Doctoral Dissertation

Studies on C-H Coupling Reactions with Small-Sized Heterocycles by Assistance of Bidentate Auxiliaries

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Preface and Acknowledgements

The studies described in this thesis have been carried out under the direction of Professor Masahiro Miura at Osaka University from October 2017 to March 2021.

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Contents

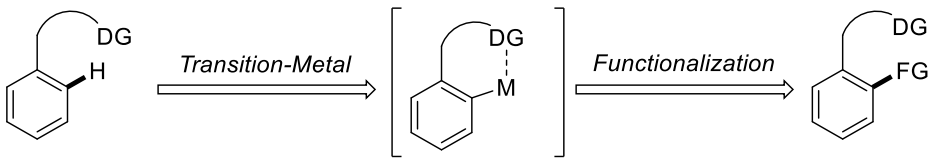
Chapter 1

General Introduction

1. Directed C-H bond functionalization

Metal-catalyzed C-C bond formation is of great importance in organic synthesis due to its wide application in the construction of structurally and functionally diverse organic molecules. Over the past few decades, the cross-coupling reactions of organic halides with organometallic reagents have been greatly developed as the efficient and useful strategies for the C-C bond formation.[1] Despite the significant progress, the prefunctionalization of the starting molecules, generation of stoichiometric wastes associated with halides and metals, and functional group compatibility are still major drawbacks to be solved. To address these problems, chemists have developed C-H bond activation strategies for the more efficient and atom-economical formation of C-C bonds as well as C-heteroatom bonds.[2] In this field, the site selectivity problem has been successfully addressed by introducing a suitable chelating auxiliary; namely, the coordination of a functional group to a metal center directs the catalyst into the proximal C-H bond in the molecule, leading to its selective cleavage and subsequent functionalization (Scheme 1).

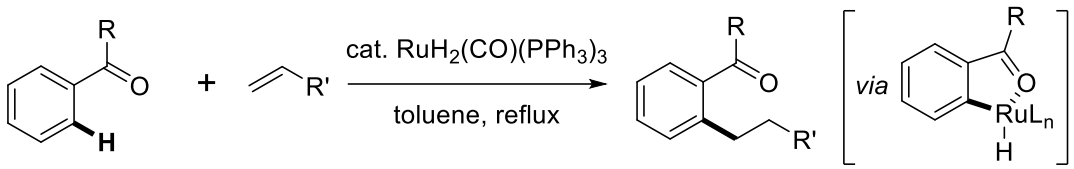
Scheme 1.



As a pioneering discovery, Murai, Kakiuchi, Chatani, and co-workers developed the ruthenium-catalyzed, directed C-H alkylation of arenes with alkenes with the assistance of a carbonyl group (Scheme 2).[3] In this transformation, the carbonyl

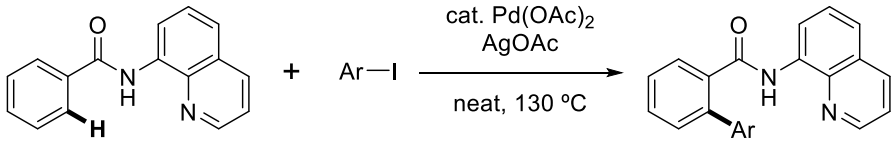
group directs *ortho* C-H bond activation to form a five-membered ruthenacycle intermediate, and subsequent migratory insertion of alkene leads to the regioselective alkylation product.

Scheme 2.



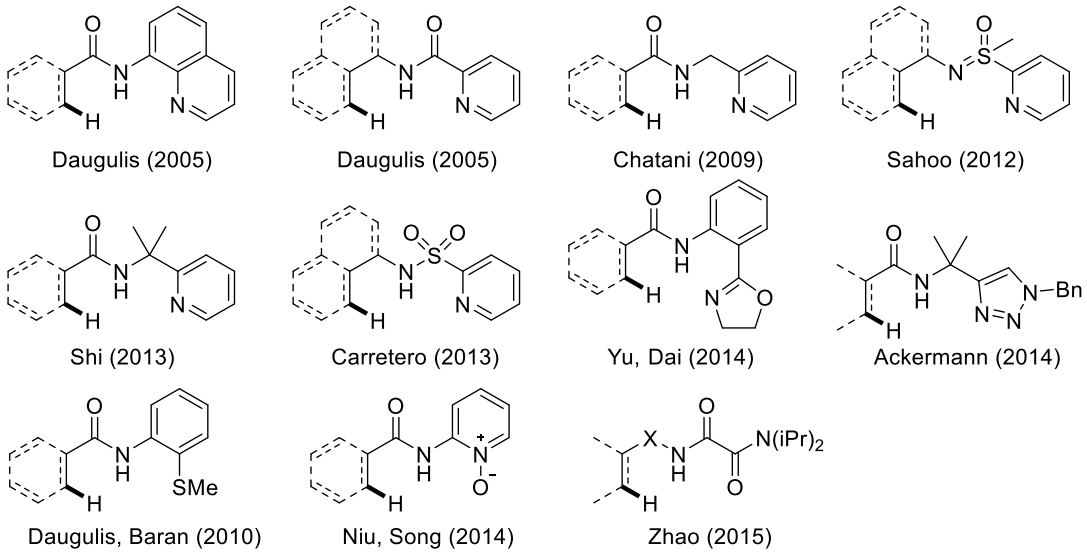
This achievement has prompted many synthetic chemists to design the suitable directing groups for directed C-H activation. As a seminal work, Daugulis developed the 8-aminoquinoline-derived *N,N*-bidentate auxiliary that enables C(sp^2)-H bond arylation of benzamides with aryl iodides under palladium catalysis (Scheme 3).[4] A related C(sp^3)-H bond arylation was also achieved under the same catalytic system.[5]

Scheme 3.



After this work, a variety of coordinating systems were reported for the various site-selective C-H bond functionalizations.[6] Among them, the heteroatom-based bidentate auxiliaries, including *N/N*, *N/S*, and *N/O* have received much attention due to the more effective coordination ability than that of monodentate ones (Scheme 4).[7] In particular, the quinoline-, pyridine-, oxazoline-, and triazole-derived *N,N*-bidentate coordinating systems, have been well established in versatile catalytic systems for the activation of C(sp^2)-H bonds and even the inert C(sp^3)-H bonds.[8]

Scheme 4



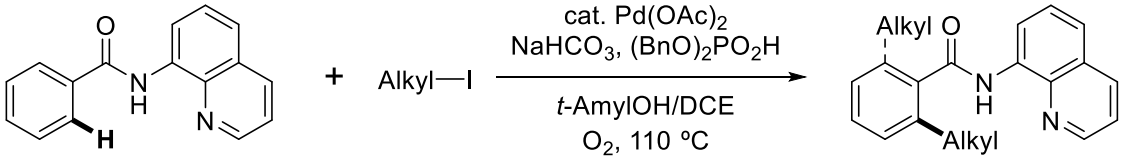
2. C-H alkylation enabled by 8-aminoquinoline-based bidentate auxiliary

Among the *N*,*N*-bidentate auxiliaries, amides derived from 8-aminoquinoline represent the most commonly used directing group and have received typical attention in the C-H bond functionalization reactions.[2o],[2p],[8] This auxiliary enables the C-H alkylation with alkyl (pseudo)halides, which is otherwise challenging transformation due to the competitive β-H elimination of alkyl metal intermediates.

In 2015, Chen group reported the Pd-catalyzed monoalkylation of 8-aminoquinoline-derived benzamides with primary as well as secondary alkyl halides (Scheme 5).[9] The mono- and dialkylation selectivity of the reaction could be controlled by adjusting the amount of $NaHCO_3$, and the phosphate additive promoted this transformation. Subsequently, the benzylation of arylacetamides was also achieved with a similar strategy. Additionally, C-H functionalization of

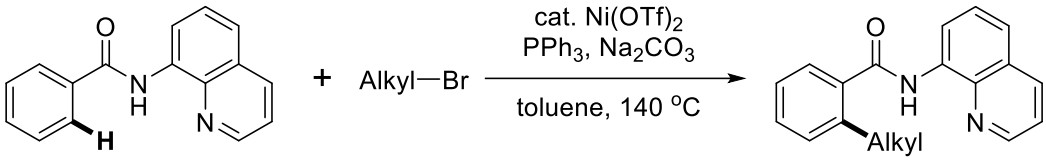
ferrocenecarboxamides with primary alkyl halides was reported under palladium catalysis by Kumar.[10]

Scheme 5.



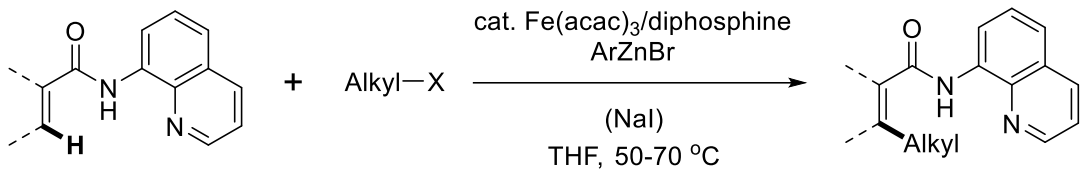
The group of Chatani first reported the Ni-catalyzed *ortho* C-H alkylation of arylcarboxamides and acrylamides with primary alkyl halides by using the aminoquinoline as the bidentate directing group.[11] The reaction proceeded with high functional group tolerance and excellent regioselectivity (Scheme 6). Under similar nickel-based catalytic systems, the related C-H alkylations with secondary alkyl halides were then developed by the same group[12] and Ackermann group,[13] independently.

Scheme 6.



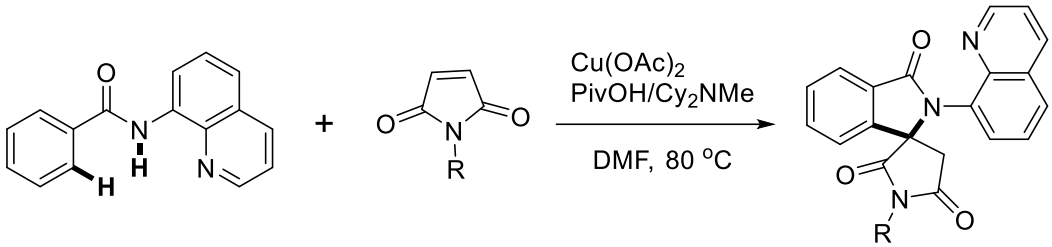
The scope of alkylating reagents was furtherly expanded in the Fe-catalyzed C-H functionalization. Ilies and Nakamura successfully employed the primary and secondary alkyl halides, tosylates, and mesylates as the alkylating reagents for the C-H alkylation process of 8-aminoquinoline-derived aryl and acryl amides (Scheme 7).[14] The ArZnBr serves as a base, which was prepared in advance through the reaction of ArMgBr and a zinc salt ($ZnBr_2$·TMEDA). Around the same time, Cook reported the related Fe-catalyzed aromatic C-H alkylation with various alkyl halides.[15]

Scheme 7.



In addition, Miura group has focused on the copper-mediated oxidative coupling of benzamides with carbon- and heteroatom-based nucleophiles by the assistance of bidentate auxiliary.[16] One contribution is the first realization of cooper-promoted aromatic formal C-H alkylation with maleimides, which undergoes successive C-H alkenylation and intramolecular Michael addition to form the structurally useful spirosuccinimides.[17]

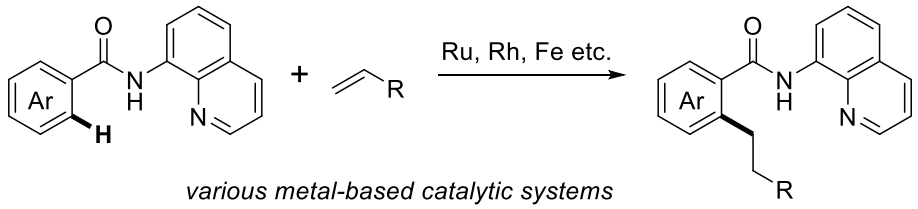
Scheme 8.



As more atom-economical alkylating reagents, alkenes have received much attention in the aminoquinoline-directed C-H alkylation reactions under various catalytic systems (Scheme 9). In 2013, Chatani reported such an alkylation with α,β-unsaturated ketones under $RuCl_2(PPh_3)$ catalysis.[18] The same group then developed the Rh(I)-catalyzed *ortho* C-H alkylation of benzamides with several alkene-derived alkylation reagents, including acrylates,[19] styrene,[20] and maleimide,[21] to construct corresponding new C-C bonds. On the other hand, Nakamura and co-workers described that the $Fe(acac)_3$ catalyst was also useful for the regioselective C-H

alkylation, in which the scope of alkenes was largely expanded: vinyl silanes, vinyl boranes, and even simple ethylene were well tolerated.[22]

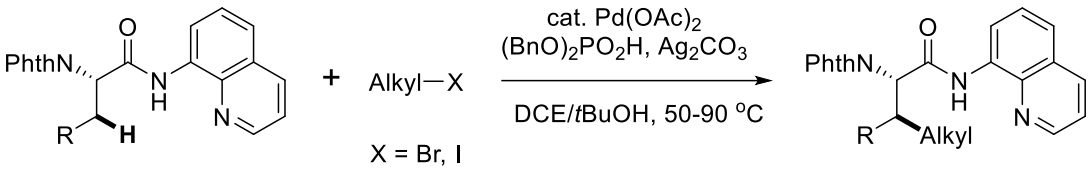
Scheme 9.



Other alkylating sources, including toluene,[23] acetonitrile,[24] alkyl Grignard reagents,[25] alkyl aluminum,[26] dicumyl peroxide,[27] and potassium malonate monoesters[28] were also reported under various catalytic systems by several research groups.

Moreover, the 8-aminoquinoline-derived amides represent the privileged auxiliary for the inert C(sp^3)-H bonds cleavage and functionalization. As a representative example, Shi group developed the aliphatic C-H alkylation of amino acid derivatives by using the 8-aminoquinoline directing group under palladium catalysis, providing an efficient strategy for the synthesis of various non-natural amino acid derivatives (Scheme 10).[29] The secondary C(sp^3)-H bonds could also be alkylated under the same catalytic system.

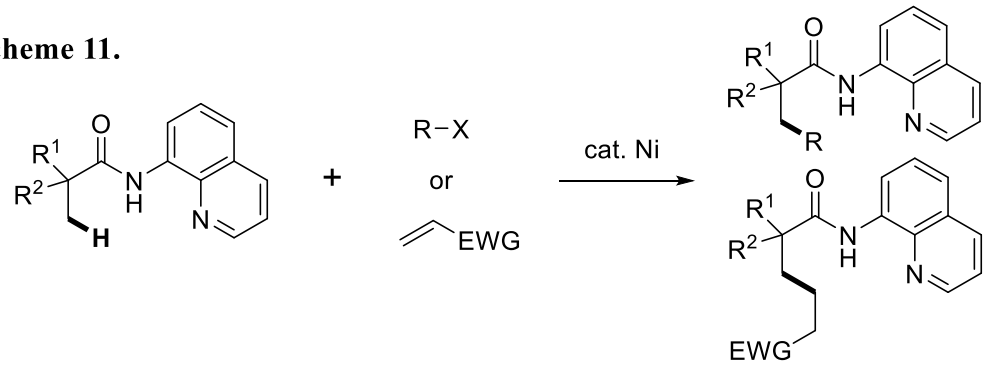
Scheme 10.



The nickel-catalyzed direct alkylation of 8-aminoquinoline-derived aliphatic amides with alkyl halides was reported by Ge (Scheme 11).[30] The reaction proceeded with

high regioselectivity: methyl C-H bond was preferably cleaved *via* a five-membered nickelacycle over the aromatic C-H bond in the cyclometallation step. Subsequently, Maiti demonstrated that the electron-deficient alkenes were also applicable for the C(sp^3)-H alkylation under nickel catalysis to provide a variety of linear alkylated amides.[31]

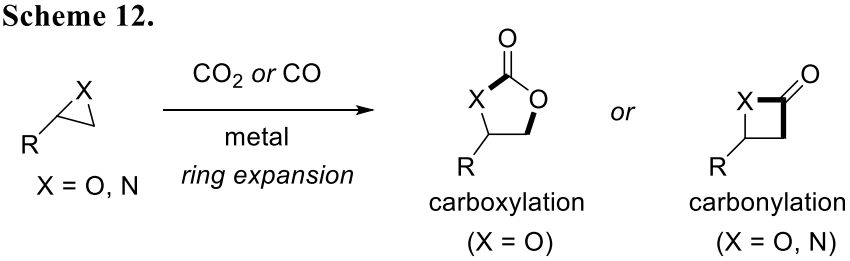
Scheme 11.



3. Metal-catalyzed ring opening reactions of small-sized heterocycles.

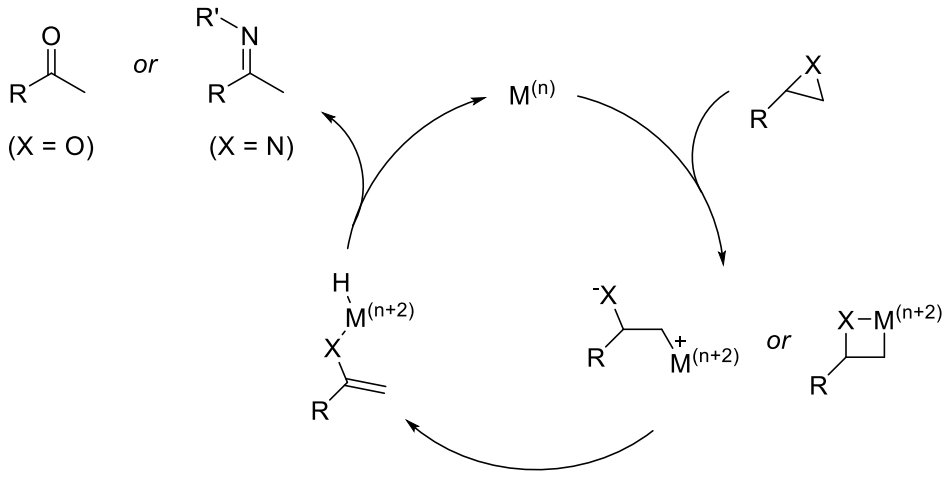
Owing to the intrinsic ring strain, small-sized heterocycles have played an indispensable role in synthetic chemistry to construct heteroatom-containing skeletons *via* ring-opening reactions.[32] Because of the considerable stability and reactivity as well as ready availability, the three-membered epoxides and aziridines have received more attention for the novel transformations. In this regard, the metal-catalyzed ring expansion reactions including carboxylation and carbonylation by the insertion of CO_2/CO were well explored with various transition metals (Scheme 12).[33]

Scheme 12.



The metal-promoted isomerization reactions of aziridines and epoxides are facile, and have been widely used for the construction of C=O/N bonds (Scheme 13). The aziridines undergo oxidative addition with a low valent metal catalyst to form a zwitterion complex or an azametallacyclobutane intermediate. Subsequent β-hydride elimination affords alkene-derived organometallic species. The final imine products are formed by the reductive elimination followed by tautomerization.[34] Similarly, the isomerization of epoxides into aldehydes or ketones *via* C-O bond cleavage was mediated by various metals and/or reagents.[35] This transformation offers convenient access to carbonyl compounds from the readily available epoxides.

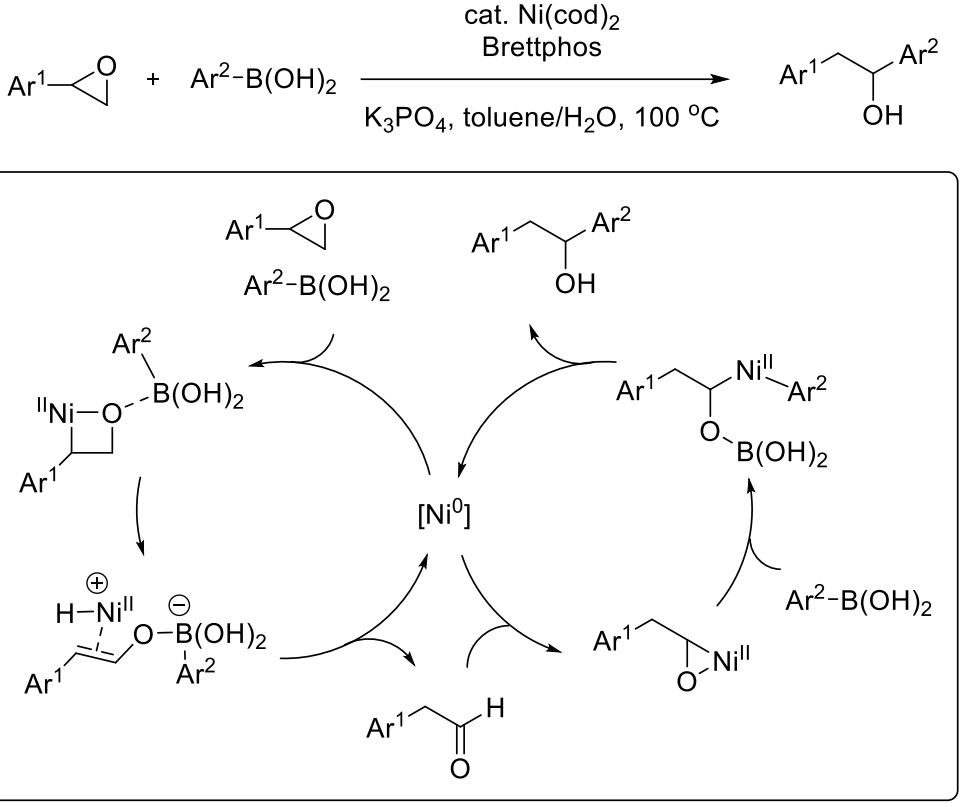
Scheme 13.



On the other hand, the three-membered heterocycles as the promising carbon electrophiles, have been investigated in the cross-coupling reactions to construct C-C bonds. However, due to the facile β-hydride elimination aforementioned in the isomerization process, the catalytic C-C bond formation with epoxides has been more challenging. In 2011, Doyle reported the Ni-catalyzed Suzuki-Miyaura-type

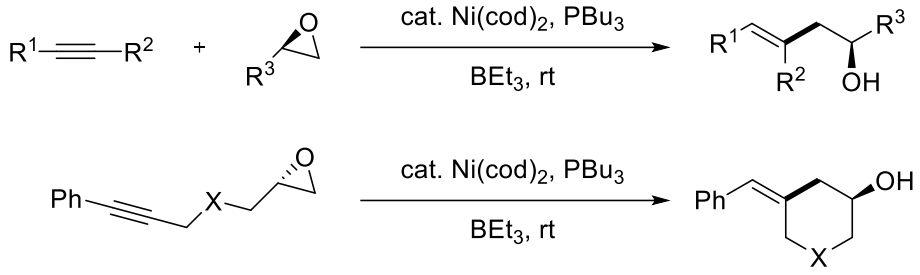
cross-coupling of styrene oxides with aryl boronic acids (Scheme 14).[36] The reaction proceeded with isomerization of styrene oxide to aldehyde by β-hydride elimination, and subsequent 1,2-arylation of the aldehyde intermediate to deliver the final product.

Scheme 14.



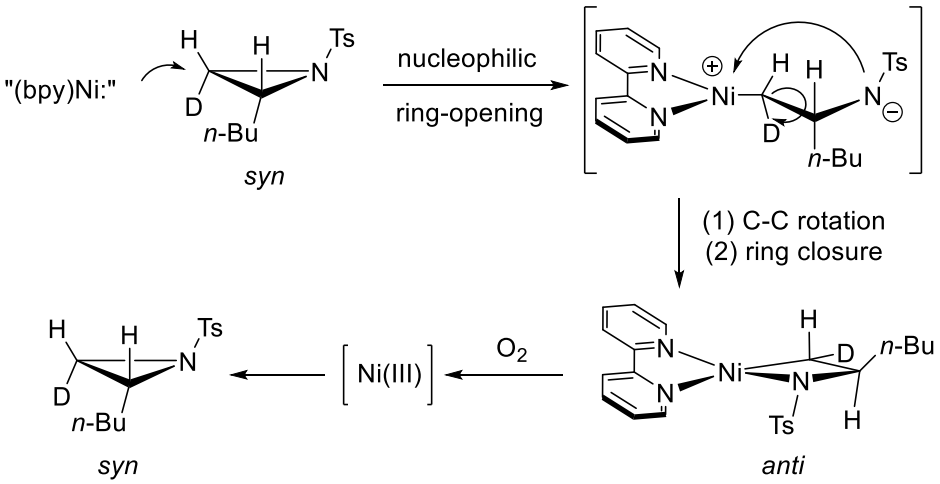
Jamison group has focused on the reductive coupling of alkynes with epoxides under $Ni(cod)_2$ catalysis to afford homoallylic alcohols (Scheme 15).[37] BEt_3 was used as the terminal reductant. Moreover, the related intramolecular reductive couplings were also realized under the same catalytic system.

Scheme 15.



Compared to epoxides, transition metal-catalyzed cross-coupling reactions between aziridines and organometallic reagents generally shows better chemo-, regio-, and stereoselectiveity, which are difficult to control in the conventinal substitution reactions. As a seminal work, Hillhouse reported the oxidative addition of alkyl aziridines to Ni(0) complexs, leading to the azametallacyclobutane intermediate.[38] The stereochemistry of the oxidative addition process was demonstrated by the reaction with a deuterium-labeled aziridine, thus indicating an S_N2 pathway involving the attack of Ni(0) to the terminal position of alkyl aziridine. Subsequent reductive elimination initiated by the oxygen afforded the net-stereoretentive aziridine product (Scheme 16).

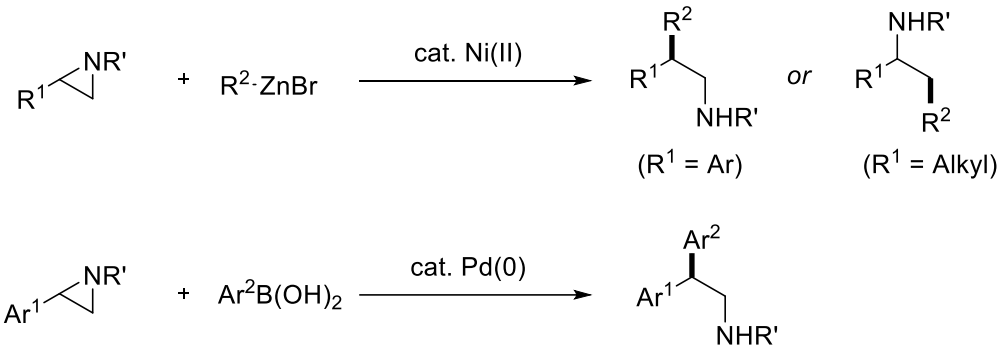
Scheme 16.



After this report, the chemistry of Negishi- and Suzuki-Miyaura-type couplings with

aziridines to construct C-C bond were well investigated by using nickel or palladium as the catalyst (Scheme 17).[39] The scope of aziridines were extended from aryl-substituted aziridines to simple aliphatic aziridines. The site selectivity of the reaction is generally dependent on the substituents on the aziridine: the aryl-substituted aziridine provides the benzylic C-N cleaved product while the more sterically accessible terminal position is substituted in the case of the alkyl-substituted aziridine.

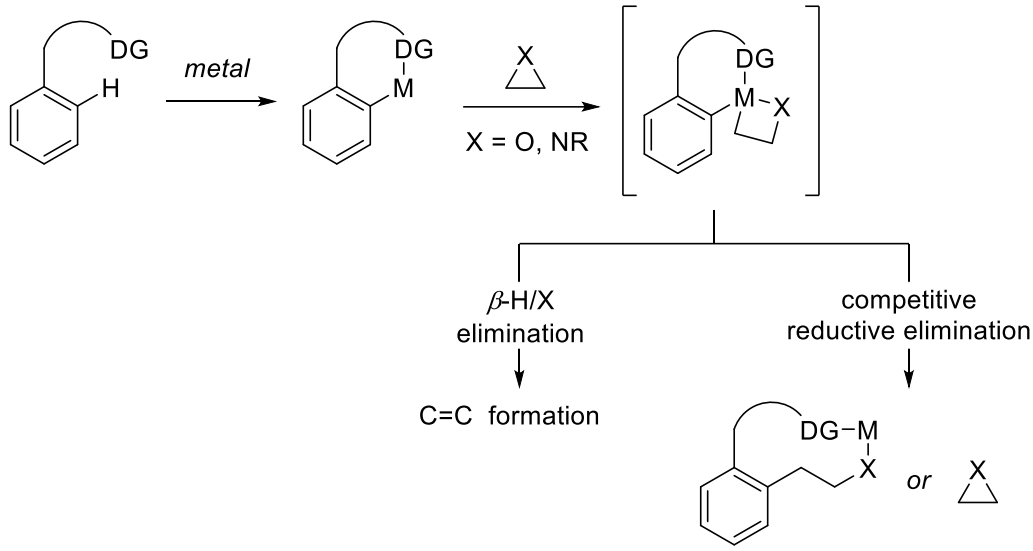
Scheme 17.



Additionally, the metal-catalyzed reactions with other small-sized heterocycles, including 2*H*-azirines, oxaziridines, thiiranes, and siliranes, also have been investigated for the preparation of valuable heteroatom-containing molecules.[33a],[40]

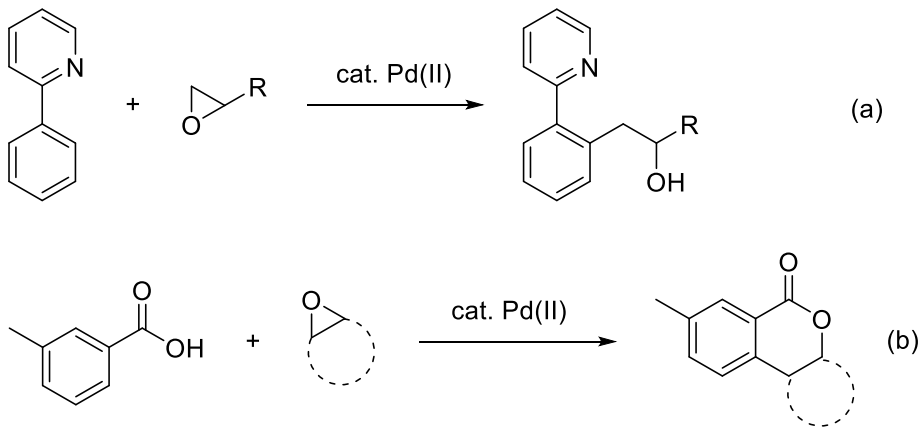
However, the catalytic C-H coupling reaction with small-sized heterocycles is less explored. As shown in Scheme 18, the potential challenges in the directed C-H functionalization with small-sized heterocycles could be ascribed to the following two points: (1) the facile β-elimination of oxa- and azametallacyclobutane intermediates results in the undesired C=C double bond formation; (2) the competitive reductive elimination leads to the conversion back into the starting heterocycles.

Scheme 18.



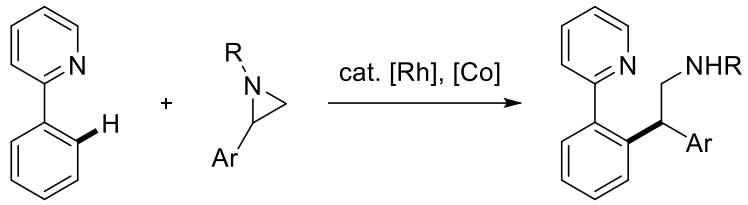
As a few successful examples, the research group of Kuninobu and Kanai,[41] and Yu[42] independently reported Pd(II)-catalyzed C-H alkylations of arylpyridines (Scheme 19a) and benzoic acids (Scheme 19b) with epoxides as alkylating reagents. More recently, Dong and co-workers also successfully employed epoxides in the palladium/norbornene-catalyzed direct annulation reaction with aryl iodides.[43] These strategies can address traditional β-hydride elimination problems associated with alkyl halide electrophiles.

Scheme 19.



In 2013, Li and co-workers first disclosed the Cp*Rh(III)-catalyzed *ortho* C-H alkylation of 2-arylpyridines with aziridines (Scheme 20).[44] Yoshikai group also developed the same transformation under Co-NHC catalysis.[45] However, these protocols are limited to the relatively activated aryl-substituted aziridines.

Scheme 20.



Aim of this thesis

Small-sized heterocycles, as readily available building blocks, have received significant interest in synthetic chemistry. However, the metal-catalyzed coupling reactions with small-sized heterocycles to form new C-C bonds mainly focused on the organohalides and organometallic reagents. The author attempted to expand this chemistry to the direct C-H functionalization by utilizing a suitable chelating auxiliary. In addition, with the assistance of a related coordinating group, a regioselective alkenyl C-H activation of allylic alcohols was also investigated. Thus, this doctoral thesis is composed of following four chapters.

Chapter 2 discloses a nickel-catalyzed stereospecific C-H coupling of benzamides with epoxides to construct isocoumarin derivatives. A unique stereospecificity with retention of configuration was observed in the reaction with internal epoxides.

Chapter 3 reveals rapid access to seven-membered benzolactons by nickel-catalyzed regioselective C-H coupling of benzamides with oxetanes.

Chapter 4 shows an 8-aminoquinoline-directed C-H alkylation of benzamides with aziridines under nickel catalysis. The C-H alkylation is followed by intramolecular amidation to form the functionalized benzolactams in single operation.

In the course of studies on the bidentate auxiliary-directed C-H functionalization reactions, a related regioselective C-H alkenylation and alkynylation of allylic alcohols under palladium catalysis with the assistance of bidentate phenanthroline auxiliary is also disclosed and shown in Chapter 5.

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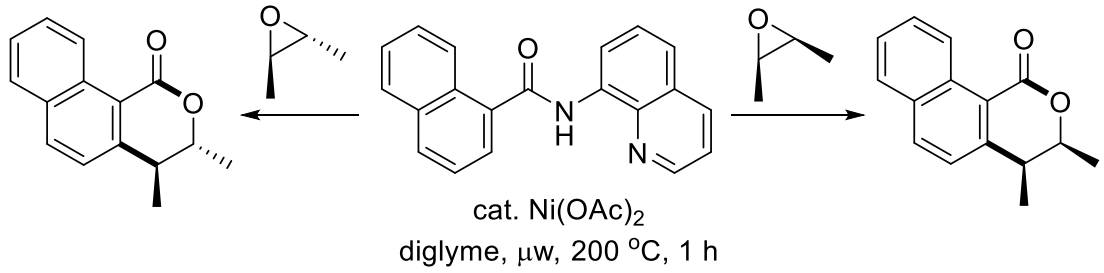
Chapter 2

Nickel-Catalyzed Stereospecific C-H Coupling of Benzamides with Epoxides

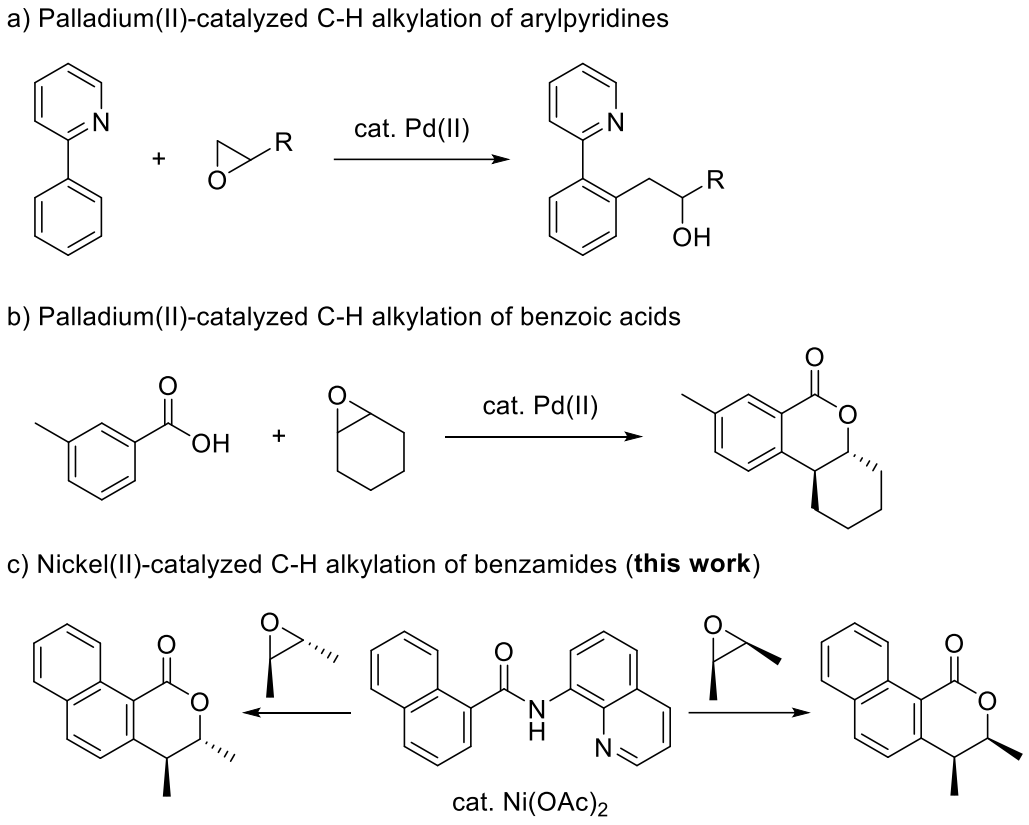
A $Ni(OAc)_2$-catalyzed C–H coupling of 8-aminoquinoline-derived benzamides with epoxides has been disclosed. The reaction proceeds with concomitant removal of the 8-aminoquinoline auxiliary to form the corresponding 3,4-dihydroisocoumarins directly. Additionally, the nickel catalysis is stereospecific, and the *cis*- and *trans*-epoxides are converted into the corresponding *cis*- and *trans*-dihydroisocoumarins with retention of configuration, which is complementary to previous palladium catalysis. Moreover, while still preliminary, the C_{sp3}–H functionalization is also achieved under the modified $NiCl_2$ catalysis.



Introduction

In recent few decades, metal-promoted C–H coupling reactions have received significant attention because of their higher atom and step economies compared to conventional cross-coupling protocols with organic halides and organometallic reagents.[1] Various electrophilic and nucleophilic components can be coupled with C–H bonds under appropriate conditions to form the corresponding C–C and C–X bonds. However, the alkylation reaction with epoxides as alkylating reagents is less explored. As limited successful examples, in 2015 the research group of Kuninobu and Kanai,[2] and Yu[3] independently reported palladium(II)-catalyzed C–H alkylations of arylpyridines and benzoic acids (Scheme 1a and 1b). These strategies can address traditional β-hydride elimination problems associated with alkyl halide electrophiles. Additionally, in the latter work, a unique stereoinvertive C–C bond formation was observed when internal epoxides were used. More recently, Dong and co-workers also successfully employed epoxides in the palladium/norbornene-catalyzed direct annulation reaction with aryl iodides.[4] A related cobalt-catalyzed C–H coupling of benzoic acids with C–C unsaturated molecules for the synthesis of lactone derivatives was also developed by Daugulis and co-workers.[5]

Scheme 1. Metal-catalyzed C–H alkylations with epoxides. (Py = 2-pyridyl, Q = 8-quinolinyl)



Meanwhile, well-designed bidentate directing groups now enable the functionalization of otherwise difficult C_{sp2}–H bonds, and even more challenging C_{sp3}–H bonds. To date, many combinations of bidentate coordination groups and transition-metal catalysts have been developed.[6] Miura group also focused on the high potential of abundant Cu salts, and succeeded in the development of unique C–H arylation, alkylation, and amination with the assistance of suitable *N*,*N*-bidentate coordination groups.[7] Given his interest in this chemistry, the author paid attention to the C–H alkylation with epoxides. Although Cu-based conditions were unsuccessful, a similar base metal, nickel,[6d,e,8] showed the promising reactivity. Herein, the author

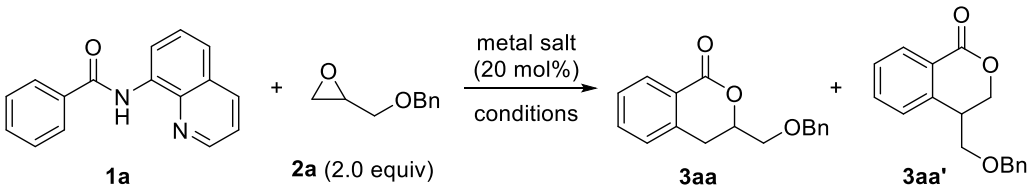
reports a nickel(II)-catalyzed C–H coupling reaction of 8-aminoquinoline-derived benzamides, a reaction originally developed by Daugulis and co-workers,[6a] with epoxides: the directed C–H alkylation is followed by intramolecular alcoholysis to deliver the corresponding 3,4-dihydroisocoumarins in one synthetic operation (Scheme 1c). Namely, the 8-aminoquinoline group is spontaneously removed and recovered, and deserves significant attention because the removal of bidentate directing groups is often tedious and problematic.[9] Thus, the present nickel catalysis can provide a potentially more effective approach to the 3,4-dihydroisocoumarin structure frequently found in natural products and bioactive molecules.[10] Additionally notable is the stereospecificity: the *cis*-epoxide can be converted to the *cis*-dihydroisocoumarin whereas the *trans* isomer is selectively formed from the *trans* epoxide. The unique stereochemical outcome with retention of configuration is complementary to that observed in previously reported palladium(II) catalysis (Scheme 1b).[3]

Results and discussion

The author commenced optimization studies with 8-aminoquinoline-derived benzamide **1a** and terminal epoxide **2a** as model substrates (Table 1). He tested several base-metal acetate catalysts in heated diglyme (150–170 ˚C), and found that only $Ni(OAc)_2•4H_2O$ showed catalytic activity to form 3,4-dihydroisocoumarins **3aa** and **3aa'** in 75% combined yield with 7.3:1 regioselectivity (entry 14). While not detected, the simply alkylated products, that is, alcohols shown in Scheme 1a can be the initial products, and subsequent intramolecular alcoholysis forms the observed **3aa** and **3aa'**. Other metal acetates including $Mn(OAc)_2•4H_2O$, $Co(OAc)_2•4H_2O$, $Fe(OAc)_2$,

and $Cu(OAc)_2$ gave no detectable amount of coupling products (entries 1, 15-17). Although the subsequent screening of various reaction parameters such as solvent, additives, and ligands did not further improve the reaction efficiency, microwave irradiation (200 ˚C) dramatically accelerated the reaction to deliver **3aa** and **3aa'** in 91% yield with somewhat higher regioisomeric ratio (9.1:1 r.r.) (entry 23).[11]

Table 1. Optimization studies[a]



1a **2a** (2.0 equiv) **3aa** **3aa'**

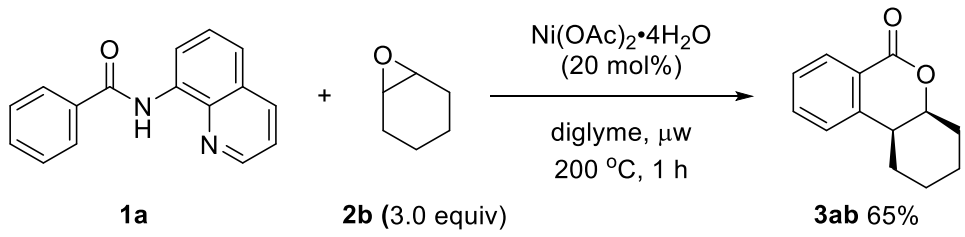
entry	$M(OAc)_2$	conditions	yield (%)[b]	**3aa**:**3aa'**[c]
1	$Cu(OAc)_2$	diglyme, 150 ˚C, 4 h	0	n.d.
2	**$Ni(OAc)_2•4H_2O$**	**none**	**69**	**n.d.**
3	$Ni(acac)_2$	none	22	n.d.
4	$NiCl_2$•glyme	none	11	n.d.
5	$NiBr_2$•diglyme	none	42	n.d.
6	NiI_2	none	42	n.d.
7	$Ni(OTf)_2$	none	4	n.d.
8	**$NiCl_2(PEt_3)_2$**	**none**	**69**	**n.d.**
9	$NiCl_2(PCy_3)_2$	none	55	n.d.
10	$Ni(cod)_2$	none	66	n.d.
11	$Ni(OAc)_2•4H_2O$	Na_2CO_3 (0.50)	52	n.d.
12	$Ni(OAc)_2•4H_2O$	PPh_3 (0.10)	67	n.d.
13	$Ni(OAc)_2•4H_2O$	AcOH (0.18)	27	n.d.
14	**$Ni(OAc)_2•4H_2O$**	**diglyme, 170 ˚C, 25 h**	**(75)**	**7.3:1**
15	$Mn(OAc)_2•4H_2O$	diglyme, 170 ˚C, 24 h	trace	n.d.
16	$Co(OAc)_2•4H_2O$	diglyme, 170 ˚C, 24 h	trace	n.d.
17	$Fe(OAc)_2$	diglyme, 170 ˚C, 24 h	0	n.d.
18	$Ni(OAc)_2•4H_2O$	HFIP, 70 ˚C, 23 h	0	n.d.
19	$Ni(OAc)_2•4H_2O$	1,4-dioxane, 115 ˚C, 24 h	4	n.d.

20	$Ni(OAc)_2•4H_2O$	DME, 110 ˚C, 24 h	10	n.d.
21	$Ni(OAc)_2•4H_2O$	DCE, 110 ˚C, 24 h	48	n.d.
22	$Ni(OAc)_2•4H_2O$	DMSO, 170 ˚C, 18 h	11	n.d.
23[d]	***$Ni(OAc)_2•4H_2O$***	***diglyme, μw, 200 ˚C, 1 h***	***(91)***	***9.1:1***

[a] Reaction conditions: metal salt (0.050 mmol), **1a** (0.25 mmol), **2a** (0.50 mmol), solvent (1.5 mL), N_2. [b] Combined yields of **3aa** and **3aa'** were estimated by GC method. Isolated yields are shown in parentheses. [c] Determined by ^1H NMR. [d] Under microwave irradiation. n.d. = not determined.

Additionally, the notable stereochemical outcome was observed when cyclohexene oxide (**2b**) was used instead of **1a** (Scheme 2): the corresponding dihydroisocoumarin **3ab** was obtained as the single *cis* isomer. The observed stereochemistry with retention of configuration is in sharp contrast to that in the previous palladium catalysis, where the internal epoxide was coupled with C–H bonds in a stereoinvertive manner.[3]

Scheme 2. Nickel-catalyzed C-H coupling of 1a and 2b with retention of configuration

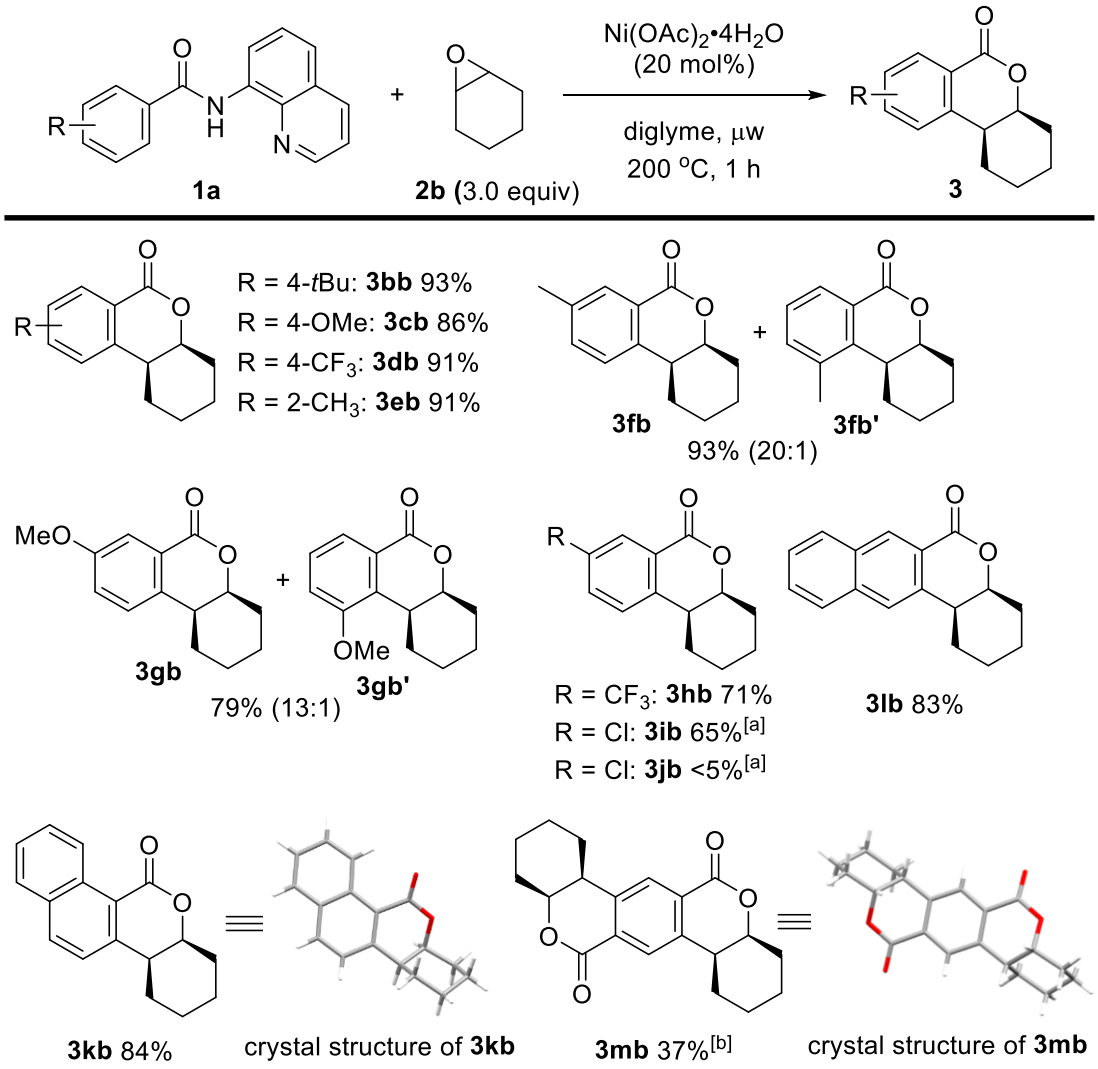


(The reaction was performed under the conditions of entry 23 in Table 1)

To check the generality of the aforementioned stereochemistry, the author investigated the scope of benzamides **1** with **2b**. Gratifyingly, the reaction proceeded uniformly with retention of configuration, and all products **3** were obtained as the *cis* isomers (Scheme 3). The reaction was compatible with electron-donating *tert*-butyl and methoxy groups as well as electron-withdrawing trifluoromethyl group to furnish the corresponding *cis*-3,4-dihydroisocoumarins **3bb**-**3db** in 86–93% yields. The

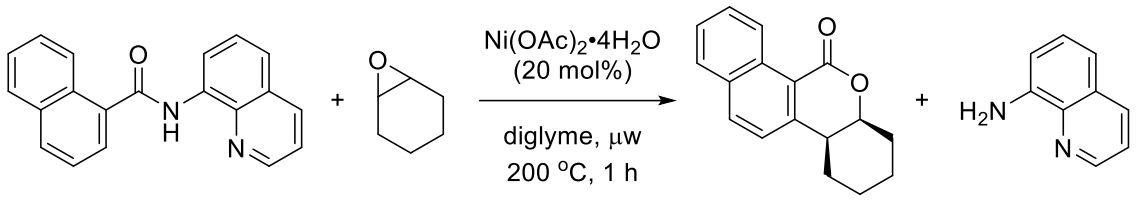
sterically demanding ortho substitution was also tolerated under the standard conditions (**3eb**). In cases of meta-substituted benzamides, more sterically accessible C–H bonds were preferably coupled with **2b** (**3fb**-**3hb**). The chloro-substituted benzamide **1i** was also converted to the dihydroisocoumarin **3ib** with an acceptable yield. However, the C–Br moiety was detrimental, and competitively reduced product was also observed (**3jb**). However, this result is somewhat informative to an oxidation state of active nickel species (see below). In contrast, condensed 1- and 2-naphthamides, **1k** and **1l**, respectively, participated in the reaction without any difficulties (**3kb** and **3lb**): the latter reaction occurred selectively at the less congested C3 position. Moreover, the double cyclization of the terephthalamide derivative **1m** was possible, forming the *syn* product **3mb** as the major isomer. The structure and stereochemistry of products **3kb** and **3mb** were unambiguously determined by the single crystallographic X-ray analysis.[12] The nickel-catalyzed reaction could be easily conducted on a 2.5 mmol scale, and the removed 8-aminoquinoline was also recovered in this case (**3kb**: 96%, 8-aminoquinoline 80%), thus indicating good reproducibility and reliability of this process (Scheme 4).

Scheme 3. Nickel-catalyzed stereospecific C–H coupling of various benzamides 1 with cyclohexene oxide (2b)



Conditions: **1** (0.25 mmol), **2b** (0.75 mmol), $Ni(OAc)_2•4H_2O$ (0.050 mmol), diglyme (1.5 mL), microwave irradiation (200 ˚C), 1 h, N_2. Yields of isolated products are given. [a] The hydrodechlorinated product **3ab** was also formed in ca. 5% yield. [b] With $Ni(OAc)_2•4H_2O$ (0.10 mmol) and **2b** (1.50 mmol). The *anti*-**3mb** and regioisomer were also detected in the crude mixture (<5%), but they could not be isolated in the pure forms.

Scheme 4. Reaction on 2.5 mmol scale

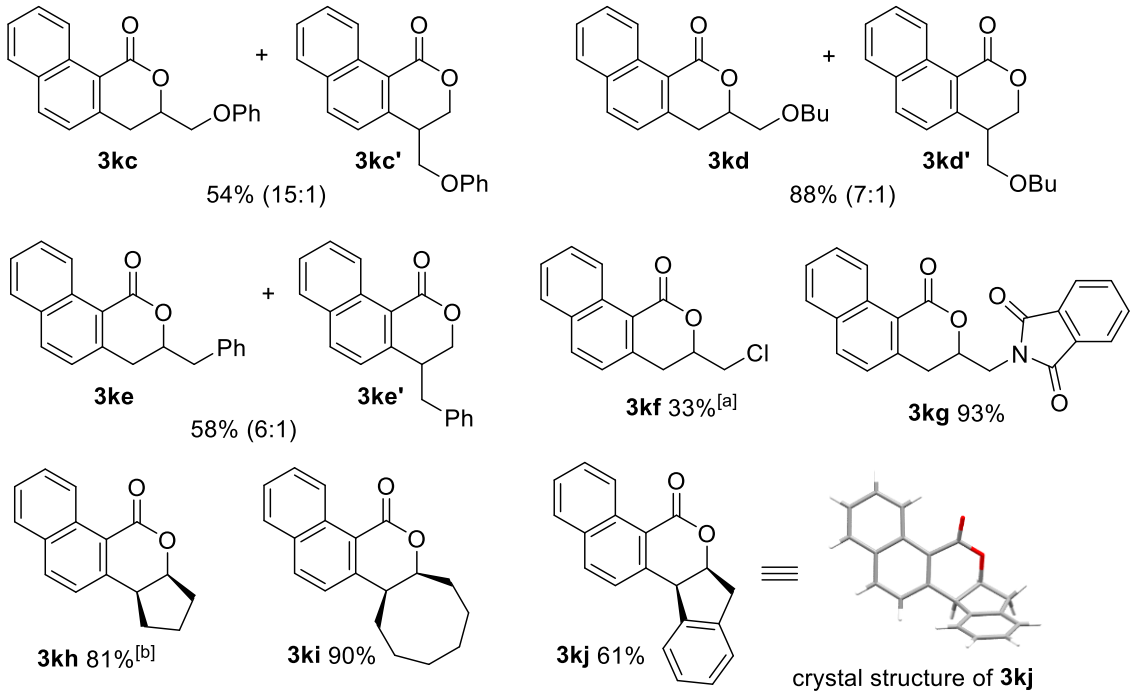


1k 2.5 mmol **2b** 3.0 equiv **3kb** 96% (609 mg) 80% (290 mg) recovery

The scope of epoxide **2** was also examined with **1k**. The product structures are illustrated in Scheme 5. As shown in Scheme 2a, terminal epoxides generally gave a regiomixture (**3kc**-**3ke**), but in good combined yields with synthetically useful regioisomeric ratios (6:1-15:1 r.r.). In contrast, the chloro- and phthalimide-substituted epoxides underwent the C–H coupling exclusively at the more accessible terminal position to deliver **3kf** and **3kg** as single isomers. Internal epoxides other than 6-membered cyclohexene oxide (**2b**) were also tested. Both the smaller (**2h**) and larger (**2i**) ring systems were accommodated, and the corresponding *cis*-dihydroisocoumarins **3kh** and **3ki** were obtained in 81% and 90% yields, respectively. Notably, in case of the indene oxide (**2j**), the regioselective benzylic C–O cleavage occurred to afford **3kj** as the single regio- and stereoisomer. Its structure was confirmed by X-ray analysis.[12] The newly developed nickel catalysis can provide rapid and concise access to various 3,4-dihydroisocoumarins particularly bearing alkyl substituents at the C3 and C4 positions, which deserves significant attention in the C–H functionalization chemistry because some related O-heterocycles can be accessed by metal-catalyzed oxidative C–H coupling of benzoic acids with

alkenes, but attempts to apply unactivated, aliphatic alkenes still remains a challenge.[1a,5]

Scheme 5. Product structures of nickel-catalyzed C–H coupling of 1-naphthamide 1k with various epoxides 2

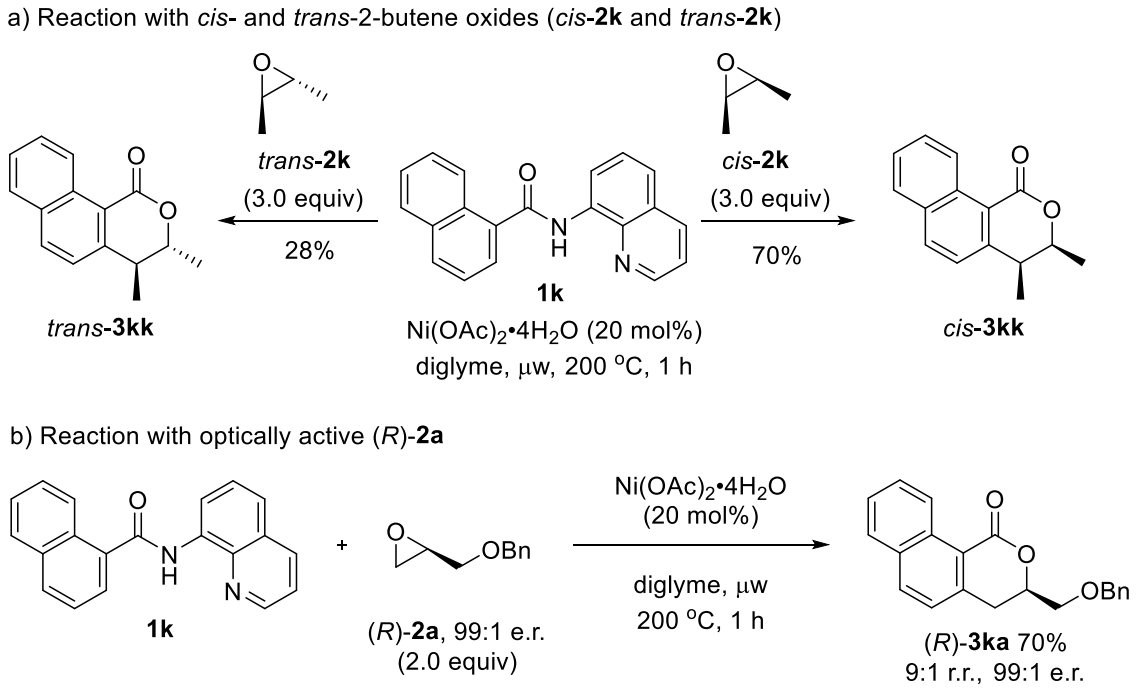


Conditions: **1k** (0.25 mmol), **2** (0.50 mmol), $Ni(OAc)_2 \cdot 4H_2O$ (0.050 mmol), diglyme (1.5 mL), microwave irradiation (200 ˚C), 1 h, N_2. Yields of isolated products are given. [a] With 1.0 mmol of **2f**. [b] With 0.75 mmol of **2h**.

To gain more insight into the stereochemistry, the author then subjected *cis*- and *trans*-2-butene oxides (*cis*-**2k** and *trans*-**2k**) to the identical conditions with **1k** (Scheme 6a). To his delight, the reaction proceeded with perfect stereospecificity: *cis*-**2k** gave the dihydroisocoumarin *cis*-**3kk** exclusively while *trans*-**3kk** was formed as the sole product from *trans*-**2k**. Again, the structure of *cis*-**3kk** was unambiguously determined by X-ray analysis.[12] Moreover, the optically active chiral epoxide (*R*)-**2a** was converted into the chiral 3,4-dihydroisocoumarin (*R*)-**3ka** without erosion of the

enantiomeric ratio (Scheme 6b). Thus, regardless of the structural and stereochemical information of starting epoxides (i.e., cyclic or acyclic as well as terminal or internal), the present nickel catalyst is stereospecific and operative with retention of configuration.

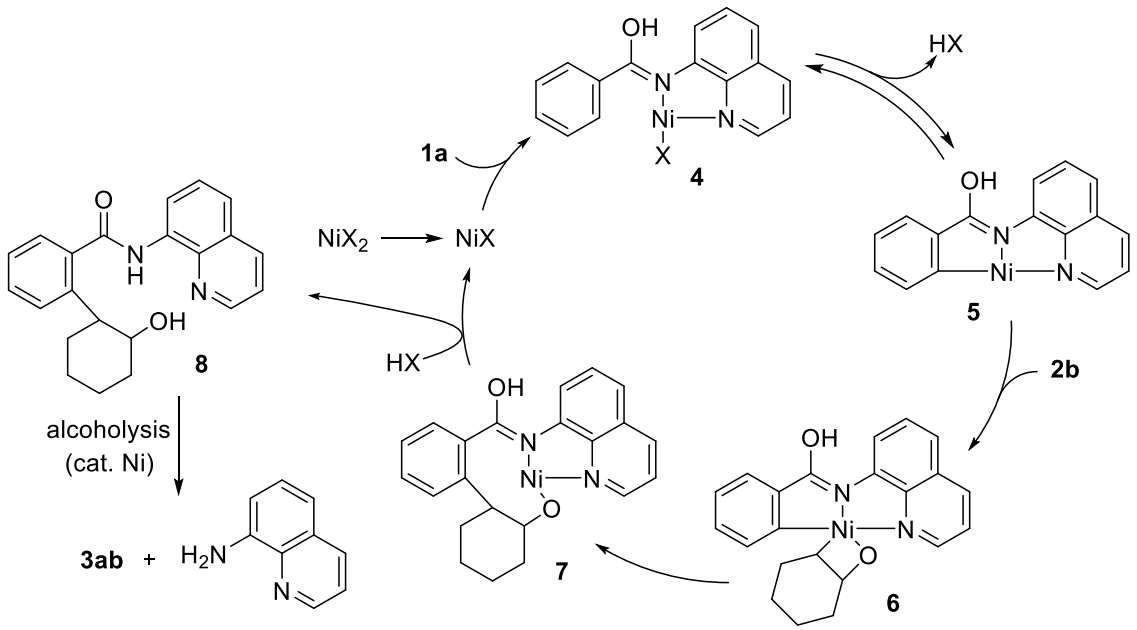
Scheme 6. Stereospecific nickel-catalyzed C–H coupling of 1-naphthamide 1k with a) *cis*- and *trans*-2-butene epoxides (*cis*-2k, *trans*-2k) and b) chiral epoxide (*R*)-2a



Although the detail still remains unclear, on the basis of the literature information and our findings,[13] we are tempted to propose the reaction mechanism of **1a** with **2b** as follows (Scheme 7). Given the incompatibility of the C–Br moiety (**3jb** in Scheme 3), an active nickel catalyst is believed to be nickel(I) rather than nickel(II).[8] Thus, the initial reduction from nickel(II) precatalyst to nickel(I) is followed by *N*,*N*-bidentate coordination with benzamide **1a** to form the intermediate **4**. The facile and reversible

C–H cleavage generates a metalacycle **5** with the liberation of HX. Subsequent oxidative addition with cyclohexene oxide **2b** (**5** to **6**) and reductive elimination (**6** to **7**) to form the C_{sp2}–C_{sp3} bond. Final protonolysis with HX regenerates the starting nickel(I) to complete the catalytic cycle. The concurrently formed alkylation product **8** undergoes the intramolecular alcoholysis to deliver the observed dihydroisocoumarin **3ab** and recovered 8-aminoquinoline. The author confirmed that this ring-closing process spontaneously occurred but was largely accelerated also by the nickel catalyst.[14] Additionally, the observed stereospecificity (retention of epoxide configuration) supports the net retention process in the Ni^{I}/Ni^{III} redox event, namely, the stereoinvertive oxidative addition/stereoinvertive reductive elimination[15] or stereoretentive oxidative addition/stereoretentive reductive elimination[16] can be operative.

Scheme 7. Plausible mechanism

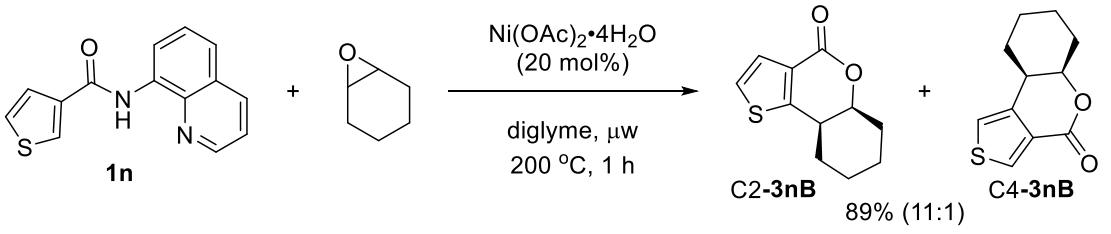


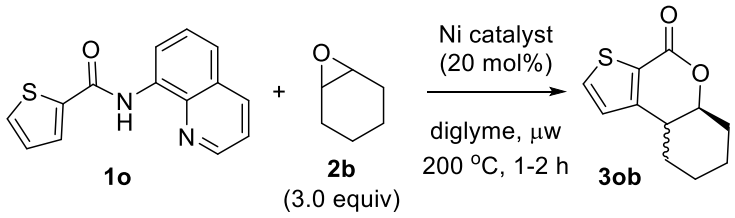
Finally, the author attempted to apply conceivably more challenging heteroaromatic thiophenecarboxamides (**1n** and **1o**; Scheme 8a). Under the standard conditions using the $Ni(OAc)_2•4H_2O$ catalyst, the reaction of thiophene-3-carboxamide **1n** and cyclohexene oxide (**2b**) occurred smoothly with good regioselectivity (89%, C2-**3nb**:C4-**3nb** = 11:1) while thiophene-2-carboxamide **1o** gave the product **3ob** in only 22% yield. However, our additional optimization studies revealed that $NiCl_2(PEt_3)_2$ showed better performance to afford **3ob** in 82% yield albeit with a lower *cis/trans* ratio of 1.7:1.[17] The complexes $NiCl_2(PCy_3)_2$ and phosphine-free $NiCl_2$•glyme were also effective, and **3ob** was formed in acceptable 75% and 50% yield, respectively, with better stereoselectivity (6:1 and >20:1).[18] Moreover, the modified $NiCl_2$-based catalyst systems also promoted the C_{sp3}–H coupling of the pivalamide **1p** with **2b** to form **3pb,** particularly with $NiCl_2(PCy_3)_2$ proving to be optimal (67% yield, *cis*/*trans* = 6:1; Scheme 8b). Also in this case, $Ni(OAc)_2•4H_2O$ was much less effective.[19] The $NiCl_2(PCy_3)_2$ catalyzed the C_{sp3}–H coupling of some additional aliphatic amides (**1q-u**) with **2b** to deliver the corresponding lactones **3qb-ub**. When the potentially reactive methyl and methylene C_{sp3}–H bonds were present, the more sterically accessible methyl C–H was selectively alkylated (**3rb** and **3tb**). Although the *cis/trans* ratio at the cyclohexyl ring fused positions was dependent on the substrate and modest in most cases, the relative stereochemistry at the position α to the carbonyl was well controlled: the stereochemistry of major isomer of **3sb** was unambiguously determined by X-ray analysis.[12] Additionally notable is the compatibility with the somewhat acidic proton at the position α to carbonyl albeit with a moderate yield (**3ub**).

While still preliminary, the obtained results demonstrate the high potential of a nickel catalyst in the even more challenging C_{sp3}–H couplings with epoxides.

Scheme 8. Nickel-catalyzed stereospecific C–H coupling of the thiophenecarboxamides 1n and 1o, and aliphatic amides 1p–u

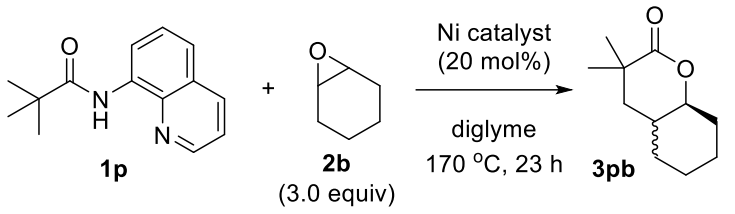
a) Reactions with thiophenecarboxamides 1n and 1o





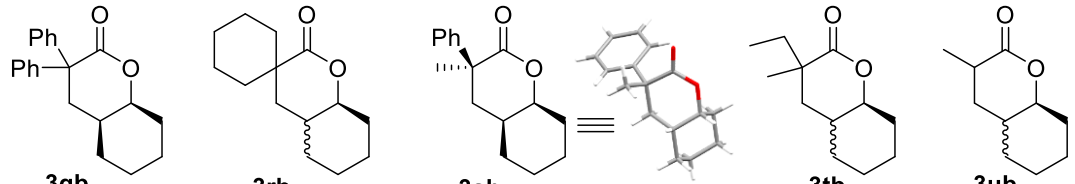
Ni catalyst	Yield, *cis/trans*
$Ni(OAc)_2•4H_2O$	22%, >20:1
$NiCl_2(PEt_3)_2$	82%, 1.7:1
$NiCl_2(PCy_3)_2$	75%, 6:1
$NiCl_2$•glyme	50%, >20:1

b) Reactions with aliphatic amides 1p-u



Ni catalyst	Yield, *cis/trans*
$Ni(OAc)_2•4H_2O$	0%, n.d.
$NiCl_2(PEt_3)_2$	32%, 10:1
$NiCl_2(PCy_3)_2$	67%, 6:1
$NiCl_2$•glyme	47%, 6:1

additional examples of aliphatic amides under $NiCl_2(PCy_3)_2$ catalysis (isolated yields, *cis/trans* ratio)



[a] The relative stereochemistry at the position α to the carbonyl is not determined. n.d. = not determined.

Summary

The author has developed a nickel-catalyzed, *N*,*N*-bidentate coordination-assisted C–H coupling of benzamides with epoxides. The reaction occurs with the concomitant removal of 8-aminoquinoline bidentate auxiliary to form the 3,4-dihydroisocoumarins directly. Additionally, the reaction is completely stereospecific in most cases: both the *cis*- and *trans*-epoxides are converted to the corresponding *cis*- and *trans*-dihydroisocoumarins with retention of configuration, which is in sharp contrast to previous palladium-catalyzed C–H coupling with epoxides.[3] Moreover, the C_{sp3}–H cleavage is also possible under $NiCl_2$/phosphine catalysis. The observed unique activity and stereochemistry associated with the nickel catalysis deserve significant attention from the viewpoint of C–H functionalization chemistry.

Instrumentation and Chemicals

^{1}H, $^{13}C\{^{1}H\}$, and $^{19}F\{^{1}H\}$ spectra were recorded at 400 MHz, 100 MHz, and 162 MHz, respectively, for $CDCl_3$ solutions. HRMS data were obtained by APCI. GC analysis was carried out using a silicon OV-17 column (i. d. 2.6 mm x 1.5 m) or CBP capillary column (i. d. 0.5 mm x 25 m). TLC analyses were performed on commercial glass plates bearing 0.25-mm layer of Merck Silica gel $60F_{254}$. Silica gel (Wakosil C-200, Wako Pure Chemical Co.) was used for column chromatography. Gel permeation chromatography (GPC) was performed by LC-6AD (pump, SHIMADZU, 3.5 mL/min $CHCl_3$) and SPD-20A (UV detector, SHIMADZU, 254 nm) with two in-line GPC H-2001 (20 x 500 mm, particle size: 15 μm) and H-2002 columns (20 x 500 mm, particle size: 15 μm) (preparative columns, Shodex) or by LC-20AR (pump, SHIMADZU, 7.5 mL/min EtOAc) and SPD-20A (UV detector, SHIMADZU, 254 nm) with two in-line YMC-GPC T2000 (20 x 600 mm, particle size: 10 μm) (preparative columns, YMC). Microwave irradiation was conducted with Initiator^{+} (Biotage), and the reaction temperature was measured by an internal probe.

Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. Diglyme was freshly distilled from CaH_2. Benzamides **1** were prepared from the corresponding benzoyl chlorides or benzoic acids and 8-aminoquinoline according to the literature.[20] Epoxides **2e**, **2g**, **2i**, and **2j** were synthesized according to the literature.[21] Others are commercially available. All reactions were carried out under nitrogen atmosphere unless otherwise noted.

Experimental Procedures

Synthesis of **3ab**. A suspension of *N*-(quinolin-8-yl)benzamide (**1a**, 62.1 mg, 0.25 mmol), cyclohexene oxide (**2b**, 73.6 mg, 0.75 mmol), $Ni(OAc)_2 \cdot 4H_2O$ (12.4 mg, 0.05 mmol) and diethylene glycol dimethyl ether (diglyme) (1.5 mL) in a sealed microwave vessel was irradiated under microwave reactor conditions at 200 °C for 1 hour under N_2 atmosphere. The resulting mixture was then quenched with water and extracted with ethyl acetate. The combined organic layer was dried over sodium sulfate. Concentration in vacuo followed by silica gel column purification with hexane/ethyl acetate (5:1, v/v) gave (4a*S**,10b*S**)-2,3,4,4a-tetrahydro-1*H*-benzo[*c*]chromen-6(10b*H*)-one (**3ab**, 33 mg, 0.163 mmol) in 65% yield.

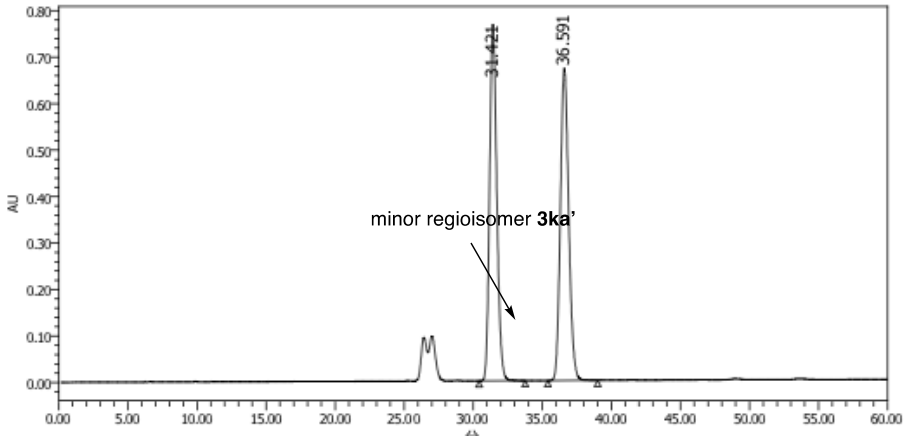
Synthesis of **3kb** (2.5 mmol scale). A suspension of *N*-(quinolin-8-yl)-1-naphthamide (**1k**, 745.9 mg, 2.5 mmol), cyclohexene oxide (**2b**, 736.1 mg, 7.5 mmol), $Ni(OAc)_2 \cdot 4H_2O$ (124.4 mg, 0.5 mmol) and diethylene glycol dimethyl ether (diglyme) (15 mL) in a sealed microwave vessel was irradiated under microwave reactor conditions at 200 °C for 1 hour under N_2 atmosphere. The resulting mixture was then quenched with water and extracted with ethyl acetate. The combined organic layer was dried over sodium sulfate. Concentration in vacuo followed by silica gel column purification with hexane/ethyl acetate (5:1, v/v) gave (6a*S**,10a*S**)-6a,7,8,9,10,10a-hexahydro-5*H*-naphtho[1,2-*c*]chromen-5-one (**3kb**, 609.0 mg, 2.41 mmol) in 96% yield and recovered 8-aminoquinoline (287.6 mg, 1.99 mmol) in 80% yield.

Synthesis of **3pb**. A suspension of *N*-(quinolin-8-yl)pivalamide (**1p**, 57.1 mg, 0.25 mmol), cyclohexene oxide (**2b,** 73.6 mg, 0.75 mmol), $NiCl_2(PCy_3)_2$ (34.5 mg, 0.05 mmol) and diethylene glycol dimethyl ether (diglyme) (1.5 mL) in a sealed tube was stirred at 170 °C by oilbath for 23 hour under N_2 atmosphere. The resulting mixture was then quenched with water and extracted with ethyl acetate. The combined organic layer was dried over sodium sulfate. After concentration in vacuo, the *cis/trans* ratio(*cis:trans* = 6:1) was confirmed by ^{1}H NMR analysis. The crude was purified by silica gel column with hexane/ethyl acetate (5:1, v/v) gave a mixture of *cis*- and *trans*-product (30.5 mg, 0.17 mmol, *cis:trans* = 6:1) in 67% yield. Then additional purification by GPC (EtOAc) gave (4a*S**,8a*S**)-3,3-dimethyloctahydro-2*H*-chromen-2-one (**3pb**, 26.1 mg, 0.14 mmol) in 56% yield.

Chiral HPLC Charts

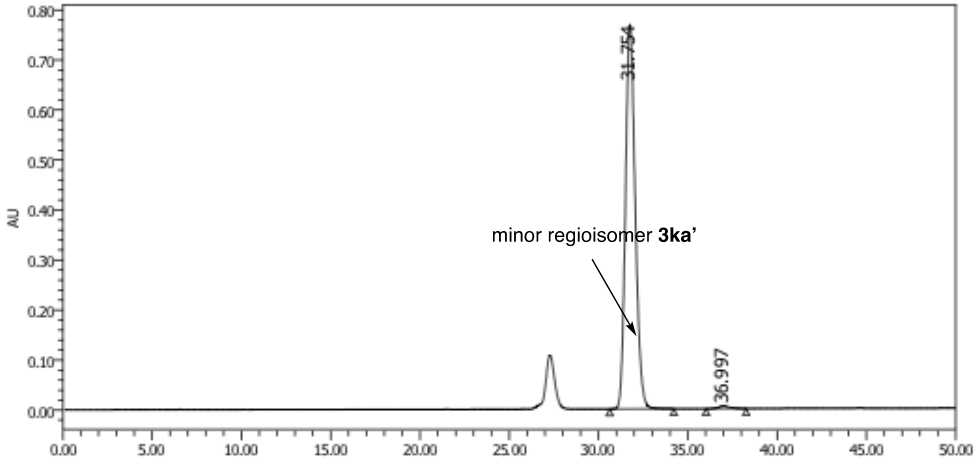
3ka: The enantiomeric ratio was determined by HPLC analysis in comparison with authentic racemic material (CHIRALCEL AD-H column, 90/10 *n*-hexane/2-propanol, 0.5 mL/min, major isomer: t_R = 31.8 min, minor isomer: t_R = 37.0dd min, UV detection at 240 nm, 30 °C).

rac-**3ka**



Peak #	Ret. Time	Area	Area %
1	31.421	27844147	49.79
2	36.591	28082736	50.21

(*R*)-**3ka**



Peak #	Ret. Time	Area	Area %
1	31.754	29238215	99.26
2	36.997	217919	0.74

Characterization Data for Products

9:1 Regiomixture of 3-((benzyloxy)methyl)isochroman-1-one (3aa) and 4-((benzyloxy)methyl)isochroman-1-one (3aa'): colorless oil; TLC R_f 0.33 (hexane/EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) for mixture δ 8.12-8.08 (m, 1H, for **3aa** + **3aa'**), 7.58-7.51 (m, 1H, for **3aa** + **3aa'**), 7.44-7.24 (m, 7H, for **3aa** + **3aa'**), 4.74-4.68 (m, 1H, for **3aa** + **3aa'**), 4.66-4.51 (m, 2.1H, for **3aa** + **3aa'**), 3.78 (qd, *J* = 10.4, 4.9 Hz, 1.8H, for **3aa**), 3.72-3.61 (m, 0.2H, for **3aa'**), 3.23-3.14 (m, 1H, for **3aa** + **3aa'**), 2.98 (dd, *J* = 16.4, 3.4 Hz, 0.9H, for **3aa**). ^{13}C NMR (100 MHz, $CDCl_3$) for mixture δ 165.0, 164.9, 140.0, 138.8, 137.7, 133.9, 133.8, 130.5, 130.3, 128.53, 128.51, 128.2, 127.9, 127.8, 127.69, 127.67, 127.6, 127.5, 125.0, 125.0, 77.2, 73.7, 73.5, 71.1, 69.9, 68.1, 38.2, 30.1. (All observed signals are shown because of complexity associated with regioisomers.) HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{17}H_{17}O_3$: 269.1172, Found: 269.1174.

(4a*S,10b*S**)-2,3,4,4a-Tetrahydro-1*H*-benzo[*c*]chromen-6(10b*H*)-one (3ab):** colorless solid; m. p. 90.7-92.4 °C (from hexane); TLC R_f 0.25 (hexane/EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.52 (td, *J* = 7.6, 1.4 Hz, 1H), 7.36 (td, *J* = 7.6, 1.2 Hz, 1H), 7.22 (dt, *J* = 8.0, 1.0 Hz, 1H), 4.68 (d, *J* = 3.1 Hz, 1H), 2.76 (ddd, *J* = 12.1, 4.5, 2.8 Hz, 1H), 2.20-2.12 (m, 1H), 1.81-1.58 (m, 5H), 1.52 (td, *J* = 12.5, 2.6 Hz, 1H), 1.47-1.35 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.0, 145.1, 133.7, 130.3, 127.4, 126.7, 124.0, 76.3, 39.2, 29.9, 29.5, 24.5, 19.4. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{13}H_{15}O_2$: 203.1067, Found: 203.1064.

(4a*S,10b*S**)-9-(*tert*-Butyl)-2,3,4,4a-tetrahydro-1*H*-benzo[*c*]chromen-6(10b*H*)-one (3bb):** colorless solid; m. p. 95.4-97.1 °C (from hexane); TLC R_f 0.30 (hexane/EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.2 Hz, 1H), 7.38 (dd, *J* = 8.3, 2.0 Hz, 1H), 7.21 (d, *J* = 2.0 Hz, 1H), 4.66 (q, *J* = 2.7 Hz, 1H), 2.74 (ddd, *J* = 12.2, 4.5, 2.8 Hz, 1H), 2.19-2.14 (m, 1H), 1.80-1.57 (m, 5H), 1.56-1.44 (m, 1H), 1.44-1.35 (m, 1H), 1.31 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.1, 157.6, 145.0, 130.1, 124.7, 123.4, 121.2, 76.3, 39.6, 35.1, 31.0, 30.0, 29.7, 24.6, 19.3. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{17}H_{23}O_2$: 259.1693, Found: 259.1694.

(4a*S,10b*S**)-9-Methoxy-2,3,4,4a-tetrahydro-1*H*-benzo[*c*]chromen-6(10b*H*)-one (3cb):** colorless solid; m. p. 82.7-84.4 °C (from hexane); TLC R_f 0.28 (hexane/EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 8.7 Hz, 1H), 6.85 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.68 (d, *J* = 2.5 Hz, 1H), 4.64 (q, *J* = 3.0 Hz, 1H), 3.84 (s, 3H), 2.72-2.67 (m, 1H), 2.17-2.12 (m, 1H), 1.80-1.48 (m, 6H),

1.44-1.33 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, 163.8, 147.5, 132.6, 116.5, 113.3, 111.3, 76.0, 55.4, 39.6, 29.9, 29.4, 24.5, 19.4. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{14}H_{17}O_3$: 233.1172, Found: 233.1179.

(4a*S,10b*S**)-9-(Trifluoromethyl)-2,3,4,4a-tetrahydro-1*H*-benzo[*c*]chromen-6(10b*H*)-one (3db):** white solid; m. p. 88.1-89.4 °C (from hexane); TLC R_f 0.38 (hexane/EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (d, *J* = 8.1 Hz, 1H), 7.62 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.51-7.50 (m, 1H), 4.72 (q, *J* = 2.9 Hz, 1H), 2.86 (dt, *J* = 12.0, 3.2 Hz, 1H), 2.19 (dt, *J* = 11.7, 5.6 Hz, 1H), 1.83-1.78 (m, 2H), 1.75-1.59 (m, 3H), 1.57-1.39 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 145.7, 135.1 (q, *J* = 32.6 Hz), 131.1, 127.1, 124.3 (q, *J* = 3.7 Hz), 123.9 (q, *J* = 3.7 Hz), 123.4 (q, *J* = 272.4 Hz), 76.4, 39.2, 29.7, 29.4, 24.4, 19.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.2. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{14}H_{14}F_3O_2$: 271.0940, Found: 271.0946.

(4a*S,10b*S**)-7-Methyl-2,3,4,4a-tetrahydro-1*H*-benzo[*c*]chromen-6(10b*H*)-one (3eb):** colorless solid; m. p. 94.1-96.0 °C (from hexane); TLC R_f 0.27 (hexane/EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (t, *J* = 7.6 Hz, 1H), 7.17 (d, *J* = 7.6 Hz, 1H), 7.05 (d, *J* = 7.5 Hz, 1H), 4.60 (d, *J* = 3.0 Hz, 1H), 2.74-2.69 (m, 1H), 2.67 (s, 3H), 2.18-2.14 (m, 1H), 1.81-1.69 (m, 3H), 1.64-1.50 (m, 3H), 1.41 (tt, *J* = 12.5, 3.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 146.2, 142.9, 132.6, 130.8, 124.7, 122.6, 75.2, 40.3, 29.8, 29.2, 24.6, 22.3, 19.3. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{14}H_{17}O_2$: 217.1223, Found: 217.1227.

(4a*S,10b*S**)-8-Methyl-2,3,4,4a-tetrahydro-1*H*-benzo[*c*]chromen-6(10b*H*)-one (3fb):** colorless solid; m. p. 98.6-99.7 °C (from hexane); TLC R_f 0.30 (hexane/EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91-7.90 (m, 1H), 7.35-7.32 (m, 1H), 7.12 (d, *J* = 7.7 Hz, 1H), 4.66 (q, *J* = 3.0 Hz, 1H), 2.73 (dt, *J* = 11.8, 3.9 Hz, 1H), 2.37 (t, *J* = 9.8 Hz, 3H), 2.16 (dt, *J* = 10.4, 6.0 Hz, 1H), 1.80-1.59 (m, 5H), 1.54-1.37 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 142.3, 137.2, 134.6, 130.6, 126.6, 123.8, 76.4, 38.9, 30.0, 29.6, 24.5, 20.9, 19.4. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{14}H_{17}O_2$: 217.1223, Found: 217.1228.

13:1 Regiomixture of (4a*S,10b*S**)-8-methoxy-2,3,4,4a-tetrahydro-1*H*-benzo[*c*]chromen-6(10b*H*)-one (3gb) and (4a*S**,10b*S**)-10-methoxy-2,3,4,4a-tetrahydro-1*H*-benzo[*c*]chromen-6(10b*H*)-one (3gb'):** colorless solid; TLC R_f 0.33 (hexane/EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) for mixture δ 7.69

(dd, *J* = 7.9, 1.1 Hz, 0.07H, for **3gb'**), 7.57 (d, *J* = 2.7 Hz, 0.93H, for **3gb**), 7.30 (t, *J* = 8.0 Hz, 0.07H, for **3gb'**), 7.14-7.04 (m, 1.93H, for **3gb + 3gb'**), 4.66-4.58 (m, 1H, for **3gb + 3gb'**), 3.85 (s, 0.21H, for **3gb'**), 3.82 (s, 2.79H, for **3gb + 3gb'**), 3.06 (ddd, *J* = 11.8, 4.4, 2.7 Hz, 0.07H, for **3gb'**), 2.73-2.68 (m, 0.93H, for **3gb**), 2.21-2.12 (m, 1H, for **3gb + 3gb'**), 1.86-1.31 (m, 7H, for **3gb + 3gb'**). ^{13}C NMR (100 MHz, $CDCl_3$) for mixture δ 166.2, 158.7, 155.2, 137.6, 133.9, 127.9, 126.4, 124.8, 121.9, 121.7, 114.7, 112.8, 76.7, 76.4, 55.6, 55.5, 38.4, 31.7, 30.0, 30.0, 25.8, 24.5, 19.4, 19.4. (All observed signals are shown because of complexity associated with regioisomers.) HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{14}H_{17}O_3$: 233.1172, Found: 233.1173.

(4a*S,10b*S**)-8-(Trifluoromethyl)-2,3,4,4a-tetrahydro-1*H*-benzo[*c*]chromen-6(10b*H*)-one (3hb):** colorless solid; m. p. 112.9-114.6 °C (from hexane); TLC R_f 0.30 (hexane/EtOAc, 5:1).^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.77 (d, *J* = 9.4 Hz, 1H), 7.39 (d, *J* = 8.0 Hz, 1H), 4.72 (d, *J* = 2.5 Hz, 1H), 2.86 (dt, *J* = 11.9, 3.9 Hz, 1H), 2.20 (dt, *J* = 11.3, 5.8 Hz, 1H), 1.83-1.63 (m, 5H), 1.60-1.39 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.7, 148.6, 130.2 (q, *J* = 33.5Hz), 130.2 (q, *J* = 3.7 Hz), 127.7, 127.6 (q, *J* = 3.7 Hz), 124.8, 123.5 (q, *J* = 272.4 Hz), 76.3, 39.2, 29.7, 29.4, 24.4, 19.2. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.79. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{14}H_{14}F_3O_2$: 271.0940, Found: 271.0940.

(4a*S,10b*S**)-8-Chloro-2,3,4,4a-tetrahydro-1*H*-benzo[*c*]chromen-6(10b*H*)-one (3ib):** colorless solid; m. p. 114.6-115.9 °C (from hexane); TLC R_f 0.38 (hexane/EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, *J* = 2.2 Hz, 1H), 7.49 (dd, *J* = 8.1, 2.3 Hz, 1H), 7.19 (d, *J* = 8.1 Hz, 1H), 4.67 (d, *J* = 3.1 Hz, 1H), 2.79-2.74 (m, 1H), 2.20-2.14 (m, 1H), 1.81-1.60 (m, 5H), 1.56-1.36 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.9, 143.4, 133.8, 133.4, 130.2, 128.3, 125.5, 76.4, 38.7, 29.8, 29.5, 24.4, 19.3. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{13}H_{14}ClO_2$: 237.0677, Found: 237.0672.

(6a*S,10a*S**)-6a,7,8,9,10,10a-Hexahydro-5*H*-naphtho[1,2-*c*]chromen-5-one (3kb):** colorless solid; m. p. 135.4-137.3 °C (from hexane); TLC R_f 0.35 (hexane/EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.26 (d, *J* = 8.7 Hz, 1H), 7.99 (d, *J* = 8.3 Hz, 1H), 7.84 (d, *J* = 7.6 Hz, 1H), 7.65 (ddd, *J* = 8.5, 6.9, 1.4 Hz, 1H), 7.52 (ddd, *J* = 8.1, 6.9, 1.1 Hz, 1H), 7.30 (d, *J* = 8.3 Hz, 1H), 4.69 (d, *J* = 2.6 Hz, 1H), 2.82 (ddd, *J* = 12.5, 4.5, 2.8 Hz, 1H), 2.26-2.21 (m, 1H), 1.91-1.75 (m, 3H), 1.70-1.55 (m, 3H), 1.49-1.38 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 146.8, 134.8, 133.1, 132.1, 128.7, 128.5, 126.5, 126.2, 124.6, 119.1, 74.9, 40.9, 29.7, 29.0, 24.7, 19.5. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{17}H_{17}O_2$: 253.1223, Found: 253.1221.

(4a*S,12b*S**)-1,2,3,4,4a,12b-Hexahydro-6*H*-naphtho[2,3-*c*]chroman-6-one (3lb):** colorless solid; m. p. 135.0-137.1 °C (from hexane); TLC R_f 0.30 (hexane/EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.72 (s, 1H), 7.95 (d, *J* = 8.2 Hz, 1H), 7.83 (d, *J* = 8.2 Hz, 1H), 7.66 (s, 1H), 7.59 (t, *J* = 7.2 Hz, 1H), 7.53-7.49 (m, 1H), 4.77 (d, *J* = 3.0 Hz, 1H), 2.99 (d, *J* = 11.8 Hz, 1H), 2.21 (d, *J* = 13.1 Hz, 1H), 1.83-1.62 (m, 6H), 1.54-1.47 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4, 139.9, 135.9, 132.6, 132.1, 129.6, 128.9, 127.3, 126.4, 125.2, 122.0, 76.7, 39.6, 30.1, 29.9, 24.6, 19.5. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{17}H_{17}O_2$: 253.1223, Found: 253.1223.

(4a*S,7b*S**,11b*S**,14b*S**)-1,2,3,4,4a,7b,8,9,10,11,11a,14b-Dodecahydrobenzo[1,2-*c*:4,5-*c*']dichromene-6,13-dione (3mb):** white solid; m. p. > 300 °C (from hexane); TLC R_f 0.27 (hexane/EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.00 (s, 2H), 4.70 (s, 2H), 2.86 (dt, *J* = 12.0, 3.3 Hz, 2H), 2.20-2.18 (m, 2H), 1.83 (dd, *J* = 11.0, 6.7 Hz, 4H), 1.75-1.64 (m, 6H), 1.54-1.42 (m, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 143.9, 129.0, 128.4, 76.8, 38.9, 29.8, 29.4, 24.4, 19.3. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{20}H_{23}O_4$: 327.1591, Found: 327.1587.

3-(Phenoxymethyl)-3,4-dihydro-1*H*-benzo[*h*]isochromen-1-one (3kc): colorless solid; m. p. 148.5-150.3 °C (from hexane); TLC R_f 0.28 (hexane/EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.22 (d, *J* = 8.7 Hz, 1H), 8.03 (d, *J* = 8.3 Hz, 1H), 7.87 (d, *J* = 8.1 Hz, 1H), 7.70-7.66 (m, 1H), 7.56 (t, *J* = 7.5 Hz, 1H), 7.37-7.29 (m, 3H), 7.00 (t, *J* = 7.4 Hz, 1H), 6.97-6.94 (m, 2H), 4.94-4.85 (m, 1H), 4.35 (dd, *J* = 9.9, 4.7 Hz, 1H), 4.25 (dd, *J* = 9.9, 5.8 Hz, 1H), 3.41 (dd, *J* = 16.5, 11.7 Hz, 1H), 3.21 (dd, *J* = 16.6, 3.2 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 158.2, 140.3, 134.9, 133.3, 131.9, 129.6, 129.0, 128.6, 126.4, 126.2, 125.1, 121.5, 120.0, 114.6, 75.1, 68.6, 31.9. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{20}H_{17}O_3$: 305.1172, Found: 305.1172.

7:1 Regiomixture of 3-(butoxymethyl)-3,4-dihydro-1*H*-benzo[*h*]isochromen-1-one (3kd) and 4-(butoxymethyl)-3,4-dihydro-1*H*-benzo[*h*]isochromen-1-one (3kd'): colorless oil; TLC R_f 0.30 (hexane/EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) for mixture δ 9.22-9.18 (m, 1H, for **3kd** + **3kd'**), 8.03-7.97 (m, 1H, for **3kd** + **3kd'**), 7.86-7.83 (m, 1H, for **3kd** + **3kd'**), 7.68-7.62 (m, 1H, for **3kd** + **3kd'**), 7.56-7.50 (m, 1H, for **3kd** + **3kd'**), 7.35 (dd, *J* = 18.7 Hz, 1H, for **3kd** + **3kd'**), 4.72-4.62 (m, 1H, for **3kd** + **3kd'**), 4.52-4.49 (m, 0.12H, for **3kd'**), 3.80-3.62 (m, 2H, for **3kd** + **3kd'**), 3.56-3.45 (m, 2H, for **3kd** + **3kd'**), 3.31-3.24 (m, 1H, for **3kd** + **3kd'**), 3.06 (dd, *J* = 16.7, 3.0 Hz, 0.88H, for **3kd**), 1.62-1.53 (m, 2H, for **3kd** + **3kd'**), 1.44-1.34 (m, 2H, for **3kd** + **3kd'**), 0.95-0.90 (m, 3H, for **3kd** + **3kd'**). ^{13}C NMR (100 MHz, $CDCl_3$) for mixture δ 164.3, 164.1, 141.8, 140.7, 134.7, 134.7,

133.4, 133.2, 131.9, 131.9, 128.8, 128.6, 126.5, 126.5, 126.3, 126.2, 125.1, 124.9, 120.2, 120.0, 76.1, 71.8, 71.7, 71.4, 69.9, 66.8, 39.9, 31.8, 31.7, 19.4, 19.3, 14.0. (All observed signals are shown because of complexity associated with regioisomers.) HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{18}H_{21}O_3$: 285.1485, Found: 285.1486.

3-Benzyl-3,4-dihydro-1*H*-benzo[*h*]isochromen-1-one (3ke): colorless solid; m. p. 153.9-155.2 °C (from hexane); TLC R_f 0.35 (hexane/EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.20 (dd, *J* = 8.7, 1.0 Hz, 1H), 7.96 (d, *J* = 8.3 Hz, 1H), 7.84 (d, *J* = 8.1 Hz, 1H), 7.66 (ddd, *J* = 8.6, 6.9, 1.4 Hz, 1H), 7.53 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 7.38-7.26 (m, 5H), 7.23 (d, *J* = 8.3 Hz, 1H), 4.77-4.70 (m, 1H), 3.30 (dd, *J* = 13.7, 5.8 Hz, 1H), 3.14-3.03 (m, 2H), 2.93 (dd, *J* = 16.5, 3.0 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.6, 140.7, 136.3, 134.6, 133.2, 131.9, 129.6, 128.8, 128.7, 128.6, 127.0, 126.3, 126.2, 125.0, 120.2, 78.0, 41.1, 34.0. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{20}H_{17}O_2$: 289.1223, Found: 289.1224.

3-(Chloromethyl)-3,4-dihydro-1*H*-benzo[*h*]isochromen-1-one (3kf): colorless solid; m. p. 139.8-141.4 °C (from hexane); TLC R_f 0.28 (hexane/EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.18 (dd, *J* = 8.7, 1.0 Hz, 1H), 8.04 (d, *J* = 8.1 Hz, 1H), 7.88-7.86 (m, 1H), 7.68 (ddd, *J* = 8.6, 6.9, 1.4 Hz, 1H), 7.56 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H), 7.35 (d, *J* = 8.3 Hz, 1H), 4.78-4.72 (m, 1H), 3.88 (dd, *J* = 11.5, 4.7 Hz, 1H), 3.79 (dd, *J* = 11.5, 6.7 Hz, 1H), 3.33 (dd, *J* = 16.4, 11.2 Hz, 1H), 3.22 (dd, *J* = 16.5, 3.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.5, 139.7, 135.1, 133.3, 131.8, 129.1, 128.6, 126.5, 126.2, 125.0, 119.7, 76.0, 44.6, 32.3. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{14}H_{12}ClO_2$: 247.0520, Found: 247.0518.

2-((1-Oxo-3,4-dihydro-1*H*-benzo[*h*]isochromen-3-yl)methyl)isoindoline-1,3-dione (3kg): pale yellow solid; m. p. 233.2-235.7 °C (from hexane); TLC R_f 0.25 (hexane/EtOAc, 3:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.15 (dd, *J* = 8.8, 1.1 Hz, 1H), 7.99 (d, *J* = 8.3 Hz, 1H), 7.88-7.82 (m, 3H), 7.75-7.71 (m, 2H), 7.65 (ddd, *J* = 8.5, 6.9, 1.3 Hz, 1H), 7.55-7.50 (m, 1H), 7.30 (d, *J* = 8.3 Hz, 1H), 4.94-4.87 (m, 1H), 4.22 (dd, *J* = 14.1, 7.0 Hz, 1H), 4.00 (dd, *J* = 14.1, 5.7 Hz, 1H), 3.27-3.14 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.1, 163.5, 139.6, 134.9, 134.3, 133.2, 131.9, 131.8, 129.0, 128.6, 126.4, 126.2, 125.0, 123.6, 120.1, 73.9, 40.9, 32.7. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{22}H_{16}NO_4$: 358.1074, Found: 358.1074.

(6a*S,9a*S**)-7,8,9,9a-Tetrahydrobenzo[*h*]cyclopenta[*c*]isochromen-5(6a*H*)-one (3kh):** colorless solid; m. p. 141.9-143.2 °C (from hexane); TLC R_f 0.30 (hexane/EtOAc, 5:1). ^{1}H NMR (400 MHz,

$CDCl_3$) δ 9.32 (dd, *J* = 8.8, 1.0 Hz, 1H), 8.00 (d, *J* = 8.3 Hz, 1H), 7.84 (d, *J* = 8.1 Hz, 1H), 7.66 (ddd, *J* = 8.6, 6.8, 1.4 Hz, 1H), 7.53 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 7.33 (d, *J* = 8.3 Hz, 1H), 5.02 (t, *J* = 4.1 Hz, 1H), 3.15 (ddd, *J* = 11.0, 8.5, 4.0 Hz, 1H), 2.35-2.27 (m, 2H), 2.18-2.05 (m, 2H), 1.95-1.79 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.1, 143.8, 134.8, 133.2, 132.1, 128.8, 128.5, 126.7, 126.2, 125.4, 118.1, 82.6, 44.3, 33.1, 32.4, 23.4. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{16}H_{15}O_2$: 239.1067, Found: 239.1071.

(6a*S,12a*S**)-6a,7,8,9,10,11,12,12a-Octahydro-5*H*-benzo[*h*]cycloocta[*c*]isochromen-5-one (3ki):** pale yellow solid; m. p. 126.4-128.1 °C (from hexane); TLC R_f 0.35 (hexane/EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.22 (dd, *J* = 8.7, 1.1 Hz, 1H), 7.98 (d, *J* = 8.3 Hz, 1H), 7.82 (dt, *J* = 8.1, 0.6 Hz, 1H), 7.63 (ddd, *J* = 8.6, 6.8, 1.5 Hz, 1H), 7.51 (ddd, *J* = 8.1, 6.9, 1.2 Hz, 1H), 7.28 (d, *J* = 8.4 Hz, 1H), 4.63 (ddd, *J* = 8.9, 5.3, 2.9 Hz, 1H), 3.14 (dt, *J* = 9.4, 2.3 Hz, 1H), 2.17-2.05 (m, 3H), 1.89-1.48 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.2, 148.4, 135.1, 133.0, 131.8, 128.7, 128.5, 126.4, 126.2, 124.7, 118.7, 79.1, 41.1, 28.7, 28.3, 28.2, 27.9, 24.2, 21.2. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{19}H_{21}O_2$: 281.1536, Found: 281.1535.

(6a*S,11b*S**)-6a,7-Dihydrobenzo[*h*]indeno[2,1-*c*]isochromen-5(11b*H*)-one (3kj):** colorless solid; m. p. 186.5-188.1 °C (from hexane); TLC R_f 0.25 (hexane/EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.36 (dd, *J* = 8.8, 1.0 Hz, 1H), 8.17 (d, *J* = 8.3 Hz, 1H), 7.91 (dt, *J* = 8.1, 0.6 Hz, 1H), 7.67 (ddd, *J* = 8.6, 6.9, 1.5 Hz, 1H), 7.62-7.55 (m, 2H), 7.36 (d, *J* = 7.4 Hz, 1H), 7.25 (tt, *J* = 7.5, 1.0 Hz, 1H), 7.16 (t, *J* = 7.4 Hz, 1H), 7.09 (d, *J* = 7.7 Hz, 1H), 5.49 (td, *J* = 4.1, 1.1 Hz, 1H), 4.51 (d, *J* = 4.3 Hz, 1H), 3.47-3.35 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4, 140.6, 140.4, 140.0, 135.2, 133.5, 132.3, 129.1, 128.7, 127.9, 127.2, 126.9, 126.6, 126.0, 125.4, 124.1, 118.7, 81.3, 47.9, 40.1. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{20}H_{15}O_2$: 287.1067, Found: 287.1069.

(3*R,4*S**)-3,4-Dimethyl-3,4-dihydro-1*H*-benzo[*h*]isochromen-1-one (*trans*-3kk):** colorless oil; TLC R_f 0.38 (hexane/EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.23 (dd, *J* = 8.8, 1.1 Hz, 1H), 8.04 (d, *J* = 8.4 Hz, 1H), 7.85 (dt, *J* = 8.1, 0.7 Hz, 1H), 7.66 (ddd, *J* = 8.6, 6.8, 1.4 Hz, 1H), 7.53 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H), 7.40 (d, *J* = 8.5 Hz, 1H), 4.52-4.46 (m, 1H), 3.05-2.99 (m, 1H), 1.46 (d, *J* = 1.4 Hz, 3H), 1.44 (d, *J* = 0.8 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 163.9, 144.9, 134.9, 133.0, 131.8, 128.8, 128.4, 126.5, 126.3, 123.7, 119.5, 78.5, 38.9, 19.6, 17.7. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{15}H_{15}O_2$: 227.1067, Found: 227.1065.

(3*S,4*S**)-3,4-Dimethyl-3,4-dihydro-1*H*-benzo[*h*]isochromen-1-one (*cis*-3kk):** colorless solid; m. p. 120.6-122.2 °C (from hexane); TLC R_f 0.32 (hexane/EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.22 (dd, *J* = 8.7, 1.0 Hz, 1H), 8.00 (d, *J* = 8.1 Hz, 1H), 7.84 (dt, *J* = 8.1, 0.6 Hz, 1H), 7.65 (ddd, *J* = 8.6, 6.8, 1.5 Hz, 1H), 7.52 (ddd, *J* = 8.1, 6.8, 1.2 Hz, 1H), 7.31 (d, *J* = 8.3 Hz, 1H), 4.75 (qd, *J* = 6.5, 2.8 Hz, 1H), 2.96 (qd, *J* = 7.2, 2.9 Hz, 1H), 1.48 (d, *J* = 6.6 Hz, 3H), 1.30 (d, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.0, 147.8, 134.9, 133.1, 131.9, 128.7, 128.5, 126.3, 126.3, 124.5, 118.9, 75.5, 38.5, 17.4, 13.6. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{15}H_{15}O_2$: 227.1067, Found: 227.1067.

9:1 Regiomixture of (*R*)-3-((benzyloxy)methyl)-3,4-dihydro-1*H*-benzo[*h*]isochromen-1-one [(*R*)-3ka] and (*R*)-4-((benzyloxy)methyl)-3,4-dihydro-1*H*-benzo[*h*]isochromen-1-one [(*R*)-3ka']: pale yellow solid; TLC R_f 0.35 (hexane/EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) for mixture δ 9.24-9.20 (m, 1H, for **3ka** + **3ka'**), 8.03-7.99 (m, 1H, for **3ka** + **3ka'**), 7.87-7.84 (m, 1H, for **3ka** + **3ka'**), 7.69-7.64 (m, 1H, for **3ka** + **3ka'**), 7.58-7.52 (m, 1H, for **3ka** + **3ka'**), 7.39-7.29 (m, 6H, for **3ka** + **3ka'**), 4.77-4.52 (m, 3.1H, for **3ka** + **3ka'**), 3.87-3.71 (m, 2H, for **3ka** + **3ka'**), 3.35-3.28 (m, 1H, for **3ka** + **3ka'**), 3.07 (dd, *J* = 16.6, 3.1 Hz, 0.9H for **3ka**). ^{13}C NMR (100 MHz, $CDCl_3$) for mixture δ 164.1, 164.0, 141.6, 140.7, 137.74, 137.71, 134.7, 133.4, 133.2, 131.9, 128.9, 128.6, 128.5, 127.9, 127.8, 127.7, 126.6, 126.5, 126.3, 126.3, 125.1, 124.9, 120.3, 120.0, 76.1, 73.7, 73.6, 71.0, 69.6, 66.9, 39.9, 31.8. (All observed signals are shown because of complexity associated with regioisomers.) HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{21}H_{19}O_3$: 319.1329, Found: 319.1331.

11:1 Regiomixture of (5a*S,9a*R**)-5a,6,7,8,9,9a-hexahydro-4*H*-thieno[3,2-*c*]chromen-4-one (C2-3nb) and (5a*R**,9a*R**)-5a,6,7,8,9,9a-hexahydro-4*H*-thieno[3,4-*c*]chromen-4-one (C4-3nb):** colorless solid; TLC R_f 0.35 (hexane/EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) for mixture δ 8.20 (d, *J* = 3.0 Hz, 0.1H, for C4-**3nb**), 7.41 (d, *J* = 5.2 Hz, 0.9H, for C2-**3nb**), 7.13 (d, *J* = 5.2 Hz, 0.9H, for C2-**3nb**), 7.05 (dd, *J* = 3.0, 0.8 Hz, 0.1H, for C4-**3nb**), 4.71 (q, *J* = 3.2 Hz, 0.9H, for C2-**3nb**), 4.63-4.60 (m, 0.1H, for C4-**3nb**), 3.05-2.97 (m, 1H, for C2-**3nb** + C4-**3nb**), 2.30-1.95 (m, 1H, for C2-**3nb** + C4-**3nb**), 1.89-1.37 (m, 7H, for C2-**3nb** + C4-**3nb**). ^{13}C NMR (100 MHz, $CDCl_3$) for C2-**3nb** δ 162.1, 155.6, 127.0, 126.8, 123.8, 77.8, 36.5, 30.4, 29.9, 24.0, 19.9. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{11}H_{13}O_2S$: 209.0631, Found: 209.0636.

1.7:1 Stereomixture of (5a*S,9a*S**)-5a,6,7,8,9,9a-hexahydro-4*H*-thieno[2,3-*c*]chromen-4-one (*cis*-3ob) and (5a*S**,9a*R**)-5a,6,7,8,9,9a-hexahydro-4*H*-thieno[2,3-*c*]chromen-4-one (*trans*-3ob):**

colorless solid; TLC R_f 0.30 (hexane/EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) for mixture δ 7.63 (dd, *J* = 5.0, 4.3 Hz, 1H, for *cis*-**3ob** + *trans*-**3ob**), 7.00-6.97 (m, 1H, for *cis*-**3ob** + *trans*-**3ob**), 4.72 (q, *J* = 3.0 Hz, 0.63H, for *cis*-**3ob**), 4.21-4.14 (m, 0.37H, for *trans*-**3ob**), 2.91-2.86 (m, 0.63H, for *cis*-**3ob**), 2.81-2.74 (m, 0.37H, for *trans*-**3ob**), 2.41-2.36 (m, 0.37H, for *trans*-**3ob**), 2.22-2.16 (m, 1H, for *cis*-**3ob** + *trans*-**3ob**), 1.85-1.33 (m, 6.63H, for *cis*-**3ob** + *trans*-**3ob**). ^{13}C NMR (100 MHz, $CDCl_3$) for mixture δ 162.1, 161.6, 153.4, 152.1, 134.6, 134.5, 126.6, 126.0, 125.9, 124.1, 84.0, 78.5, 40.3, 36.9, 31.1, 29.7, 28.9, 28.1, 25.0, 24.3, 24.1, 19.9. (All observed signals are shown because of complexity associated with stereoisomers.) HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{11}H_{13}O_2S$: 209.0631, Found: 209.0636.

(4a*S,8a*S**)-3,3-Dimethyloctahydro-2*H*-chromen-2-one (3pb):** colorless oil; TLC R_f 0.35 (hexane/EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.50 (dt, *J* = 8.1, 4.2 Hz, 1H), 2.25-2.16 (m, 1H), 1.86 (dd, *J* = 13.9, 8.9 Hz, 1H), 1.82-1.67 (m, 3H), 1.66-1.43 (m, 5H), 1.42-1.32 (m, 2H), 1.31 (s, 3H), 1.28 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.9, 79.3, 37.9, 37.4, 31.5, 29.7, 29.5, 29.1, 28.3, 22.3, 22.0. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{11}H_{19}O_2$: 183.1380, Found: 183.1381.

(4a*S,8a*S**)-3,3-Diphenyloctahydro-2*H*-chromen-2-one (3qb):** colorless oil; TLC R_f 0.27 (hexane/EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (d, *J* = 4.3 Hz, 4H), 7.39-7.35 (m, 1H), 7.27-7.18 (m, 3H), 6.99-6.97 (m, 2H), 4.30 (dt, *J* = 5.9, 4.0 Hz, 1H), 2.96-2.89 (m, 1H), 2.29 (dd, *J* = 14.9, 7.5 Hz, 1H), 2.21-2.13 (m, 1H), 1.91-1.84 (m, 1H), 1.73-1.59 (m, 5H), 1.47-1.39 (m, 1H), 1.37-1.27 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 145.1, 139.8, 129.1, 128.6, 127.9, 127.8, 127.7, 126.8, 76.6, 56.9, 38.6, 31.6, 30.3, 29.6, 23.3, 21.3. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{21}H_{23}O_2$: 307.1693, Found: 307.1697.

3:1 Stereomixture of (4a*S,8a*S**)-hexahydrospiro[chromene-3,1'-cyclohexan]-2(4*H*)-one (*cis*-3rb) and (4a*S**,8a*R**)-hexahydrospiro[chromene-3,1'-cyclohexan]-2(4*H*)-one (*trans*-3rb):** colorless oil; TLC R_f 0.33 (hexane/EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) for mixture δ 4.55-4.44 (m, 1H, for *cis*-**3rb** + *trans*-**3rb**), 2.29-2.23 (m, 0.25H, for *trans*-**3rb**), 2.12-2.00 (m, 1.75H, for *cis*-**3rb** + *trans*-**3rb**), 1.91-1.30 (m, 19H, for *cis*-**3rb** + *trans*-**3rb**). ^{13}C NMR (100 MHz, $CDCl_3$) for mixture δ 178.2, 178.1, 78.2, 77.8, 41.4, 40.8, 36.2, 36.0, 35.5, 33.4, 32.3, 32.0, 29.9, 29.6, 27.9, 26.7, 25.3, 23.2, 23.1, 23.0, 22.8, 21.5, 21.1, 21.0, 20.97, 20.6, 19.8. (All observed signals are shown because of complexity associated with stereoisomers.) HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{14}H_{23}O_2$: 223.1693, Found: 223.1700.

(3*S,4a*S**,8a*S**)-3-Methyl-3-phenyloctahydro-2*H*-chromen-2-one (3sb):** colorless solid; m. p. 99.7-101.7 °C (from hexane/DCM); TLC R_f 0.33 (hexane/EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30-7.36 (m, 4H), 7.26-7.22 (m, 1H), 4.58 (dt, *J* = 8.6, 4.2 Hz, 1H), 2.47-2.39 (m, 2H), 2.03-1.98 (m, 1H), 1.86-1.71 (m, 6H), 1.65-1.50 (m, 2H), 1.40-1.30 (m, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9, 146.1, 128.6, 126.7, 126.0, 80.6, 47.2, 39.8, 30.9, 29.6, 28.4, 27.2, 23.3, 20.9. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{16}H_{21}O_2$: 245.1536, Found: 245.1535.

1.5:1 Stereomixture of (4a*S,8a*S**)-3-ethyl-3-methyloctahydro-2*H*-chromen-2-one (*cis*-3tb) and (4a*S**,8a*R**)-3-ethyl-3-methyloctahydro-2*H*-chromen-2-one (*trans*-3tb):** colorless oil; TLC R_f 0.35 (hexane/EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) for mixture δ 4.50-4.42 (m, 1H, for *cis*-**3tb** + *trans*-**3tb**), 2.33-2.66 (m, 0.4H, for *trans*-**3tb**), 2.09-2.01 (m, 1H, for *cis*-**3tb** + *trans*-**3tb**), 1.90-1.81 (m, 2H, for *cis*-**3tb** + *trans*-**3tb**), 1.78-1.71 (m, 0.6H, for *cis*-**3tb**), 1.69-1.55 (m, 5H, for *cis*-**3tb** + *trans*-**3tb**), 1.52-1.38 (m, 3H, for *cis*-**3tb** + *trans*-**3tb**), 1.36-1.30 (m, 1H, for *cis*-**3tb** + *trans*-**3tb**), 1.28 (s, 1.2H, for *trans*-**3tb**), 1.24 (s, 1.8H, for *cis*-**3tb**), 0.92-0.88 (m, 3H, for *cis*-**3tb** + *trans*-**3tb**). ^{13}C NMR (100 MHz, $CDCl_3$) for mixture δ 177.7, 177.1, 79.4, 78.6, 41.8, 40.9, 36.4, 34.8, 33.5, 32.6, 30.6, 30.2, 29.5, 28.8, 28.2, 27.6, 27.3, 23.4, 23.0, 21.2, 21.1, 8.9, 8.8. (All observed signals are shown because of complexity associated with stereoisomers.) HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{12}H_{21}O_2$: 197.1536, Found: 197.1543.

2:1 Stereomixture of (4a*S,8a*S**)-3-methyloctahydro-2*H*-chromen-2-one (*cis*-3ub) and (4a*S**,8a*R**)-3-methyloctahydro-2*H*-chromen-2-one (*trans*-3ub):** colorless oil; TLC R_f 0.35 (hexane/EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) for mixture δ 4.49-4.46 (m, 1H, for *cis*-**3ub** + *trans*-**3ub**), 2.65-2.51 (m, 1H, for *cis*-**3ub** + *trans*-**3ub**), 2.28 (td, *J* = 9.2, 13.7 Hz, 0.7H, for *cis*-**3ub**), 2.02-1.96 (m, 1.6H, for *cis*-**3ub** + *trans*-**3ub**), 1.93-1.81 (m, 0.7H, for *cis*-**3ub**), 1.76-1.43 (m, 6H, for *cis*-**3ub** + *trans*-**3ub**), 1.38-1.23 (m, 2.3H, for *cis*-**3ub** + *trans*-**3ub**), 1.17 (d, *J* = 6.6 Hz, 2H, for *cis*-**3ub**), 1.07-1.00 (m, 0.7H, for *cis*-**3ub**). ^{13}C NMR (100 MHz, $CDCl_3$) for mixture δ 176.5, 175.2, 79.4, 75.9, 34.4, 33.5, 33.4, 33.3, 32.5, 31.6, 30.8, 29.7, 29.6, 25.0, 24.6, 24.56, 20.3, 19.7, 18.1, 15.9. (All observed signals are shown because of complexity associated with stereoisomers.) HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{10}H_{17}O_2$: 169.1223, Found: 169.1221.

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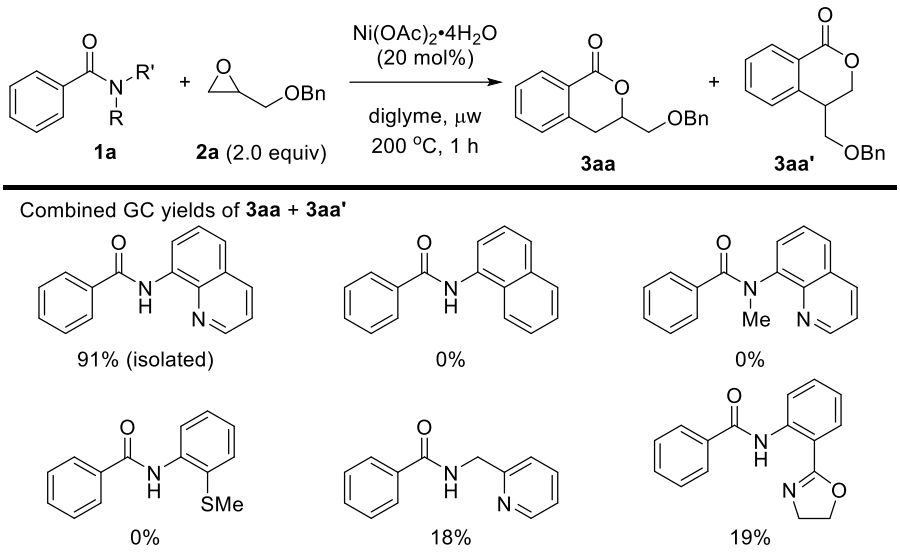
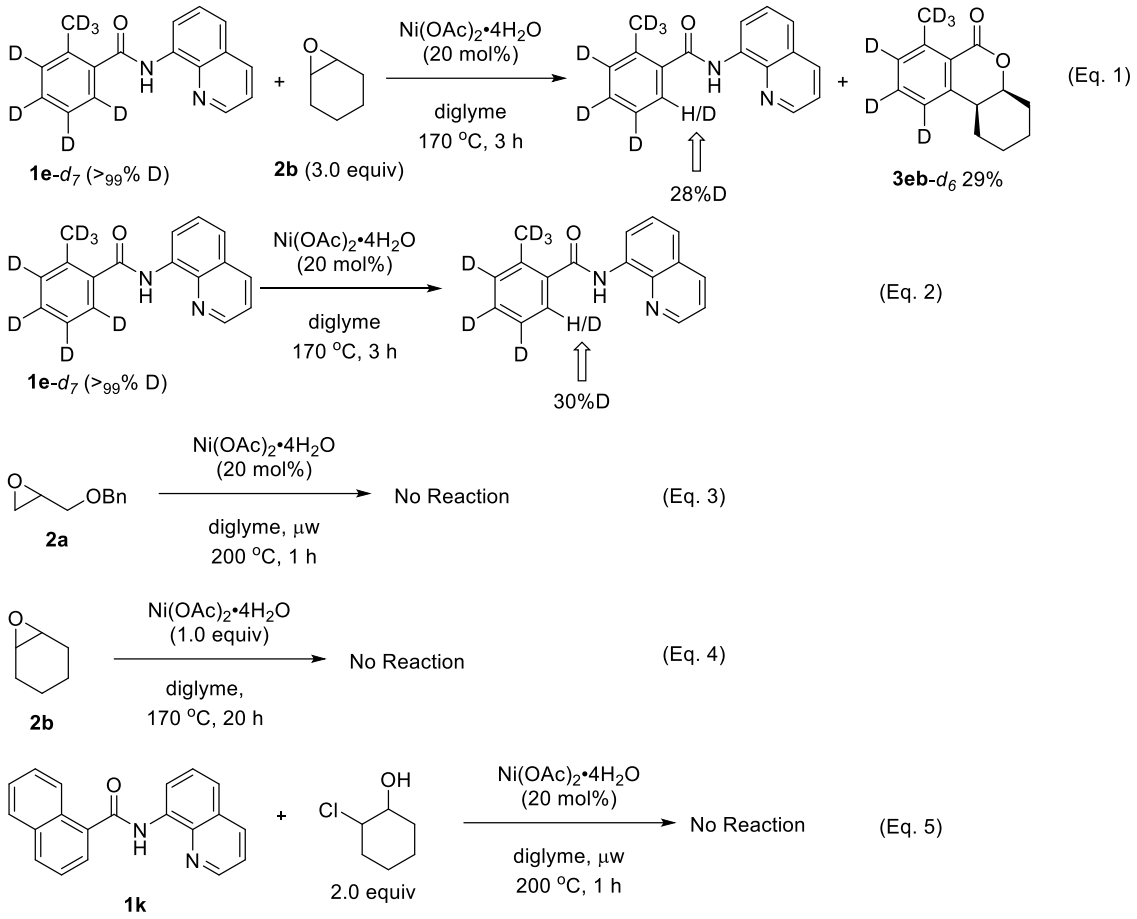
[11] Benzamides that bear other bidentate or monodentate directing groups showed either no or much lower reactivity.



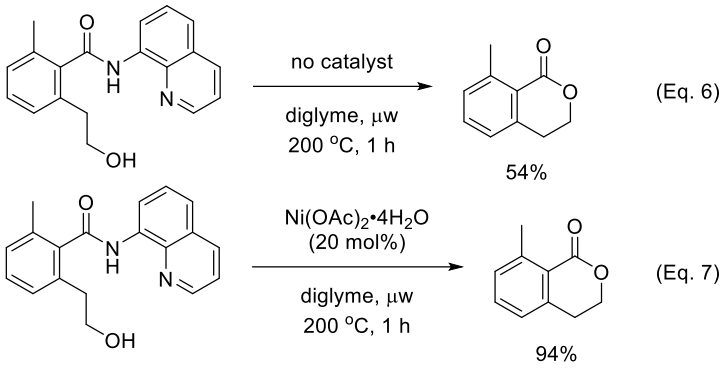
[12] CCDC 1842695 (**3kb**), 1842697 (**3mb**), 1842696 (**3kj**), 1842698 (*cis*-**3kk**), and 1853295 (**3sb**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[13] The author performed several control experiments to gain some mechanistic insight: (1) the deuterium-labeled benzamide rapidly underwent the H/D exchange reaction, thus indicating the

reversible and non-rate-limiting C–H cleavage (Eq. 1 and 2); (2) in the absence of benzamide, no reaction of epoxide occurred (Eq. 3 and 4); (3) 2-chlorocyclohexanol was not the intermediate of the reaction (Eq. 5).



[14] The author independently prepared the following simply alkylated product and subjected it into reaction conditions. Even without any Ni catalysts, the corresponding dihydroisocoumarin was formed in 54% yield (Eq. 6). The $Ni(OAc)_2•4H_2O$ catalyst apparently accelerated the reaction (Eq. 7). These results suggest that in the nickel-catalyzed reaction of 8-aminoquinoline-derived amide and epoxide, the simply alkylated product is initially formed, and subsequent nickel-promoted intramolecular alcoholysis affords the observed dihydroisocoumarin. In addition, Ohshima recently reported the related nickel(II)-catalyzed alcoholysis of 8-aminoquinoline amides. Deguchi, T.; Xin, H.-L.; Morimoto, H.; Ohshima, T. *ACS Catal.* **2017**, *7*, 3157.



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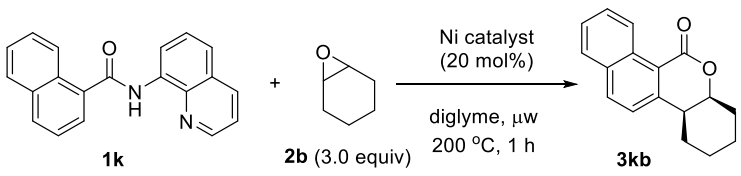
[16] For recent elegant studies on the stereoretentive oxidative addition of epoxides to nickel by a bimolecular mechanism, see: Denoyer, A. N.; Bowes, E. G.; Patrick, B. O.; Love, J. A. *J. Am. Chem. Soc.* **2015**, *137*, 12748.

[17] The isolated *cis*-**3ob** underwent no *cis/trans* isomerization under $NiCl_2(PEt_3)_2$ catalysis, even with prolonged reaction periods. Thus, the *trans*-**3ob** might be kinetically formed.

[18] The $NiCl_2(PEt_3)_2$ and $NiCl_2(PCy_3)_2$ salts also catalyzed the reaction of other amides, such as the parent **1a**, with efficiency comparable to $Ni(OAc)_2•4H_2O$, but we identified $Ni(OAc)_2•4H_2O$ to be best from the view point of cost ($NiCl_2(PEt_3)_2$: 4166 JPY/g (ALFA AESAR), $NiCl_2(PCy_3)_2$: 3940 JPY/g (TCI), $Ni(OAc)_2•4H_2O$: 13 JPY/g (Aldrich)). Additionally, the stereochemical erosion was unique to the thiophene **1o**: in the reaction of nonheteroaromatic **1k** and **2b** $Ni(OAc)_2•4H_2O/PPh_3$, $NiCl_2(PEt_3)_2$, and $NiCl_2(PCy_3)_2$ all afforded **3kb** with high *cis* selectivity (16:1–>20:1).



Ni catalyst	Yield, *cis/trans*
$Ni(OAc)_2•4H_2O$	84%, >20:1
$Ni(OAc)_2•4H_2O/PPh_3$	80%, >20:1
$NiCl_2(PEt_3)_2$	66%, 16:1
$NiCl_2(PCy_3)_2$	87%, 16:1

[19] Several attempts to apply microwave irradiation with aliphatic amides **1p–u** resulted in an explosion, although we have no explanation for the reason. Thus, we performed the reaction under conventional heating conditions with an oil bath.

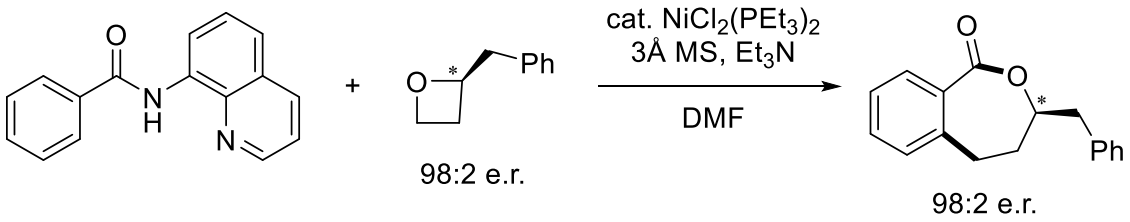
[20] Nishino, M.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 4457.

[21] (a) Shaw, M. H.; Croft, R. A.; Whittingham, W. G.; Bower, J. F. *J. Am. Chem. Soc.* **2015**, *137*, 8054. (b) Halimehjani, A. Z.; Hooshmand, S. E.; Shamiri, E. V. *Tetrahedron Lett.* **2014**, *55*, 5454. (c) Monaco, M. R.; Fazzi, D.; Tsuji, N.; Leutzsch, M.; Liao, S.; Thiel, W.; List, B. *J. Am. Chem. Soc.* **2016**, *138*, 14740.

Chapter 3

Synthesis of Seven-Membered Benzolactones by Nickel-Catalyzed C-H Coupling of Benzamides with Oxetanes

A $NiCl_2(PEt_3)_2$-catalyzed regioselective C–H coupling of 8-aminoquinoline-derived benzamides with oxetanes has been developed. The reaction proceeds with concomitant removal of the 8-aminoquinoline auxiliary to directly form the corresponding seven-membered benzolactones, which frequently occurr in natural products and bioactive molecules. Additionally, no stereochemical erosion is observed during the course of the reaction, and the use of enantioenriched and substituted oxetane thus provides a new avenue to the optically active benzolactone.



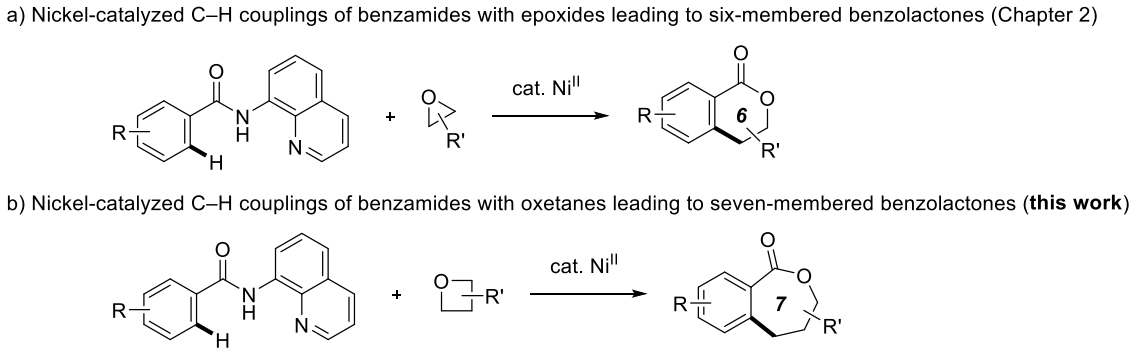
Introduction

Oxetane constitutes an important class of cyclic ethers in organic synthetic chemistry and polymer synthesis. Owing to its high strain energy,[1] it can undergo a variety of ring-opening reactions with highly reactive organometallic reagents and heteroatom nucleophiles in the presence or absence of Brønsted and Lewis acid promotors to form the corresponding three-carbon homologated, oxygenated products and/or polyethers.[2] However, redox-active transition-metal-catalyzed coupling reactions with oxetane are relatively limited, compared to a three-membered analogue, epoxide, probably because of slightly less distortion energy (oxetane: 107 kJ mol^{-1} vs. epoxide: 114 kJ mol^{-1}).[1] As an early work, Murai and coworkers developed the rhodium-catalyzed silylformylation of oxetanes with hydrosilanes and carbon monoxide.[3] Gansäuer also reported the titanocene-catalyzed ring-opening reductive dimerization to provide 1,6-hexanediols.[4] Recently, some research groups developed unique coupling reactions of oxetanes, including the rhodium-catalyzed carbene insertion[5] and gold-nanoparticle-catalyzed silaboration[6]. The iron-catalyzed oxidative C–H coupling was also disclosed,[7] in this course, the C-H functionalization with oxetane-based carbon radical are followed by the oxidation and annulation to give the ring-opening of oxetane. However, the synthetic strategy of directed C-H functionalization with oxetanes under transition-metal catalysis still remains underdeveloped.

Meanwhile, Miura group recently reported the nickel-catalyzed C–H coupling reaction[8] of benzamides with epoxides (Scheme 1a).[9,10] The reaction was promoted

by the *N*,*N*-bidentate coordinated aminoquinoline auxiliary, which was originally developed by Daugulis,[11] and the corresponding six-membered benzolactones were directly obtained with the concomitant removal of aminoquinoline directing group. During our continuing interest in this chemistry, we next envisioned the C–H coupling reaction with oxetanes. Herein, we report a nickel-catalyzed coupling reaction of quinoline amides with oxetanes via the *N*,*N*-double chelation-assisted C–H cleavage (Scheme 1b). As observed in our previous work with epoxides,[9a] a successive ring-closing reaction occurred[12] to directly deliver the corresponding seven-membered benzolactones of prevalent medium-sized ring system found in natural products and bioactive molecules.[13]

Scheme 1. Nickel-catalyzed C–H couplings of quinoline benzamides with epoxides (a) and oxetanes (b)



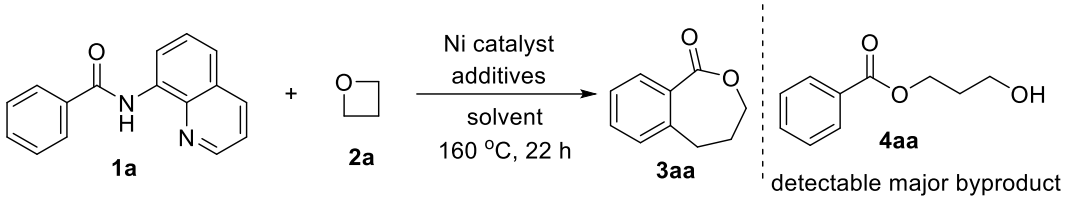
Results and discussion

The author selected benzamide **1a** and parent oxetane (**2a**) as model substrates and started optimization studies (Table 1). In an early experiment, treatment of **1a** with **2a** (4.0 equiv) and 20 mol% $NiCl_2(PCy_3)_2$ in diglyme at 160 ˚C (our previous optimal

conditions[9a]) afforded the seven-membered benzolactone **3aa** in 30% ^{1}H NMR yield (entry 1). Subsequent brief screening of nickel catalysts revealed that $NiCl_2(PEt_3)_2$ showed better performance (entries 2-4). Solvent and concentration effects were also critical: DMF further increased the yield to 56% yield, particularly under higher concentration (entries 5 and 6), whereas the reaction in other solvents including NMP, DMSO, and toluene was almost sluggish (entries 7-9). On the other hand, an additional survey of phosphine ligands combined with the $NiCl_2$•glyme salt in the DMF solvent provided no improvement of the yield (entries 10-14). The use of nickel(0) catalyst, $Ni(cod)_2$, also gave almost no conversion (entry 15), while the $NiCl_2$ without any ligand resulted in a 40% formation of the coupling product (entry 16). The higher nickel catalyst loading (30 mol%) slightly improved the yield (entry 17); however, at this point we found the formation of the ester **4aa** as the major byproduct (≈30%), which apparently suggests occurrence of the ring-opening side reaction of oxetane (**2a**) with contaminated water. Thus, the author tested the addition of several dehydrating agents (entries 18-21). Pleasingly, 3Å MS effectively suppressed the byproduct **4aa** to furnish **3aa** in 74% isolated yield (entry 21) with good reproducibility. Finally, with the Et_3N additive (20 mol%), the targeted benzolactone **3aa** was isolated in slightly higher yield of 78% (entry 22). Additional observations worth noting are that other organic bases such as 1,4-diazabicyclo[2.2.2]octane (DABCO) and 4-dimethylaminopyridine (DMAP) were detrimental (data not shown); the aminoquinoline auxiliary was indispensable, and other monodentately and bidentately coordinating amide substrates showed sluggish reactivity under the present conditions.

Unfortunately, both long reaction time and high reaction temperature were necessary for good conversion and reproducibility.

Table 1. Optimization studies[a]

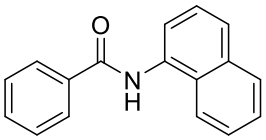


entry	Ni cat. (loading [mol%])	additives	solvent [mL]	yield [%][b]
1	$NiCl_2(PCy_3)_2$ (20)	none	diglyme (1.0)	30
2	$NiCl_2(PEt_3)_2$ (20)	none	diglyme (1.0)	36
3	$NiCl_2$•glyme (20)	none	diglyme (1.0)	25
4	$Ni(acac)_2$ (20)	none	diglyme (1.0)	0
5	$NiCl_2(PEt_3)_2$ (20)	none	DMF (1.0)	33
6	$NiCl_2(PEt_3)_2$ (20)	none	DMF (0.5)	56
7	$NiCl_2(PEt_3)_2$ (20)	none	NMP (1.0)	8
8	$NiCl_2(PEt_3)_2$ (20)	none	DMSO (1.0)	0
9	$NiCl_2(PEt_3)_2$ (20)	none	toluene (1.0)	0
10	$NiCl_2$•glyme (20)/dppbz (20)	none	DMF (0.5)	30
11	$NiCl_2$•glyme (20)/dppe (20)	none	DMF (0.5)	9
12	$NiCl_2$•glyme (20)/PPh_3 (40)	none	DMF (0.5)	30
13	$NiCl_2$•glyme (20)/PBu_3 (40)	none	DMF (0.5)	8
14	$NiCl_2$•glyme (20)/P(*t*Bu)$_3$ (40)	none	DMF (0.5)	26
15	$Ni(cod)_2$ (20)	none	DMF (0.5)	trace
16	$NiCl_2$ (20)	none	DMF (0.5)	40
17	$NiCl_2(PEt_3)_2$ (30)	none	DMF (0.5)	59
18	$NiCl_2(PEt_3)_2$ (30)	Na_2SO_4	DMF (0.5)	41
19	$NiCl_2(PEt_3)_2$ (30)	$MgSO_4$	DMF (0.5)	39
20	$NiCl_2(PEt_3)_2$ (30)	4Å MS	DMF (0.5)	56–68[c]
21	$NiCl_2(PEt_3)_2$ (30)	3Å MS	DMF (0.5)	(74)

22	$NiCl_2(PEt_3)_2$ (30)	3Å MS/Et_3N[d]	DMF (0.5)	(78)

[a] Conditions: **1a** (0.20 mmol), **2a** (0.80 mmol), Ni cat., additives, solvent, 160 ˚C, 22 h, N_2. [b] Estimated by ^{1}H NMR with triphenylmethane as an internal standard. Yields of isolated material in parentheses. [c] Poor reproducibility. [d] 20 mol% of Et_3N. Abbreviations: acac = acetylacetonate, cod = 1,5-cyclooctadiene, DMF = *N*,*N*-dimethylformamide, DMSO = dimethylsulfoxide, dppbz = 1,2-bis(diphenylphosphino)benzene, dppe = 1,2-bis(diphenylphosphino)ethane, NMP = *N*-methylpyrrolidone.

substrates with lower or no reactivity under conditions in entry 6 (^{1}H NMR yield of **3aa** is shown)



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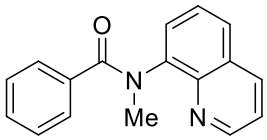

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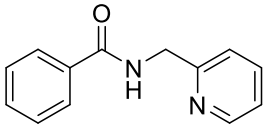

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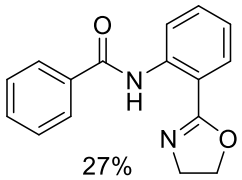
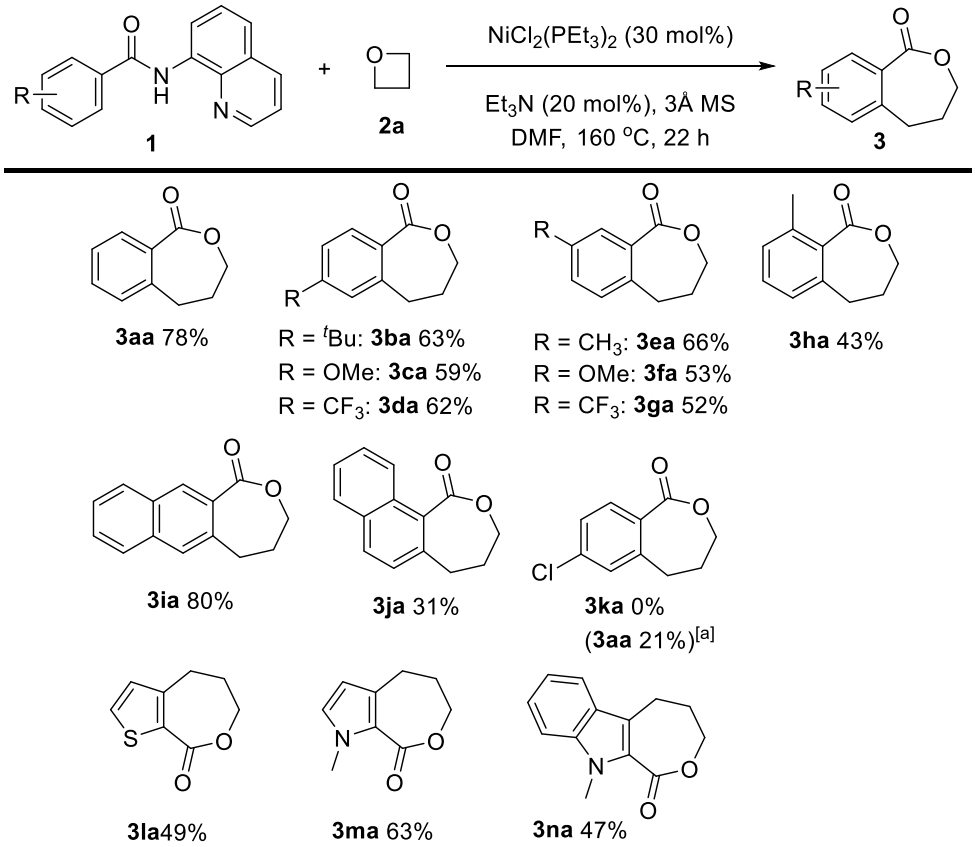


27%

With good conditions in hand (entry 21 in Table 1), the author investigated the scope and limitations of benzamide substrates **1** with the parent oxetane (**2a**; Scheme 2). The nickel catalyst was equally compatible with electron-neutral, -donating, and withdrawing groups (*t*Bu, MeO, CF_3) at the *para* position to form the corresponding benzolactones **3ba**-**da** in good yields. In the case of *meta*-substituted benzamides, the reaction occurred selectively at the more sterically accessible C–H bond, regardless of the electronic nature of substituents (**3ea**-**ga**). Albeit with somewhat lower efficiency, the substitution at the *ortho* position was also tolerated (**3ha**). Higher fused naphthalene derivatives **1i** and **1j** could also be employed: the 2-naphthalenecarboxamide was coupled with **2a** at the sterically less hindered C3 position to form the corresponding tricyclic system **3ia** in 80% yield, whereas the 1-naphthyl isomer showed lower reactivity (**3ja**, 31%) probably due to steric factors similar to the result of **3ha**. Unfortunately, the reaction of chloro-substituted

benzamide **1k** was sluggish, and only the protodechlorinated product **3aa** was observed (not **3ka**); however, the unsuccessful result gave information about the oxidation state of active nickel species (vide infra). Additional advantage is accommodation of some heteroaromatics. Thiophene-, pyrrole-, and indole-derived carboxamides underwent the C–H coupling-cyclization cascade to deliver **3la-na** in synthetically acceptable yields.[14]

Scheme 2. Nickel-catalyzed C–H coupling of various benzamides 1 with oxetane (2a)

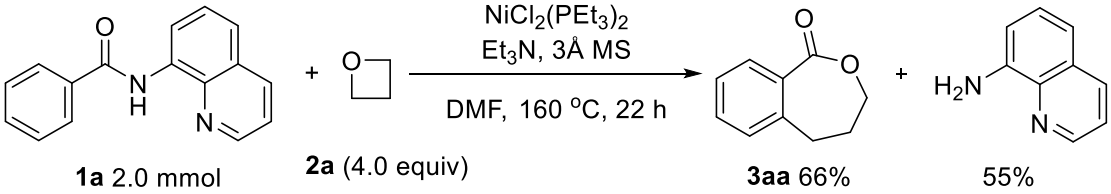


Conditions: **1** (0.20 mmol), **2a** (0.80 mmol), $NiCl_2(PEt_3)_2$ (0.060 mmol), Et_3N (0.040 mmol), 3Å MS (100 mg), DMF (0.50 mL), 160 ˚C, 22 h, N_2. Yields of isolated products are given. [a] Only the protodechlorinated product **3aa** was formed.

An additional feature of this nickel catalysis is the spontaneous removal and successful recycling of directing group (Scheme 3). The model reaction of **1a** with **2a**

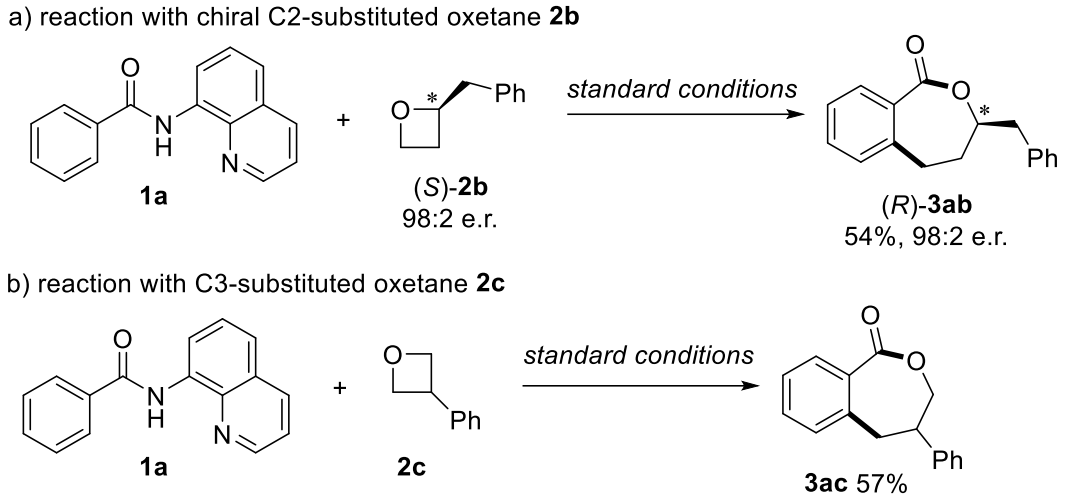
could also be performed on a 2.0 mmol scale, and the desired **3aa** was isolated in 66% yield along with 55% recovery of 8-aminoquinoline auxiliary; the result deserves some attention from synthetic point of view, because the removal of such a bidentate directing group often requires tedious and additional experimental operations.[12]

Scheme 3. Reaction on 2.0 mmol scale



The scope and limitation of oxetanes **2** was then briefly surveyed. In the reaction with the C2-substituted oxetane (*S*)-**2b**, the more sterically accessible C4–O bond was selectively cleaved to form the benzolactone (*R*)-**3ab** as the sole regioisomer (Scheme 4a). Additionally, its chirality was successfully transferred without erosion of enantiomeric excess, thus providing a new route to chiral seven-membered benzolactones from relatively easily prepared enantioenriched oxetanes. The C3-substituted oxetane **2c** was also coupled with **1a**, and the corresponding **3ac** was obtained in 57% yield (Scheme 4b). On the other hand, unsuccessful oxetanes included 2,2- and 3,3-disubstituted oxetanes. In the former case, the ring-opening isomerization predominantly occurred to form the corresponding homoallylic alcohol, whereas the latter substrates resulted in no conversion probably because of steric factors (data not shown).

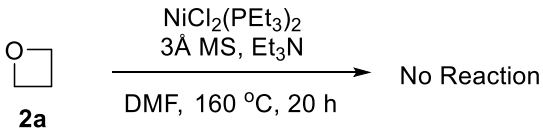
Scheme 4. Nickel-catalyzed C–H coupling of benzamide 1a with some substituted oxetanes 2 (under the conditions of Scheme 2)



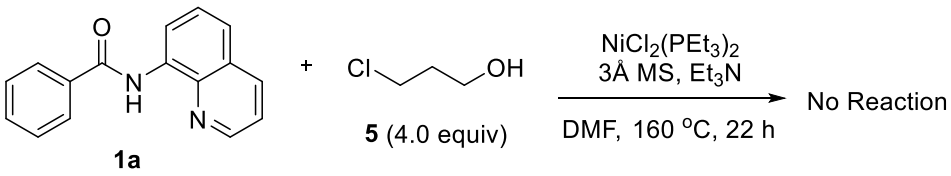
To get some insight into the reaction mechanism, the author implemented the following control experiments. In the absence of the benzamide **1**, the parent oxetane (**2a**) gave no detectable amount of ring-opening side products (Scheme 5a). Additionally, the reaction of **1a** with 3-chloropropanol (**5**), which is the most conceivable ring-opening side product promoted by the $NiCl_2$ salt, resulted in no conversion (Scheme 5b). These outcomes suggest that the oxetane itself is directly coupled with **1a**. Deuterium-labeling experiments with [D_5]-**1a** were also performed (Scheme 5c). In the presence and absence of oxetane (**2a**), significant *ortho*-H/D scrambling occurred even at an early stage of the reaction, thus indicating that the C–H cleavage process is facile and not the rate-limiting step.[15]

Scheme 5. Control experiments

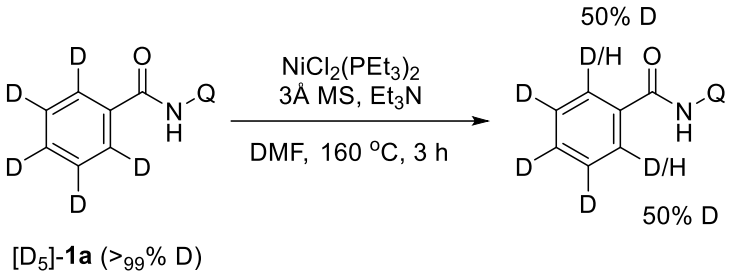
a) reaction of oxetane (**2a**) without benzamide **1**

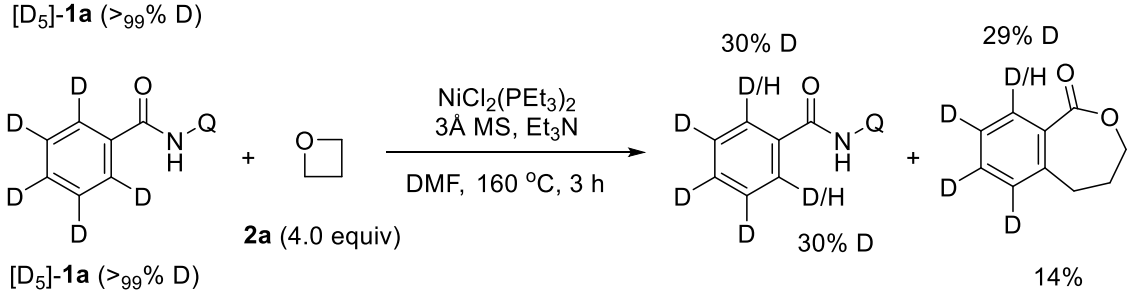


b) reaction of **1a** with 3-chloropropanol (**5**) instead of oxetane (**2a**)



c) deuterium-labeling experiments with [D_5]-**1a** (Q = 8-quinolinyl)

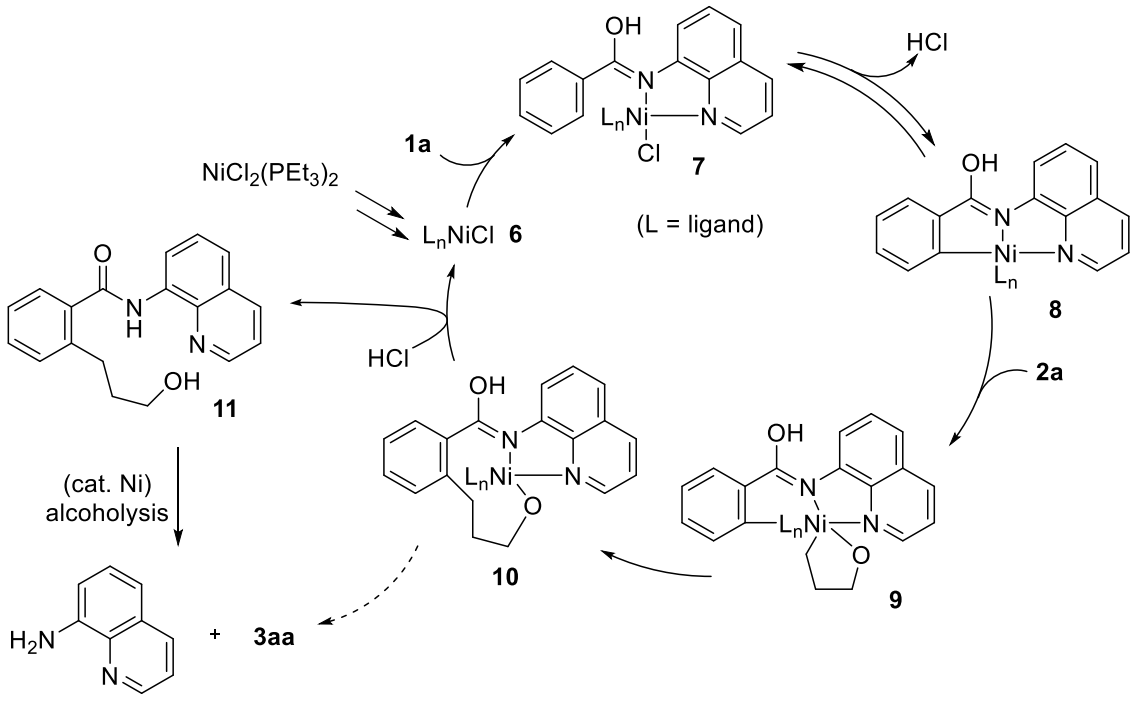




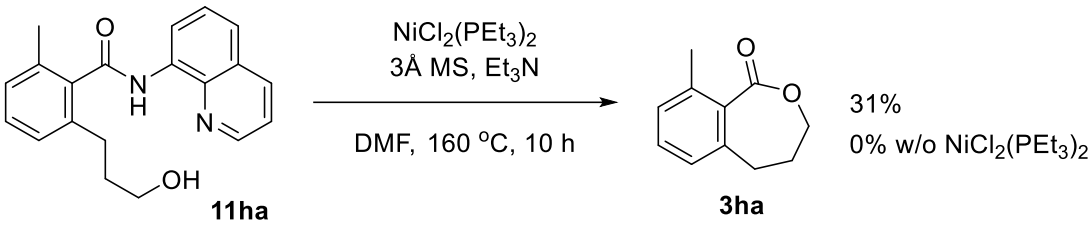
Based on the above findings, a possible reaction mechanism of **1a** with **2a** is proposed as shown in Scheme 6. First, the nickel(II) precatalyst $NiCl_2(PEt_3)_2$ is believed to be reduced to nickel(I) species **6**.[16] The observed incompatibility with the ArCl moiety (Scheme 2, **3ka**) can support the intermediacy of nickel at the lower oxidation state. Although the exact reductant remains to be elucidated, the benzamide substrate or PEt_3 can be a good candidate.[17] The coordination of benzamide **1a** (**6** to **7**) is followed by *N*,*N*-bidentate coordination-assisted reversible C–H cleavage to form the nickelacycle **8**. The chelated nickel complex **8** then undergoes oxidative addition

with **2a** (**8** to **9**), and subsequent reductive elimination generates the C–H alkylated intermediate **10**. Acceleration of the aforementioned and somewhat challenging oxidative addition of oxetane can be an additional role of PEt_3 ligand. Upon protonolysis with HCl, the corresponding alcohol **11** is liberated along with regeneration of the starting nickel **6**. Final intramolecular alcoholysis delivers the observed seven-membered benzolactone **3aa** and free 8-aminoquinoline. The role of Et_3N additive is unclear at this stage, but it can work as a proton shuttle in the catalytic cycle. The cyclization event can also be accelerated by the nickel catalyst. The $NiCl_2(PEt_3)_2$ catalyst successfully converted the independently prepared **11ha** to the lactone **3ha**, whereas no reaction occurred in the absence of any nickel catalyst (Scheme 7).[18]

Scheme 6. Plausible mechanism



Scheme 7. Effects of nickel catalyst in intramolecular alcoholysis



Summary

A nickel-catalyzed C–H coupling of 8-aminoquinoline-derived benzamides with oxetanes has been developed. The reaction occurs with the spontaneous removal of the 8-aminoquinoline bidentate auxiliary to form the corresponding seven-membered benzolactones directly. The present nickel catalysis can provide a new avenue to such medium-sized lactones of frequent occurrence in bioactive molecules and natural products. Additionally, this is one of the limited successful applications of oxetanes under the redox-active transition-metal catalysis.

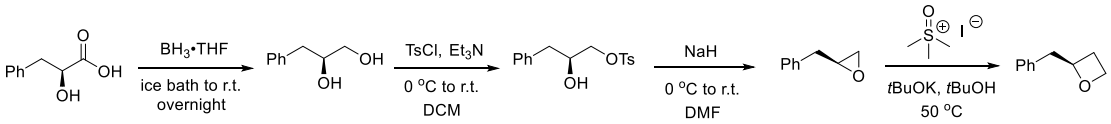
Instrumentation and Chemicals

^{1}H, $^{13}C\{^{1}H\}$, and $^{19}F\{^{1}H\}$ spectra were recorded at 400 MHz, 100 MHz, and 162 MHz, respectively, for $CDCl_3$ solutions. HRMS data were obtained by APCI using TOF. GC analysis was carried out using a silicon OV-17 column (i. d. 2.6 mm x 1.5 m) or CBP capillary column (i. d. 0.5 mm x 25 m). TLC analyses were performed on commercial glass plates bearing 0.25-mm layer of Merck Silica gel $60F_{254}$.

Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. DMF was dried on a Glass Contour Solvent dispensing system (Nikko Hansen & Co., Ltd.) prior to use. Powdered 3Å MS was commercially available from Aldrich and dried with a heat gun under reduced pressure for 30 min before use. Benzamides **1** were prepared from the corresponding benzoyl chlorides or benzoic acids and 8-aminoquinoline according to the literature.[19] The parent oxetane (**2a**) is commercially available. The substituted **2c**[20] was synthesized according to the literature. The synthetic procedure of (*S*)-**2b** was shown in the following section (S3). All reactions were carried out under nitrogen atmosphere unless otherwise noted.

Experimental Procedures

Preparation of chiral oxetane (*S*)-**2b** (Scheme 4a).[21]



Step 1: To a solution of (*S*)-2-hydroxy-3-phenylpropanoic acid (2.49g, 15.0 mmol, commercially available from TCI) in 50 mL of anhydrous THF was added slowly BH_3•THF complex (45 mL, 1M in THF, 3.0 equiv.) with ice cooling under N_2. The solution was stirred overnight at room temperature, and the reaction was quenched with water. After evaporation of the solvent, the residue was diluted with water and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to afford the crude product, which was purified by flash column chromatography on silica gel using hexane/ethyl acetate (1/1) as the eluent to afford *(S)*-3-phenylpropane-1,2-diol (2.05 g, 90%) as a colorless oil.

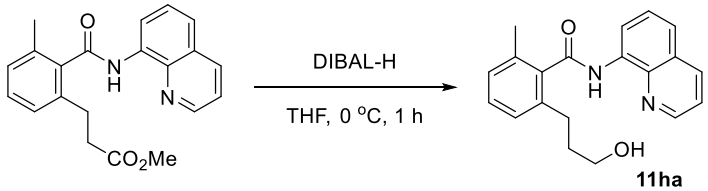
Step 2: To a dried round-bottom flask was added *(S)*-3-phenylpropane-1,2-diol (1.52 g, 10.0 mmol), Et_3N (1.41 mL, 10.0 mmol), and dry DCM (20 mL). It was cooled to 0 °C and then TsCl

(1.90 g, 10.0 mmol) was added in one portion. After stirring at 0 °C for 1 h, the solution was stirred for another 1 h at room temperature. The resulting mixture was quenched with water, and the organic layer was washed with a saturated aqueous solution of $NaHCO_3$ (15 mL) then with brine (15 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude product was purified by flash column chromatography on silica gel using hexane/ethyl acetate (2/1) as the eluent to give the *(S)*-2-hydroxy-3-phenylpropyl 4-methylbenzenesulfonate (1.80 g, 59%) as a colorless oil.

Step 3: The tosylate (1.8 g, 5.88 mmol) was then dissolved in DMF (20 mL) followed by the addition of NaH (60% oil dispersion, 258.7 mg) at 0 °C under N_2. After stirring at 0 °C for 2 h, TLC analysis demonstrated complete conversion. The reaction was quenched with water, and the aqueous layer was extracted with ethyl acetate (3 x 25 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo, the crude product was purified by flash column chromatography on silica gel using hexane/ethyl acetate (20/1) as the eluent to give the *(S)*-2-benzyloxirane (0.54 g, 68%) as a colorless oil.

Step 4: To a stirred solution of trimethylsulfoxonium iodide (1.77 g, 8.04 mmol) in *tert*-butanol (15 mL) at 50 °C was added potassium *tert*-butoxide (0.90 g, 8.04 mmol). After 0.5 h, a solution of *(S)*-2-benzyloxirane (0.54 g, 4.02 mmol) in *tert*-butanol (4 mL) was added dropwise, and the reaction was stirred for 3 days at 50 °C. After the reaction, solvent was evaporated, and water was added to the residue. After extraction with hexane (3 x 25 mL) and evaporation, the crude product was purified by flash column chromatography on silica gel (hexane/ethyl acetate (10/1)) to give the *(S)*-2-benzyloxetane as a slightly yellow liquid in 65% yield (387.3 mg, 2.62 mmol, 98:2 e.r.). The enantiomeric ratio was determined by HPLC analysis on a chiral stationary phase: CHIRALCEL OJ-H column, 95/5 *n*-hexane/2-propanol, 0.5 mL/min, major isomer: t_R = 19.4 min, minor isomer: t_R = 23.4 min, UV detection at 254 nm, 30 °C.

Preparation of **11ha** (Scheme 7).



11ha

A 100 mL round-bottom flask was charged with THF (10 mL) and methyl 3-(3-methyl-2-(quinolin-8-ylcarbamoyl)phenyl)propanoate (1.60 g, 4.6 mmol), which was prepared according to the literature.[22] The solution was cooled to 0 ˚C, and DIBAL-H (1.0 M toluene solution, 18 mL, 18 mmol) was added dropwise. The resulting mixture was stirred at the same

temperature for 1 h before addition of 1 M HCl aq. Extraction with ethyl acetate (20 mL) three times and evaporation under reduced pressure afforded the crude product. The targeted 2-(3-hydroxypropyl)-6-methyl-*N*-(quinolin-8-yl)benzamide (**11ha**, 0.18 g, 0.56 mmol, 12%, not optimized) was isolated by column chromatography on silica gel with hexane/ethyl acetate (2/1, v/v). The copy of ^{1}H NMR spectrum was attached in the last part.

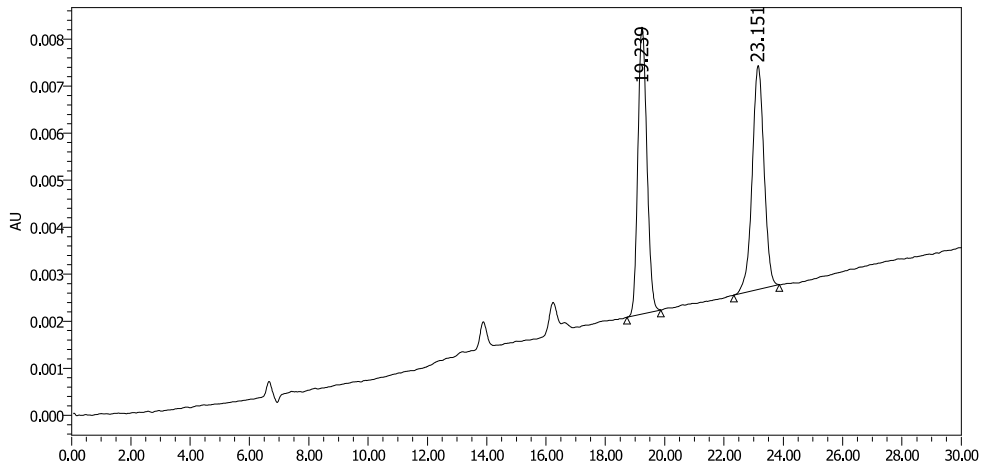
Synthesis of **3aa**. In the glovebox filled with nitrogen, *N*-(quinolin-8-yl)benzamide (**1a**, 49.66 mg, 0.20 mmol), $NiCl_2(PEt_3)_2$ (22.0 mg, 0.06 mmol), and molecular seive 3Å (100 mg, activated powder) were added to a 5 mL sealed microwave vessel, and the vessel was then taken out from the glovebox. DMF (0.5 mL), oxetane (**2a,** 46.46 mg, 0.80 mmol), and triethylamine (4.05 mg, 0.04 mmol) were added by syringe subsequently. The reaction mixture was heated at 160 °C for 22 hours under N_2 atmosphere. The resulting mixture was then quenched with water and extracted with ethyl acetate. The combined organic layer was dried over sodium sulfate. Concentration in vacuo followed by silica gel column purification with hexane/ethyl acetate (5:1, v/v) gave 4,5-dihydrobenzo[*c*]oxepin-1(3*H*)-one (**3aa**, 25.3 mg, 0.156 mmol) in 78% yield.

Synthesis of **3aa** (2.0 mmol scale). In the glovebox filled with nitrogen, *N*-(quinolin-8-yl)benzamide (**1a**, 496.6 mg, 2.0 mmol), $NiCl_2(PEt_3)_2$ (220.0 mg, 0.60 mmol), and molecular seive 3Å (1.0 g, activated powder) were added to a 20 mL sealed microwave vessel, and the vessel was then taken out from the glovebox. DMF (5.0 mL), oxetane (**2a,** 464.6 mg, 8.0 mmol), and triethylamine (40.5 mg, 0.40 mmol) were added by syringe subsequently. The reaction mixture was heated at 160 °C for 22 hours under N_2 atmosphere. The resulting mixture was then quenched with water and extracted with ethyl acetate. The combined organic layer was dried over sodium sulfate. Concentration in vacuo followed by silica gel column purification with hexane/ethyl acetate (5:1, v/v) gave 4,5-dihydrobenzo[*c*]oxepin-1(3*H*)-one (**3aa**, 215.3 mg, 1.32 mmol) in 66% yield and recovered quinolin-8-amine (158.2 mg, 1.10 mmol) in 55% yield.

Chiral HPLC Charts

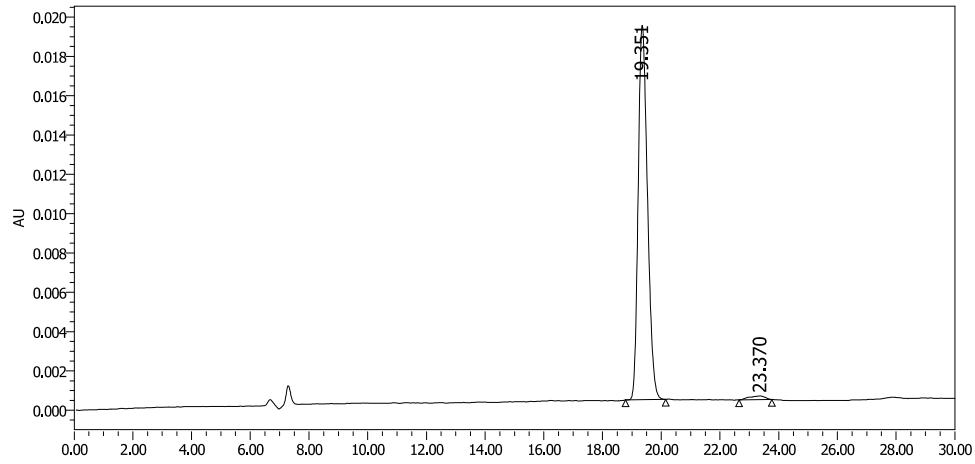
2b: The enantiomeric ratio was determined by HPLC analysis in comparison with authentic racemic material (CHIRALCEL OJ-H column, 95/5 *n*-hexane/2-propanol, 0.5 mL/min, major isomer: t_R = 19.4 min, minor isomer: t_R = 23.4 min, UV detection at 254 nm, 30 ºC).

rac-**2b**



Peak #	Ret. Time	Area	Area %
1	19.239	129656	49.52
2	23.151	132178	50.48

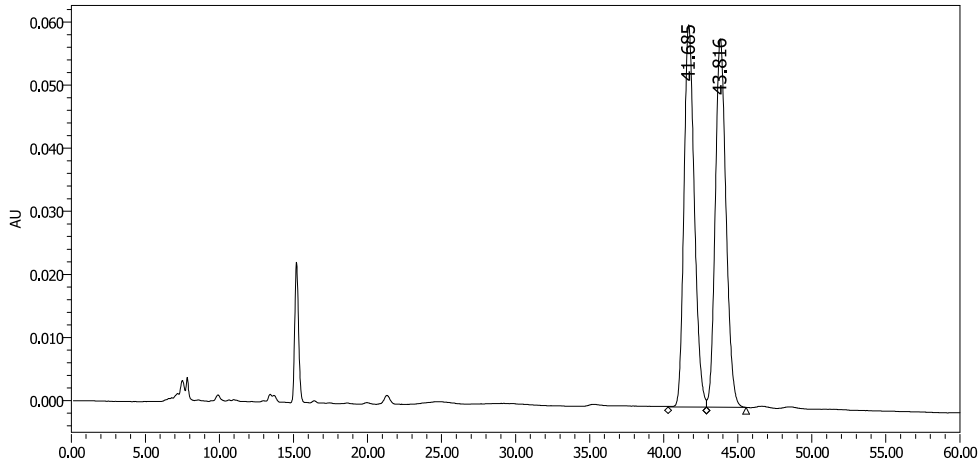
(*S*)-**2b**



Peak #	Ret. Time	Area	Area %
1	19.351	417691	98.36
2	23.370	6979	1.64

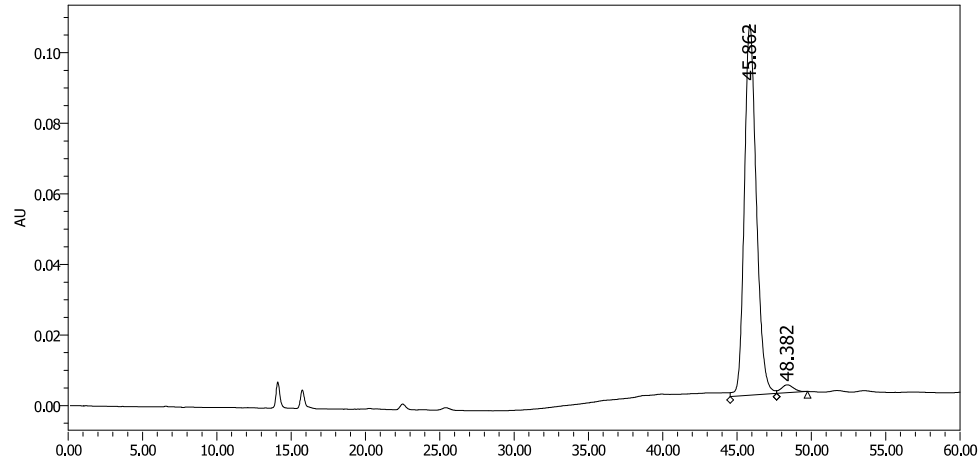
3ab: The enantiomeric ratio was determined by HPLC analysis in comparison with authentic racemic material (CHIRALPAK AD-H column, 98/2 *n*-hexane/2-propanol, 0.5 mL/min, major isomer: t_R = 45.9 min, minor isomer: t_R = 48.4 min, UV detection at 254 nm, 30 °C).

rac-**3ab**



Peak #	Ret. Time	Area	Area %
1	41.685	2949270	49.96
2	43.816	2953820	50.04

(*R*)-**3ab**



Peak #	Ret. Time	Area	Area %
1	45.862	5878709	97.79
2	48.382	132742	2.21

Characterization Data for Products

4,5-Dihydrobenzo[*c*]oxepin-1(3*H*)-one (3aa): colorless oil; TLC R_f 0.30 (hexane/EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (dd, *J* = 7.6, 1.3 Hz, 1H), 7.49 (td, *J* = 7.4, 1.3 Hz, 1H), 7.37 (td, *J* = 7.5, 1.2 Hz, 1H), 7.22 (dd, *J* = 7.4, 0.6 Hz, 1H), 4.16 (t, *J* = 6.3 Hz, 2H), 2.91 (t, *J* = 7.2 Hz, 2H), 2.17-2.10 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 137.5, 132.6, 131.6, 130.2, 128.6, 127.4, 66.5, 29.4, 27.8. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{10}H_{11}O_2$: 163.0754, Found: 163.0756.

7-(*tert*-Butyl)-4,5-dihydrobenzo[*c*]oxepin-1(3*H*)-one (3ba): light yellow oil; TLC R_f 0.35 (hexane/EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.2 Hz, 1H), 7.37 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.20 (d, *J* = 1.8 Hz, 1H), 4.16 (t, *J* = 6.3 Hz, 2H), 2.89 (t, *J* = 7.2 Hz, 2H), 2.16-2.09 (m, 2H), 1.33 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 156.4, 137.4, 130.2, 128.7, 125.7, 124.4, 66.6, 35.0, 31.1, 29.9, 27.8. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{14}H_{19}O_2$: 219.1380, Found: 219.1388.

7-Methoxy-4,5-dihydrobenzo[*c*]oxepin-1(3*H*)-one (3ca): colorless oil; TLC R_f 0.32 (hexane/EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, *J* = 8.5 Hz, 1H), 6.85 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.72 (d, *J* = 2.5 Hz, 1H), 4.16 (t, *J* = 6.3 Hz, 2H), 3.85 (s, 3H), 2.87 (t, *J* = 7.3 Hz, 2H), 2.15-2.08 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 163.0, 140.1, 132.7, 123.8, 114.5, 112.1, 66.6, 55.4, 29.9, 27.7. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{11}H_{13}O_3$: 193.0859, Found: 193.0843.

7-(Trifluoromethyl)-4,5-dihydrobenzo[*c*]oxepin-1(3*H*)-one (3da): colorless oil; TLC R_f 0.30 (hexane/EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.7 Hz, 1H), 7.63 (d, *J* = 7.7 Hz, 1H), 7.50 (s, 1H), 4.17 (t, *J* = 6.3 Hz, 2H), 3.0 (t, *J* = 7.4 Hz, 2H), 2.21-2.14 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 138.3, 135.0, 134.0 (q, *J* = 33.2 Hz), 130.7, 125.6 (q, *J* = 3.6 Hz), 124.0 (q, *J* = 3.6 Hz), 123.5 (q, *J* = 272.8 Hz), 66.5, 29.3, 27.3. ^{19}F NMR (376 MHz, $CDCl_3$) δ -63.1. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{11}H_{10}F_3O_2$: 231.0627, Found: 231.0616.

8-Methyl-4,5-dihydrobenzo[*c*]oxepin-1(3*H*)-one (3ea): colorless oil; TLC R_f 0.28 (hexane/EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, *J* = 1.0 Hz, 1H), 7.27 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.09 (d, *J* = 7.7 Hz, 1H), 4.14 (t, *J* = 6.3 Hz, 2H), 2.85 (t, *J* = 7.2 Hz, 2H), 2.36 (s, 3H), 2.13-2.06 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 137.2, 134.5, 133.3, 131.4, 130.7, 128.6, 66.6, 28.9, 27.8,

20.9. HRMS (APCI) m/z ([M+H]$^+$) Calcd for $C_{11}H_{13}O_2$: 177.0910, Found: 177.0916.

8-Methoxy-4,5-dihydrobenzo[*c*]oxepin-1(3*H*)-one (3fa): colorless oil; TLC R_f 0.32 (hexane/EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (d, *J* = 2.7 Hz, 1H), 7.11 (d, *J* = 8.4 Hz, 1H), 7.00 (dd, *J* = 8.4, 2.7 Hz, 1H), 4.16 (t, *J* = 6.3 Hz, 2H), 3.82 (s, 3H), 2.83 (t, *J* = 7.3 Hz, 2H), 2.12-2.05 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.3, 158.7, 132.4, 129.9, 129.7, 119.1, 114.1, 66.8, 55.6, 28.4, 27.9. HRMS (APCI) m/z ([M+H]$^+$) Calcd for $C_{11}H_{13}O_3$: 193.0859, Found: 193.0869.

8-(Trifluoromethyl)-4,5-dihydrobenzo[*c*]oxepin-1(3*H*)-one (3ga): colorless oil; TLC R_f 0.38 (hexane/EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 1.1 Hz, 1H), 7.74 (dd, *J* = 7.8, 1.1 Hz, 1H), 7.37 (d, *J* = 7.8 Hz, 1H), 4.18 (t, *J* = 6.9 Hz, 2H), 3.00 (t, *J* = 7.8 Hz, 2H), 2.21-2.14 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 141.4, 132.4, 130.1 (q, *J* = 33.8 Hz), 129.4, 129.3 (q, *J* = 3.5 Hz), 127.3 (q, *J* = 3.8 Hz), 123.6 (q, *J* = 272.2 Hz), 66.5, 29.4, 27.3. ^{19}F NMR (376 MHz, $CDCl_3$) δ -62.7. HRMS (APCI) m/z ([M+H]$^+$) Calcd for $C_{11}H_{10}F_3O_2$: 231.0627, Found: 231.0629.

9-Methyl-4,5-dihydrobenzo[*c*]oxepin-1(3*H*)-one (3ha): colorless oil; TLC R_f 0.36 (hexane/EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (t, *J* = 7.6 Hz, 1H), 7.18 (d, *J* = 7.8 Hz, 1H), 7.02 (d, *J* = 7.5 Hz, 1H), 4.09 (t, *J* = 6.2 Hz, 2H), 2.28 (t, *J* = 7.1 Hz, 2H), 2.45 (s, 3H), 2.08-2.01 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 138.5, 136.8, 131.3, 130.5, 129.7, 125.8, 65.8, 29.4, 27.7, 20.2. HRMS (APCI) m/z ([M+H]$^+$) Calcd for $C_{11}H_{13}O_2$: 177.0910, Found: 177.0920.

4,5-Dihydronaphtho[2,3-*c*]oxepin-1(3*H*)-one (3ia): white solid; m. p. 130.3-130.8 ºC (from hexane); TLC R_f 0.30 (hexane/EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (s, 1H), 7.91 (dd, *J* = 8.1, 0.6 Hz, 1H), 7.82 (dd, *J* = 8.1, 0.4 Hz, 1H), 7.65 (s, 1H), 7.60-7.56 (m, 1H), 7.54-7.50 (m, 1H), 4.19 (t, *J* = 6.3 Hz, 2H), 3.05 (t, *J* = 7.1 Hz, 2H), 2.20-2.14 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.4, 135.3, 133.6, 131.8, 131.4, 130.1, 128.8, 128.3, 127.3, 127.1, 126.5, 66.7, 29.6, 28.1. HRMS (APCI) m/z ([M+H]$^+$) Calcd for $C_{14}H_{13}O_2$: 213.0910, Found: 213.0916.

4,5-Dihydronaphtho[1,2-*c*]oxepin-1(3*H*)-one (3ja): white solid; m. p. 85.3-85.7 ºC (from hexane); TLC R_f 0.40 (hexane/EtOAc, 5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.27 (dd, *J* = 8.4, 0.7 Hz, 1H), 7.95 (d, *J* = 8.2 Hz, 1H), 7.88-7.84 (m, 1H), 7.60-7.56 (m, 1H), 7.53-7.49 (m, 1H), 7.33 (d, *J* = 8.3 Hz, 1H), 4.16 (t, *J* = 6.3 Hz, 2H), 3.03 (t, *J* = 7.2 Hz, 2H), 2.19-2.12 (m, 2H). ^{13}C NMR (100 MHz,

$CDCl_3$) δ 170.9, 135.6, 132.7, 132.3, 130.9, 128.2, 127.9, 127.1, 126.4, 126.1, 125.2, 65.9, 29.7, 27.6. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{14}H_{13}O_2$: 213.0910, Found: 213.0913.

5,6-Dihydrothieno[2,3-*c*]oxepin-8(4*H*)-one (3la): colorless oil; TLC R_f 0.33 (hexane/EtOAc, 5:1). ^1H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, *J* = 5.1 Hz, 1H), 6.92 (d, *J* = 5.1 Hz, 1H), 4.43-4.41 (m, 2H), 3.07 (t, *J* = 6.8 Hz, 2H), 2.29-2.23 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 144.9, 133.3, 130.3, 130.0, 68.7, 29.5, 26.7. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_8H_9O_2S$: 169.0318, Found: 169.0317.

1-Methyl-1,4,5,6-tetrahydro-8*H*-oxepino[3,4-*b*]pyrrol-8-one (3ma): colorless oil; TLC R_f 0.35 (hexane/EtOAc, 5:1). ^1H NMR (400 MHz, $CDCl_3$) δ 6.80 (d, *J* = 2.5 Hz, 1H), 5.98 (d, *J* = 2.5 Hz, 1H), 4.34-4.31 (m, 2H), 3.86 (s, 3H), 2.90 (t, *J* = 7.2 Hz, 2H), 2.17-2.10 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 164.4, 130.8, 130.2, 119.1, 108.6, 68.3, 37.3, 27.0, 25.2. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_9H_{12}NO_2$: 166.0863, Found: 166.0861.

10-Methyl-3,4,5,10-tetrahydro-1*H*-oxepino[3,4-*b*]indol-1-one (3na): light yellow solid; m. p. 55.8-56.1 °C (from hexane); TLC R_f 0.31 (hexane/EtOAc, 5:1). ^1H NMR (400 MHz, $CDCl_3$) δ 7.64 (dt, *J* = 8.1, 0.9 Hz, 1H), 7.43-7.37 (m, 2H), 7.20-7.16 (m, 1H), 4.45-4.43 (m, 2H), 3.98 (s, 3H), 3.19 (t, *J* = 7.3 Hz, 2H), 2.34-2.28 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 139.5, 126.0, 125.7, 124.3, 121.2, 120.4, 120.2, 110.3, 68.4, 31.9, 26.8, 22.1. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{13}H_{14}NO_2$: 216.1019, Found: 216.1021.

***(R)*-3-Benzyl-4,5-dihydrobenzo[*c*]oxepin-1(3*H*)-one ((*R*)-3ab):** colorless oil; 98:2 e.r.; TLC R_f 0.40 (hexane/EtOAc, 5:1). ^1H NMR (400 MHz, $CDCl_3$) δ 7.68 (d, *J* = 7.6 Hz, 1H), 7.44 (t, *J* = 7.4 Hz, 1H), 7.34 (t, *J* = 7.5 Hz, 1H), 7.29-7.25 (m, 2H), 7.23-7.15 (m, 4H), 4.28-4.21 (m, 1H), 3.15 (dd, *J* = 13.9, 6.8 Hz, 1H), 3.00 (td, *J* = 13.4, 8.1 Hz, 1H), 2.90 (dd, *J* = 13.9, 6.1 Hz, 1H), 2.73 (dd, *J* = 13.9, 7.2 Hz, 1H), 2.15 (td, *J* = 13.0, 8.8 Hz, 1H), 1.96-1.86 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 137.8, 137.0, 132.5, 131.9, 130.1, 129.4, 128.6, 128.5, 127.3, 126.8, 78.8, 41.1, 33.6, 29.7. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{17}H_{17}O_2$: 253.1223, Found: 253.1226. Chiralpak AD-H column, 98/2 hexane/2-propanol, 0.5 mL/min, major isomer: t_R = 45.86 min, minor isomer: t_R = 48.38 min.

4-Phenyl-4,5-dihydrobenzo[*c*]oxepin-1(3*H*)-one (3ac): colorless oil; TLC R_f 0.35 (hexane/EtOAc,

5:1). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.53 (td, *J* = 7.5, 1.5 Hz, 1H), 7.43 (td, *J* = 7.6, 1.2 Hz, 1H), 7.35-7.32 (m, 2H), 7.30-7.24 (m, 4H), 4.40-4.29 (m, 2H), 3.51-3.45 (m, 1H), 3.24 (dd, *J* = 14.1, 7.5 Hz, 1H), 3.06 (dd, *J* = 14.1, 7.4 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.1, 142.1, 137.0, 132.8, 131.4, 130.6, 129.4, 128.9, 127.7, 127.5, 127.3, 71.4, 45.4, 38.2. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{16}H_{15}O_2$: 239.1067, Found: 239.1077.

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[15] The source of H might still be contaminated water. We confirmed the partial deuterium incorporation (22% D) at the ortho position of **1a** when a mixture of **1a**, D_2O (1.0 equiv), and nickel catalyst was simply heated in DMF.

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[18] Ohshima reported the related nickel(II)-catalyzed alcoholysis of 8-aminoquinoline amides. T. Deguchi, H.-L. Xin, H. Morimoto, T. Ohshima, *ACS Catal.* **2017**, *7*, 3157. The yield of **3ha** was lower than that observed in Scheme 2, which suggests another lactonization pathway, such as the direct conversion of Ni-associated intermediate **10** to the benzolactone **3aa** (Scheme 6).

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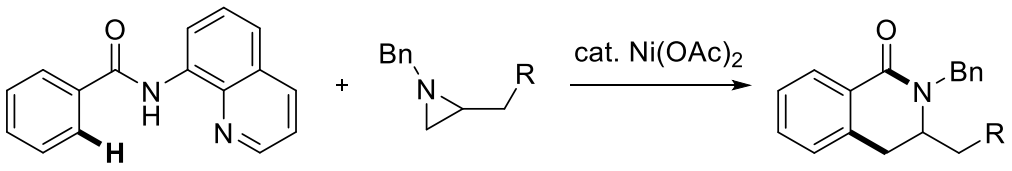
Chapter 4

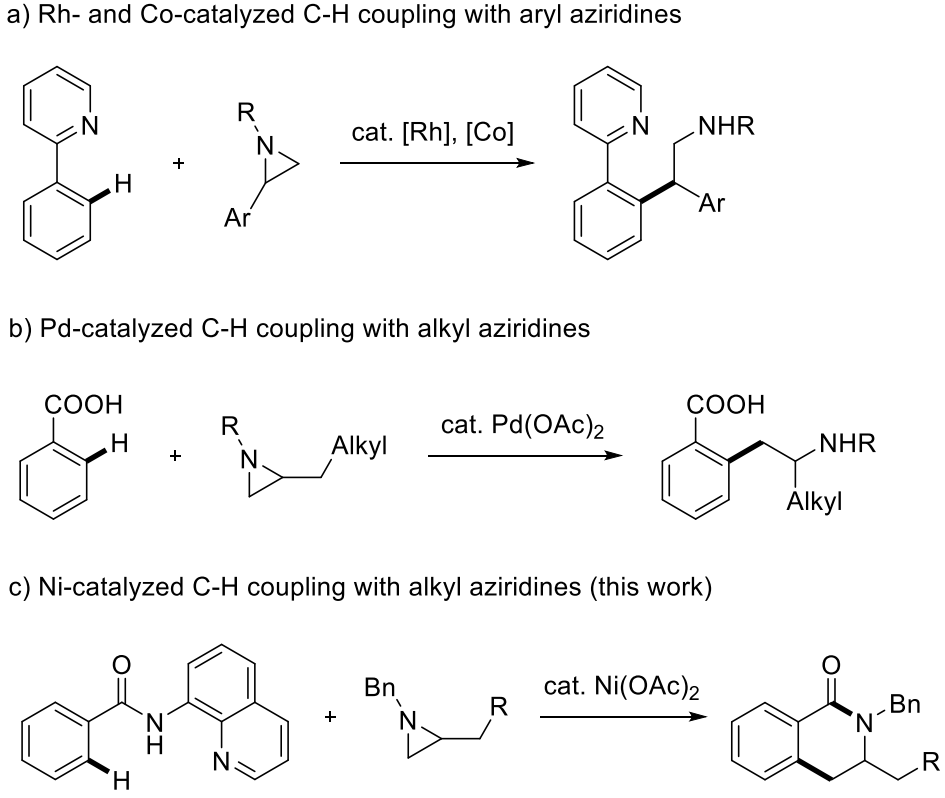
Synthesis of Benzolactams by Nickel-Catalyzed C-H Coupling of Benzamides with Aziridines

A nickel-catalyzed C-H coupling of 8-aminoquinoline-derived benzamides with aziridines has been disclosed. This protocol provides rapid access to benzolactams by the C-H alkylation-amidation cascade event with the concomitant removal of aminoquinoline auxiliary. Moreover, the alkyl-substituted aziridines are also well tolerated to afford the corresponding products.



Transition-metal-catalyzed C-H activation has emerged as an efficient and step- and atom-economic strategy for the C-C/C-X bond formation. Among them, the chelating auxiliary directed C-H functionalization has attracted much attention from synthetic chemists because it can achieve otherwise challenging C-H bond activation.[1] On the other hand, aziridines, as strained small ring systems, have served as important building blocks in synthetic organic chemistry *via* the ring-opening reactions.[2] The Lewis acid promoted Friedel-Crafts alkylation[3] and cross-coupling reaction with organometallic regents[4] have been the main topics for new C-C bond formations with aziridines. Despite the certain progress in this field, the restriction in substrate scope and tedious multi-step preparation of starting organometallic coupling partners limit its wide application in organic synthesis. Thus, synthetic chemists have paid efforts to explore the possibility of directed aromatic C-H alkylation with aziridines. As a seminal work, Li and co-workers disclosed the Cp*Rh(III)-catalyzed *ortho* C-H alkylation of 2-arylpyridines *via* the ring opening of aziridines,[5] and Yoshikai group developed the same transformation under Co-NHC catalysis[6] (Scheme 1a). However, these protocols are limited to the relatively activated aryl-substituted aziridines, and the C-H coupling reaction with alkyl-substituted aziridines is less explored. As only one successful example, Zhao and co-workers recently achieved the Pd-catalyzed C-H alkylation of benzoic acids with aliphatic aziridines (Scheme 1b).[7] Based on previous work on the 8-aminoquinoline-directed[8] C-H alkylation with epoxides and oxetanes,[9] the author envisioned the nickel-catalyzed[10] C-H coupling of benzamides with aliphatic aziridines to construct the corresponding benzolactams (Scheme 1c).

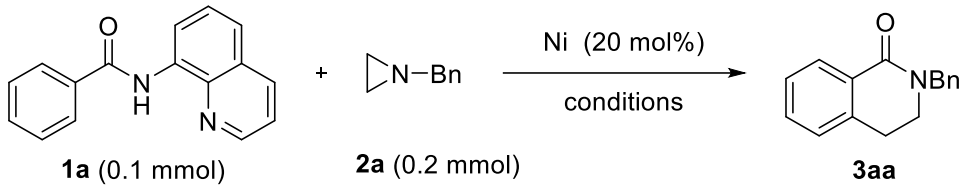
Scheme 1. Metal-catalyzed C-H alkylation with aziridines.



Benzamide **1a** and *N*-benzyl aziridine **2a** were selected as model substrates, and the author commenced optimization studies (0.1 mmol scale; Table 1). Several nickel catalysts were initially tested in heated toluene (150 °C) (entries 1-6), and $Ni(OAc)_2 \cdot 4H_2O$ showed the best reactivity with the formation of benzolactam **3aa** in 40% yield (entry 1). Subsequent screening of solvent revealed that diglyme showed a better performance (entries 7-13). The NaOAc additive resulted in no increasing in yield (entry 14). Pleasingly, the reaction was accelerated by microwave irradiation to deliver the desired benzolactam in 72% yield within 1 h (entry 15). The $NiCl_2$ gave low efficiency (entry 16). Additional screening of the external phosphine ligands provided no improvement (entries 17 and 18). The higher loading of **2a** increased the

conversion of benzamide to form the corresponding lactam in 81% isolated yield (entry 19). Further investigation of the reaction time and temperature did not give significant improvement (entries 20 and 21). The substituent group on N atom of aziridine was critical: the *N*-Ts substitution resulted in decomposition of aziridine, while *N*-Ph aziridine gave no reaction (entry 22).

Table 1. Optimization studies.



1a (0.1 mmol) **2a** (0.2 mmol) **3aa**

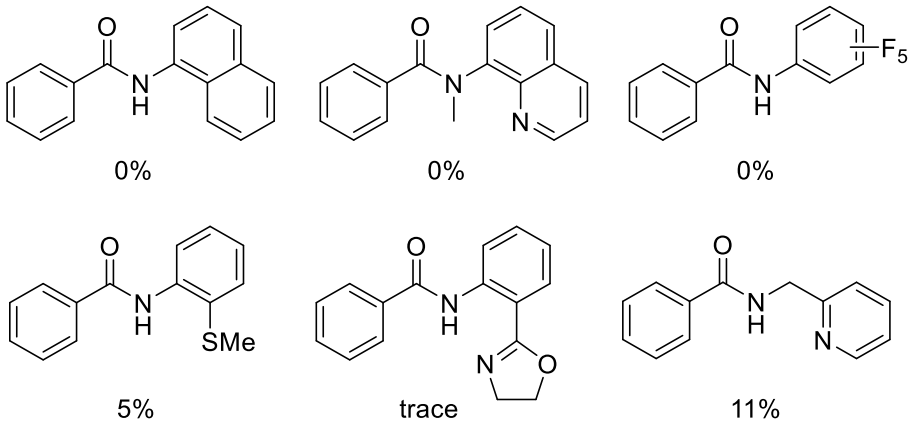
Entry	Ni salts	Additives (mol%)	Solvent (mL)	Conditions	Yield (%)[a]
					3aa
1	$Ni(OAc)_2·4H_2O$		toluene (0.5)	150 °C, 20 h	40
2	$NiCl_2$·glyme		toluene (0.5)	150 °C, 20 h	37
3	$NiCl_2(PEt_3)_2$		toluene (0.5)	150 °C, 20 h	31
4	$NiCl_2(PCy_3)_2$		toluene (0.5)	150 °C, 20 h	26
5	$NiBr_2$·diglyme		toluene (0.5)	150 °C, 20 h	14
6	$Ni(cod)_2$		toluene (0.5)	150 °C, 20 h	trace
7	$Ni(OAc)_2·4H_2O$		*O*-xylene (0.5)	150 °C, 23 h	55
8	$Ni(OAc)_2·4H_2O$		PhCl (0.5)	150 °C, 23 h	43
9	$Ni(OAc)_2·4H_2O$		DCE (0.5)	160 °C, 23 h	10
10	$Ni(OAc)_2·4H_2O$		DMF (0.5)	150 °C, 23 h	33
11	$Ni(OAc)_2·4H_2O$		DMSO (0.5)	150 °C, 23 h	15
12	$Ni(OAc)_2·4H_2O$		dioxane (0.5)	150 °C, 23 h	47
13	$Ni(OAc)_2·4H_2O$		diglyme (0.5)	150 °C, 23 h	68
14	$Ni(OAc)_2·4H_2O$	NaOAc (100)	diglyme (0.5)	150 °C, 23 h	59
15	**$Ni(OAc)_2·4H_2O$**		**diglyme (0.5)**	**μw, 200 °C, 1 h**	**72**
16	$NiCl_2$		diglyme (0.5)	μw, 200 °C, 1 h	40
17	$Ni(OAc)_2·4H_2O$	PPh_3 (40)	diglyme (0.5)	μw, 200 °C, 1 h	60

18	$Ni(OAc)_2 \cdot 4H_2O$	PMe_3 (40)	diglyme (0.5)	μw, 200 °C, 1 h	65
19[b]	**$Ni(OAc)_2 \cdot 4H_2O$**		**diglyme (0.5)**	**μw, 200 °C, 1 h**	**83(81)**
20[b]	$Ni(OAc)_2 \cdot 4H_2O$		diglyme (0.5)	μw, 250 °C, 1 h	59
21[b]	$Ni(OAc)_2 \cdot 4H_2O$		diglyme (0.5)	μw, 200 °C, 1.5 h	81
22[c]	$Ni(OAc)_2 \cdot 4H_2O$		diglyme (0.5)	μw, 200 °C, 1 h	0

[a] NMR yields with CH_2Br_2 as an internal standard. Isolated yields in parentheses. [b] With 0.3 mmol of **2a**. [c] *N*-tosyl- or *N*-phenyl-substituted aziridine was used instead of *N*-benzyl-substituted aziridine.

Under the conditions in entry 19 Table 1, the effects of other directing groups were evaluated. As shown in Table 2, the monodentate auxiliaries did not give any product, and other *N,S*- and *N,N*-bidentate coordinating groups showed sluggish reactivity, which demonstrated that aminoquinoline auxiliary was indispensable in this transformation.

Table 2. Effects of directing groups.[a]

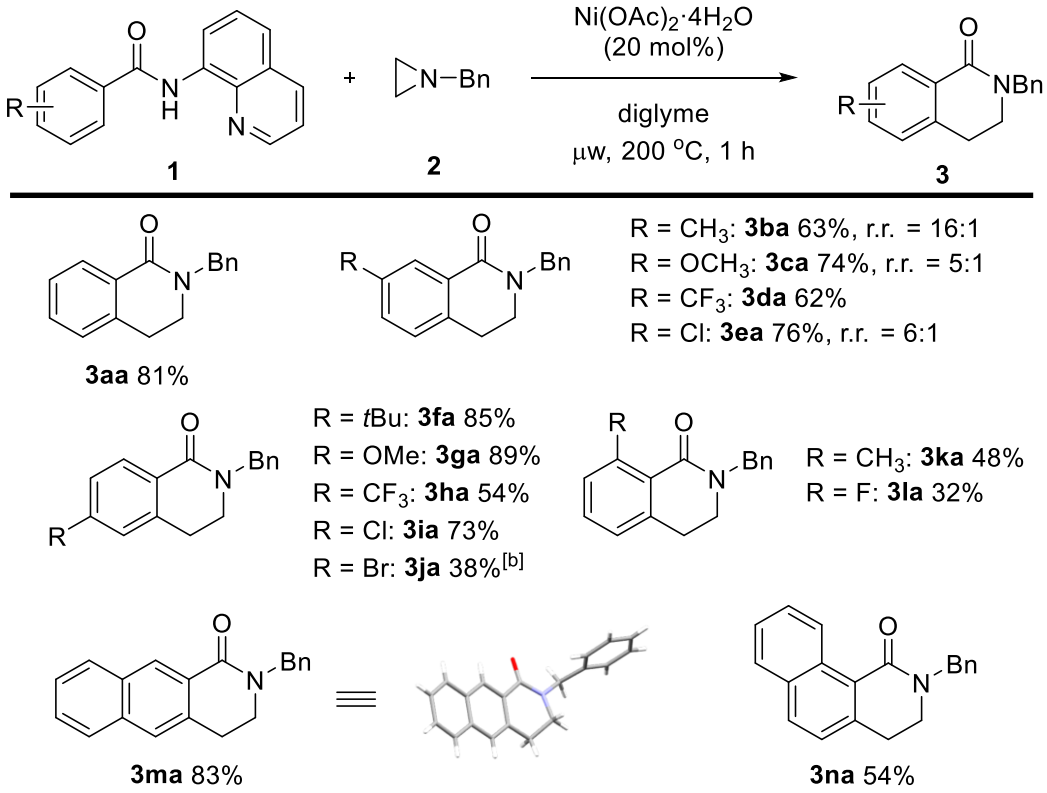


[a] ^{1}H NMR yield of **3aa** is shown.

With the optimal reaction conditions in hand, a variety of benzamides **1** were examined with *N*-Bn aziridine **2a** to explore the generality of this transformation. As shown in Table 3, the *meta*-substituted benzamides were well tolerated, and the reaction preferably occurred at the less sterically hindered position to form the benzolactams

3ba-ea in good yields with acceptable regioselectivity. The benzamides bearing electron-donating and -withdrawing groups at the *para* position smoothly furnished the coupling products (**3fa-ha**). Notably, the chloro substitution was well tolerated in the catalytic system (**3ia**), while the bromo moiety afforded the corresponding lactam **3ja** in a synthetically useful yield but with the formation of protodebrominated byproduct **3aa**. Additionally, the sterically demanding *ortho*-substituted benzamides also successfully underwent the C-H coupling to produce the functionalized lactams (**3ka-la**) albeit with somewhat lower efficiency. Moreover, the 2-naphthalenecarboxamide derivative **1b** was well tolerated and regioselectively formed the benzolactam **3ma** in 83% yield, whereas the more sterically hindered 1-naphthyl isomer showed lower reactivity (**3na**, 54%). The structure of **3ma** was unambiguously confirmed by the single crystallographic X-ray analysis.[11]

Table 3. Nickel-catalyzed C-H coupling of benzamides 1 with aziridines 2a.[a]



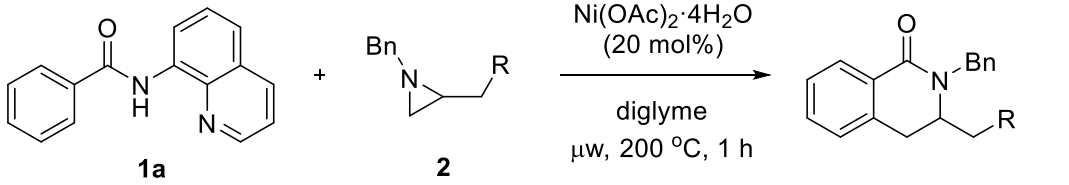
[a] Reaction conditions: **1** (0.10 mmol), **2a** (0.30 mmol), $Ni(OAc)_2 \cdot 4H_2O$ (0.020 mmol), diglyme (0.5 mL), microwave irradiation (200 °C), 1 h, N_2. Yields of isolated products are given. [b] The hydrodebrominated product **3aa** was also formed in ca. 27% yield.

The scope and limitation of aziridines **2** were then investigated. The reaction with the unactivated aliphatic aziridine **2b** preferably occurred at the sterically less hindered terminal position and resulted in the formation of corresponding benzolactam **3ab** with good regioselectivity (Scheme 1a). Moreover, the aziridines **2c** and **2d** with *O*-containing alkyl substitutions were well compatible for the C-H coupling-cyclization cascade process to deliver **3ac-ad** in good yields with high regioselectivity. Additionally, the benzyl-substituted optically active aziridine (*S*)-**2e** furnished the benzolactam (*S*)-**3ae** with excellent regioselectivity (Scheme 1b). Notably, its chirality was successfully transferred without losing the enantiopurity, thus providing a new

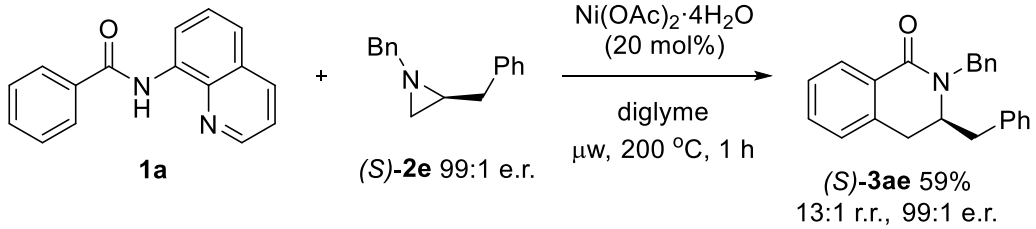
route to chiral benzolactams from easily prepared enantioenriched aziridines. In the reaction with the phenyl-substituted aziridine (*S*)-**2f** (Scheme 1c), the relatively activated benzylic C-N bond was preferably cleaved to afford (*S*)-**3af**[12] in a stereoinvertive manner[13],[4b] albeit with some erosion of the enantiopurity, which probably underwent an S_N2-type nucleophilic ring-opening pathway of aziridine. However, the attempts with more challenging 1,2-disubstituted aziridines were still unsuccessful (data not shown).

Scheme 1. Nickel-catalyzed C-H coupling of benzamide 1a with substituted aziridines 2.

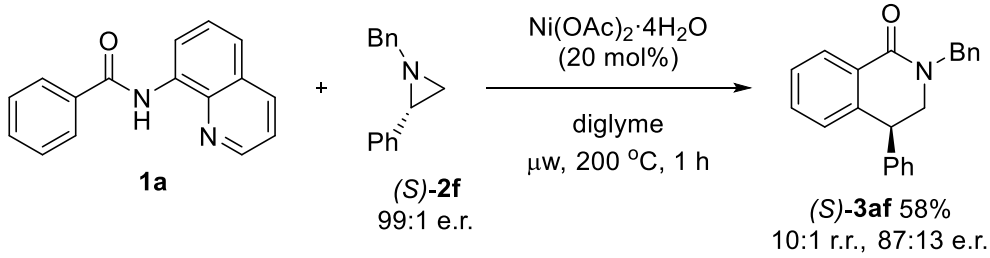
a) reaction with substituted aliphatic aziridines



b) reaction with chiral substituted aliphatic aziridine **2e**

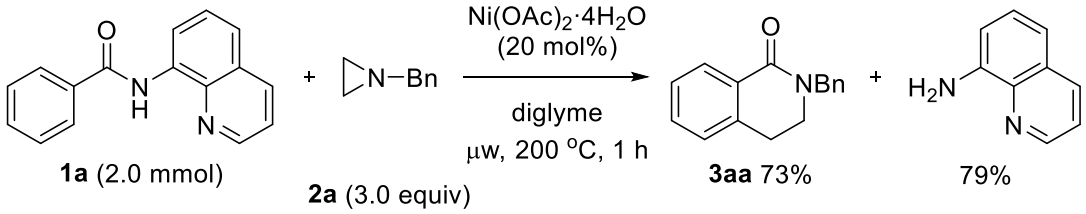


c) reaction with chiral substituted phenyl aziridine **2f**



Additionally, the model reaction could be performed effectively on a 20-fold larger scale, and the desired **3aa** was isolated in 73% yield along with 79% recovery of 8-aminoquinoline auxiliary (Scheme 2). The result demonstrates a practical feature of this synthetic methodology, whereas the removal of such a bidentate auxiliary often requires tedious and additional operations.[14]

Scheme 2. Reaction on 2.0 mmol scale.



Summary

In chapter 3, a $Ni(OAc)_2$-catalyzed C-H coupling reaction of 8-aminoquinoline-derived benzamides with aziridines was described. The reaction proceeded with the C-H alkylation and subsequent intramolecular amidation to deliver the corresponding benzolactams in one operation with the recovery of 8-aminoquinoline auxiliary. Additionally, the alkyl-substituted aziridines were also tolerated to couple with benzamides preferably at the terminal position.

Experimental Section

Instrumentation and Chemicals

^{1}H, $^{13}C\{^{1}H\}$, and $^{19}F\{^{1}H\}$ spectra were recorded at 400 MHz, 100 MHz, and 162 MHz, respectively, for $CDCl_3$ solutions. HRMS data were obtained by APCI. GC analysis was carried out using a silicon OV-17 column (i. d. 2.6 mm x 1.5 m) or CBP capillary column (i. d. 0.5 mm x 25 m). TLC analyses were performed on commercial glass plates bearing 0.25-mm layer of Merck Silica gel $60F_{254}$. Silica gel (Wakosil C-200, Wako Pure Chemical Co.) was used for column chromatography. Gel permeation chromatography (GPC) was performed by LC-20AR (pump, SHIMADZU, 7.5 mL/min EtOAc or $CHCl_3$) and SPD-20A (UV detector, SHIMADZU, 254 nm) with two in-line YMC-GPC T2000 (20 x 600 mm, particle size: 10 μm) (preparative columns, YMC). Microwave irradiation was conducted with Initiator^{+} (Biotage), and the reaction temperature was measured by an internal probe.

Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. Diglyme was freshly distilled from CaH_2. Benzamides **1** were prepared from the corresponding benzoyl chlorides or benzoic acids and 8-aminoquinoline according to the literature.[15] Aziridines **2a-f** were synthesized according to the literature.[16] All reactions were carried out under nitrogen atmosphere unless otherwise noted.

Experimental Procedures

Synthesis of **3aa**. A suspension of *N*-(quinolin-8-yl)benzamide (**1a**, 24.8 mg, 0.10 mmol), *N*-Bn aziridine (**2a**, 39.9 mg, 0.30 mmol), $Ni(OAc)_2 \cdot 4H_2O$ (5.0 mg, 0.02 mmol), and diethylene glycol dimethyl ether (diglyme) (0.5 mL) in a sealed microwave vessel was irradiated under microwave reactor conditions at 200 °C for 1 hour under N_2 atmosphere. The resulting mixture was then quenched with water and extracted with ethyl acetate. The combined organic layer was dried over sodium sulfate. Concentration in vacuo followed by silica gel column purification with hexane/ethyl acetate (5:1, v/v) gave 2-benzyl-3,4-dihydroisoquinolin-1(2*H*)-one (**3aa**, 19.2 mg, 0.081 mmol) in 81% yield.

2.0 mmol scale: A suspension of *N*-(quinolin-8-yl)benzamide (**1a**, 496.0 mg, 2.0 mmol), *N*-Bn aziridine (**2a**, 798.0 mg, 3.0 mmol), $Ni(OAc)_2 \cdot 4H_2O$ (100.0 mg, 0.2 mmol), and diethylene glycol dimethyl ether (diglyme) (10.0 mL) in a sealed microwave vessel was irradiated under microwave reactor conditions at 200 °C for 1 hour under N_2 atmosphere. The resulting mixture was then

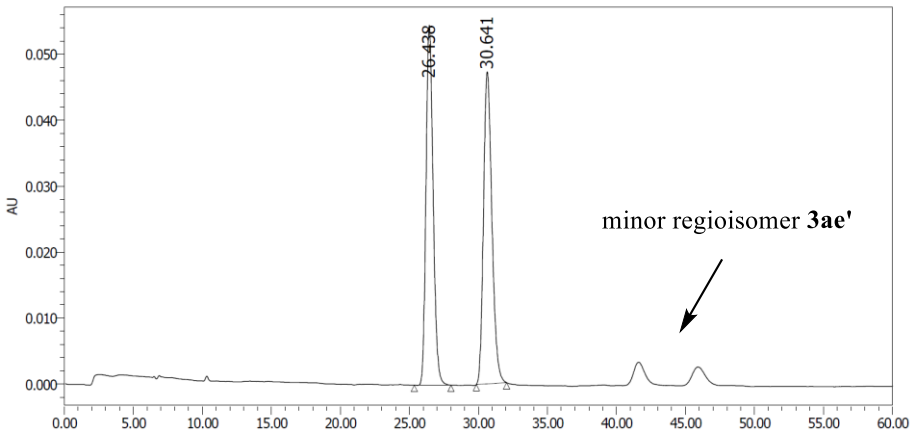
quenched with water and extracted with ethyl acetate. The combined organic layer was dried over sodium sulfate. Concentration in vacuo followed by silica gel column purification with hexane/ethyl acetate (5:1, v/v) gave 2-benzyl-3,4-dihydroisoquinolin-1(2*H*)-one (**3aa**, 346.5 mg, 1.460 mmol) in 73% yield and recovered 8-aminoquinoline (227.5 mg, 1.58 mmol) in 79% yield.

Synthesis of (*S*)-**3af-H**.[17] To a solution of (*S*)-**3af** (31.3 mg, 0.1 mmol) and toluene (0.5 mL) was added triflic acid (0.04 mL, 0.4 mmol). The resulting mixture was stirred for 15 min at 150 °C under microwave irradiation. After cooling to rt, the resulting mixture was then quenched with saturated aqueous $NaHCO_3$ and extracted with ethyl acetate. The combined organic layer was washed with brine and dried over sodium sulfate. Concentration in vacuo followed by silica gel column purification with hexane/ethyl acetate (2:1, v/v) gave (*S*)-4-phenyl-3,4-dihydroisoquinolin-1(2*H*)-one ((*S*)-**3af-H**, 26.2 mg, 0.076 mmol) in 76% yield.

Chiral HPLC Charts

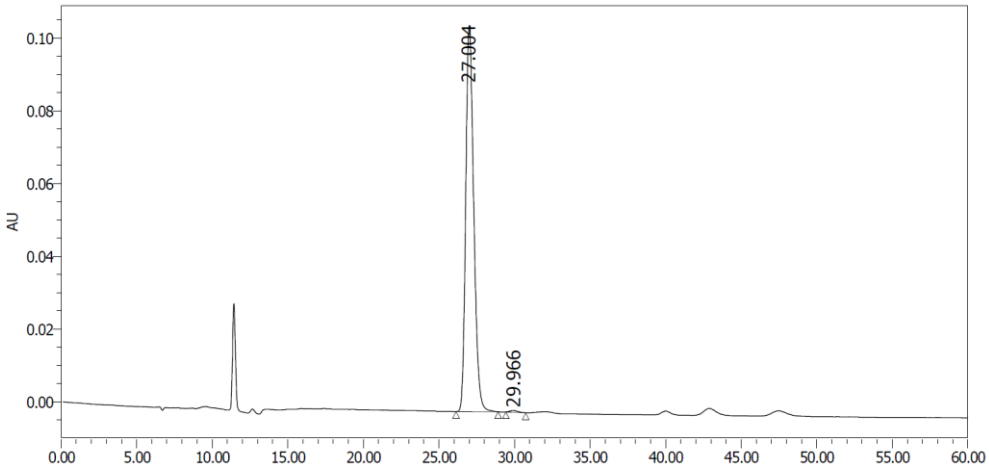
3ae: The enantiomeric ratio was determined by HPLC analysis in comparison with authentic racemic material (CHIRALCEL OD-H column, 95/5 *n*-hexane/2-propanol, 0.5 mL/min, major isomer: t_R = 27.0 min, minor isomer: t_R = 30.0dd min, UV detection at 240 nm, 30 °C).

rac-**3ae**



Peak #	Ret. Time	Area	Area %
1	26.438	1951763	48.93
2	30.641	2036931	51.07

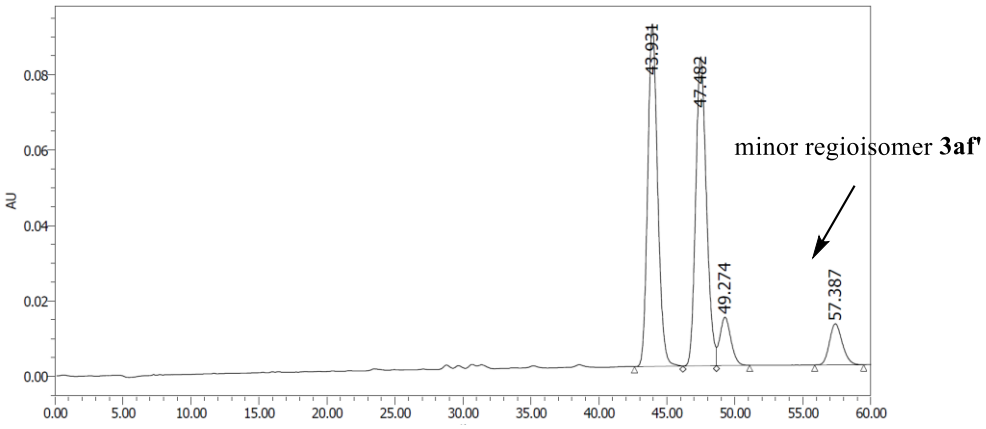
(*S*)-**3ae**



Peak #	Ret. Time	Area	Area %
1	27.004	3909088	99.57
2	29.966	16873	0.43

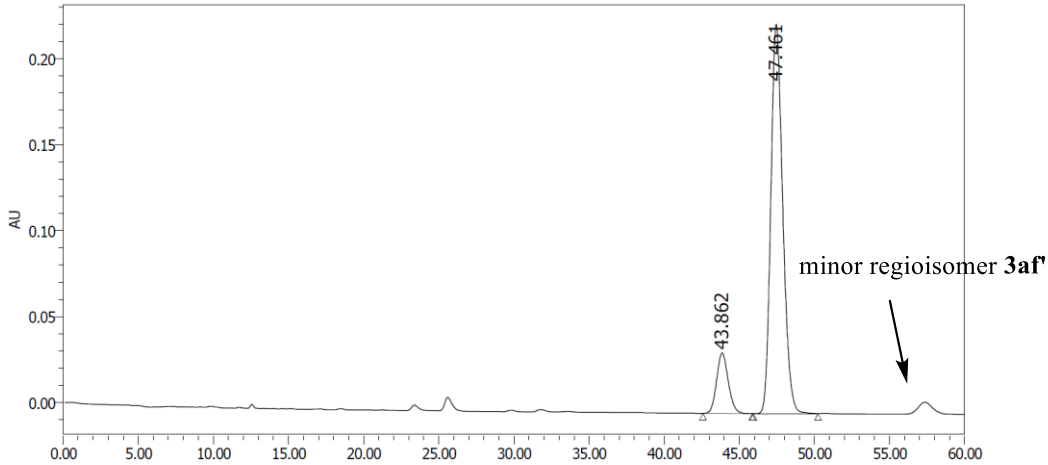
3af: The enantiomeric ratio was determined by HPLC analysis in comparison with authentic racemic material (CHIRALPAK AD-H column, 93/7 *n*-hexane/2-propanol, 0.5 mL/min, major isomer: t_R = 47.5 min, minor isomer: t_R = 43.9dd min, UV detection at 240 nm, 30 °C).

rac-**3af**



Peak #	Ret. Time	Area	Area %
1	43.931	4621907	43.76
2	47.482	4498519	42.59
3	49.274	724411	6.86
4	57.387	717729	6.80

(*S*)-**3af**



Peak #	Ret. Time	Area	Area %
1	43.862	1891585	13.14
2	47.461	12503070	86.86

Characterization Data for Products

2-Benzyl-3,4-dihydroisoquinolin-1(2*H*)-one (3aa): colorless solid (19.2 mg, 81% yield); m.p. 120.7-122.4 °C (from hexane); TLC R_f 0.20 (hexane/EtOAc, 5:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.15 (dd, *J* = 7.5, 1.2 Hz, 1H), 7.42 (td, *J* = 7.4, 1.5 Hz, 1H), 7.38-7.36 (m, 1H), 7.34-7.33 (m, 4H), 7.32-7.27 (m, 1H), 7.16 (dd, *J* = 7.4, 0.7 Hz, 1H), 4.80 (s, 2H), 3.49 (t, *J* = 6.5 Hz, 2H), 2.94 (t, *J* = 6.5 Hz, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 164.6, 138.1, 137.5, 131.7, 129.4, 128.7, 128.5, 128.1, 127.5, 127.1, 126.9, 50.5, 45.4, 28.1. HRMS (APCI) m/z ([M+H]$^+$) Calcd for $C_{16}H_{16}NO$: 238.1227, Found: 238.1230.

16:1 Regiomixture of 2-benzyl-7-methyl-3,4-dihydroisoquinolin-1(2H)-one (3ba) and 2-benzyl-5-methyl-3,4-dihydroisoquinolin-1(2*H*)-one (3ba'): colorless oil (15.8 mg, 63% yield); TLC R_f 0.22 (hexane/EtOAc, 5:1). ^{1}H NMR ($CDCl_3$, 400 MHz) for mixture δ 8.04 (d, *J* = 7.9 Hz, 0.06H, for **3ba'**), 7.97 (d, *J* = 1.1 Hz, 0.94H, for **3ba**), 7.33-7.30 (m, 4H, for **3ba** + **3ba'**), 7.30-7.27 (m, 1H, for **3ba** + **3ba'**), 7.23 (dd, *J* = 7.7, 1.4 Hz, 1H, for **3ba** + **3ba'**), 7.05 (d, *J* = 7.7 Hz, 1H, for **3ba** + **3ba'**), 4.80 (s, 2H, for **3ba** + **3ba'**), 3.48-3.45 (m, 2H, for **3ba** + **3ba'**), 2.91-2.87 (m, 2H, for **3ba** + **3ba'**), 2.39 (s, 2.8 H, for **3ba**), 2.37 (s, 0.2 H, for **3ba'**). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) for

3ba δ 164.8, 137.5, 136.8, 135.1, 132.5, 129.1, 128.8, 128.6, 128.1, 127.4, 126.8, 50.5, 45.5, 27.7, 21.1. HRMS (APCI) m/z ([M+H]$^+$) Calcd for $C_{17}H_{18}NO$: 252.1383, Found: 252.1386.

5:1 Regiomixture of 2-benzyl-7-methoxy-3,4-dihydroisoquinolin-1(2*H*)-one (3ca) and 2-benzyl-5-methoxy-3,4-dihydroisoquinolin-1(2*H*)-one (3ca'): colorless oil (19.8 mg, 74% yield); TLC R_f 0.25 (hexane/EtOAc, 4:1). ^{1}H NMR ($CDCl_3$, 400 MHz) for mixture δ 7.78 (dd, *J* = 7.8, 0.9 Hz, 0.18H, for **3ca'**), 7.69 (d, *J* = 2.8 Hz, 0.82H, for **3ca**), 7.35-7.30 (m, 4.18H, for **3ca** + **3ca'**), 7.29-7.27 (m, 1H, for **3ca** + **3ca'**), 7.07 (d, *J* = 8.3 Hz, 0.82H, for **3ca**), 6.98 (dd, *J* = 8.3, 2.8 Hz, 1H, for **3ca** + **3ca'**), 4.80 (s, 1.64H, for **3ca**), 4.79 (s, 0.36H, for **3ca'**), 3.86 (s, 2.46H, for **3ca**), 3.84 (s, 0.54H, for **3ca'**), 3.48-3.43 (m, 2H, for **3ca** + **3ca'**), 2.92-2.85 (m, 2H, for **3ca** + **3ca'**). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) for mixture δ 164.6, 158.8, 155.4, 137.5, 137.4, 130.5, 130.3, 130.2, 128.7, 128.6, 128.1, 127.5, 127.4, 127.3, 126.9, 120.4, 119.3, 113.1, 111.6, 55.6, 55.5, 50.6, 50.5, 45.7, 45.0, 27.2, 21.3. (All observed signals are shown because of complexity associated with regioisomers.) HRMS (APCI) m/z ([M+H]$^+$) Calcd for $C_{17}H_{18}NO_2$: 268.1333, Found: 268.1348.

2-Benzyl-7-(trifluoromethyl)-3,4-dihydroisoquinolin-1(2*H*)-one (3da): colorless solid (18.9 mg, 62% yield); m.p. 100.6-102.4 °C (from hexane); TLC R_f 0.24 (hexane/EtOAc, 5:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.44 (d, *J* = 0.8 Hz, 1H), 7.66 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.39-7.32 (m, 4H), 7.31-7.27 (m, 2H), 4.81 (s, 2H), 3.52 (t, *J* = 6.5 Hz, 2H), 3.00 (t, *J* = 6.5 Hz, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 163.3, 141.7, 137.0, 130.0, 129.8 (q, *J* = 33.0 Hz), 128.8, 128.2 (q, *J* = 4.2 Hz), 128.1, 127.7, 127.6, 125.7 (q, *J* = 4.2 Hz), 123.9 (q, *J* = 272.2 Hz), 50.6, 45.0, 28.0. ^{19}F{^{1}H} NMR ($CDCl_3$, 376 MHz) δ -62.6. HRMS (APCI) m/z ([M+H]$^+$) Calcd for $C_{17}H_{15}F_3NO$: 306.1101, Found: 306.1108.

6:1 Regiomixture of 2-benzyl-7-chloro-3,4-dihydroisoquinolin-1(2*H*)-one (3ea) and 2-benzyl-5-chloro-3,4-dihydroisoquinolin-1(2*H*)-one (3ea'): colorless oil (20.6 mg, 76% yield); TLC R_f 0.30 (hexane/EtOAc, 5:1). ^{1}H NMR ($CDCl_3$, 400 MHz) for mixture δ 8.15 (dd, *J* = 7.6, 1.2 Hz, 0.14H, for **3ea'**), 8.12 (d, *J* = 2.2 Hz, 0.86H, for **3ea**), 7.44-7.26 (m, 6H, for **3ea** + **3ea'**), 7.16 (dd, *J* = 7.3, 0.7 Hz, 0.14H, for **3ea'**), 7.10 (d, *J* = 8.1 Hz, 0.86H, for **3ea**), 4.80 (s, 0.28H, for **3ea'**), 4.78 (s, 1.72H, for **3ea**), 3.50-3.45 (m, 2H, for **3ea** + **3ea'**), 2.95-2.88 (m, 2H, for **3ea** + **3ea'**). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) for mixture δ 164.6, 163.4, 138.1, 137.5, 137.1, 136.3, 133.1, 131.7, 131.6, 130.9, 129.4, 128.7, 128.6, 128.5, 128.4, 128.1, 127.6, 127.5, 127.1, 126.9, 50.6, 50.5, 45.4, 45.2, 28.1, 27.5. (All observed signals are shown because of complexity associated with regioisomers.) HRMS (APCI) m/z ([M+H]$^+$) Calcd for $C_{16}H_{15}ClNO$: 272.0837, Found: 272.0814.

2-Benzyl-6-(*tert*-butyl)-3,4-dihydroisoquinolin-1(2*H*)-one (3fa): colorless solid (24.9 mg, 85% yield); m.p. 115.6-116.8 °C (from hexane); TLC R_f 0.20 (hexane/EtOAc, 5:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.08 (d, *J* = 8.2 Hz, 1H), 7.39 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.33-7.30 (m, 4H), 7.28-7.26 (m, 1H), 7.16 (s, 1H), 4.80 (s, 2H), 3.48 (t, *J* = 6.5 Hz, 2H), 2.93 (t, *J* = 6.5 Hz, 2H), 1.33 (s, 9H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 164.7, 155.3, 137.8, 137.6, 128.6, 128.3, 128.1, 127.4, 126.8, 124.2, 123.9, 50.4, 45.5, 35.0, 31.2, 28.4. HRMS (APCI) m/z ([M+H]$^+$) Calcd for $C_{20}H_{24}NO$: 294.1853, Found: 294.1870.

2-Benzyl-6-methoxy-3,4-dihydroisoquinolin-1(2*H*)-one (3ga): colorless solid (23.8 mg, 89% yield); m.p. 92.7-94.4 °C (from hexane); TLC R_f 0.22 (hexane/EtOAc, 5:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.09 (d, *J* = 8.6 Hz, 1H), 7.33-7.30 (m, 4H), 7.29-7.24 (m, 1H), 6.86 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.65 (d, *J* = 2.5 Hz, 1H), 4.78 (s, 2H), 3.84 (s, 3H), 3.46 (t, *J* = 6.5 Hz, 2H), 2.90 (t, *J* = 6.5 Hz, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 164.6, 162.3, 140.2, 137.7, 130.6, 128.6, 128.0, 127.4, 122.3, 112.5, 112.0, 55.4, 50.3, 45.4, 28.4. HRMS (APCI) m/z ([M+H]$^+$) Calcd for $C_{17}H_{18}NO_2$: 268.1333, Found: 268.1335.

2-Benzyl-6-(trifluoromethyl)-3,4-dihydroisoquinolin-1(2*H*)-one (3ha): colorless solid (16.5 mg, 54% yield); m.p. 104.1-105.9 °C (from hexane); TLC R_f 0.27 (hexane/EtOAc, 5:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.26 (d, *J* = 8.1 Hz, 1H), 7.62 (d, *J* = 8.1 Hz, 1H), 7.44 (s, 1H), 7.37-7.28 (m, 5H), 4.81 (s, 2H), 3.52 (t, *J* = 6.5 Hz, 2H), 3.00 (t, *J* = 6.5 Hz, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 163.3, 138.7, 137.0, 133.3 (q, *J* = 32.2 Hz), 132.4, 129.1, 128.8, 128.1, 127.7, 124.0 (q, *J* = 4.2 Hz), 123.9 (q, *J* = 4.2 Hz), 123.8 (q, *J* = 273.1 Hz), 50.6, 45.1, 28.0. ^{19}F{^{1}H} NMR ($CDCl_3$, 376 MHz) δ -62.9. HRMS (APCI) m/z ([M+H]$^+$) Calcd for $C_{17}H_{15}F_3NO$: 306.1101, Found: 306.1073.

2-Benzyl-6-chloro-3,4-dihydroisoquinolin-1(2*H*)-one (3ia): colorless solid (19.8 mg, 73% yield); m.p. 95.7-97.2 °C (from hexane); TLC R_f 0.33 (hexane/EtOAc, 5:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.08 (d, *J* = 8.3 Hz, 1H), 7.38-7.28 (m, 6H), 7.16-7.15 (m, 1H), 4.78 (s, 2H), 3.48 (t, *J* = 6.5 Hz, 2H), 2.91 (t, *J* = 6.5 Hz, 2H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 163.8, 139.7, 137.8, 137.2, 130.1, 128.7, 128.1, 127.9, 127.6, 127.4, 126.9, 50.5, 45.2, 27.9. HRMS (APCI) m/z ([M+H]$^+$) Calcd for $C_{16}H_{15}ClNO$: 272.0837, Found: 272.0811.

2-Benzyl-6-bromo-3,4-dihydroisoquinolin-1(2*H*)-one (3ja): colorless oil (12.0 mg, 38% yield); TLC R_f 0.30 (hexane/EtOAc, 5:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.00 (d, *J* = 8.3 Hz, 1H), 7.49 (dd,

J = 8.3, 2.0 Hz, 1H), 7.34-7.28 (m, 6H), 4.78 (s, 2H), 3.48 (t, *J* = 6.5 Hz, 2H), 2.91 (t, *J* = 6.5 Hz, 2H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 163.9, 139.9, 137.1, 130.4, 130.3, 129.9, 128.7, 128.3, 128.1, 127.6, 126.4, 50.5, 45.2, 27.8. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{16}H_{15}BrNO$: 316.0332, Found: 316.0330.

2-Benzyl-8-methyl-3,4-dihydroisoquinolin-1(2*H*)-one (3ka): colorless solid (12.1 mg, 48% yield); m.p. 90.3-91.4 °C (from hexane); TLC R_f 0.35 (hexane/EtOAc, 5:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.34-7.33 (m, 4H), 7.29-7.24 (m, 2H), 7.15 (d, *J* = 7.7 Hz, 1H), 6.99 (d, *J* = 7.7 Hz, 1H), 4.78 (s, 2H), 3.43 (t, *J* = 6.5 Hz, 2H), 2.86 (t, *J* = 6.5 Hz, 2H), 2.75 (s, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 165.2, 141.0, 139.5, 137.9, 131.0, 130.7, 128.6, 128.0, 127.9, 127.4, 124.9, 50.2, 45.2, 29.6, 22.6. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{17}H_{18}NO$: 252.1383, Found: 252.1367.

2-Benzyl-8-fluoro-3,4-dihydroisoquinolin-1(2*H*)-one (3la): colorless solid (8.1 mg, 32% yield); m.p. 93.7-95.4 °C (from hexane); TLC R_f 0.30 (hexane/EtOAc, 5:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39-7.31 (m, 5H), 7.30-7.27 (m, 1H), 7.04 (dd, *J* = 10.9, 2.5 Hz, 1H), 6.94 (d, *J* = 7.5 Hz, 1H), 4.78 (s, 2H), 3.46 (t, *J* = 6.5 Hz, 2H), 2.90 (t, *J* = 6.5 Hz, 2H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 162.4 (d, *J* = 261.7 Hz), 161.6 (d, *J* = 3.6 Hz), 141.2, 137.4, 132.8 (d, *J* = 10.0 Hz), 128.7, 128.2, 127.5, 122.6 (d, *J* = 4.0 Hz), 117.7 (d, *J* = 5.5 Hz), 115.9 (d, *J* = 22.6 Hz), 50.0, 45.0, 29.0 (d, *J* = 2.1 Hz). $^{19}F\{^{1}H\}$ NMR ($CDCl_3$, 376 MHz) δ -111.6. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{16}H_{15}FNO$: 256.1132, Found: 256.1131.

2-Benzyl-3,4-dihydrobenzo[*g*]isoquinolin-1(2*H*)-one (3ma): colorless solid (23.9 mg, 83% yield); m.p. 129.1-130.5 °C (from hexane); TLC R_f 0.22 (hexane/EtOAc, 4:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.72 (s, 1H), 7.97 (dd, *J* = 8.1, 0.5 Hz, 1H), 7.78 (d, *J* = 8.1 Hz, 1H), 7.58 (s, 1H), 7.56-7.46 (m, 2H), 7.39-7.27 (m, 5H), 4.87 (s, 2H), 3.54 (t, *J* = 6.5 Hz, 2H), 3.10 (t, *J* = 6.5 Hz, 2H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 164.7, 137.4, 134.9, 134.3, 132.2, 129.6, 129.4, 128.7, 128.1, 127.9, 127.5, 127.4, 127.1, 126.0, 125.1, 50.7, 45.7, 28.6. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{20}H_{18}NO$: 288.1383, Found: 288.1365. The X-ray quality crystal was grown from DCM/Hexane.

2-Benzyl-3,4-dihydrobenzo[*h*]isoquinolin-1(2*H*)-one (3na): colorless solid (15.5 mg, 54% yield); m.p. 106.3-107.7 °C (from hexane); TLC R_f 0.25 (hexane/EtOAc, 4:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.47 (d, *J* = 8.8 Hz, 1H), 7.89 (d, *J* = 8.3, 1H), 7.82 (dd, *J* = 8.1, 0.5 Hz, 1H), 7.63-7.59 (m, 1H), 7.51-7.47 (m, 1H), 7.41-7.39 (m, 2H), 7.37-7.33 (m, 2H), 7.31-7.24 (m, 2H), 4.89 (s, 2H), 3.53 (t, *J*

= 6.5 Hz, 2H), 3.02 (t, *J* = 6.5 Hz, 2H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 165.1, 139.0, 138.0, 133.3, 132.5, 131.9, 128.7, 128.2, 128.0, 127.8, 127.4, 127.0, 125.7, 125.1, 124.4, 50.4, 44.8, 30.0. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{20}H_{18}NO$: 288.1383, Found: 288.1364.

9:1 Regiomixture of 2-benzyl-3-ethyl-3,4-dihydroisoquinolin-1(2*H*)-one (3ab) and 2-benzyl-4-ethyl-3,4-dihydroisoquinolin-1(2*H*)-one (3ab'): colorless oil (18.6 mg, 70% yield); TLC R_f 0.20 (hexane/EtOAc, 4:1). ^{1}H NMR ($CDCl_3$, 400 MHz) for mixture δ 8.15 (d, *J* = 7.6 Hz, 0.1H, for **3ab'**), 8.10 (d, *J* = 7.6 Hz, 0.9H, for **3ab**), 7.44-7.28 (m, 7H, for **3ab** + **3ab'**), 7.14 (d, *J* = 7.6 Hz, 1H, for **3ab** + **3ab'**), 5.64 (d, *J* = 15.0 Hz, 0.9H, for **3ab**), 5.01 (d, *J* = 14.4 Hz, 0.1H, for **3ab'**), 4.53 (d, *J* = 14.4 Hz, 0.1H, for **3ab'**), 3.96 (d, *J* = 15.0 Hz, 0.9H, for **3ab**), 3.65 (dd, *J* = 12.3, 4.3 Hz, 0.1H, for **3ab'**), 3.45-3.39 (m, 0.9H, for **3ab**), 3.29 (dd, *J* = 12.3, 3.0 Hz, 0.1H, for **3ab'**), 3.15 (dd, *J* = 15.9, 5.9 Hz, 0.9H, for **3ab**), 2.78 (d, *J* = 15.9 Hz, 0.9H, for **3ab**), 2.66-2.61 (m, 0.1H, for **3ab'**), 1.67-1.59 (m, 1H, for **3ab** + **3ab'**), 1.52-1.40 (m, 1H, for **3ab** + **3ab'**), 0.84 (t, *J* = 7.5 Hz, 2.7H, for **3ab**), 0.71 (t, *J* = 7.5 Hz, 0.3H, for **3ab'**). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) for mixture δ 163.9, 142.3, 138.2, 136.2, 131.8, 131.6, 129.3, 128.7, 128.6, 128.1, 127.9, 127.8, 127.5, 127.4, 127.4, 127.0, 126.8, 56.4, 50.5, 48.8, 48.5, 39.3, 31.1, 26.7, 24.3, 11.5, 11.1. (All observed signals are shown because of complexity associated with regioisomers.) HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{18}H_{20}NO$: 266.1540, Found: 266.1521.

2-Benzyl-3-(phenoxymethyl)-3,4-dihydroisoquinolin-1(2*H*)-one (3ac): colorless oil (26.7 mg, 78% yield); TLC R_f 0.22 (hexane/EtOAc, 3:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.13 (dd, *J* = 7.6 1.3 Hz, 1H), 7.42 (td, *J* = 7.4 1.5 Hz, 1H), 7.39-7.31 (m, 5H), 7.31-7.26 (m, 1H), 7.25-7.20 (m, 2H), 7.15 (d, *J* = 7.4 Hz, 1H), 6.93 (tt, *J* = 7.4, 1.0 Hz, 1H), 6.75-6.73 (m, 2H), 5.62 (d, *J* = 14.9 Hz, 1H), 4.22 (d, *J* = 14.9 Hz, 1H), 4.01-3.92 (m, 2H), 3.82 (dd, *J* = 8.9, 8.3 Hz, 1H), 3.24 (dd, *J* = 16.1, 5.8 Hz, 1H), 3.04 (dd, *J* = 16.1, 1.4 Hz, 1H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 163.9, 158.1, 137.9, 135.7, 132.2, 129.5, 128.9, 128.8, 128.4, 128.1, 128.0, 127.6, 127.3, 121.3, 114.4, 66.7, 53.8, 49.4, 29.8. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{23}H_{22}NO_2$: 344.1646, Found: 344.1667.

9:1 Regiomixture of 2-benzyl-3-(butoxymethyl)-3,4-dihydroisoquinolin-1(2*H*)-one (3ad) and 2-benzyl-4-(butoxymethyl)-3,4-dihydroisoquinolin-1(2*H*)-one (3ad'): colorless oil (19.7 mg, 61% yield); TLC R_f 0.25 (hexane/EtOAc, 3:1). ^{1}H NMR ($CDCl_3$, 400 MHz) for mixture δ 8.15 (d, *J* = 7.6, 1.4 Hz, 0.1H, for **3ad'**), 8.10 (dd, *J* = 7.6, 1.2 Hz, 0.9H, for **3ad**), 7.44-7.40 (m, 1H, for **3ad** + **3ad'**), 7.37-7.25 (m, 6H, for **3ad** + **3ad'**), 7.20 (d, *J* = 6.8 Hz, 0.1H, for **3ad'**), 7.15 (d, *J* = 7.4 Hz, 0.9H, for

3ad), 5.57 (d, *J* = 14.9 Hz, 0.9H, for **3ad**), 4.98 (d, *J* = 14.4 Hz, 0.1H, for **3ad'**), 4.52 (d, *J* = 14.4 Hz, 0.1H, for **3ad'**), 4.14 (d, *J* = 14.9 Hz, 0.9H, for **3ad**), 3.77-3.72 (m, 0.9H, for **3ad**), 3.64-3.62 (m, 0.1H, for **3ad'**), 3.40 (dd, *J* = 9.4, 5.6 Hz, 1H, for **3ad** + **3ad'**), 3.35-3.22 (m, 3H, for **3ad** + **3ad'**), 3.14 (dd, *J* = 15.9, 5.9 Hz, 0.9H, for **3ad**), 3.08-3.06 (m, 0.1H, for **3ad'**), 3.05-2.99 (m, 0.1H, for **3ad'**), 2.91 (dd, *J* = 15.9, 1.5 Hz, 0.9H, for **3ad**), 1.49-1.42 (m, 2H, for **3ad** + **3ad'**), 1.35-1.25 (m, 2H, for **3ad** + **3ad'**), 0.90-0.86 (m, 3H, for **3ad** + **3ad'**). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) for **3ad** δ 163.9, 138.1, 136.1, 131.9, 129.0, 128.6, 128.2, 128.1, 127.8, 127.4, 127.0, 71.2, 70.1, 54.2, 49.4, 31.6, 29.9, 19.3, 13.9. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{21}H_{26}NO_2$: 324.1959, Found: 324.1957.

13:1 Regiomixture of (*S*)-2,3-dibenzyl-3,4-dihydroisoquinolin-1(2*H*)-one (3ae) and 2,4-dibenzyl-3,4-dihydroisoquinolin-1(2*H*)-one (3ae'): colorless oil (19.3 mg, 59% yield); TLC R_f 0.28 (hexane/EtOAc, 3:1). ^{1}H NMR ($CDCl_3$, 400 MHz) for mixture δ 8.22-8.17 (m, 1H, for **3ae + 3ae'**), 7.50-7.46 (m, 1H, for **3ae + 3ae'**), 7.43-7.18 (m, 9.07H, for **3ae + 3ae'**), 7.15 (d, *J* = 7.4 Hz, 0.93H, for **3ae**), 7.05-7.01 (m, 1.86H, for **3ae**), 6.77-6.75 (m, 0.14 H, for **3ae'**), 5.55 (d, *J* = 14.9 Hz, 0.93H, for **3ae**), 4.95 (d, *J* = 14.4 Hz, 0.07H, for **3ae'**), 4.57 (d, *J* = 14.4 Hz, 0.07H, for **3ae'**), 3.83 (d, *J* = 14.9 Hz, 0.93H, for **3ae**), 3.74-3.68 (m, 0.93H, for **3ae**), 3.58 (dd, *J* = 12.7, 4.5 Hz, 0.07H, for **3ae'**), 3.20 (dd, *J* = 12.7, 2.4 Hz, 0.07H, for **3ae'**), 3.04 (dd, *J* = 15.9, 5.9 Hz, 0.93H, for **3ae**), 2.88 (dd, *J* = 13.2, 5.3 Hz, 0.93H, for **3ae**), 2.80 (dd, *J* = 13.6, 5.7 Hz, 0.07H, for **3ae'**), 2.68-2.58 (m, 0.14H, for **3ae** + **3ae'**), 2.64 (dd, *J* = 15.9, 1.4 Hz, 0.93H, for **3ae**), 2.60 (dd, *J* = 13.2, 9.6 Hz, 0.93H, for **3ae**). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) for **3ae** δ 163.8, 138.0, 137.9, 136.1, 132.1, 129.3, 129.2, 128.8, 128.7, 128.4, 128.1, 128.0, 127.5, 127.2, 126.7, 56.6, 48.9, 37.7, 31.1. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{23}H_{22}NO$: 328.1696, Found: 328.1672.

10:1 Regiomixture of (*S*)-2-benzyl-4-phenyl-3,4-dihydroisoquinolin-1(2*H*)-one (3af) and 2-benzyl-3-phenyl-3,4-dihydroisoquinolin-1(2*H*)-one (3af'): colorless oil (18.2 mg, 58% yield); TLC R_f 0.25 (hexane/EtOAc, 4:1). ^{1}H NMR ($CDCl_3$, 400 MHz) for mixture δ 8.27-8.20 (m, 1H, for **3af + 3af'**), 7.42-7.40 (m, 2H, for **3af + 3af'**), 7.36-7.24 (m, 4H, for **3af + 3af'**), 7.22-7.19 (m, 3H, for **3af + 3af'**), 7.16-7.14 (m, 1H, for **3af + 3af'**), 7.06-7.04 (m, 2H, for **3af + 3af'**), 6.95-6.93 (m, 1H, for **3af + 3af'**), 5.81 (d, *J* = 15.0 Hz, 0.1H, for **3af'**), 4.76 (d, *J* = 14.7 Hz, 0.9H, for **3af**), 4.70 (d, *J* = 14.7 Hz, 0.9H, for **3af**), 4.26 (dd, *J* = 7.6, 5.2 Hz, 0.9H, for **3af**), 3.72 (dd, *J* = 12.5, 5.2 Hz, 0.9H, for **3af**), 3.66-3.62 (m, 0.1H, for **3af'**), 3.61 (dd, *J* = 12.5, 7.6 Hz, 0.9H, for **3af**), 3.58-3.52 (m, 0.2H, for **3af'**), 2.97 (dd, *J* = 15.9, 3.2 Hz, 0.1H, for **3af'**). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) for **3af** δ

164.5, 140.6, 140.4, 136.8, 132.1, 129.5, 128.7, 128.6, 128.5, 128.4, 128.1, 127.5, 127.4, 127.3, 127.2, 52.4, 50.5, 43.9. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{22}H_{20}NO$: 314.1540, Found: 314.1558.

(*S*)-4-Phenyl-3,4-dihydroisoquinolin-1(2*H*)-one (3af-H): colorless solid (26.2 mg, 76% yield); m.p. 133.5-135.1 ^oC (from hexane); TLC R_f 0.23 (hexane/EtOAc, 2:1); $[\alpha]^{20}_D$ = -30.8 (*c* = 0.15, $CHCl_3$). ^1H NMR ($CDCl_3$, 400 MHz) δ 8.16-8.14 (m, 1H), 7.44-7.37 (m, 2H), 7.36-7.27 (m, 3H), 7.19-7.17 (m, 2H), 6.98-6.96 (m, 1H), 6.66 (bs, 1H), 4.32 (dd, *J* = 7.7, 5.4 Hz, 1H), 3.81 (ddd, *J* = 12.2, 5.3, 2.9 Hz, 1H), 3.71 (ddd, *J* = 12.2, 7.7, 2.9 Hz, 1H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 166.2, 141.4, 140.6, 132.5, 129.0, 128.8, 128.6, 128.1, 127.7, 127.4, 127.3, 47.2, 44.3. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{15}H_{14}NO$: 224.1070, Found: 224.1075.

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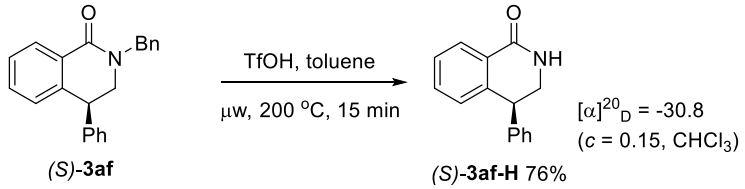

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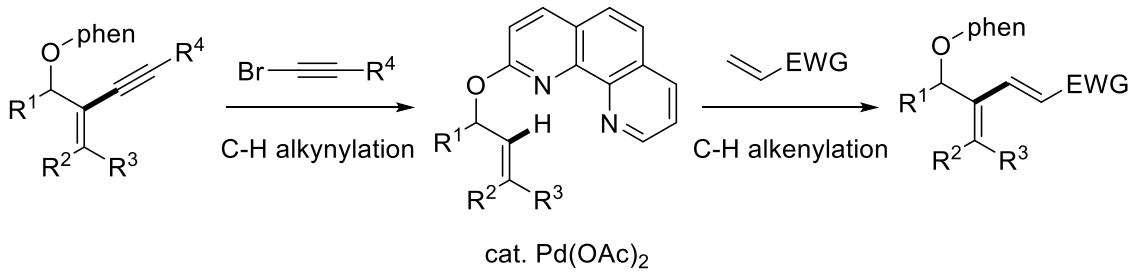
Chapter 5

Pd-Catalyzed Regioselective C-H Alkenylation and Alkynylation of Allylic Alcohols with the Assistance of Phenanthroline Bidentate Auxiliary

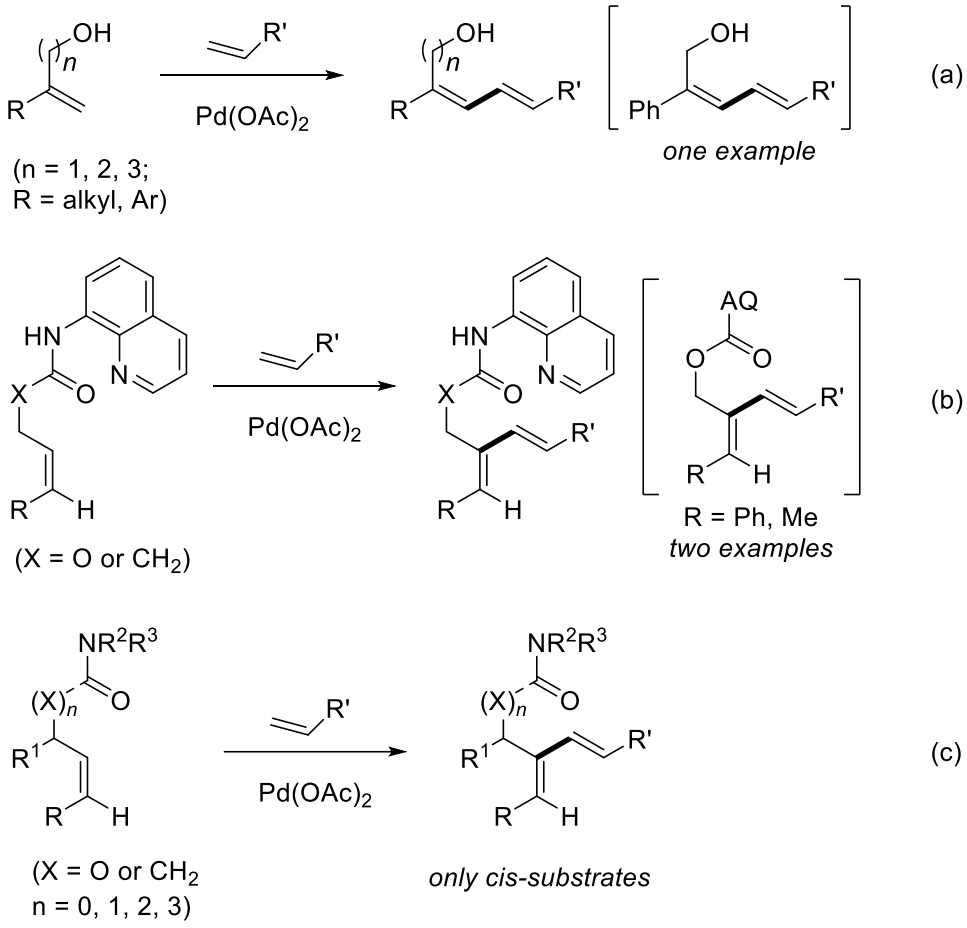
A Pd-catalyzed regioselective C–H alkenylation of allylic alcohols with electron-deficient alkenes has been developed. The key to success is the introduction of bidentately coordinating phenanthroline directing group, which enables the otherwise challenging and regioselective C–H activation at the proximal alkenyl C–H bonds over the conceivably competitive allylic C–O bond activation. The same Pd/phenanthroline system is efficient for the C–H alkynylation of allylic alcohols with alkynyl bromides.



Introduction

Allylic alcohols are important building blocks in organic synthesis and also frequently used as the site of fragment coupling in the synthesis of complex natural products.[1] Accordingly, synthetic chemists have developed numerous methodologies for the preparation of allylic alcohols, particularly multisubstituted derivatives, such as reductive coupling reactions of alkynes with carbonyls[2] and Cr/Ni-mediated Nozaki-Hiyama-Kishi-Takai-type reactions.[3] On the other hand, a decoration of relatively simple allylic alcohols via metal-mediated alkenyl C–H functionalizations[4] is considered to be a good alternative. In particular, the Pd-catalyzed regioselective C–H alkenylation is an attractive strategy to deliver the conjugated dienyl alcohols. However, due to their potential lability and capability of formation of π-allyl metal species *via* allylic C–O bond activation,[5] there are a few successful examples in the literature. Xu and Loh reported the Pd-catalyzed OH-directed C–H alkenylation of alkenyl alcohols, but only one allylic alcohol was employed and limited to the 1,1-disubstituted Ph-conjugated substrate (Scheme 1a).[6] Engle also developed the 8-aminoquinoline-directed,[7] Pd-catalyzed regioselective C–H alkenylation but with just two examples of allylic alcohols (Scheme 1b).[8] Very recently, Zhang and Zhong disclosed the more general C–H alkenylation strategy by using the carbamate directing group (Scheme 1c).[9] However, all reported procedures are still restricted in scope: only terminal or *cis*-allylic alcohols could be employed.

Scheme 1. Pd-catalyzed regioselective C–H alkenylation of allylic alcohol derivatives



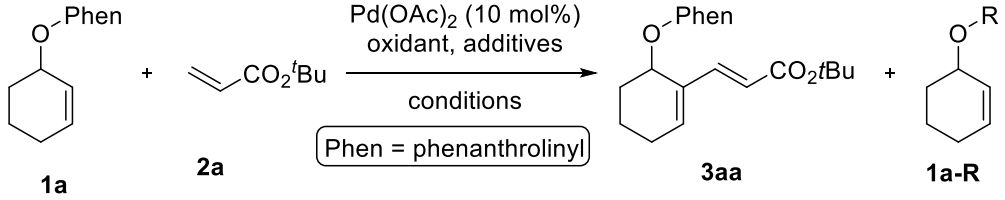
Recently, Miura group originally developed a phenanthroline-based directing group and successfully achieved the copper-promoted regioselective C–H amination, sulfenylation, and selenation of phenols. Given the continuing interest in the chemistry of bidentate auxiliary-directed C–H functionalizations, the author herein reports a phenanthroline-directed, Pd-catalyzed regioselective C–H alkenylation of allylic alcohols: a bidentate chelating nature of phenanthroline auxiliary enables the C–H activation selectively at the proximal position over the conceivable allylic C–O activation. The Pd catalysis accommodates *cis*-, *trans*-, and even more challenging

trisubstituted substrates. The conjugated dienyl alcohol derivatives obtained are also readily converted to the dienyl amines and ethers as well as free OH alcohols. The author also describes a related C–H alkynylation of allylic alcohols, which is unprecedented in the literature.

Results and discussion

The author selected the 2-cyclohexenol derivative **1a** and *tert*-butyl acrylate (**2a**; 2.0 equiv) as model substrates and started optimization studies (Table 1). After extensive screening of various reaction parameters, we pleasingly found that the reaction proceeded in the presence of $Pd(OAc)_2$ catalyst, AgTFA oxidant (2.0 equiv), and 2-phenylisobutyric acid/benzoquinone (BQ) additives (100 and 10 mol %, respectively) in heated MeCN (50 ˚C) to form the corresponding dienyl alcohol **3aa** in 76% ^{1}H NMR yield as the single regio- and stereoisomer (entry 29). The acid and BQ additives were not indispensable but improved the reaction efficiency.

Table 1. Optimization studies for alkenylation[a]



entry	oxidant (equiv)	additives (mol %)	conditions	yield (%)[b]	
				3aa	**1a-R**
1	MnO_2 (3.0)	PivOH (100), BQ (10)	MeCN, 80 ˚C, air	11	n.d.
2	MnO_2 (3.0)	PivOH (100), BQ (10)	MeCN, 80 ˚C, N_2	10	n.d.
3	***AgOAc (2.0)***	***PivOH (100), BQ (10)***	***MeCN, 80 ˚C, air***	***23***	***n.d.***

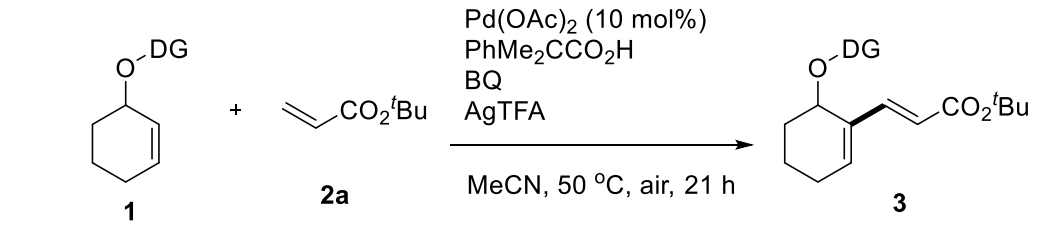
4	Ag_2CO_3 (1.0)	PivOH (100), BQ (10)	MeCN, 80 ˚C, air	14	n.d.
5	Ag_2O (1.0)	PivOH (100), BQ (10)	MeCN, 80 ˚C, air	0	n.d.
6	$AgNO_3$ (2.0)	PivOH (100), BQ (10)	MeCN, 80 ˚C, air	0	n.d.
7	AgOTf (2.0)	PivOH (100), BQ (10)	MeCN, 80 ˚C, air	0	n.d.
8	$AgSbF_6$ (2.0)	PivOH (100), BQ (10)	MeCN, 80 ˚C, air	0	n.d.
9	$Cu(OAc)_2$ (1.1)	PivOH (100), BQ (10)	MeCN, 80 ˚C, air	0	n.d.
10	AgOAc (2.0)	PivOH (100)	MeCN, 80 ˚C, air	12	n.d.
11	none	PivOH (100)	MeCN, 80 ˚C, air	trace	n.d.
12	***AgOAc (2.0)***	***PivOH (100), BQ (10)***	***MeCN, 50 ˚C, air***	***35***	***28***
13	***AgOAc (2.0)***	***2-NpCO_2H (100), BQ (10)***	***MeCN, 50 ˚C, air***	***31***	***36***
14	AgOAc (2.0)	HFIP (100), BQ (10)	MeCN, 50 ˚C, air	0	n.d.
15	AgOAc (2.0)	BQ (10)	MeCN, 50 ˚C, air	8	n.d.
16	AgOAc (2.0)	2-NpCO_2H (100), BQ (10)	HFIP, 50 ˚C, air	13	n.d.
17	AgOAc (2.0)	2-NpCO_2H (100), BQ (10)	dioxane, 50 ˚C, air	8	n.d.
18	AgOAc (2.0)	2-NpCO_2H (100), BQ (10)	hexane, 50 ˚C, air	0	n.d.
19	AgOAc (2.0)	2-NpCO_2H (100), BQ (10)	toluene, 50 ˚C, air	8	n.d.
20	AgOAc (2.0)	2-NpCO_2H (100), BQ (10)	THF, 50 ˚C, air	0	n.d.
21	AgOAc (2.0)	2-NpCO_2H (100), BQ (10)	DCE, 50 ˚C, air	12	n.d.
22	AgOAc (2.0)	2-NpCO_2H (100), BQ (10)	DMF, 50 ˚C, air	19	n.d.
23	AgOAc (2.0)	2-NpCO_2H (100), BQ (10)	DMSO, 50 ˚C, air	27	n.d.
24	AgOAc (2.0)	2-NpCO_2H (100), BQ (10)	*t*BuOH, 50 ˚C, air	11	n.d.
25	AgOAc (2.0)	2-NpCO_2H (100), BQ (10)	DCM, 50 ˚C, air	11	n.d.
26	AgOAc (2.0)	2-NpCO_2H (100), BQ (10)	NMP, 50 ˚C, air	8	n.d.
27	AgTFA (2.0)	2-NpCO_2H (100), BQ (10)	MeCN, 50 ˚C, air	50	21
28	AgTFA (2.0)	PivOH (100), BQ (10)	MeCN, 50 ˚C, air	69	n.d.
29	***AgTFA (2.0)***	***PhMe_2CCO_2H (100), BQ (10)***	***MeCN, 50 ˚C, air***	***76***	***10***
30	AgTFA (2.0)	*i*PrCO_2H (100), BQ (10)	MeCN, 50 ˚C, air	68	8
31	AgTFA (2.0)	1-AdCO_2H (100), BQ (10)	MeCN, 50 ˚C, air	59	5
32	AgTFA (2.0)	Ph_2MeCO_2H (100), BQ (10)	MeCN, 50 ˚C, air	49	n.d.
33	AgTFA (2.0)	MesCO_2H (100), BQ (10)	MeCN, 50 ˚C, air	52	n.d.
34	AgTFA (2.0)	9-Anthroic acid (100), BQ (10)	MeCN, 50 ˚C, air	59	n.d.
35	AgTFA (2.0)	Ac-Gly-OH (100), BQ (10)	MeCN, 50 ˚C, air	54	n.d.

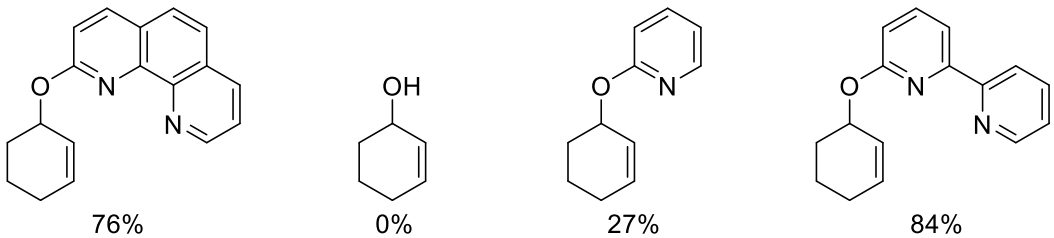
36	AgTFA (2.0)	$PhMe_2CCO_2H$ (100), BQ (10)	MeCN, 50 °C, O_2	20	n.d.
37	AgTFA (2.0)	$PhMe_2CCO_2H$ (200), BQ (10)	MeCN, 50 °C, air	54	n.d.
38	AgTFA (2.0)	$PhMe_2CCO_2H$ (50), BQ (10)	MeCN, 50 °C, air	63	n.d.
39	AgTFA (2.0)	$PhMe_2CCO_2H$ (25), BQ (10)	MeCN, 50 °C, air	60	n.d.
40	***AgTFA (2.0)***	***$PhMe_2CCO_2H$ (25), BQ (20)***	***MeCN, 50 °C, air***	***80 (78)***	***6***

[a] Reaction conditions: $Pd(OAc)_2$ (0.010 mmol), **1a** (0.10 mmol), **2a** (0.20 mmol), oxidant, additives, solvent (1.0 mL), 16-21 h. [b] Determined by ^1H NMR using CH_2Br_2 as the internal standard. Isolated yields are in parentheses. n.d. = not determined.

On the other hand, the choice of directing group was critical (Scheme 1): the free alcohol (**1a-OH**) and monodentate pyridine-directed substrate (**1a-Py**) resulted in no and much less formation of alkenylated products, respectively. Only a similarly bidentately coordinating **1a-bpy** showed a comparable reactivity. However, given the more ready availability of phenanthroline-based directing group (easily prepared on a decagram scale from commercially available simple phenanthroline),[10],[11] subsequent studies were performed with **1a**.

Scheme 1. Effects of directing groups in Pd-catalyzed regioselective C–H alkenylation of cyclohexenols 1 with 2a[a]





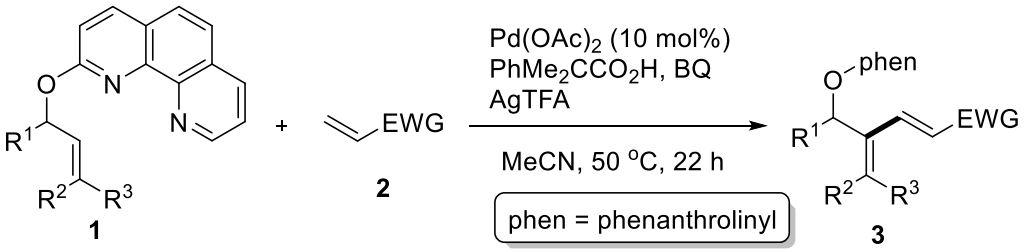
[a] Conditions: **1** (0.10 mmol), **2a** (0.20 mmol), $Pd(OAc)_2$ (0.010 mmol), $PhMe_2CCO_2H$ (0.10 mmol), BQ (0.010 mmol), AgTFA (0.20 mmol), MeCN (1.0 mL), 50 ˚C, 21 h.

Additional fine tunings finally revealed that the desired **3aa** was isolated in 78% yield with 10 mol % $Pd(OAc)_2$, 25 mol % acid, and 20 mol % BQ (entry 40, Table 1). Under the optimal conditions, the generality of reaction was investigated (Scheme 2). The α,β-unsaturated esters were good coupling partners toward **1a**, and primary (**2b**-**e**) and secondary alkyl (**2f**) acrylates provided the corresponding conjugated 1,3-dienes **3ab**-**af** in good to high yields. The somewhat labile phenyl and ethylene glycol esters **2g** and **2h** also underwent the reaction smoothly (**3ag** and **3ah**). Additionally, the unsaturated ketone, nitrile, and sulfone were amenable to the reaction, giving the functionalized dienols **3ai**-**ak** in 68-81% yields.

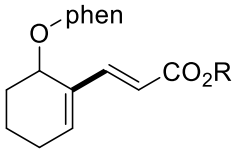
The salient feature of Pd catalysis with the phenanthroline bidentate auxiliary is that the scope of allylic alcohols was broader than that of reported procedures.[6],[8],[9] The reaction was compatible with the 4,4-dimethylcyclohexenol **1b** as well as larger seven-membered and smaller five-membered allylic alcohols **1c** and **1d** (**3ba**-**da**). The structure of **3ba** was unambiguously confirmed by X-ray crystallography (CCDC 1990132). The linear *cis*-allylic alcohols **2e**-**g** also afforded the C–H alkenylated products **3ea**-**ga** albeit with some erosion of stereochemistry of allyl moiety.[12] It is noteworthy that the more sterically demanding *trans*-allylic alcohols also reacted with **1a** to furnish **3fa** and **3ga** in favor of *trans* geometry. Particularly notable is the successful transformation of the sterically hindered trisubstituted substrates: the prenyl alcohol **2h** was converted to the multisubstituted 1,3-diene **3ha** in a synthetically useful

yield. The cyclic substructure on the alkene terminus was also accommodated to form the cyclohexylidene- and cyclopentylidene-containing systems **3ia** and **3ja**. Moreover, the *O*- and *N*-heterocycles were also tolerated under reaction conditions: tetrahydropyran (**3ka**), piperidine (**3la** and **3ma**), and bicyclic tropinone derivatives (**3na**) were obtained in good yields. The reaction could be set up without any special precautions to exclude air and moisture and thus easily performed on a 10-fold larger scale (**3aa**).[13]

Scheme 2. Products of phenanthroline-directed, Pd-catalyzed regioselective C–H alkenylation of allylic alcohols 1 with electron-deficient alkenes 2[a]

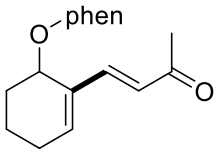


• *scope of alkenes* ***2***

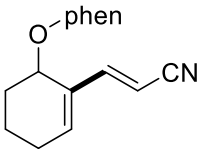


R = *t*Bu: **3aa** 78% (71%)[b]
R = Me: **3ab** 77%
R = Et: **3ac** 79%[c]
R = Bu: **3ad** 91%

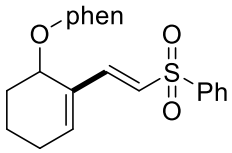
R = *i*Bu: **3ae** 85%
R = Cy: **3af** 68%
R = Ph: **3ag** 75%
R = $CH_2CH_2OCH_3$: **3ah** 79%



3ai 76%[d]



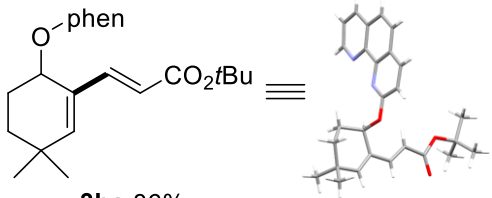
3**aj** 81%[d]



3**ak** 68%

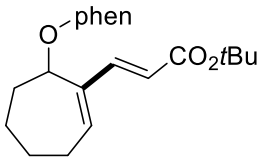
• *scope of allylic alcohols* **1**[d]

from *cis*-allylic alcohols

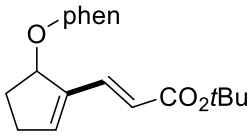


3ba 86%

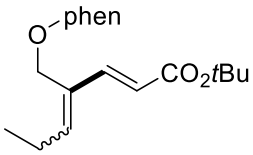
crystal structure of **3ba**



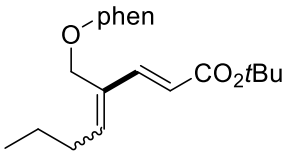
3ca 69%[c]



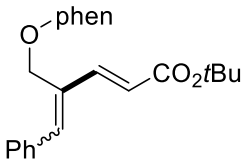
3da 58%[e]



3ea 61%
cis/trans = 7:3

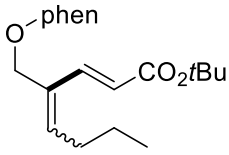


3fa 67%
cis/trans = 3:1

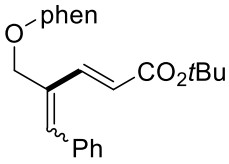


3ga 81%
cis/trans = 4:1[c]

from *trans*-allylic alcohols

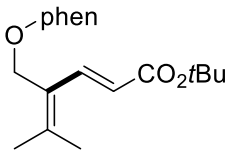


3fa 49%
cis/trans = 1:3

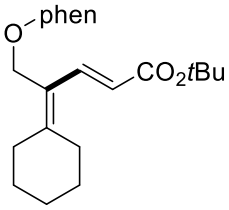


3ga 46%
cis/trans = 2:3

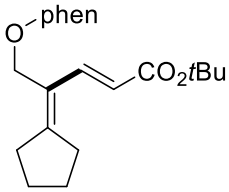
from trisubstituted allylic alcohols



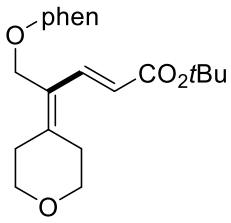
3ha 53%



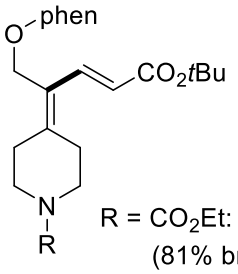
3ia 59%



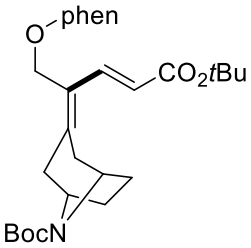
3ja 67%



3ka 60%



R = CO_2Et: **3la** 43%
(81% brsm)[c],[f]
R = Boc: **3ma** 49%
(70% brsm)[c]



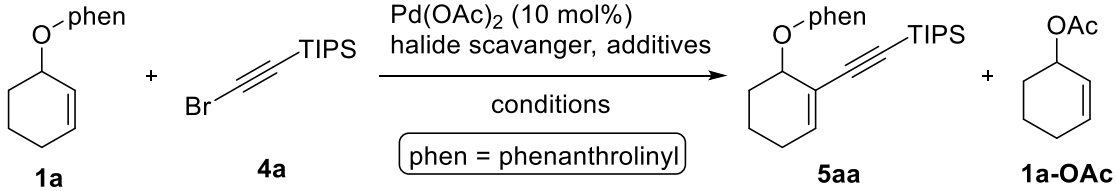
3na 63%
(84% brsm)[c]

[a] Conditions: **1** (0.20 mmol), **2** (0.40 mmol), $Pd(OAc)_2$ (0.020 mmol), $PhMe_2CCO_2H$ (0.050 mmol), BQ (0.040 mmol), AgTFA (0.40 mmol), MeCN (1.0 mL), 50 ˚C, 22 h. Isolated yields are shown. [b] On a 2.0 mmol scale. [c] With $PhMe_2CCO_2H$ (0.10

mmol). [d] At 65 ˚C. [e] With **2a** (0.60 mmol) and AgTFA (0.30 mmol) at 50 ˚C. [f] 36 h.

The Pd/phenanthroline system was also applicable to the regioselective alkenyl C–H alkynylation of allylic alcohols, which is unprecedented and one of the limited successful examples of the Pd-catalyzed directed C–H alkynylation of unconjugated internal alkenes.[14] After extensive optimization studies shown in Table 2, treatment of **1a** with TIPS-substituted alkynyl bromide **4a** in the presence of $Pd(OAc)_2$ catalyst and $AgBF_4$/NaOAc additives in heated 1,2-dichloroethane (DCE; 90 ˚C) afforded the conjugated enyne **5aa** in 73% isolated yield (entry 37). Both additives were critical: $AgBF_4$ could abstract Br derived from **4a** to enable the catalytic turnover of Pd, whereas NaOAc greatly improved the mass balance of the reaction.

Table 2. Optimization studies for alkynylation[a]



1a **4a** **5aa** **1a-OAc**

entry	halide scavenger (equiv)	additives (mol %)	conditions	yield (%)[b]	
				5aa	**1a-OAc**
1	***AgOAc (1.0)***	***PivOH (20)***	***DCE (1.0 mL), 100 ˚C, 6 h, air***	***12***	***n.d.***
2	AgOAc (1.0)	PivOH (20)	DCE (1.0 mL), 100 ˚C, 6 h, N_2	14	n.d.
3	AgTFA (1.0)	PivOH (20)	DCE (1.0 mL), 100 ˚C, 6 h, N_2	trace	n.d.
4	AgOAc (1.0)	PivOH (20)	MeCN (1.0 mL), 100 ˚C, 6 h, air	8	n.d.
5	AgOAc (1.0)	PivOH (20)	1,4-dioxane (1.0 mL), 100 ˚C, 6 h, air	0	n.d.
6	AgOAc (1.0)	PivOH (20)	toluene (1.0 mL), 100 ˚C, 6 h, air	0	n.d.
7	AgOAc (1.0)	PivOH (20)	HFIP (1.0 mL), 100 ˚C, 6 h, air	trace	trace
8	AgOAc (1.0)	PivOH (20) BQ (50)	DCE (1.0 mL), 100 ˚C, 17 h, air	12	n.d.

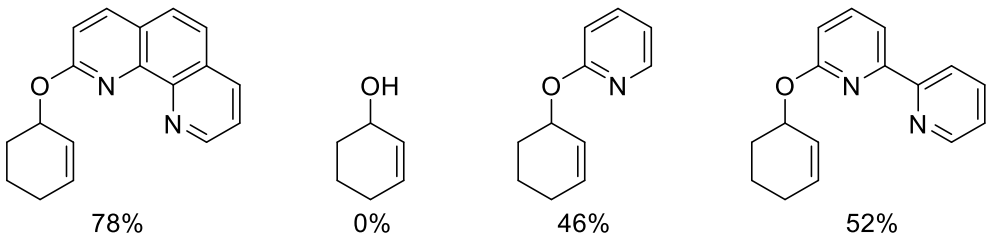
9	AgOAc (1.0)	PivOH (20) K_2CO_3 (100)	DCE (1.0 mL), 100 ˚C, 18 h, air	14	n.d.
10	AgOAc (1.0)	LiCl (100)	DCE (1.0 mL), 100 ˚C, 18 h, air	0	n.d.
11	AgOAc (1.0)	none	DCE (1.0 mL), 100 ˚C, 17 h, air	12	n.d.
12	***AgOAc (1.0)***	***none***	***DCE (0.5 mL), 100 ˚C, 22 h, air***	***22***	n.d.
13[c]	Ag_2O (0.5)	none	DCE (0.5 mL), 100 ˚C, 12 h, air	trace	n.d.
14[c]	$AgNO_3$ (1.0)	none	DCE (0.5 mL), 100 ˚C, 12 h, air	10	n.d.
15	AgOPiv (1.0)	none	DCE (0.5 mL), 100 ˚C, 22 h, N_2	18	n.d.
16	AgOTf (1.0)	none	DCE (0.5 mL), 100 ˚C, 22 h, N_2	0	n.d.
17	$Cu(OPiv)_2$ (1.0)	none	DCE (1.0 mL), 100 ˚C, 14 h, air	0	n.d.
18	$Cu(OAc)_2$ (1.0)	none	DCE (1.0 mL), 100 ˚C, 14 h, air	0	n.d.
19	$Cu(OTf)_2$ (1.0)	none	DCE (1.0 mL), 100 ˚C, 14 h, air	0	n.d.
19	KOAc (1.0)	none	DCE (1.0 mL), 100 ˚C, 15 h, air	3	n.d.
20	CsOPiv (1.0)	none	DCE (0.5 mL), 90 ˚C, 22 h, air	0	n.d.
21	Cy_2NH (2.0)	none	DCE (0.5 mL), 110 ˚C, 18 h, air	0	n.d.
22	***AgOAc (1.5)***	***NaOAc (100)***	***DCE (1.0 mL), 110 ˚C, 22 h, air***	***41***	***21***
23	AgOAc (1.5)	CsOAc (100)	DCE (1.0 mL), 110 ˚C, 22 h, air	22	n.d.
24	AgOAc (1.5)	KOAc (100)	DCE (1.0 mL), 110 ˚C, 22 h, air	30	n.d.
25	AgOAc (1.5)	LiOAc (100)	DCE (1.0 mL), 110 ˚C, 22 h, air	18	n.d.
26	AgOAc (1.5)	NaTFA (100)	DCE (1.0 mL), 110 ˚C, 22 h, air	36	n.d.
27	AgOAc (1.5)	Bu_4NOAc (100)	DCE (1.0 mL), 110 ˚C, 22 h, air	20	n.d.
28	AgOAc (1.5)	Na_2CO_3 (100)	DCE (1.0 mL), 120 ˚C, 19 h, air	trace	n.d.
29	AgOAc (1.5)	KOPiv (100)	DCE (1.0 mL), 120 ˚C, 19 h, air	26	n.d.
30	AgOAc (1.5)	NaOBz (100)	DCE (1.0 mL), 120 ˚C, 19 h, air	11	n.d.
31[d]	Ag_2CO_3 (1.0)	NaOAc (100)	DCE (1.0 mL), 110 ˚C, 22 h, air	0	n.d.
32[d]	AgF (1.0)	NaOAc (100)	DCE (1.0 mL), 110 ˚C, 19 h, air	18	21
33[d]	Ag_3PO_4 (1.0)	NaOAc (100)	DCE (1.0 mL), 110 ˚C, 19 h, air	10	26
34[d]	$AgSbF_6$ (1.0)	NaOAc (100)	DCE (1.0 mL), 110 ˚C, 19 h, air	0	n.d.
35[d]	***$AgBF_4$ (1.0)***	***NaOAc (100)***	***DCE (1.0 mL), 110 ˚C, 19 h, air***	***71***	***18***
36[d]	***$AgNTf_2$ (1.0)***	***NaOAc (100)***	***DCE (1.0 mL), 110 ˚C, 19 h, air***	***71***	***20***

37[d]	***$AgBF_4$ (1.0)***	***NaOAc (100)***	***DCE (1.0 mL), 90 ˚C, 16 h, air***	***78 (73)***	***13***
38[d]	$AgBF_4$ (1.0)	NaOAc (50)	DCE (1.0 mL), 90 ˚C, 16 h, air	31	21
39	$AgBF_4$ (1.0)	NaOAc (100)	DCE (1.0 mL), 90 ˚C, 16 h, air	63	26
40	$AgBF_4$ (1.5)	NaOAc (100)	DCE (1.0 mL), 90 ˚C, 16 h, air	30	43
41[d]	$AgPF_6$ (1.0)	NaOAc (100)	DCE (1.0 mL), 90 ˚C, 16 h, air	(66)	8
42[d]	$AgBF_4$ (1.0)	none	DCE (1.0 mL), 110 ˚C, 19 h, air	0	n.d.
43[d,e]	$AgBF_4$ (1.0)	NaOAc (100)	DCE (1.0 mL), 110 ˚C, 19 h, air	trace	trace

[a] Reaction conditions: $Pd(OAc)_2$ (0.010 mmol), **1a** (0.10 mmol), **4a** (0.15 mmol), halide scavanger, additive, solvent. [b] Determined by ^1H NMR using dibenzyl ether as the internal standard. Isolated yields are in parentheses. [c] With 0.30 mmol of **4a**. [d] With 0.20 mmol of **4a**. [e] Without $Pd(OAc)_2$. n.d. = not determined.

Under the optimal conditions, the effects of other directing groups were evaluated for the alkynylation (Table 3). As seen in the alkenylation, the phenanthroline bidentate auxiliary was necessary for the acceptable conversion.

Table 3. Effects of directing groups



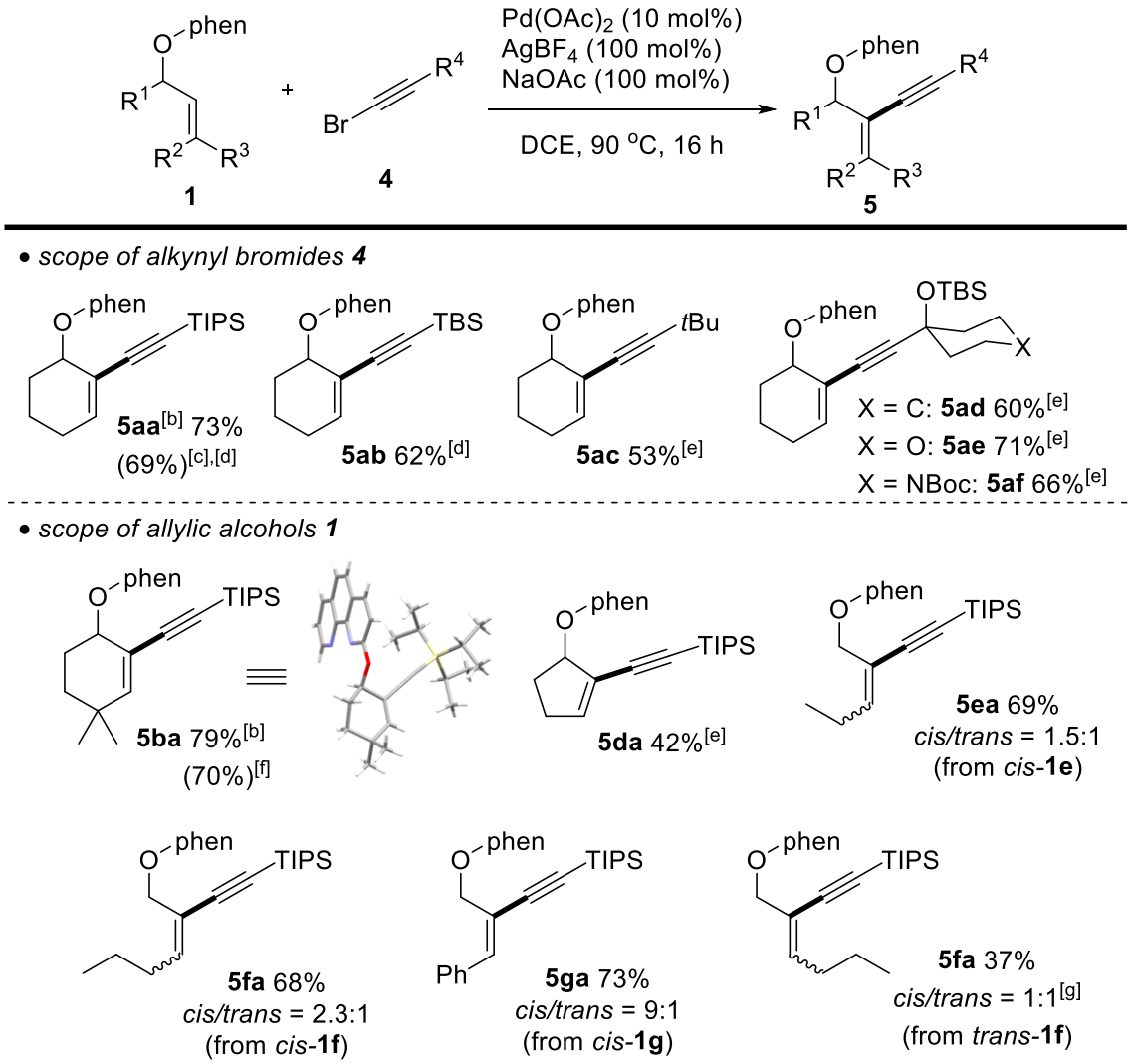
78% 0% 46% 52%

^1H NMR yields of corresponding C-H alkynylated products under conditions of entry 37 in Table 2.

As shown in Scheme 3, several other bulky alkynyl bromides **4** were successfully coupled with **1a**. For example, the reaction with TBS- and *tert*-butyl-substituted alkynyl bromides **4b** and **4c** provided **5ab** and **5ac**, respectively, in good yields. The Pd catalysis was also tolerated with the protected propargylic alcohol derivatives that bear the cyclohexyl as well as the heterocyclic pyran and piperidine rings (**5ad-af**). At

higher reaction temperature (110 ˚C), the corresponding alkynyl chloride was also available for use (**5aa**). As a general trend, $AgPF_6$ showed better performance than $AgBF_4$ when the alkyl-substituted alkynyl bromides were employed. The scope of allylic alcohols **1** was also evaluated. The 4,4-dimethylcyclohexenol **1b** smoothly reacted with **4a** to form the corresponding conjugated enyne **5ba** in 79% yield; the structure of which was determined by the single X-ray crystallographic analysis (CCDC 2022024). The reaction was scalable and easily conducted on a 2.0 mmol scale. The reactivity of cyclopentenol derivative was somewhat lower, but the targeted **5da** was isolated in a synthetically useful yield. The linear *cis*-allylic alcohols were also amenable, and the corresponding C–H alkynylated products **5ea**-**ga** were obtained albeit with variable stereospecificity (*cis*/*trans* = 1.5:1-9:1). Moreover, the conceivably more challenging *trans*-allylic alcohol formed the desired product **5fa**.[15]

Scheme 3. Products of phenanthroline-directed, Pd-catalyzed regioselective C–H alkynylation of allylic alcohols 1 with alkynyl bromides 4[a]

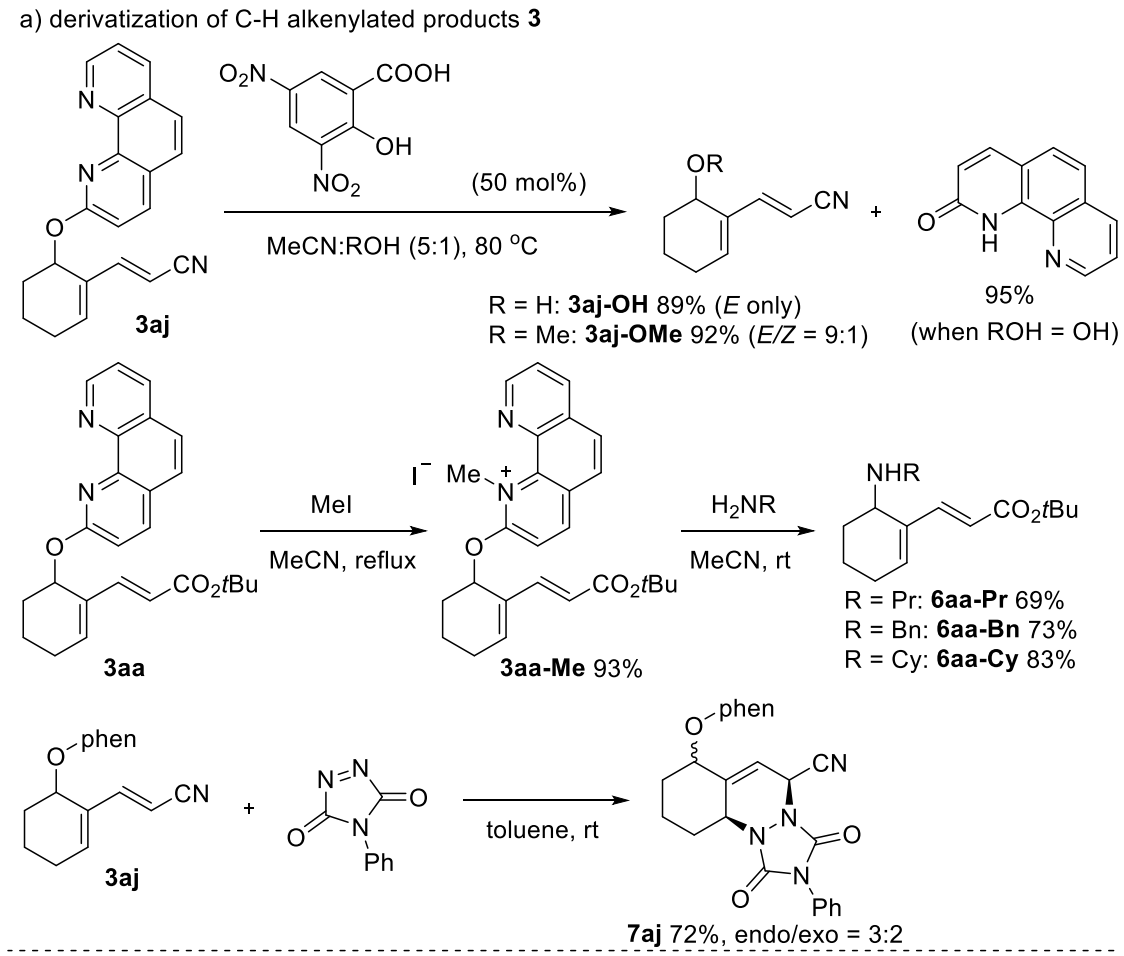


[a] Conditions: **1** (0.20 mmol), **4** (0.40 mmol), $Pd(OAc)_2$ (0.020 mmol), $AgBF_4$ (0.20 mmol), NaOAc (0.20 mmol), DCE (2.0 mL), 90 ˚C, 16 h. [b] On a 0.10 mmol scale. [c] With the corresponding alkynyl chloride instead of **4a**. [d] At 110 ˚C. [e] With $AgPF_6$ instead of $AgBF_4$. [f] On a 2.0 mmol scale. [g] At 100 ˚C.

The phenanthroline auxiliary in the products could be easily removed and manipulated (Scheme 4). The Brønsted acid catalyzed[16] substitution of **3aj** with H_2O proceeded smoothly to deliver the corresponding free dienyl alcohol **3aj-OH** and

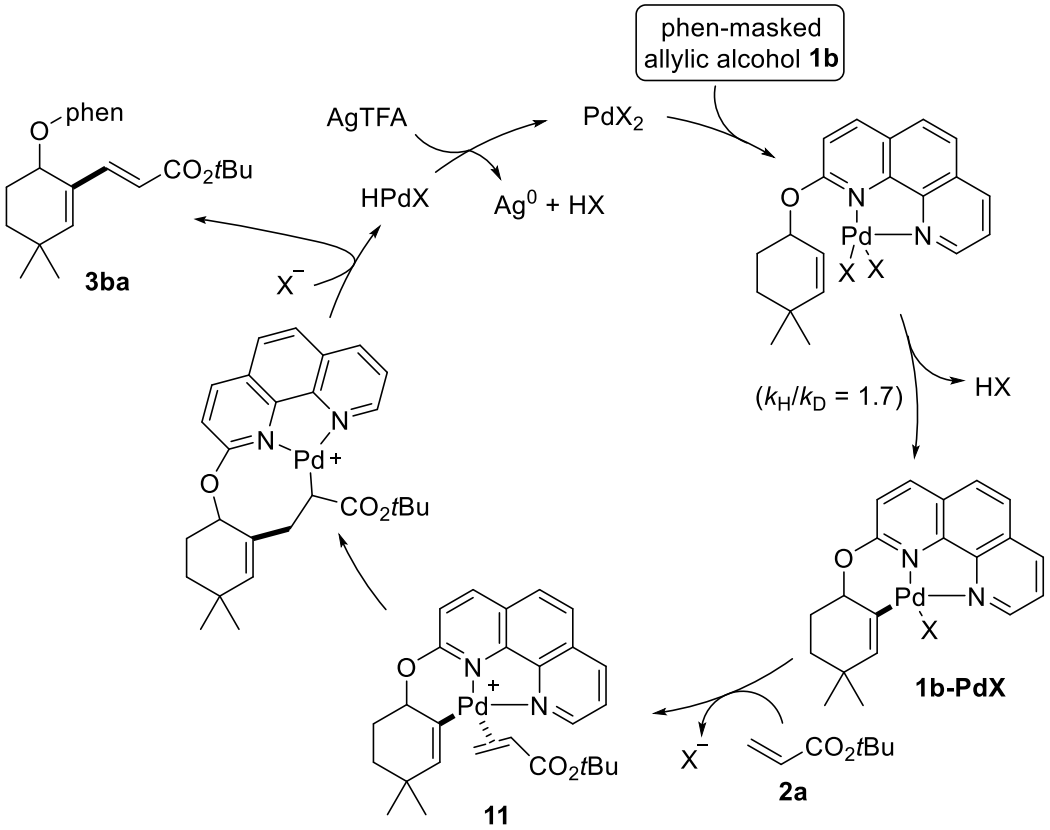
2-phenanthrolinone in 89 and 95% yields, respectively.[17] The latter was easily recycled via conversion back into the diecting group precursor.[10a] The etherification with the alcohol nucleophile was also feasible (**3aj-OMe**). Moreover, the dienylamines **6aa-Pr-Cy** were obtained by the quaternary-driven nucleophilic amination with primary amines. On the other hand, the formed 1,3-diene moiety was a reactive enophile, and Diels-Alder reaction with the triazoledione was possible to afford the cycloadduct **7aj** in a good yield. The C–H alkynylated product **5ba** was also readily and regioselectively converted to the free alcohol **5ba-OH** along with phenanthrolinone under the aforementioned acid-mediated conditions. The cleavage of the TIPS moiety with TBAF (**5ba-OH** to **8**) was followed by the Cu-catalyzed azide-alkyne cycloaddition to afford the functionalized triazole **9** in a good overall yield. Additionally, the direct desilylative Sonogashira coupling of **5aa** could also be performed to form the aryl-conjugated enyne **10**, which overcomes the limitation of alkynyl bromides in the C–H alkynylation.[15]

Scheme 4. Derivatization of C–H alkenylated and alkynylated products 3 and 5



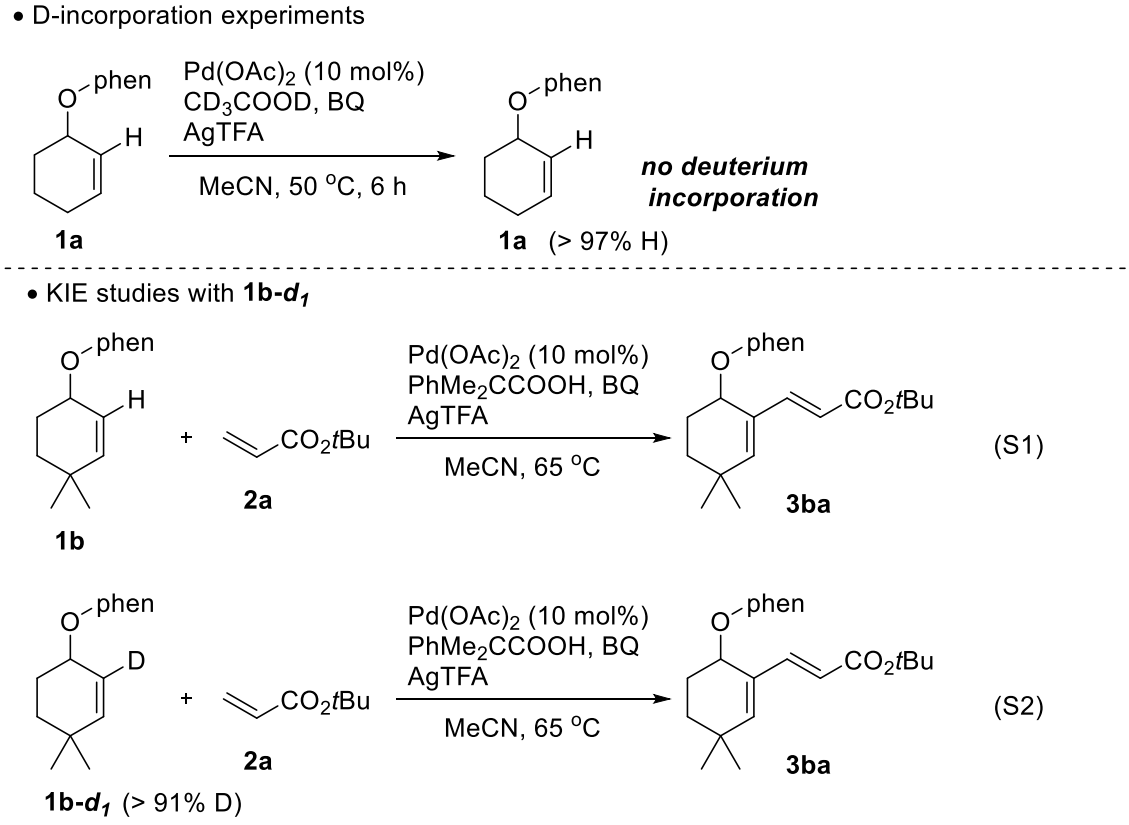
The proposed reaction mechanism for the phenanthroline-directed Pd-catalyzed alkenylation of **1b** with **2a** is shown in Scheme 5. The initial coordination of phenanthroline moiety of **1b** to PdX_2 (X = OAc, $OCOCMe_2Ph$, or TFA) is followed by C–H cleavage to form the 6-membered palladacycle intermediate **1b-PdX**. Subsequent ligand exchange on Pd between the alkene **2a** and X^- occurs to afford an alkene-coordinated cationic Pd species **11**. The C–H alkenylated product **3ba** is formed by successive insertion and β-H elimination. The liberation of HX and reoxidation with AgTFA regenerate the starting PdX_2 to complete the catalytic cycle.

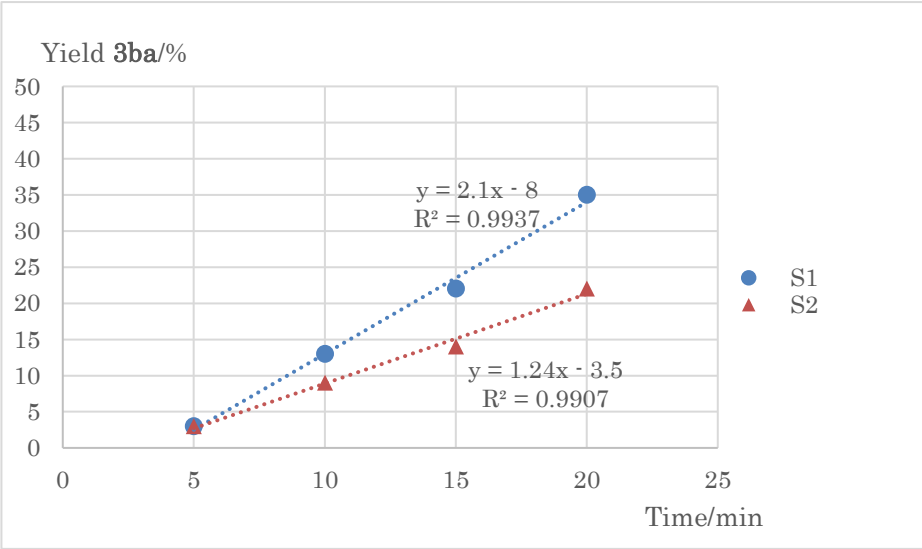
Scheme 5. Plausible reaction mechanism of 1b and 2a



The deuterium incorporation experiments and KIE studies with the deuterated **1b** suggest the irreversible and rate-limiting C–H cleavage (Scheme 6). Given the better reactivity of **1a** and **1a-bpy** than **1a-Py** observed in Scheme 1 and our previous Cu-catalyzed phenanthroline-directed C–H amination of phenols,[10a] the chelating nature of phenanthroline (and bipyridine) moiety accelerates the otherwise challenging C–H cleavage step. Additionally, the positive effects of acid additive can support the operation of acetate-ligand-promoted concerted metalation-deprotonation mechanism.[18] The exact role of BQ is not clear at this stage, but it can coordinate to Pd(0) to avoid the formation of catalytically inactive Pd black.[19]

Scheme 6. Deuterium-Labeling studies





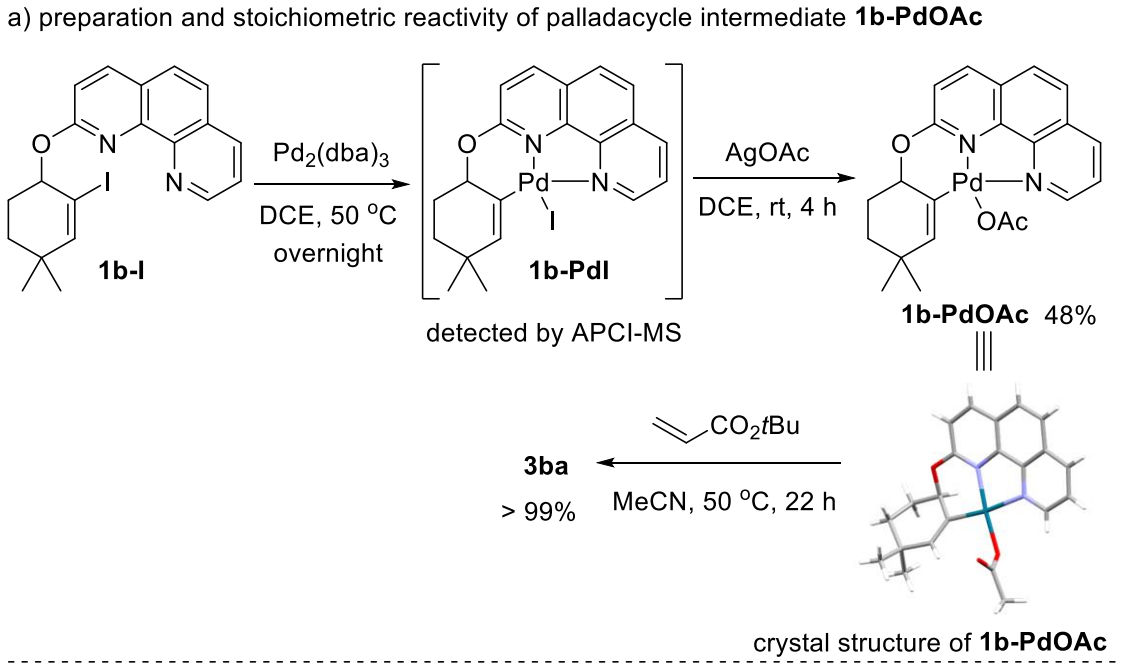
According to the above data, the ratio of initial rate constants was calculated as follows.

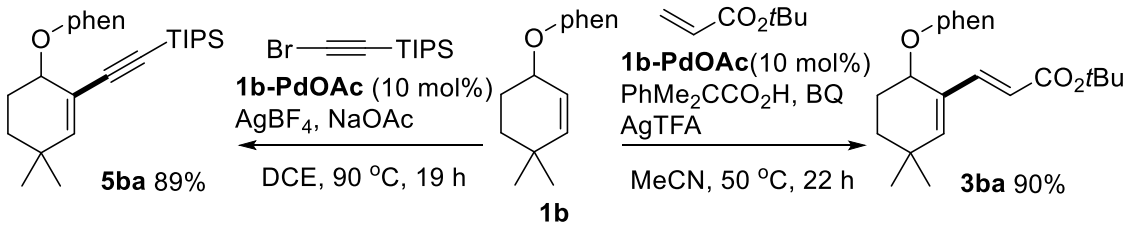
$$k_H/k_D = 2.1/1.24 = 1.69 \quad \text{(eq S1 vs eq S2)}$$

All attempts to detect and isolate the key palladacycle intermediate **1b-PdX** from **1b** and $Pd(OAc)_2$ remained unsuccessful, but the author was pleased to prepare the corresponding acetate complex **1b-PdOAc** from the alkenyl iodide **1b-I** and $Pd_2(dba)_3$ (Scheme 7a). Oxidative addition of **1b-I** to the Pd proceeded smoothly in DCE at 50 ˚C, and complete consumption of **1b-I** and formation of **1b-PdI** were assigned by APCI-HRMS. Subsequent addition of AgOAc at room temperature promoted I/OAc ligand exchange to give the targeted **1b-PdOAc** as a bench-stable white solid in 48% overall yield. The structure was confirmed by $^{1}H/^{13}C$ NMR, ESI-HRMS, and X-ray crystallography (CCDC 2022025); **1b-PdOAc** has a typical tetracoordinated planar structure with 360.05˚ sum of bond angle around Pd. The stoichiometric reaction of **1b-PdOAc** with **2a** in the absence of any external additives formed the alkenylated product **3ba** in a quantitative yield. Additionally, **1b-PdOAc** worked well as the

catalyst to couple **1b** and **2a** with comparable efficiency to that under standard conditions in Scheme 2 (Scheme 7b). Similarly high catalytic activity of **1b-PdOAc** was also observed in the reaction of **1b** with the alkynyl bromide **4a**. Thus, a related palladacycle intermediate would be involved in the catalytic cycle of both C–H alkenylation and alkynylation.[20]

Scheme 7. (a) Preparation and stoichiometric reactivity of 6-membered palladacycle; (b) Catalytic activity of 6-membered palladacycle





Summary

The author has developed a phenanthroline-directed Pd-catalyzed C–H alkenylation of allylic alcohols with electron-deficient alkenes. The bidentate coordinating nature of phenanthroline enables the otherwise challenging and regioselective C–H activation at the proximal alkenyl C–H bond over the competitive allylic C–O bond activation (conventional π-allyl Pd chemistry). The same phenanthroline/Pd system is applicable to the C–H alkynylation of allylic alcohols, which is unprecedented, to the best of his knowledge. Some mechanistic studies with the independently prepared 6-membered palladacycle intermediate suggest that the regioselective, directed C–H palladation is the key step in the C–H alkenylation and alkynylation.

Instrumentation and Chemicals

^{1}H and $^{13}C\{^{1}H\}$ NMR spectra were recorded at 400 MHz and 100 MHz, respectively, for $CDCl_3$ solutions. HRMS data were obtained by APCI, ESI, or FAB using a TOF (APCI, ESI) or a magnetic sector (FAB), respectively. GC analysis was carried out using a silicon OV-17 column (i. d. 2.6 mm x 1.5 m) or CBP capillary column (i. d. 0.5 mm x 25 m). TLC analyses were performed on commercial glass plates bearing 0.25-mm layer of Merck Silica gel $60F_{254}$. Silica gel (Wakosil C-200, Wako Pure Chemical Co.) was used for column chromatography. Gel permeation chromatography (GPC) was performed by LC-20AR (pump, SHIMADZU, 7.5 mL/min $CHCl_3$ or EtOAc) and SPD-20A (UV detector, SHIMADZU, 254 nm) with two in-line YMC-GPC T2000 (20 x 600 mm, particle size: 10 μm) (preparative columns, YMC).

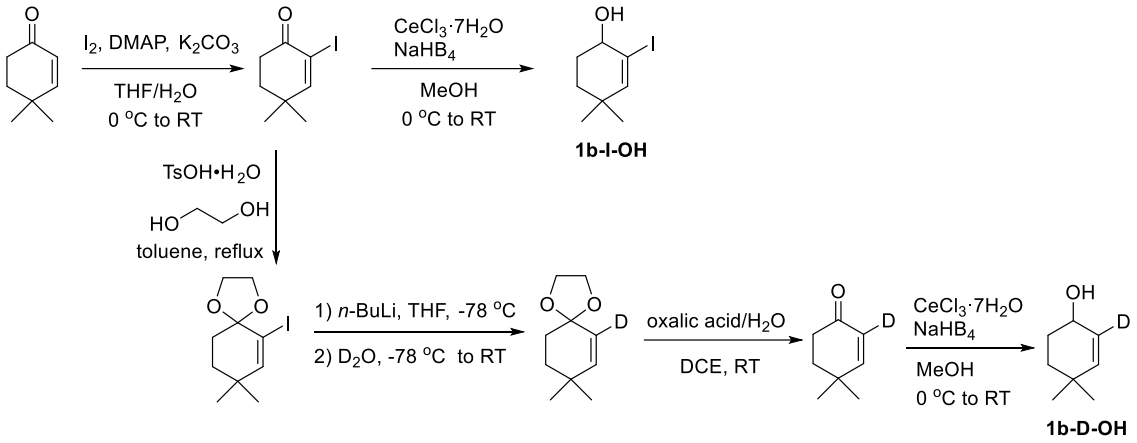
Unless otherwise noted, materials obtained from commercial suppliers were used without further purification. MeCN was dried on a Glass Contour Solvent dispensing system (Nikko Hansen & Co., Ltd.) prior to use. DCE was freshly distilled from CaH_2 prior to use. Substrates **1** were prepared from the corresponding allylic alcohols and 2-chlorophenanthroline[10] via condensation (see the following experimental section for details). The electron-withdrawing alkenes **2** are commercially available. The alkynyl bromides **4** were synthesized according to the literature.[21] Unless otherwise noted, all reaction were performed under nitrogen conditions.

Experimental Procedures

1. Preparation of starting allylic alcohol derivatives 1

Substrates **1** were prepared from the corresponding allylic alcohols **1-OH**. The **1a-OH**, *cis*-**1e-OH**, *cis*-**1f-OH,** *trans*-**1f-OH**, *trans*-**1g-OH**, and **1h** are commercially available. The **1b-OH, 1c-OH**, and **1d-OH** were prepared from the commercially available corresponding a,b-unsaturated ketones by the typical Luche reduction using $CeCl_3$, $NaBH_4$, and MeOH. The *cis*-**1g-OH**[22] was prepared according to the literature method. The **1b-I-OH**[23] and **1b-D-OH**[24] were synthesized as follows (Scheme S1).

Scheme S1. Preparation of allylic alcohols **1b-I-OH** and **1b-D-OH**



Procedure for synthesis of 1b-I-OH: To a solution of 4,4-dimethyl-2-cyclohexan-1-one (1.280 g, 10.40 mmol) in THF/water (48 mL, 1:1, v/v) was added K_2CO_3 (1.720 g, 12.40 mmol), I_2 (3.940 g, 15.60 mmol), and DMAP (254 mg, 2.0 mmol) successively at 0 °C. The mixture was warmed to room temperature and stirred for 3 h. The reaction mixture was then diluted with ethyl acetate (30 mL) and quenched with saturated aqueous sodium sulfite (50 mL). The separated aqueous phase was extracted with ethyl acetate (2 × 20 mL), and the combined organic phases were washed with saturated aqueous sodium sulfite (30 mL), hydrochloric acid (50 mL, 0.1 M), and brine (1 × 50 mL). The organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography with hexane/ethyl acetate (10:1, v/v) to give 2-iodo-4,4-dimethylcyclohex-2-en-1-one (72%, 1.872 g, 7.488 mmol).

To a solution of 2-iodo-4,4-dimethylcyclohex-2-en-1-one (1,170 g, 4.680 mmol) and $CeCl_3·7H_2O$ (1.740 g, 4.680 mmol) in MeOH (15 mL) was added $NaHB_4$ (212.5 mg, 5.616 mmol) at 0 °C and then warmed to room temperature. After 1 h, the reaction was quenched with H_2O (15 mL), and MeOH was removed in vacuo. The resulting residue was extracted with ethyl acetate (3 × 20 mL), and the combined organic phases were washed with brine (20 mL), dried over Na_2SO_4, and concentrated in vacuo. The target **1b-I-OH** (97%, 1.150 g, 4.560 mmol) was obtained and used directly in the next step without further purification.

Procedure for synthesis of 1b-D-OH: A solution of 2-iodo-4,4-dimethylcyclohex-2-en-1-one (1.40 g, 5.60 mmol), ethylene glycol (3.3 mL), *p*-TsOH (71 mg, 0.336 mmol), in toluene (50 mL) was heated at reflux overnight. The water formed during the reaction was removed by a Dean-Stark trap. The reaction was cooled to room temperature and exacted with Et_2O (3 x 30 mL). The combined organic layer were sequentially washed with saturated aqueous $NaHCO_3$ (20 mL) and

brine (20 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography with hexane/ethyl acetate (20:1 to 10:1, v/v) to give 6-iodo-8,8-dimethyl-1,4-dioxaspiro[4.5]dec-6-ene (84%, 1.380 g, 4.70 mmol).

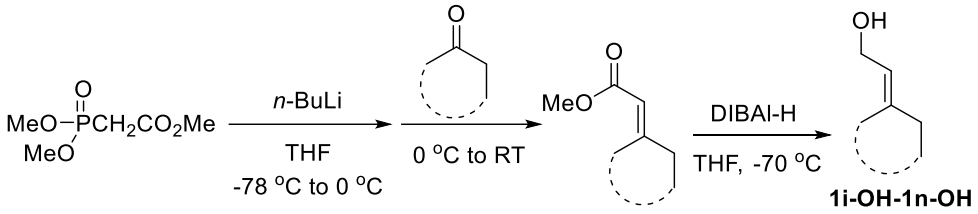
To a solution of 6-iodo-8,8-dimethyl-1,4-dioxaspiro[4.5]dec-6-ene (1.380 g, 4.70 mmol) in THF (40 mL) was added *n*-BuLi (3.67 mL, 1.6 M in hexane) dropwise at -78 °C and stirred for 1 h. The reaction was quenched with D_2O (0.5 mL) at -78 °C, warmed to room temperature, and stirred for 1 h. The resulting mixture was quenched with saturated aqueous NH_4Cl (50 mL) and extracted with Et_2O (3 x 30 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo to afford the 6-deuterio-8,8-dimethyl-1,4-dioxaspiro[4.5]dec-6-ene (795.4 mg, quantitative, 91% D), which was used directly in the next step without further purification.

A solution of oxalic acid (1.610 g, 17.888 mmol) in water (25 mL) was added to a solution of 6-deuterio-8,8-dimethyl-1,4-dioxaspiro[4.5]dec-6-ene (945 mg, 5.59 mmol) in DCE (25 mL) at room temperature. The mixture was stirred vigorously until the hydrolysis was completed. The aqueous layer was extracted with ether (3 x 30 mL), and the combined organic layers were washed with saturated aqueous $NaHCO_3$ (30 mL) and brine (30 mL), dried over Na_2SO_4, and concentrated in vacuo. The 2-deuterio-4,4-dimethylcyclohex-2-en-1-one (83%, 580.0 mg, 4.640 mmol) was obtained and was used directly in the next step without further purification.

To a solution of 2-deuterio-4,4-dimethylcyclohex-2-en-1-one (580.0 mg, 4.640 mmol) and $CeCl_3 \cdot 7H_2O$ (1.730 g, 4.640 mmol) in MeOH (15 mL) was added $NaHB_4$ (202.0 mg, 5.336 mmol) at 0 °C and then warmed to room temperature. After 1 h, the reaction was quenched with H_2O (15 mL), and MeOH was removed in vacuo. The resulting residue was extracted with ethyl acetate (3 × 20 mL), and the combined organic phases were washed with brine (20 mL), dried over Na_2SO_4, and concentrated in vacuo. The target **1b-D-OH** (63%, 368.0 mg, 2.898 mmol) was obtained and used directly in the next step without further purification.

The trisubstituted allylic alcohols **1i-OH**–**1n-OH** were synthesized via HWE reaction (Scheme S2).[25]

Scheme S2. Preparation of allylic alcohols **1i-OH**–**1n-OH**

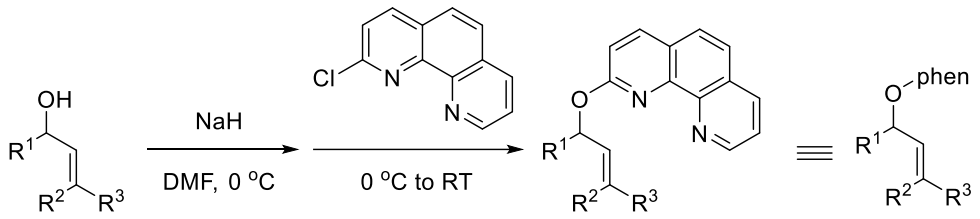


To a solution of trimethyl phosphonoacetate (0.87 mL, 6 mmol) in dry THF (50 mL) was added *n*-BuLi (3.8 mL, 1.59 M in hexane) dropwise at -78 °C. The mixture was warmed to 0 °C and stirred for 1 h. The corresponding ketone (6 mmol) was then added dropwise at 0 °C and stirred for overnight at room temperature. The reaction was quenched with water (50 mL) at 0 °C and the resulting mixture was extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4 and concentrated in vacuo to afford the desired unsaturated ester, which was used directly in the next step without further purification.

To a solution of the unsaturated ester (5 mmol) in THF (50 mL) was added DIBAL-H (11.0 mL, 1.0 M in toluene) dropwise at -70 °C. After completed, the reaction was quenched with saturated aqueous NH_4Cl (1.0 mL). The suspension was filtered through a short plug of activated alumina. The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography with hexane/ethyl acetate (2:1 to 1:1, v/v) to afford the desired trisubstituted allylic alcohol. Note: for **1l-OH**, after adding DIBAL-H, the mixture was stirred for 3 h at -70 °C, then warmed to -20 °C and stirred for 2 h.

The allylic alcohols **1-OH** were converted to the starting substrates **1** via condensation with chlorophenanthroline (Scheme S3).

Scheme S3. Preparation of the starting substrates **1**



To a suspension of NaH (88.0 mg, 2.20 mmol) in DMF (4.0 mL) was added the corresponding allylic alcohol (2.0 mmol) at 0 °C. After stirring for 0.5 h, the 2-chlorophenanthroline (429.3, 2.0 mmol)[1] was added in portion at 0 °C. Then the mixture was warmed to room temperature and stirred for 15 h. The reaction was quenched with water (10 mL) and extracted with EtOAc (3 x 25 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography with hexane/ethyl acetate (3:1 to 1:1, v/v) to give **1**. Note: for the synthesis of **1a-Py** and **1-bpy** (control experiment substrates in Scheme 1 and Scheme S4), 2-chloropyridine and 6-bromo-2,2'-bipyridine, respectively, was used instead of 2-chlorophenanthroline.

2. General procedure for palladium-catalyzed C–H alkenylation of allylic alcohols (Scheme 2)

A 0.2 mmol scale reaction: To a 15 mL screw cap test tube were added the allylic alcohol substrate (**1**, 0.20 mmol), 2-phenylisobutyric acid (8.2 mg, 0.05 mmol), 1,4-benzoquinone (4.4 mg, 0.04 mmol), AgTFA (88.4 mg, 0.40 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), MeCN (1.0 mL), and alkene coupling partner (**2**, 0.40 mmol) under ambient atmosphere. The tube was sealed with a screw-top septum cap and stirred at 50 °C (oil bath) for 22 h. The reaction was allowed to cool to room temperature, saturated aqueous $NaHCO_3$ (2.0 mL) was added, and the aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography to give the desired product **3**. (Note: **3la**, **3ma,** and **3na** were further purified by GPC ($CHCl_3$).)

A 2.0 mmol scale reaction: To a 25 mL two-neck round-bottom flask were added the allylic alcohol substrate (**1a**, 553.0 mg, 2.0 mmol), 2-phenylisobutyric acid (82.0 mg, 0.50 mmol), 1,4-benzoquinone (44.0 mg, 0.40 mmol), AgTFA (884.0 mg, 4.0 mmol), $Pd(OAc)_2$ (45.0 mg, 0.20 mmol), MeCN (10.0 mL), and alkene coupling partner (**2a**, 513.0 mg, 4.0 mmol) under ambient atmosphere. The flask was sealed with a septum and stirred at 50 °C (oil bath) for 22 h. The reaction was allowed to cool to room temperature, and saturated aqueous $NaHCO_3$ (15.0 mL) was added. The aqueous layer was extracted with EtOAc (3 x 25 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography with hexane/EtOAc (1:1, v/v) to give the desired product **3aa** (71%, 571.3 mg, 1.42 mmol).

3. General procedure for palladium-catalyzed C–H alkynylation of allylic alcohols (Scheme 3)

A 0.2 mmol scale reaction: To a 15 mL screw cap test tube were added the allylic alcohol substrate (**1**, 0.20 mmol), NaOAc (16.4 mg, 0.20 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), $AgBF_4$ (39.0 mg, 0.20 mmol), DCE (2.0 mL) and alkynyl bromide (**4**, 0.40 mmol) under ambient atmosphere. The tube was sealed with a cap and stirred at 90 °C (oil bath) for 16 h. The reaction was allowed to cool to room temperature, and the mixture was filtered through a short plug of activated alumina (EtOAc as eluent) and concentrated in vacuo. The residue was purified by silica gel column chromatography to give the desired product **5**. (Note: **5da** was further purified by GPC (EtOAc).)

A 2.0 mmol scale reaction: To a 50 mL two-neck round-bottom flask were added the allylic alcohol substrate (**1b**, 608.8 mg, 2.0 mmol), NaOAc (164.0 mg, 2.0 mmol), $Pd(OAc)_2$ (45.0 mg, 0.20 mmol), $AgBF_4$ (390.0 mg, 2.0 mmol), DCE (20.0 mL), and alkynyl bromide (**4a**, 1.045 g, 4.0 mmol) under ambient atmosphere. The flask was sealed with a glass stopper and stirred at 90 °C (oil

bath) for 16 h. The reaction was allowed to cool to room temperature, and the mixture was filtered through a short plug of activated alumina (EtOAc as eluent) and concentrated in vacuo. The residue was purified by silica gel column chromatography with hexane/EtOAc (3:1, v/v) to give the desired product **5ba** (70%, 678.6 mg, 1.40 mmol).

4. Derivatizations of Products (Scheme 4)

Procedure for synthesis of 3aj-OH: To a 10 mL microwave vessel were added **3aj** (81.8 mg, 0.25 mmol), MeCN (2.5 mL), H_2O (0.5 mL), and 3,5-dinitrosalicylic acid (28.5 mg, 0.125 mmol). The vessel was sealed and stirred at 80 °C (oil bath) overnight. The reaction was allowed to cool to room temperature, saturated aqueous $NaHCO_3$ (4.0 mL) was added, and the aqueous layer was extracted with EtOAc (3 x 15 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography with hexane/ethyl acetate (5:1 to 1:2, v/v) to give the product **3aj-OH** (89%, 33.2 mg, 0.223 mmol) and phenanthrolinone (95%, 46.5 mg, 0.2375 mmol).

Procedure for synthesis of 3aj-OMe: To a 10 mL microwave vessel were added **3aj** (32.7 mg, 0.10 mmol), MeCN (1.0 mL), MeOH (0.2 mL), and 3,5-dinitrosalicylic acid (11.4 mg, 0.05 mmol). The vessel was sealed and stirred at 80 °C (oil bath) overnight. The reaction was allowed to cool to room temperature, saturated aqueous $NaHCO_3$ (2.0 mL) was added, and the aqueous layer was extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography with hexane/ethyl acetate (5:1, v/v) to give the product **3aj-OMe** (92%, 15.0 mg, 0.092 mmol).

Procedure for synthesis of 3aa-Me: To a 10 mL microwave vessel were added **3aa** (201.2 mg, 0.50 mmol), MeCN (2.0 mL), and MeI (94 μL, 212.9 mg, 1.50 mmol). The vessel was sealed and stirred at reflux (oil bath) for 3 h. After **3aa** was fully consumed, the solvent was removed in vacuo and obtained a yellow solid **3aa-Me** (93%, 253.1 mg, 0.465 mmol).

Procedure for synthesis of 6aa: To a 5 mL microwave vessel were added **3aa-Me** (32.6 mg, 0.06 mmol), MeCN (1.0 mL), and the corresponding primary amine (1.20 mmol, 20.0 equiv). The vessel was sealed and stirred at room temperature for 15 h. The crude was filtered through a short plug of silica gel ($CHCl_3$ as eluent) and concentrated in vacuo. The residue was purified by GPC ($CHCl_3$) to obtain the product **6aa**.

Procedure for synthesis of 7aj: To a 5 mL microwave vessel were added **3aj** (32.7 mg, 0.10 mmol), toluene (1.0 mL), and triazoledione (35.0 mg, 0.20 mmol). The vessel was sealed and stirred under dark at room temperature for 15 h. The solvent was removed in vacuo and purified by silica gel column chromatography with hexane/ethyl acetate (1:1, v/v) to give **7aj** (72%, 36.1 mg, 0.072 mmol, *endo/exo* = 3:2).

Procedure for synthesis of 5ba-OH: To a 25 mL microwave vessel were added **5ba** (484.7 mg, 1.0 mmol), MeCN (12.5 mL), H_2O (2.5 mL), and 3,5-dinitrosalicylic acid (114.1 mg, 0.50 mmol). The vessel was sealed and stirred at 80 °C (oil bath) overnight. The reaction was allowed to cool to room temperature, saturated aqueous $NaHCO_3$ (15 mL) was added, and the aqueous layer was extracted with EtOAc (3 x 25 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography with hexane/ethyl acetate (5:1 to 1:2, v/v) to give the product **5ba-OH** (95%, 291.2 mg, 0.950 mmol) and phenanthrolinone (93%, 182.2 mg, 0.930 mmol).

Procedure for synthesis of 8: To a solution of **5ba-OH** (275.9 mg, 0.90 mmol) in THF (10 mL) was added TBAF (1.0 M in THF, 1.9 mL) dropwise at 0 °C. The mixture was stirred at 0 °C for 20 min and subsequently at room temperature for 2.5 h. The reaction mixture was diluted with water (30 mL) and extracted with EtOAc (3 x 25 mL). The combined organic layers were washed with water (20 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by silica gel column chromatography with hexane/ethyl acetate (5:1, v/v) to give **8** (89%, 120.3 mg, 0.801 mmol).

Procedure for synthesis of 9: To a solution of **8** (30.0 mg, 0.20 mmol) and benzylazide (26.6 mg, 0.20 mmol) in a mixture of *t*BuOH/H_2O (0.45/0.45 mL) were added a freshly prepared aqueous sodium ascorbate (21 μL, 1.0 M) and aqueous $CuSO_4$ (7 μL, 0.32 M). The resulting mixture was stirred at room temperature for 16 h, and then diluted with water (5.0 mL) and extracted with EtOAc (3 x 15 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography with hexane/ethyl acetate (1:1, v/v) to give **9** (quantitative, 56.7 mg, 0.20 mmol).

Procedure for synthesis of 10: To a 5 mL microwave vessel were added **5aa** (45.6 mg, 0.10 mmol), 4-iodotoluene (43.6 mg, 0.20 mmol), $Pd(PPh_3)_2Cl_2$ (7.1 mg, 0.01 mmol), and CuI (3.8 mg, 0.02

mmol) under N_2 atmosphere. THF (1.0 mL), Et_3N (0.18 mL), and TBAF (1.0 M in THF, 0.20 mL) were subsequently added via syringe, and the mixture was stirred at 50 °C (oil bath) for 17 h. The reaction was allowed to cool to room temperature, quenched with saturated aqueous NH_4Cl (10 mL), and extracted with EtOAc (3 x 15 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel column chromatography with hexane/ethyl acetate (2:1, v/v) to give **10** (63%, 24.5 mg, 0.063 mmol).

5. Procedure for preparing palladacycle intermediate 1b-PdOAc (Scheme 7a)

In a 50 mL Schlenk tube were placed **1b-I** (215.2 mg, 0.50 mmol), $Pd_2(dba)_3$ (229.0 mg, 0.25 mmol), and DCE (12.0 mL) under N_2 atmosphere. The mixture was stirred at 50 °C (oil bath) overnight. The resulting solution was allowed to cool to room temperature and followed by the addition of AgOAc (83.5 mg, 0.50 mmol). The mixture was stirred at room temperature for another 4 h. The precipitates were collected by filtration and washed with EtOAc (2 x 1.0 mL). The filter cake was dissolved in $CHCl_3$ (3 x 25 mL) and filtered through a short plug of silica gel. Concentration in vacuo gave a white powder **1b-PdOAc** (48%, 112.5 mg, 0.24 mmol).

Characterization Data for Substrates and Products

2-(Cyclohex-2-en-1-yloxy)-1,10-phenanthroline (1a): pale yellow solid (486.0 mg, 88% yield); m. p. 87.3-89.8 °C (from hexane); TLC R_f 0.20 (hexane/EtOAc, 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.15 (dd, *J* = 4.3, 1.8 Hz, 1H), 8.21 (dd, *J* = 8.1, 1.8 Hz, 1H), 8.09 (d, *J* = 8.7 Hz, 1H), 7.73 (d, *J* = 8.7 Hz, 1H), 7.64 (d, *J* = 8.7 Hz, 1H), 7.57 (dd, *J* = 8.1, 4.3 Hz, 1H), 7.10 (d, *J* = 8.7 Hz, 1H), 6.29-6.27 (m, 1H), 6.11-6.07 (m, 1H), 6.05-6.00 (m, 1H), 2.22-2.08 (m, 3H), 2.04-1.97 (m, 1H), 1.95-1.86 (m, 1H), 1.83-1.74 (m, 1H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 162.4, 150.0, 145.4, 144.5, 138.9, 136.0, 132.2, 129.1, 126.8, 126.3, 124.7, 123.5, 122.3, 114.5, 68.7, 28.6, 25.2, 19.1. HRMS (APCI) m/z ([M+H]$^+$) Calcd for $C_{18}H_{17}N_2O$: 277.1335, Found: 277.1324.

2-(Cyclohex-2-en-1-yloxy)pyridine (1a-Py): colorless oil (252.1 mg, 72%); TLC R_f 0.35 (hexane/EtOAc, 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.14 (ddd, *J* = 5.1, 2.0, 0.9 Hz, 1H), 7.54 (ddd, *J* = 9.1, 7.1, 2.0 Hz, 1H), 6.83 (ddd, *J* = 7.1, 5.1, 0.9 Hz, 1H), 6.71 (dt, *J* = 8.4, 0.9 Hz, 1H), 6.00-5.95 (m, 1H), 5.91-5.86 (m, 1H), 5.61-5.57 (m, 1H), 2.18-2.09 (m, 1H), 2.07-1.96 (m, 2H), 1.90-1.78 (m, 2H), 1.73-1.63 (m, 1H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 163.4, 146.8, 138.5, 132.0, 126.8, 116.4, 111.7, 68.4, 28.5, 25.1, 19.2. HRMS (APCI) m/z ([M+H]$^+$) Calcd for $C_{11}H_{14}NO$: 176.1070, Found: 176.1042.

6-(Cyclohex-2-en-1-yloxy)-2,2'-bipyridine (1a-bpy): colorless oil (347.9 mg, 69% yield); TLC R_f 0.33 (hexane/EtOAc, 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.65 (dq, *J* = 4.8, 0.9 Hz, 1H), 8.35 (dt, *J* = 8.0, 0.9 Hz, 1H), 7.98 (dd, *J* = 7.5, 0.9 Hz, 1H), 7.79 (td, *J* = 7.5, 1.8 Hz, 1H), 7.69 (dd, *J* = 8.2, 7.5 Hz, 1H), 7.27 (ddd, *J* = 7.5, 4.8, 1.2 Hz, 1H), 6.75 (dd, *J* = 8.2, 0.9 Hz, 1H), 6.04-5.98 (m, 2H), 5.78-5.75 (m, 1H), 2.21-2.13 (m, 1H), 2.10-2.02 (m, 2H), 2.00-1.83 (m, 2H), 1.77-1.68 (m, 1H). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ 162.7, 156.2, 153.3, 149.1, 139.5, 136.8, 132.1, 126.9, 123.4, 120.9, 113.4, 111.9, 68.5, 28.5, 25.2, 19.2. HRMS (APCI) m/z ([M+H]$^+$) Calcd for $C_{16}H_{17}N_2O$: 253.1335, Found: 253.1319.

2-((4,4-Dimethylcyclohex-2-en-1-yl)oxy)-1,10-phenanthroline (1b): colorless solid (553.6 mg, 91% yield); m. p. 125.5-127.2 °C (from hexane); TLC R_f 0.25 (hexane/EtOAc, 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.15 (dd, *J* = 4.3, 1.8 Hz, 1H), 8.21 (dd, *J* = 8.1, 1.8 Hz, 1H), 8.08 (d, *J* = 8.7 Hz, 1H), 7.73 (d, *J* = 8.7 Hz, 1H), 7.64 (d, *J* = 8.7 Hz, 1H), 7.57 (dd, *J* = 8.1, 4.3 Hz, 1H), 7.10 (d, *J* = 8.7 Hz, 1H), 6.23-6.19 (m, 1H), 5.92 (dd, *J* = 10.0, 3.4 Hz, 1H), 5.71 (dt, *J* = 10.0, 0.6 Hz, 1H),

2.26-2.18 (m, 1H), 2.02-1.95 (m, 1H), 1.77-1.71 (m, 1H), 1.65-1.59 (m, 1H), 1.10 (s, 3H), 1.05 (s, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 162.5, 150.0, 145.4, 144.5, 142.1, 138.9, 136.0, 129.1, 126.3, 124.6, 124.3, 123.5, 122.3, 114.5, 69.0, 33.7, 32.0, 29.3, 28.8, 25.7. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{20}H_{21}N_2O$: 305.1648, Found: 305.1675.

2-((2-Iodo-4,4-dimethylcyclohex-2-en-1-yl)oxy)-1,10-phenanthroline (1b-I): yellow solid (748.3 mg, 87% yield); m. p. 140.7-142.4 ºC (from hexane); TLC R_f 0.23 (hexane/EtOAc, 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.16 (dd, *J* = 4.3, 1.8 Hz, 1H), 8.22 (dd, *J* = 8.1, 1.8 Hz, 1H), 8.14 (d, *J* = 8.7 Hz, 1H), 7.74 (d, *J* = 8.7 Hz, 1H), 7.65 (d, *J* = 8.7 Hz, 1H), 7.57 (dd, *J* = 8.1, 4.3 Hz, 1H), 7.19 (d, *J* = 8.7 Hz, 1H), 6.48 (s, 1H), 6.29 (t, *J* = 4.5 Hz, 1H), 2.51-2.42 (m, 1H), 2.29-2.22 (m, 1H), 1.77-1.70 (m, 1H), 1.66-1.60 (m, 1H), 1.12 (s, 3H), 1.07 (s, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 162.1, 152.6, 150.0, 145.4, 144.3, 139.2, 136.0, 129.2, 126.3, 125.0, 123.8, 122.4, 114.4, 96.2, 74.4, 37.4, 32.1, 29.2, 27.6, 26.7. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{20}H_{20}IN_2O$: 431.0615, Found: 431.0627.

2-((2-Deuterio-4,4-dimethylcyclohex-2-en-1-yl)oxy)-1,10-phenanthroline ($[D_1]$1b): colorless solid (549.3 mg, 90% yield); m. p. 105.6-107.9 (from hexane); TLC R_f 0.25 (hexane/EtOAc, 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.15 (dd, *J* = 4.3, 1.8 Hz, 1H), 8.21 (dd, *J* = 8.1, 1.8 Hz, 1H), 8.08 (d, *J* = 8.7 Hz, 1H), 7.73 (d, *J* = 8.7 Hz, 1H), 7.64 (d, *J* = 8.7 Hz, 1H), 7.57 (dd, *J* = 8.1, 4.3 Hz, 1H), 7.10 (d, *J* = 8.7 Hz, 1H), 6.21 (t, *J* = 5.4 Hz, 1H), 5.71 (s, 1H), 2.26-2.18 (m, 1H), 2.02-1.95 (m, 1H), 1.77-1.71 (m, 1H), 1.65-1.59 (m, 1H), 1.10 (s, 3H), 1.05 (s, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 162.5, 150.0, 145.4, 144.5, 142.0, 138.9, 136.0, 129.1, 126.3, 124.6, 124.0 (t, *J* = 23.9 Hz), 123.4, 122.3, 114.5, 69.0, 33.7, 31.9, 29.3, 28.8, 25.7. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{20}H_{20}DN_2O$: 306.1711, Found: 306.1703.

2-(Cyclohept-2-en-1-yloxy)-1,10-phenanthroline (1c): colorless solid (412.0 mg, 71% yield); m. p. 117.3-119.8 (from hexane); TLC R_f 0.28 (hexane/EtOAc, 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.14 (dd, *J* = 4.3, 1.8 Hz, 1H), 8.21 (dd, *J* = 8.1, 1.8 Hz, 1H), 8.11 (d, *J* = 8.7 Hz, 1H), 7.73 (d, *J* = 8.7 Hz, 1H), 7.64 (d, *J* = 8.7 Hz, 1H), 7.57 (dd, *J* = 8.1, 4.3 Hz, 1H), 7.11 (d, *J* = 8.7 Hz, 1H), 6.34-6.32 (m, 1H), 5.99-5.87 (m, 2H), 2.31-2.26 (m, 2H), 2.20-2.15 (m, 1H), 2.06-1.97 (m, 1H), 1.95-1.88 (m, 2H), 1.86-1.76 (m, 1H), 1.61-1.52 (m, 1H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 162.2, 150.0, 145.4, 144.6, 138.9, 135.9, 134.4, 131.6, 129.1, 126.2, 124.6, 123.5, 122.4, 114.3, 75.0, 32.7, 28.6, 27.0, 26.2. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{19}H_{19}N_2O$: 291.1492, Found: 291.1482.

2-(Cyclopent-2-en-1-yloxy)-1,10-phenanthroline (1d): colorless solid (340.7 mg, 65% yield); m. p. 109.8-111.5 (from hexane); TLC R_f 0.25 (hexane/EtOAc, 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.15 (dd, *J* = 4.3, 1.8 Hz, 1H), 8.19 (dd, *J* = 8.1, 1.8 Hz, 1H), 8.07 (d, *J* = 8.7 Hz, 1H), 7.70 (d, *J* = 8.7 Hz, 1H), 7.61 (d, *J* = 8.7 Hz, 1H), 7.55 (dd, *J* = 8.1, 4.3 Hz, 1H), 7.07 (d, *J* = 8.7 Hz, 1H), 6.68-6.65 (m, 1H), 6.19-6.15 (m, 2H), 2.69-2.58 (m, 2H), 2.47-1.39 (m, 1H), 2.07-1.99 (m, 1H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 162.7, 149.9, 145.5, 144.5, 138.9, 136.9, 136.0, 130.6, 129.1, 126.3, 124.6, 123.5, 122.4, 114.3, 81.7, 31.3, 30.3. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{17}H_{15}N_2O$: 263.1179, Found: 263.1188.

(*Z*)-2-(Pent-2-en-1-yloxy)-1,10-phenanthroline (1e): colorless solid (433.2 mg, 82% yield); m. p. 67.2-68.9 (from hexane); TLC R_f 0.32 (hexane/EtOAc, 2:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.17 (dd, *J* = 4.3, 1.8 Hz, 1H), 8.23 (dd, *J* = 8.1, 1.8 Hz, 1H), 8.10 (d, *J* = 8.7 Hz, 1H), 7.74 (d, *J* = 8.7 Hz, 1H), 7.66 (d, *J* = 8.7 Hz, 1H), 7.58 (dd, *J* = 8.1, 4.3 Hz, 1H), 7.14 (d, *J* = 8.7 Hz, 1H), 5.83-5.71 (m, 2H), 5.33-5.32 (m, 2H), 2.33-2.26 (m, 2H), 1.04 (t, *J* = 7.5 Hz, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 162.9, 150.0, 145.4, 144.4, 138.9, 136.9, 136.1, 129.1, 126.3, 124.8, 123.8, 123.7, 122.4, 114.2, 62.3, 21.2, 14.3. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{17}H_{17}N_2O$: 265.1335, Found: 265.1311.

(*Z*)-2-(Hex-2-en-1-yloxy)-1,10-phenanthroline (*cis*-1f): colorless solid (472.8 mg, 85% yield); m. p. 68.1-70.6 (from hexane); TLC R_f 0.30 (hexane/EtOAc, 2:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.17 (dd, *J* = 4.3, 1.8 Hz, 1H), 8.23 (dd, *J* = 8.1, 1.8 Hz, 1H), 8.11 (d, *J* = 8.7 Hz, 1H), 7.75 (d, *J* = 8.7 Hz, 1H), 7.67 (d, *J* = 8.7 Hz, 1H), 7.59 (dd, *J* = 8.1, 4.3 Hz, 1H), 7.15 (d, *J* = 8.7 Hz, 1H), 5.87-5.80 (m, 1H), 5.78-5.72 (m, 1H), 5.33 (d, *J* = 6.5 Hz, 2H), 2.25 (q, *J* = 7.1 Hz, 2H), 1.50-1.41 (m, 2H), 0.95 (t, *J* = 7.3 Hz, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 162.9, 150.0, 145.4, 144.4, 138.9, 136.1, 135.2, 129.1, 126.3, 124.8, 124.5, 123.7, 122.4, 114.2, 62.4, 29.8, 22.8, 13.8. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{18}H_{19}N_2O$: 279.1492, Found: 279.1487.

(*Z*)-2-((3-Phenylallyl)oxy)-1,10-phenanthroline (*cis*-1g): colorless oil (493.2 mg, 79% yield); TLC R_f 0.38 (hexane/EtOAc, 2:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.15 (dd, *J* = 4.3, 1.8 Hz, 1H), 8.24 (dd, *J* = 8.1, 1.8 Hz, 1H), 8.14 (d, *J* = 8.7 Hz, 1H), 7.76 (d, *J* = 8.7 Hz, 1H), 7.68 (d, *J* = 8.7 Hz, 1H), 7.59 (dd, *J* = 8.1, 4.3 Hz, 1H), 7.43 (d, *J* = 7.2 Hz, 2H), 7.37 (t, *J* = 7.4 Hz, 2H), 7.27 (tt, *J* = 7.2, 1.3 Hz, 1H), 7.17 (d, *J* = 8.7 Hz, 1H), 6.78 (d, *J* = 11.7 Hz, 1H), 6.14 (dt, *J* = 11.7, 6.8 Hz, 1H), 5.55 (dd, *J* = 6.8, 1.5 Hz, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 162.2, 149.9, 145.3, 144.3, 139.1, 136.4, 136.2, 133.2, 129.1, 129.0, 128.4, 127.3, 127.1, 126.3, 124.9, 123.8, 122.5, 114.1, 63.0. HRMS (APCI) m/z

([M+H]$^+$) Calcd for $C_{21}H_{17}N_2O$: 313.1335, Found: 313.1341.

(*E*)-2-(Hex-2-en-1-yloxy)-1,10-phenanthroline (*trans*-1f): colorless oil (422.7 mg, 76% yield); TLC R_f 0.30 (hexane/EtOAc, 2:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.18 (dd, *J* = 4.3, 1.8 Hz, 1H), 8.22 (dd, *J* = 8.1, 1.8 Hz, 1H), 8.10 (d, *J* = 8.7 Hz, 1H), 7.74 (d, *J* = 8.7 Hz, 1H), 7.65 (d, *J* = 8.7 Hz, 1H), 7.58 (dd, *J* = 8.1, 4.3 Hz, 1H), 7.14 (d, *J* = 8.7 Hz, 1H), 6.01-5.94 (m, 1H), 5.89-5.81 (m, 1H), 5.22 (dd, *J* = 6.4, 1.0 Hz, 2H), 2.10 (q, *J* = 7.1 Hz, 2H), 1.50-1.41 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 162.8, 150.0, 145.4, 144.4, 138.9, 136.1, 136.0, 129.1, 126.3, 124.9, 124.8, 123.6, 122.4, 114.1, 67.3, 34.5, 22.2, 13.7. HRMS (APCI) m/z ([M+H]$^+$) Calcd for $C_{18}H_{19}N_2O$: 279.1492, Found: 279.1496.

(*E*)-2-((3-Phenylallyl)oxy)-1,10-phenanthroline (*trans*-1g): colorless solid (518.2 mg, 83% yield); m. p. 86.0-87.6 (from hexane); TLC R_f 0.38 (hexane/EtOAc, 2:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.20 (dd, *J* = 4.3, 1.8 Hz, 1H), 8.24 (dd, *J* = 8.1, 1.8 Hz, 1H), 8.14 (d, *J* = 8.7 Hz, 1H), 7.76 (d, *J* = 8.7 Hz, 1H), 7.68 (d, *J* = 8.7 Hz, 1H), 7.60 (dd, *J* = 8.1, 4.3 Hz, 1H), 7.47-7.45 (m, 2H), 7.35-7.31 (m, 2H), 7.27-7.23 (m, 1H), 7.19 (d, *J* = 8.7 Hz, 1H), 6.89 (d, *J* = 16.0 Hz, 1H), 6.59 (dt, *J* = 15.9, 6.2 Hz, 1H), 5.46 (dd, *J* = 6.2, 1.3 Hz, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 162.6, 150.1, 145.4, 144.4, 139.1, 136.7, 136.1, 133.6, 129.2, 128.6, 127.8, 126.7, 126.3, 124.9, 124.6, 123.8, 122.5, 114.0, 67.0. HRMS (APCI) m/z ([M+H]$^+$) Calcd for $C_{21}H_{17}N_2O$: 313.1335, Found: 313.1314.

2-((3-Methylbut-2-en-1-yl)oxy)-1,10-phenanthroline (1h): colorless solid (422.6 mg, 80% yield); m. p. 55.1-56.8 (from hexane); TLC R_f 0.31 (hexane/EtOAc, 2:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.17 (dd, *J* = 4.3, 1.8 Hz, 1H), 8.23 (dd, *J* = 8.1, 1.8 Hz, 1H), 8.10 (d, *J* = 8.7 Hz, 1H), 7.74 (d, *J* = 8.7 Hz, 1H), 7.65 (d, *J* = 8.7 Hz, 1H), 7.58 (dd, *J* = 8.1, 4.3 Hz, 1H), 7.14 (d, *J* = 8.7 Hz, 1H), 5.63 (tt, *J* = 7.3, 1.3 Hz, 1H), 5.27 (d, *J* = 7.3 Hz, 2H), 1.84 (bs, 6H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 163.0, 150.0, 145.4, 144.4, 139.0, 138.9, 136.1, 129.1, 126.3, 124.8, 123.6, 122.4, 119.5, 114.2, 63.3, 26.0, 18.4. HRMS (APCI) m/z ([M+H]$^+$) Calcd for $C_{17}H_{17}N_2O$: 265.1335, Found: 265.1341.

6-((3-Methylbut-2-en-1-yl)oxy)-2,2'-bipyridine (1h-bpy): pale yellow oil (1.0 mmol scale, 120.0 mg, 50% yield); TLC R_f 0.25 (hexane/EtOAc, 5:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.65 (dq, *J* = 4.8, 1.0 Hz, 1H), 8.39 (dt, *J* = 8.0, 1.0 Hz, 1H), 8.01 (dd, *J* = 7.4, 0.7 Hz, 1H), 7.78 (td, *J* = 7.5, 1.7 Hz, 1H), 7.68 (dd, *J* = 8.2, 0.7 Hz, 1H), 7.28-7.25 (m, 1H), 6.78 (dd, *J* = 8.2, 0.7 Hz, 1H), 5.62-5.58 (m, 1H), 4.96 (d, *J* = 7.2 Hz, 2H), 1.80 (bs, 6H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 163.2, 156.2, 153.4,

149.1, 139.4, 138.2, 136.7, 123.5, 121.0, 120.0, 113.6, 111.4, 62.5, 25.9, 18.2. HRMS (APCI) m/z ([M+H]$^+$) Calcd for $C_{15}H_{17}N_2O$: 241.1335, Found: 241.1331.

2-(2-Cyclohexylideneethoxy)-1,10-phenanthroline (1i): colorless oil (444.1 mg, 73% yield); TLC R_f 0.27 (hexane/EtOAc, 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.17 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.22 (dd, *J* = 8.1, 1.7 Hz, 1H), 8.09 (d, *J* = 8.7 Hz, 1H), 7.73 (d, *J* = 8.7 Hz, 1H), 7.64 (d, *J* = 8.7 Hz, 1H), 7.57 (dd, *J* = 8.1, 4.3 Hz, 1H), 7.14 (d, *J* = 8.7 Hz, 1H), 5.57 (t, *J* = 7.2 Hz, 1H), 5.28 (d, *J* = 7.2 Hz, 2H), 2.35 (bs, 2H), 2.20 (t, *J* = 4.7 Hz, 2H), 1.57 (bs, 6H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 163.1, 149.9, 146.7, 145.3, 144.3, 138.8, 136.2, 129.1, 126.4, 124.7, 123.5, 122.4, 116.1, 114.3, 62.7, 37.2, 29.3, 28.4, 27.8, 26.7. HRMS (APCI) m/z ([M+H]$^+$) Calcd for $C_{20}H_{21}N_2O$: 305.1648, Found: 305.1649.

6-(2-Cyclohexylideneethoxy)-2,2'-bipyridine (1i-bpy): pale yellow oil (1.0 mmol scale, 155.3 mg, 55%); TLC R_f 0.25 (hexane/EtOAc, 5:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.64 (dq, *J* = 4.8, 1.0 Hz, 1H), 8.39 (dt, *J* = 8.0, 1.0 Hz, 1H), 8.00 (dd, *J* = 7.4, 0.7 Hz, 1H), 7.77 (td, *J* = 7.4, 1.7 Hz, 1H), 7.68 (dd, *J* = 8.2, 0.7 Hz, 1H), 7.27-7.23 (m, 1H), 6.77 (dd, *J* = 8.2, 0.7 Hz, 1H), 5.53 (tt, *J* = 7.2, 1.0 Hz, 1H), 4.97 (d, *J* = 7.2 Hz, 2H), 2.30 (bs, 2H), 2.17-2.15 (m, 2H), 1.57-1.56 (m, 6H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 163.2, 156.2, 153.4, 149.1, 145.9, 139.3, 136.7, 123.4, 121.0, 116.7, 113.6, 111.4, 61.8, 37.1, 29.2, 28.4, 27.8, 26.7. HRMS (APCI) m/z ([M+H]$^+$) Calcd for $C_{18}H_{21}N_2O$: 281.1648, Found: 281.1649.

2-(2-Cyclopentylideneethoxy)-1,10-phenanthroline (1j): colorless oil (452.6 mg, 78% yield); TLC R_f 0.25 (hexane/EtOAc, 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.17 (dd, *J* = 4.3, 1.8 Hz, 1H), 8.23 (dd, *J* = 8.1, 1.8 Hz, 1H), 8.10 (d, *J* = 8.7 Hz, 1H), 7.74 (d, *J* = 8.7 Hz, 1H), 7.66 (d, *J* = 8.7 Hz, 1H), 7.58 (dd, *J* = 8.1, 4.3 Hz, 1H), 7.14 (d, *J* = 8.7 Hz, 1H), 5.75-5.70 (m, 1H), 5.26 (dt, *J* = 7.2, 1.0 Hz, 2H), 2.48 (t, *J* = 7.2 Hz, 2H), 2.38 (t, *J* = 7.2 Hz, 2H), 1.74-1.64 (m, 4H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 163.0, 150.5, 150.0, 145.4, 144.4, 138.9, 136.1, 129.1, 126.3, 124.7, 123.6, 122.4, 114.9, 114.2, 64.9, 34.0, 29.1, 26.4, 26.1. HRMS (APCI) m/z ([M+H]$^+$) Calcd for $C_{19}H_{19}N_2O$: 291.1492, Found: 291.1491.

2-(2-(Tetrahydro-4*H*-pyran-4-ylidene)ethoxy)-1,10-phenanthroline (1k): colorless oil (495.9 mg, 81% yield); TLC R_f 0.34 (hexane/EtOAc, 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.16 (dd, *J* = 4.3, 1.8 Hz, 1H), 8.23 (dd, *J* = 8.1, 1.8 Hz, 1H), 8.10 (d, *J* = 8.7 Hz, 1H), 7.74 (d, *J* = 8.7 Hz, 1H), 7.65 (d, *J*

= 8.7 Hz, 1H), 7.58 (dd, *J* = 8.1, 4.3 Hz, 1H), 7.13 (d, *J* = 8.7 Hz, 1H), 5.66 (t, *J* = 7.2 Hz, 1H), 5.31 (d, *J* = 7.2 Hz, 2H), 3.71 (t, *J* = 5.4 Hz, 2H), 3.67 (t, *J* = 5.4 Hz, 2H), 2.55 (t, *J* = 5.6 Hz, 2H), 2.31 (t, *J* = 5.6 Hz, 2H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 162.8, 149.8, 145.1, 144.2, 141.0, 139.0, 136.3, 129.1, 126.4, 124.8, 123.6, 122.4, 118.2, 114.2, 69.3, 68.8, 62.2, 36.9, 30.3. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{19}H_{19}N_2O_2$: 307.1441, Found: 307.1426.

Ethyl 4-(2-((1,10-phenanthrolin-2-yl)oxy)ethylidene)piperidine-1-carboxylate (1l): colorless oil (565.8 mg, 75% yield); TLC R_f 0.33 (hexane/EtOAc, 1:2). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.16 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.23 (dd, *J* = 8.1, 1.7 Hz, 1H), 8.11 (d, *J* = 8.7 Hz, 1H), 7.75 (d, *J* = 8.7 Hz, 1H), 7.66 (d, *J* = 8.7 Hz, 1H), 7.58 (dd, *J* = 8.1, 4.3 Hz, 1H), 7.13 (d, *J* = 8.7 Hz, 1H), 5.71 (t, *J* = 7.2 Hz, 1H), 5.31 (d, *J* = 7.2 Hz, 2H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.50-3.46 (m, 4H), 2.50 (bs, 2H), 2.27 (bs, 2H), 1.26 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 162.7, 155.5, 150.0, 145.3, 144.3, 141.4, 139.0, 136.1, 129.2, 126.3, 124.8, 123.7, 122.5, 119.2, 114.1, 62.2, 61.3, 45.3, 44.7, 35.8, 28.8, 14.7. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{22}H_{24}N_3O_3$: 378.1812, Found: 378.1828.

***tert*-Butyl 4-(2-((1,10-phenanthrolin-2-yl)oxy)ethylidene)piperidine-1-carboxylate (1m):** colorless oil (640.2 mg, 79% yield); TLC R_f 0.31 (hexane/EtOAc, 1:2). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.17 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.24 (dd, *J* = 8.1, 1.7 Hz, 1H), 8.11 (d, *J* = 8.7 Hz, 1H), 7.75 (d, *J* = 8.7 Hz, 1H), 7.66 (d, *J* = 8.7 Hz, 1H), 7.59 (dd, *J* = 8.1, 4.3 Hz, 1H), 7.13 (d, *J* = 8.7 Hz, 1H), 5.69 (t, *J* = 7.2 Hz, 1H), 5.31 (d, *J* = 7.2 Hz, 2H), 3.47-3.41 (m, 4H), 2.49 (bs, 2H), 2.26 (bs, 2H), 1.46 (s, 9H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 162.7, 154.7, 149.9, 145.2, 144.3, 141.7, 139.0, 136.2, 129.2, 126.3, 124.8, 123.7, 122.5, 118.9, 114.1, 79.5, 62.2, 45.7, 44.9, 35.9, 28.9, 28.5. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{24}H_{28}N_3O_3$: 406.2125, Found: 406.2135.

***tert*-Butyl**
3-(2-((1,10-phenanthrolin-2-yl)oxy)ethylidene)-8-azabicyclo[3.2.1]octane-8-carboxylate (1n): colorless oil (698.6 mg, 81% yield); TLC R_f 0.26 (hexane/EtOAc, 1:2). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.16 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.23 (dd, *J* = 8.1, 1.7 Hz, 1H), 8.11 (d, *J* = 8.7 Hz, 1H), 7.75 (d, *J* = 8.7 Hz, 1H), 7.66 (d, *J* = 8.7 Hz, 1H), 7.58 (dd, *J* = 8.1, 4.3 Hz, 1H), 7.13 (d, *J* = 8.7 Hz, 1H), 5.77 (t, *J* = 7.1 Hz, 1H), 5.40 (bs, 1H), 5.18 (bs, 1H), 4.30 (bs, 1H), 4.20 (bs, 1H), 2.79 (d, *J* = 13.8 Hz, 1H), 2.68-2.54 (m, 1H), 2.42-2.28 (m, 1H), 2.10 (d, *J* = 13.8 Hz, 1H), 1.89-1.82 (m, 2H), 1.63-1.54 (m, 2H), 1.48 (s, 9H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 162.8, 153.6, 149.9, 145.2, 144.3, 139.0, 138.9, 136.2, 129.1, 126.3, 124.8, 123.7, 123.1, 122.4, 114.1, 79.3, 62.1, 54.2, 53.6, 42.4, 41.6, 35.4,

34.7, 28.5. HRMS (APCI) m/z ([M+H]$^+$) Calcd for $C_{26}H_{30}N_3O_3$: 432.2282, Found: 432.2270.

***tert*-Butyl (*E*)-3-(6-((1,10-phenanthrolin-2-yl)oxy)cyclohex-1-en-1-yl)acrylate (3aa):** colorless oil (62.5 mg, 78% yield); TLC R_f 0.20 (hexane/EtOAc, 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.17 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.21 (dd, *J* = 8.1, 1.7 Hz, 1H), 8.10 (d, *J* = 8.6 Hz, 1H), 7.73 (d, *J* = 8.6 Hz, 1H), 7.65 (d, *J* = 8.6 Hz, 1H), 7.57 (dd, *J* = 8.1, 4.4 Hz, 1H), 7.22 (d, *J* = 15.9 Hz, 1H), 7.10 (d, *J* = 8.6 Hz, 1H), 6.49-6.46 (m, 2H), 5.95 (d, *J* = 15.9 Hz, 1H), 2.50-2.38 (m, 2H), 2.30-2.26 (m, 1H), 1.97 (tt, *J* = 13.4, 3.4 Hz, 1H), 1.90-1.79 (m, 1H), 1.71-1.69 (m, 1H), 1.33 (s, 9H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 167.0, 162.0, 150.0, 145.5, 144.5, 144.4, 141.9, 139.1, 136.0, 134.4, 129.2, 126.3, 124.9, 123.7, 122.4, 118.6, 114.5, 79.8, 66.7, 28.1, 27.7, 26.7, 17.1. HRMS (APCI) m/z ([M+H]$^+$) Calcd for $C_{25}H_{27}N_2O_3$: 403.2016, Found: 403.2011.

Methyl (*E*)-3-(6-((1,10-phenanthrolin-2-yl)oxy)cyclohex-1-en-1-yl)acrylate (3ab): colorless oil (55.3 mg, 77% yield); TLC R_f 0.30 (hexane/EtOAc, 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.16 (dd, *J* = 4.3, 1.8 Hz, 1H), 8.21 (dd, *J* = 8.1, 1.8 Hz, 1H), 8.10 (d, *J* = 8.7 Hz, 1H), 7.73 (d, *J* = 8.7 Hz, 1H), 7.65 (d, *J* = 8.7 Hz, 1H), 7.57 (dd, *J* = 8.1, 4.3 Hz, 1H), 7.33 (d, *J* = 15.9 Hz, 1H), 7.08 (d, *J* = 8.6 Hz, 1H), 6.54-6.51 (m, 2H), 6.00 (d, *J* = 15.9 Hz, 1H), 3.59 (s, 3H), 2.48-2.39 (m, 2H), 2.31-2.23 (m, 1H), 2.00 (tt, *J* = 13.3, 3.5 Hz, 1H), 1.91-1.80 (m, 1H), 1.73-1.70 (m, 1H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 168.0, 161.9, 149.9, 145.8, 145.4, 144.5, 142.9, 139.2, 136.1, 134.4, 129.2, 126.3, 124.9, 123.7, 122.4, 116.2, 114.4, 66.5, 51.3, 27.7, 26.7, 17.2. HRMS (APCI) m/z ([M+H]$^+$) Calcd for $C_{22}H_{21}N_2O_3$: 361.1547, Found: 361.1533.

Ethyl (*E*)-3-(6-((1,10-phenanthrolin-2-yl)oxy)cyclohex-1-en-1-yl)acrylate (3ac): colorless oil (59.0 mg, 79% yield); TLC R_f 0.28 (hexane/EtOAc, 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.16 (dd, *J* = 4.3, 1.8 Hz, 1H), 8.21 (dd, *J* = 8.1, 1.8 Hz, 1H), 8.10 (d, *J* = 8.7 Hz, 1H), 7.73 (d, *J* = 8.7 Hz, 1H), 7.65 (d, *J* = 8.7 Hz, 1H), 7.57 (dd, *J* = 8.1, 4.3 Hz, 1H), 7.32 (d, *J* = 15.9 Hz, 1H), 7.08 (d, *J* = 8.6 Hz, 1H), 6.54 (s, 1H), 6.51 (dd, *J* = 4.8, 3.4 Hz, 1H), 6.01 (d, *J* = 15.9 Hz, 1H), 4.13-3.98 (m, 2H), 2.48-2.39 (m, 2H), 2.31-2.24 (m, 1H), 1.98 (tt, *J* = 13.2, 3.4 Hz, 1H), 1.91-1.79 (m, 1H), 1.72-1.68 (m, 1H), 1.12 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 167.6, 161.9, 149.9, 145.5, 145.4, 144.4, 142.6, 139.2, 136.1, 134.4, 129.2, 126.3, 124.9, 123.7, 122.4, 116.7, 114.5, 66.5, 60.0, 27.7, 26.7, 17.1, 14.2. HRMS (APCI) m/z ([M+H]$^+$) Calcd for $C_{23}H_{23}N_2O_3$: 375.1703, Found: 375.1705.

Butyl (*E*)-3-(6-((1,10-phenanthrolin-2-yl)oxy)cyclohex-1-en-1-yl)acrylate (3ad): colorless oil

(73.1 mg, 91% yield); TLC R_f 0.28 (hexane/EtOAc, 2:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.16 (dd, *J* = 4.3, 1.8 Hz, 1H), 8.21 (dd, *J* = 8.1, 1.8 Hz, 1H), 8.10 (d, *J* = 8.7 Hz, 1H), 7.72 (d, *J* = 8.7 Hz, 1H), 7.64 (d, *J* = 8.7 Hz, 1H), 7.56 (dd, *J* = 8.1, 4.3 Hz, 1H), 7.31 (d, *J* = 15.9 Hz, 1H), 7.08 (d, *J* = 8.6 Hz, 1H), 6.54 (s, 1H), 6.50 (dd, *J* = 4.8, 3.3 Hz, 1H), 6.05 (d, *J* = 15.9 Hz, 1H), 4.06-3.92 (m, 2H), 2.48-2.39 (m, 2H), 2.30-2.23 (m, 1H), 1.98 (tt, *J* = 13.5, 3.4 Hz, 1H), 1.91-1.80 (m, 1H), 1.72-1.69 (m, 1H), 1.49-1.42 (m, 2H), 1.25-1.15 (m, 2H), 0.79 (t, *J* = 7.4 Hz, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 167.7, 161.9, 149.9, 145.5, 144.5, 142.6, 139.2, 136.0, 134.4, 129.2, 126.3, 124.9, 123.7, 122.4, 116.8, 114.4, 66.5, 63.9, 30.6, 27.7, 26.7, 19.0, 17.1, 13.7 (two sp^2 C are overlapping). HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{25}H_{27}N_2O_3$: 403.2016, Found: 403.2046.

Isobutyl (*E*)-3-(6-((1,10-phenanthrolin-2-yl)oxy)cyclohex-1-en-1-yl)acrylate (3ae): colorless oil (68.3 mg, 85% yield); TLC R_f 0.25 (hexane/EtOAc, 2:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.16 (dd, *J* = 4.3, 1.8 Hz, 1H), 8.21 (dd, *J* = 8.1, 1.8 Hz, 1H), 8.10 (d, *J* = 8.7 Hz, 1H), 7.72 (d, *J* = 8.6 Hz, 1H), 7.64 (d, *J* = 8.6 Hz, 1H), 7.56 (dd, *J* = 8.1, 4.3 Hz, 1H), 7.31 (d, *J* = 15.9 Hz, 1H), 7.08 (d, *J* = 8.6 Hz, 1H), 6.56 (t, *J* = 2.9 Hz, 1H), 6.50 (dd, *J* = 4.8, 3.2 Hz, 1H), 6.08 (d, *J* = 15.9 Hz, 1H), 3.82 (dd, *J* = 10.7, 6.6 Hz, 1H), 3.72 (dd, *J* = 10.7, 6.6 Hz, 1H), 2.49-2.39 (m, 2H), 2.30-2.24 (m, 1H), 1.98 (tt, *J* = 13.6, 3.5 Hz, 1H), 1.92-1.81 (m, 1H), 1.79-1.69 (m, 2H), 0.76 (d, *J* = 6.7 Hz, 6H), 0.74 (d, *J* = 6.7 Hz, 6H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 167.7, 161.9, 150.0, 145.4, 144.4, 142.5, 139.2, 136.0, 134.5, 129.2, 126.2, 124.9, 123.7, 122.4, 116.8, 114.4, 70.2, 66.4, 27.7, 27.6, 26.7, 19.0, 17.1 (two sp^2 C are overlapping). HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{25}H_{27}N_2O_3$: 403.2016, Found: 403.2012.

Cyclohexyl (*E*)-3-(6-((1,10-phenanthrolin-2-yl)oxy)cyclohex-1-en-1-yl)acrylate (3af): colorless oil (58.2 mg, 68% yield); TLC R_f 0.35 (hexane/EtOAc, 2:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.19 (dd, *J* = 4.3, 1.6 Hz, 1H), 8.25 (dd, *J* = 8.1, 1.6 Hz, 1H), 8.10 (d, *J* = 8.7 Hz, 1H), 7.75 (d, *J* = 8.7 Hz, 1H), 7.66 (d, *J* = 8.7 Hz, 1H), 7.59 (dd, *J* = 8.1, 4.3 Hz, 1H), 7.30 (d, *J* = 16.0 Hz, 1H), 7.10 (d, *J* = 8.6 Hz, 1H), 6.55 (s, 1H), 6.50 (dd, *J* = 4.8, 3.3 Hz, 1H), 6.02 (d, *J* = 16.0 Hz, 1H), 4.72-4.67 (m, 1H), 2.49-2.45 (m, 2H), 2.31-2.24 (m, 1H), 2.00 (tt, *J* = 13.6, 3.5 Hz, 1H), 1.91-1.80 (m, 1H), 1.74-1.69 (m, 3H), 1.58-1.53 (m, 2H), 1.45-1.42 (m, 1H), 1.30-1.21 (m, 4H), 1.15-1.10 (m, 1H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 167.0, 162.0, 149.7, 145.2, 144.2, 142.3, 139.1, 136.4, 134.4, 129.2, 126.4, 124.9, 123.6, 122.4, 117.4, 114.7, 72.1, 66.7, 31.6, 31.5, 27.7, 26.7, 25.4, 23.6, 17.1 (two sp^2 C are overlapping). HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{27}H_{29}N_2O_3$: 429.2173, Found: 429.2147.

Phenyl (*E*)-3-(6-((1,10-phenanthrolin-2-yl)oxy)cyclohex-1-en-1-yl)acrylate (3ag): colorless solid (63.3 mg, 75% yield); m. p. 66.8-68.5 (from hexane); TLC R_f 0.30 (hexane/EtOAc, 2:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.18 (dd, *J* = 4.3, 1.8 Hz, 1H), 8.22 (dd, *J* = 8.1, 1.7 Hz, 1H), 8.14 (d, *J* = 8.7 Hz, 1H), 7.75 (d, *J* = 8.7 Hz, 1H), 7.67 (d, *J* = 8.7 Hz, 1H), 7.57 (dd, *J* = 8.1, 4.3 Hz, 1H), 7.51 (d, *J* = 16.0 Hz, 1H), 7.30-7.26 (m, 2H), 7.15-7.11 (m, 2H), 6.99-6.96 (m, 2H), 6.63-6.59 (m, 2H), 6.25 (d, *J* = 16.0 Hz, 1H), 2.50-2.45 (m, 2H), 2.35-2.29 (m, 1H), 2.03 (tt, *J* = 13.6, 3.9 Hz, 1H), 1.96-1.85 (m, 1H), 1.77-1.74 (m, 1H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 166.0, 161.9, 150.8, 150.0, 147.5, 145.5, 144.5, 144.0, 139.3, 136.0, 134.5, 129.3, 129.2, 126.3, 125.4, 125.0, 123.8, 122.4, 121.6, 115.8, 114.4, 66.4, 27.7, 26.8, 17.1. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{27}H_{23}N_2O_3$: 423.1703, Found: 423.1715.

2-Methoxyethyl (*E*)-3-(6-((1,10-phenanthrolin-2-yl)oxy)cyclohex-1-en-1-yl)acrylate (3ah): colorless oil (63.8 mg, 79% yield); TLC R_f 0.40 (hexane/EtOAc, 2:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.18 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.23 (dd, *J* = 8.1, 1.6 Hz, 1H), 8.10 (d, *J* = 8.7 Hz, 1H), 7.74 (d, *J* = 8.7 Hz, 1H), 7.65 (d, *J* = 8.7 Hz, 1H), 7.58 (dd, *J* = 8.1, 4.3 Hz, 1H), 7.35 (d, *J* = 16.0 Hz, 1H), 7.08 (d, *J* = 8.6 Hz, 1H), 6.53-6.51 (m, 2H), 6.03 (d, *J* = 16.0 Hz, 1H), 4.23-4.10 (m, 2H), 3.46 (t, *J* = 4.7 Hz, 2H), 3.22 (s, 3H), 2.48-2.39 (m, 2H), 2.31-2.23 (m, 1H), 1.99 (tt, *J* = 13.5, 3.3 Hz, 1H), 1.90-1.78 (m, 1H), 1.72-1.68 (m, 1H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 167.5, 161.9, 149.7, 146.2, 143.1, 139.2, 136.4, 136.3, 134.3, 129.2, 126.4, 125.0, 123.6, 122.4, 116.2, 114.6, 70.5, 66.6, 63.2, 58.9, 27.6, 26.7, 17.1 (two sp^2 C are overlapping). HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{24}H_{25}N_2O_4$: 405.1809, Found: 405.1833.

(*E*)-4-(6-((1,10-Phenanthrolin-2-yl)oxy)cyclohex-1-en-1-yl)but-3-en-2-one (3ai): colorless oil (52.2 mg, 76% yield); TLC R_f 0.35 (hexane/EtOAc, 2:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.17 (dd, *J* = 4.3, 1.8 Hz, 1H), 8.24 (dd, *J* = 8.1, 1.8 Hz, 1H), 8.12 (d, *J* = 8.7 Hz, 1H), 7.76 (d, *J* = 8.7 Hz, 1H), 7.67 (d, *J* = 8.7 Hz, 1H), 7.59 (dd, *J* = 8.1, 4.3 Hz, 1H), 7.19 (d, *J* = 16.1 Hz, 1H), 7.09 (d, *J* = 8.7 Hz, 1H), 6.60-6.56 (m, 2H), 6.45 (d, *J* = 16.1 Hz, 1H), 2.48-2.42 (m, 2H), 2.32-2.26 (m, 1H), 2.07 (s, 3H), 2.02-1.94 (m, 2H), 1.76-1.71 (m, 1H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 199.0, 161.9, 150.0, 145.4, 144.4, 144.2, 143.5, 139.2, 136.1, 134.7, 129.2, 126.3, 125.6, 124.9, 123.8, 122.5, 114.4, 66.3, 27.9, 27.8, 26.9, 17.1. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{22}H_{21}N_2O_2$: 345.1598, Found: 345.1596.

(*E*)-3-(6-((1,10-Phenanthrolin-2-yl)oxy)cyclohex-1-en-1-yl)acrylonitrile (3aj): colorless oil (52.9 mg, 81% yield); TLC R_f 0.33 (hexane/EtOAc, 2:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.17 (dd, *J* = 4.3,

1.7 Hz, 1H), 8.25 (dd, *J* = 8.1, 1.7 Hz, 1H), 8.14 (d, *J* = 8.6 Hz, 1H), 7.76 (d, *J* = 8.7 Hz, 1H), 7.69 (d, *J* = 8.7 Hz, 1H), 7.60 (dd, *J* = 8.1, 4.3 Hz, 1H), 7.08 (d, *J* = 8.7 Hz, 1H), 6.99 (d, *J* = 16.6 Hz, 1H), 6.69 (t, *J* = 2.7 Hz, 1H), 6.46 (dd, *J* = 4.8, 3.4 Hz, 1H), 6.04 (d, *J* = 16.6 Hz, 1H), 2.50-2.43 (m, 1H), 2.33-2.25 (m, 2H), 1.97-1.89 (m, 2H), 1.78-1.74 (m, 1H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 161.6, 151.1, 150.1, 145.3, 144.2, 143.5, 139.5, 136.1, 134.6, 129.3, 126.2, 125.0, 124.0, 122.6, 119.2, 114.2, 95.9, 64.9, 28.2, 26.6, 16.8. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{21}H_{18}N_3O$: 328.1444, Found: 328.1445.

(*E*)-2-((2-(2-(Phenylsulfonyl)vinyl)cyclohex-2-en-1-yl)oxy)-1,10-phenanthroline (3ak): colorless oil (60.1 mg, 68% yield); TLC R_f 0.28 (hexane/EtOAc, 2:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.10 (dd, *J* = 4.3, 1.6 Hz, 1H), 8.22 (dd, *J* = 8.1, 1.6 Hz, 1H), 8.02 (d, *J* = 8.7 Hz, 1H), 7.69 (d, *J* = 8.7 Hz, 1H), 7.64 (d, *J* = 8.7 Hz, 1H), 7.59 (dd, *J* = 8.1, 4.3 Hz, 1H), 7.41-7.22 (m, 5 H), 7.03-6.99 (m, 2H), 6.96 (d, *J* = 8.7 Hz, 1H), 6.67 (s, 1H), 6.59 (dd, *J* = 4.9, 3.1 Hz, 1H), 2.52-2.45 (m, 1H), 2.35-2.22 (m, 2H), 2.00-1.85 (m, 2H), 1.78-1.75 (m, 1H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 161.7, 150.1, 145.1, 144.9, 143.9, 142.7, 140.9, 139.1, 135.9, 133.6, 132.2, 129.1, 128.3, 126.8, 126.1, 124.7, 123.7, 122.5, 114.1, 65.2, 28.4, 26.7, 16.8 (two sp^2 C are overlapping). HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{26}H_{23}N_2O_3S$: 443.1424, Found: 443.1401.

***tert*-Butyl (*E*)-3-(6-((1,10-phenanthrolin-2-yl)oxy)-3,3-dimethylcyclohex-1-en-1-yl)acrylate (3ba):** colorless solid (73.9 mg, 86% yield); m. p. 184.5-186.1 °C (from hexane); TLC R_f 0.22 (hexane/EtOAc, 2:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.15 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.18 (dd, *J* = 8.1, 1.8 Hz, 1H), 8.07 (d, *J* = 8.7 Hz, 1H), 7.69 (d, *J* = 8.7 Hz, 1H), 7.61 (d, *J* = 8.7 Hz, 1H), 7.54 (dd, *J* = 8.1, 4.3 Hz, 1H), 7.19 (d, *J* = 15.9 Hz, 1H), 7.08 (d, *J* = 8.7 Hz, 1H), 6.42 (t, *J* = 3.4 Hz, 1H), 6.14 (s, 1H), 5.94 (d, *J* = 15.9 Hz, 1H), 2.40-2.34 (m, 1H), 2.15 (tt, *J* = 13.4, 3.5 Hz, 1H), 2.15 (td, *J* = 13.4, 3.1 Hz, 1H), 1.48-1.45 (m, 1H), 1.33 (s, 9H), 1.15 (s, 3H), 1.06 (s, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 166.8, 162.0, 151.4, 149.9, 145.4, 144.6, 144.4, 139.1, 136.0, 131.9, 129.2, 126.3, 124.8, 123.7, 122.3, 119.3, 114.4, 79.7, 66.6, 33.3, 31.7, 30.1, 28.1, 26.9, 24.9. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{27}H_{31}N_2O_3$: 431.2329, Found: 431.2301.

***tert*-Butyl (*E*)-3-(7-((1,10-phenanthrolin-2-yl)oxy)cyclohept-1-en-1-yl)acrylate (3ca):** colorless solid (57.4 mg, 69% yield); m. p. 119.0-120.7 (from hexane); TLC R_f 0.28 (hexane/EtOAc, 2:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.18 (dd, *J* = 4.3, 1.8 Hz, 1H), 8.20 (dd, *J* = 8.1, 1.8 Hz, 1H), 8.10 (d, *J* = 8.7 Hz, 1H), 7.72 (d, *J* = 8.7 Hz, 1H), 7.64 (d, *J* = 8.7 Hz, 1H), 7.56 (dd, *J* = 8.1, 4.3 Hz, 1H), 7.24

(d, *J* = 15.9 Hz, 1H), 7.12 (d, *J* = 8.7 Hz, 1H), 6.62 (d, *J* = 6.7 Hz, 1H), 6.45 (t, *J* = 6.7 Hz, 1H), 6.39 (d, *J* = 15.9 Hz, 1H), 2.72-2.62 (m, 2H), 2.36-2.29 (m, 1H), 2.10-2.01 (m, 1H), 1.91-1.77 (m, 3H), 1.64-1.55 (m, 1H), 1.42 (s, 9H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 167.3, 161.9, 150.0, 146.3, 145.5, 145.2, 144.6, 140.6, 139.0, 135.8, 129.1, 126.1, 124.8, 123.6, 122.3, 118.6, 114.0, 79.7, 71.1, 29.3, 28.2, 28.1, 26.6, 24.5. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{26}H_{29}N_2O_3$: 417.2173, Found: 417.2155.

***tert*-Butyl (*E*)-3-(5-((1,10-phenanthrolin-2-yl)oxy)cyclopent-1-en-1-yl)acrylate (3da):** colorless oil (45.0 mg, 58% yield); TLC R_f 0.30 (hexane/EtOAc, 2:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.17 (dd, *J* = 4.3, 1.8 Hz, 1H), 8.22 (dd, *J* = 8.1, 1.8 Hz, 1H), 8.11 (d, *J* = 8.7 Hz, 1H), 7.75 (d, *J* = 8.7 Hz, 1H), 7.66 (d, *J* = 8.7 Hz, 1H), 7.58 (dd, *J* = 8.1, 4.3 Hz, 1H), 7.42 (d, *J* = 15.9 Hz, 1H), 7.11 (d, *J* = 8.7 Hz, 1H), 6.79 (dd, *J* = 5.1, 2.3 Hz, 1H), 6.49 (t, *J* = 2.6 Hz, 1H), 6.02 (dd, *J* = 15.9, 0.6 Hz, 1H), 2.96-2.87 (m, 1H), 2.76-2.68 (m, 1H), 2.58-2.49 (m, 1H), 2.15-2.09 (m, 1H), 1.39 (s, 9H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 166.8, 162.3, 150.0, 145.5, 144.4, 143.9, 140.3, 139.0, 137.4, 136.0, 129.2, 126.3, 124.8, 123.7, 122.4, 121.6, 114.3, 80.0, 79.5, 31.8, 31.3, 28.1. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{24}H_{25}N_2O_3$: 389.1860, Found: 389.1882.

7:3 Stereomixture of *tert*-butyl (2*E*,4*Z*)-4-(((1,10-phenanthrolin-2-yl)oxy)methyl)hepta-2,4-dienoate (*cis*-3ea) and *tert*-butyl (2*E*,4*E*)-4-(((1,10-phenanthrolin-2-yl)oxy)methyl)hepta-2,4-dienoate (*trans*-3ea): colorless oil (47.5 mg, 61% yield); TLC R_f 0.35 (hexane/EtOAc, 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz) for mixture δ 9.19-9.17 (m, 1H, for ***cis*** + ***trans***), 8.26-8.23 (m, 1H, for ***cis*** + ***trans***), 8.14-8.11 (m, 1H, for ***cis*** + ***trans***), 7.77-7.75 (m, 1H, for ***cis*** + ***trans***), 7.71-7.67 (m, 1.3H, for ***cis*** + ***trans***), 7.61-7.58 (m, 1H, for ***cis*** + ***trans***), 7.29 (d, *J* = 15.9 Hz, 0.7H, for ***cis***), 7.18-7.14 (m, 1H, for ***cis*** + ***trans***), 6.26 (t, *J* = 7.6 Hz, 0.3H, for ***trans***), 6.21 (t, *J* = 7.6 Hz, 0.7H, for ***cis***), 6.09 (d, *J* = 15.9 Hz, 0.3H, for ***trans***), 5.98 (d, *J* = 15.9 Hz, 0.7H, for ***cis***), 5.45 (s, 1.4H, for ***cis***), 5.38 (s, 0.6H, for ***trans***), 2.51-2.36 (m, 2H, for ***cis*** + ***trans***), 1.47 (s, 2.7H, for ***trans***), 1.45 (s, 6.3H, for ***cis***), 1.09-1.04 (m, 3H, for ***cis*** + ***trans***). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) for mixture δ 166.9, 166.8, 162.7, 162.6, 150.0, 148.0, 145.8, 145.3, 144.9, 144.3, 139.0, 137.6, 136.2, 132.2, 130.4, 129.2, 129.1, 126.3, 125.0, 124.9, 123.9, 123.8, 122.5, 121.1, 119.0, 114.2, 114.1, 80.2, 80.0, 68.3, 60.6, 28.2, 22.3, 21.5, 13.9. (All observed signals are shown because of complexity associated with stereoisomers.) HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{24}H_{27}N_2O_3$: 391.2016, Found: 391.2033.

3:1 Stereomixture of *tert*-butyl (2*E*,4*Z*)-4-(((1,10-phenanthrolin-2-yl)oxy)methyl)octa-2,4-dienoate (*cis*-3fa) and *tert*-butyl (2*E*,4*E*)-4-(((1,10-phenanthrolin-2-yl)oxy)methyl)octa-2,4-dienoate (*trans*-3fa): colorless oil (54.1 mg, 67% yield); TLC R_f 0.32 (hexane/EtOAc, 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz) for mixture δ 9.20-9.18 (m, 1H, for ***cis*** + ***trans***), 8.26-8.24 (m, 1H, for ***cis*** + ***trans***), 8.14-8.12 (m, 1H, for ***cis*** + ***trans***), 7.78-7.75 (m, 1H, for ***cis*** + ***trans***), 7.72-7.67 (m, 1.25H, for ***cis*** + ***trans***), 7.62-7.58 (m, 1H, for ***cis*** + ***trans***), 7.29 (d, *J* = 15.9 Hz, 0.75H, for ***cis***), 7.18-7.14 (m, 1H, for ***cis*** + ***trans***), 6.29 (t, *J* = 7.7 Hz, 0.25H, for ***trans***), 6.22 (t, *J* = 7.7 Hz, 0.75H, for ***cis***), 6.10 (d, *J* = 15.9 Hz, 0.25H, for ***trans***), 5.98 (d, *J* = 15.9 Hz, 0.75H, for ***cis***), 5.46 (s, 1.5H, for ***cis***), 5.38 (s, 0.5H, for ***trans***), 2.43 (q, *J* = 7.5 Hz, 1.5H, for ***cis***), 2.36 (q, *J* = 7.5 Hz, 0.5H, for ***trans***), 1.51-1.45 (m, 11H, for ***cis*** + ***trans***), 0.96-0.91 (m, 3H, for ***cis*** + ***trans***). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) for mixture δ 167.0, 166.9, 162.7, 162.6, 150.0, 146.5, 145.8, 145.3, 144.3, 144.5, 139.0, 137.7, 136.2, 132.8, 131.1, 129.2, 126.3, 125.0, 124.9, 123.9, 123.8, 122.5, 121.0, 119.0, 114.2, 80.2, 80.0, 68.4, 60.7, 30.9, 30.1, 28.2, 22.6, 22.5, 13.8, 13.7. (All observed signals are shown because of complexity associated with stereoisomers.) HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{25}H_{29}N_2O_3$: 405.2173, Found: 405.2147.

4:1 Stereomixture of *tert*-butyl (2*E*,4*Z*)-4-(((1,10-phenanthrolin-2-yl)oxy)methyl)-5-phenylpenta-2,4-dienoate (*cis*-3ga) and *tert*-butyl (2*E*,4*E*)-4-(((1,10-phenanthrolin-2-yl)oxy)methyl)-5-phenylpenta-2,4-dienoate (*trans*-3ga): colorless oil (70.9 mg, 81% yield); TLC R_f 0.24 (hexane/EtOAc, 2:1). ^{1}H NMR ($CDCl_3$, 400 MHz) for mixture δ 9.21 (dd, *J* = 4.3, 1.8 Hz, 0.2H, for ***trans***), 9.15 (dd, *J* = 4.3, 1.8 Hz, 0.8H, for ***cis***), 8.27-8.22 (m, 1H, for ***cis*** + ***trans***), 8.19-8.14 (m, 1H, for ***cis*** + ***trans***), 7.83-7.76 (m, 1.2H, for ***cis*** + ***trans***), 7.69 (d, *J* = 8.7 Hz, 1H, for ***cis*** + ***trans***), 7.63-7.56 (m, 1H, for ***cis*** + ***trans***), 7.50-7.43 (m, 2H, for ***cis*** + ***trans***), 7.39-7.35 (m, 1H, for ***cis*** + ***trans***), 7.31-7.20 (m, 4.8H, for ***cis*** + ***trans***), 6.27 (d, *J* = 15.9 Hz, 0.2H, for ***trans***), 6.12 (d, *J* = 15.9 Hz, 0.8H, for ***cis***), 5.58 (s, 0.4H, for ***trans***), 5.54 (s, 1.6H, for ***cis***), 1.46 (s, 1.8H, for ***trans***), 1.45 (s, 7.2H, for ***cis***). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) for mixture δ 166.7, 166.6, 162.5, 150.1, 145.9, 145.3, 144.4, 144.3, 142.9, 139.5, 139.2, 139.0, 136.2, 136.1, 135.9, 135.7, 133.4, 132.1, 129.7, 129.4, 129.2, 129.1, 128.6, 128.4, 128.3, 128.1, 126.3, 125.1, 125.0, 124.0, 123.9, 122.7, 122.5, 122.4, 120.9, 114.1, 80.3, 80.2, 68.1, 61.8, 28.2. (All observed signals are shown because of complexity associated with stereoisomers.) HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{28}H_{27}N_2O_3$: 439.2016, Found: 439.2026.

1:3 Stereomixture of *tert*-butyl (2*E*,4*Z*)-4-(((1,10-phenanthrolin-2-yl)oxy)methyl)octa-2,4-dienoate (*cis*-3fa) and *tert*-butyl

(2*E*,4*E*)-4-(((1,10-phenanthrolin-2-yl)oxy)methyl)octa-2,4-dienoate (*trans*-3fa): colorless oil (39.6 mg, 49% yield); TLC R_f 0.32 (hexane/EtOAc, 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz) for mixture δ 9.20-9.18 (m, 1H, for ***cis*** + ***trans***), 8.26-8.24 (m, 1H, for ***cis*** + ***trans***), 8.14-8.12 (m, 1H, for ***cis*** + ***trans***), 7.78-7.75 (m, 1H, for ***cis*** + ***trans***), 7.72-7.67 (m, 1.75H, for ***cis*** + ***trans***), 7.62-7.58 (m, 1H, for ***cis*** + ***trans***), 7.29 (d, *J* = 15.9 Hz, 0.25H, for ***cis***), 7.18-7.14 (m, 1H, for ***cis*** + ***trans***), 6.29 (t, *J* = 7.7 Hz, 0.75H, for ***trans***), 6.22 (t, *J* = 7.7 Hz, 0.25H, for ***cis***), 6.10 (d, *J* = 15.9 Hz, 0.75H, for ***trans***), 5.98 (d, *J* = 15.9 Hz, 0.25H, for ***cis***), 5.46 (s, 0.5H, for ***cis***), 5.38 (s, 1.5H, for ***trans***), 2.43 (q, *J* = 7.5 Hz, 0.5H, for ***cis***), 2.36 (q, *J* = 7.5 Hz, 1.5H, for ***trans***), 1.50-1.45 (m, 11H, for ***cis*** + ***trans***), 0.96-0.91 (m, 3H, for ***cis*** + ***trans***). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) for mixture δ 167.0, 166.9, 162.7, 162.6, 150.0, 146.5, 145.8, 145.2, 144.2, 143.5, 139.0, 137.7, 136.2, 132.8, 131.1, 129.2, 126.4, 125.0, 124.9, 123.8, 123.8, 122.5, 121.0, 119.0, 114.2, 80.2, 80.0, 68.4, 60.7, 30.9, 30.1, 28.2, 22.6, 22.5, 13.8, 13.7. (All observed signals are shown because of complexity associated with stereoisomers.) HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{25}H_{29}N_2O_3$: 405.2173, Found: 405.2193.

2:3 Stereomixture of *tert*-butyl (2*E*,4*Z*)-4-(((1,10-phenanthrolin-2-yl)oxy)methyl)-5-phenylpenta-2,4-dienoate (*cis*-3ga) and *tert*-butyl (2*E*,4*E*)-4-(((1,10-phenanthrolin-2-yl)oxy)methyl)-5-phenylpenta-2,4-dienoate (*trans*-3ga): colorless oil (40.2 mg, 46% yield); TLC R_f 0.24 (hexane/EtOAc, 2:1). ^{1}H NMR ($CDCl_3$, 400 MHz) for mixture δ 9.21 (dd, *J* = 4.3, 1.8 Hz, 0.6H, for ***trans***), 9.15 (dd, *J* = 4.3, 1.8 Hz, 0.4H, for ***cis***), 8.27-8.23 (m, 1H, for ***cis*** + ***trans***), 8.19-8.15 (m, 1H, for ***cis*** + ***trans***), 7.83-7.77 (m, 1.6H, for ***cis*** + ***trans***), 7.69 (d, *J* = 8.7 Hz, 1H, for ***cis*** + ***trans***), 7.63-7.56 (m, 1H, for ***cis*** + ***trans***), 7.51-7.44 (m, 1.4H, for ***cis*** + ***trans***), 7.39-7.35 (m, 3H, for ***cis*** + ***trans***), 7.33-7.26 (m, 2H, for ***cis*** + ***trans***), 7.24-7.20 (m, 1H, for ***cis*** + ***trans***), 6.27 (dd, *J* = 15.9, 0.5 Hz, 0.6H, for ***trans***), 6.12 (d, *J* = 15.9 Hz, 0.4H, for ***cis***), 5.58 (bs, 1.2H, for ***trans***), 5.54 (s, 0.8H, for ***cis***), 1.46 (s, 5.4H, for ***trans***), 1.45 (s, 3.6H, for ***cis***). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) for mixture δ 166.7, 166.6, 162.5, 150.1, 145.9, 145.3, 144.4, 144.3, 142.9, 139.5, 139.2, 139.0, 136.2, 136.1, 135.9, 135.7, 133.4, 132.1, 129.7, 129.4, 129.2, 129.1, 128.6, 128.4, 128.3, 128.1, 126.3, 125.1, 125.0, 124.0, 123.9, 122.7, 122.5, 122.4, 120.9, 114.1, 80.3, 80.2, 68.1, 61.8, 28.2. (All observed signals are shown because of complexity associated with stereoisomers.) HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{28}H_{27}N_2O_3$: 439.2016, Found: 439.2027.

***tert*-Butyl (*E*)-4-(((1,10-phenanthrolin-2-yl)oxy)methyl)-5-methylhexa-2,4-dienoate (3ha):** colorless oil (41.3 mg, 53% yield); TLC R_f 0.32 (hexane/EtOAc, 2:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ

9.20 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.25 (dd, *J* = 8.1, 1.7 Hz, 1H), 8.12 (d, *J* = 8.7 Hz, 1H), 7.83 (d, *J* = 15.7 Hz, 1H), 7.77 (d, *J* = 8.7 Hz, 1H), 7.68 (d, *J* = 8.7 Hz, 1H), 7.60 (dd, *J* = 8.1, 4.3 Hz, 1H), 7.15 (d, *J* = 8.7 Hz, 1H), 5.98 (d, *J* = 15.7 Hz, 1H), 5.47 (s, 2H), 2.08 (s, 3H), 2.07 (s, 3H), 1.44 (s, 9H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 167.4, 163.0, 149.9, 147.8, 145.2, 144.3, 140.6, 139.0, 136.3, 129.2, 126.6, 126.4, 124.9, 123.7, 122.4, 118.7, 114.2, 79.9, 62.7, 28.2, 22.7, 21.5. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{24}H_{27}N_2O_3$: 391.2016, Found: 391.2012.

***tert*-Butyl (*E*)-4-(([2,2'-bipyridin]-6-yloxy)methyl)-5-methylhexa-2,4-dienoate (3ha-bpy):** colorless oil (44.0 mg, 60% yield); TLC R_f 0.22 (hexane/EtOAc, 5:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.66 (dq, *J* = 4.8, 1.0 Hz, 1H), 8.40 (d, *J* = 8.0 Hz, 1H), 8.03 (dd, *J* = 7.5, 0.7 Hz, 1H), 7.84-7.78 (m, 2H), 7.71 (dd, *J* = 8.1, 0.7 Hz, 1H), 7.28 (ddd, *J* = 7.5, 4.8, 1.1 Hz, 1H), 6.79 (dd, *J* = 8.1, 0.7 Hz, 1H), 5.94 (d, *J* = 15.7 Hz, 1H), 5.16 (s, 2H), 2.06 (s, 3H), 2.03 (s, 3H), 1.47 (s, 9H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 167.3, 163.2, 156.0, 153.4, 149.1, 147.5, 140.7, 139.5, 136.8, 126.8, 123.5, 121.0, 118.5, 114.0, 111.6, 80.1, 61.6, 28.2, 22.5, 21.4. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{22}H_{27}N_2O_3$: 367.2016, Found: 367.1993.

***tert*-Butyl (*E*)-5-((1,10-phenanthrolin-2-yl)oxy)-4-cyclohexylidenepent-2-enoate (3ia):** colorless oil (50.7 mg, 59% yield); TLC R_f 0.27 (hexane/EtOAc, 2:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.20 (dd, *J* = 4.3, 1.8 Hz, 1H), 8.25 (dd, *J* = 8.1, 1.8 Hz, 1H), 8.12 (d, *J* = 8.7 Hz, 1H), 7.91 (d, *J* = 15.7 Hz, 1H), 7.77 (d, *J* = 8.7 Hz, 1H), 7.68 (d, *J* = 8.7 Hz, 1H), 7.60 (dd, *J* = 8.1, 4.3 Hz, 1H), 7.15 (d, *J* = 8.7 Hz, 1H), 6.03 (d, *J* = 15.7 Hz, 1H), 5.47 (s, 2H), 2.59-2.52 (m, 4H), 1.68-1.62 (m, 6H), 1.45 (s, 9H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 167.5, 163.0, 156.1, 150.1, 145.3, 144.4, 140.3, 138.9, 136.2, 129.2, 126.4, 124.9, 123.8, 123.4, 122.4, 119.1, 114.2, 79.9, 62.3, 32.7, 31.3, 28.7, 28.5, 28.2, 26.6. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{27}H_{31}N_2O_3$: 431.2329, Found: 431.2329.

***tert*-Butyl (*E*)-5-([2,2'-bipyridin]-6-yloxy)-4-cyclohexylidenepent-2-enoate (3ia-bpy):** colorless oil (46.4 mg, 57% yield); TLC R_f 0.23 (hexane/EtOAc, 5:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.66 (dq, *J* = 4.8, 1.0 Hz, 1H), 8.40 (td, *J* = 8.0, 0.8 Hz, 1H), 8.03 (dd, *J* = 7.5, 0.7 Hz, 1H), 7.90 (d, *J* = 15.7 Hz, 1H), 7.81 (td, *J* = 7.7, 1.7 Hz, 1H), 7.70 (dd, *J* = 8.1, 0.7 Hz, 1H), 7.28 (ddd, *J* = 7.5, 4.8, 1.1 Hz, 1H), 6.79 (dd, *J* = 8.1, 0.7 Hz, 1H), 5.98 (d, *J* = 15.7 Hz, 1H), 5.17 (s, 2H), 2.55 (t, *J* = 6.1 Hz, 2H), 2.46 (bs, 2H), 1.67-1.62 (m, 6H), 1.47 (s, 9H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 167.4, 163.2, 156.1, 155.9, 153.4, 149.1, 140.4, 139.4, 136.8, 123.6, 123.5, 121.1, 118.9, 113.9, 111.7, 80.1, 61.2, 32.6, 31.3, 28.7, 28.5, 28.2, 26.6. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{25}H_{31}N_2O_3$: 407.2329,

Found: 407.2323.

***tert*-Butyl (*E*)-5-((1,10-phenanthrolin-2-yl)oxy)-4-cyclopentylidenepent-2-enoate (3ja):** colorless oil (55.7 mg, 67% yield); TLC R_f 0.25 (hexane/EtOAc, 2:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.18 (dd, *J* = 4.3, 1.8 Hz, 1H), 8.25 (dd, *J* = 8.1, 1.8 Hz, 1H), 8.12 (d, *J* = 8.7 Hz, 1H), 7.76 (d, *J* = 8.7 Hz, 1H), 7.68 (d, *J* = 8.7 Hz, 1H), 7.64-7.58 (m, 2H), 7.16 (d, *J* = 8.7 Hz, 1H), 5.95 (d, *J* = 15.7 Hz, 1H), 5.44 (s, 2H), 2.74 (t, *J* = 5.8 Hz, 2H), 2.74 (t, *J* = 5.8 Hz, 2H), 1.78-1.73 (m, 4H), 1.45 (s, 9H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 167.4, 163.0, 161.0, 150.1, 145.4, 144.4, 141.6, 138.9, 136.1, 129.2, 126.3, 124.9, 123.8, 123.7, 122.4, 117.8, 114.2, 79.9, 64.1, 32.5, 31.8, 28.2, 26.3, 26.2. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{26}H_{29}N_2O_3$: 417.2173, Found: 417.2158.

***tert*-Butyl**
(*E*)-5-((1,10-phenanthrolin-2-yl)oxy)-4-(tetrahydro-4*H*-pyran-4-ylidene)pent-2-enoate (3ka): colorless oil (51.8 mg, 60% yield); TLC R_f 0.28 (hexane/EtOAc, 1:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.18 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.25 (dd, *J* = 8.1, 1.7 Hz, 1H), 8.13 (d, *J* = 8.7 Hz, 1H), 7.81 (d, *J* = 15.7 Hz, 1H), 7.77 (d, *J* = 8.7 Hz, 1H), 7.69 (d, *J* = 8.7 Hz, 1H), 7.60 (dd, *J* = 8.1, 4.3 Hz, 1H), 7.14 (d, *J* = 8.7 Hz, 1H), 6.13 (d, *J* = 15.7 Hz, 1H), 5.50 (s, 2H), 3.76 (t, *J* = 5.4 Hz, 2H), 3.69 (t, *J* = 5.4 Hz, 2H), 2.76 (t, *J* = 5.4 Hz, 2H), 2.68 (t, *J* = 5.4 Hz, 2H), 1.46 (s, 9H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 167.2, 162.6, 150.0, 149.2, 145.3, 144.3, 139.3, 139.1, 136.2, 129.2, 126.3, 125.2, 125.0, 123.9, 122.5, 120.3, 114.1, 80.2, 69.0, 68.6, 61.7, 33.0, 31.7, 28.2. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{26}H_{29}N_2O_4$: 433.2122, Found: 433.2133.

Ethyl
(*E*)-4-(1-((1,10-phenanthrolin-2-yl)oxy)-5-(*tert*-butoxy)-5-oxopent-3-en-2-ylidene)piperidine-1-carboxylate (3la): colorless oil (43.2 mg, 43% yield); TLC R_f 0.20 (hexane/EtOAc, 1:2). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.18 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.25 (dd, *J* = 8.1, 1.7 Hz, 1H), 8.13 (d, *J* = 8.7 Hz, 1H), 7.81-7.76 (m, 2H), 7.69 (d, *J* = 8.7 Hz, 1H), 7.60 (dd, *J* = 8.1, 4.3 Hz, 1H), 7.13 (d, *J* = 8.7 Hz, 1H), 6.13 (d, *J* = 15.3 Hz, 1H), 5.50 (s, 2H), 4.13 (q, *J* = 7.1 Hz, 2H), 3.54 (bs, 2H), 3.49 (t, *J* = 5.5 Hz, 2H), 2.75 (bs, 2H), 2.66 (t, *J* = 5.5 Hz, 2H), 1.46 (s, 9H), 1.25 (t, *J* = 7.1 Hz, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 167.1, 162.5, 155.4, 150.0, 149.3, 145.2, 144.2, 139.3, 139.1, 136.2, 129.2, 126.3, 126.1, 125.0, 123.9, 122.5, 120.6, 114.1, 80.3, 61.9, 61.4, 44.4, 44.1, 31.3, 30.1, 28.2, 14.7. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{29}H_{34}N_3O_5$: 504.2493, Found: 504.2464.

***tert*-Butyl**

(*E*)-4-(1-((1,10-phenanthrolin-2-yl)oxy)-5-(*tert*-butoxy)-5-oxopent-3-en-2-ylidene)piperidine-1-carboxylate (3ma): colorless oil (52.0 mg, 49% yield); TLC R_f 0.23 (hexane/EtOAc, 1:2). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.18 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.25 (dd, *J* = 8.1, 1.7 Hz, 1H), 8.13 (d, *J* = 8.7 Hz, 1H), 7.80 (d, *J* = 15.7 Hz, 1H), 7.76 (d, *J* = 8.7 Hz, 1H), 7.69 (d, *J* = 8.7 Hz, 1H), 7.60 (dd, *J* = 8.1, 4.3 Hz, 1H), 7.13 (d, *J* = 8.7 Hz, 1H), 6.14 (d, *J* = 15.7 Hz, 1H), 5.50 (s, 2H), 3.50 (bs, 2H), 3.44 (bs, 2H), 2.76 (bs, 2H), 2.64 (t, *J* = 5.4 Hz, 2H), 1.46 (s, 9H), 1.45 (s, 9H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 167.1, 162.5, 154.7, 150.0, 149.7, 145.3, 144.3, 139.3, 139.1, 136.2, 129.2, 126.3, 125.9, 125.0, 123.9, 122.5, 120.5, 114.1, 80.2, 79.7, 61.8, 44.8, 43.9, 31.4, 30.2, 28.4, 28.2. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{31}H_{38}N_3O_5$: 532.2806, Found: 532.2800.

***tert*-Butyl**

(*E*)-3-(1-((1,10-phenanthrolin-2-yl)oxy)-5-(*tert*-butoxy)-5-oxopent-3-en-2-ylidene)-8-azabicyclo[3.2.1]octane-8-carboxylate (3na): colorless oil (70.2 mg, 63% yield); TLC R_f 0.22 (hexane/EtOAc, 1:2). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.17 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.23 (dd, *J* = 8.1, 1.1 Hz, 1H), 8.11 (d, *J* = 8.6 Hz, 1H), 7.79-7.73 (m, 2H), 7.67 (d, *J* = 8.6 Hz, 1H), 7.58 (dd, *J* = 8.1, 4.3 Hz, 1H), 7.12 (d, *J* = 8.7 Hz, 1H), 6.12 (d, *J* = 15.7 Hz, 1H), 5.58 (d, *J* = 11.9 Hz, 1H), 5.35 (d, *J* = 11.9 Hz, 1H), 4.37-4.20 (m, 1H), 3.10 (d, *J* = 15.0 Hz, 1H), 2.94 (d, *J* = 15.0 Hz, 1H), 2.60-2.44 (m, 2H), 1.89-1.82 (m, 1H), 1.75 (bs, 1H), 1.48-1.44 (m, 21H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 167.2, 162.6, 153.5, 150.0, 147.4, 145.2, 144.2, 139.4, 139.1, 136.2, 129.7, 129.2, 126.3, 125.0, 123.9, 122.5, 120.2, 114.1, 80.2, 79.5, 61.9, 54.0, 53.7, 37.8, 37.0, 36.6, 36.0, 28.5, 28.2. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{33}H_{40}N_3O_5$: 558.2963, Found: 558.2948.

2-((2-((Triisopropylsilyl)ethynyl)cyclohex-2-en-1-yl)oxy)-1,10-phenanthroline (5aa): colorless oil (33.3 mg, 73% yield); TLC R_f 0.28 (hexane/EtOAc, 3:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.16 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.22 (dd, *J* = 8.1, 1.7 Hz, 1H), 8.07 (d, *J* = 8.7 Hz, 1H), 7.73 (d, *J* = 8.7 Hz, 1H), 7.64 (d, *J* = 8.7 Hz, 1H), 7.57 (dd, *J* = 8.1, 4.3 Hz, 1H), 7.14 (d, *J* = 8.7 Hz, 1H), 6.49-6.46 (m, 2H), 2.31-2.14 (m, 4H), 1.88-1.74 (m, 2H), 0.82-0.74 (m, 21H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 162.6, 149.7, 145.2, 144.2, 140.0, 138.8, 136.2, 129.1, 126.3, 124.9, 123.4, 122.3, 122.2, 114.6, 106.6, 89.0, 69.7, 28.3, 25.9, 18.4, 18.2, 11.1. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{29}H_{37}N_2OSi$: 457.2669, Found: 457.2654.

2-((2-((*tert*-Butyldimethylsilyl)ethynyl)cyclohex-2-en-1-yl)oxy)-1,10-phenanthroline (5ab):

colorless oil (51.3 mg, 62% yield); TLC R_f 0.32 (hexane/EtOAc, 2:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.15 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.22 (dd, *J* = 8.1, 1.7 Hz, 1H), 8.10 (d, *J* = 8.7 Hz, 1H), 7.73 (d, *J* = 8.7 Hz, 1H), 7.64 (d, *J* = 8.7 Hz, 1H), 7.57 (dd, *J* = 8.1, 4.3 Hz, 1H), 7.16 (d, *J* = 8.7 Hz, 1H), 6.49-6.47 (m, 2H), 2.31-2.14 (m, 4H), 1.86-1.74 (m, 2H), 0.62 (s, 9H), -0.17 (s, 3H), -0.18 (s, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 162.6, 149.8, 145. 4, 144.3, 140.3, 138.9, 136.0, 129.1, 126.3, 124.9, 123.5, 122.3, 122.0, 114.5, 105.4, 91.2, 69.5, 28.2, 25.9, 25.8, 18.1, 16.3, -4.8. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{26}H_{31}N_2OSi$: 415.2200, Found: 415.2198.

2-((2-(3,3-Dimethylbut-1-yn-1-yl)cyclohex-2-en-1-yl)oxy)-1,10-phenanthroline (5ac): colorless oil (37.7 mg, 53% yield); TLC R_f 0.25 (hexane/EtOAc, 2:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.16 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.22 (dd, *J* = 8.1, 1.7 Hz, 1H), 8.10 (d, *J* = 8.7 Hz, 1H), 7.74 (d, *J* = 8.7 Hz, 1H), 7.64 (d, *J* = 8.7 Hz, 1H), 7.57 (dd, *J* = 8.1, 4.3 Hz, 1H), 7.17 (d, *J* = 8.7 Hz, 1H), 6.40 (t, *J* = 4.3 Hz, 1H), 6.30 (t, *J* = 3.9 Hz, 1H), 2.28-2.16 (m, 4H), 1.86-1.71 (m, 2H), 0.90 (s, 9H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 162.8, 149.9, 145.4, 144.4, 138.8, 137.5, 136.0, 129.1, 126.3, 124.8, 123.4, 122.3, 122.0, 114.6, 97.4, 78.4, 70.2, 30.7, 28.3, 27.5, 25.8, 18.3. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{24}H_{25}N_2O$: 357.1961, Found: 357.1954.

2-((2-((1-((*tert*-Butyldimethylsilyl)oxy)cyclohexyl)ethynyl)cyclohex-2-en-1-yl)oxy)-1,10-phenanthroline (5ad): colorless oil (61.4 mg, 60% yield); TLC R_f 0.30 (hexane/EtOAc, 5:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.15 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.21 (dd, *J* = 8.1, 1.7 Hz, 1H), 8.09 (d, *J* = 8.7 Hz, 1H), 7.73 (d, *J* = 8.7 Hz, 1H), 7.64 (d, *J* = 8.7 Hz, 1H), 7.56 (dd, *J* = 8.1, 4.3 Hz, 1H), 7.13 (d, *J* = 8.7 Hz, 1H), 6.44 (t, *J* = 4.3 Hz, 1H), 6.36 (t, *J* = 3.9 Hz, 1H), 2.32-2.18 (m, 4H), 1.89-1.72 (m, 2H), 1.48-1.41 (m, 2H), 1.32-1.06 (m, 6H), 0.99-0.92 (m, 1H), 0.87-0.82 (m, 1H), 0.77 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 162.5, 149.8, 145.4, 144.4, 138.8, 138.3, 136.0, 129.1, 126.3, 124.8, 123.5, 122.3, 121.7, 114.5, 92.4, 84.5, 69.6, 69.4, 41.0, 40.9, 28.3, 25.9, 25.8, 25.1, 22.6, 22.5, 18.1, 18.0, -2.95, -2.96. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{32}H_{41}N_2O_2Si$: 513.2932, Found: 513.2934.

2-((2-((4-((*tert*-Butyldimethylsilyl)oxy)tetrahydro-2*H*-pyran-4-yl)ethynyl)cyclohex-2-en-1-yl)oxy)-1,10-phenanthroline (5ae): colorless oil (72.9 mg, 71% yield); TLC R_f 0.35 (hexane/EtOAc, 3:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.14 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.21 (dd, *J* = 8.1, 1.7 Hz, 1H), 8.09 (d, *J* = 8.7 Hz, 1H), 7.73 (d, *J* = 8.7 Hz, 1H), 7.64 (d, *J* = 8.7 Hz, 1H), 7.56 (dd, *J* = 8.1, 4.3 Hz, 1H), 7.12 (d, *J* = 8.7 Hz, 1H), 6.45 (t, *J* = 4.3 Hz, 1H), 6.39 (t, *J* = 3.9 Hz, 1H), 3.49-3.42 (m, 2H),

3.34-3.26 (m, 2H), 2.32-2.17 (m, 4H), 1.89-1.73 (m, 2H), 1.57-1.43 (m, 4H), 0.77 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 162.4, 149.8, 145.3, 144.3, 139.3, 138.9, 136.1, 129.1, 126.3, 124.8, 123.6, 122.4, 121.4, 114.4, 90.8, 85.3, 69.5, 66.6, 64.3, 64.2, 41.1, 41.0, 28.2, 25.9, 25.7, 18.1, 18.0, -2.9, -3.0. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{31}H_{39}N_2O_3Si$: 515.2724, Found: 515.2715.

***tert*-Butyl 4-((6-((1,10-phenanthrolin-2-yl)oxy)cyclohex-1-en-1-yl)ethynyl)-4-((*tert*-butyldimethylsilyl)oxy) piperidine-1-carboxylate (5af):** colorless oil (80.9 mg, 66% yield); TLC R_f 0.33 (hexane/EtOAc, 2:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.14 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.21 (dd, *J* = 8.1, 1.7 Hz, 1H), 8.09 (d, *J* = 8.7 Hz, 1H), 7.72 (d, *J* = 8.7 Hz, 1H), 7.63 (d, *J* = 8.7 Hz, 1H), 7.56 (dd, *J* = 8.1, 4.3 Hz, 1H), 7.10 (d, *J* = 8.7 Hz, 1H), 6.43 (t, *J* = 4.3 Hz, 1H), 6.38 (t, *J* = 3.9 Hz, 1H), 3.23 (bs, 2H), 3.03-2.97 (m, 2H), 2.33-2.24 (m, 1H), 2.20-2.14 (m, 3H), 1.89-1.71 (m, 2H), 1.45-1.35 (m, 4H), 1.35 (s, 9H), 0.75 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 162.4, 154.4, 149.8, 145.3, 144.3, 139.3, 138.9, 136.0, 129.1, 126.3, 124.8, 123.6, 122.3, 121.3, 114.4, 90.5, 85.5, 79.0, 69.4, 67.5, 40.6, 40.1, 28.4, 28.2, 25.9, 25.7, 18.0, 17.9, -3.0. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{36}H_{48}N_3O_4Si$: 614.3409, Found: 614.3414.

2-((4,4-Dimethyl-2-((triisopropylsilyl)ethynyl)cyclohex-2-en-1-yl)oxy)-1,10-phenanthroline (5ba): colorless solid (38.2 mg, 79% yield); m. p. 119.5-121.2 °C (from hexane); TLC R_f 0.30 (hexane/EtOAc, 3:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.15 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.21 (dd, *J* = 8.1, 1.7 Hz, 1H), 8.07 (d, *J* = 8.7 Hz, 1H), 7.73 (d, *J* = 8.7 Hz, 1H), 7.64 (d, *J* = 8.7 Hz, 1H), 7.56 (dd, *J* = 8.1, 4.3 Hz, 1H), 7.13 (d, *J* = 8.7 Hz, 1H), 6.42 (t, *J* = 5.1 Hz, 1H), 6.15 (d, *J* = 0.8 Hz, 1H), 2.36-2.28 (m, 1H), 2.18-2.10 (m, 1H), 1.70 (ddd, *J* = 13.3, 9.6, 3.3 Hz, 1H), 1.64-1.58 (m, 1H), 1.13 (s, 3H), 1.08 (s, 3H), 0.80-0.78 (m, 21H). $^{13}C\{^{1}H\}$ NMR ($CDCl_3$, 100 MHz) δ 162.7, 149.8, 149.1, 145.5, 144.3, 138.8, 136.0, 129.1, 126.3, 124.8, 123.4, 122.2, 120.1, 114.6, 106.5, 88.9, 69.8, 32.9, 32.8, 29.1, 28.4, 25.5, 18.5, 18.4, 11.1. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{31}H_{41}N_2OSi$: 485.2983, Found: 485.2968.

2-((2-((Triisopropylsilyl)ethynyl)cyclopent-2-en-1-yl)oxy)-1,10-phenanthroline (5da): colorless oil (37.1 mg, 42% yield); TLC R_f 0.24 (hexane/EtOAc, 3:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.15 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.22 (dd, *J* = 8.1, 1.7 Hz, 1H), 8.09 (d, *J* = 8.7 Hz, 1H), 7.73 (d, *J* = 8.7 Hz, 1H), 7.64 (d, *J* = 8.7 Hz, 1H), 7.57 (dd, *J* = 8.1, 4.3 Hz, 1H), 7.13 (d, *J* = 8.7 Hz, 1H), 6.84-6.80 (m, 1H),

6.43-6.41 (m, 1H), 2.90-2.82 (m, 1H), 2.70-2.62 (m, 1H), 2.56-2.48 (m, 1H), 2.11-2.03 (m, 1H), 0.87-0.86 (m, 21H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 162.7, 149.9, 145.5, 144.4, 142.4, 138.9, 136.0, 129.1, 126.2, 126.0, 124.8, 123.5, 122.3, 114.3, 102.2, 93.3, 82.1, 31.2, 30.9, 18.5, 18.4, 11.1. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{28}H_{35}N_2OSi$: 443.2514, Found: 443.2515.

1.5:1 Stereomixture of (*Z*)-2-((2-((triisopropylsilyl)ethynyl)pent-2-en-1-yl)oxy)-1,10-phenanthroline (*cis*-5ea) and (*E*)-2-((2-((triisopropylsilyl)ethynyl)pent-2-en-1-yl)oxy)-1,10-phenanthroline (*trans*-5ea): pale yellow oil (61.3 mg, 69% yield); TLC R_f 0.30 (hexane/EtOAc, 2:1). ^1H NMR ($CDCl_3$, 400 MHz) for mixture δ 9.17-9.15 (m, 1H, for ***cis*** + ***trans***), 8.23 (dd, *J* = 8.1, 1.7 Hz, 1H, for ***cis*** + ***trans***), 8.11 (dd, *J* = 8.7, 1.1 Hz, 1H, for ***cis*** + ***trans***), 7.74 (dd, *J* = 8.7, 1.5 Hz, 1H, for ***cis*** + ***trans***), 7.66 (dd, *J* = 8.7, 1.3 Hz, 1H, for ***cis*** + ***trans***), 7.58 (dd, *J* = 8.1, 4.3 Hz, 1H, for ***cis*** + ***trans***), 7.17 (d, *J* = 8.7, 3.1 Hz, 1H, for ***cis*** + ***trans***), 6.27-6.22 (m, 1H, for ***cis*** + ***trans***), 5.35 (s, 1.2H, for ***cis***), 5.28 (d, *J* = 0.8 Hz, 0.8H, for ***trans***), 2.46-2.36 (m, 2H, for ***cis*** + ***trans***), 1.09-1.01 (m, 24H, for ***cis*** + ***trans***). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) for mixture δ 162.9, 162.8, 150.0, 149.9, 145.4, 145.3, 144.3, 144.0, 139.0, 138.9, 136.1, 129.1, 126.4, 126.3, 124.9, 124.8, 123.7, 122.4, 119.2, 118.9, 114.3, 114.2, 107.7, 103.6, 95.7, 88.2, 69.2, 63.7, 24.0, 22.1, 18.6, 13.8, 13.3, 11.3, 11.2. (All observed signals are shown because of complexity associated with stereoisomers.) HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{28}H_{37}N_2OSi$: 445.2669, Found: 445.2678.

2.3:1 Stereomixture of (*Z*)-2-((2-((triisopropylsilyl)ethynyl)hex-2-en-1-yl)oxy)-1,10-phenanthroline and (*cis*-5fa) (*E*)-2-((2-((triisopropylsilyl)ethynyl)hex-2-en-1-yl)oxy)-1,10-phenanthroline (*trans*-5fa): pale yellow oil (62.3 mg, 68% yield); TLC R_f 0.28 (hexane/EtOAc, 3:1). ^1H NMR ($CDCl_3$, 400 MHz) for mixture δ 9.17-9.15 (m, 1H, for ***cis*** + ***trans***), 8.22 (dd, *J* = 8.1, 1.7 Hz, 1H, for ***cis*** + ***trans***), 8.10 (d, *J* = 8.7 Hz, 1H, for ***cis*** + ***trans***), 7.74 (dd, *J* = 8.7, 2.0 Hz, 1H, for ***cis*** + ***trans***), 7.65 (dd, *J* = 8.7, 1.7 Hz, 1H, for ***cis*** + ***trans***), 7.58 (dd, *J* = 8.1, 4.3 Hz, 1H, for ***cis*** + ***trans***), 7.16 (d, *J* = 8.6, 2.7 Hz, 1H, for ***cis*** + ***trans***), 6.29-6.23 (m, 1H, for ***cis*** + ***trans***), 5.36 (s, 1.4H, for ***cis***), 5.28 (d, *J* = 0.7 Hz, 0.6H, for ***trans***), 2.42-2.33 (m, 2H, for ***cis*** + ***trans***), 1.52-1.42 (m, 2H, for ***cis*** + ***trans***), 1.05-1.01 (m, 21H, for ***cis*** + ***trans***), 0.96-0.91 (m, 3H, for ***cis*** + ***trans***). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) for mixture δ 162.9, 162.8, 150.0, 149.9, 145.3, 144.3, 143.7, 142.4, 139.0, 138.9, 136.1, 129.1, 126.4, 126.3, 124.9, 124.8, 123.7, 122.4, 119.9, 119.5, 114.3, 114.2, 107.8, 103.8, 95.5, 88.2, 69.2, 63.8, 32.6, 30.8, 22.5, 22.1, 18.6, 13.9, 13.8, 11.3, 11.2. (All observed signals are shown because of complexity

associated with stereoisomers.) HRMS (APCI) m/z ([M+H]$^+$) Calcd for $C_{29}H_{39}N_2OSi$: 459.2826, Found: 459.2810.

9:1 Stereomixture of (*Z*)-2-((2-benzylidene-4-(triisopropylsilyl)but-3-yn-1-yl)oxy)-1,10-phenanthroline (*cis*-5ga) and (*E*)-2-((2-benzylidene-4-(triisopropylsilyl)but-3-yn-1-yl)oxy)-1,10-phenanthroline (*trans*-5ga): pale yellow oil (71.8 mg, 73% yield); TLC R_f 0.25 (hexane/EtOAc, 3:1). ^{1}H NMR ($CDCl_3$, 400 MHz) for mixture δ 9.19 (dd, *J* = 4.3, 1.8 Hz, 0.1H, for ***trans***), 9.14 (dd, *J* = 4.3, 1.8 Hz, 0.9H, for ***cis***), 8.25-8.21 (m, 1H, for ***cis*** + ***trans***), 8.15-8.12 (m, 1H, for ***cis*** + ***trans***), 8.03-8.01 (m, 0.2H, for ***trans***), 7.76 (d, *J* = 8.7 Hz, 1H, for ***cis*** + ***trans***), 7.68-7.66 (m, 1H, for ***cis*** + ***trans***), 7.61-7.56 (m, 1H, for ***cis*** + ***trans***), 7.43-7.41 (m, 1.8H, for ***cis***), 7.34-7.31 (m, 2H, for ***cis*** + ***trans***), 7.27-7.19 (m, 3H, for ***cis*** + ***trans***), 5.54 (d, *J* = 0.5 Hz, 1.8H, for ***cis***), 5.54 (d, *J* = 1.0 Hz, 0.2H, for ***trans***), 1.09-1.02 (m, 21H, for ***cis*** + ***trans***). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) for ***cis*-5ga** δ 162.7, 149.9, 145.3, 144.3, 140.8, 139.0, 136.1, 135.6, 129.1, 128.5, 128.1, 128.0, 126.3, 125.0, 123.8, 122.4, 120.9, 114.3, 108.0, 91.5, 64.5, 18.7, 18.6, 11.3. HRMS (APCI) m/z ([M+H]$^+$) Calcd for $C_{32}H_{37}N_2OSi$: 493.2669, Found: 493.2644.

1:1 Stereomixture of (*Z*)-2-((2-((triisopropylsilyl)ethynyl)hex-2-en-1-yl)oxy)-1,10-phenanthroline (*cis*-5fa) and (*E*)-2-((2-((triisopropylsilyl)ethynyl)hex-2-en-1-yl)oxy)-1,10-phenanthroline (*trans*-5fa): pale yellow oil (33.9 mg, 37% yield); TLC R_f 0.28 (hexane/EtOAc, 3:1). ^{1}H NMR ($CDCl_3$, 400 MHz) for mixture δ 9.17-9.15 (m, 1H, for ***cis*** + ***trans***), 8.24-8.22 (m, 1H, for ***cis*** + ***trans***), 8.10 (d, *J* = 8.7 Hz, 1H, for ***cis*** + ***trans***), 7.74 (dd, *J* = 8.7, 2.0 Hz, 1H, for ***cis*** + ***trans***), 7.65 (dd, *J* = 8.7, 1.7 Hz, 1H, for ***cis*** + ***trans***), 7.58 (ddd, *J* = 8.1, 4.3, 0.8 Hz, 1H, for ***cis*** + ***trans***), 7.16 (d, *J* = 8.6, 2.7 Hz, 1H, for ***cis*** + ***trans***), 6.29-6.23 (m, 1H, for ***cis*** + ***trans***), 5.36 (s, 1H, for ***cis***), 5.28 (d, *J* = 0.7 Hz, 1H, for ***trans***), 2.42-2.33 (m, 2H, for ***cis*** + ***trans***), 1.52-1.42 (m, 2H, for ***cis*** + ***trans***), 1.05-1.02 (m, 21H, for ***cis*** + ***trans***), 0.96-0.91 (m, 3H, for ***cis*** + ***trans***). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) for mixture δ 162.9, 162.8, 150.0, 149.9, 145.3, 144.3, 143.7, 142.4, 139.0, 138.9, 136.1, 129.1, 126.4, 126.3, 124.9, 124.8, 123.7, 122.4, 119.9, 119.5, 114.3, 114.2, 107.8, 103.8, 95.5, 88.2, 69.2, 63.8, 32.6, 30.8, 22.5, 22.1, 18.6, 13.9, 13.8, 11.3, 11.2. (All observed signals are shown because of complexity associated with stereoisomers.) HRMS (APCI) m/z ([M+H]$^+$) Calcd for $C_{29}H_{39}N_2OSi$: 459.2826, Found: 459.2833.

(*E*)-3-(6-Hydroxycyclohex-1-en-1-yl)acrylonitrile (3aj-OH): colorless oil (46.5 mg, 95% yield); TLC R_f 0.30 (hexane/EtOAc, 4:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.93 (d, *J* = 16.5 Hz, 1H), 6.25 (t, *J* = 4.1 Hz, 1H), 5.64 (dd, *J* = 16.5, 0.5 Hz, 1H), 4.39 (t, *J* = 3.4 Hz, 1H), 2.36-2.29 (m, 1H), 2.23-2.14 (m, 1H), 1.93-1.86 (m, 1H), 1.78-1.65 (m, 3H), 1.52 (d, *J* = 6.9 Hz, 1H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 151.5, 141.9, 136.1, 118.8, 95.2, 63.1, 31.5, 26.5, 16.7. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_9H_{12}NO$: 150.0913, Found: 150.0929.

9:1 Stereomixture of (*E*)-3-(6-methoxycyclohex-1-en-1-yl)acrylonitrile (*trans*-3aj-OMe) and (*Z*)-3-(6-methoxycyclohex-1-en-1-yl)acrylonitrile (*cis*-3aj-OMe): colorless oil (15.0 mg, 92% yield); TLC R_f 0.35 (hexane/EtOAc, 5:1). ^{1}H NMR ($CDCl_3$, 400 MHz) for mixture δ 6.93 (d, *J* = 16.5 Hz, 0.9H, for ***trans***), 6.58 (d, *J* = 12.3 Hz, 0.1H, for ***cis***), 6.44 (t, *J* = 4.1 Hz, 0.1H, for ***cis***), 6.28 (t, *J* = 3.9 Hz, 0.9H, for ***trans***), 5.37 (d, *J* = 16.5 Hz, 0.9H, for ***trans***), 5.16 (d, *J* = 12.3 Hz, 0.1H, for ***cis***), 4.35 (t, *J* = 3.6 Hz, 0.1H, for ***cis***), 3.88 (t, *J* = 3.3 Hz, 0.9H, for ***trans***), 3.44 (s, 0.3H, for ***cis***), 3.36 (s, 2.7H, for ***trans***), 2.34-2.26 (m, 1H, for ***trans*** + ***cis***), 2.21-2.07 (m, 2H, for ***trans*** + ***cis***), 1.77-1.66 (m, 1H, for ***trans*** + ***cis***), 1.63-1.46 (m, 2H, for ***trans*** + ***cis***). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) for ***trans*** δ 151.8, 142.6, 134.8, 118.9, 94.3, 71.7, 55.9, 26.6, 25.2, 16.7. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{10}H_{14}NO$: 164.1070, Found: 164.1072.

(*E*)-2-((2-(3-(*tert*-butoxy)-3-oxoprop-1-en-1-yl)cyclohex-2-en-1-yl)oxy)-1-methyl-1,10-phenanthrolin-1-ium iodide (3aa-Me): yellow solid (253.1 mg, 93% yield); m. p. 124.0-125.7 °C (from MeCN). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.31 (d, *J* = 5.6 Hz, 1H), 9.24 (d, *J* = 7.7 Hz, 1H), 8.42-8.36 (m, 2H), 8.15 (dd, *J* = 13.1, 8.8 Hz, 2H), 7.31 (d, *J* = 8.8 Hz, 1H), 7.21 (d, *J* = 15.9 Hz, 1H), 6.55 (dd, *J* = 5.0, 2.9 Hz, 1H), 5.91 (s, 1H), 5.53 (s, 3H), 5.51 (d, *J* = 15.9 Hz, 1H), 2.46-2.41 (m, 1H), 2.32-2.29 (m, 2H), 1.80-1.75 (m, 3H), 1.38 (s, 9H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 166.3, 161.4, 152.0, 147.1, 144.3, 143.2, 140.6, 138.7, 136.0, 132.5, 132.4, 130.6, 128.9, 124.7, 124.4, 117.8, 117.5, 80.5, 68.4, 54.5, 28.1, 27.5, 26.4, 16.9. HRMS (FAB) m/z ($[M–I]^+$) Calcd for $C_{26}H_{29}N_2O_3$: 417.2173, Found: 417.2181.

***tert*-Butyl (*E*)-3-(6-(propylamino)cyclohex-1-en-1-yl)acrylate (6aa-Pr):** pale yellow oil (11.0 mg, 69% yield); TLC R_f 0.38 (hexane/EtOAc, 2:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.12 (d, *J* = 15.9 Hz, 1H), 6.17 (t, *J* = 3.9 Hz, 1H), 5.83 (d, *J* = 15.9 Hz, 1H), 3.36 (bs, 1H), 2.73-2.66 (m, 1H), 2.59-2.53 (m, 1H), 2.29-2.22 (m, 1H), 2.17-2.09 (m, 1H), 1.97 (dd, *J* = 13.5, 3.5 Hz, 1H), 1.82-1.70 (m, 1H), 1.59-1.51 (m, 3H), 1.49 (s, 9H), 1.41 (tt, *J* = 13.5, 3.5 Hz, 2H), 0.93 (t, *J* = 7.4 Hz, 3H). $^{13}C\{^1H\}$

NMR ($CDCl_3$, 100 MHz) δ 167.0, 145.9, 140.0, 136.7, 116.8, 80.1, 50.9, 50.0, 28.2, 26.6, 26.0, 23.4, 16.5, 11.9. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{16}H_{28}NO_2$: 266.2115, Found: 266.2117.

***tert*-Butyl (*E*)-3-(6-(benzylamino)cyclohex-1-en-1-yl)acrylate (6aa-Bn):** pale yellow oil (13.7 mg, 73% yield); TLC R_f 0.38 (hexane/EtOAc, 2:1). ^1H NMR ($CDCl_3$, 400 MHz) δ 7.37-7.31 (m, 4H), 7.28-7.23 (m, 1H), 7.09 (d, *J* = 15.9 Hz, 1H), 6.17 (t, *J* = 3.8 Hz, 1H), 5.65 (d, *J* = 15.9 Hz, 1H), 3.91 (d, *J* = 13.1 Hz, 1H), 3.76 (d, *J* = 13.1 Hz, 1H), 3.40 (bs, 1H), 2.30-2.23 (m, 1H), 2.19-2.10 (m, 1H), 2.06-2.02 (m, 1H), 1.88-1.77 (m, 1H), 1.63-1.57 (m, 1H), 1.49 (s, 9H), 1.41 (tt, *J* = 13.4, 3.7 Hz, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 167.0, 145.6, 140.4, 140.0, 136.7, 128.5, 128.4, 127.0, 116.9, 80.0, 51.7, 49.7, 28.2, 26.6, 25.7, 16.5. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{20}H_{28}NO_2$: 314.2115, Found: 314.2105.

***tert*-Butyl (*E*)-3-(6-(cyclohexylamino)cyclohex-1-en-1-yl)acrylate (6aa-Cy):** pale yellow oil (15.1 mg, 83% yield); TLC R_f 0.25 (hexane/EtOAc, 2:1). ^1H NMR ($CDCl_3$, 400 MHz) δ 7.09 (d, *J* = 15.9 Hz, 1H), 6.15 (t, *J* = 3.9 Hz, 1H), 5.91 (d, *J* = 15.9 Hz, 1H), 3.54 (bs, 1H), 2.57 (tt, *J* = 10.3, 3.5 Hz, 1H), 2.28-2.21 (m, 1H), 2.06-1.93 (m, 2H), 1.78-1.69 (m, 4H), 1.62-1.54 (m, 2H), 1.49 (s, 9H), 1.37 (tt, *J* = 13.5, 3.5 Hz, 2H), 1.31-1.03 (m, 6H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 167.1, 145.9, 139.6, 137.2, 117.1, 79.9, 54.3, 47.4, 35.3, 33.1, 28.2, 26.6, 26.4, 26.1, 25.4, 25.1, 16.2. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{19}H_{32}NO_2$: 306.2428, Found: 306.2401.

3:2 Stereomixture of (5*S,7*R**,10a*S**)-7-((1,10-phenanthrolin-2-yl)oxy)-1,3-dioxo-2-phenyl-2,3,5,7,8,9,10,10a-octahydro-1*H*-[1,2,4]triazolo[1,2-*a*]cinnoline-5-carbonitrile (*anti*-7aj) and (5*S**,7*S**,10a*S**)-7-((1,10-phenanthrolin-2-yl)oxy)-1,3-dioxo-2-phenyl-2,3,5,7,8,9,10,10a-octahydro-1*H*-[1,2,4]triazolo[1,2-*a*]cinnoline-5-carbonitrile (*syn*-7aj)** (the stereochemistry was tentatively assigned)**:** colorless oil (36.1 mg, 72% yield); TLC R_f 0.22 (hexane/EtOAc, 1:1). ^1H NMR ($CDCl_3$, 400 MHz) for mixture δ 9.16-9.13 (m, 1H, for ***anti*** + ***syn***), 8.25-8.22 (m, 1H, for ***anti*** + ***syn***), 8.17-8.13 (m, 1H, for ***anti*** + ***syn***), 7.76 (d, *J* = 2.6 Hz, 0.4H, for ***syn***), 7.74 (d, *J* = 2.6 Hz, 0.6H, for ***anti***), 7.69 (d, *J* = 2.6 Hz, 0.6H, for ***anti***), 7.66 (d, *J* = 2.6 Hz, 0.4H, for ***syn***), 7.63-7.58 (m, 1H, for ***anti*** + ***syn***), 7.52-7.44 (m, 4H, for ***anti*** + ***syn***), 7.40-7.34 (m, 1H, for ***anti*** + ***syn***), 7.15 (d, *J* = 8.7 Hz, 0.4H, for ***syn***), 7.10 (d, *J* = 8.7 Hz, 0.6H, for ***anti***), 6.81 (dd, *J* = 5.3, 1.6 Hz, 0.6H, for ***anti***), 6.62 (dd, *J* = 5.3, 1.6 Hz, 0.4H, for ***syn***), 6.53-6.50 (m, 1H, for ***anti*** + ***syn***), 5.28 (d, *J* = 5.3 Hz, 0.4H, for ***syn***), 5.13 (dd, *J* = 5.3, 2.2 Hz, 0.6H, for ***anti***), 4.90 (dd, *J* = 11.6, 3.5 Hz, 0.4H, for ***syn***),

4.62-4.58 (m, 0.6H, for ***anti***), 3.16-3.13 (m, 0.6H, for ***anti***), 2.54-2.40 (m, 1.4H, for ***anti*** + ***syn***), 2.18-2.10 (m, 1H, for ***anti*** + ***syn***), 1.96-1.69 (m, 2.6H, for ***anti*** + ***syn***), 1.63-1.53 (m, 0.4H, for ***syn***). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) for mixture δ 161.2, 161.1, 152.8, 152.7, 151.1, 150.8, 150.1, 149.9, 145.4, 144.2, 144.1, 140.7, 139.4, 139.3, 138.8, 136.1, 130.6, 130.5, 129.3, 129.2, 129.19, 129.18, 128.6, 128.5, 126.2, 126.1, 125.5, 125.4, 125.0, 124.9, 124.2, 124.1, 122.7, 122.6, 115.8, 114.0, 113.7, 113.3, 73.3, 73.2, 55.4, 53.1, 44.0, 42.8, 32.0, 31.9, 31.4, 29.7, 19.1, 18.4. (All observed signals are shown because of complexity associated with stereoisomers.) HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{29}H_{23}N_6O_3$: 503.1826, Found: 503.1854.

4,4-Dimethyl-2-((triisopropylsilyl)ethynyl)cyclohex-2-en-1-ol (5ba-OH): colorless oil (291.2 mg, 95% yield); TLC R_f 0.28 (hexane/EtOAc, 5:1). ^1H NMR ($CDCl_3$, 400 MHz) δ 5.95 (s, 1H), 4.13-4.10 (m, 1H), 2.15 (d, *J* = 2.8 Hz, 1H), 1.97-1.89 (m, 1H), 1.74-1.65 (m, 1H), 1.61-1.55 (m, 1H), 1.45-1.38 (m, 1H), 1.08 (bs, 21H), 1.05 (s, 3H), 1.00 (s, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 146.9, 122.5, 105.7, 91.0, 67.2, 33.0, 32.9, 28.9, 28.7, 27.4, 18.7, 11.3. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{19}H_{35}OSi$: 307.2452, Found: 307.2442.

2-Ethynyl-4,4-dimethylcyclohex-2-en-1-ol (8): colorless oil (120.3 mg, 89% yield); TLC R_f 0.30 (hexane/EtOAc, 5:1). ^1H NMR ($CDCl_3$, 400 MHz) δ 6.02 (s, 1H), 4.16-4.12 (m, 1H), 2.91 (s, 1H), 2.05 (d, *J* = 4.0 Hz, 1H), 1.97-1.89 (m, 1H), 1.75-1.67 (m, 1H), 1.62-1.56 (m, 1H), 1.46-1.40 (m, 1H), 1.05 (s, 3H), 1.00 (s, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 148.4, 121.1, 82.7, 77.2, 66.9, 32.9, 32.7, 28.7, 28.5, 27.8. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{10}H_{15}O$: 151.1118, Found: 151.1129.

2-(1-Benzyl-1*H*-1,2,3-triazol-4-yl)-4,4-dimethylcyclohex-2-en-1-ol (9): colorless solid (56.7 mg, quantitative); m. p. 88.1-88.9 °C (from hexane); TLC R_f 0.25 (hexane/EtOAc, 1:1). ^1H NMR ($CDCl_3$, 400 MHz) δ 7.51 (s, 1H), 7.38-7.33 (m, 3H), 7.27-7.24 (m, 2H), 6.05 (s, 1H), 5.50 (d, *J* = 17.6 Hz, 1H), 5.46 (d, *J* = 17.6 Hz, 1H), 4.58 (t, *J* = 4.9 Hz, 1H), 3.59 (bs, 1H), 2.03-1.95 (m, 1H), 1.88-1.81 (m, 1H), 1.68-1.62 (m, 1H), 1.44 (ddd, *J* = 13.0, 8.3, 3.2 Hz, 1H), 1.07 (s, 3H), 1.00 (s, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 148.5, 137.9, 134.6, 129.1, 128.8, 128.1, 127.8, 119.4, 65.7, 54.2, 32.8, 32.4, 29.4, 28.5, 27.9. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{17}H_{22}N_3O$: 284.1757, Found: 284.1760.

2-((2-(*p*-Tolylethynyl)cyclohex-2-en-1-yl)oxy)-1,10-phenanthroline (10): colorless oil (24.5 mg,

63% yield); TLC R_f 0.22 (hexane/EtOAc, 2:1). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.15 (dd, *J* = 4.3, 1.7 Hz, 1H), 8.22 (dd, *J* = 8.1, 1.7 Hz, 1H), 8.09 (d, *J* = 8.7 Hz, 1H), 7.73 (d, *J* = 8.7 Hz, 1H), 7.64 (d, *J* = 8.7 Hz, 1H), 7.57 (dd, *J* = 8.1, 4.3 Hz, 1H), 7.19 (d, *J* = 8.7 Hz, 1H), 6.98 (d, *J* = 8.1 Hz, 2H), 6.88 (d, *J* = 8.1 Hz, 2H), 6.51-6.47 (m, 2H), 2.37-2.29 (m, 1H), 2.27-2.15 (m, 3H), 2.22 (s, 3H), 1.88-1.74 (m, 2H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 162.7, 149.8, 145.4, 144.4, 139.3, 138.9, 137.6, 136.1, 131.2, 129.1, 128.7, 126.3, 124.9, 123.5, 122.4, 121.8, 120.4, 114.7, 88.6, 88.5, 69.9, 28.1, 26.1, 21.4, 17.9. HRMS (APCI) m/z ($[M+H]^+$) Calcd for $C_{27}H_{23}N_2O$: 391.1805, Found: 391.1806.

Palladacycle intermediate (1b-PdOAc): colorless solid (112.5 mg, 48% yield); m. p. 184.8-187.3 °C (from DCM/hexane). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.79 (dd, *J* = 4.8, 1.5 Hz, 1H), 8.38 (dd, *J* = 8.3, 1.5 Hz, 1H), 8.25 (d, *J* = 8.7 Hz, 1H), 7.83 (d, *J* = 8.7 Hz, 1H), 7.77 (d, *J* = 8.7 Hz, 1H), 7.73 (dd, *J* = 8.3, 4.8 Hz, 1H), 7.18 (d, *J* = 8.7 Hz, 1H), 5.41 (s, 1H), 4.82 (t, *J* = 4.0 Hz, 1H), 2.25 (s, 3H), 2.20-2.09 (m, 2H), 1.68-1.61 (m, 1H), 1.50-1.45 (m, 1H), 1.06 (s, 3H), 1.03 (s, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ 177.9, 169.1, 166.3, 163.1, 149.2, 142.3, 139.3, 137.4, 129.4, 127.2, 126.4, 124.9, 124.5, 124.4, 118.3, 75.5, 33.7, 33.3, 30.6, 28.0, 26.1, 24.6. HRMS (ESI) m/z ($[M–OAc]^+$) Calcd for $C_{20}H_{19}N_2OPd$: 409.0532, Found: 409.0528.

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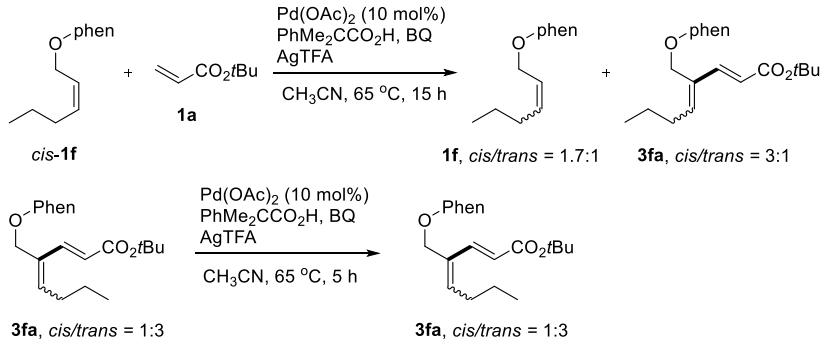
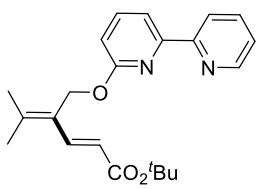
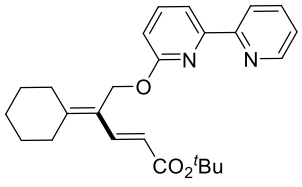
[12] We checked the trans/cis isomerization of both starting substrate and product. While the starting substrate gradually underwent the isomerization, the stereochemistry of initially formed product remained under the optimal conditions. See refs 8 and 15c and references cited therein.



[13] We also prepared the bipyridine-derived trisubstituted allylic alcohol substrates **1h-bpy** and **1i-bpy** and investigated their reactivity. However, we found no significant improvement, and almost the same isolated yields of the corresponding alkenylated products were obtained.



3ha-bpy: 60%



3ia-bpy: 57%

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[15] In the alkynylation reaction, attempts to apply less sterically demanding TMS-, aryl-substituted alkynyl bromides and simple terminal alkynes (e.g., H-C≡C-TIPS) as well as the trisubstituted allylic alcohols such as **1h** remained unsuccessful.

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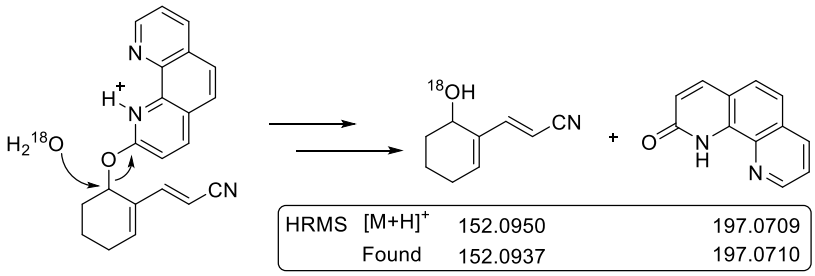

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Conclusions

The research described in this thesis is studies on the C-H coupling reactions *via N,N*-bidentate auxiliaries directed C-H bond activation. The auxiliary directed C-H alkylations of benzamides with small-sized heterocycles were disclosed under nickel catalysis, providing efficient access to the structurally useful benzolactones and benzolactams. The stereochemistry observed in this thesis shows unique nature of nickel catalyst in the C-H coupling process with small-sized heterocycles. Additionally, the C-H functionalizations of allylic alcohols were achieved with the assistance of a related bidentate directing group under palladium catalysis. The broad scope of allylic alcohols demonstrates the salient feature of the catalytic system and will find wide application in the development of related alkenyl C-H activation reactions.

The author has focused on exploring the possibility of small-sized heterocycles as the alkylating regents in the directed C-H functionalization reactions. With the assistance of 8-aminoquinoline-derived bidentate auxiliary, the nickel-catalyzed C-H alkylation of benzamides with epoxides to construct isocoumarin derivatives was developed (Chapter 2). A unique stereospecificity with retention of configuration was observed in the reaction with internal epoxides. Moreover, the four-membered oxetanes (Chapter 3) and three-membered aziridines (Chapter 4) were also applicable to the related C-H alkylations of 8-aminoquinoline-derived benzamides to form the corresponding benzolactones and benzolactams, respectively, under nickel catalysis. Additionally, in the course of studies on the bidentate auxiliary-directed C-H functionalization reactions, a related regioselective C-H alkenylation and alkynylation of allylic alcohols under palladium catalysis with the assistance of bidentate phenanthroline auxiliary was also disclosed (Chapter 5). This protocol shows significant advantage in the scope of allylic alcohols: *cis*-, *trans*-, and even more challenging trisubstituted substrates were tolerated. The bidentate auxiliaries are essential for these novel transformations, probably because of their capability to facilitate the otherwise challenging C-H bond activation and also inhibit β-elimination

of the metallacycle intermediates.

The author believes that the findings presented in this thesis possess great potential in the formation of C-C bonds and heterocyclic compounds.

Publication List

1. Nickel-Catalyzed Stereospecific C-H Coupling of Benzamides with Epoxides
   Shibo Xu, Kazutaka Takamatsu, Koji Hirano, Masahiro Miura
   Angew. Chem. Int. Ed. **2018**, *57*, 11797.

2. Synthesis of Seven-Membered Benzolactones by Nickel-Catalyzed C-H Coupling of Benzamides with Oxetanes
   Shibo Xu, Kazutaka Takamatsu, Koji Hirano, Masahiro Miura
   Chem. Eur. J. **2019**, *25*, 9400.

3. Synthesis of Benzolactams by Nickel-Catalyzed C-H Coupling of Benzamides with Aziridines
   Shibo Xu, Koji Hirano, Masahiro Miura
   Manuscript in preparation.

4. Palladium-Catalyzed Regioselective C-H Alkenylation and Alkynylation of Allylic Alcohols with the Assistance of a Bidentate Phenanthroline Auxiliary
   Shibo Xu, Koji Hirano, Masahiro Miura
   Org. Lett. **2020**, *22*, 9059.