane/EtOAc = 9/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.76 (d, *J* = 7.3 Hz, 1H), 7.59 (t, *J* = 7.3 Hz, 1H), 7.43 (d, *J* = 7.8 Hz, 1H), 7.37 (dd, *J* = 7.7, 7.3 Hz, 1H), 4.71 (d, *J* = 40.3 Hz, 2H), 3.30 (d, *J* = 16.9 Hz, 1H), 2.83 (d, *J* = 16.9 Hz, 1H), 2.53 (d, *J* = 13.7 Hz, 1H), 2.34 (d, *J* = 13.7 Hz, 1H), 1.56 (s, 3H), 1.21 (s, 3H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 211.2, 153.0, 142.8, 135.8, 135.0, 127.5, 126.8, 124.5, 114.6, 48.9, 45.8, 39.5, 25.7, 24.0.

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{14}H_{17}O$: 201.1274, found: 201.1271.

2-Allyl-2-benzyl-2,3-dihydro-1*H*-inden-1-one (6d). CAS [1362388-09-7]



6d

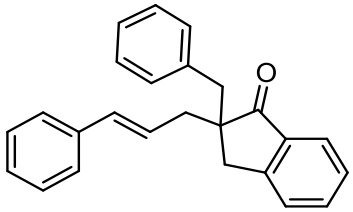
Yellow oil (50 mg, 93%). R_f 0.33 (SiO_2, hexane/EtOAc = 4/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.70 (d, *J* = 8.2 Hz, 1H), 7.50–7.46 (m, 1H), 7.30–7.25 (m, 2H), 7.18–7.09 (m, 5H), 5.64–5.54 (m, 1H), 5.08–4.96 (m, 2H), 3.13–3.09 (m, 2H), 2.95 (d, *J* = 17.4 Hz, 1H), 2.82 (dd, *J* = 13.5, 1.6 Hz, 1H), 2.55 (q, *J* = 6.6 Hz, 1H), 2.36–2.27 (m, 1H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 210.4, 153.2, 137.4, 136.9, 134.9, 133.5, 130.3, 128.2, 127.3, 126.5, 126.4, 123.9, 118.8, 53.8, 42.8, 42.6, 35.4.

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{19}H_{19}O$: 263.1430, found: 263.1431.

2-Benzyl-2-cinnamyl-2,3-dihydro-1*H*-inden-1-one (6e). CAS [1972646-94-8]



6e

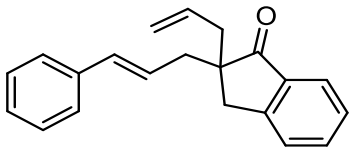
Colorless solid (67 mg, 98%). R_f 0.49 (SiO_2, hexane/EtOAc = 4/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.71 (d, *J* = 7.3 Hz, 1H), 7.49–7.45 (m, 1H), 7.32– 7.27 (m, 2H), 7.25–7.12 (m, 10H), 6.41 (d, *J* = 16.0 Hz, 1H), 6.02–5.94 (m, 1H), 3.19–3.12 (m, 2H), 3.01 (d, *J* = 17.4 Hz, 1H), 2.87 (d, *J* = 13.3 Hz, 1H), 2.74–2.65 (m, 1H), 2.50–2.45 (m, 1H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 210.4, 153.1, 137.4, 137.3, 136.8, 135.0, 133.7, 130.4, 128.6, 128.2, 127.41, 127.35, 126.6, 126.5, 126.3, 125.3, 124.0, 54.5, 42.9, 41.7, 35.6.

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{25}H_{23}O$: 339.1743, found: 339.1740.

2-Allyl-2-cinnamyl-2,3-dihydro-1*H*-inden-1-one (6f).



6f

Yellow oil (46 mg, 82%). R_f 0.46 (SiO_2, hexane/EtOAc = 4/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.75 (d, *J* = 7.8 Hz, 1H), 7.62–7.54 (m, 1H), 7.44–7.32 (m, 2H), 7.25–7.12 (m, 5H), 6.43 (d, *J* = 16.0 Hz, 1H), 6.06–5.96 (m, 1H), 5.71–5.56 (m, 1H), 5.13–4.97 (m, 2H), 3.12–3.07 (m, 2H), 2.63–2.56 (m, 1H), 2.55–2.43 (m, 2H), 2.40–2.32 (m, 1H).

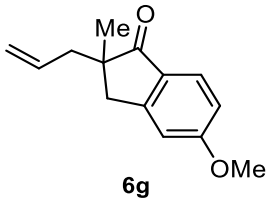
^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 210.2, 153.1, 137.3, 136.7, 135.1, 133.6, 133.5, 128.6, 127.5, 127.3, 126.6, 126.2, 125.3, 124.1, 118.7, 52.9, 41.9, 41.0, 36.3.

IR (KBr, cm^{-1}): 3075 w, 3059 w, 3026 w, 2920 w, 1707 s, 1607 m, 1589 w, 1494 w, 1474 w, 1464 w, 1447 w, 1432 w, 1294 w, 1208 w, 1185 w, 967 w, 917 w, 790 w, 737 m, 693 w.

MS, m/z (relative intensity, %): 288 (M^+, 8.8), 247 (39), 128 (11), 118 (12), 117 (100), 116 (10), 115 (51), 91 (35).

HRMS (DART) *m/z* [M+H^+] calcd for $C_{21}H_{21}O$: 289.1587, found: 289.1584.

2-Allyl-5-methoxy-2-methyl-2,3-dihydro-1*H*-inden-1-one (6g).



6g

Yellow oil (19 mg, 43%). R_f 0.44 (SiO_2, hexane/EtOAc = 3/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.68 (d, *J* = 8.2 Hz, 1H), 6.89 (d, *J* = 8.2 Hz, 1H), 6.85 (s, 1H), 5.71–5.51 (m, 1H), 5.22–4.86 (m, 2H), 3.93–3.75 (m, 3H), 3.11(d, *J* = 17.4 Hz, 1H), 2.78 (d, *J* = 16.9 Hz, 1H), 2.44–2.15 (m, 2H), 1.21 (s, 3H).

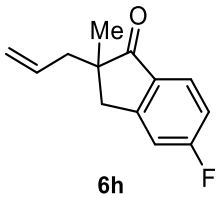
^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 209.1, 165.6, 155.7, 134.2, 129.2, 126.0, 118.3, 115.6, 109.8, 55.7, 49.1, 42.8, 39.5, 24.1.

IR (KBr, cm^{-1}): 2961 w, 2925 w, 1701 s, 1598 s, 1489 w, 1455 w, 1436 w, 1338 w, 1255 s, 1104 w, 1089 m, 1026 w, 917 w, 784 w, 754 w.

MS, m/z (relative intensity, %): 216 (M^+, 68), 217 (10), 201 (41), 176 (38), 175 (100), 174 (20), 173 (21), 159 (14), 158 (12), 148 (21), 147 (29), 132 (12), 131 (17), 129 (12), 128 (17), 120 (17), 117 (12), 116 (12), 115 (44), 103 (22), 91 (48), 89 (13), 78 (15), 77 (33), 65 (11), 63 (18), 51 (17), 41 (18).

HRMS (DART) *m/z* [M+H^+] calcd for $C_{14}H_{17}O_2$: 217.1223, found: 217.1224.

2-Allyl-5-fluoro-2-methyl-2,3-dihydro-1*H*-inden-1-one (6h).



6h

Yellow oil (24 mg, 60%). R_f 0.44 (SiO_2, hexane/EtOAc = 3/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.75 (dd, J = 8.2, 7.8 Hz, 1H), 7.11–7.03 (m, 2H), 5.70–5.56 (m, 1H), 5.12–4.97 (m, 2H), 3.15 (d, J = 17.4 Hz, 1H), 2.82 (d, J = 17.4 Hz, 1H), 2.44–2.34 (m, 1H), 2.33–2.23 (m, 1H), 1.22 (s, 3H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 209.0, 167.5 (d, J_F = 255.9 Hz), 155.6 (d, J_F = 9.6 Hz), 133.7, 132.4, 126.6 (d, J_F = 10.5 Hz), 118.7, 115.9 (d, J_F = 24.0 Hz), 113.3 (d, J_F = 22.0 Hz), 49.4, 42.7, 39.4, 24.0.

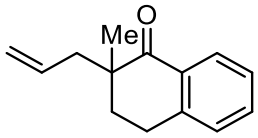
^{19}F NMR ($CDCl_3$, 376 MHz) δ: -105.5.

IR (KBr, cm^{-1}): 2360 w, 1712 s, 1616 m, 1593 m, 1433 w, 1335 w, 1249 s, 1191 m, 1178 w, 1085 m, 984 w, 938 w, 917 w, 859 w, 786 s, 758 s, 459 w.

MS, m/z (relative intensity, %): 204 (M^+, 57), 189 (71), 176 (14), 164 (39), 162 (29), 161 (19), 149 (14), 147 (22), 146 (31), 136 (38), 135 (66), 134 (28), 133 (77), 115 (39), 109 (41), 108 (43), 107 (33), 94 (10), 83 (17), 63 (10), 57 (10), 41 (23).

HRMS (DART) *m/z* [M+H^+] calcd for $C_{13}H_{14}FO$: 205.1023, found: 205.1022.

2-Allyl-2-methyl-3,4-dihydronaphthalen-1(2*H*)-one (6i). CAS [223690-77-5]



6i

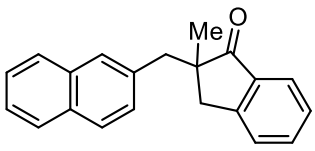
Colorless oil (27 mg, 67%). R_f 0.49 (SiO_2, hexane/EtOAc = 4/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 8.04 (d, J = 7.8 Hz, 1H), 7.48–7.44 (m, 1H), 7.30 (t, J = 7.6 Hz, 1H), 7.22 (d, J = 7.8 Hz, 1H), 5.84–5.73 (m, 1H), 5.10–5.06 (m, 2H), 3.00–2.96 (m, 2H), 2.47 (q, J = 7.0 Hz, 1H), 2.27 (dd, J = 13.7, 7.8 Hz, 1H), 2.11–2.05 (m, 1H), 1.94–1.87 (m, 1H), 1.19 (s, 3H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 202.3, 143.5, 134.1, 133.2, 131.7, 128.8, 128.2, 126.8, 118.4, 44.8, 41.2, 33.5, 25.5, 22.1.

HRMS (DART) *m/z* [M+H^+] calcd for $C_{14}H_{17}O$: 201.1274, found: 201.1271.

2-Methyl-2-(naphthalen-2-ylmethyl)-2,3-dihydro-1*H*-inden-1-one (6j).



6j

Colorless oil (15 mg, 53%). R_f 0.48 (SiO_2, hexane/EtOAc = 4/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.76 (d, *J* = 7.3 Hz, 3H), 7.69 (d, *J* = 8.7 Hz, 1H), 7.61 (s, 1H), 7.51 (td, J = 7.4, 1.1 Hz, 1H), 7.45–7.39 (m, 2H), 7.34–7.28 (m, 3H), 3.32 (d, J = 17.4 Hz, 1H), 3.23 (d, J = 13.7 Hz, 1H), 2.99 (d, J = 13.7 Hz, 1H), 2.77 (d, J = 17.4 Hz, 1H), 1.30 (s, 3H).

^{13}C NMR (CD_2Cl_2, 100.53 MHz) δ: 211.0, 152.6, 135.8, 135.7, 135.0, 133.4, 132.2, 128.9, 128.8, 127.7, 127.7, 127.6, 127.5, 126.7, 126.0, 125.5, 124.4, 50.7, 43.4, 39.0, 25.1.

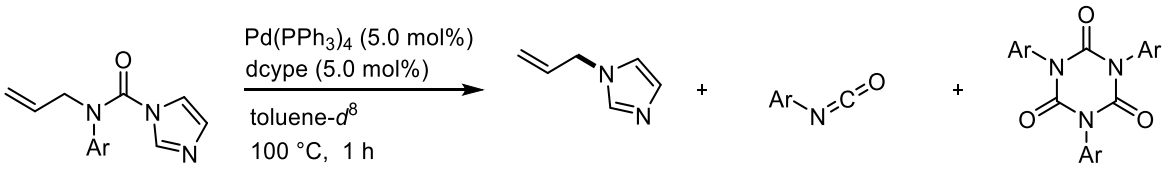
IR (KBr, cm^{-1}): 3053 w, 3020 w, 2959 w, 2924 w, 1709 sm 1607 m, 1588 w, 1508 w, 1464 w, 1455 w, 1432 w, 1370 w, 1327 w, 1285 w, 1204 w, 1090 w, 981 w, 956 w, 859 w, 815 w, 798 w, 754 w, 638 w, 480 w.

MS, m/z (relative intensity, %): 286 (M^+, 39), 271 (27), 145 (14), 143 (11), 142 (57), 141 (100), 115 (50).

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{21}H_{19}O$: 287.1430, found: 287.1431.

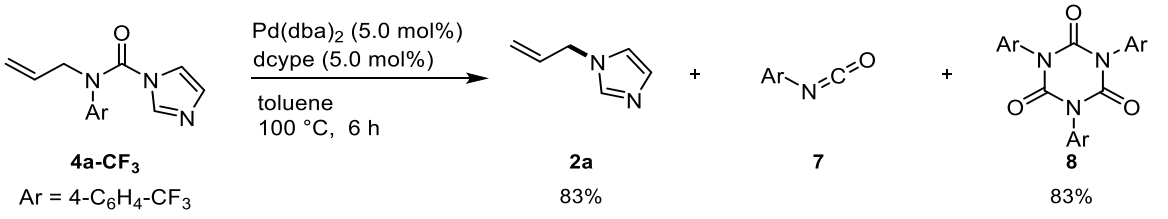
VIII. Mechanistic Studies

VIII-1. Observation of Eliminated Isocyanate and Its Cyclic Trimer



In a glovebox filled with nitrogen, $Pd(PPh_3)_4$ (5.8 mg, 0.0050 mmol), dcype (2.3 mg, 0.0050 mmol) and toluene-d_8 (1.0 mL) were added to a 10 mL vial with a Teflon-sealed screwcap, and stirred for 5 min at room temperature. **1aa-CF$_3$** (29.5 mg, 0.10 mmol) were then added, and the cap was applied to seal the vial. The vessel was heated at 100 °C for 1 h. NMR analysis of the crude mixture revealed that in addition to the formation of allylamine **2aa**, of the corresponding isocyanate **7** (δ = - 62.2 ppm) and the isocyanurate **8** (δ = - 64.1 ppm), which was generated by trimerization of isocyanate **7**. The yield of isocyanate **7** and isocyanurate **8** was determined to be 10 % and 83% (based on isocyanate monomer) respectively using perfluorobenzene as an internal standard.

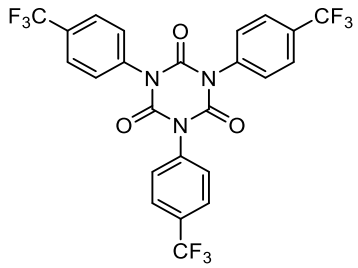
VIII-2. Isolation of isocyanurate 8



In a glovebox filled with nitrogen, $Pd(dba)_2$ (8.6 mg, 0.015 mmol), dcype (6.3 mg, 0.015 mmol) and toluene (1.5 mL) were added to a 10 mL vial with a Teflon-sealed screw cap, and the mixture was stirred for 5 min at rt. Amide **1aa-CF$_3$** (90.2 mg, 0.30 mmol) was added, and the cap was applied to seal the vial. The vessel was heated at 100 °C for 6 h. After being cooled to rt, the crude mixture was filtered through a pad of celite, and the filtrate was concentrated *in vacuo* to form a solid. The solid was washed with hexane to afford isocyanurate **8** as a colorless solid (45.5 mg,

83%).

***N,N′,N″*-tri{p-(trifluoromethyl)phenyl}isocyanurate (8).** CAS [2360979-94-6]



8

Colorless solid (46 mg, 83%). R_f 0.80 (SiO_2, hexane/EtOAc = 1/1).

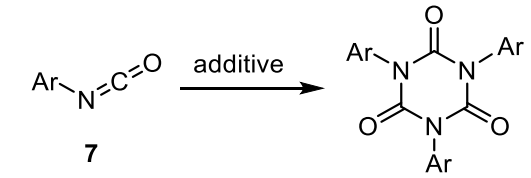
^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.80 (d, J = 8.2 Hz, 6H), 7.55 (d, J = 8.2 Hz, 6H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 147.9, 136.2, 132.0 (q, J_{CF} = 33.5 Hz), 129.2, 126.9 (q, J_{CF} = 3.8 Hz), 123.6 (q, J_{CF} = 272.2 Hz).

^{19}F NMR ($CDCl_3$, 376 MHz) δ: -64.1.

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{24}H_{13}F_9N_3O_3$: 562.0808, found: 562.0813.

VIII-3. Control experiment of trimerization of isocyanate 7



7 (Ar = 4-C_6H_4-CF_3)

8

additive		trimer **8**
$Pd(PPh_3)_4$	dcype	
−	−	n.d.
+	+	observed
+	−	n.d.
−	+	n.d.

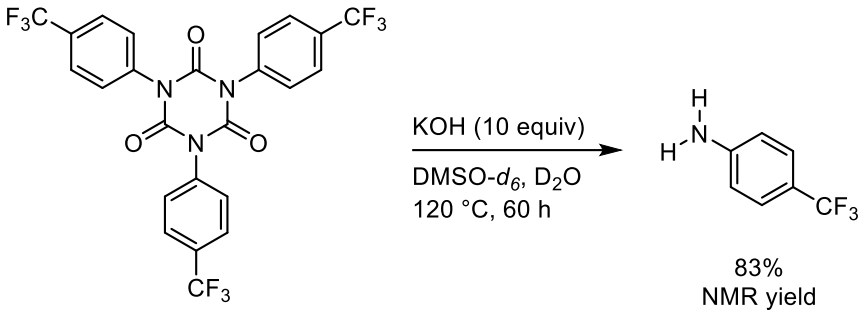
+ : added − : not added

Figure S3. Control experiment of trimerization of isocyanate **7**.[a]

[a]Reaction conditions: **7** (0.20 mmol) and $Pd(PPh_3)_4$/dcype (5.0 mol%) in toluene (1.0 mL) for 6 h at 100 °C.

As the result of these control experiments, the trimerization of **7** proceeded only when the Pd catalyst and dcype are both present. In addition, the corresponding cyclic trimer was not formed in the reactions of substrates that contain an electron-donating group on the isocyanate (*i.e.*, Ar = 4-$MeOC_6H_4$). These results indicate that the higher tendency of isocyanates bearing electron-withdrawing groups to trimerize can lead to the higher reactivity of CF_3-substituted urea substrates in this Pd/dcype-catalyzed UFC.

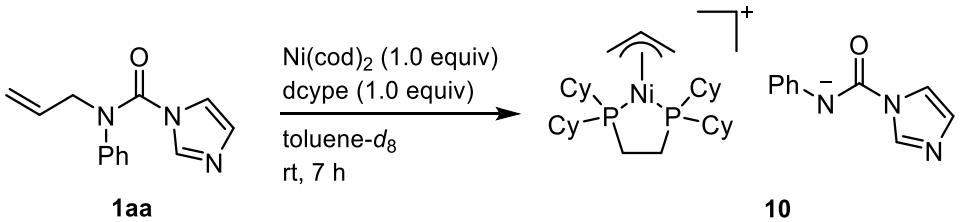
VIII-4. Procedure for hydrolysis of isocyanurate 8



8 **9**

Isocyanurate **8** (20.2 mg, 0.036 mmol) and DMSO-d_6 (0.61 mL) were added to an NMR tube having a J-Young volve. A solution of KOH (2.0 M in D_2O, 0.12 mL, 0.24 mmol) was added, and the NMR tube was sealed, shaken vigorously and the tube was heated at 120 °C for 60 h. The tube was cooled to rt and analyzed by ^{19}F NMR, which revealed that 4-aminobenzotrifluoride was formed in 83 % yield using trifluoromethylbenzene as an internal standard.

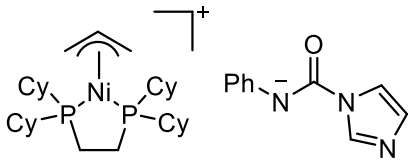
VIII-5-1. Isolation of an intermediate complex using Ni



1aa **10**

In a glovebox filled with nitrogen, $Ni(cod)_2$ (0.13 g, 0.50 mmol), dcype (0.37 g, 0.50 mmol) and toluene-d_8 (3.0 mL) were added to a 10 mL vial with a Teflon-sealed screwcap and stirred for 5 min at rt. Urea **1aa** (120 mg, 0.50 mmol) was then added, and the cap was applied to seal the vial. The vessel was stirred at rt for 7 h, after which a yellow solid was formed. The solid was collected by filtration and washed with hexane to give Ni complex **10** (0.32g, 90%).

π-Allyl Ni complex 10.



10

Yellow solid (0.32 g, 90%).

^1H NMR (CD_2Cl_2, 399.78 MHz) δ: 8.23 (s, 1H), 7.64 (s, 1H), 7.43 (d, J = 7.3 Hz, 2H), 7.14 (t, J = 7.8 Hz, 2H), 6.84 (s, 1H), 6.73 (t, J = 6.9 Hz, 1H), 5.04 (quin, J = 11.5 Hz, 1H), 2.04–1.11 (m, 48 H).

^{31}P NMR (CD_2Cl_2, 161.83 MHz) δ: 76.6.

VIII-5-2. Recrystallization of an intermediate complex with Ni complex 10

11 was obtained by recrystallization from THF and toluene. X-ray crystallography confirmed the cationic π-allylnickel framework in **10**, with the counter anion being hydrolyzed by a small amount of water upon recrystallization (*i.e.*, **11**).

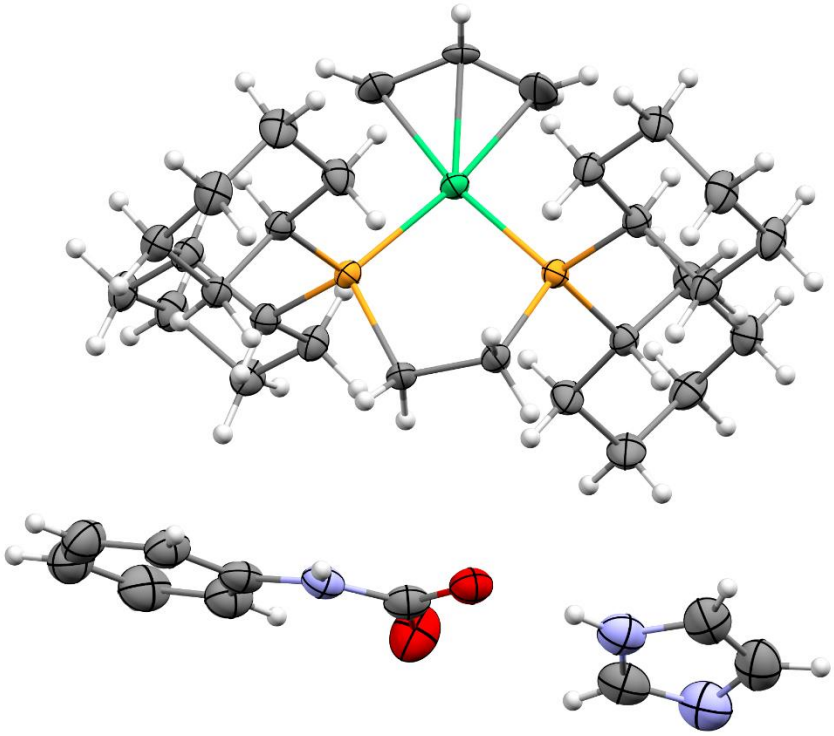
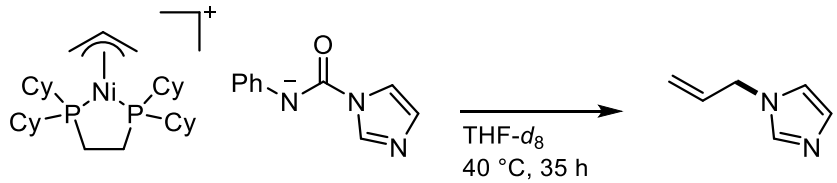


Figure S4. ORTEP drawing of **11** with thermal ellipsoids set at the 50% probability level.[a]

[a]Crystal data for **11**, monoclinic, space group $P\,2_1/c$ (no. 14), $a = 12.30869(13)$ Å, $b = 19.9187(2)$ Å, $c = 15.72761(19)$ Å, $\beta = 100.1891(11)$ °, $V = 3795.18(7)$ Å^3, $T = 123$ K, $Z = 4$, $R1$ ($wR2$) = 0.0394 (0.1083) for 433 parameters and 7671 unique reflections. GOF = 1.026. CCDC 2145093.

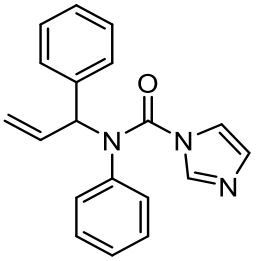
VIII-5-3. Elimination of isocyanate and reductive elimination from 9



In a glovebox filled with nitrogen, **10** (7.4 mg, 0.010 mmol) and THF-d_8 (0.6 mL) were added to a 10 mL vial with a Teflon-sealed screwcap and the cap was applied to seal the vial. The vessel was stirred at 40 °C for 35 h. After this reaction, the reaction was cooled to room temperature, and was analyzed by ^{1}H NMR. This NMR analysis revealed to the formation of *N*-allylimidazole (**2aa)**. The yield of aniline was determined to be 57 % using trifluoromethylbenzene (2.4 mg, 0.0142 mmol) as an internal standard.

VIII-6. A UFC reaction with a branched allyl urea

***N*-Phenyl-*N*-(1-phenylallyl)-1*H*-imidazole-1-carboxamide (1ia).**



1ia

Urea **1ia** was prepared according to General Procedure B.

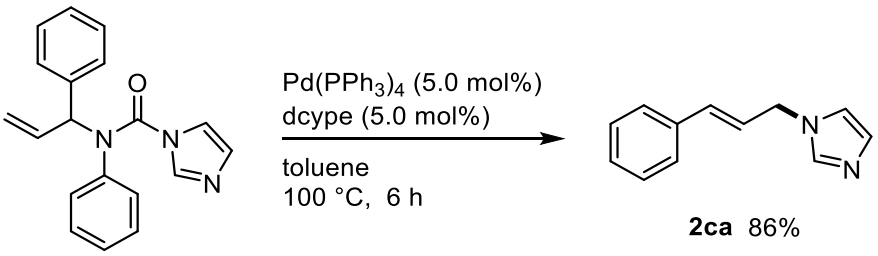
Yellow oil (0.86 g, 60%). R_f 0.10 (SiO_2, hexane/EtOAc = 1/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.55 (t, *J* = 1.1 Hz, 1H), 7.35–7.25 (m, 8H), 6.90 (d, *J* = 5.5 Hz, 2H), 6.84 (t, *J* = 1.4 Hz, 1H), 6.77 (s, 1H), 6.24–6.17 (m, 2H), 5.48–5.40 (m, 2H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 150.2, 139.5, 138.4, 138.0, 133.9, 129.9, 129.0, 128.9, 128.8, 128.7, 128.3, 128.2, 120.5, 118.6, 66.4.

IR (KBr, cm^{-1}): 2360 s, 2342 m, 1698 s, 1685 s, 1594 m, 1492 m, 1473 m, 1455 m, 1386 s, 1300 s, 1252 m, 1228 w, 1005 m, 753 m, 717 m, 698 s, 668 w, 650 m.

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{19}H_{18}N_3O$: 304.1444, found: 304.1448.

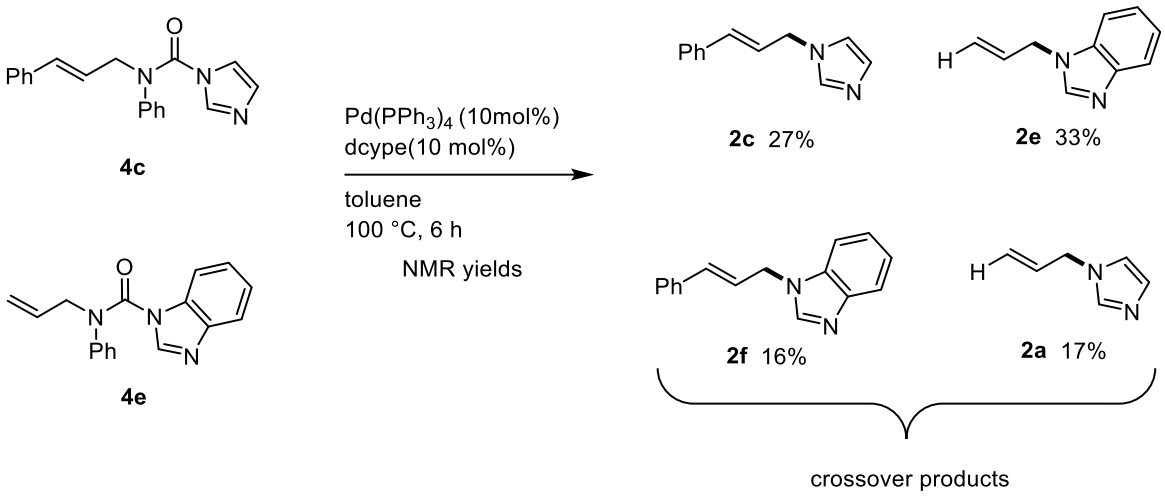


1ia **2ca** 86%

In a glovebox filled with nitrogen, $Pd(PPh_3)_4$ (11.7 mg, 0.010 mmol), dcype (4.6 mg, 0.010 mmol) and toluene (1.0 mL) were added to a 10 mL vial with a Teflon-sealed screwcap, and stirred for 5 min at rt. Urea **1ia** (60.6 mg, 0.25 mmol) was then added, and the cap was applied to seal the vial. The vessel was heated at 100 °C for 6 h. After being cooled to rt, the crude mixture was filtered through a pad of celite, and the filtrate was concentrated *in vacuo.* The residue was purified by flash column chromatography over silica gel to give the mixture of allylamine **2ca** as a colorless solid (41 mg, 86%).

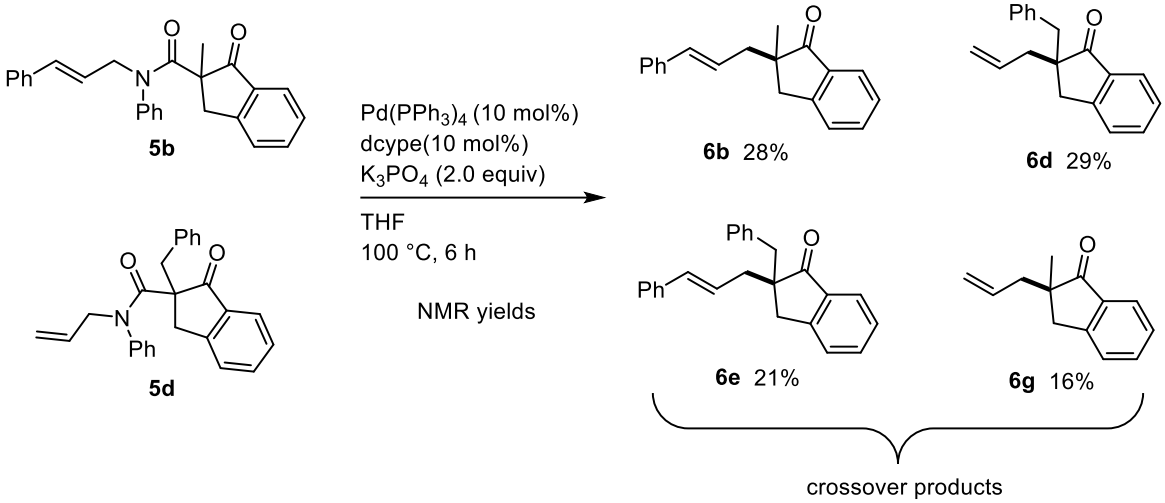
VIII-7. Crossover Experiments

VIII-7-1. C-N bond formation reaction



In a glovebox filled with nitrogen, $Pd(PPh_3)_4$ (11.6 mg, 0.010 mmol), dcype (4.5 mg, 0.011 mmol) and toluene (1.0 mL) were added to a 10 mL vial with a Teflon-sealed screwcap, and stirred for 5 min at rt. A mixture of **4c** (30.9 mg, 0.10 mmol) and **4e** (27.6 mg, 0.10 mmol) were then added, and the cap was applied to seal the vial. The vessel was heated at 100 °C for 6 h. After being cooled to rt, the crude mixture was filtered through a pad of celite. The filtrate was analyzed by ^{1}H-NMR using 1,3,5-trimethoxybenzene (6.9 mg) as an internal standard, which revealed that **2c**, **2e**, **2f** and **2a** were formed in 27%, 33%, 16% and 17%, respectively.

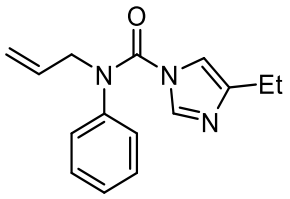
VIII-7-2. C-C bond formation reaction



In a glovebox filled with nitrogen, $Pd(PPh_3)_4$ (11.5 mg, 0.010 mmol), dcype (5.1 mg, 0.012 mmol) and THF (1.0 mL) were added to a 10 mL vial with a Teflon-sealed screwcap, and stirred for 5 min at rt. A mixture of **5b** (41.2 mg, 0.090 mmol), **5d** (29.6 mg, 0.097 mmol) and K_3PO_4 (27.1 mg, 0.20 mmol) were then added, and the cap was applied to seal the vial. The vessel was heated at 100 °C for 6 h. After being cooled to rt, the crude mixture was filtered through a pad of celite. The filtrate was analyzed by ^{1}H-NMR using 1,3,5-trimethoxybenzene (13 mg) as an internal standard, which revealed that **6b**, **6d**, **6e** and **6g** were formed in 28%, 29%, 21% and 16%, respectively.

VIII-8. Order of *N*-allylation and elimination of isocyanate in the UFC

***N*-Allyl-4-ethyl-*N*-phenyl-1*H*-imidazole-1-carboxamide (1at).**



1at

Urea **1at** was prepared with General Procedure A using 4-ethylimidazole (4.3 g, 4.7 mmol).

Yellow oil (1.3 g, 90%). R_f 0.10 (SiO_2, hexane/EtOAc = 1/1).

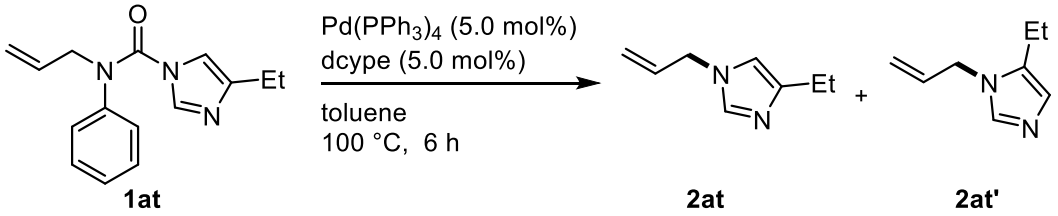
^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.45 (s, 1H), 7.39–7.29 (m, 3H), 7.12–7.10 (m, 2H), 6.56 (d, *J* = 0.9 Hz, 1H), 6.02–5.92 (m, 1H), 5.23–5.18 (m, 2H), 4.43 (d, *J* = 6.4 Hz, 2H), 2.42 (q, *J* = 7.5 Hz, 2H), 1.07 (t, *J* = 7.6 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 150.1, 144.5, 141.9, 137.3, 132.0, 130.1, 128.2, 126.8, 119.1, 113.6, 55.3, 21.4, 13.0.

IR (KBr, cm^{-1}): 2360 w, 2342 w, 1697 s, 1653 w, 1646 w, 1595 w, 1506 w, 1494 m, 1474 w, 1456 m, 1434 m, 1419 m, 1396 s, 1361 w, 1293 m, 1265 s, 1226 w, 1038 w, 1026 w, 753 m, 700 m.

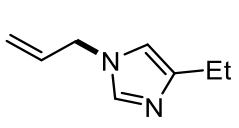
MS, m/z (relative intensity, %): 255 (M^+, 28), 240 (21), 161 (13), 160 (88), 132 (62), 119 (17), 77 (12), 41 (100).

HRMS (DART) *m/z* [M+H^+] calcd for $C_{15}H_{18}N_3O$: 256.1444, found: 256.1444.

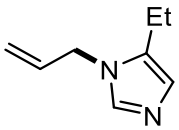


In a glovebox filled with nitrogen, $Pd(PPh_3)_4$ (11.7 mg, 0.010 mmol), dcype (4.6 mg, 0.010 mmol) and toluene (1.0 mL) were added to a 10 mL vial with a Teflon-sealed screwcap, and stirred for 5 min at rt. Urea **1at** (51 mg, 0.20 mmol) was then added, and the cap was applied to seal the vial. The vessel was heated at 100 °C for 6 h. After being cooled to rt, the crude mixture was filtered through a pad of celite. The filtrate was concentrated *in vacuo* to give a residue, which was analyzed by ^{1}H-NMR using 1,3,5-trimethoxybenzene (17 mg) as an internal standard. This analysis revealed that **2at** and **2at'** were formed in 83% combined yield with a ratio of 2.3:1, respectively. The crude product was purified by flash column chromatography over silica gel to give a mixture of allylamine **2at** and **2at'** as a colorless oil (18 mg, 66%).

1-Allyl-4-ethyl-1*H*-imidazole (2at and 2at')



2at



2at'

Colorless oil (18 mg, 66%). R_f 0.030 (SiO_2, EtOAc).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.40 (s, 1H: **2at'**), 7.37 (s, 1H: **2at**), 6.78 (s, 1H: **2at'**), 6.61 (s, 1H: **2at**), 5.98–5.89 (m, 1H + 1H: **2at** and **2at'**), 5.26–5.15 (m, 2 H+1H: **2at** and **2at'**), 4.98 (d, *J* = 16 Hz, 1H: **2at'**), 4.48–4.44 (m, 2H + 2H: **2at** and **2at'**), 2.59 (q, *J* = 8.2 Hz, 2H: **2at**), 2.51 (q, *J* = 7.3 Hz, 2H: **2at'**), 1.25 (t, *J* = 7.3 Hz, 3H: **2at'**), 1.25 (t, *J* = 8.2 Hz, 3H: **2at**).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 145.18, 136.33, 133.17, 118.48, 117.65, 114.50, 49.49 (**2au**), 46.98 (**2at'**), 21.81 (**2at**), 17.35 (**2at'**), 13.70 (**2at**), 12.51 (**2at'**).

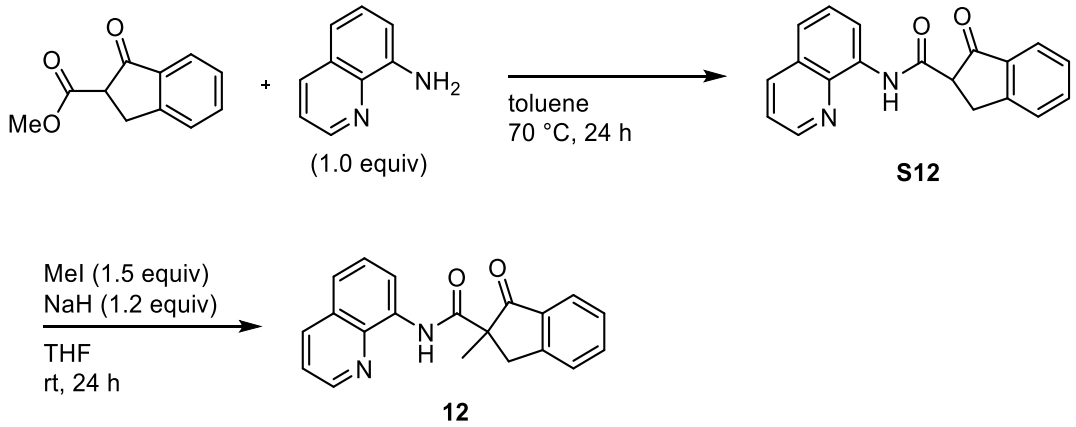
IR (KBr, cm^{-1}): 2970 m, 2931 m, 2853 w, 1498 s, 1445 m, 1421 w, 1247 w, 1227 w, 1159 m, 1109 m, 995 m, 923 m, 817 m, 756 w, 665 m.

MS, m/z (relative intensity, %): 136 (M^+, 61), 135 (21), 121 (100), 95 (45), 94 (15), 81 (14), 68 (11), 67 (14), 54 (12), 41 (92).

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_8H_{13}N_2$: 137.1073, found: 137.1073.

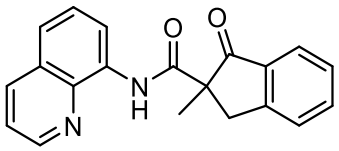
IX. Synthetic Application via Directed C(sp^3)–H Arylation

IX-1. Procedure for synthesis of 12



Methyl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (7.8 g, 40 mmol)[11] and 8-aminoquinoline (6.0 g, 40 mmol) in toluene (100 mL) were stirred at 70 °C for 24 h. After being cooled to rt, the solution was concentrated and resulting crude product was purified by flash chromatography (hexane/EtOAc = 9/1) to give 8-aminoquinolinyl amide **S12** as brown solid (3.5 g, 29%). This material was used in the next step without further purification. 8-Aminoquinolino amide **S12** (1.7 g, 5.5 mmol) was added slowly to a suspension of NaH (300 mg, 8.3 mmol, 60% dispersion in mineral oil) in THF (20 mL), and MeI (0.50 mL, 6.6 mmol) was then added dropwise. The reaction was stirred at rt for 12 h, and H_2O was then added. The mixture was extracted with EtOAc, and the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The resulting crude product was purified by flash chromatography (hexane/EtOAc = 9/1) to give amide **12** as colorless solid (1.35 g, 77%).

2-Methyl-1-oxo-*N*-(quinolin-8-yl)-2,3-dihydro-1*H*-indene-2-carboxamide (12).



12

Colorless solid (1.4 g, 77%). Mp 124 °C. R_f 0.48 (SiO_2, hexane/EtOAc = 3/1).

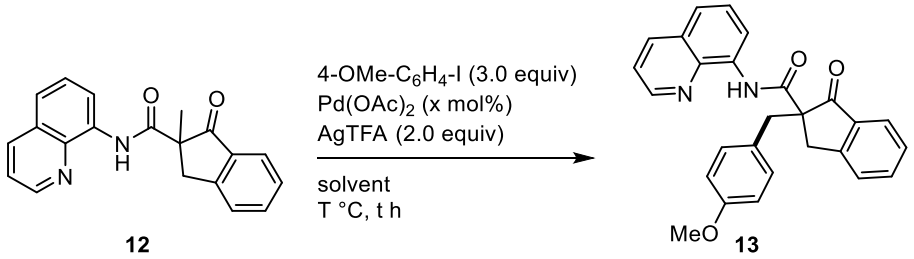
^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 11.35 (s, 1H), 9.00 (dd, *J* = 4.4 Hz, 1H), 8.75 (t, *J* = 4.6 Hz, 1H), 8.16 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.85 (d, *J* = 7.8 Hz, 1H), 7.66 (td, *J* = 7.8, 1.1 Hz, 1H), 7.55–7.51 (m, 3H), 7.50–7.46 (m, 1H), 7.41 (t, *J* = 7.1 Hz, 1H), 4.22 (d, *J* = 17.9 Hz, 1H), 3.10 (d, J = 17.9 Hz, 1H), 1.80 (s, 3H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 206.8, 169.5, 153.1, 148.9, 139.2, 136.4, 136.0, 134.4, 136.0, 128.2, 127.9, 127.3, 126.8, 125.1, 122.0, 121.7, 117.0, 57.9, 38.3, 26.3.

IR (ATR, cm^{-1}): 3329 m, 2930 m, 2870 w, 2342 w, 1681 s, 1587 w, 1487 w, 1420 m, 1377 m, 1299 w, 1265 m, 1216 m, 1158 2, 1078 m, 971 s, 916 s, 806 m, 756 s, 715 m, 679 m, 557 m.

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{20}H_{17}N_2O_2$: 317.1285, found: 317.1287.

IX -2-1. Optimization for palladium-catalyzed C(sp^3)-H arylation of 12



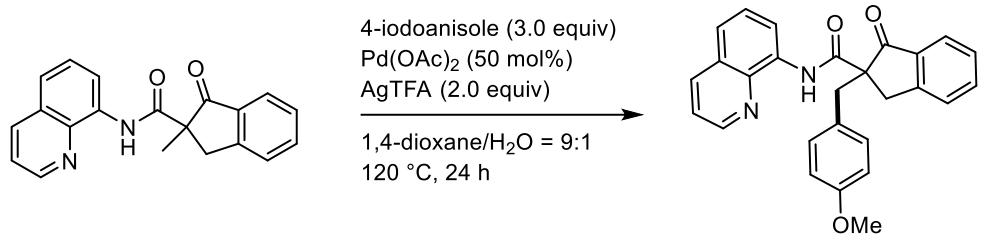
Entry	x (mol%)	solvent	T (°C)	t (h)	isolated yields (%) A	SM
1	10	TCE/H_2O=1:1	rt	60	0	81
2	10	TCE/H_2O=1:1	90	24	5	81
3	50	TCE/H_2O=1:1	90	24	20	46
4	50	dioxane/H_2O=9:1	90	24	30	36
5	50	TCE/H_2O=1:1	90	48	29	51
6	50	dioxane/H_2O=9:1	90	48	37	32
7	25	dioxane/H_2O=9:1	90	24	24	trace
	then 25	dioxane/H_2O=9:1	90	24		
8	50	dioxane/H_2O=9:1	120	24	45	32
9	50	dioxane/H_2O=9:1	120	48	34	15

Figure S5. Optimization for Palladium-Catalyzed C(sp^3)-H Arylation

The aminoquinolinyl amide-directed C(sp^3)–H bond activation reactions were optimized according to literature

procedures.[17] As the result of these optimization studies, the conditions shown in entry 8 of Figure S5 was found to be most efficient.

IX -2-2. Procedure for palladium-catalyzed C(sp^3)-H arylation of 12

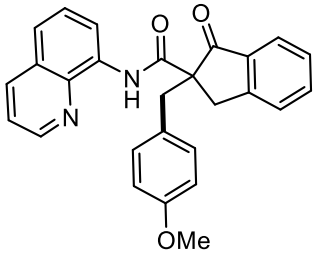


12 **13**

45%

$Pd(OAc)_2$ (24.0 mg, 0. 10 mmol), 4-iodoanisole (147 mg, 0.60 mmol), AgTFA (8.8 mg, 0.40 mmol), **12** (69 mg, 0.20 mmol) and 1,4-dioxane/H_2O = 9/1 (2.0 mL) were added to a 10 mL vial with a Teflon-sealed screwcap, and the cap was applied to seal the vial. The vessel was heated at 120 °C for 24 h, then cooled to rt. H_2O and Et_2O were added, and the organic extracts were washed with H_2O several times. The organic extracts were dried over anhydrous Na_2SO_4. The filtrate was then concentrated *in vacuo.* The crude product was purified by flash column chromatography over silica gel to give allylamine **13** as a colorless solid (0.38 g, 45%).

2-(4-Methoxybenzyl)-1-oxo-*N*-(quinolin-8-yl)-2,3-dihydro-1*H*-indene-2-carboxamide (13).



13

Pale yellow solid (0.38 g, 45%). Mp 159 °C. R_f 0.54 (SiO_2, hexane/EtOAc = 3/1).

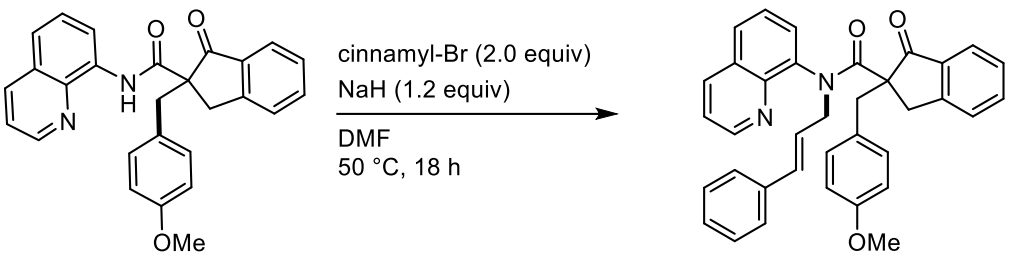
^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 11.52 (s, 1H), 9.03 (dd, *J* = 4.0, 2.0 Hz, 1H), 8.74 (t, *J* = 4.6 Hz, 1H), 8.17 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.80 (d, *J* = 7.8 Hz, 1H), 7.59–7.48 (m, 4H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.34 (t, *J* = 7.3 Hz, 1H), 7.07 (d, *J* = 8.0 Hz, 2H), 6.68 (dt, *J* = 9.3, 2.5 Hz, 2H), 4.05 (d, *J* = 17.9 Hz, 1H), 3.70 (s, 3H), 3.43 (q, *J* = 8.0 Hz, 2H), 3.24 (d, J = 17.9 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 206.3, 168.0, 158.8, 153.7, 149.0, 139.3, 136.3, 135.9, 135.3, 134.9, 131.0, 128.2, 127.8, 127.7, 127.3, 126.6, 124.8, 122.0, 121.8, 116.8, 113.8, 63.6, 55.2, 44.3, 34.2.

IR (KBr, cm^{-1}): 3064 m, 3030 w, 2960 w, 2937 m, 2837 m, 1682 s, 1595 m, 1512 s, 1463 m, 1384 s, 1325 m, 1302 m, 1243 s, 1195 m, 1182 s, 1050 m, 913 s, 841 m, 815 w, 791 s, 742 s, 647 w.

HRMS (DART) *m/z* [M+H^+] calcd for $C_{27}H_{23}N_2O_3$: 423.1703, found: 423.1711.

IX -3. Procedure for generation of 14 via *N*-alkylation of 13

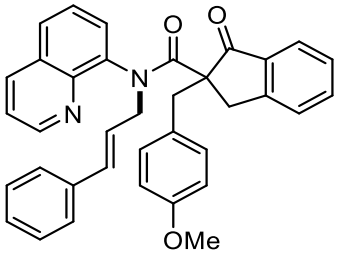


13 **14**

43%

C-H activation product **13** (0.42 g, 1.0 mmol) was added slowly at 0 °C to a suspension of NaH (48 mg, 1.2 mmol, 60% dispersion in mineral oil) in DMF (20 mL). The mixture was stirred at rt for 1 h, and cinnamyl bromide (0.39 mg, 2.0 mmol) was added dropwise. The reaction was stirred at 50 °C for 18 h and then H_2O and Et_2O were added. The organic extracts were washed with H_2O several times, dried over anhydrous Na_2SO_4 and filtered. The filtrate was then concentrated *in vacuo.* The residue was purified by flash column chromatography over silica gel to give allylamine **14** as a yellow oil (0.23 g, 43%).

***N*-Cinnamyl-2-(4-methoxybenzyl)-1-oxo-*N*-(quinolin-8-yl)-2,3-dihydro-1*H*-indene-2-carboxamide (14)**



14

Yellow oil (0.23 mg, 43%). R_f 0.20 (SiO_2, hexane/EtOAc = 1/1).

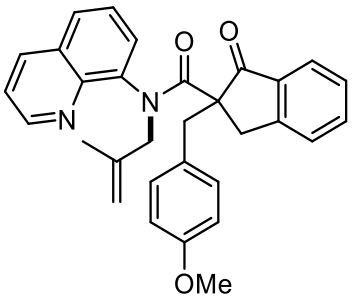
^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 8.89 (dd, *J* = 4.0, 2.0 Hz, 1H), 7.76 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.34 (dd, *J* = 7.3, 1.4 Hz, 1H), 7.28–7.22 (m, 6H), 7.21–7.16 (m, 1H), 7.09 (t, *J* = 7.8 Hz, 1H), 7.03–7.00 (m, 1H), 6.90 (d, *J* = 8.7 Hz, 2H), 6.84–6.76 (m, 2H), 6.48 (d, *J* = 8.7 Hz, 2H), 6.44–6.38 (m, 1H), 6.19–6.15 (m, 2H), 5.27 (dd, *J* = 14.2, 4.6 Hz, 1H), 3.85 (dd, *J* = 14.7, 8.2 Hz, 1H), 3.56 (s, 3H), 3.54–3.47 (m, 3H), 2.83 (d, *J* = 18.3 Hz, 1H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 206.5, 172.1, 158.0, 152.0, 150.4, 144.7, 136.9, 136.6, 136.1, 136.0, 135.8, 133.4, 133.3, 131.8, 129.6, 128.8, 128.5, 128.0, 127.5, 126.5, 126.2, 125.6, 125.0, 124.1, 123.0, 121.3, 113.0, 61.1, 55.0, 54.0, 41.4, 35.4.

IR (KBr, cm^{-1}): 2911 w, 2360 s, 2342 s, 1733 w, 1715 s, 1699 s, 1684 w, 1670 w, 1652 m, 1546 w, 1636 m, 1609 m, 1558 m, 1540 m, 1508 s, 1497 m, 1489 w, 1464 m, 1448 w, 1419 w, 1249 m, 1034 m, 792 w, 722 w, 668.

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{36}H_{31}N_2O_3$: 539.2329, found: 539.2333.

2-(4-Methoxybenzyl)-*N*-(2-methylallyl)-1-oxo-*N*-(quinolin-8-yl)-2,3-dihydro-1*H*-indene-2-carboxamide (16).



16

Yellow oil (0.13 mg, 26%). R_f 0.47 (SiO_2, hexane/EtOAc = 1/1).

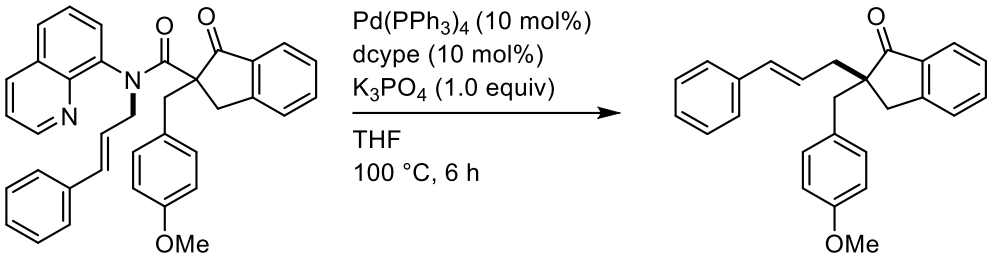
^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 8.87 (dd, *J* = 2.0, 6.0 Hz, 1H), 7.76 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.37 (dd, *J* = 7.3, 1.8 Hz, 1H), 7.27–7.23 (m, 2H), 7.10 (t, *J* = 7.8 Hz, 1H), 7.04–7.02 (m, 1H), 6.88 (d, *J* = 8.7 Hz, 2H), 6.83–6.79 (m, 2H), 6.46 (d, *J* = 8.7 Hz, 2H), 6.16–6.14 (m, 1H), 5.30 (d, *J* = 15.1 Hz, 1H), 4.78 (s, 1H), 4.63 (s, 1H), 3.56–3.34 (m, 7H), 2.77 (d, *J* = 18.3 Hz, 1H), 1.87 (s, 3H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 206.8, 172.2, 158.0, 151.9, 150.4, 144.7, 141.3, 136.8, 136.0, 136.0, 135.78, 133.4, 131.8, 129.5, 128.7, 128.0, 126.2, 125.6, 124.2, 123.0, 121.2, 113.3, 113.0, 61.0, 57.2, 55.1, 41.6, 35.2, 20.7.

IR (KBr, cm^{-1}): 2961 m, 2834 m, 1697 s, 1646 s, 1609 m, 1514 s, 1496 m, 1466 m, 1423 m, 1389 m, 1273 w, 1246 m, 1185 s, 1122 w, 1037 s, 970 m, 923 m, 914 w, 902 m, 855 m, 832 m, 808 m, 795 s, 760 m, 746 s.

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{31}H_{29}N_2O_3$: 477.2173, found: 477.2180.

IX -4. Procedure for palladium-catalyzed elimination of isocyanate to 15 from 14

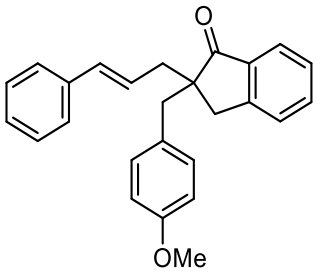


14 **15**

86%

In a glovebox filled with nitrogen, $Pd(PPh_3)_4$ (20 mg, 0.017 mmol), dcype (7.2 mg, 0.017 mmol) and THF (1.0 mL) were added to a 10 mL vial with a Teflon-sealed screwcap, and stirred for 5 min at rt. Amide **14** (92 mg, 0.17 mmol) and K_3PO_4 (36 mg, 0.17 mmol) were then added, and the cap was applied to seal the vial. The vessel was heated at 100 °C for 6 h. After being cooled to rt, the crude mixture was filtered through a pad of celite, and the filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography over silica gel to give **15** as a colorless oil (54 mg, 86%).

2-Cinnamyl-2-(4-methoxybenzyl)-2,3-dihydro-1*H*-inden-1-one (15).



15

Colorless oil. (54 mg, 86%). R_f 0.55 (SiO_2, hexane/EtOAc = 4/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.01 (d, *J* = 7.8 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 1H), 7.31–7.15 (m, 7H), 7.04 (d, *J* = 8.7 Hz, 2H), 6.71 (d, *J* = 8.7 Hz, 2H), 6.41 (d, *J* = 15.6 Hz, 1H), 6.02–5.94 (m, 1H), 3.72 (s, 3H), 3.15–3.08 (m, 2H), 3.00 (d, *J* = 17.4 Hz, 1H), 2.81 (d, *J* = 13.3 Hz, 1H), 2.67 (dd, *J* = 6.9, 6.0 Hz, 1H), 2.46 (dd, *J* = 13.7, 8.2 Hz, 1H).

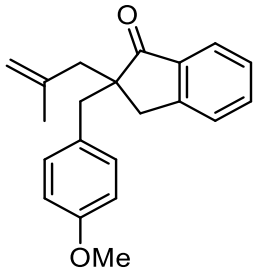
^{13}C NMR ($CDCl_3$, 100.53 MHz) δ 210.5, 158.3, 153.2, 137.3, 136.8, 135.0, 133.6, 131.3, 129.5, 128.5, 127.4, 127.3, 126.5, 126.2, 125.4, 124.0, 113.6, 55.3, 54.6, 42.0, 41.7, 35.6.

IR (KBr, cm^{-1}):2360 s, 2342 s, 1715 s, 1699 s, 1684 m, 1652 m, 1646 w, 1636 w, 1609 m, 1558 m, 1540 m, 1508 s, 1497 m, 1489 m, 1473 m, 1464 m, 1457 m, 1436 m, 1295 m, 1249 s, 1179 m, 1034 m, 968 w, 736 m, 693 m, 668 w.

MS, m/z (relative intensity, %): 368 (M^+, 2.7), 247 (18), 121 (100), 117 (20), 115 (16), 91 (16).

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{26}H_{25}O_2$: 369.1849, found: 369.1854.

2-(4-Methoxybenzyl)-2-(2-methylallyl)-2,3-dihydro-1*H*-inden-1-one (17).



17

Colorless oil. (29 mg, 46%). R_f 0.60 (SiO_2, hexane/EtOAc = 1/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.67 (d, *J* = 7.8 Hz, 1H), 7.49–7.45 (m, 1H), 7.29–7.25 (m, 2H), 6.99 (dd, *J* = 11.4, 2.7 Hz, 2H), 6.67 (dt, *J* = 9.3, 2.5 Hz, 2H), 4.68 (d, *J* = 34.3 Hz, 2H), 3.70 (s, 3H), 3.14–2.99 (m, 3H), 2.72 (d, *J* = 13.3 Hz, 1H), 2.64 (d, *J* = 13.3 Hz, 1H), 2.37 (d, *J* = 13.7 Hz, 1H) 1.50 (s, 3H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 210.9, 158.2, 153.5, 142.4, 137.0, 134.8, 131.4, 129.3, 127.3, 126.4, 123.9, 115.1, 113.5, 55.2, 53.8, 45.7, 43.5, 35.2, 24.2.

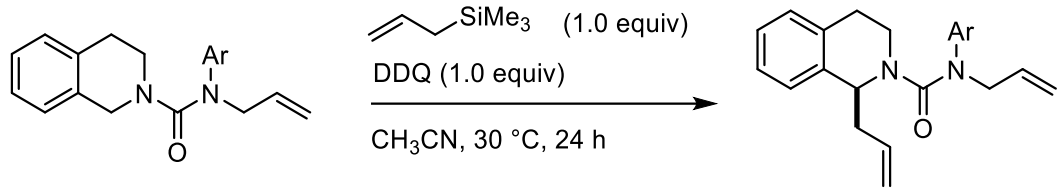
IR (KBr, cm^{-1}):2933 w, 2913 w, 1707 s, 1609 m, 1511 s, 1463 w, 1439 w, 1298 w, 1248 m, 1179 w, 1035 w, 894 w, 739 m.

MS, m/z (relative intensity, %): 306 (M^+, 6.3), 251 (45), 250 (50), 122 (82), 121 (100), 115 (16), 91 (18), 78 (12), 77 (21).

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{21}H_{23}O_2$: 307.1693, found: 307.1690.

X. Synthetic Application via Oxidative α-Functionalization of Cyclic Amines

X-1. Procedure for oxidative α-functionalization of cyclic amine 1ah-CF_3[18]

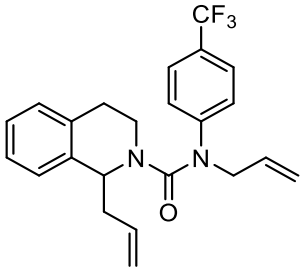


1ah-CF_3
Ar = *p*-C_6H_4-CF_3

18
88%

A 100 mL two-necked flask with a magnetic stirring bar was evacuated and backfilled with nitrogen three times. *N*-allylurea derivative **1ah-CF_3** (2.2 g, 6.6 mmol), DDQ (2.1 g, 6.66 mmol) and dry MeCN (50 mL) were added to the flask. The mixture was cooled at 0 °C and allyltrimethylsilane (1.3 mL, 9.0 mmol) was slowly added to the flask. The reaction was stirred at room temperature overnight, and the reaction mixture was concentrated in vacuum to give crude product. The crude product was purified by flash chromatography (Hexane/EtOAc = 9/1) to give protected α-allylamine **18** as yellow oil (2.34 g, 88%).

***N*,1-Diallyl-*N*-(4-(trifluoromethyl)phenyl)-3,4-dihydroisoquinoline-2(1*H*)-carboxamide (18)**



18

Yellow oil. (2.34 g, 88%). R_f 0.24 (SiO_2, hexane/EtOAc = 9/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.47 (d, *J* = 8.7 Hz, 2H), 7.18–7.10 (m, 4H), 7.06–6.97 (m, 2H), 5.97–5.80 (m, 2H), 5.25–5.04 (m, 5H), 4.39–4.319 (m, 2H), 3.80 (dd, *J* = 13.5, 4.4 Hz, 1H), 3.27–3.20 (m, 1H), 2.71 (dd, *J* = 11.0, 6.4 Hz, 1H), 2.64–2.54 (m, 3H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 159.9, 148.8, 136.7, 135.3, 134.6, 133.4, 128.9, 127.1, 126.8, 126.5 (q, J_{CF} = 3.83 Hz), 126.1, 125.5 (q, J_{CF} = 32.6 Hz), 124.2 (q, J_{CF} = 271.3 Hz), 122.3, 117.7, 117.1, 55.44, 54.1, 41.3, 39.9, 28.2.

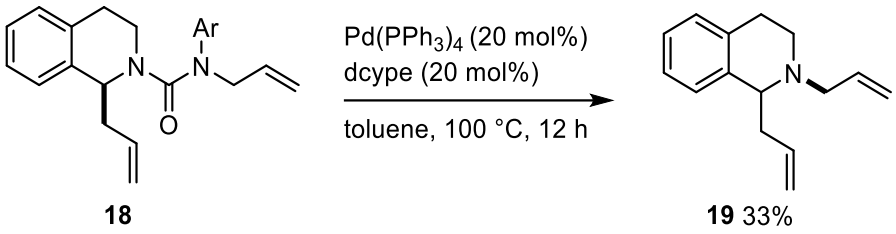
^{19}F NMR ($CDCl_3$, 376 MHz) δ: -63.3.

IR (KBr, cm^{-1}): 3077 w, 2930 w, 1656 s, 1614 s, 1581 w, 1519 m, 1493 w, 1430 m, 1325 s, 1294 m, 1243 w, 1218 m, 1191 w, 1165 m, 1117 s, 1070 s, 919 m, 841 m, 763 m, 746 m, 610 w.

MS, m/z (relative intensity, %): 400 (M$^+$, 0), 360 (27), 359 (95), 228 (55), 172 (11), 132 (16), 131 (20), 130 (38), 129 (11), 103 (12), 41 (100).

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{23}H_{24}N_2OF_3$: 401.1835, found: 401.1840.

X-2. Procedure for palladium-catalyzed elimination of isocyanate to 19 from 18

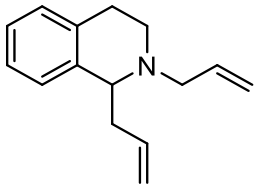


18 **19** 33%

Ar = *p*-C_6H_4-CF_3

In a glovebox filled with nitrogen, $Pd(PPh_3)_4$ (45 mg, 0.040 mmol), dcype (18 mg, 0.040 mmol) and toluene (1.0 mL) were added to a 10 mL vial with a Teflon-sealed screwcap, and stirred for 5 min at rt. Protected α-allylamine **18** (80 mg, 0.20 mmol) were then added, and the cap was applied to seal the vial. The vessel was heated at 100 °C for 12 h, then cooled at rt. To quench the generated isocyanate **7**, $^tBuNH_2$ (0.10 mL) were added to the reaction vessel and then stirred at 70 °C for 5 h. Ant then, the crude mixture was filtered through a pad of Celite. The filtrate was then concentrated *in vacuo*. The crude product was purified by flash column chromatography over silica gel to give α-allylated cyclic amine **19** as a colorless oil (14 mg, 33%).

1,2-Diallyl-1,2,3,4-tetrahydroisoquinoline (19) CAS [287480-38-0]



19

Colorless oil (14 mg, 33%). R_f 0.57 (SiO_2, hexane/EtOAc = 3/1).

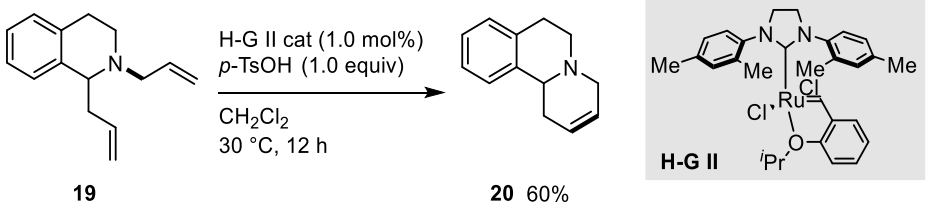
^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.15–7.04 (m, 4H), 5.96–5.86 (m, 2H), 5.21–5.13 (m, 2H), 5.07–5.02 (m, 2H), 3.78 (t, *J* = 6.4 Hz, 1H), 3.28–3.19 (m, 3H), 2.93–2.84 (m, 2H), 2.67–2.55 (m, 2H), 2.49–2.44 (m, 1H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 138.1, 136.8, 136.5, 134.7, 129.0, 128.0, 126.1, 125.7, 117.3, 116.0, 60.3, 57.0, 44.0, 40.1, 25.2.

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{15}H_{20}N$: 214.1590, found: 214.1590.

X-3. Procedure for ring-closing metathesis of 19

Benzodehydro[*a*]quinolidine 20.[19]

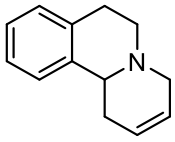


19 **20** 60%

In a glovebox filled with nitrogen, *p*-TsOH (20 mg, 0.16 mmol), α-allylated cyclic amine **19** (33 mg, 0.16 mmol) and dry CH_2Cl_2 (1.0 mL) were added to a 10 mL vial with a Teflon-sealed screwcap and stirred for 30 min at rt. Hoveyda-

Grubbs catalyst II (2.0 mg, 1.0 mol%) was then added, and the cap was applied to seal the vial. The vessel was stirred at 30 °C for 15 h, then cooled at rt and the crude mixture was filtered through a pad of Celite. The filtrate was then concentrated *in vacuo*. The crude product was purified by flash column chromatography over silica gel to give compound **20** as a colorless oil (17.7 mg, 60%).

1,6,7,11b-Tetrahydro-4*H*-pyrido[2,1-*a*]isoquinoline (20).



20

Colorless oil. (17.7 mg, 60%). R_f 0.18 (SiO_2, hexane/EtOAc = 1/3).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.26-7.10 (m, 4H), 5.87-5.76 (m, 2H), 3.55-3.38 (m, 2H), 3.24-3.02 (m, 3H), 2.73-2.52 (m, 3H), 2.26-2.17 (m, 1H).

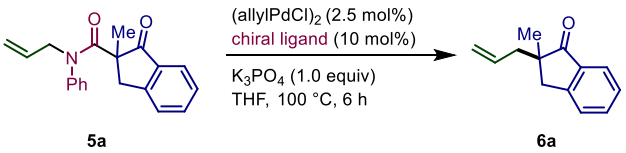
^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 138.3, 134.6, 128.9, 126.1, 126.0 (two overlapping peaks), 125.6, 125.5 (two overlapping peaks), 125.4, 59.2, 55.5, 51.4, 33.5, 29.6.

IR (KBr, cm^{-1}): 2923 s, 1652 w, 1558 w, 1539 w, 1520 w, 1455 m, 1324 m, 1101 w, 734 s, 658 m.

MS, m/z (relative intensity, %): 185 (M^+, 44), 184 (35), 132 (10), 131 (71), 130 (100), 115 (11), 104 (21), 103 (17), 78 (10), 77 (15).

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{13}H_{16}N$: 186.1277, found: 186.1279.

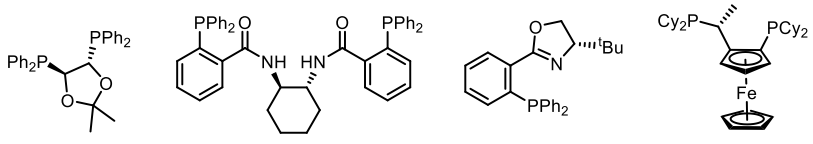
XI. Palladium-Catalyzed Elimination of Isocyanate from *N*-Allyl-β-Ketoamide Derivatives Using a Chiral Ligand



5a **6a**

entry	ligand	solvent	NMR yield [%]	ee [%]
1	**L1**	THF	28	-
2	**L2**	THF	n.d.	-
3	**L3**	THF	n.d.	-
4	**L4**	THF	70	5
5	**L4**	toluene	64	10

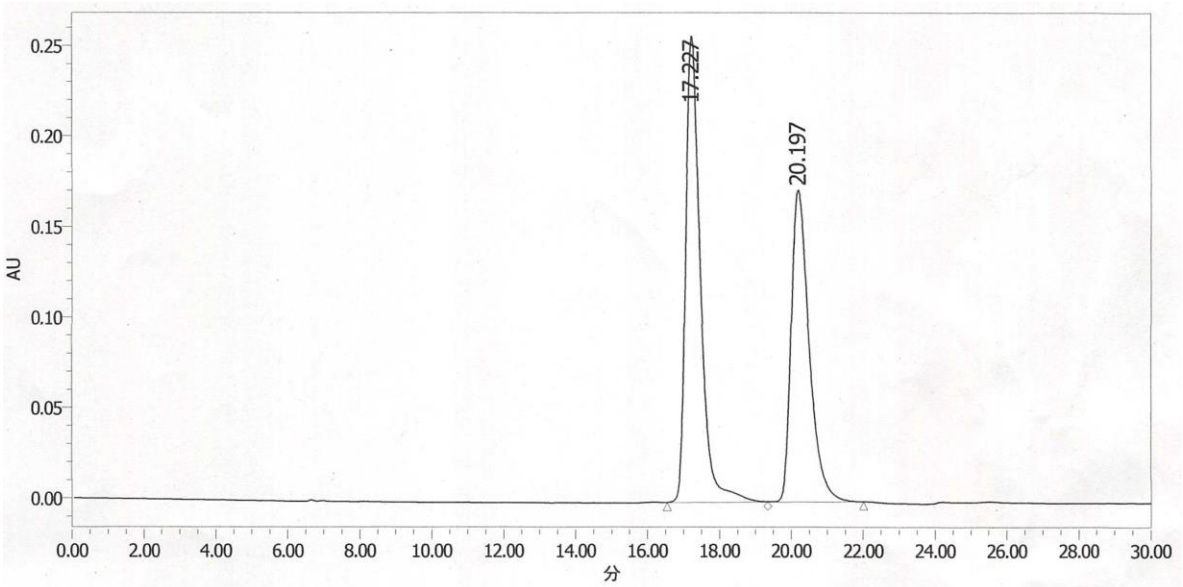
chiral ligands:



L1 **L2** **L3** **L4**

In a glovebox filled with nitrogen, (allylPdCl)$_2$ (11.6 mg, 0.010 mmol), dcype (4.2 mg, 0.010 mmol) toluene (1.0 mL) are added to a 10 mL vial with a Teflon-sealed screwcap, and stirred for 5 min at rt. Amide **5a** (61.1 mg, 0.20

mmol) and K_3PO_4 (27.6 mg, 0.20 mmol) were then added, and the cap was applied to seal the vial and the vessel was heated at 100 °C for 6 h. After being cooled to rt, the crude mixture was filtered through a pad of celite, and the filtrate was concentrated *in vacuo.* The residue was analyzed by ^{1}H-NMR using 1,3,5-trimethoxybenzene (17 mg) as an internal standard. The residue was purified by flash column chromatography over silica gel to give indanone derivative **6a** as a yellow solid (23.9 mg, 64%). The enantiomeric excess was determined by HPLC analysis[22] (CHIRALCEL OB-H column, 99:1 hexane/Isopropanpl, 0.5 mL/min, 6a-A: tR = 17.2 min, 6a-B: tR = 20.2 min, UV detection at 220 nm, 30 °C).



	Ret. time (min)	Area (μVs)	%Area	height (μV)
1	17.227	7315975	55.02	257703
2	20.197	5980188	44.98	172304

Figure S6. Chiral HPLC Chart of **6a** using a chiral phosphine ligand **L4**.

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Chapter 2

Palladium-Catalyzed Unimolecular Fragment Coupling of *N*-Allylamides Bearing a Tethered Nucleophile with the Translocation of an Amide Group

2.1. Introduction

In contrast to the fact that a myriad of methods are available for constructing frameworks of a wide variety of molecules, the development of methods for modifying them lags far behind, despite the great demand for late-stage molecular transformations in organic synthesis.[1] The difficulty of editing molecular frameworks is largely attributed to the inertness of chemical bonds that constitute the frameworks, as represented by C–C bonds. However, advancements in activating strong bonds by transition metal catalysts[2] as well as the renaissance associated with photochemistry has allowed notable developments of methods for editing molecular frameworks. Methods that have been reported to date can be classified into three types: 1) insertion,[3–5] 2) deletion[6,7] and 3) substitution[8] (Figure 1a). Insertion is defined as a class of reactions, in which an atom or a group is inserted into the chemical bond that constitutes the framework of the substrate. Deletion is the reverse process of insertion, in which a new chemical bond is forged by the ejection of an atom or a group from the substrate with the remaining fragments being recombined. Decarbonylation[6a] and decarboxylation[6b,c] reactions are typical examples of deletion reactions. Substitution is a type of transformation that is a combination of deletion and insertion. Namely, an atom or a group is removed from the substrate backbone and a new component is inserted into the same site.[8] A new type of editing of molecular frameworks would be "cut-and-paste" type reactions, in which a fragment of the molecular skeleton is removed and is then attached to a different site in the molecule, thus resulting in the construction of a new molecular framework. Although this mode of editing is attractive, to the best of our knowledge, it has not been reported as a single step transformation.[9]

Our laboratory recently reported the palladium-catalyzed unimolecular fragment coupling (UFC) of amides, in which an amide moiety is deleted from the substrate (Figure 1b, top).[6e] In this reaction, an amide group is eliminated in the form of an isocyanate. In our preliminary study, the author also found that when amide substrates bearing an unprotected alcohol group are used, the eliminated isocyanate is trapped by the alcohol moiety (Figure 1b, bottom). The overall transformation is the catalytic translocation of an amide group, which can be viewed as a cut-and-paste type editing of a molecular framework. The author reports herein on a detailed investigation on this migratory UFC reaction of amides.

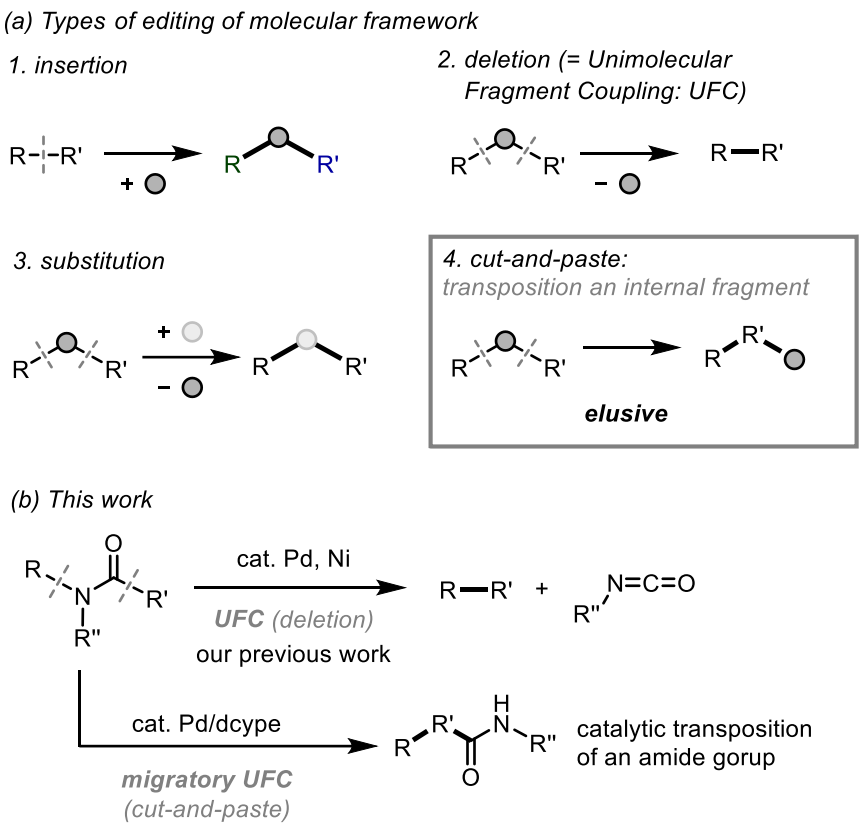


Figure 1. Types of editing of molecular frameworks and migratory UFC of amides.

2.2. Results and Discussion

In our previous investigation related to the palladium-catalyzed UFC of amides,[6e] the author found that, when a *N*-allylthiocarbamate bearing a primary alcohol group (i.e., **1a**) is used as a substrate, the eliminated isocyanate is trapped by the hydroxy group, resulting in the formation of the carbamate product **2a** in 68% yield (Figure 2).

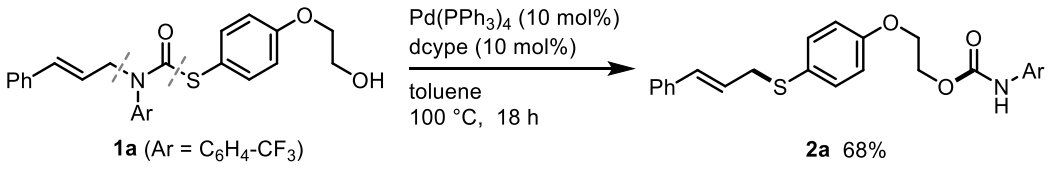
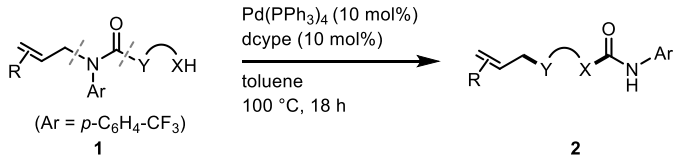


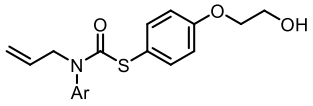
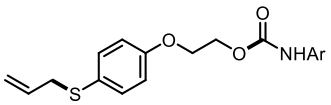
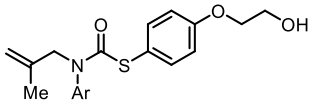
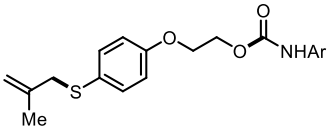
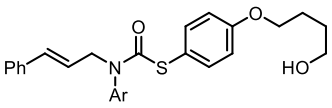
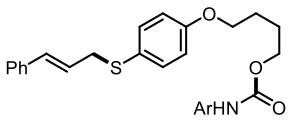
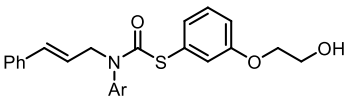
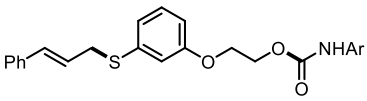
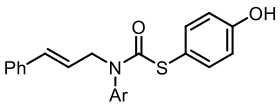
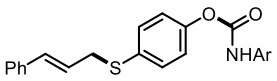
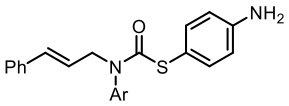
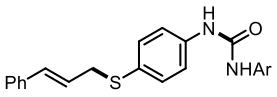
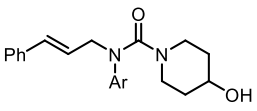
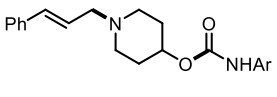
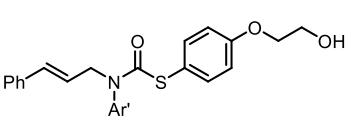
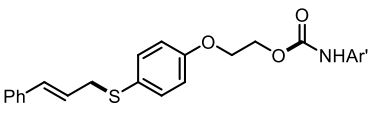
Figure 2. Pd-catalyzed unimolecular fragment coupling with translocation of an amide group.

On the basis of these preliminary results, the author examined the UFC reactions using *N*-allylamides bearing various tethered nucleophiles (Table 1). Regarding an allylic fragment, in addition to a cinnamyl derivative **1a**, non-substituted allyl (**1b**) and 2-methylallyl (**1c**) groups can also be used in the migratory UFC to form the corresponding *N*-allylthioesters **2b** and **2c**, respectively. Concerning the linker to tether a primary alcohol, a longer alkyl chain (**1d**) and a *meta*-phenylene group (**1e**) were also found to be acceptable, affording the translocated products **2d** and **2e**, respectively. Regarding the nature of the tethered nucleophile, not only primary alcohols but also phenolic hydroxy (**1d**) and aniline (**1e**) groups could be used to successfully capture the eliminated isocyanate (**2d**: 40% yield; **2e**: 61% yield). The author also found that this migratory UFC is not limited to C–S bond formation using N-

allylthiocarbamates, but C–N bond formation using urea derivatives is also possible. For example, *N*-allylurea with a secondary alcohol moiety (i.e., **1h**) participated in this reaction to yield carbamate **2h** in 59% yield. The author also examined the effect of the nitrogen substituent that is to be eliminated. Although the author routinely used *p*-$CF_3C_6H_4$ as a migrating group based on its efficient elimination behavior in our previous UFC studies, a simple phenyl group also functioned successfully, as exemplified by an efficient migratory UFC of **1i**. On the other hand, the reaction did not proceed efficiently when an electron-donating methoxy group was introduced to the migrating group (*i.e.*, **1j**), as was observed in our previous UFC reaction.[6e,10]

Table 1. Scope of Pd-catalyzed migratory UFC of *N*-allylamides



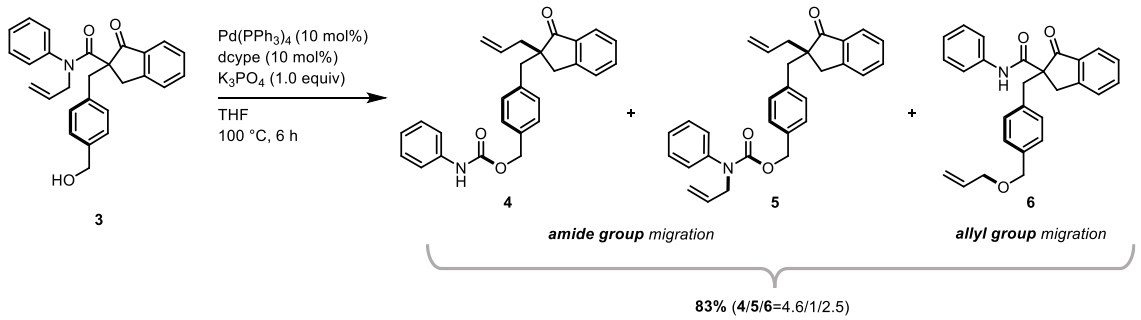
substrate	product
 **1b**	 **2b** 92%
 **1c**	 **2c** 65%
 **1d**	 **2d** 50%[b]
 **1e**	 **2e** 54%
 **1f**	 **2f** 40%
 **1g**	 **2g** 61%
 **1h**	 **2h** 59%[c,d]
 **1i** (Ar' = Ph) **1j** (Ar' = *p*-C6H4-OMe)	 **2i** 78% **2j** 15%

[a]Reaction conditions: **1** (0.10 mmol), $Pd(PPh_3)_4$ (0.010 mmol), dcype (0.010 mmol), in toluene (0.5 mL) for 18 h at 100 °C. [b]0.050 mmol scale. [c]0.20 mmol scale. [d]Run for 12 h at 140 °C.

The author next investigated the issue of whether this catalytic migratory UFC could be applied to C–C bond formation. Our previous study revealed that the use of *N*-allyl-β-ketoamide as a substrate allowed for the UFC of

amides to form a C–C bond.[6e] Therefore, the author envisioned that *N*-allyl-β-ketoamide with a primary alcohol moiety would also participate in this migratory UFC reaction with the formation of a C–C bond. When ketoamide **3** was reacted under the conditions used for C–C bond forming UFC reaction,[6e] the expected amide translocation product **4** was formed, along with a doubly allylated product (i.e., **5**), which was likely formed by the further reaction of **4** with another π-allylpalladium species (Figure 3). In addition, the *O*-allylated product **6** was formed as a minor product, presumably because the UFC of ketoamide substrates is slower than that for thiocarbamate or urea substrates **1**,[6e] thereby allowing the π-allylpalladium intermediate to react with a tethered alcohol. Compounds **4**/**5**/**6** were obtained in a combined yield of 83% with a ratio of 4.6/1/2.5.

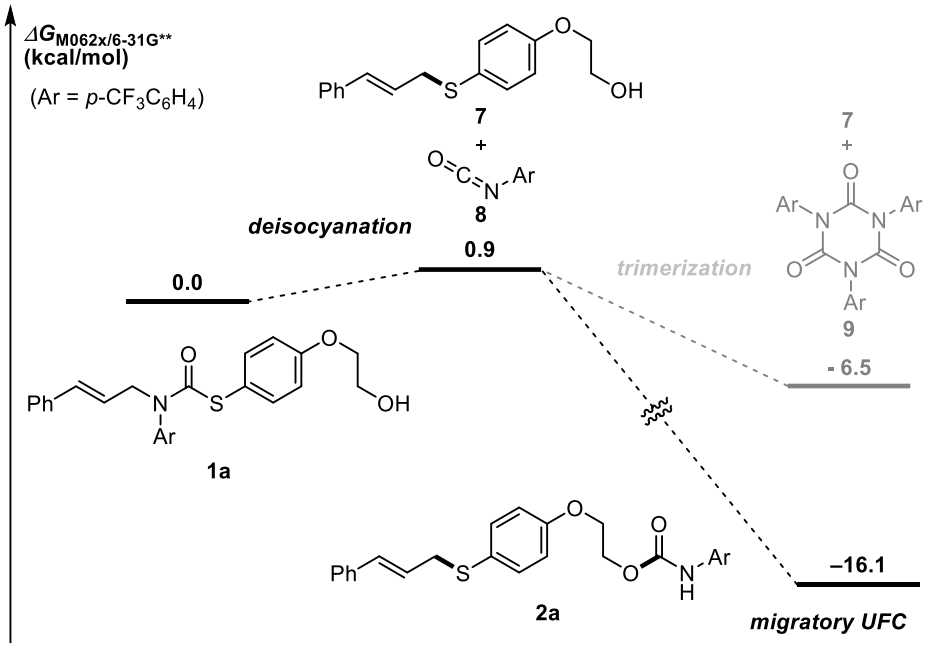
Figure 3. Pd-catalyzed C-C bond forming migratory UFC using β-ketoamides



[a] Reaction conditions: **3** (0.10 mmol), $Pd(PPh_3)_4$ (0.010 mmol), dcype (0.010 mmol), K_3PO_4 (0.10 mmol) in THF (1.0 mL) for 6 h at 100 °C.

In our deisocyanative UFC, the trimerization of the eliminated isocyanate to form a stable cyclic trimer (i.e., isocyanurate) serves as one of the driving forces for this reaction.[6e] In contrast, in this migratory UFC, the eliminated isocyanate is captured by a tethered nucleophile before it trimerizes. To obtain insights into the thermodynamics of these processes, the free energies of starting thiocarbamate **1a**, UFC product **7**, isocyanate **8**, cyclic trimer **9** and migratory UFC product **2a** were estimated by DFT calculations (Figure 4). Although the UFC process of **1a** to afford **7** and **8** is endothermic by 0.9 kcal/mol, the subsequent trimerization of **8** to **9** renders the overall process exothermic by 6.5 kcal/mol. The formation of **2a** by the intramolecular capture of **8** provides an even greater free energy gain of 17.0 kcal/mol, thereby making the migratory UFC a highly favored pathway ($\Delta G = -16.1$ kcal/mol).

Figure 4. Relative free energy changes in UFC and migratory UFC of **1a**



2.3. Conclusion

In conclusion, the author report on the palladium-catalyzed migratory UFC of *N*-allylamides bearing a tethered nucleophile, such as an alcohol. In this reaction, an amide moiety located in the middle of the molecular framework is removed and transferred to the end of the molecule. Additional developments of catalytic methods for use in this type of cut-and-paste editing of molecular frameworks is currently underway in our laboratory.

2.4. Experimental Section

I. General Information

^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a JEOL ECS-400 spectrometer in $CDCl_3$. The chemical shifts in ^{1}H NMR spectra were recorded relative to $CHCl_3$ (δ = 7.26). The chemical shifts in ^{13}C NMR spectra were recorded relative to $CDCl_3$ (δ = 77.16). The chemical shifts in ^{19}F NMR spectra were recorded relative to perfluorobenzene (δ = -163.0). The data is reported as follows: chemical shift (δ =) in ppm, coupling constant (Hz), and integration. Infrared spectra (IR) were obtained using a JASCO FT/IR-4200 spectrometer. Absorption is reported in reciprocal centimeters (cm-1) with the following relative intensities: s (strong), m (medium), or w (weak). High resolution mass spectra (HRMS) were obtained using a JEOL JMS-T100LP spectrometer. Melting points were determined using a Yamato melting point apparatus. Column chromatography was performed with Biotage Isolera® equipped with Biotage SNAP Ultra or SNAP Isolute NH_2 Cartridge. DFT calculations were performed with the Gaussian 09 (G09RevD.01) program. Geometry optimizations and frequency calculations for all reported structures were performed using the M06-2X density functional with the 6-31G(d.p) basis set. Compounds **1a**, **1f** and **1g** were prepared according to the previously reported procedure.6e See the Supporting Information for details of materials.

II. Materials

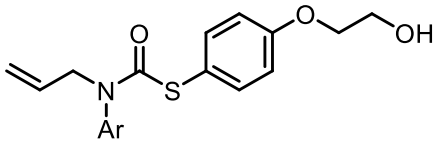
All commercially available reagents and solvents were supplied from TCI, WAKO and Aldrich. These

corresponding *N*-allylamine including *N*-allyl-4-(trifluoromethyl)aniline [CAS:949535-52-8],[1] *N*-cinnamylaniline [CAS:1142-24-1],[1] *N*-(2-methylallyl)aniline [CAS:22774-81-8],[1] *N*-cinnamyl-4-(trifluoromethyl)aniline [CAS:1191260-11-3],[2] were prepared according to literature procedures. Other compounds including, *S*-(4-hydroxyphenyl) cinnamyl(4-(trifluoromethyl)phenyl)carbamothioate (**1g**) [CAS:2792717-42-9],[3] *N*-cinnamyl-4-hydroxy-*N*-(4-(trifluoromethyl)phenyl)piperidine-1-carboxamide (**1f**) [2792717-34-9],[3] and 4-[(phenylmethylene)amino]benzenethiol [CAS:259875-34-8],[4] were also prepared according to our previously reported procedure.

III. Typical Procedure for *N*-Allylamide Derivatives (Ar = *p*-C_6H_4-CF_3)

A 100 mL two-necked flask with a magnetic stirring bar was evacuated and backfilled with nitrogen three times. After adding triphosgene (1.4 g, 5.0 mmol) and dry EtOAc (30 mL) to the flask, the mixture was cooled at 0 °C and pyridine (1.6 mL, 20 mmol) was slowly added to the flask. After stirring the mixture at 0 °C for 15 min, *N*-allyl-4-(trifluoromethyl)aniline (2.4 g, 10 mmol) was slowly added to the mixture. The mixture was warmed to rt and stirred for 6 h. The resulting mixture was carefully quenched by adding HCl (1 M, 15 mL) and was extracted with EtOAc (20 mL × 3). The organic layer was washed with H_2O, and then dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure to give the corresponding carbamoyl chloride as a dark oil. This material was used in the next step without further purification. 4-Mercaptophenol (1.4 g, 10 mmol) and Et_3N (3.4 mL, 20 mmol) were dissolved in THF (20 mL) and the mixture was stirred at rt for 15 min. To this mixture, carbamoyl chloride and DMAP (0.20 g, 1.5 mmol) were then added and was stirred at rt for 12 h. The resulting mixture was quenched with H_2O (10 mL) and extracted with EtOAc (20 mL× 3). The organic layer was washed H_2O (20 mL) and dried over Na_2SO_4. After filtration, the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (hexane/EtOAc = 1/1) to afford the crude *S*-(4-hydroxyphenyl) allyl(4-(trifluoromethyl)phenyl)carbamothioate as a yellow solid (2.0 g, ca. 60% yield), which was used in the next step without further purification. The corresponding amide (0.36 g, 1.0 mmol) was added portion-wise to a suspension of NaH (48 mg, 1.2 mmol, 60% dispersion in mineral oil) in THF (17 mL), and 2-bromoethanol (0.10 mL, 1.5 mmol) was then added dropwise. The reaction was stirred at rt for 12 h, and H_2O (5.0 mL) was added. The mixture was extracted with EtOAc (10 mL× 3), and the combined extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated. The resulting crude product was purified by flash chromatography (hexane/EtOAc = 1/1) to give **1b** as colorless oil (0.21 g, 17% yield).

***S*-(4-(2-Hydroxyethoxy)phenyl) Allyl(4-(trifluoromethyl)phenyl)carbamothioate (1b)**



1b

Yield: 0.21 g (53%); white solid; R_f 0.17 (silica gel, hexane/EtOAc = 1/1); mp 99 °C.

IR (KBr): 3488 s, 1651 s, 1592 s, 1496 s, 1377 s, 1324 s, 1256 m, 1177 m, 1105 m, 1068 s, 1033 m, 937 m, 830 s, 754 m, 702 m, 683 m, 561 m cm^{-1}.

^{1}H NMR (399.78 MHz, $CDCl_3$): δ = 7.71 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.36 (dt, *J* = 9.6, 2.5 Hz, 2H), 6.91 (dt, *J* = 9.5, 2.5 Hz, 2H), 5.87 (dd, *J* = 16.8, 10.2 Hz, 1H), 5.19–5.10 (m, 2H), 4.34 (d, *J* = 6.4 Hz, 2H), 4.05 (t, *J* = 4.6 Hz, 2H), 3.92 (t, *J* = 4.4 Hz, 2H), 2.31 (s, 1H).

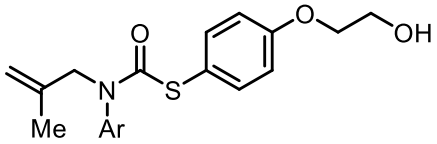
^{13}C NMR (100.53 MHz, $CDCl_3$): δ = 167.9, 159.8, 143.6, 137.3, 132.2, 130.7 (q, J_{CF} = 32.6 Hz), 129.8, 126.7 (q, J_{CF} = 3.8 Hz), 123.8 (q, J_{CF} = 272.2 Hz), 119.9, 119.2, 115.3, 69.3, 61.3, 53.8.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -63.8.

MS: m/z (%) = 397 (34) [M^+], 229 (14), 228 (92), 169 (11), 126 (11), 125 (89), 97 (12), 45 (25), 42 (10), 41 (100).

HRMS (DART): *m/z* [M+H^+] calcd for $C_{19}H_{19}NO_3F_3S$: 398.1032, found: 398.1033.

***S*-(4-(2-Hydroxyethoxy)phenyl) (2-Methylallyl)(4-(trifluoromethyl)phenyl)carbamothioate (1c)**



1c

Typical Procedure was followed using *N*-(2-methylallyl)-4-(trifluoromethyl)aniline (1.8 g, 8.2 mmol). The subsequent alkylation was run on a 3.0 mmol scale.

Yield: 0.22 g (18%); colorless oil; R_f 0.20 (silica gel, hexane/EtOAc = 1/1).

IR (KBr): 3467 s, 2946 m, 1644 s, 1592 s, 1496 s, 1376 m, 1069 m, 906 s, 858 m, 833 m, 753 s, 717 m, 620 s, 559 m cm^{-1}.

^{1}H NMR (399.78 MHz, $CDCl_3$): δ = 7.70 (d, *J* = 8.2 Hz, 2H), 7.48 (d, *J* = 8.2 Hz, 2H), 7.36 (d, *J* = 8.7 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 4.82 (s, 1H), 4.77 (s, 1H), 4.31 (s, 2H), 4.02 (t, *J* = 4.6 Hz, 2H), 3.90 (t, *J* = 4.4 Hz, 2H), 2.47 (s, 1H), 1.77 (s, 3H).

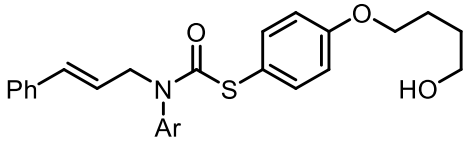
^{13}C NMR (100.53 MHz, $CDCl_3$): δ = 168.2, 159.8, 143.7, 139.9, 137.2, 130.5 (q, J_{CF} = 32.6 Hz), 129.31, 126.5 (q, J_{CF} = 3.8 Hz), 123.8 (q, J_{CF} = 272.2 Hz), 119.9, 115.3, 114.4, 69.3, 61.3, 56.9, 20.2.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -63.8.

MS, m/z (%): 411 (15) [M^+], 243 (10), 242 (73), 170 (23), 126 ’15), 125 (72), 55 (100), 45 (20).

HRMS (DART): *m/z* [M+H^+] calcd for $C_{20}H_{21}NO_3F_3S$: 412.1189, found: 412.1193.

***S*-(4-(4-Hydroxybutoxy)phenyl)cinnamyl (4-(Trifluoromethyl)phenyl)carbamothioate (1d)**



1d

Typical Procedure was followed using 4-bromo-1-butanol (0.16 g, 1.05 mmol). The subsequent alkylation was run on a 0.70 mmol scale.

Yield: 30 mg (10%); white solid; R_f 0.40 (silica gel, hexane/EtOAc = 1/1); mp 124 °C.

IR (KBr): 3535 m, 1648 s, 1609 s, 1593 s, 1570 m, 1495 s, 1367 m, 1323 s, 1242 s, 1193 m, 1170 s, 1121 s, 1105 m,

1066 m, 1018 m, 967 m, 831 s, 751 m, 619 m cm^{-1}.

^1H NMR (399.78 MHz, $CDCl_3$,): δ = 7.71 (d, *J* = 8.2 Hz, 2H), 7.51 (d, *J* = 8.2 Hz, 2H), 7.38–7.25 (m, 7H), 6.92–6.89 (m, 2H), 6.42 (d, *J* = 15.6 Hz, 1H), 6.31–6.25 (m, 1H), 4.49 (d, *J* = 6.9 Hz, 2H), 4.01 (t, *J* = 6.2 Hz, 2H), 3.71 (t, *J* = 6.4 Hz, 2H), 1.90–1.85 (m, 2H), 1.78–1.70 (m, 3H).

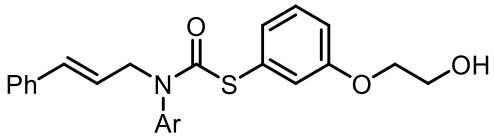
^{13}C NMR (100.53 MHz, $CDCl_3$): δ = 168.1, 160.1, 143.7, 137.2, 136.3, 134.4, 130.8 (q, J_{CF} = 30.7 Hz), 130.0, 128.7, 128.1, 126.8 (q, J_{CF} = 3.8 Hz), 126.6, 123.8 (q, J_{CF} = 272.2 Hz), 123.4, 119.4, 115.3, 67.9, 62.6, 53.5, 29.5, 25.8.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -63.8.

MS, m/z (%): 501 (1) [M^+], 118 (10), 117 (100), 115 (14).

HRMS (DART): *m/z* [M+H^+] calcd for $C_{27}H_{27}NO_3F_3S$: 502.1658, found: 502.1656.

(3-(2-Hydroxyethoxy)phenyl) Cinnamyl(4-(trifluoromethyl)phenyl)carbamothioate (1e)



1e

Typical Procedure was followed using 3-mercaptophenol (1.1 mL, 11 mmol). The subsequent alkylation was run on a 1.3 mmol scale.

Yield: 0.14 g (22%); colorless oil; R_f 0.20 (silica gel, hexane/EtOAc = 1/1).

IR (KBr): 3419 w, 1806 m, 1775 m, 1669 m, 1612 m, 1589 m, 1477 w, 1371 w, 1324 s, 1246 m, 1167 m, 1127 m, 1068 m, 968 w, 774 m, 691 w, 620 w cm^{-1}.

^1H NMR (399.78 MHz, $CDCl_3$): δ = 7.72 (d, *J* = 8.4 Hz, 2H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.35–7.27 (m, 6H), 7.10–7.04 (m, 2H), 6.98–6.94 (m, 1H), 6.42 (d, *J* = 15.6 Hz, 1H), 6.30–6.25 (m, 1H), 4.49 (d, *J* = 6.9 Hz, 2H), 4.08 (t, *J* = 4.6 Hz, 2H), 3.94 (q, *J* = 4.3 Hz, 2H), 2.05 (t, *J* = 6.0 Hz, 1H).

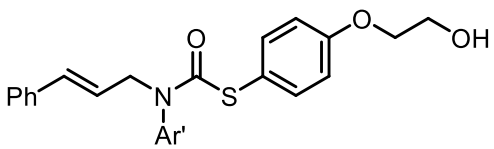
^{13}C NMR (100.53 MHz, $CDCl_3$): δ = 167.1, 158.8, 143.5, 136.3, 134.5, 131.0 (q, J_{CF} = 32.6 Hz), 130.1, 130.0, 129.9, 128.8, 128.3, 128.2, 126.8 (q, J_{CF} = 2.9 Hz), 126.7, 123.8 (q, J_{CF} = 272.2 Hz), 123.2, 121.4, 116.2, 69.4, 61.5, 53.6.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -63.9.

MS, m/z (%): 473 (2) [M^+], 118 (11), 117 (100), 115 (17).

HRMS (DART): *m/z* [M+H^+] calcd for $C_{25}H_{23}NO_3F_3S$: 474.1345, found: 474.1338.

***S*-(4-(2-Hydroxyethoxy)phenyl) Cinnamyl(phenyl)carbamothioate (1i)**



1i (Ar' = Ph)

Typical Procedure was followed using *N*-cinnamylaniline (2.1 g, 10 mmol). The subsequent alkylation was run on a 1.0 mmol scale.

Yield: 61 mg (15%); white solid; R_f 0.20 (silica gel, hexane/EtOAc = 1/1); mp 127 °C.

IR (KBr): 3489 s, 1657 s, 1639 s, 1591 s, 1572 m, 1494 s, 1483 m, 1374 s, 1301 m, 1288 s, 1273 s, 1253 s, 1219 m, 1175 m, 1068 m, 1036 m, 963 m, 834 s, 727 s, 695 m cm^{-1}.

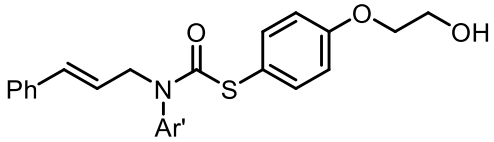
^1H NMR (399.78 MHz, $CDCl_3$): δ = 7.48–7.24 (m, 12H), 6.92 (d, *J* = 8.7 Hz, 2H), 6.44–6.27 (m, 2H), 4.48 (d, *J* = 6.4 Hz, 2H), 4.07 (t, *J* = 4.6 Hz, 2H), 3.94 (t, *J* = 4.6 Hz, 2H), 2.23 (s, 1H).

^{13}C NMR (100.53 MHz, $CDCl_3$): δ = 168.2, 159.6, 140.2, 137.2, 136.6, 134.0, 129.8, 129.6, 129.0, 128.6, 127.9, 126.6, 123.8, 120.7, 115.2, 69.3, 61.3, 53.5.

MS, m/z (%): 405 (1) [M^+], 118 (10), 117 (100), 115 (17).

HRMS (DART): *m/z* [M+H^+] calcd for $C_{24}H_{24}NO_3S$: 406.1471, found: 406.1472.

_S_-(4-(2-Hydroxyethoxy)phenyl) Cinnamyl(4-methoxyphenyl)carbamothioate (1j)



1j (Ar' = *p*-C_6H_4-OMe)

Typical Procedure was followed using *N*-cynnamyl-4-(methoxy)aniline (2.4 g, 10 mmol). The subsequent alkylation was run on a 1.0 mmol scale.

Yield: 0.11g (25%); white solid; R_f 0.20 (silica gel, hexane/EtOAc = 1/1); mp 96 °C.

IR (KBr): 3421 m, 1672 s, 1646 s, 1593 m, 1509 s, 1493 s, 1455 m, 1375 m, 1297 w, 1242 s, 1174 m, 1093 w, 916 m, 834 s, 733 m, 629 w, 465 w, 444 m, 433 m, 420 m, 410 m cm^{-1}.

^1H NMR (399.78 MHz, $CDCl_3$): δ = 7.40–7.24 (m, 9H), 6.96–6.91 (m, 4H), 6.40 (d, *J* = 16.0 Hz, 1H), 6.27 (d, *J* = 15.6 Hz, 1H), 4.43 (d, *J* = 6.4 Hz, 2H), 4.07 (t, *J* = 4.6 Hz, 2H), 3.94 (t, *J* = 4.4 Hz, 2H), 3.84 (s, 3H), 2.15 (s, 1H).

^{13}C NMR (100.53 MHz, $CDCl_3$): δ = 168.6, 159.9, 159.6, 137.2, 136.6, 134.0, 132.7, 131.1, 128.6, 127.9, 126.6, 123.9, 121.1, 115.2, 114.7, 69.3, 61.4, 55.6, 53.6.

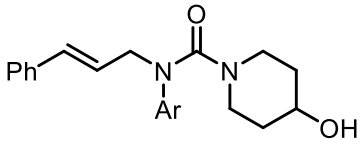
MS, m/z (%): 435 (1) [M^+], 118 (10), 117 (100), 115 (15).

HRMS (DART): *m/z* [M+H^+] calcd for $C_{25}H_{26}NO_4S$: 436.1571, found: 436.1579.

Procedure for the Synthesis of _S_-(4-Aminophenyl) Allyl(phenyl)carbamothioate (1h)

N-Benzylidene protected **1h** was prepared using (*E*)-4-(benzylideneamino)benzenethiol[11] according to the typical procedure on a 10 mmol scale. A white solid (3.7 g, ca. 98%) was obtained, and this material was used in the next step without further purification. Thus obtained protected **1h** (3.7 g, ca. 10 mmol) was dissolved in HCl (1.0 M, 80 mL), and the solution was stirred at rt for 1 h. The mixture was then quenched with an aqueous solution of NaOH (2.0 M, 100 mL), and the resulting mixture was extracted with EtOAc (30 mL × 3). The combined extracts were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated. The resulting crude product was purified by flash chromatography (hexane/EtOAc = 1/1) to give **1h** as a white solid (1.53 g, 54% yield).

_S_-(4-Aminophenyl) Allyl(phenyl)carbamothioate (1h)



1h

Yield: 1.53 g (54%); white solid; R_f 0.32 (silica gel, hexane/EtOAc = 1/1); mp 96 °C.

IR (KBr): 3651 m, 3373 s, 1655 m, 1652 w, 1618 w, 1592 w, 1514 s, 1452 w, 1435 m, 1363 s, 1335 w, 1295 s, 1250 s, 1217 s, 1176 s, 1170 s, 1128 w, 1073 m, 1018 w, 1003 w cm^{-1}.

^1H NMR (399.78 MHz, $CDCl_3$): δ = 7.46–7.42 (m, 3H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 2H), 6.62 (d, *J* = 8.0 Hz, 2H), 5.95–5.85 (m, 1H), 5.16–5.10 (m, 2H), 4.33 (d, *J* = 6.4 Hz, 2H), 3.76 (s, 2H).

^{13}C NMR (100.53 MHz, $CDCl_3$): δ = 168.7, 147.8, 140.4, 137.0, 132.8, 129.6, 129.4, 128.7, 118.5, 116.6, 115.4, 53.8.

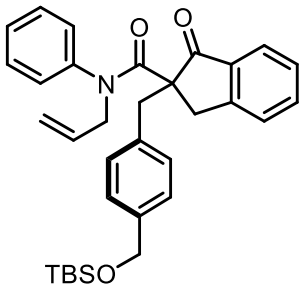
MS, m/z (%): 284 (33) [M^+], 160 (64), 132 (27), 125 (10), 123 (72), 80 (26), 41 (100).

HRMS (DART): *m/z* [M+H^+] calcd for $C_{16}H_{17}N_2OS$: 285.1056, found: 285.1056.

Procedure for the Synthesis for β-Keto Amide 3

Synthesis of TBS-protected 3: A 100 mL two-necked flask with a magnetic stirring bar was evacuated and backfilled with nitrogen three times. Methyl 1-oxo-2,3-dihydro-1*H*-indene-2-carboxylate (2.2 g, 12 mmol) and *N*-allylaniline (5.0 mL, 24 mmol) were added to the flask. The mixture was stirred at 70 °C for 48 h, and then cooled to rt. The residue was concentrated and purified by column chromatography on silica gel (hexane/EtOAc = 9/1) to afford crude *N*-allyl-1-oxo-*N*-phenyl-2,3-dihydro-*1H*-indene-2-carboxamide as a yellow solid (0.92 g, ca. 28% yield), which was used in the next step without further purification. This amide (0.60 g, 2.0 mmol) was added to a suspension of NaH (0.16 g, 4 mmol, 60% dispersion in mineral oil) in THF, and (4-(bromomethyl)benzyl)(tert-butyl)dimethylsilane (10 mmol, 0.61 mL) was then added dropwise. The reaction was stirred at rt for 12 h, and then H_2O (15 mL) was added. The residue was extracted with EtOAc (15 mL × 3), and the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4, and concentrated. The resulting crude product was purified by flash chromatography (Hexane/EtOAc, = 8/2) to give TBS-protected **3** as a white solid (0.42 g, 81% yield).

***N*-Allyl-2-(4-(((tert-butyldimethylsilyl)oxy)methyl)benzyl)-1-oxo-N-phenyl-2,3-dihydro-1H-indene-2-carboxamide (TBS-protected 3)**



TBS-protected 3

Yield: 0.42g (81%); white solid; R_f 0.54 (silica gel, hexane/EtOAc = 1/1); mp 108 °C.

IR (KBr): 1703 s, 1652 m, 1641 s, 1494 w, 1381 w, 1272 w, 1258 w, 1092 w, 1079 m, 835 m, 784 w, 703 m cm^{-1}.

^{1}H NMR (399.78 MHz, $CDCl_3$): δ = 7.12–7.08 (m, 2H), 6.89 (q, *J* = 8.1 Hz, 9H), 6.82 (d, *J* = 7.8 Hz, 1H), 6.75 (t, *J* = 6.9 Hz, 1H), 5.91–5.84 (m, 1H), 5.09–4.99 (m, 2H), 4.46 (s, 2H), 4.22 (dd, *J* = 7.8, 6.4 Hz, 2H), 3.47–3.34 (m, 3H), 3.16 (d, *J* = 17.9 Hz, 1H), 0.80 (t, *J* = 2.7 Hz, 9H), -0.12 (q, *J* = 2.7 Hz, 6H).

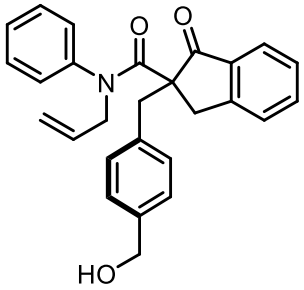
^{13}C NMR (100.53 MHz, $CDCl_3$): δ = 205.5, 171.1, 151.3, 139.4, 139.0, 137.1, 134.2, 134.0, 132.7, 130.4, 128.3, 126.6, 125.4, 125.2, 123.4, 118.1, 64.6, 60.4, 55.1, 42.0, 37.0, 25.9, 18.3, -5.3.

MS, m/z (%): 525 (2) [M^+], 393 (28), 349 (29), 348 (100), 233 (26), 133 (15), 132 (35), 104 (36), 91 (13), 75 (16), 73 (62), 41 (29).

HRMS (DART): *m/z* [M+H^+] calcd for $C_{33}H_{40}NO_3Si$: 526.2772, found: 526.2768.

Deprotection of TBS-protected 3: TBS-protected **3** (0.42 g, 0.80 mmol) was dissolved in THF (15 mL), and 1.0 M THF solution of tetrabutylammonium fluoride (1.4 mL, 14 mmol) was added to the THF solution. The mixture was stirred at rt overnight. The mixture was then quenched with a saturated aqueous solution of NH_4Cl (5.0 mL), and the resulting mixture was extracted with EtOAc (6.0 mL × 3). The combined extracts were washed with brine (6.0 mL), dried over anhydrous Na_2SO_4, and concentrated. The resulting crude product was purified by flash chromatography (hexane/EtOAc = 1/9) to give **3** as white solid (0.29 g, 88% yield).

***N*-Allyl-2-(4-(hydroxymethyl)benzyl)-1-oxo-N-phenyl-2,3-dihydro-1H-indene-2-carboxamide (3)**



Yield: 0.29g (88%); white solid; R_f 0.49 (silica gel, EtOAc); mp 88 °C.

IR (KBr): 3470 m, 1713 s, 1635 s, 1608 m, 1594 m, 1495 m, 1436 m, 1387 s, 1258 s, 1015 m, 983 m, 922 m, 745 m, 702 s cm^{-1}.

^{1}H NMR (399.78 MHz, $CDCl_3$): δ = 7.15 (q, *J* = 6.6 Hz, 2H), 6.97–6.85 (m, 10H), 6.79 (s, 2H), 5.94–5.84 (m, 1H), 5.12–5.02 (m, 2H), 4.44 (s, 2H), 4.24 (m, 2H), 3.47–3.37 (m, 3H), 3.16 (d, *J* = 18.3 Hz, 1H).

^{13}C NMR (100.53 MHz, $CDCl_3$): δ = 205.4, 171.2, 151.4, 139.1, 139.0, 137.1, 135.3, 134.2, 132.8, 131.0, 128.4, 128.3, 126.8, 126.4, 125.4, 123.7, 118.3, 65.1, 60.6, 55.3, 42.2, 37.2.

MS, m/z (%): 411 (7) [M^+], 393 (11), 290 (19), 262 (12), 261 (20), 251 (10), 233 (26), 157 (20), 133 (30), 132 (100), 131 (11), 121 (67), 115 (24), 106 (13), 105 (21), 104 (23), 93 (34), 91 (77), 77 (50), 41 (29).

HRMS (DART): *m/z* [M+H^+] calcd for $C_{27}H_{26}NO_3$: 412.1907, found: 412.1913.

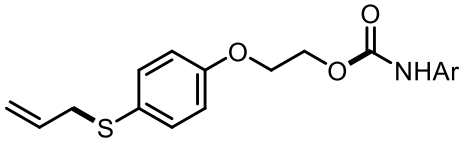
IV. Typical Procedure for the Palladium-Catalyzed Elimination of Isocyanate from N-Allylamide Derivatives

2 (Ar = *p*-C_6H_4-CF_3)

In a glovebox filled with nitrogen, $Pd(PPh_3)_4$ (11.6 mg, 0.010 mmol), dcype (4.7 mg, 0.010 mmol) and toluene (1.0 mL) were added to a 10 mL-vial with a Teflon-sealed screwcap, and the mixture was stirred at rt for 5 min. The amide **1b** (39.7 mg, 0.10 mmol) was then added, and the cap was applied to seal the vial. The vessel was heated at 100 °C

for 18 h, then cooled to rt and the crude mixture was filtered through a pad of celite. The crude product was purified by flash column chromatography on silica gel to give **2b** as a white solid (36.5 mg, 92%).

2-(4-(Allylthio)phenoxy)ethyl (4-(Trifluoromethyl)phenyl)carbamate (2b)



2b

Yield: 36.5 mg (92%); white solid; R_f 0.68 (silica gel, hexane/EtOAc = 1/1); mp 103 °C.

IR (KBr): 3322 s, 1702 s, 1597 s, 1540 s, 1495 s, 1455 m, 1413 m, 1329 s, 1281 m, 1232 m, 1118 m, 1091 m, 1069 m, 1016 m, 931 m, 831 m, 648 m, 515 m cm^{-1}.

^1H NMR (399.78 MHz, $CDCl_3$): δ = 7.57 (d, *J* = 8.7 Hz, 2H), 7.50 (d, *J* = 8.7 Hz, 2H), 7.34 (td, *J* = 6.0, 3.5 Hz, 2H), 6.91 (s, 1H), 6.85 (dt, *J* = 9.5, 2.6 Hz, 2H), 5.87–5.79 (m, 1H), 5.03–4.97 (m, 2H), 4.54 (dd, *J* = 5.3, 3.9 Hz, 2H), 4.20 (t, *J* = 4.6 Hz, 2H), 3.44 (dt, *J* = 7.0, 1.1 Hz, 2H).

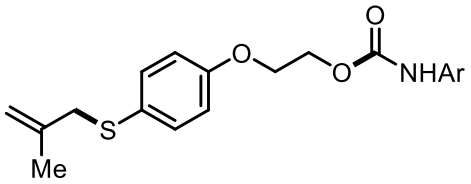
^{13}C NMR (100.53 MHz, $CDCl_3$): δ = 157.8, 152.9, 140.8, 134.0, 133.8, 126.8, 126.5 (q, J_{CF} = 3.8 Hz), 125.5 (q, J_{CF} = 32.6 Hz), 124.2 (q, J_{CF} = 271.2 Hz), 118.2, 117.5, 115.1, 66.2, 63.9, 39.2.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -63.3.

MS, m/z (%): 397 (7) [M^+], 233 (11), 232 (100), 188 (13), 166 (36), 160 (10), 145 (11), 125 (31), 45 (49), 41 (21).

HRMS (DART): *m/z* [M+H^+] calcd for $C_{19}H_{19}NO_3F_3S$: 398.1032, found: 398.1031.

2-(4-((2-Methylallyl)thio)phenoxy)ethyl (4-(Trifluoromethyl)phenyl)carbamate (2c)



2c

Yield: 27.2 mg (65%); white solid; R_f 0.72 (silica gel, hexane/EtOAc = 1/1); mp 101 °C.

IR (KBr): 3269 s, 1693 s, 1597 m, 1545 m, 1495 s, 1455 m, 1408 m, 1339 s, 1282 m, 1236 m, 1164 s, 1114 m, 1082 m, 1070 m, 904 s, 832 s, 784 m, 767 m, 672 m, 530 m, 508 m cm^{-1}.

^1H NMR (399.78 MHz, $CDCl_3$): δ = 7.56 (d, *J* = 8.4 Hz, 2H), 7.49 (d, *J* = 8.4 Hz, 2H), 7.33 (td, *J* = 4.6, 2.4 Hz, 2H), 6.90 (s, 1H), 6.86–6.83 (m, 2H), 4.74 (q, *J* = 1.5 Hz, 1H), 4.65 (d, *J* = 0.9 Hz, 1H), 4.54 (t, *J* = 4.6 Hz, 2H), 4.20 (dd, *J* = 5.3, 3.9 Hz, 2H), 3.41 (d, *J* = 0.9 Hz, 2H), 1.84 (s, 3H).

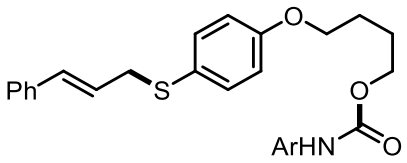
^{13}C NMR (100.53 MHz, $CDCl_3$): δ = 157.8, 152.9, 141.2, 140.9, 133.9, 127.4, 126.5 (q, J_{CF} = 3.1 Hz), 125.6 (q, J_{CF} = 32.3 Hz), 124.2 (q, J_{CF} = 272.2 Hz), 118.2, 115.1, 114.0, 66.2, 64.0, 44.0, 21.1.

^{19}F NMR (376 MHz, $CDCl_3$,): δ = -63.3.

MS, m/z (%): 411 (9) [M^+], 233 (11), 232 (100), 207 (19), 188 (13), 180 (40), 160 (10), 147 (17), 125 (24), 55 (32), 45 (46).

HRMS (DART): *m/z* [M+H^+] calcd for $C_{20}H_{21}NO_3F_3S$: 412.1189, found: 412.1191.

4-(4-(Cinnamylthio)phenoxy)butyl (4-(Trifluoromethyl)phenyl)carbamate (2d)



2d

Run on a 0.050 mmol scale.

Yield: 14.2 mg (56%); white solid; R_f 0.68 (silica gel, hexane/EtOAc = 1/1); mp 138 °C.

IR (KBr): 3355 w, 1710 s, 1619 w, 1598 w, 1539 m, 1517 m, 1493 m, 1473 w, 1413 w, 1336 s, 1269 w, 1233 s, 1182 w, 1164 w, 1114 m, 1072 m, 819 w, 505 w, 433 w, 422 w cm^{-1}.

^1H NMR (399.78 MHz, $CDCl_3$): δ = 7.56 (d, *J* = 8.7 Hz, 2H), 7.48 (d, *J* = 8.7 Hz, 2H), 7.38–7.28 (m, 6H), 7.22 (dt, *J* = 6.1, 2.5 Hz, 1H), 6.81 (dt, *J* = 9.5, 2.6 Hz, 2H), 6.73 (s, 1H), 6.30–6.20 (m, 2H), 4.26 (t, *J* = 6.0 Hz, 2H), 3.98 (t, *J* = 5.7 Hz, 2H), 3.58 (q, *J* = 3.1 Hz, 2H), 1.90–1.87 (m, 4H).

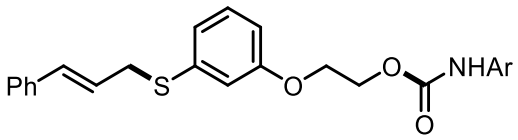
^{13}C NMR (100.53 MHz, $CDCl_3$): δ = 158.6, 153.3, 141.1, 137.0, 134.5, 132.6, 128.6, 127.6, 126.5 (q, J_{CF} = 3.8 Hz), 126.4, 125.9, 125.7, 125.3 (q, J_{CF} = 32.6 Hz), 124.3 (q, J_{CF} = 272.2 Hz), 118.1, 115.1, 67.4, 65.4, 39.3, 25.9, 25.8.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -63.3.

MS, m/z (%): 501 (0) [M^+], 314 (6) [M^+-isocyanate], 126 (42), 118 (12), 117 (100), 115 (26), 91 (11).

HRMS (DART): *m/z* [M+H^+] calcd for $C_{27}H_{27}NO_3F_3S$: 502.1658, found: 502.1652.

2-(3-(Cinnamylthio)phenoxy)ethyl (4-(Trifluoromethyl)phenyl)carbamate (2e)



2e

Yield: 25.7 mg (54%); white solid; R_f 0.57 (silica gel, hexane/EtOAc = 1/1); mp 98 °C.

IR (KBr): 3330 m, 2361 s, 2340 m, 1704 s, 1592 m, 1567 m, 1540 s, 1475 m, 1457 m, 1416 m, 1336 s, 1283 m, 1232 m, 1161 m, 1113 m, 1088 m, 971 m, 945 m, 836 m, 757 m, 505 m, 473 m, 422 m, 412 m cm^{-1}.

^1H NMR (399.78 MHz, $CDCl_3$,): δ = 7.57 (d, *J* = 8.7 Hz, 2H), 7.49 (d, *J* = 8.7 Hz, 2H), 7.33–7.27 (m, 4H), 7.23–7.19 (m, 2H), 6.99 (d, *J* = 7.8 Hz, 1H), 6.94 (t, *J* = 1.8 Hz, 1H), 6.87 (s, 1H), 6.75 (dd, *J* = 8.2, 2.3 Hz, 1H), 6.46 (d, *J* = 15.6 Hz, 1H), 6.29–6.22 (m, 1H), 4.50 (t, *J* = 4.6 Hz, 2H), 4.16 (t, *J* = 4.4 Hz, 2H), 3.73–3.71 (m, 2H).

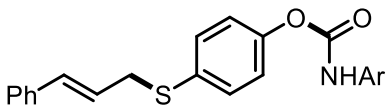
^{13}C NMR (100.53 MHz, $CDCl_3$,): δ = 158.6, 152.9, 140.9, 137.6, 136.8, 133.1, 129.9, 128.7, 127.8, 126.53 (q, J_{CF} = 3.8 Hz), 126.46, 125.5 (q, J_{CF} = 32.6 Hz), 125.0, 124.2 (q, J_{CF} = 271.3 Hz), 122.7, 118.2, 116.0, 112.8, 66.2, 63.9, 36.9.

^{19}F NMR (376 MHz, $CDCl_3$,): δ = -63.3.

MS, m/z (%): 473 (0) [[M^+], 286 (4) [M^+-isocyanate], 118 (10), 117 8100), 115 (28), 91 (11).

HRMS (DART): *m/z* [M+H^+] calcd for $C_{25}H_{23}NO_3F_3S$: 474.1345, found: 474.1347.

1-Cinnamylpiperidin-4-yl (4-(Trifluoromethyl)phenyl)carbamate (2f)



2f

Yield: 24 mg (59%); white solid; R_f 0.16 (silica gel, EtOAc); mp 128 °C.

In addition to **2f**, a UFC product (isocyanate is not trapped by the OH group) was obtained (4,1 mg, 19% isolated yield). Note that **2f** was decomposed to form the UFC product, when NH silica was used for its isolation.

IR (KBr): 3342 m, 1700 s, 1617 m, 1536 m, 1511 m, 1410 m, 1331 s, 1238 m, 1162 m, 1121 s, 1072 s, 833 m, 691 m cm^{-1}.

^1H NMR (399.78 MHz, $CDCl_3$): δ = 7.53 (dd, *J* = 19.5, 8.9 Hz, 4H), 7.39–7.37 (m, 2H), 7.31 (t, *J* = 7.6 Hz, 2H), 7.26–7.22 (m, 1H), 7.04 (s, 1H), 6.52 (d, *J* = 15.6 Hz, 1H), 6.27 (dt, *J* = 15.6, 6.9 Hz, 1H), 4.85–4.81 (m, 1H), 3.19–3.17 (m, 2H), 2.82 (br, 2H), 2.32 (br, 2H), 2.04–2.00 (m, 2H), 1.83–1.74 (m, 2H).

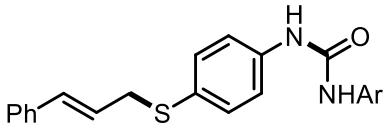
^{13}C NMR (100.53 MHz, $CDCl_3$): δ = 152.8, 141.3, 136.9, 133.3, 128.7, 127.7, 126.5 (q, J_{CF} = 4.8 Hz), 126.4, 125.2 (q, J_{CF} = 32.6 Hz), 122.1, 121.6 (q, J_{CF} = 271.3 Hz), 118.1, 71.7, 61.1, 51.0, 31.2.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -63.2.

MS, m/z (%): 404 (31) [M^+], 281 (16), 207 (33), 118 (100), 73 (11).

HRMS (DART): *m/z* [M+H^+] calcd for $C_{22}H_{24}N_2O_2F_3$: 405.1784, found: 405.1782.

4-(Cinnamylthio)phenyl (4-(Trifluoromethyl)phenyl)carbamate (2g)



2g

Yield: 17.1 mg (40%); white solid; R_f 0.43 (silica gel, hexane/EtOAc = 2/1); mp 179 °C.

IR (KBr): 2931 m, 2853 w, 1748 m, 1615 m, 1540 m, 1478 m, 1411 w, 1324 s, 1198 s, 1184 s, 1163 m, 1115 m, 1067 s, 1004 w, 842 m, 753 w, 433 m, 422 m, 411 w cm^{-1}.

^1H NMR (399.78 MHz, $CDCl_3$): δ = 7.58 (q, *J* = 9.2 Hz, 4H), 7.42 (d, *J* = 8.7 Hz, 2H), 7.34–7.23 (m, 5H), 7.12 (d, *J* = 8.7 Hz, 2H), 7.08 (s, 1H), 6.43 (d, *J* = 15.6 Hz, 1H), 6.29–6.21 (m, 1H), 3.70 (d, *J* = 6.9 Hz, 2H).

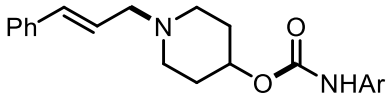
^{13}C NMR (100.53 MHz, $CDCl_3$): δ = 151.2, 149.2, 140.5, 136.8, 133.4, 133.1, 132.0, 128.7, 127.8, 126.6 (q, J_{CF} = 2.9 Hz), 126.5, 125.7 (q, J_{CF} = 33.6 Hz), 125.0, 124.2 (q, J_{CF} = 271.3 Hz), 122.1, 118.4, 37.9.

^{19}F NMR (376 MHz, $CDCl_3$): δ = -63.4.

MS, m/z (%): 429 (1) [M^+], 118 (10), 117 (100), 115 (19).

HRMS (DART): *m/z* [M+H^+] calcd for $C_{23}H_{19}NO_2F_3S$: 430.1083, found: 430.1089.

1-(4-(Allylthio)phenyl)-3-Phenylurea (2h)



2h

Run on a 0.20 mmol scale.

Yield: 43.6 mg (77%); white solid; R_f 0.80 (silica gel, EtOAc); mp 126 °C.

IR (KBr): 3306 m, 1639 s, 1594 s, 1585 m, 1562 m, 1557 s, 1552 s, 1538 w, 1532 w, 1519 w, 1496 m, 1443 m, 1439 m, 1395 w, 1313 w, 1294 w, 1288 w, 1261 w, 1234 m, 924 w cm^{-1}.

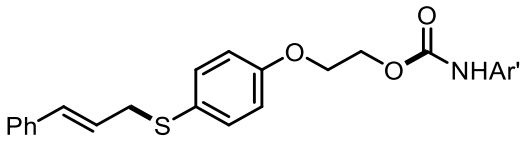
^1H NMR (399.78 MHz, $CDCl_3$): δ = 7.25–7.20 (m, 5H), 7.14 (dd, *J* = 11.4, 8.7 Hz, 3H), 7.09–7.04 (m, 1H), 5.87–5.77 (m, 1H), 5.07–5.01 (m, 2H), 3.44 (*d*, J = 6.9 Hz, 2H).

^{13}C NMR (100.53 MHz, $CDCl_3$): δ = 154.7, 137.8, 136.8, 133.6, 131.6, 130.1, 129.1, 124.0, 121.2, 120.7, 117.7, 38.2.

MS, m/z (%): 284 (0) [M^+], 165 (22) [M^+-isocyanate], 124 (100), 80 (26).

HRMS (DART): *m/z* [M+H^+] calcd for $C_{16}H_{17}N_2OS$: 285.1056, found: 285.1058.

2-(4-(Cinnamylthio)phenoxy)ethyl Phenylcarbamate (2i)



2i

Run on a 0.15 mmol scale.

Yield: 47.7 mg (78%); white solid; R_f 0.73 (silica gel, hexane/EtOAc = 1/1); mp 106 °C.

IR (KBr): 3293 m, 1698 s, 1597 m, 1537 m, 1492 m, 1442 m, 1312 w, 1243 m, 1224 m, 1176 w, 1064 m, 1025 w, 928 w, 834 m, 420 w cm^{-1}.

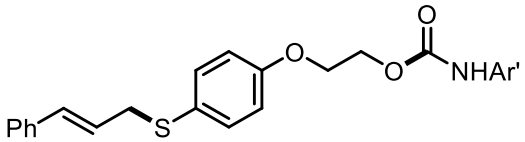
^1H NMR (399.78 MHz, $CDCl_3$): δ = 7.38–7.26 (m, 10H), 7.23–7.20 (m, 1H), 7.10–7.05 (m, 1H), 6.85 (dt, *J* = 9.5, 2.5 Hz, 2H), 6.71 (s, 1H), 6.31–6.18 (m, 2H), 4.52–4.50 (m, 2H), 4.18 (t, *J* = 4.8 Hz, 2H), 3.59 (d, *J* = 6.4 Hz, 2H).

^{13}C NMR (100.53 MH, $CDCl_3$): δ = 158.2, 153.3, 137.7, 137.0, 134.4, 132.6, 129.3, 128.7, 127.6, 126.6, 126.4, 125.6, 123.8, 118.9, 115.2, 66.5, 63.6, 39.2.

MS, m/z (%): 405 (0) [M^+], 286 (8) [M^+-isocyanate], 118 (10), 117 (100), 115 (26).

HRMS (DART): *m/z* [M+H^+] calcd for $C_{24}H_{24}NO_3S$: 406.1471, found: 406.1464.

2-(4-(Cinnamylthio)phenoxy)ethyl (4-Methoxyphenyl)carbamate (2j)



2j

Run on a 0.12 mmol scale.

Yield: 8.0 mg (15%); white solid; R_f 0.62 (silica gel, hexane/EtOAc = 1/1); mp 139 °C.

IR (KBr): 3344 m, 1698 s, 1535 m, 1491 m, 1451 w, 1415 w, 1240 s, 1222 s, 1185 w, 1088 m, 1066 m, 1024 m, 970 w, 816 m, 758 m cm^{-1}.

^1H NMR (399.78 MHz, $CDCl_3$): δ = 7.38–7.33 (m, 2H), 7.31–7.28 (m, 7H), 7.22 (td, *J* = 4.2, 2.1 Hz, 1H), 6.86–6.84 (m, 4H), 6.30–6.19 (m, 2H), 4.49 (t, *J* = 4.6 Hz, 2H), 4.18 (t, *J* = 4.6 Hz, 2H), 3.78 (s, 3H), 3.59 (d, *J* = 6.4 Hz, 2H).

^{13}C NMR (100.53 MHz, $CDCl_3$): δ = 158.2, 156.3, 137.0, 134.4, 134.3, 132.6, 130.7, 128.7, 127.6, 126.5, 126.4, 125.6, 120.9, 115.2, 114.4, 66.5, 63.5, 55.6, 39.2.

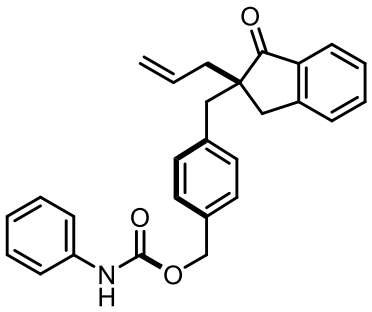
MS, m/z (%): 435 (0) [M^+], 286 (8) [M^+-isocyanate], 118 (10), 117 (100), 115 (26), 91 (10).

HRMS (DART): *m/z* [M+H^+] calcd for $C_{25}H_{26}NO_4S$: 436.1577, found: 436.1574.

Procedure for the Palladium-Catalyzed Elimination of Isocyanate from *N*-Allyl-β-ketoamide 3

In a glovebox filled with nitrogen, $Pd(PPh_3)_4$ (11.6 mg, 0.010 mmol), dcype (4.7 mg, 0.010 mmol) and toluene (1.0 mL) were added to a 10 mL-vial with a Teflon-sealed screwcap, and the mixture was stirred at rt for 5 min. The amide **3** (41.1 mg, 0.10 mmol) and K_3PO_4 (13.8 mg, 0.10 mmol) were then added, and the cap was applied to seal the vial. The vessel was heated at 100 °C for 6 h, then cooled at rt and the crude mixture was filtered through a pad of celite. The crude product was purified by flash column chromatography over silica gel to give a mixture of **4**, **5** and **6** as a colorless oil (35 mg, 83% yield) with a ratio of 4.2/1/2.5 by ^1H NMR analysis. A part of each product was obtained in pure form through purification by GPC.

4-((2-Allyl-1-oxo-2,3-dihydro-1*H*-inden-2-yl)methyl)benzyl Phenylcarbamate (4)



4

Yield: 35 mg (83%, **4**/5/6 = **4.2**/1/2.5); colorless oil; R_f 0.70 (silica gel, hexane/EtOAc = 1/1).

IR (KBr): 1717 w, 1704 m, 1700 m, 1696 m, 1558 w, 1539 m, 786 s, 757 s, 418 m cm^{-1}.

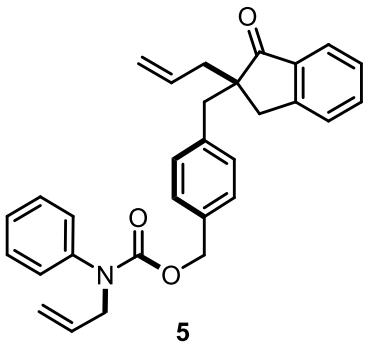
^1H NMR (399.78 MHz, $CDCl_3$): δ = 7.70 (d, *J* = 7.8 Hz, 1H), 7.51–7.47 (m, 1H), 7.36 (d, *J* = 7.8 Hz, 2H), 7.31–7.26 (m, 4H), 7.20 (d, *J* = 7.8 Hz, 2H), 7.11 (d, *J* = 7.8 Hz, 2H), 7.08–7.04 (m, 1H), 6.67 (s, 1H), 5.63–5.53 (m, 1H), 5.08–5.04 (m, 3H), 4.99–4.96 (m, 1H), 3.13–3.07 (m, 2H), 2.95 (d, *J* = 17.4 Hz, 1H), 2.82 (d, *J* = 13.5 Hz, 1H), 2.53 (q, *J* = 6.7 Hz, 1H), 2.30 (dd, *J* = 13.5, 8.0 Hz, 1H).

^{13}C NMR (100.53 MHz $CDCl_3$): δ = 210.2, 153.1, 137.9, 137.8, 136.8, 135.0, 134.2, 133.4, 130.6, 129.2, 128.3, 127.4, 126.5, 124.0, 123.6, 118.9, 118.7, 66.8, 53.9, 42.6, 42.4, 35.5.

MS, m/z (%): 411 (0) [M^+], 292 (3) [M^+-isocyanate], 236 (29), 235 (32), 234 (43), 132 (22), 131 (44), 120 (15), 119 (21), 117 (11), 115 (18), 105 (24), 104 (100), 103 (22), 91 (82), 90 (12), 89 (10), 77 (15), 41 (22).

HRMS (DART): *m/z* [M+H^+] calcd for $C_{27}H_{26}NO_3$: 412.1907, found: 412.1909.

4-((2-Allyl-1-oxo-2,3-dihydro-1*H*-inden-2-yl)methyl)benzyl Allyl(phenyl)carbamate (5)



5

Yield: 35 mg (83%, 4/**5**/6 = 4.2/**1**/2.5); colorless oil; R_f 0.70 (silica gel, hexane/EtOAc = 1/1).

IR (KBr): 1706 s, 1607 w, 1598 w, 1496 m, 1464 w, 1443 w, 1436 w, 1396 m, 1360 w, 1295 m, 1275 m, 1253 m, 1229 m, 1147 m, 1018 w, 993 w, 921 w, 700 m cm^{-1}.

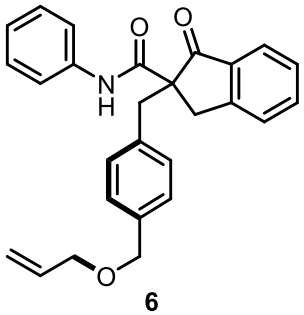
^1H NMR (399.78 MHz, $CDCl_3$): δ = 7.69 (d, *J* = 7.3 Hz, 1H), 7.48 (td, *J* = 7.4, 1.1 Hz, 1H), 7.33–7.27 (m, 4H), 7.23–7.18 (m, 3H), 7.06 (s, 4H), 5.92–5.82 (m, 1H), 5.61–5.53 (m, 1H), 5.12–4.96 (m, 6H), 4.24 (dt, *J* = 6.0, 1.4 Hz, 2H), 3.10–3.05 (m, 2H), 2.94 (d, *J* = 17.4 Hz, 1H), 2.79 (d, *J* = 13.3 Hz, 1H), 2.53 (q, *J* = 6.6 Hz, 1H), 2.30 (dd, *J* = 13.7, 8.2 Hz, 1H).

^{13}C NMR (100.53 MHz, $CDCl_3$): δ = 210.3, 155.3, 153.1, 137.1, 136.8, 135.0, 134.8, 133.8, 133.4, 130.4, 129.0, 127.5, 127.4, 126.8, 126.6, 126.5, 123.9, 118.9, 117.4, 117.2, 67.1, 53.9, 53.4, 42.6, 42.4, 35.5

MS, m/z (%): 451 (1) [M^+], 407 (13), 281 (19), 276 (11), 275 (42), 236 (12), 235 (71), 234 (100), 233 (11), 208 (12), 207 (59), 132 (14), 131 (12), 128 (10), 117 (12), 115 (12), 105 (13), 104 (39), 103 (14), 91 (28), 77 (14), 73 (17), 41 (16).

HRMS (DART): *m/z* [M+H^+] calcd for $C_{30}H_{30}NO_3$: 452.2220, found: 452.2219.

2-(4-((Allyloxy)methyl)benzyl)-1-oxo-*N*-phenyl-2,3-dihydro-1*H*-indene-2-carboxamide (6)



6

Yield: 35 mg (83%, 4/5/**6** = 4.2/1/**2.5**); colorless oil; R_f 0.70 (silica gel, hexane/EtOAc = 1/1).

IR (KBr): 3328 w, 2854 w, 1699 s, 1598 s, 1539 s, 1498 w, 1466 w, 1442 w, 1311 m, 1299 w, 1080 w, 935 w, 913 w, 755 m, 692 m, 505 w cm^{-1}.

^1H NMR (399.78 MHz, $CDCl_3$): 9.20 (s, 1H), 7.75 (d, *J* = 7.8 Hz, 1H), 7.60–7.54 (m, 3H), 7.36 (td, *J* = 15.5, 7.8 Hz, 4H), 7.17–7.07 (m, 5H), 5.96–5.86 (m, 1H), 5.29–5.17 (m, 2H), 4.43 (s, 2H), 3.97–3.92 (m, 3H), 3.35 (d, *J* = 13.7 Hz, 1H), 3.26 (d, *J* = 3.7 Hz, 1H), 3.22 (d, *J* = 8.2 Hz, 1H).

^{13}C NMR (100.53 MHz, $CDCl_3$): 207.2, 167.6, 153.5, 137.8, 137.5, 136.3, 135.1, 134.8, 134.6, 130.1, 129.1, 127.8, 127.7, 126.7, 124.6, 124.5, 120.1, 117.3, 71.8, 71.1, 62.2, 45.3, 34.9.

MS, m/z (%): 411 (0) [M^+], 292 (41) [M^+-isocyanate], 234 (22), 233 (479, 171 812), 161 (18), 131 (13), 129 (10), 128 (20), 119 (52), 117 (11), 115 (19), 105 (20), 104 (27), 91 (100), 90 (11), 55 (10), 41 (37).

HRMS (DART): *m/z* [$M+H^+$] calcd for $C_{27}H_{26}NO_3$: 412.1907, found: 412.1908.

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Chapter 3

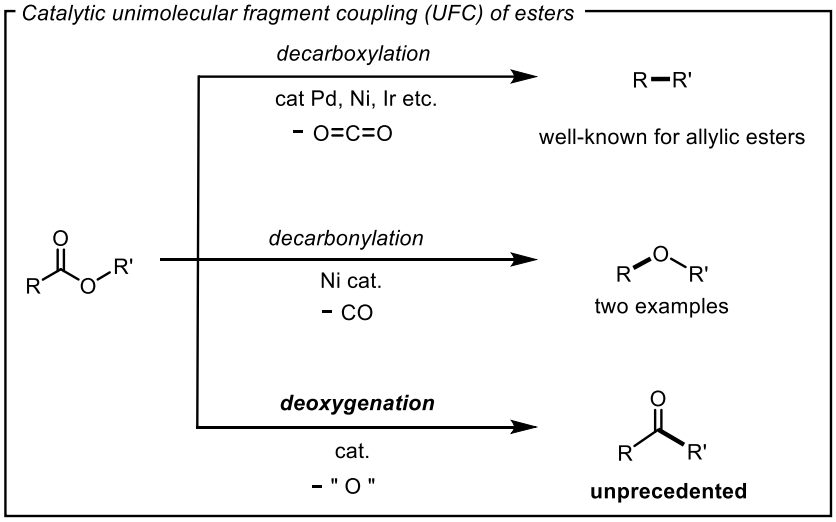
Nickel/photoredox Dual-catalyzed Unimolecular Fragment Coupling of Allyl Esters to Ketones by the Formal Deletion of an Oxygen Atom

3.1. Introduction

Unimolecular fragment coupling (UFC) is defined as reaction format, in which the linker of a molecule is eliminated and the remaining fragments are then coupled. Typical examples include the decarboxylation of esters[1] or the decarbonylation of carbonyl compounds.[2] UFC reactions are potentially valuable methods because readily available starting materials are used and no other reagents, except for catalysts are required, thus making it suitable for late-stage bond formation. In addition to decarboxylation and decarbonylation, other examples for UFC include the release of SO_2,[3] an amino group,[4] or an oxygen atom.[5]

Regarding catalytic UFC reactions of esters, there are three types of reactions in which certain atoms or groups are eliminated from the ester moiety, leading to the formation of new bonds (Scheme 1). The first type involves decarboxylation (removal of CO_2), in which all atoms that constitute an ester group are eliminated to form C–C or C–heteroatom bonds. This type of reaction has been well-documented for allyl or benzyl esters.[1] The second type is decarbonylation, which involves the elimination of CO, resulting in the formation of an ether.[6] Although this reaction category is much less common, two examples using pyridyl esters[6a] and cyclic esters[6b] have been reported. The third type involves the formal elimination of an oxygen atom from an ester, which would generate a ketone. Although this mode of catalytic deoxygenative UFC of esters is attractive, it has not been reported to date, to the best of our knowledge.[7]

Herein, the author reports that this deoxygenative UFC of esters can be achieved when the dual use of nickel and photoredox catalysts are used. This transformation involves the deletion of an oxygen atom in an ester framework to the corresponding ketone, a reaction that can be viewed as a "*retro* Baeyer-Villiger reaction".

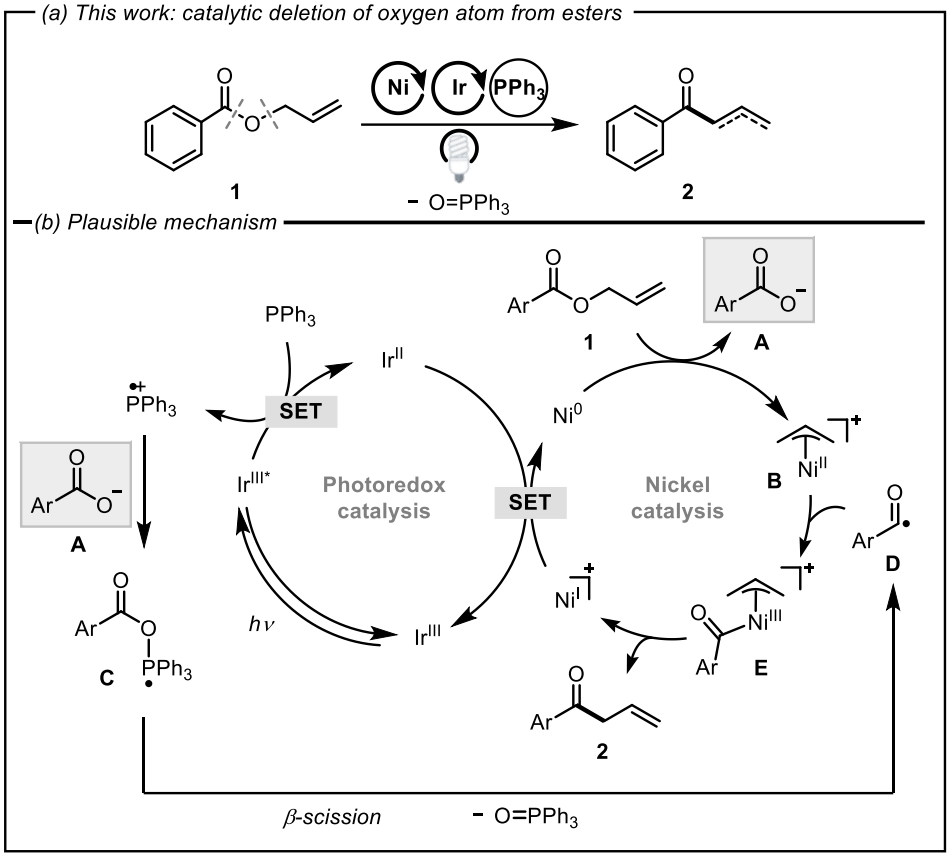


Scheme 1. Types of catalytic unimolecular fragment coupling of esters.

3.2. Results and Disccusion

Our group recently reported the palladium or nickel catalyzed UFC of amides via the elimination of isocyanate from allylic amide.[8] In this report, the author found that the reaction of allylamide with a nickel catalyst produces a cationic π-allyl nickel species and the corresponding amide anion. As indicated by this finding and previous studies about decarboxylation of allylesters[9], allylesters would also react with nickel catalyst to form ion-paired intermediates including carboxylates and a cationic π-allyl nickel species. The author therefore envisaged if it would be possible to remove the oxygen atom from this carboxylate in this ion-paired nickel complex. To achieve this, the author focused on the reactivity of phosphine radical cation and carboxylates, in which seminal independent studies have recently been reported by Zhu[10], Rovis and Doyle[11].

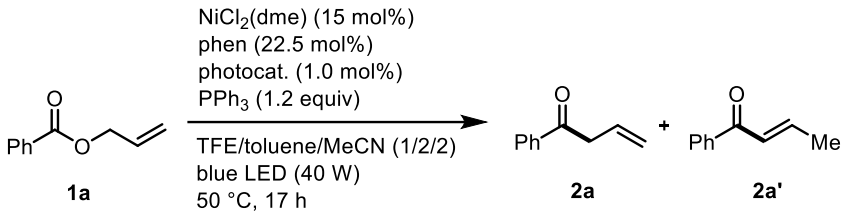
His mechanistic design is detailed in Scheme 2b. The author envisioned that allylester **1** would first be activated by oxidative addition with nickel catalyst to give carboxylate **A** and a cationic π-allyl nickel species **B**. Concurrently, the photoexcited *[Ir(dF(CF_3)ppy)$_2$(dtbbpy)]PF_6 {$E_{1/2}^{red}$[*Ir^{III}/Ir^{II}] = +0.97 V versus saturated calomel electrode (SCE)}[12] causes single-electron transfer (SET) oxidation of triphenylphosphine {$E_{1/2}$ = +0.98 V versus SCE}[13,14], resulting the formation of triphenylphosphine radical cation. This phosphine radical cation then reacted with carboxylate **A** to form the phosphoranyl radical **C**, which leads to the elimination of oxygen atom and the formation of acyl radical **D** with phosphine oxide via β-scission promoted by the strong affinity between the phosphoranyl radical and oxygen. Subsequently, this acyl radical **D** was trapped by a cationic π-allyl nickel species **B** to obtained a new π-allyl nickel complex **E**. Reductive elimination from this complex **E** would furnished the desired UFC product **2**.



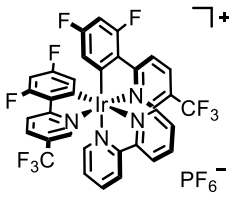
Scheme 2. Working Hypothesis

As a result of extensive optimization,[15] the desired deoxygenative UFC of allyl ester **1a** was found to proceed when the reaction was conducted in the presence of $NiCl_2$(dme) (15 mol%), phenanthroline (phen, 22.5 mol%), iridium photoredox catalyst **PC1** (1.0 mol%) and PPh_3 (1.2 equiv) in a mixed solvent (trifluoroethanol (TFE), toluene, and MeCN) at 50 °C for 17 h under irradiation with blue LED (460 nm). The deoxygenated product was obtained in 40% yield as a conjugated ketone **2a'**, rather than allyl ketone **2a**, since the double bond had undergone isomerization in the reaction system.[16] Control experiments revealed that a photoredox catalyst, a nickel catalyst, PPh_3, and light irradiation are all essential for the success of this UFC reaction (Entry 2-5). In addition to **2a'**, trifluoroethoxy esters, which are generated from the reaction with TFE, was also observed (ca. 10%). However, the highest yield was achieved when a solvent mixture containing all three solvents was used. For example, the reaction in the absence of TFE was less effective (13% yield, Entry 6). Interestingly, lowering the reaction temperature to 40 °C resulted in the formation of an approximately 1:1 mixture of the allyl ketone **2a** and the conjugated ketone **2a'** in 41% combined yield (Entry 7). Although the products were a mixture of isomers, the combined yields were generally higher in the case of other substrates when the reactions were conducted at 40 °C (see Scheme 3).

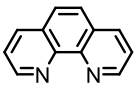
Table 1 Nickel/photo redox-catalyzed deoxygenation of **1a**[a]



Entry	Deviation from above conditions	Isolated yield [%] (**2a**:**2a'**)
1	None	40 (**2a'** only)
2	Without photocat.	0
3	Without Ni/phen	0
4	Without PPh_3	0
5	Without blue LED	0
6	Without TFE	13 (**2a'** only)[b]
7	At 40 °C	41 (1:1.1)



photocat.



phen

CF_3CH_2OH
TFE

[a]Reaction conditions: allylester **1** (0.20 mmol), $NiCl_2$(dme) (0.030 mmol), phen (0.045 mmol), photochem. (0.020 mmol) and PPh_3 (0.24 mmol) in TFE (0.50 mL), toluene (1.0 mL) and MeCN (1.0 mmol) at 50 °C for 17 h. [b]The yield determined by NMR analysis. dme = 1,2-dimethoxyethane

With the optimized reaction conditions in hand, the author then examined the substrate scope for this reaction (Scheme 3). With regard to the acyl group, a MeO group (**1b**) and a phenyl group (**1c**) on aromatic ring was found to be compatible with this reaction, resulting in the formation of deoxygenated products [52% (**2b**:**2b'**=2.7:1) and 60% (**2c**:**2c'**=1:2.3), respectively]. Halogen groups such as *p*-chloro (**1d**) and *p*-fluoro (**1k**) substituent was tolerated, allowing the resulting ketones to be amenable to further structural elaboration via common C−X bond functionalization reactions. It should also be noted that this reaction can be performed on a 1.0 mmol scale by simply applying the standard protocol, and deoxygenated products **2d** and **2d'** were obtained in a combined yield of 63% in a ratio of 1:2.2.[17] On the other hand, electron-withdrawing groups, such as an ester (**1e**) was found to be less effective substrates for this reaction.

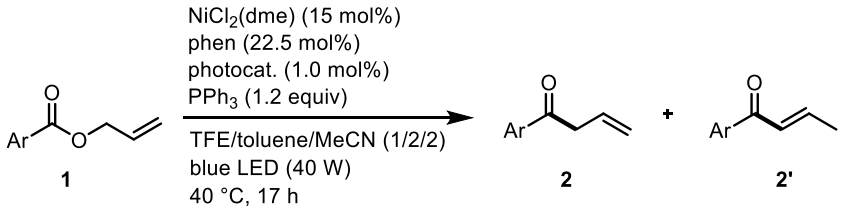
This reaction also proceeds using substrates bearing two substituents at the ortho and para positions, including those containing both electron-withdrawing and electron-donating groups (**1f** and **1g**), or two electron-donating groups (**1h**). An allyl ester with *m*-chloro and *p*-methoxy groups (**1f**) participated in this UFC reaction to form the corresponding products in 82% combined yield (**2f**:**2f'** = 1:1.3). In addition, this deoxygenative UFC is applicable to

sterically hindered allylic esters bearing an *o*-phenyl or *o*-methyl group (i.e., **1i** and **1j**). Allylic esters bearing heteroaryl groups (**1l** and **1m**) also successfully participated in this deoxygenative UFC reaction.

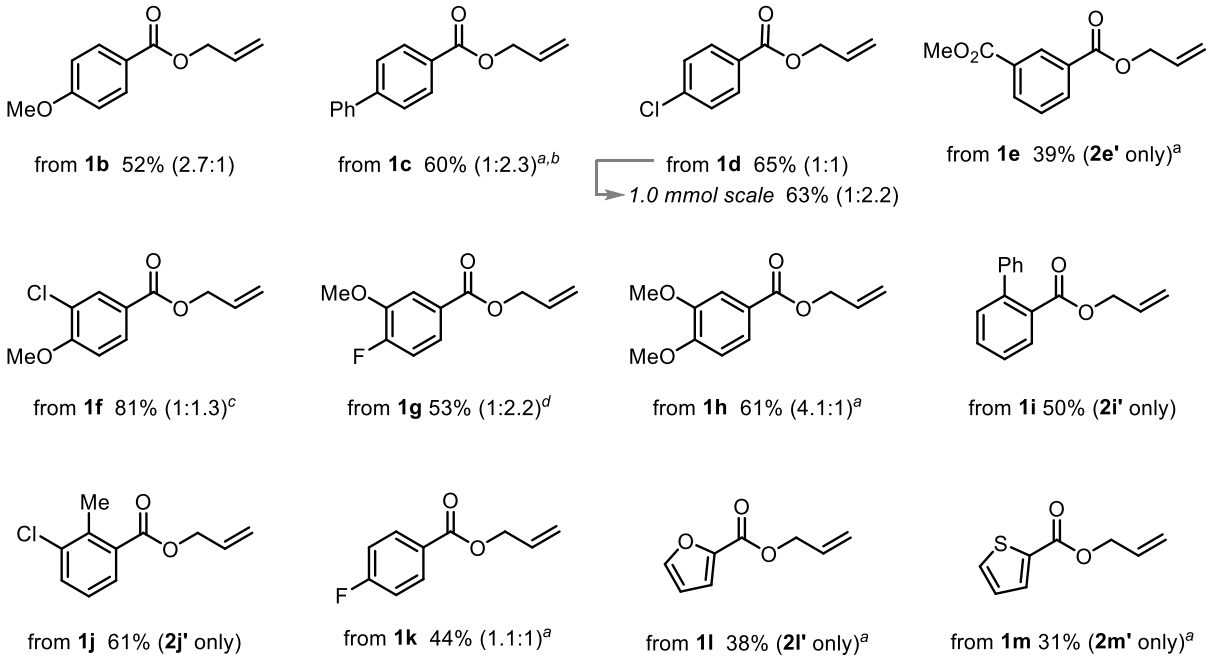
Regarding the allylic fragment, several substituted derivatives were found to be applicable. For example, an oxygen atom was eliminated from the terminal substituted **1n** with the formation of the corresponding allyl ketone **2n** and the conjugated ketone **2n'** in 64% combined yield (**2b**:**2b'** = 1:2.5). Both 2-methylallyl **1o** and 3-methylallyl derivative **1p** participated in this reaction to produce the ketones **2o'** or allyl ketone **2p** as the sole products.

Although the reaction afforded a mixture of non-conjugated (i.e., **2**) and conjugated (i.e., **2'**) ketones in several cases, the mixture can be converted into a pure **2'** by simply treating it with DABCO afterwards without any loss in yield (see SI for details).

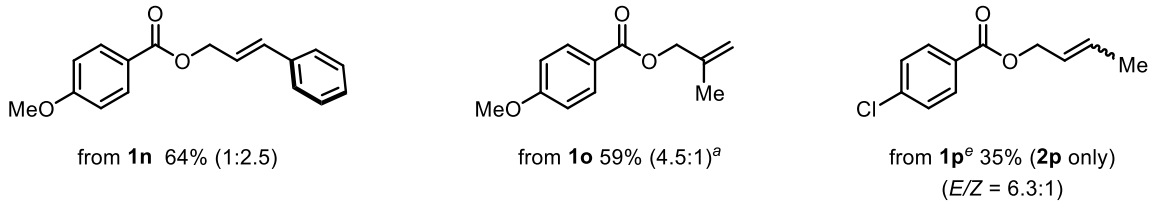
Scheme 3. Scope of Nickel/Photoredox-Catalyzed Deoxygenation of Allyl Esters.



aryl group variation



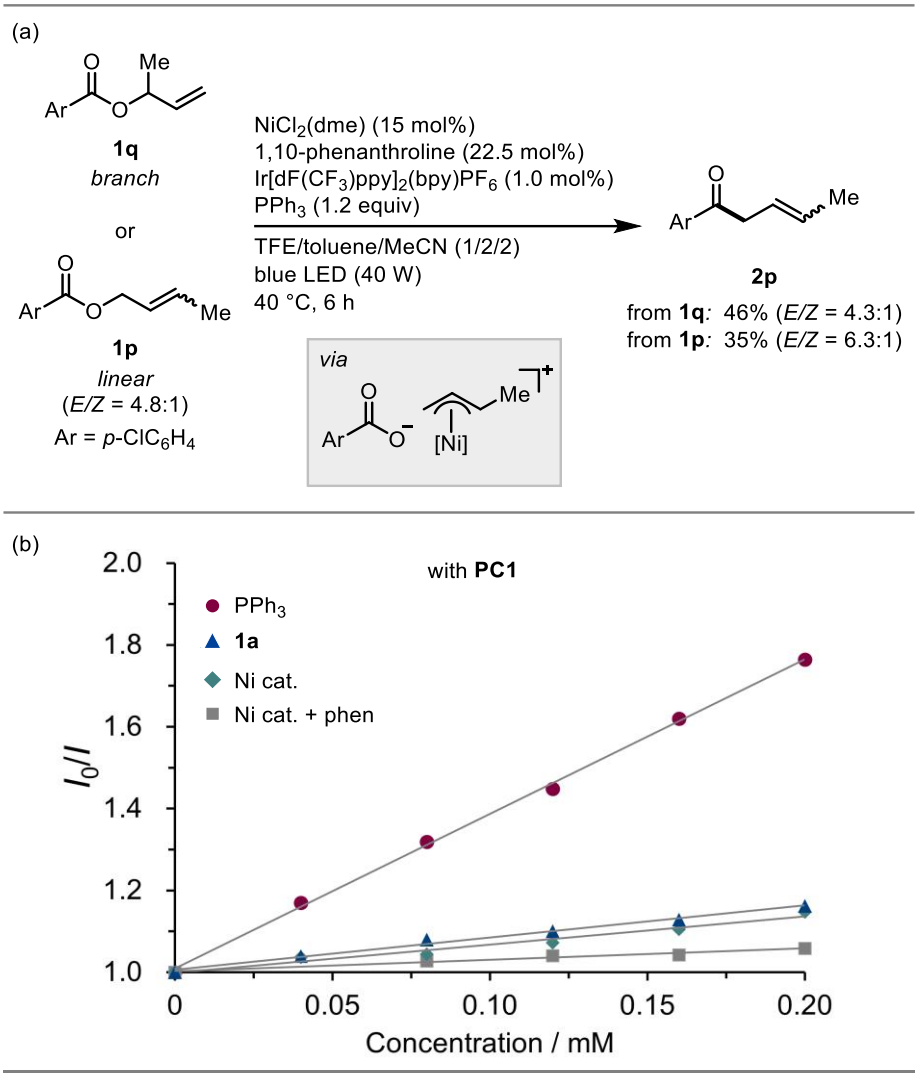
allyl group variation



[a]Run for 6 h. [b]**2d'** was formed as a mixture of *E/Z* geometric isomer (7.4/1). [c]**2f'** was formed as a mixture of *E/Z* geometric isomer (1/1.3). [d]**2g'** was formed as a mixture of *E/Z* geometric isomer (1/1). [e]**1p** is a mixture of *E/Z* geometric isomer (4.8/1).

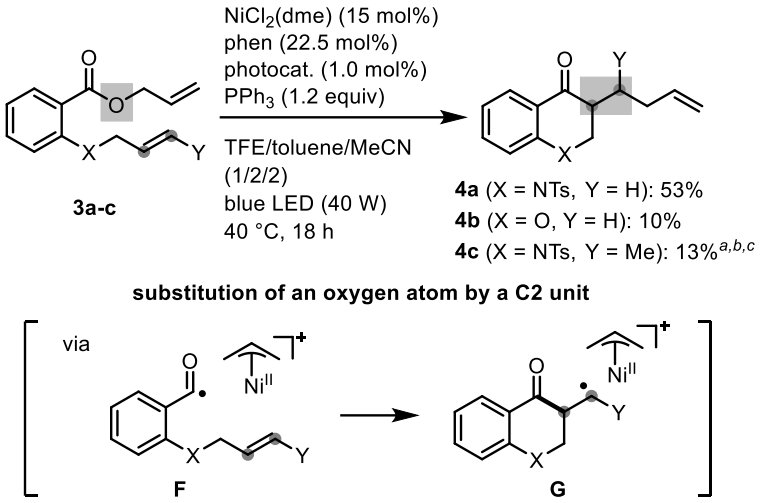
To obtain some supporting evidence for this reaction mechanism, several mechanistic studies were performed. For example, allyl esters bearing branched (**1q**) and linear (**1p**) allyl groups both afforded linear allylated product **2p** under the standard conditions, which suggests that both reactions proceed via a common □-allynickel intermediate (Scheme 4a). The author also performed luminescence-quenching experiments on the iridium photocatalysts **PC1**. Stern−Volmer plots revealed that an excited state of **PC1** is most efficiently quenched by PPh_3, resulting in the

formation of a triphenylphosphine radical cation as the author originally envisioned (Scheme 4b). In addition, the postulated acyl radical intermediate was intercepted with an external alkene under these conditions (see SI for details)



Scheme 4. Mechanistic studies: (a) Support for the intermediacy of π-allynickel complex. (b) Stern−Volmer experiment with **PC1**.

This UFC reaction can be used, not only for the removal of the oxygen atom from an ester, but also for the substitution of the oxygen atom with a two-carbon unit. For example, when an allyl ester bearing a tethered alkene moiety (i.e., **3**) was reacted under the Ni/photocat conditions, the cyclic ketone **4** was obtained (Scheme 5). This transformation can be viewed as the substitution of the oxygen atom in **3** (colored in red in Scheme 5) with a tethered alkene moiety (colored in orange in Scheme 5). The formation of **4** can be rationalized by assuming the generation of an acyl radical **F** and a π-allyl nickel intermediate via the elimination of phosphine oxide, 6-exo cyclization of the acyl radical **F**, followed by the recombination of the resulting alkyl radical species **G** with the π-aryl nickel species.



Scheme 5. Catalytic Deoxygenative Insertion of a Tethered Alkene into Allyl Ester **3**. [a]0.40 mmol scale. [b]**3c** is a mixture of *E/Z* geometric isomer (5.9/1). [c]d.r. = 1.3/1., d.r. = diastereoisomeric ratio.

3.3. Conclusion

In summary, the author reports on the nickel and photoredox dual-catalyzed UFC of allyl esters. The reaction proceeds via the formal elimination of oxygen atom, thus providing a new strategy for the generation of ketones from esters. The key feature of this reaction is that it involves a combination of a nickel-catalyzed oxidative addition/reductive elimination cycle and a photoredox-catalyzed deoxygenation process of carboxylates using PPh_3 in a single reaction system. The author have also demonstrated that this UFC allows the formal catalytic substitution of the ester oxygen atom by a C2 unit. These UFC reactions of esters provide a new option for modifying ester skeletons. Further studies directed at the development of new catalytic UFC reactions using other esters and related compounds are currently underway in our laboratory.

3.4. Experimental Section

I. General Information

^1H, ^{13}C, and ^{19}F NMR spectra were recorded on a JEOL ECS-400 spectrometer in $CDCl_3$. The chemical shifts in ^1H NMR spectra were recorded relative to $CHCl_3$ (δ 7.26). The chemical shifts in ^{13}C NMR spectra were recorded relative to $CDCl_3$ (δ 77.16). The chemical shifts in ^{19}F NMR spectra were recorded relative to perfluorobenzene (-163.0 ppm). The data is reported as follows: chemical shift (δ) in ppm, coupling constant (Hz), and integration. Infrared spectra (IR) were obtained using a JASCO FT/IR-4200 spectrometer. Absorption is reported in reciprocal centimeters (cm^{-1}) with the following relative intensities: s (strong), m (medium), or w (weak). High resolution mass spectra (HRMS) were obtained using JEOL JMS-700 spectrometer (EI-double-focusing) or a JEOL JMS-T100LP spectrometer (DART-TOF). Melting points were determined using a Yamato melting point apparatus. Column chromatography was performed with Biotage Isolera® equipped with Biotage SNAP Ultra or SNAP Isolute NH_2 Cartridge. All photo reactions were carried out using Blue Kessil A160WE Tuna Blue and glass oil bath (MOB-200D, Techno Sigma).

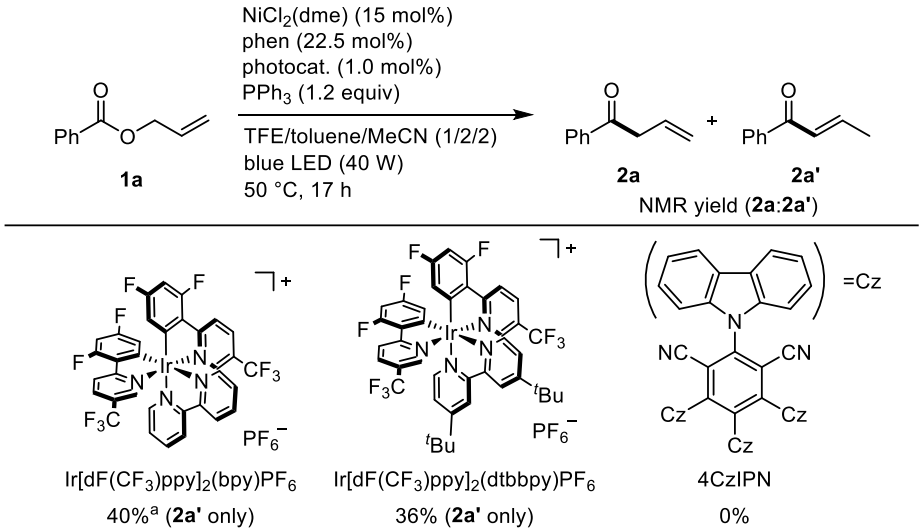
II. Materials

All commercially available reagents and solvents were supplied from TCI, WAKO and Aldrich. These corresponding allylesters including **1b** [CAS:6941-68-0],[3] **1c** [CAS:115694-59-2],[1] **1d** [CAS:15784-28-8],[1] **1e** [CAS:52255-63-7],[2] **1h** [CAS:128863-83-2],[1] **1i** [CAS:61422-02-4],[1] **1k** [CAS:53409-01-1],[1] **1l** [CAS:131323-45-0],[1] **1m** [CAS:431948-67-3],[1] **1n** [CAS:204453-96-3],[1] **1o** [CAS:34301-32-1],[1] **1p** [CAS:99893-77-3],[2] **1q** [CAS:1384266-61-8][1] and **3b** [CAS:89844-08-6][4] were prepared according to literature procedures.

III. Optimization Studies

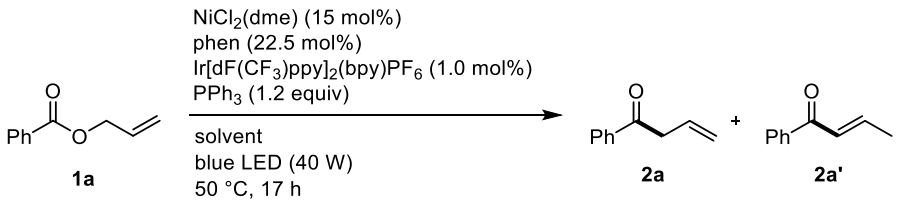
A procedure for optimization studies. In a glovebox filled with nitrogen, $NiCl_2$•dme (5–15 mol%), ligands (7.5–22.5 mol%), photocat. (1.0 mol%), aromatic carboxylic ester (0.20 mmol), phosphine reagents (0.24 mmol) and solvents (2.5 mL) were added to a 10 mL vial with a Teflon-sealed screwcap. The tube was then sealed and was placed at a distance (ca. 4.0 cm) from blue LEDs (45 W × 2), and the mixture was stirred at 40 or 50 °C for 18 h. Then, the reaction mixture was removed from the light and the crude mixture was filtered through a pad of celite. The filtrate was then concentrated *in vacuo*. The crude product was then analyzed by ^{1}H NMR with 1,1,2,2-tetrachloroethane as an external standard.

Table S1. Optimization of photocatalysts.



a) Isolated yield.

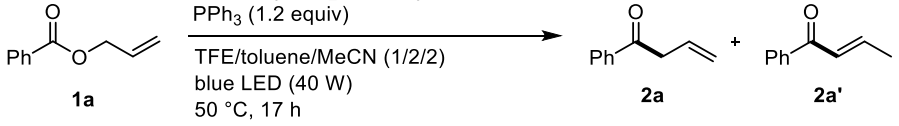
Table S2. Optimization of solvents.



entry	solvent (2.5 mL)	NMR yields (%) (2a:2a')
0	MeCN + toluene + TFE (2:2:1)	45 (40)[a] (**2a'** only)
1	MeCN	24 (**2a'** only)
2	toluene	0
3	THF	0
4	HFIP	0
5	TFE	0
6	MeCN + toluene (1:1)	13 (**2a'** only)
7	MeCN + TFE (1:1)	22 (**2a'** only)
8	MeCN + toluene + HFIP (2:2:1)	36 (**2a'** only)
9	MeCN + toluene + *t*-BuOH (2:2:1)	18 (**2a'** only)
10	MeCN + toluene + *i*-PrOH (2:2:1)	20 (**2a'** only)

a) Isolated yield.

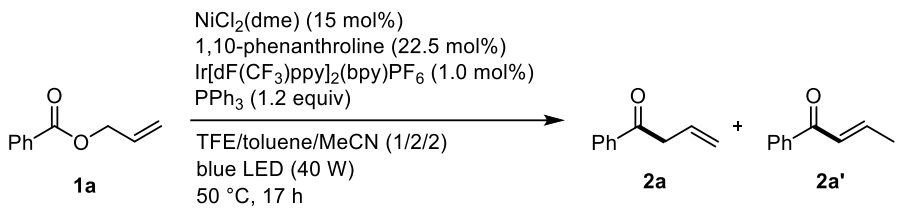
Table S3. Optimization of ligands.



entry	Ligand	NMR yields (%) (**2a**:**2a'**)
0	1,10-phenanthroline	45 (40)[a] (**2a'** only)
1	dcype	0
2	dtbbpy	43 (13:1)
3	2,2'-bipyridine	32 (**2a'** only)
4	4,4'-di(trifluoromethyl)bipyridine	43 (1:13)
5	ICy•HBF_4	15 (**2a'** only)
6	none	44 (1.2:1)

a) Isolated yield.

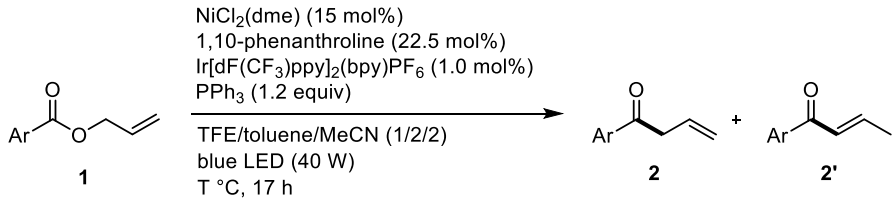
Table S4. Optimization of phosphine and other reagents for deoxygenation step.

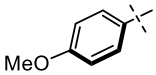
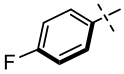


entry	PR_3	NMR yields (%) (**2a**:**2a'**)
0	PPh_3	45 (40)[a] (**2a'** only)
1	$P(p\text{-}MeOC_6H_4)_3$	trace (**2a'** only)
2	$P(p\text{-}CF_3C_6H_4)_3$	0
3	$PCyPh_2$	9 (**2a'** only)
4	$P(OEt)_3$	0
5	DMDC	0 (**1a**: quant)
6	Boc_2O	0 (**1a**: quant)

a) Isolated yield.

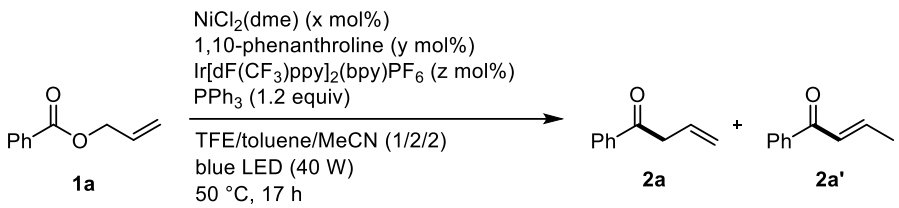
Table S5. Optimization of reaction temperatures with several allyl esters.



entry	Ar	T (°C)	NMR yields (**2**:**2'**)
1		50	40%[a] (**2'** only)
2		40	41%[a] (1:1.1)
3		50	34% (1.6:1)
4		40	50% (3.2:1)
5		50	36% (**2'** only)
6		40	54% (1.1:1)

a) Isolated yield.

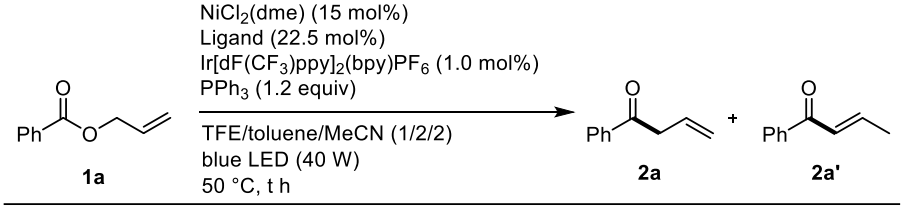
Table S6. Optimization of catalyst loading.



entry	x (mol%)	y (mol%)	z (mol%)	NMR yields (%) (**2a**:**2a'**)
0	15	22.5	1	45 (40)[a] (**2a'** only)
1	15	22.5	2	42 (**2a'** only)
2	10	15	1	40 (**2a'** only)
3	5	7.5	1	29 (**2a'** only)

a) Isolated yield.

Table S7. Optimization of reaction time.

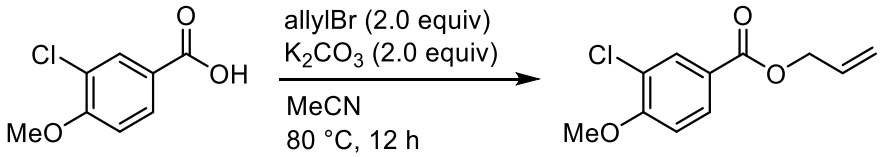


entry	t (h)	NMR yields (%) (**2a**:**2a'**)	recovered **1a**
1	3	47 (1.1:1)	0
2	6	46 (1:4.8)	0
3	17	45 (**2'** only)	0
4	40	23 (1:1)	0

a) Isolated yield.

IV. Preparation of Starting Materials for Nickel/Photo Redox-Catalyzed Deoxygenation of Allyl Esters for Nickel/Photo Redox-Catalyzed Deoxygenation of Allyl Esters

Allyl ester derivatives were prepared based on General Procedure.[1] These corresponding carboxylic acids were supplied from TCI.

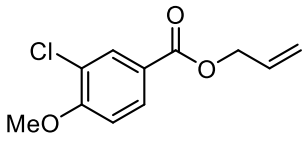


1f

To a stirred solution of 3-Chloro-4-methoxybenzoic acid [37908-96-6] (0.93 g, 5.0 mmol) in 25 mL of MeCN, K_2CO_3 (1.5 g, 10 mmol), and allyl bromide (1.0 mL, 10 mmol) were added, and the reaction mixture was stirred at 80 °C for 12 h. The reaction was quenched with H_2O, extracted with EtOAc, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (hexane/EtOAc = 10/1) to afford **1f**

as a colorless oil (0.33 g, 29%).

Allyl 3-chloro-4-methoxybenzoate (1f)



1f

Colorless oil (0.33 g, 29%). R_f 0.16 (SiO_2, hexane/EtOAc = 9/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 8.07 (d, *J* = 1.8 Hz, 1H), 7.96 (dd, *J* = 8.9, 2.5 Hz, 1H), 6.95 (d, *J* = 8.2 Hz, 1H), 6.06–5.98 (m, 1H), 5.40 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.29 (dd, *J* = 10.5, 1.5 Hz, 1H), 4.80 (dt, *J* = 5.6, 1.5 Hz, 2H), 3.96 (s, 3H).

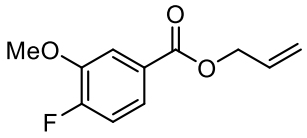
^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 165.1, 158.8, 132.3, 131.8, 130.1, 123.5, 122.7, 118.5, 111.4, 65.8, 56.5.

IR (KBr, cm^{-1}): 1717 s, 1600 m, 1502 m, 1312 m, 1269 s, 1233 m, 1116 m, 1062 w, 1020 w, 762 m, 707 w.

MS, m/z (relative intensity, %): 226 (M^+, 10), 171 (36), 170 (11), 169 (100), 77 (12), 63 (12), 41 (15).

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{11}H_{12}O_3{}^{35}Cl$: 227.0470, found: 227.0472.

Allyl 4-fluoro-3-methoxybenzoate (1g)



1g

Colorless oil (1.2 g, >99%). R_f 0.40 (SiO_2, hexane/EtOAc = 9/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.69–7.64 (m, 2H), 7.12 (dd, *J* = 11.0, 8.7 Hz, 1H), 6.07–6.00 (m, 1H), 5.41 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.30 (dd, *J* = 10.5, 1.5 Hz, 1H), 4.82 (dt, *J* = 6.0, 1.5 Hz, 2H), 3.94 (s, 3H)

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 165.5, 155.7 (d, J_F = 254.95), 147.8 (d, J_F = 11.50), 132.3, 126.8, 123.3 (d, J_F = 7.67), 118.6, 116.1 (d, J_F = 19.17), 114.7 (d, J_F = 3.83), 65.9, 56.5.

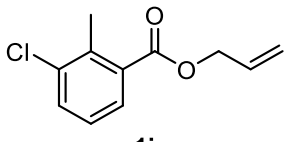
^{19}F NMR (376 MHz) δ: -128.8.

IR (KBr, cm^{-1}): 3750 w, 1717 s, 1541 w, 1509 m, 1416 m, 1285 s, 1211 m, 1180 m, 760 m.

MS, m/z (relative intensity, %): 210 (M^+, 12), 154 (12), 153 (100), 125 (25), 95 (12), 41 (15).

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{11}H_{12}O_3F$: 211.0765, found: 211.0766.

Allyl 3-chloro-2-methylbenzoate (1j)



1j

Colorless oil (0.44g, 42%). R_f 0.42 (SiO_2, hexane/EtOAc = 9/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.73 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.51 (dd, *J* = 8.0, 1.1 Hz, 1H), 7.18 (t, *J* = 7.8 Hz,

1H), 6.07–6.00 (m, 1H), 5.44–5.29 (m, 2H), 4.81 (dt, *J* = 6.0, 1.1 Hz, 2H), 2.61 (s, 3H).

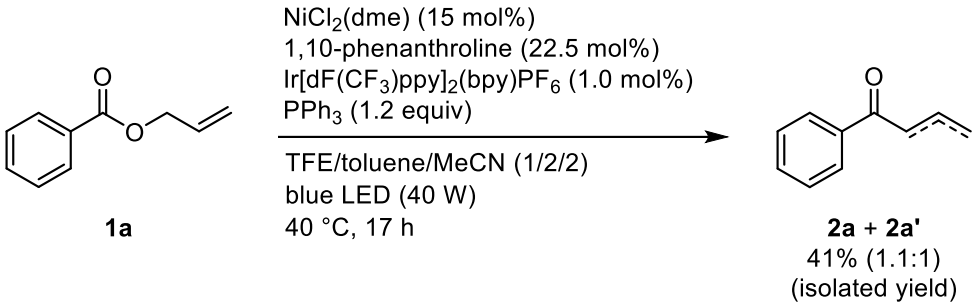
^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 13C-NMR (101 MHz, CHLOROFORM-D) δ 167.2, 137.3, 136.3, 132.7 (two overlapping peaks), 132.1, 128.7, 126.5, 118.8, 66.0, 17.6.

IR (KBr, cm^{-1}): 3854 w, 3750 w, 1724 s, 1541 w, 1438 m, 1249 s, 1213 m, 1103 w, 1016 m, 754 m.

MS, m/z (relative intensity, %): 210 (M^+, 5), 181 (23) 171 (32), 170 (17), 169 (100), 168 (13), 157 (15), 155 (23), 153 (72), 127 (18), 125 (56), 99 (12), 90 (13), 89 (53), 77 (30), 63 (28), 41 (44).

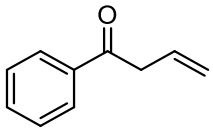
HRMS (DART) *m/z* [M+H^+] calcd for $C_{11}H_{12}O_3{}^{35}Cl$: 211.0520, found: 211.0522.

V. Typical Procedure for Nickel/Photo Redox-Catalyzed Deoxygenation of Allyl Esters 1



In a glovebox filled with nitrogen, $NiCl_2$•dme (6.9 mg, 15 mol%), 1,10-phenanthroline (8.2 mg, 22.5 mol%), Ir[dF(CF_3)ppy]$_2$(bpy)PF_6 (2.0 mg, 1 mol%), allyl ester **1a** (32.8 mg, 0.20 mmol, 1.0 equiv), PPh_3 (61.4 mg, 0.24 mmol, 1.2 equiv), TFE (0.50 mL), toluene (1.0 mL) and MeCN (1.0 mL) were added to a 10 mL vial with a Teflon-sealed screwcap. The tube was then sealed and was placed at a distance (ca. 4.0 cm) from blue LEDs (45 W × 2), and the mixture was stirred at 40 °C for 17 h. Then, the reaction mixture was removed from the light and the crude mixture was filtered through a pad of celite. The filtrate was then concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (hexane/EtOAc = 10/1) to afford **2a** as colorless oil (6.2 mg, 21%) and **2a'** as colorless oil (5.8 mg, 20%).

1-Phenyl-but-3-en-1-one (2a). CAS [6249-80-5]



2a

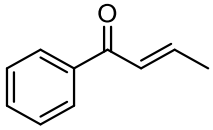
Colorless oil (6.2 mg, 21%). R_f 0.40 (SiO_2, hexane/EtOAc = 9/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.99–7.96 (m, 2H), 7.58 (t, *J* = 7.6 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 2H), 6.15–6.05 (m, 1H), 5.26–5.20 (m, 2H), 3.77 (dt, *J* = 6.8, 1.6 Hz, 2H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 198.2, 136.7, 133.3, 131.2, 128.8, 128.4, 118.9, 43.6.

HRMS (DART) *m/z* [M+H^+] calcd for $C_{10}H_{11}O$: 147.0804, found: 147.0808.

(*E*)-1-Phenylbut-2-en-1-one (2a'). CAS [35845-66-0]



2a'

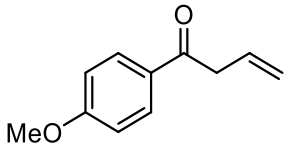
Colorless oil (5.8 mg, 20%). R_f 0.34 (SiO_2, hexane/EtOAc = 9/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.93–7.91 (m, 2H), 7.57-7.54 (m, 1H), 7.47 (t, *J* = 7.3 Hz, 2H), 7.12–7.03 (m, 1H), 6.91 (dd, *J* = 15.1, 1.4 Hz, 1H), 2.01 (dd, *J* = 6.9, 1.4 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 191.0, 145.2, 138.0, 132.7, 128.6 (two overlapping peaks), 127.7, 18.8.

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{10}H_{11}O$: 147.0804, found: 147.0807.

1-(4-Methoxyphenyl)but-3-en-1-one (2b). CAS [85234-21-5]



2b

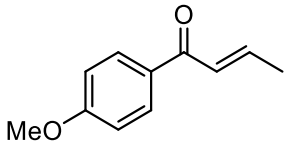
Colorless oil (13.5 mg, 38%). R_f 0.26 (SiO_2, hexane/EtOAc = 9/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.96 (d, *J* = 8.0 Hz, 2H), 6.94 (d, *J* = 8.0 Hz, 2H), 6.12–6.05 (m, 1H), 5.23–5.18 (m, 2H), 3.87 (s, 3H), 3.72 (dd, *J* = 6.9, 1.4 Hz, 2H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 196.7, 163.6, 131.5, 130.7, 129.7, 118.6, 113.8, 55.6, 43.3.

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{11}H_{13}O_2$: 177.0910, found: 177.0906.

(*2E*)-1-(4-Methoxyphenyl)-but-2-en-1-one (2b'). CAS [97060-29-2]



2b'

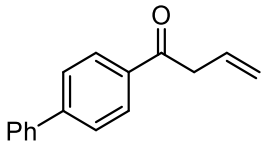
Colorless oil (4.9 mg, 14%). R_f 0.14 (SiO_2, hexane/EtOAc = 9/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.95 (dt, *J* = 9.5, 2.5 Hz, 2H), 7.11–7.02 (m, 1H), 6.97–6.90 (m, 3H), 3.88 (s, 3H), 1.99 (dd, *J* = 6.9, 1.4 Hz, 3H).

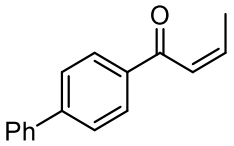
^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 189.1, 163.4, 144.1, 130.9 (two overlapping peaks), 127.3, 113.9, 55.6, 18.7.

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{11}H_{13}O_2$: 177.0910, found: 177.0908.

1-(Biphenyl-4-yl)but-3-en-1-one (2c) CAS [929606-64-4] and **(2*E*)-1-([1,1'-Biphenyl]-4-yl)but-2-en-1-one (2c").** CAS [1453859-80-7]



2c



2c"

Run for 6 h.

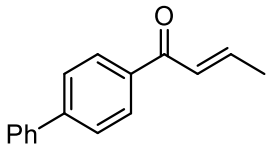
White solid (9.2 mg, 23% (**2c/2c"** = 3.6/1)). R_f 0.37 (SiO_2, hexane/EtOAc = 9/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 8.07–8.01 (m, 2H+2H, **2c**+**2c"**), 7.71–7.63 (m, 4H+4H, **2c**+**2c"**), 7.50–7.40 (m, 3H+3H, **2c**+**2c"**), 6.94–6.82 (1H, **2c"**), 6.56–6.37 (1H, **2c"**), 6.12 (dd, *J* = 17.0, 10.5 Hz, 1H), 5.28–5.22 (m, 2H), 3.80 (dt, *J* = 6.7, 1.5 Hz, 2H), 2.18 (dd, *J* = 7.3, 1.8 Hz, 3H, **2c"**).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 197.8, 146.0, 144.1 (**2c"**), 140.0, 135.3, 131.2, 129.1, 129.0, 128.4, 128.3 (**2c"**), 127.42, 127.37 (**2c"**), 125.4, 119.0, 43.7, 16.4 (**2c"**).

HRMS (EI) *m/z* [M^+] calcd for $C_{16}H_{14}O$: 222.1045, found: 222.1044 (**2c**) and 222.1042 (**2c"**).

(*2E*)-1-([1,1'-Biphenyl]-4-yl)but-2-en-1-one (2c'). CAS [1360924-05-5]



2c'

Run for 6 h.

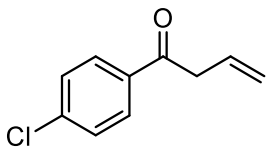
White solid (15.2 mg, 37%). R_f 0.26 (SiO_2, hexane/EtOAc = 9/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 8.02 (d, *J* = 8.7 Hz, 2H), 7.70–7.63 (m, 4H), 7.49–7.45 (m, 2H), 7.42–7.38 (m, 1H), 7.16–7.07 (m, 1H), 6.96 (dd, *J* = 15.3, 1.6 Hz, 1H), 2.02 (dd, *J* = 6.9, 1.4 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 190.3, 145.5, 145.1, 140.1, 136.7, 129.3, 129.1, 128.3, 127.5, 127.4, 127.3, 18.8.

HRMS (DART) *m/z* [$M+H^+$] calcd for $C_{16}H_{15}O$: 223.1117, found: 223.1119.

1-(4-Chlorophenyl)but-3-en-1-one (2d). CAS [95827-00-2]



2d

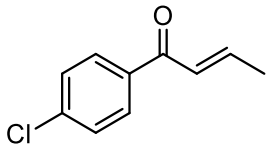
Colorless oil (12.4 mg, 33%). R_f 0.37 (SiO_2, hexane/EtOAc = 9/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.91 (dt, *J* = 8.9, 2.2 Hz, 2H), 7.45 (dt, *J* = 9.0, 2.1 Hz, 2H), 6.12–6.02 (m, 1H), 5.27–5.19 (m, 2H), 3.74 (dt, *J* = 6.6, 1.5 Hz, 2H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 197.0, 139.8, 134.9, 130.8, 129.9, 129.1, 119.2, 43.6.

HRMS (DART) *m/z* [$M+H^+$] calcd for $C_{10}H_{10}O^{35}Cl$: 181.0415, found: 181.0413.

(*2E*)-1-(4-Chlorophenyl)but-2-en-1-one (2d'). CAS [95826-96-3]



2d'

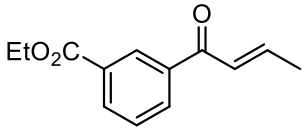
Colorless oil (11.9 mg, 32%). R_f 0.31 (SiO_2, hexane/EtOAc = 9/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.88–7.86 (m, 2H), 7.44 (dt, *J* = 9.0, 2.1 Hz, 2H), 7.14–7.05 (m, 1H), 6.87 (dt, *J* = 15.3, 1.6 Hz, 1H), 2.01 (dd, *J* = 6.9, 1.4 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 189.5, 145.8, 139.2, 136.3, 130.1, 129.0, 127.2, 18.8.

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{10}H_{10}O^{35}Cl$: 181.0415, found: 181.0418.

Methyl 3-[(*2E*)1-oxo-2-buten-1-yl]benzoate (2e'). CAS [1824823-41-7]



2e'

Run for 6 h.

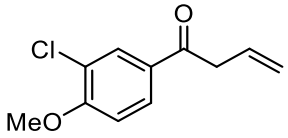
Colorless oil (15.0 mg, 39%). R_f 0.12 (SiO_2, hexane/EtOAc = 9/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 8.57 (t, *J* = 1.6 Hz, 1H), 8.23 (dt, *J* = 7.8, 1.4 Hz, 1H), 8.13 (dt, *J* = 7.6, 1.5 Hz, 1H), 7.57 (t, *J* = 7.8 Hz, 1H), 7.17–7.08 (m, 1H), 6.96 (dq, *J* = 15.2, 1.5 Hz, 1H), 3.96 (s, 3H), 2.03 (dd, *J* = 6.9, 1.4 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 189.9, 166.5, 146.2, 138.3, 133.6, 132.9, 130.6, 129.7, 129.0, 127.3, 52.5, 18.8.

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{12}H_{13}O_3$: 205.0859, found: 205.0854.

1-(3-Chloro-4-methoxyphenyl)but-3-en-1-one (2f)



2f

White solid (15 mg, 36%). R_f 0.16 (SiO_2, hexane/EtOAc = 9/1). M.p. 80 °C.

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 8.00 (d, *J* = 2.3 Hz, 1H), 7.88 (dd, *J* = 8.7, 2.3 Hz, 1H), 6.97 (d, *J* = 8.7 Hz, 1H), 6.11–6.01 (m, 1H), 5.25–5.18 (m, 2H), 3.97 (s, 3H), 3.69 (dt, *J* = 6.4, 1.4 Hz, 2H).

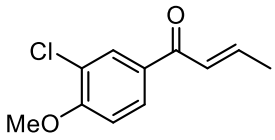
^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 195.8, 159.0, 131.1, 130.8, 130.3, 128.9, 123.1, 119.0, 111.5, 56.5, 43.3.

IR (KBr, cm^{-1}): 1671 s, 1567 m, 1445 m, 1326 m, 1281 s, 1201 s, 1012 s, 813 m 701 w.

MS, m/z (relative intensity, %): 210 (M$^+$, 1), 171 (32), 169 (100), 141 (11), 126 (13), 77 (17), 63 (13).

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{11}H_{12}O_2{}^{35}Cl$: 211.0520, found: 211.0524.

(*2E*)-1-(3-Chloro-4-methoxyphenyl)but-2-en-1-one (2f')



2f'

White solid (9.2 mg, 22%). R_f 0.14 (SiO_2, hexane/EtOAc = 9/1). M.p. 101 °C.

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 8.00 (d, *J* = 1.8 Hz, 1H), 7.87 (dd, *J* = 8.7, 2.3 Hz, 1H), 7.11–7.03 (m, 1H), 6.98 (d, *J* = 8.7 Hz, 1H), 6.90–6.85 (m, 1H), 3.97 (s, 3H), 2.00 (dd, *J* = 6.9, 1.8 Hz, 3H).

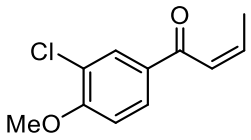
^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 188.1, 158.7, 145.0, 131.5, 131.0, 129.1, 126.8, 123.0, 111.5, 56.5, 18.7.

IR (KBr, cm^{-1}): 3749 w, 1619 s, 1560 m, 1506 m, 1411 m, 1303 m, 1257 s, 1190 w, 1017 s, 934 w, 808 s, 679 w.

MS, m/z (relative intensity, %): 212 (M^++2, 13), 210 (M^+, 40), 195 (11), 175 (21), 171 (32), 169 (100), 141 (13), 126 (16), 111 (11), 77 (22), 75 (11), 69 (49), 63 (23), 41 (33).

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{11}H_{12}O_2{}^{35}Cl$: 211.0520, found: 211.0525.

(2*Z*)-1-(3-Chloro-4-methoxyphenyl)but-2-en-1-one (2f")



2f"

White solid (10 mg, 24%). R_f 0.16 (SiO_2, hexane/EtOAc = 9/1). M.p. 86 °C.

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.99 (d, *J* = 2.3 Hz, 1H), 7.86 (dd, *J* = 8.7, 2.3 Hz, 1H), 6.97 (d, *J* = 8.7 Hz, 1H), 6.76 (dd, *J* = 11.9, 1.8 Hz, 1H), 6.42 (dd, *J* = 11.9, 7.3 Hz, 1H), 3.97 (s, 3H), 2.13 (dd, *J* = 7.3, 1.8 Hz, 3H).

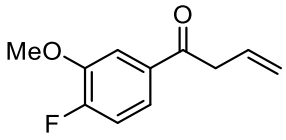
^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 189.9, 158.6, 144.0, 132.3, 130.9, 128.9, 125.0, 123.0, 111.5, 56.5, 16.4.

IR (KBr, cm^{-1}): 3749 w, 1647 w, 1592 m, 1499 m, 1313 m, 1255 s, 1057 s, 787 m.

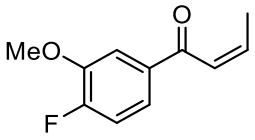
MS, m/z (relative intensity, %): 212 (M^++2, 12), 210 (M^+, 35), 195 (14), 175 (92), 174 (34), 171 (30), 169 (100), 141 (25), 126 (35), 115 (16), 77 (55), 69 (67), 63 (57), 41 (72).

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{11}H_{12}O_2{}^{35}Cl$: 211.0520, found: 211.0526.

1-(4-Fluoro-3-methoxyphenyl)but-3-en-1-one (2g) and **(2*Z*)-1-(4-Fluoro-3-methoxyphenyl)but-2-en-1-one (2g")**



2g



2g"

Colorless oil (13 mg, 34% (**2g**/**2g"**=1/1)). R_f 0.32 (SiO_2, hexane/EtOAc = 9/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.63–7.60 (m, 1H+1H, **2g**+**2g"**), 7.56–7.48 (m, 1H+1H, **2g**+**2g"**), 7.16–7.10 (m, 1H+1H, **2g**+**2g"**), 6.79 (dq, *J* = 11.5, 1.8 Hz, 1H, **2g"**), 6.48–6.4 (m, 1H, **2g"**), 6.12–6.02 (m, 1H, **2g**), 5.26–5.19 (m,

2H, **2g**), 3.95 (s, 3H), 3.94 (s, 3H), 3.73 (dt, *J* = 6.7, 1.5 Hz, 2H, **2g**), 2.14 (dd, *J* = 7.1, 1.8 Hz, 3H, **2g"**).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 196.6 (**2g"**), 190.7 (**2g**), 155.8 (d, J_F = 255.91), 155.6 (d, J_F = 254.95), 148.2 (d, J_F = 10.54, **2g**), 148.1 (d, J_F = 11.50, **2g"**), 144.3 (**2g**), 135.4 (d, J_F = 3.83), 133.4 (d, J_F = 3.83), 131.1 (**2g"**), 125.0 (**2g**), 122.33 (d, J_F = 6.71, **2g"**), 122.26 (d, J_F = 7.67, **2g**), 119.0 (**2g"**), 116.0 (d, J_F = 19.17), 115.9 (d, J_F = 19.17), 113.1 (d, J_F = 2.88), 113.0 (d, J_F = 2.88), 56.43, 56.39, 43.4 (**2g"**), 18.8 (**2g**).

^{19}F NMR (376 MHz) δ: -128.1 and -129.0.

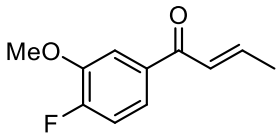
IR (KBr, cm^{-1}): 3750 w, 1684 m, 1669 m, 1604 m, 1514 s, 1457 w, 1413 w, 1275 s, 1198 w, 1167 m, 1126 w, 1025 m, 772 m.

MS, m/z (relative intensity, %) **2g**: 194 (M^+, 1), 153 (100), 125 (30), 110 (12), 95 (18), 82 (11).

2g": 194 (M^+, 47), 179 (26), 163 (98), 153 (91), 125 (74), 110 (36), 95 (51), 82 (42), 77 (26), 69 (100), 41 (95).

HRMS (EI) *m/z* [M^+] calcd for $C_{11}H_{11}O_2F$: 194.0743, found: 194.0738 (**2g**) and 194.0739 (**2g"**).

(2*E*)-1-(4-Fluoro-3-methoxyphenyl)but-2-en-1-one (2g')



2g'

Colorless oil (7.7 mg, 20%). R_f 0.20 (SiO_2, hexane/EtOAc = 9/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.60 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.50 (qd, *J* = 4.2, 2.1 Hz, 1H), 7.16–7.06 (m, 2H), 6.92–6.87 (m, 1H), 3.95 (s, 3H), 2.01 (dd, *J* = 6.9, 1.8 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 189.1, 155.6 (d, J_F = 253.99), 148.2 (d, J_F = 10.54), 145.3, 134.7 (d, J_F = 3.83), 127.0, 122.3 (d, J_F = 7.67), 115.9 (d, J_F = 19.17), 113.4 (d, J_F = 2.88), 56.5, 18.8.

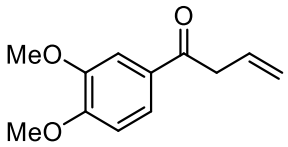
^{19}F NMR (376 MHz) δ: -129.0.

IR (KBr, cm^{-1}): 3750 w, 1671 w, 1624 w, 1602 w, 1509 s, 1456 m, 1415 m, 1297 s, 1272 s, 1169 m, 766 m.

MS, m/z (relative intensity, %): 194 (M^+, 42), 179 (39), 163 (10), 153 (100), 125 (40), 110 (16), 95 (22), 82 (18), 77 (12), 69 (79), 41 (42).

HRMS (DART) *m/z* [M+H^+] calcd for $C_{11}H_{12}O_2F$: 195.0816, found: 195.0816.

1-(3,4-Dimethoxyphenyl)but-3-en-1-one (2h). CAS [184165-65-9]



2h

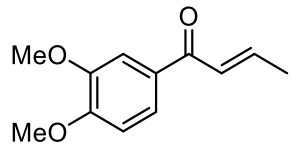
Run for 6 h.

Colorless oil (20 mg, 49%). R_f 0.16 (SiO_2, hexane/EtOAc = 9/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.59 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.54–7.52 (m, 1H), 6.88 (d, *J* = 8.5 Hz, 1H), 6.12–6.02 (m, 1H), 5.22–5.18 (m, 2H), 3.94 (s, 3H), 3.93 (s, 3H), 3.71 (d, *J* = 6.9 Hz, 2H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 196.7, 153.5, 149.2, 131.6, 130.0, 123.2, 118.6, 110.5, 110.2, 56.2, 56.1, 43.3.
HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{12}H_{15}O_3$: 207.1016, found: 207.1016.

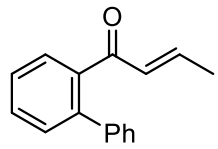
(2*E*)-1-(3,4-Dimethoxyphenyl)but-2-en-1-one (2h'). CAS [4693-35-0]



2h'

Run for 6 h.
Colorless oil (5.0 mg, 12%). R_f 0.14 (SiO_2, hexane/EtOAc = 9/1).
^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.57 (td, *J* = 7.9, 2.2 Hz, 2H), 7.10–7.02 (m, 1H), 6.96–6.88 (m, 2H), 3.947 (s, 3H), 3.945 (s, 3H), 1.99 (dd, *J* = 6.9, 1.4 Hz, 3H).
^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 189.0, 153.3, 149.3, 144.1, 131.1, 127.1, 123.2, 111.0, 110.1, 56.2, 56.2, 18.7.
HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{12}H_{15}O_3$: 207.1016, found: 207.1013.

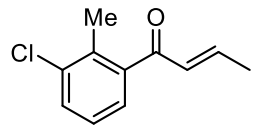
(*2E*)-1-([1,1'-Biphenyl]-2-yl)but-2-en-1-one (2i'). CAS [4693-35-0]



2i'

Colorless oil (22.2 mg, 50%). R_f 0.12 (SiO_2, hexane/EtOAc = 9/1).
^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.51 (td, *J* = 6.9, 1.8 Hz, 2H), 7.43–7.29 (m, 7H), 6.54 (dd, *J* = 15.6, 6.9 Hz, 1H), 6.01–5.96 (m, 1H), 1.66 (dd, *J* = 6.9, 1.8 Hz, 3H).
^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 197.4, 145.4, 140.9, 140.7, 139.8, 132.4, 130.4, 130.2, 129.2, 128.62, 128.56, 127.7, 127.4, 18.3.
HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{16}H_{15}O$: 223.1117, found: 223.1116.

(2*E*)-1-(3-Chloro-2-methylphenyl)but-2-en-1-one (2j')

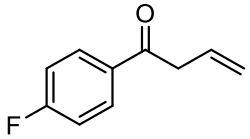


2j'

Colorless oil (23.6 mg, 61%). R_f 0.12 (SiO_2, hexane/EtOAc = 9/1).
^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.40 (q, *J* = 3.5 Hz, 1H), 7.15 (dd, *J* = 6.8, 3.5 Hz, 2H), 6.67–6.59 (m, 1H), 6.40 (dd, *J* = 15.8, 1.5 Hz, 1H), 2.32 (s, 3H), 1.93 (dd, *J* = 6.8, 1.5 Hz, 3H).
^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 196.9, 148.4, 141.6, 135.9, 134.0, 132.9, 130.8, 126.5, 125.9, 18.7, 17.2.

IR (KBr, cm^{-1}): 3750 w, 1682 m, 1654 s, 1620 m, 1437 s, 1292 s, 1263 w, 1192 m, 1007 w, 971 m, 786 m, 726 m.
MS, m/z (relative intensity, %): 194 (M^+, 3), 181 (33), 180 (12), 179 (100), 165 (11), 153 (25), 144 (80), 127 (17), 125 (42), 116 (13), 115 (23), 99 (13), 90 (12), 89 (49), 69 (67), 63 (32), 51 (10), 41 (60).
HRMS (DART) *m/z* [M+H^+] calcd for $C_{11}H_{12}O^{35}Cl$: 195.0571, found: 195.0578.

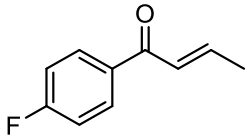
1-(4-Fluorophenyl)but-3-en-1-one (2k). CAS [61668-02-8]



2k

Colorless oil (7.9 mg, 22%). R_f 0.17 (SiO_2, hexane/EtOAc = 9/1).
^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 8.02–7.99 (m, 2H), 7.16–7.11 (m, 2H), 6.13–6.03 (m, 1H), 5.27–5.19 (m, 2H), 3.74 (dt, *J* = 6.6, 1.5 Hz, 2H).
^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 196.6, 165.9 (d, J_F = 254.95), 133.1 (d, J_F = 2.88), 131.1 (d, J_F = 9.58), 131.0, 119.1, 115.9 (d, J_F = 22.04), 43.5.
^{19}F NMR (376 MHz) δ: -106.3.
HRMS (DART) *m/z* [M+H^+] calcd for $C_{10}H_{10}OF$: 165.0710, found: 165.0706.

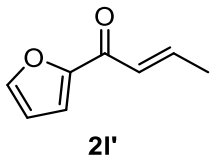
(*2E*)-1-(4-Fluorophenyl)but-2-en-1-one (2k'). CAS [604007-01-4]



2k'

Colorless oil (7.9 mg, 22%). R_f 0.11 (SiO_2, hexane/EtOAc = 9/1).
^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.99–7.94 (m, 2H), 7.17–7.04 (m, 3H), 6.89 (dq, *J* = 15.3, 1.6 Hz, 1H), 2.01 (dd, *J* = 6.9, 1.4 Hz, 3H).
^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 188.2, 165.6 (d, J_F = 253.99), 145.4, 134.3 (d, J_F = 2.88), 131.2 (d, J_F = 9.58), 127.2, 115.7 (d, J_F = 22.04), 18.7.
^{19}F NMR (376 MHz) δ: -107.3.
HRMS (DART) *m/z* [M+H^+] calcd for $C_{10}H_{10}OF$: 165.0710, found: 165.0709.

(*2E*)-1-(2-Furanyl)-2-buten-1-one (2l'). CAS [131323-45-0]



2l'

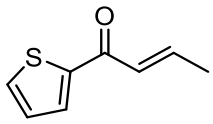
Run for 6 h.
Colorless oil (10 mg, 38%). R_f 0.21 (SiO_2, hexane/EtOAc = 9/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.62 (d, *J* = 0.9 Hz, 1H), 7.27–7.13 (m, 2H), 6.83 (dd, *J* = 15.3, 1.6 Hz, 1H), 6.56 (q, *J* = 1.7 Hz, 1H), 1.99 (dd, *J* = 6.9, 1.4 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 178.2, 153.4, 146.6, 144.5, 126.5, 117.6, 112.4, 18.7.

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_8H_9O_2$: 137.0597, found: 137.0594.

(*2E*)-1-(2-Thienyl)-2-buten-1-one (2m'). CAS [13196-29-7]



2m'

Run for 6 h.

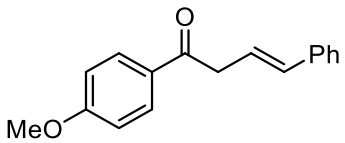
Colorless oil (11.4 mg, 31%). R_f 0.32 (SiO_2, hexane/EtOAc = 9/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.76 (dd, *J* = 3.7, 0.9 Hz, 1H), 7.65 (dd, *J* = 5.0, 1.4 Hz, 1H), 7.18–7.09 (m, 2H), 6.84 (dq, *J* = 15.1, 1.7 Hz, 1H), 2.00 (dd, *J* = 6.9, 1.8 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 182.3, 145.2, 144.4, 133.8, 131.9, 128.3, 127.0, 18.6.

HRMS (DART) *m/z* [M+H$^+$] calcd for C_8H_9OS: 153.0369, found: 153.0368.

(*2E*)-1-(4-methoxyphenyl)-4-phenylbut-3-en-1-one (2n). CAS [84066-68-2]



2n

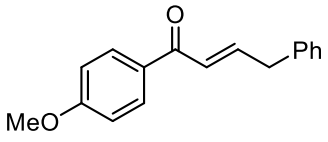
Colorless oil (9.0 mg, 18%). R_f 0.20 (SiO_2, hexane/EtOAc = 9/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 8.00–7.97 (m, 2H), 7.38 (d, *J* = 7.8 Hz, 2H), 7.30 (t, *J* = 7.8 Hz, 2H), 7.21 (t, *J* = 7.3 Hz, 1H), 6.95 (dd, *J* = 11.4, 2.7 Hz, 2H), 6.57–6.45 (m, 2H), 3.88 (s, 3H), 3.86 (d, *J* = 6.0 Hz, 2H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 196.6, 163.7, 137.1, 132.0, 130.7, 129. 8, 128.8, 128.5, 127.2, 124.5, 113.9, 55.6, 38.2.

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{17}H_{17}O_2$: 253.1223, found: 253.1224.

(2*E*)-1-(4-methoxyphenyl)-4-phenylbut-2-en-1-one (2n'). CAS [1955487-56-5]



2n'

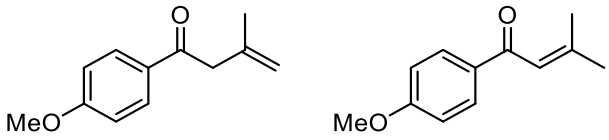
Colorless oil (23.3 mg, 46%). R_f 0.28 (SiO_2, hexane/EtOAc = 9/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.93–7.90 (m, 2H), 7.39–7.26 (m, 5H), 6.93–6.90 (m, 2H), 6.71 (d, *J* = 11.4 Hz, 1H), 6.08–6.02 (m, 1H), 3.95 (dd, *J* = 7.3, 1.8 Hz, 2H), 3.86 (s, 3H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 196.6, 163.7, 137.1, 132.0, 130.7, 129.8, 128.8, 128.5, 127.2, 124.5, 113.9, 55.6, 38.2.

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{17}H_{17}O_2$: 253.1223, found: 253.1220.

1-(4-Methoxyphenyl)-3-methylbut-3-en-1-one (2o) CAS [1368940-60-6] and **1-(4-methoxyphenyl)-3-methylbut-2-en-1-one (2o')** CAS [32097-05-5].



2o **2o'**

Run for 6 h.

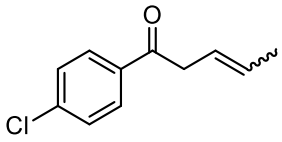
Colorless oil [22.5 mg, 59% (**2o**:**2o'**=4.5:1)]. R_f 0.36 (SiO_2, hexane/EtOAc = 9/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) **2o** δ: 7.96 (d, *J* = 9.2 Hz, 2H), 6.93 (d, *J* = 9.2 Hz, 2H), 4.96 (s, 1H), 4.84 (s, 1H), 3.86 (s, 3H), 3.63 (s, 2H), 1.81 (s, 3H); **2o'** δ: 7.93 (d, *J* = 9.2 Hz, 2H), 6.93 (d, *J* = 9.2 Hz, 2H), 6.71 (t, *J* = 1.1 Hz, 1H), 3.86 (s, 3H), 2.18 (d, *J* = 1.4 Hz, 3H), 2.00 (d, *J* = 0.9 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) **2o** δ: 196.8, 163.6, 140.3, 130.9, 130.6, 114.8, 113.8, 55.6, 47.7, 23.0; **2o'** δ: 190.5, 162.9, 155.3, 132.3, 130.1, 121.3, 113.7, 55.6, 28. 0, 21.2.

HRMS (EI) *m/z* [M$^+$] calcd for $C_{12}H_{14}O_2$: 190.0994, found: 190.0994 (**2o**) and 190.0993 (**2o'**).

1-(4-Chloro-phenyl)-pent-3-en-1-one (2p). CAS [1334518-96-5]



2p

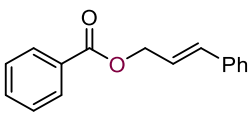
White solid (16.1 mg, 35% (*E*/*Z* = 6.3/1)). R_f 0.37 (SiO_2, hexane/EtOAc = 9/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.91 (dq, *J* = 8.8, 2.5 Hz, 2H), 7.45–7.42 (m, 2H), 5.69–5.62 (m, 2H), 3.74–3.71 (m, 2H (*Z* isomer)), 3.66–3.65 (m, 2H), 1.71 (dd, *J* = 8.5, 5.3 Hz, 3H).

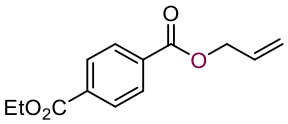
^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 197.6, 139.6, 135.0, 130.0, 129.9, 129.0, 128.7 (*Z* isomer), 128.0 (*Z* isomer), 123.2, 122.0 (*Z* isomer), 42.6, 37.3 (*Z* isomer), 18.3.

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{11}H_{12}O^{35}Cl$: 195.0571, found: 195.0571.

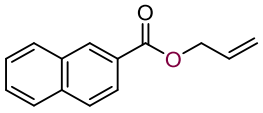
List of unsuccessful substrates.



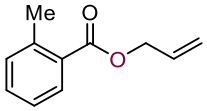
S1
27% (1:4.3)



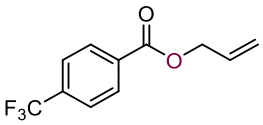
S2
27% (**proS2'** only)



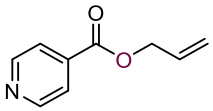
S3
39% (**proS3'** only)



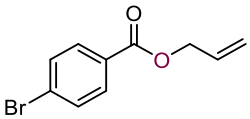
S4
42% (**proS4'** only)



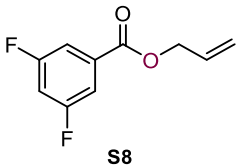
S5
13% (**proS5'** only)



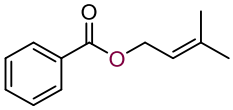
S6
0%



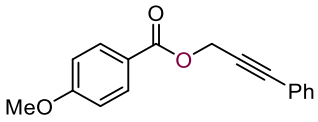
S7
10% (NMR yield)



S8
19% (**proS8'** only)

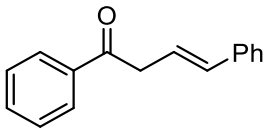


S9
0%



S10
0%

(*3E*)-1,4-Diphenylbut-3-en-1-one (proS1). CAS [3420-52-8]



proS1

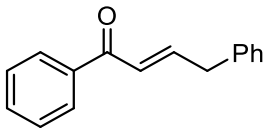
White solid (2 mg, 5%). R_f 0.34 (SiO_2, hexane/EtOAc = 9/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 8.02–8.00 (m, 2H), 7.59 (s, 1H), 7.50 (d, *J* = 7.8 Hz, 2H), 7.39 (d, *J* = 7.3 Hz, 2H), 7.31 (t, *J* = 7.6 Hz, 2H), 7.23 (s, 1H), 6.58–6.45 (m, 2H), 3.93 (d, *J* = 6.4 Hz, 2H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 198.2, 137.1, 136.7, 133.7, 133.4, 128.8, 128.7, 128.5, 127.6, 126.4, 122.7, 42.9.

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{16}H_{15}O$: 223.1117, found: 223.1114.

(*2E*)-1,4-Diphenylbut-2-en-1-one (proS1'). CAS [167645-90-1]



proS1'

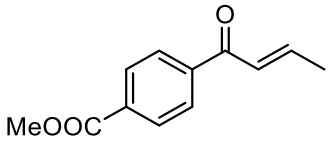
White solid (9.4 mg, 22%). R_f 0.40 (SiO_2, hexane/EtOAc = 9/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.94 (dt, *J* = 8.4, 1.5 Hz, 2H), 7.58–7.54 (m, 1H), 7.47–7.43 (m, 2H), 7.39–7.35 (m, 2H), 7.31–7.26 (m, 3H), 6.73 (d, *J* = 11.4 Hz, 1H), 6.10–6.03 (m, 1H), 4.00 (dd, *J* = 7.3, 1.8 Hz, 2H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 198.1, 137.0, 136.6, 133.4, 132.3, 128.8 (two overlapping peaks), 128.5, 128.4, 127.2, 124.0, 38.4.

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{16}H_{15}O$: 223.1117, found: 223.1113.

Methyl 4-[(*2E*)-1-oxo-2-buten-1-yl]benzoate (proS2'). CAS [1313028-22-6]



proS2'

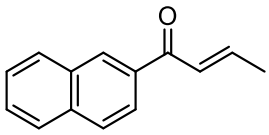
Colorless oil (11.1 mg, 27%). R_f 0.20 (SiO_2, hexane/EtOAc = 9/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 8.13 (dd, *J* = 6.9, 1.8 Hz, 2H), 7.96 (dd, *J* = 6.9, 1.8 Hz, 2H), 7.10 (q, *J* = 7.3 Hz, 1H), 6.92–6.88 (m, 1H), 3.95 (s, 3H), 2.02 (dd, *J* = 6.9, 1.8 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 190.5, 166.5, 146.5, 141.5, 133.5, 129.9, 128.5, 127.6, 52.6, 18.9.

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{12}H_{13}O_3$: 205.0859, found: 205.0863.

(*2E*)-1-(2-Naphthalenyl)-2-buten-1-one (proS3'). CAS [944344-75-6]



proS3'

Run for 6 h.

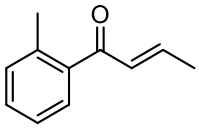
White solid (15.0 mg, 39%). R_f 0.29 (SiO_2, hexane/EtOAc = 9/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 8.44 (s, 1H), 8.04–7.87 (m, 4H), 7.57 (dtd, *J* = 18.5, 7.4, 1.5 Hz, 2H), 7.19–7.05 (m, 2H), 2.05 (d, *J* = 5.5 Hz, 3H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 190.7, 145.1, 135.5, 135.3, 132.7, 130.1, 129.6, 128.6, 128.4, 127.9, 127.6, 126.8, 124.7, 18.8.

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{14}H_{13}O$: 197.0961, found: 197.0962.

(*2E*)-1-(*o*-Tolyl)but-2-en-1-one (proS4'). CAS [944344-74-5]



proS4'

Run for 6 h.

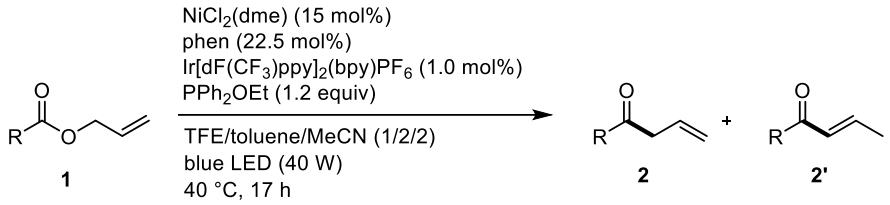
White solid (15.1 mg, 42%). R_f 0.35 (SiO_2, hexane/EtOAc = 9/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.38–7.32 (m, 2H), 7.23 (q, *J* = 7.9 Hz, 2H), 6.73 (dd, *J* = 15.6, 6.9 Hz, 1H), 6.50 (dd, *J* = 15.6, 1.4 Hz, 1H), 2.38 (s, 3H), 1.95 (dd, *J* = 6.6, 1.6 Hz, 3H).

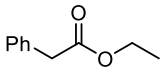
^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 197.2, 147.0, 139.1, 136.8, 132.5, 131.2, 130.3, 128.1, 125.4, 20.2, 18.7.

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{11}H_{13}O$: 161.0961, found: 161.0958.

Examination of aliphatic esters.

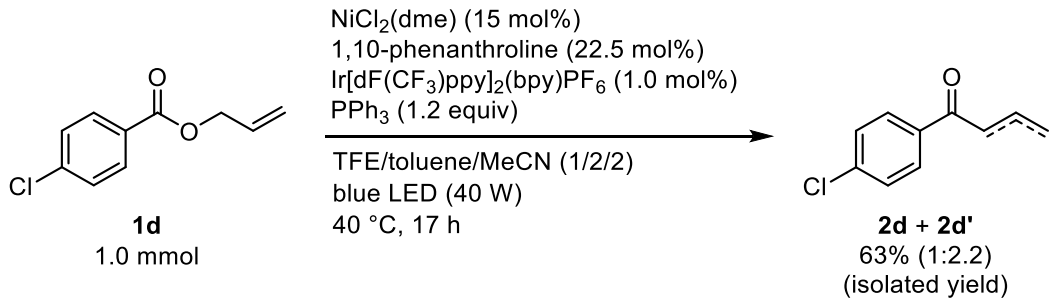


Entry	R	NMR yields (%) (**2a**:**2a'**)
1	$PhCH_2$	0%[a]
2	C_5H_{11}	0%

a  was formed in 65% isolated yield.

No desired products were formed under the standard reaction conditions, possibly due to the mismatch of the oxidation potential. Based on the report by Doyle[5], the use of $PPh_2(OEt)$ as a reductant was examined. However, no desired products were formed, even though the starting esters were completely consumed.

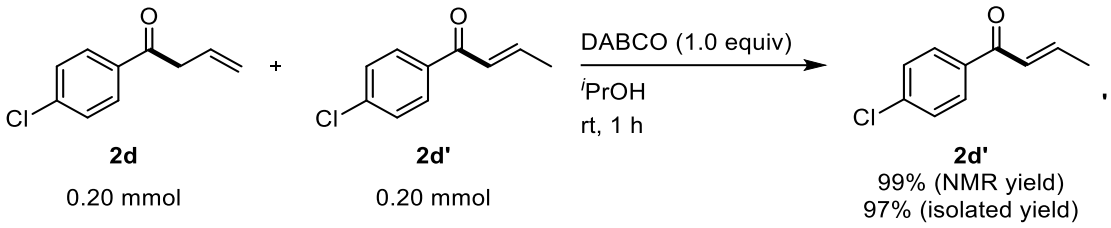
VI. A 1.0 mmol Scale Experiment



Procedure for a 1.0 mmol scale reaction. In a glovebox filled with nitrogen, $NiCl_2$•dme (35.1 mg, 15 mol%), 1,10-phenanthroline (39.6 mg, 22.5 mol%), $Ir[dF(CF_3)ppy]_2(bpy)PF_6$ (10.3 mg, 1 mol%), allyl ester **1d** (202 mg, 1.0 mmol, 1.0 equiv), PPh_3 (318 mg, 1.2 mmol, 1.2 equiv), TFE (2.50 mL), toluene (5.0 mL) and MeCN (5.0 mL) were added to a 50 mL vial. The tube was then sealed and was placed at a distance (ca. 4.0 cm) from blue LEDs (45 W × 2), and the mixture was stirred at 40 °C for 17 h. The reaction mixture was then removed from the light and the crude mixture was filtered through a pad of celite. The filtrate was then concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (hexane/EtOAc = 10/1) to afford **2d** as colorless oil (37.3 mg, 20%) and **2d'** as colorless oil (79.8 mg, 43%).

VII. Isomerization of β,γ-Unsaturated Ketone to α,β-Unsaturated Ketone

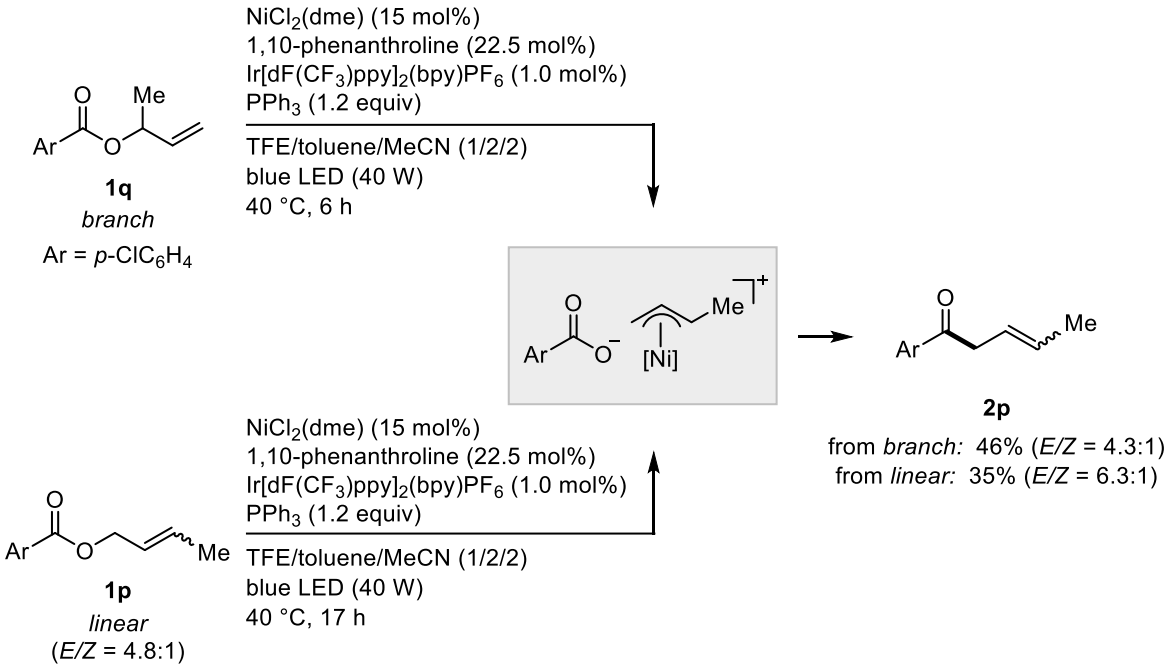
Procedure for isomerization of 2d[6]



To a 20 mL flask with a magnetic stirring bar, ketone **2d** (36 mg, 0.20 mmol), **2d'** (36 mg, 0.20 mmol), DABCO (44.8, 0.40 mmol) and ^{i}PrOH (2.0 mL) were added. The mixture was stirred at rt for 1 h. The organic solvent was then removed *in vacuo*. The crude product was purified by column chromatography on silica gel (hexane/EtOAc = 99/1) to afford **2d'** as colorless oil (70 mg, 97%).

VIII. Mechanistic Studies

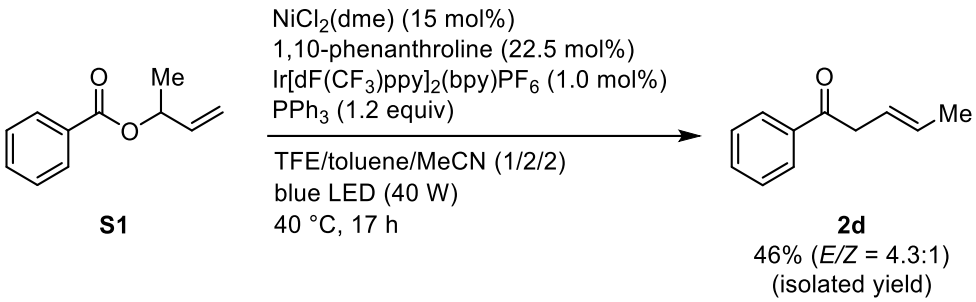
VIII-1. Experimental support of the intermediacy of an ionic-paired π-allylnickel complex.



Scheme S1.

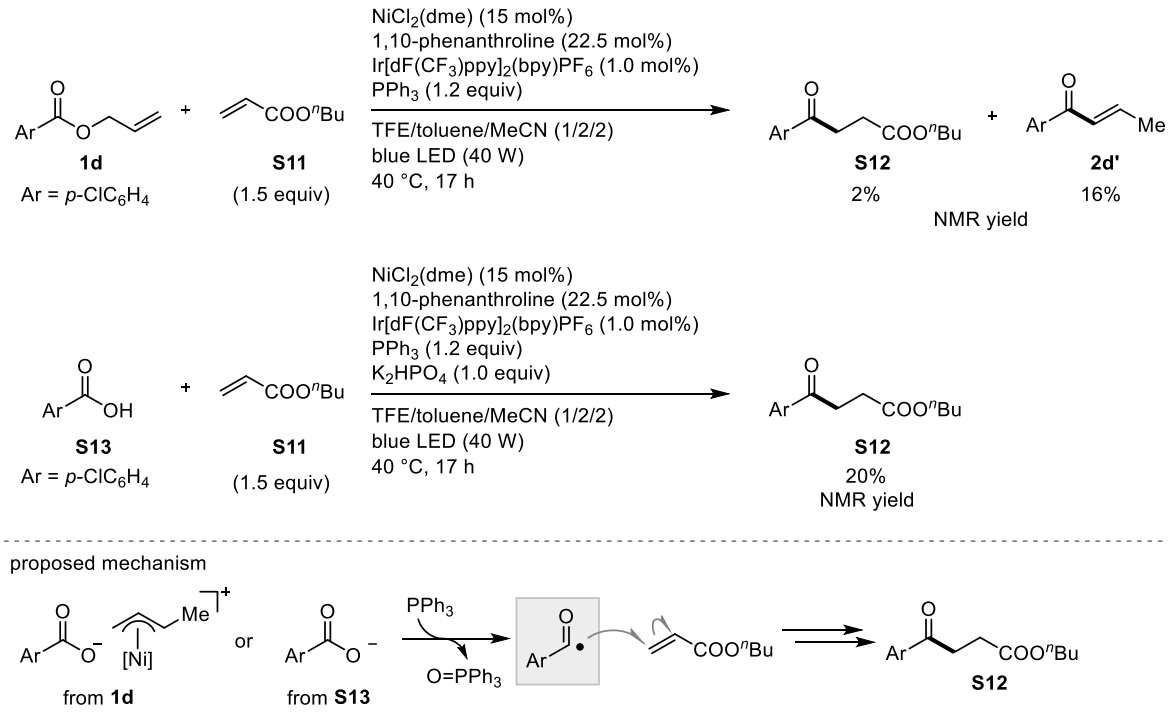
Allyl esters bearing branched (**1q**) or linear (**1p**) allyl groups both afforded linear allylated product **2p** under the Ni/photoredox-catalyzed conditions, which suggests that both reactions proceed via a common π-allylnickel intermediate.[7]

A procedure for nickel/photo redox-catalyzed deoxygenation of branch allyl esters 1q.



In a glovebox filled with nitrogen, $NiCl_2$•dme (6.7 mg, 15 mol%), 1,10-phenanthroline (8.2 mg, 22.5 mol%), Ir[dF(CF3)ppy]$_2$(bpy)PF_6 (2.0 mg, 1 mol%), allylic ester **1q** (41.2 mg, 0.20 mmol, 1.0 equiv), Ph_3P (64.4 mg, 0.24 mmol, 1.2 equiv), TFE (0.50 mL), toluene (1.0 mL) and MeCN (1.0 mL) were added to a 10 mL vial with a Teflon-sealed screwcap. The tube was then sealed and was placed at a distance (ca. 4.0 cm) from blue LEDs (45 W × 2), and the mixture was stirred at 40 °C for 6 h. Then, the reaction mixture was removed from the light and the crude mixture was filtered through a pad of celite. The filtrate was then concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (hexane/EtOAc = 10/1) to afford **2p** as a white solid (17.3 mg, 46%).

VIII-2. Experimental support of the generation of acyl radical species.



Scheme S2.

When butyl acrylate (**S11**) was reacted with allyl ester **1d** under the optimized conditions, the intermolecular adduct **S12** was obtained in 2% NMR yield, which was formed by reaction with butyl acrylate (**S11**) and acyl radical generated from **1d**, along with the deoxygenative UFC product **2d'** (16% NMR yield). In addition, when benzoic

acid **S13**, in place if **1k**, was reacted in the presence of K_2HPO_4 under the standard conditions, ketone **S12** was formed, similar to the reaction using allyl ester **1d**.[8] These results support that an acyl radical was generated from a carboxylate anion of an ion-pared π-allylnickel intermediate under the Ni/photoredox-catalyzed conditions.

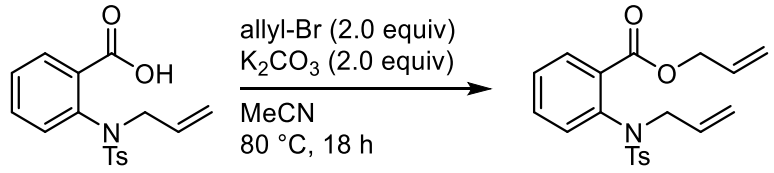
Procedures for nickel/photo redox-catalyzed deoxygenation with Michael acceptor.

Using allyl ester 1d as a starting material. In a glovebox filled with nitrogen, $NiCl_2$•dme (6.9 mg, 15 mol%), 1,10-phenanthroline (8.2 mg, 22.5 mol%), $Ir[dF(CF_3)ppy]_2(bpy)PF_6$ (2.0 mg, 1 mol%), allylester **1d** (42 mg, 0.21 mmol, 1.0 equiv), Ph_3P (62.9 mg, 0.24 mmol, 1.2 equiv), TFE (0.50 mL), toluene (1.0 mL) and MeCN (1.0 mL) were added to a 10 mL vial with a Teflon-sealed screwcap. Butyl acrylate (**S11**) (37.6 mg, 0.29 mmol, 1.5 equiv) was then added, and the tube was sealed and was placed at a distance (ca. 4.0 cm) from blue LEDs (45 W × 2), and the mixture was stirred at 40 °C for 17 h. Then, the reaction mixture was removed from the light and the crude mixture was filtered through a pad of celite. The filtrate was then concentrated *in vacuo* to afford the crude corresponding ketone **S12** and the deoxygenative UFC product **2d'** [2% and 16% yield by ^{1}H-NMR analysis using 1,1,2,2-tetrachloroethane (14.4 mg) as an internal standard, respectively].

Using benzoic acid S13 as a starting material. In a glovebox filled with nitrogen, $NiCl_2$•dme (7.0 mg, 15 mol%), 1,10-phenanthroline (7.9 mg, 22.5 mol%), $Ir[dF(CF_3)ppy]_2(bpy)PF_6$ (2.1 mg, 1 mol%), benzoic acid **S13** (30.8 mg, 0.20 mmol, 1.0 equiv), Ph_3P (61.4 mg, 0.24 mmol, 1.2 equiv), K_2HPO_4 (33.8 mg, 0.20 mmol, 1.0 equiv), TFE (0.50 mL), toluene (1.0 mL) and MeCN (1.0 mL) were added to a 10 mL vial with a Teflon-sealed screwcap. Butyl acrylate (**S11**) (39.1 mg, 0.30 mmol, 1.5 equiv) was then added, and the tube was sealed and was placed at a distance (ca. 4.0 cm) from blue LEDs (45 W × 2), and the mixture was stirred at 40 °C for 17 h. Then, the reaction mixture was removed from the light and the crude mixture was filtered through a pad of celite. The filtrate was then concentrated *in vacuo* to afford the crude corresponding ketone **S12** [20% yield by ^{1}H-NMR analysis using 1,1,2,2-tetrachloroethane (10.5 mg) as an internal standard].

IX. Catalytic Deoxygenative Insertion of a Tethered Alkene into Allyl Ester

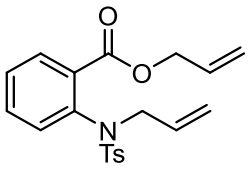
IX -1. Procedure for the synthesis of 3



4.5 mmol **3a**

2-((*N*-allyl-4-methylphenyl)sulfonamido)benzoic acid [324057-41-2] was prepared according to the literature procedure.[9] To a stirred solution of 2-((*N*-allyl-4-methylphenyl)sulfonamido)benzoic acid (1.5 g, 4.5 mmol) in 25 mL of MeCN, K_2CO_3 (1.3 g, 9.0 mmol), and allyl bromide (0.80 mL, 9.0 mmol) were added, and the reaction mixture was stirred at 80 °C for 18 h. The reaction was quenched with H_2O, extracted with EtOAc, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (hexane/EtOAc = 1/1) to afford **3a** as a white solid (0.68 g, 41%).

Allyl 2-((*N*-allyl-4-methylphenyl)sulfonamido)benzoate (3a).



3a

White solid (0.68 g, 41%). R_f 0.53 (SiO_2, hexane/EtOAc = 1/1). M.p. 58 °C.

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.89–7.86 (m, 1H), 7.52–7.50 (m, 2H), 7.42–7.36 (m, 2H), 7.24 (d, *J* = 7.8 Hz, 2H), 6.92–6.89 (m, 1H), 6.04 (dd, *J* = 16.9, 10.5 Hz, 1H), 5.91 (dd, *J* = 16.7, 10.3 Hz, 1H), 5.42–5.37 (m, 1H), 5.29 (dq, *J* = 10.3, 1.2 Hz, 1H), 5.05 (d, *J* = 0.9 Hz, 1H), 5.03-5.00 (m, 1H), 4.69 (d, *J* = 6.0 Hz, 2H), 4.27 (d, *J* = 6.9 Hz, 2H), 2.41 (s, 3H).

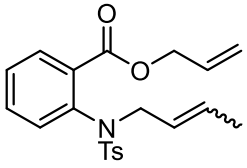
^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 165.9, 143.4, 138.0, 137.0, 133.4, 132.8, 132.2, 132.1, 131.5, 131.0, 129.6, 128.4, 127.7, 119.2, 118.9, 66.2, 54.7, 21.7.

IR (KBr, cm^{-1}): 3074 w, 1719 s, 1597 s, 1488 s, 1450 s, 1421 w, 1341 s, 1298 s, 1252 s, 1213 m, 1183 m, 1164 s, 1158 s, 1128 m, 1088 m, 1046 m, 993 m, 969 w, 929 s, 889 w, 871 m, 810 m, 780 m, 715 s, 666 s, 629 w.

MS, m/z (relative intensity, %): 371 (M^+, 1), 307 (17), 216 (50), 207 (20), 174 (19), 159 (11), 157 (100), 156 (25), 132 (11), 131 (76), 130 (54), 128 (11), 103 (30), 91 (32), 77 (18), 65 (14), 41 (42).

HRMS (DART) *m/z* [M+H^+] calcd for $C_{20}H_{22}NO_4S$: 372.1260, found: 372.1271.

Allyl-2-((*N*-(but-2-en-1-yl)-4-methylphenyl)sulfonamido)benzoate (3c).



3c

2-((*N*-(But-2-en-1-yl)-4-methylphenyl)sulfonamido)benzoic acid was prepared according to the procedure for the synthesis **3**.[9]

Colorless oil (1.6 g, 89% (*E*/*Z* = 10/1)). R_f 0.38 (SiO_2, hexane/EtOAc = 1/1).

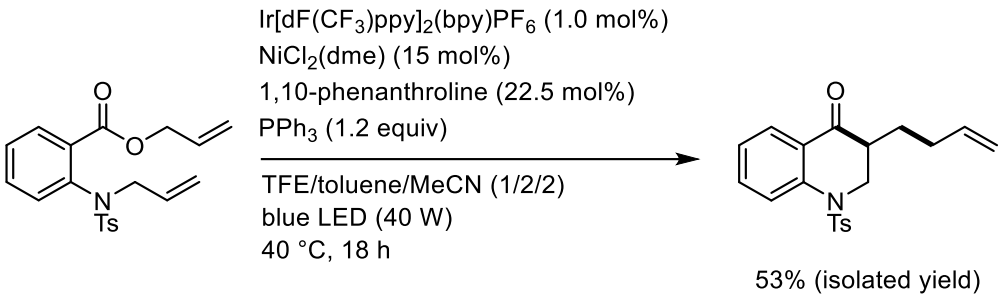
^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.88–7.85 (m, 1H), 7.54–7.50 (m, 2H), 7.42–7.35 (m, 2H), 7.25–7.22 (m, 2H), 6.92–6.89 (m, 1H), 6.09–5.99 (m, 1H), 5.54–5.37 (m, 3H), 5.28 (dq, *J* = 10.5, 1.3 Hz, 1H (*E* isomer)), 4.71–4.68 (m, 2H), 4.34 (d, *J* = 5.5 Hz, 2H (*Z* isomer)), 4.20 (d, *J* = 6.4 Hz, 2H (*E* isomer)), 2.41 (s, 3H), 1.59–1.55 (m, 3H), 1.42 (d, *J* = 5.5 Hz, 2H (*Z* isomer)).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 166.0, 143.24 (*Z* isomer), 143.18, 138.2 (*Z* isomer), 138.1, 137.2 (*Z* isomer), 137.1, 132.9, 132.3, 132.0, 131.4, 131.3, 130.9 (*Z* isomer), 130.6, 129.47, 129.46 (*Z* isomer), 128.6 (*Z* isomer), 128.3 (*Z* isomer), 128.2, 127.7, 126.0, 125.0 (*Z* isomer), 118.8, 66.2, 54.1, 48.1 (*Z* isomer), 21.7, 17.8, 12.7 (*Z* isomer).

IR (KBr, cm^{-1}): 2940 w, 1718 s, 1490 m, 1341 s, 1250 m, 1171 s, 1090 w, 998 m, 949 m, 840 m, 770 w, 728 m, 665 s, 545 m.

MS, m/z (relative intensity, %): 385 (M^+, 0.2), 231 (11), 230 (67), 173 (12), 172 (100), 91 (24), 41 (21).
HRMS (DART) *m/z* [M+H^+] calcd for $C_{21}H_{24}NO_4S$: 386.1421, found: 386.1430.

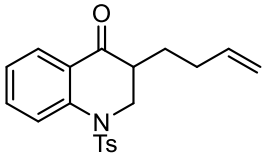
IX -2. Procedure for catalytic deoxygenative insertion of a tethered alkene into allyl ester



53% (isolated yield)

In a glovebox filled with nitrogen, $NiCl_2$•dme (6.6 mg, 15 mol%), 1,10-phenanthroline (8.8 mg, 22.5 mol%), Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 (2.2 mg, 1.0 mol%), aromatic carboxylic ester **3** (85 mg, 0.23 mmol, 1.0 equiv), Ph_3P (63 mg, 0.24 mmol, 1.2 equiv), TFE (0.50 mL), toluene (1.0 mL) and MeCN (1.0 mL) were added to a 10 mL vial with a Teflon-sealed screwcap. The tube was then sealed and was placed at a distance (ca. 4.0 cm) from blue LEDs (45 W × 2), and the mixture was stirred at 40 °C for 18 h. Then, the reaction mixture was removed from the light and the crude mixture was filtered through a pad of celite. The filtrate was then concentrated in vacuo. The crude product was purified by column chromatography on silica gel (hexane/EtOAc = 10/1) to afford **4** as colorless oil (42 mg, 53%).

3-(But-3-en-1-yl)-1-tosyl-2,3-dihydroquinolin-4(1*H*)-one (4a).

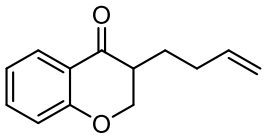


4a

Colorless oil (42 mg, 53%). R_f 0.40 (SiO_2, hexane/EtOAc = 1/1).
^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.95 (dd, *J* = 8.0, 1.6 Hz, 1H), 7.85 (d, *J* = 9.2 Hz, 1H), 7.60–7.58 (m, 2H), 7.55–7.51 (m, 1H), 7.24–7.20 (m, 3H), 5.79–5.70 (m, 1H), 5.11–5.02 (m, 2H), 4.46 (dd, *J* = 14.0, 4.8 Hz, 1H), 3.74 (dd, *J* = 14.0, 11.9 Hz, 1H), 2.39–2.31 (m, 4H), 2.22–2.19 (m, 1H), 2.13–1.99 (m, 2H), 1.43–1.35 (m, 1H).
^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 195.3, 144.7, 142.3, 137.4, 136.8, 134.7, 130.2, 128.3, 127.0, 125.2, 124.9, 123.1, 116.1, 50.5, 44.4, 30.8, 26.5, 21.8.
IR (KBr, cm^{-1}): 2970 w, 1688 s, 1598 s, 1476 m, 1457 m, 1355 s, 1294 m, 1186 w, 1166 s, 1089 m, 1039 w, 962 w, 881 w, 813 w, 759 w, 740 w, 664 m, 574 s, 545 w, 533 w.
MS, m/z (relative intensity, %): 355 (M^+, 4), 301 (25), 300 (11), 200 (24), 199 (14), 158 (37), 146 (100), 145 (44), 130 (17), 155 (12), 92 (10), 91 (63), 77 (23), 65 (16), 55 (14).

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{20}H_{22}NO_3S$: 356.1315, found: 356.1315.

3-(But-3-en-1-yl)chroman-4-one (4b). CAS [177748-57-1]



4b

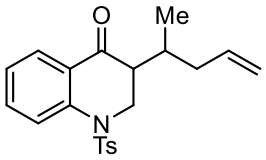
Colorless oil (4.0 mg, 10%). R_f 0.40 (SiO_2, hexane/EtOAc = 9/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.89 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.49–7.44 (m, 1H), 7.03–6.95 (m, 2H), 5.86–5.76 (m, 1H), 5.10–5.01 (m, 2H), 4.53 (dd, *J* = 11.4, 4.6 Hz, 1H), 4.27 (dd, *J* = 11.4, 8.7 Hz, 1H), 2.74–2.67 (m, 1H), 2.21 (td, *J* = 15.7, 6.9 Hz, 2H), 2.07–1.98 (m, 1H), 1.62–1.57 (m, 1H).

^{13}C NMR ($CDCl_3$, 100.53 MHz) δ: 194.6, 161.8, 137.6, 135.9, 127.6, 121.5, 120.8, 117.8, 115.8, 70.5, 45.3, 31.2, 25.5.

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{13}H_{15}O_2$: 203.1067, found: 203.1069.

3-(Pent-4-en-2-yl)-1-tosyl-2,3-dihydroquinolin-4(1H)-one (4c).



4c

Run at 0.40 mmol scale. These products were obtained as a mixture of stereoisomers (1.3:1) determined by ^{1}H NMR.

Colorless oil (20 mg, 13%). R_f 0.20 (SiO_2, hexane/EtOAc = 9/1).

^{1}H NMR ($CDCl_3$, 399.78 MHz) δ: 7.95–7.92 (2H (1H (major), 1H (minor)), 7.89–7.84 (2H (1H (major), 1H (minor)), 7.59–7.51 (6H (3H (major), 3H (minor)), 7.25–7.19 (6H (3H (major), 3H (minor)), 5.74–5.63 (2H (1H (major), 1H (minor)), 5.15 (dq, *J* = 17.2, 1.8 Hz, 1H, major), 5.09 (d, *J* = 10.5 Hz, 1H, major), 5.00–4.94 (m, 2H, minor), 5.15 (dd, *J* = 14.2, 5.0 Hz, 1H, major), 4.36 (dd, *J* = 14.2, 4.6 Hz, 1H, minor), 3.91 (dd, *J* = 14.2, 11.9 Hz, 1H, minor), 3.80 (t, *J* = 14.2 Hz, 1H, major), 2.49–2.35 (10H (5H (major), 5H (minor)), 2.49–2.44 (2H (1H (major), 1H (minor)), 2.27–2.22 (2H (1H (major), 1H (minor)), 2.14–1.90 (4H (2H (major), 2H (minor)), 0.93 (d, *J* = 6.9 Hz, 3H, minor), 0.81 (d, *J* = 6.9 Hz, 3H, major).

^{13}C NMR ($CDCl_3$, 100.53 MHz) major; δ: 195.3, 144.6, 142.3, 136.9, 136.5, 134.6, 130.1, 128.2, 127.1, 126.0, 125.4, 123.7, 117.2, 48.4, 46.7, 38.7, 30.6, 21.7, 15.4.

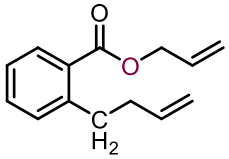
minor; δ: 194.8, 144.7, 142.2, 137.0, 136.5, 134.6, 130. 2, 128.2, 127.0, 125.8, 125.2, 123.4, 116.8, 49.5, 47.8, 37.7, 31.1, 21.7, 17.0.

IR (KBr, cm^{-1}): 2926 w, 1687 s, 1598 s, 1457 s, 1360 m, 1295 w, 1166 s, 1089 m, 916 w, 762 m, 673 m, 573 s.

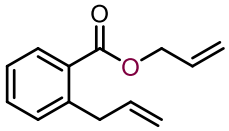
MS, m/z (relative intensity, %): 369 (M$^+$, 3), 301 (24), 300 (12), 214 (21), 213 (11), 207 (10), 172 (16), 147 (11), 146 (100), 145 (48), 132 (12), 91 (59), 65 (14), 77 (20), 41 (20).

HRMS (DART) *m/z* [M+H$^+$] calcd for $C_{21}H_{24}NO_3S$: 370.1471, found: 370.1481.

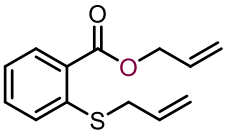
The list of unsuccessful substrates.



0%



trace



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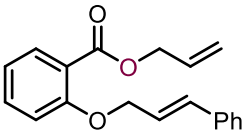

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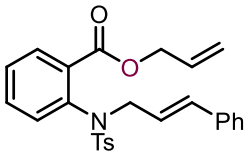
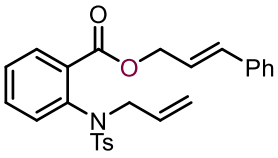
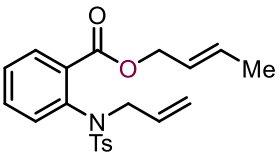


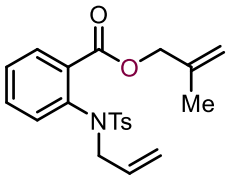
ca. 10%



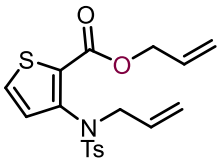
trace
(SM 12 %)



n.d.
(SM 57 %)



n.d.
(SM 44 %)



n.d.

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For Experimental Section

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Conclusion

The research reported in this thesis focuses on new types of catalytic UFC reactions using amides and esters.

In Chapter 1, the first unimolecular fragment coupling of amides through the elimination of isocyanate is described. Several mechanistic experiments have indicated that this UFC reaction proceeds through a sequence that involves the oxidative addition of the C(allyl)–N bond to form a π-allyl complex, the extrusion of isocyanate, and reductive elimination. This UFC of amides allows for the late-stage conversion of amide moieties into allyl groups in a one-step process, which should be useful in the synthetic elaboration of products that are synthesized by C–H functionalization reactions.

In Chapter 2, the palladium-catalyzed migratory UFC of *N*-allylamides bearing a tethered nucleophile such as an alcohol is described. In this reaction, an amide moiety located in the middle of the molecular framework is removed and transferred to the terminal of the molecule. These types of reactions are defined as "cut-and-paste" types of reactions, in which a fragment of the molecular skeleton is removed and is then attached to a different site in the molecule, which results in the construction of a new molecular framework.

In Chapter 3, the nickel/photoredox dual-catalyzed deoxygenative UFC of allyl esters is described. This transformation involves the deletion of an oxygen atom in an ester framework to the corresponding ketone, which could be viewed as a "*retro* Baeyer-Villiger reaction". The key feature of this UFC is that it involves the fusion of a nickel-catalyzed oxidative addition/reductive elimination cycle and a photoredox-catalyzed deoxygenation process of carboxylates using PPh_3 as a stoichiometric reductant. This protocol also allows the formal catalytic substitution of the ester oxygen atom by a C2 unit.

In this thesis study, novel reaction formats were developed for transition metal-catalyzed UFCs using *N*-allylamides via the elimination and translocation of isocyanates using allyl esters via the elimination of oxygen atoms as triphenylphosphine oxides. However, the scope of UFC reactions remains limited primarily to substrates that contain reactive bonds, which includes allylic and benzylic substrates, because their elementary reactions in the UFC mechanism are applicable to the limited class of relatively reactive chemical bonds. Therefore, there is a need to broaden and diversify the scope of substrates in order to fully demonstrate the powerful potential of the UFC strategy. The author anticipates that knowledge gained from this thesis will contribute to a future expansion of the scope of the UFC strategy and to further development into general methods for "skeletal editing" reactions.

List of Publications

1. **Shimazumi,R.**; Tanimoto, R.; Kodama, T.; Tobisu, M.
   Palladium-Catalyzed Unimolecular Fragment Coupling of *N*-Allylamides via Elimination of Isocyanate,
   J. Am. Chem. Soc., **2022**, *144*, 11033–11043.
2. **Shimazumi,R.**; Kodama, T.; Tobisu, M.
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   Synthesis, **2024**, *56*, 134–142.
3. **Shimazumi,R.**; Tanimoto, R.; Tobisu, M.
   Nickel/Photoredox Dual-Catalyzed Conversion of Allyl Esters to Ketones via the Formal Deletion of Oxygen,
   Org. Lett. **2023**, *25*, 6440–6445.

Supplementary List of Publication

1. **Shimazumi, R.**; Igarashi, T.; Tobisu, M.
   Palladium-Catalyzed *B*-Diarylation of Diethylaminoborane for the Synthesis of Diarylborinic Acids,
   Chem. Lett. **2020**, *49*, 760–763.
2. **Shimazumi, R**.; Morita, K.; Yoshida, T.; Yasui, K.; Tobisu, M.
   Late-Stage Derivatization of Buflavine by Nickel-Catalyzed Direct Substitution of a Methoxy Group via C–O Bond Activation,
   Synthesis, **2021**, *53*, 3037–3044.
3. Igarashi, T.; **Shimazumi, R.**; Tobisu, M.
   Nickel-catalyzed direct methylation of arylphosphines via carbon–phosphorus bond cleavage using $AlMe_3$,
   Chem. Commun. **2023**, *59*, 9722–9725.
4. Pearson, T.J.; **Shimazumi, R.**; Driscoll, J.L.; Dherange, B.D.; Park, D.; Levin, M.D.
   Aromatic Nitrogen Scanning by Ipso-Selective Nitrene Internalization,
   Science **2023**, *381*, 1474–1479.
5. **Shimazumi, R.**; Morimoto, M.; Tobisu, M.
   KO^{t}Bu-Catalyzed Transformation from N-Benzyl Amides Bearing an ortho Alkynyl Group to Isoindole Derivatives Involving 1,2-Acyl Shift,
   Manuscript in preparation
6. **Shimazumi, R.**; Tobisu, M.
   Unimolecular Fragment Coupling: A New Bond-Forming Methodology via Deletion of Atom(s)
   Manuscript in preparation