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Cobalt-catalyzed arylation and alkenylation of alpha-bromo eneformamides and enecarbamates by cross-coupling with organic bromides: Application to the synthesis of functionalized piperidines and azepanes

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ABSTRACT

The synthesis of α-arylated and alkenylated piperidine and azepane derivatives has been accomplished through cross-coupling of α-bromo eneformamides or enecarbamates with feedstock organic halides such as aryl and vinyl bromides, under cobalt catalysis. The coupling products, which themselves are synthetic intermediates for accessing other functionalized piperidines and azepanes are obtained in good to excellent yields.

Introduction

The piperidine and azepane structural motifs constitute the core of several alkaloids and pharmaceuticals (selected examples of which are depicted in Fig. 1) that represent over thirty therapeutic areas including antidepressants and analgesics [1].

Fittingly, these motifs continue to inspire researchers toward the development of increasingly more efficient strategies for their construction and functionalization [2–8]. One such strategy that provides efficient access to functionalized piperidine and azepane derivatives is to employ an eneformamide or enecarbamate as a substrate for subsequent functionalization. In addition to offering latent functionality at the α and β positions (see **VI**, Fig. 2), cyclic enamides or enecarbamates offer several other advantages as a starting point for access to functionalized azaheterocycles [9–19].

As detailed in many previous reports, C-2 functionalization has primarily been achieved by utilizing the corresponding vinyl triflate [20–22], phosphate [23], stannane [24], or boronate [21,25] in cross-coupling manifolds (Fig. 2, top). The double bond of the

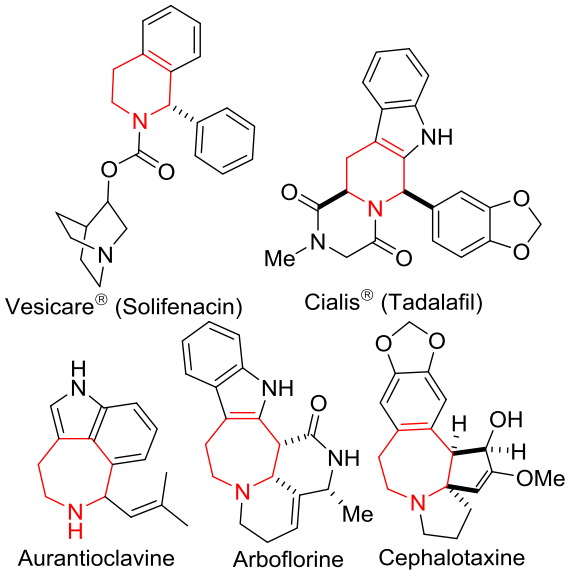

Fig. 1. Examples of bioactive piperidines and azepanes.

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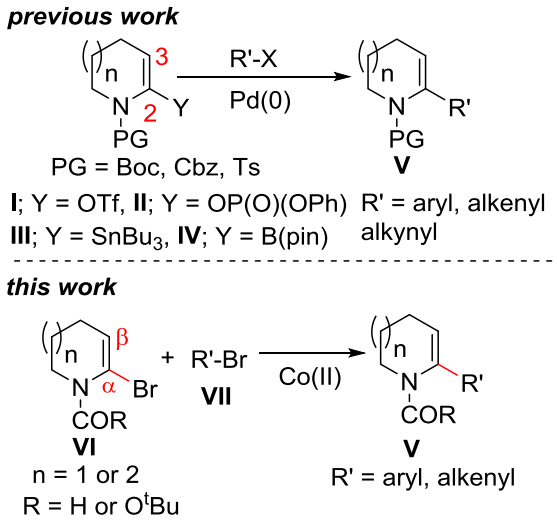


Fig. 2. C-2 functionalization strategies.

enamide or enecarbamate may also be reduced or oxidized [15,16,26,27], cyclopropanated [28], or engaged in allylic functionalization protocols [29].

Seeking a complementary approach to these established reactivity modes for the synthesis of α-arylated and vinylated *N*-heterocycles, we reasoned that cross-coupling of two readily available electrophilic organic bromides such as **VI** and **VII** (Fig. 2, bottom), catalyzed by an inexpensive and nontoxic metal such as cobalt, offered an attractive and conceptually sagacious approach [30]. Communicated herein is the *Co-catalyzed cross-coupling of bromo eneformamides* and *enecarbamates* with *organic bromides* to afford *α-substituted dehydropiperidines* and *azepenes*, which are further elaborated to other synthetically useful intermediates.

Results and discussion

Gleaning from Gosmini's insightful reports on Co-catalyzed cross-coupling of aromatic halides with α-halostyrenes [31], we commenced studies on the α-arylation of halo eneformamides by coupling bromo eneformamide **1a** [32] with bromobenzene in the presence of $CoBr_2$, a phosphine ligand, and a reductant such as manganese. Starting with a monodentate phosphine ligand such as triphenylphosphine [31,33,34], and after performing the reaction using the conditions described in Table 1, it was ascertained that acetonitrile was the most suitable solvent (see entries 1–3); consistent with Gosmini's findings [31]. In lieu of previous observations that the bite angle of a Co-bound phosphine ligand can have a dramatic effect on the efficiency of cross-couplings [33,35–41], several bidentate ligands were also evaluated (entries 4–12). Fortuitously, resounding success was achieved when bis-1,2-diphenylphosphinopropane (dppp) was utilized (entry 4). Ligands with smaller bite angles such as bis-1,2-diphenylphosphinomethane (dppm, entry 6) or larger bite angles such as bis-1,2-diphenylphosphinohexane (dpph, entry 8) have an adverse effect on the efficacy of the coupling.

Furthermore, no coupling is observed in the presence of *rac*-BINAP (entry 10), bipyridine (entry 11), or in the absence of any ligand (entry 12). Additionally, shortening the reaction time by performing the coupling at 40 °C has no noticeable beneficial effect on the yield (entry 13). Although the efficiency of the arylation marginally improves when bromo eneformamide **1a** is slowly introduced over the course of an hour (presumably due to the minimization of dimerization events, entry 14), the operational simplicity of the procedure employed in entry 4 still endows it with a practical advantage. In somewhat unsurprising results, chlorobenzene and chloro eneformamide **1b** are incompetent reactive partners when respectively coupled with eneformamide **1a** or bromobenzene (entries 15 & 16).

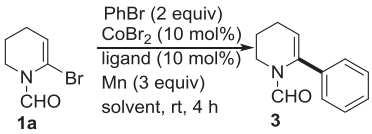
With satisfactory conditions in hand (Table 1, entry 4 or 14), the scope of the α-arylation with respect to the aryl bromide coupling partner was briefly explored (Scheme 1). Sterically demanding, electron-rich, electron-deficient, and π-deficient aryl bromides were surveyed. A highly electron-rich aryl bromide undergoes faster and more efficient coupling compared to an electron-neutral aryl bromide (**6** *vs* **3**). Of note, ortho substitution is tolerated on the aryl bromide (see **4**). Not surprisingly, π-deficient heteroaryl bromides are less competent coupling partners and afford the products in modest yields (see **7**). The α-alkenylation of **1a** also proceeds satisfactorily as coupling with β-bromostyrene affords *N*-formyl amino diene **8** in good yield. Vinylated adducts of dehydropiperidines such as **8** are highly desired since they serve as a diene component in [4 + 2]-cycloaddition reactions [42].

We have found that the Co-catalyzed reductive cross-coupling of two electrophilic organic bromides is not limited to the piperidine heterocycle. For example, homologous azepane bromo eneformamide **2** also undergoes efficient α-arylation and vinylation to afford the corresponding α-functionalized azepenes in good yields (see **9**–**12**).

When Co-catalyzed arylation of bromo enecarbamate **13a** with 2-bromonaphthalene was attempted, slow reactivity was encountered. Gratifyingly, heating to 40 °C for 4 h affords enecarbamate **14** in good yield (Scheme 2). Consistent with observations made when bromo eneformamide **1a** was employed, coupling with electron-rich aryl bromides proceeds highly efficiently (see **15** and **16**). Furthermore, regioselective α-alkenylation of **13a** with 1-bromopropene proceeds satisfactorily and furnishes conjugated diene **17**.

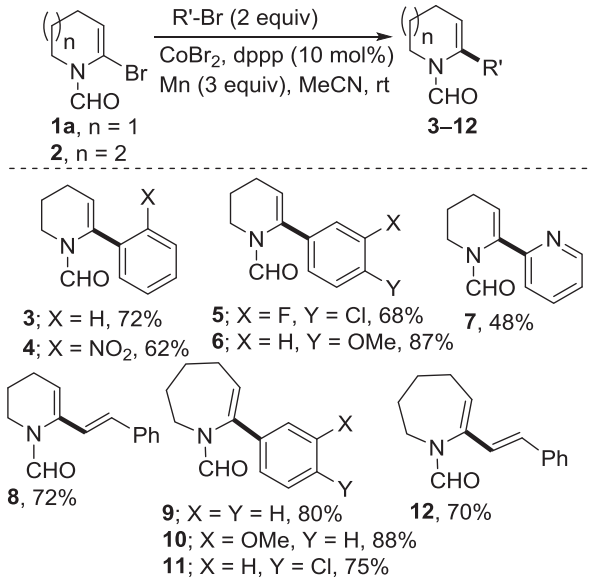
In a finding of great significance, particularly in the context of stereoselective construction of polysubstituted piperidines, these

Table 1
Optimization of the Co-catalyzed coupling of bromo eneformamide **1a** with phenyl bromide.



Entry	Ligand	Solvent	% Yield (by GC)
1	PPh_3	DMF	30
2	PPh_3	MeCN	61
3	PPh_3	THF	0
4	dppp	MeCN	86
5	dppe	MeCN	71
6	dppm	MeCN	46
7	dppb	MeCN	67
8	dpph	MeCN	22
9	dppf	MeCN	36
10	*rac*-BINAP	MeCN	0
11	bipyridine	MeCN	0
12	none	MeCN	0
13[a]	dppp	MeCN	80
14[b]	dppp	MeCN	94
15[c]	dppp	MeCN	26
16[d]	dppp	MeCN	<5

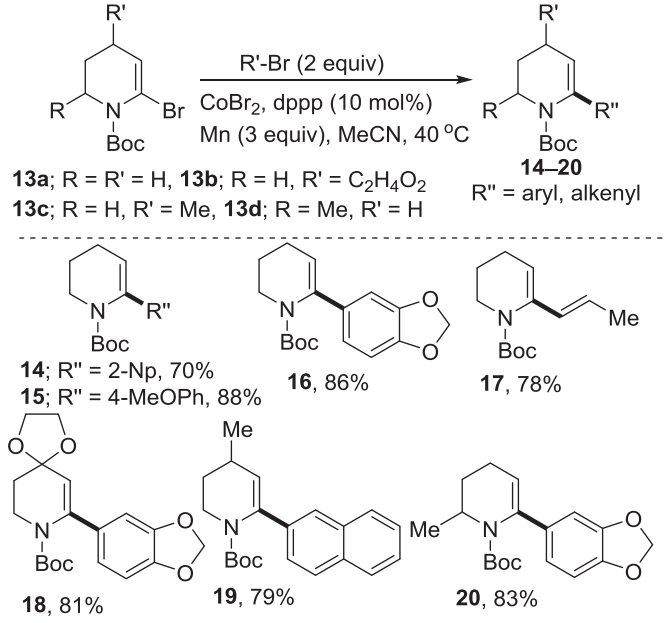
(c) using PhCl, (d) using chloro eneformamide **1b.**
[a] at 40 °C for 1 h.
[b] **1a** added slowly over 60 min.



Scheme 1. α-Functionalization of eneformamides **1a** and **2.**

studies have revealed that γ- and α′-substituted bromo enecarbamates such as **13b/c/d** undergo efficient α-arylation under similar reaction conditions to afford 2,4- and 2,6-disubstituted dehydropiperidines (see **18**–**20**). The utility of protected dihydropyridones such as **18** in alkaloid synthesis has been amply demonstrated [43–58].

While the detailed mechanistic features of the cobalt-catalyzed reductive cross-coupling described herein have not been fully investigated at this point, we suspect that a mechanism analogous to that first proposed by Gosmini [31] is operative. The general features include manganese-mediated reduction of Co(II) to Co(I), oxidative addition of one of the organic bromide coupling partners, a second reduction from Co (III) to Co (I), oxidative addition of the other bromide coupling partner, and subsequent reductive elimination.



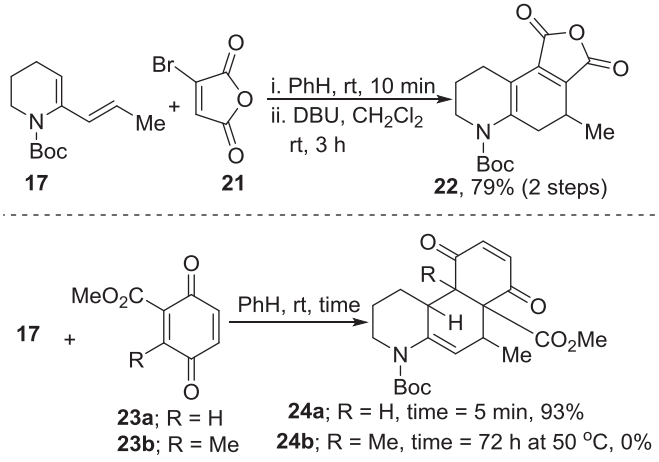
Scheme 2. Cobalt-catalyzed α-functionalization of enecarbamates **15a/b/c/d.**

The utility of α-vinylated adducts of dehydropiperidines in hexannelation reactions has been demonstrated. When diene **17** is subjected to a [4 + 2] cycloaddition reaction with bromomaleic anhydride (**21**) at room temperature in benzene, a single stereo- and regioisomer of the isomerized bromo adduct (not shown) is formed, which slowly dehydrobrominates upon standing. As such, this intermediate was converted to tricycle **22** upon treatment with DBU (Scheme 3). Treatment of diene **17** with activated ester quinone **23a** [59] gives rise to a single isomer of [6-6-6] tricycle **24a,** bearing four contiguous stereocenters, one of which is quaternary. As a testament to the challenges associated with the formation of vicinal quaternary centers in sterically congested environments, we find that methyl-bearing quinone **23b** fails to react with diene **17**, even after 3 days at 50 °C.

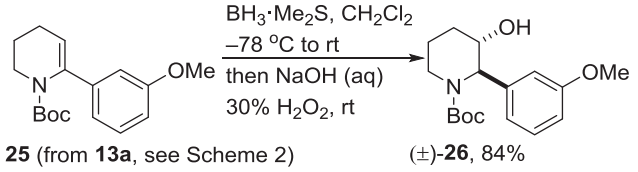
The α-arylated cyclic enecarbamates prepared in Scheme 2 may be further elaborated to other synthetically useful piperidine derivatives. For example, hydroboration-oxidation of crude **25** using conditions first introduced by Dhimane and coworkers [60] affords vicinally functionalized piperidine derivative **26** as a single diastereomer (Scheme 4). Of note, 2-aryl-3-hydroxypiperidines such as **26** serve as important intermediates in the synthesis of commodity chemicals such as 3-hydroxypipecolic acid [61–63] and alkaloids such as *epi*-L-773,060 [64,65].

The synthesis of 2,6-disubstituted dehydropiperidines such as **20** sets the stage for accessing α,α,α′-trisubstituted piperidines. Illustratively, catalytic hydrogenation of enecarbamate **27** over Pearlman's catalyst, then benzylic lithiation-transmetalation and copper-mediated allylation [66] affords a single diastereomer of trisubstituted piperidine **27**, bearing two α-amino stereocenters, one of which is *quaternary* (Scheme 5). NOESY experiments established the relative configuration of **27** as having the α-aryl group and the α′-methyl group *cis*. In this two-step sequence, highly diastereoselective reduction of **27** and subsequent net stereoretentive allylation are implicated. Instructively, the presence of an allyl moiety on a piperidine skeleton offers several advantages for the synthesis of piperidine alkaloids and pharmaceuticals since the double bond may be oxidized [67–72], reduced [69,72,73], carbolithiated [74–77], engaged in metathesis reactions [78], or hydrozirconated [79].

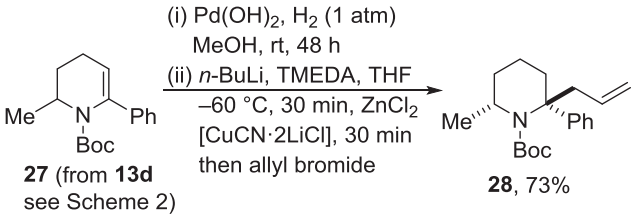
The synthesis of α,α-disubstituted azepanes and of γ′-functionalized azepane derivatives is possible through careful manipulation of the coupling products obtained using methodology described herein. For example, base-mediated cleavage of the formyl group in arylated azepene **11** followed by addition of allylmagnesium bromide to the resulting imine tautomer affords



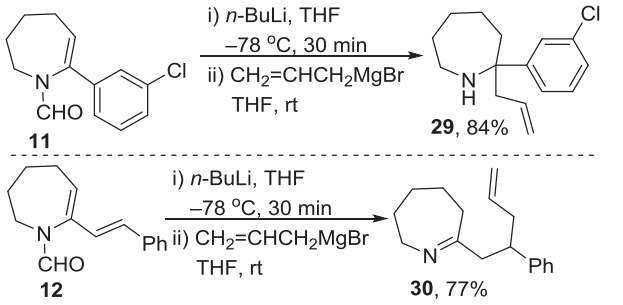
Scheme 3. Hexannelation of α-vinylated enecarbamate **17.**



Scheme 4. Hydroboration-oxidation of enecarbamate **25.**



Scheme 5. Stereocontrolled preparation of saturated trisubstituted piperidine **19.**



Scheme 6. 1,2- and 1,4-addition of allylmagnesium bromide to cyclic amines and imino dienes, respectively.

quaternary cyclic amine **29** (Scheme 6). When the same sequence of events is repeated on vinylated azepene **12**, conjugate addition out-competes 1,2-addition and furnishes γ'-allylated cyclic imine **30**.

Conclusion

In summary, cobalt-catalyzed α-arylation and alkenylation of cyclic α-bromo eneformamides and enecarbamates with vastly available organic bromides have been accomplished on two different classes of azaheterocycles, The 2-substituted enecarbamates and eneformamides are amenable to further functionalization under different modes of reactivity including cycloaddition, hydroboration-oxidation, stereoselective benzylic lithiation/allylation, 1,2- or 1,4-addition of nucleophiles to their corresponding imine tautomers. This short synthetic sequence sets the stage for the synthesis of α- and α,β-functionalized piperidine or azepane alkaloids and pharmaceuticals. Studies aimed at fully understanding the mechanistic details of the Co-catalyzed cross-coupling are underway.

Experimental

General information

All experiments involving air and moisture-sensitive reagents such as cobalt precatalysts, phosphine ligands, and organolithium reagents were carried out under an inert atmosphere of nitrogen and using freshly distilled solvents. All electrophiles such as aryl and vinyl bromides were newly purchased and used without further purification. TMEDA was distilled on a short path, over CaH_2. Column chromatography was performed on silica gel (230–400 mesh). Thin-layer chromatography (TLC) was performed on silica plates. Visualization of the TLC plates was aided by UV irradiation at 254 nm or by $KMnO_4$ staining. Unless otherwise indicated, ^1H, ^{13}C, DEPT-135, COSY 45, HMQC, and NOESY NMR spectra were acquired using C_6D_6 or $CDCl_3$ as solvent at room temperature. Chemical shifts are quoted in parts per million (ppm).

General procedure A. Arylation of halo eneformamides

To a solution of $CoBr_2$ (22 mg, 0.10 mmol, 10 mol%), bis-1,2-diphenylphosphinopropane (41.2 mg, 0.10 mmol, 10 mol%), and manganese powder (165 mg, 3 mmol, 3 equiv) in acetonitrile (5 mL) was added the aryl bromide (2 mmol, 2 equiv) at the desired temperature (rt for the bromo eneformamides or 40 °C for the bromo enecarbamates). A solution of the bromo eneformamide (1 mmol, 1 equiv) in acetonitrile (5 mL) was added slowly. After completion (as judged by TLC and GC–MS), the reaction mixture was treated with a mild acid such as 10% H_3PO_4 (aq) and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford the desired coupling product as an oil. Purification was carried out by flash chromatography on silica (pretreated with 1% Et_3N).

*Compound **3***

Prepared from **1a** (190 mg, 1.0 mmol) and phenyl bromide (314 mg, 2.0 equiv), using General Procedure A. T = 23 °C, time = 4 h; Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (70:30). Yield = 135 mg, 72%. ^1H NMR (400 MHz, C_6D_6) δ 8.39 (1H), 7.07 to 6.98 (5H), 4.76 (1H), 3.66 to 3.63 (2H), 1.72 to 1.68 (2H), 1.37 to 1.28 (2H). ^{13}C NMR (101 MHz, C_6D_6) δ 160.4, 138.5, 137.0, 128.5, 128.0, 127.8, 111.4, 39.0, 23.0, 21.9. HRMS calc for $C_{12}H_{13}NO$ 187.0997, found 187.0995.

*Compound **4***

Prepared from **1a** (190 mg, 0.10 mmol) and *o*-nitro-bromobenzene (400 mg, 2 equiv) using **General Procedure A** at room temperature for 12 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (20:80). Yield = 14.5 mg, 62%. ^1H NMR (400 MHz, C_6D6) δ 8.09 (1H), 7.30 to 7.28 (1H), 6.70 to 6.54 (3H), 4.40 to 4.38 (1H), 3.71 to 3.68 (2H), 1.60 to 1.56 (2H), 1.34 to 1.25 (2H). ^{13}C NMR (101 MHz, C_6D6) δ 160.0, 134.6, 132.9, 132.0, 131.4, 129.7, 124.7, 111.7, 39.9, 23.3, 21.6. . HRMS calc for $C_{12}H_{12}N_2O_3$ 232.0848, found 232.0844.

*Compound **5***

Prepared from **1a** (190 mg, 1.0 mmol) and 1-bromo-3-chloro-4-fluorobenzene (418 mg, 2 equiv) using **General Procedure A** at rt for 8 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (90:10). Yield = 18 mg, 68%. ^1H NMR (400 MHz, C_6D_6) δ 8.04 (1H), 6.97 to 6.95 (1H), 6.47 to 6.45 (2H), 4.48 to 4.46 (1H), 3.53 to 3.50 (2H), 1.64 to 1.60 (2H), 1.28 to 1.25 (2H). ^{13}C NMR (101 MHz, C_6D_6) δ 160.3, 136.1, 134.3, 129.9, 127.4, 127.3, 116.6, 116.4, 112.6, 39.0, 22.8, 21.7. HRMS calc for $C_{12}H_{11}ClFNO$ 239.0513, found 239.0511.

*Compound **6***

Prepared from **1a** (190 mg, 1.0 mmol) and 4-bromoanisole (374 mg, 2 equiv) using **General Procedure A.** Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (50:50). Yield = 173.6 mg, 80%. ^1H NMR (400 MHz, C_6D_6) δ 8.43 (1H), 7.04 to 7.01 (2H), 6.68 to 6.65 (2H), 4.81 to 4.79 (1H), 3.69 to 3.66 (2H), 3.33 (3H), 1.82 to 1.78 (2H), 1.43, 1.36 (2H). ^{13}C NMR (101 MHz, C_6D_6) δ 160.6, 159.7, 138.2, 133.5, 129.1, 129.1,

114.0, 110.4, 54.6, 39.1, 23.0, 22.1. HRMS calc for $C_{13}H_{15}NO_2$ 217.1103, found 217.1106.

Compound ***7***

Prepared from **1a** (190, 1.0 mmol) and 2-bromopyridine (320 mg, 2 equiv) using General Procedure A. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (20:80 to 0:100). Yield = 9.6 mg, 51%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.83 (1H), 8.81 (1H), 8.34 to 8.32 (1H), 7.56 to 7.44 (1H), 7.25 to 7.23 (1H), 5.17 to 5.15 (1H), 3.72 to 3.68 (2H), 2.18 to 2.13 (2H), 1.73 to 1.66 (2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.5, 150.0, 141.9, 138.8, 128.3, 125.0, 122.7, 109.5, 41.2, 23.7, 21.0. HRMS calc for $C_{11}H_{12}N_2O$ 188.0950, found 188.0953.

Compound ***8***

Prepared from **1a** (190 mg, 1.0 mmol) and β-bromostyrene (2 equiv) using General Procedure A. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (70:30). Yield = 173 mg, 81^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (1H), 7.65 to 7.32 (6H), 7.14 & 7.12 (1H), 5.13 to 5.10 (1H), 3.68 to 3.64 (2H), 2.13 to 2.09 (2H), 1.73 to 1.70 (2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.0, 145.3, 132.7, 129.5, 129.2, 109.5, 41.2, 23.8, 21.1. HRMS calc for $C_{14}H_{15}NO$ 213.1154, found 213.1157.

Compound ***9***

Prepared from **2** (20.5 mg, 0.1 mmol) and bromobenzene (2 equiv) using **General Procedure A**. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (70:30). Yield = 16 mg, 80%. Data as reported [80].

Compound ***10***

Prepared from **2** (20.5 mg, 0.1 mmol) and 4-bromoanisole (2 equiv) using **General Procedure A**. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (50:50). Yield = 203.5 mg, 80%. Data as reported [80].

Compound ***11***

Prepared from **2** (102.5 mg, 0.5 mmol) and 1-bromo-3-chlorobenzene using **General Procedure A**. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (80:20). Yield = 88 mg, 75%. Data as reported [80].

Compound ***12***

Prepared from **2** (102.5 mg, 0.5 mmol) and β-bromostyrene (2 equiv) using **General Procedure A**. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with hexane/EtOAc (90:10). Yield = 80 mg, 70%. Data as reported [80].

Compound ***14***

Prepared from **13a** (26.1 mg, 0.10 mmol) and 2-bromonaphthalene (41.4 mg, 2 equiv) using **General Procedure A** but at 40 °C for 4 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with PE/DCM (2:1). Yield = 21.6 mg; 70%. ^{1}H NMR (400 MHz, C_6D_6) δ 8.03 (1H), 7.81 to 7.20 (6H), 5.18 to 5.17 (1H), 3.75 to 3.73 (2H), 1.88 to 1.83 (2H), 1.55 to 1.52 (2H), 0.98 (9H). ^{13}C NMR (101 MHz, C_6D_6) δ 153.71, 140.51, 138.91, 133.61, 132.79, 128.52, 128.27, 127.81, 127.56, 127.22, 126.00, 125.37, 124.51, 123.77, 114.90, 79.58, 44.22, 27.37, 23.62, 23.45. HRMS calc for $C_{20}H_{23}NO_2$ 309.1729, found 309.1733. **Note:** The aromatic region is contaminated with the byproduct of biaryl coupling.

Compound ***15***

Prepared from **13a** (26.1 mg, 0.1 mmol) and 4-bromoanisole (2 equiv) using **General Procedure A** but at 40 °C for 2 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with PE/DCM (1:3). Yield = 25.2 mg; 88%. Data as reported [81]. ^{1}H NMR (400 MHz, C_6D6) δ 7.26, 7.23 (2H), 6.77, 6.75 (2H), 5.07 to 5.05 (1H), 3.70 to 3.67 (2H), 3.33 (3H), 1.87 to 1.82 (2H), 1.55 to 1.46 (2H), 1.14 (9H). ^{13}C NMR (101 MHz, C_6D6) δ 158.98, 153.81, 140.30, 134.07, 126.54, 114.22, 113.20, 79.33, 54.51, 44.33, 27.54, 23.52, 23.45. **Note:** The aromatic region is contaminated with the byproduct of biaryl coupling.

Compound ***16***

Prepared from **13a** (26.1 mg, 0.1 mmol) and 5-bromobenzo[*d*][1,3]dioxole (2 equiv) using **General Procedure A** at 40 °C for 2 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with PE/DCM (1:3). Yield = 26 mg; 86%. ^{1}H NMR (400 MHz, C_6D_6) δ 6.94 (1H), 6.79 to 6.63 (1H), 5.33 (1H), 5.02 to 5.00 (2H), 3.65 to 3.62 (2H), 1.80 to 1.76 (2H), 1.52 to 1.19 (11H). ^{13}C NMR (101 MHz, C_6D_6) δ 154.37, 148.29, 147.34, 140.91, 136.14, 119.52, 114.04, 109.08, 107.07, 101.27, 80.15, 44.96, 28.31, 24.13, 24.08. HRMS calc for $C_{17}H_{21}NO_4$ 303.1471, found 303.1466.

Compound ***17***

Prepared from **13a** (261 mg, 1.0 mmol) and 1-bromopropene (2 equiv) using **General Procedure A** at 40 °C for 3 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with PE/DCM (2:1). Data as reported [82]. Yield = 175 mg; 78%.

Compound ***18***

Prepared from **13b** (32.0 mg, 0.10 mmol) and 5-bromobenzo[*d*][1,3]dioxole (2 equiv) using **General Procedure A** at 40 °C for 2 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with DCM/MeOH (95:2). Yield = 28 mg; 77%. ^{1}H NMR (400 MHz, C_6D_6) δ 6.85 (1H), 6.77 to 6.71 (1H), 6.54 to 6.52 (1H), 5.32 to 5.23 (3H), 4.05 to 4.02 (1H), 3.53, 3.52, 3.50, 3.49, 3.49, 3.48, 3.47, 3.46, 3.44, 3.44, 3.43, 3.43, 3.42, 3.41, 3.37, 3.34, 1.98, 1.97, 1.95, 1.95, 1.54, 1.48, 1.48, 1.47, 1.44, 1.44, 1.41, 1.41, 1.39, 1.38, 1.33, 1.33, 1.30, 1.28, 1.26, 1.11, 1.10. ^{13}C NMR (101 MHz, C_6D6) δ 154.15, 153.10, 147.54, 147.31, 143.16, 134.37, 119.69, 112.79, 107.64, 106.91, 104.91, 100.70, 80.08, 78.66, 64.07, 63.98, 63.88, 44.97, 35.46, 28.10, 27.40. HRMS calc for $C_{19}H_{23}NO_6$ 361.1525, found 361.1534.

Compound ***19***

Prepared from **13c** (27.6 mg, 0.10 mmol) and 2-bromonaphthalene (2 equiv) using **General Procedure A** at 40 °C for 4 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N). PE/DCM (2:1). Yield = 25.6 mg; 79%. ^{1}H NMR (400 MHz, C_6D_6, mixture of rotamers) δ 8.03 to 7.84 (1H), 7.76 to 7.21 (6H), 5.17 & 5.16 (1H), 3.81 to 3.76 (2H), 2.16 to 2.09 (1H), 1.74 to 1.66 (1H), 1.52 to 0.98 (11H), 0.82 to 0.65 (3H). ^{13}C NMR (101 MHz, C_6D_6) δ 153.65, 139.51, 138.81, 133.59, 132.81, 127.79, 127.57, 127.20, 126.02, 125.40, 124.68, 123.95, 120.72, 79.65, 42.91, 31.62, 29.04, 27.36, 21.18. HRMS calc for $C_{21}H_{25}NO_2$ 323.1885, found 323.1879.

Compound ***20***

Prepared from **13d** (27.6 mg, 0.10 mmol) and 5-bromobenzo[*d*][1,3]dioxole (2 equiv) using **General Procedure A** at 40 °C for 2 h. Purification: Flash chromatography on silica (pretreated with 1% Et_3N). PE/DCM (1:3). Yield = 26.3 mg; 83%. ^{1}H NMR (400 MHz, C_6D_6, mixture of rotamers) δ 6.94 to 6.91 (1H), 6.79 to 6.76 (1H), 6.66 (1H), 5.37 to 5.32 (2H), 5.02 to 5.01 (1H), 4.90 to 4.72 (1H), 1.83, to 1.01 (16H). ^{13}C NMR (101 MHz, C_6D_6, mixture of rotamers) δ 153.54, 148.28, 147.62, 146.94, 146.55, 137.10, 136.84, 135.43, 120.28, 118.58, 113.11, 108.37, 107.69, 107.52, 106.22, 100.72, 100.57, 98.30, 80.17,

79.37, 48.84, 46.80, 27.97, 27.79, 27.64, 27.36, 19.83, 18.19, 15.47, 15.33. HRMS calc for $C_{18}H_{23}NO_4$ 317.1627, found 317.1630.

*Compound **22***

Cycloaddition. A 5 mL tube was flame-dried, evacuated and flushed with nitrogen. A solution of the dienophile (1.0 mL, 0.10 M in benzene) was added to a solution of the diene (1.0 mL, 0.10 M in benzene) under nitrogen. After 10 min, the solvent was removed *in vacuo* to obtain the bromo adduct (35 mg, 87%). No further purification is necessary. ^{1}H NMR (400 MHz, C_6D_6) δ 3.65 to 3.60 (1H), 3.46 (1H), 2.91 to 2.85 (1H), 2.55 to 2.41 (2H), 2.22 to 2.10 (1H), 1.84 to 1.75 (1H), 1.49 to 1.29 (14H), 1.24 (3H). ^{13}C NMR (101 MHz, C_6D_6) δ 168.21, 167.79, 153.27, 136.42, 111.36, 81.31, 60.14, 58.94, 44.61, 37.29, 35.31, 28.51, 25.73, 23.19, 17.30.

Caution. The product is acid (and base) sensitive and should not be put on silica (unless pretreated with 1% Et_3N). The adduct also readily eliminates HBr upon standing.

Dehydrobromination. To the bromo adduct (20 mg, 0.05 mmol) dissolved in distilled CH_2Cl_2 (5 mL) was added DBU (3 equiv) dropwise. After 3 h at room temperature, the reaction was quenched by addition of *sat*. aqueous NH_4Cl. The mixture was diluted with DCM and the layers were separated. The aqueous layer was further extracted with DCM and the combined organic layers were washed with brine, dried over Na_2SO_4 (30 min), filtered, and concentrated under reduced pressure. Purification by flash chromatography on silica (pretreated with 1% Et_3N) eluting with PE/DCM (1:3) afforded 11.32 mg of the desired product in 79% yield (from diene **17**). ^{1}H NMR (400 MHz, C_6D_6) δ 3.38 to 3.22 (1H), 3.20 to 3.16 (1H), 2.69 to 2.09 (6H), 1.47 to 1.20 (10H), 0.91 & 0.89 (3H). ^{13}C NMR (101 MHz, C_6D_6) δ 163.45, 152.15, 143.29, 140.42, 134.18, 110.47, 81.30, 44.65, 35.04, 27.74, 25.31, 22.02, 21.99, 16.17. HRMS calc for $C_{17}H_{21}NO_5$ 319.1420, found 319.1418.

*Compound **24a***

A 5 mL tube was flame-dried, evacuated and flushed with nitrogen. A solution of dienophile **23a** (1.0 mL, 0.1 M in benzene) was added to a solution of diene **17** (1.0 mL, 0.1 M in benzene) under nitrogen. After 5 min, the solvent was removed *in vacuo* to obtain the crude product (35.1 mg, 93%). ^{1}H NMR (400 MHz, C_6D_6) δ 6.26 (1H), 6.06 (1H), 5.69 to 5.56 (1H), 4.15 (1H), 3.82 (1H), 3.29 to 3.19 (6H), 2.85 to 2.79 (1H), 2.61 to 2.54 (1H), 2.41 to 2.34 (1H), 1.46 to 1.09 (13H). ^{13}C NMR (101 MHz, C_6D_6) δ 197.74, 195.10, 171.80, 154.19, 142.87, 140.18, 137.68, 124.86, 79.92, 61.97, 54.83, 52.87, 46.67, 36.78, 35.70, 30.14, 28.73, 26.10, 17.12. HRMS calc for $C_{21}H_{27}NO_6$ 389.1838, found 389.1845.

Caution. The product is acid (and base) sensitive and should not be put on silica (unless pretreated with 1% Et_3N). Even residual acid in $CDCl_3$ destroys the compound.

*Compound **26***

To a solution of the crude enecarbamate **25** (58 mg, 0.20 mmol, 1.0 equiv) in freshly distilled CH_2Cl_2 (4 mL) at −78 °C was added dropwise a 2 M solution of $BH_3 \cdot SMe_2$ in THF (100 μL, 1 equiv). After a few minutes, the mixture was warmed to room temperature and stirring was continued for 6 h. It was then cooled to 0 °C and a few drops of 10% NaOH (aq) were added slowly followed by 0.5 mL of 30% H_2O_2. The mixture was returned to room temperature and stirred for 3 h. Water was added and the mixture was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated under reduced pressure to afford crude product as an oil. Purification by flash chromatography on silica eluting with hexanes:EtOAc (40:60) gave 52.8 mg of the *trans*-**26** in 84% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 to 7.23 (1H), 6.83 to 6.75 (3H), 5.35 to 5.33 (1H), 4.48 to 4.46 (1H), 4.12 to 4.06 (1H), 3.80 to 3.77 (3H), 3.13 (1H), 2.92 to 2.85 (1H), 2.04 to 1.25 (13H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.9, 156.6, 140.2, 129.6, 118.6, 112.5, 111.7, 79.9, 67.3, 60.1, 55.1, 40.1, 28.5, 28.4, 26.0, 18.8. HRMS calc for $C_{17}H_{25}NO_4$ 307.1784, found 307.1780.

*Compound **28***

Hydrogenation. $Pd(OH)_2$ (102 mg, 0.4 mmol) was added to a solution of crude enecarbamate **27** (27.3 mg, 0.1 mmol) in freshly distilled MeOH (4 mL) under hydrogen (1 atm) at room temperature. After complete consumption of the **27** (based on LC-MS and TLC monitoring, ~48 h), the mixture was filtered through a plug of Celite, concentrated under reduced pressure, and dried extensively on a high vacuum line.

Benzylic lithiation. To an oven-dried, septum-capped round bottom flask equipped with a stir bar, was added freshly distilled TMEDA (0.02 mL, 0.12 mmol, 1.2 equiv) and a solution of the reduced enecarbamate (0.1 mmol, 1.0 equiv) in THF (2 mL) under nitrogen. The mixture was cooled to −60 °C and a solution of *n*-BuLi (0.10 mL, 2.0 M in hexanes, 0.2 mmol, 2.0 equiv) was added slowly. After 1 h at this temperature, a solution of $ZnCl_2$ (0.13 mL, 1.0 M in THF, 1.3 equiv) was added slowly. After 30 min, a solution of $CuCN \cdot 2LiCl$ [prepared from CuCN (1.2 equiv) and LiCl (2.5 equiv)] in THF (1.0 mL) was added. After 30 min, allyl bromide (1.1 equiv) was added. The mixture was allowed to stir for 10 h at this temperature prior to the addition of MeOH (0.2 mL) and warming to room temperature. A solution of NH_4Cl (2 mL) was added and the aqueous layer was extracted with Et_2O. The combined organic layers were dried over Na_2SO_4 and evaporated to give the crude product. Purification by flash chromatography on silica eluting with hexane-EtOAc (98:2) afforded 23 mg of **28** in 73% yield from **13d**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 to 7.12 (5H), 6.05 (1H), 5.19 to 5.08 (2H), 4.45 (1H), 3.17 to 2.96 (2H), 2.14 to 0.85 (18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 150.4, 136.2, 128.0, 125.8, 125.5, 117.3, 79.5, 62.4, 48.2, 45.3, 37.3, 28.3, 27.3, 22.5, 14.5. HRMS calc for $C_{20}H_{29}NO_2$ 315.2198, found 315.2194.

*Compound **29***

Imine formation. To eneformamide **11** (59 mg, 0.25 mmol, 1.0 equiv) dissolved in freshly distilled THF (5 mL) was added *n*-BuLi (0.15 mL, 0.30 mmol, 2.0 M in hexanes, 1.2 equiv) at −78 °C. After complete deprotection of the eneformamide (~30 min, as indicated by TLC and LCMS-monitoring), the mixture was quenched with H_2O and diluted with EtOAc. It was washed with *sat*. $NaHCO_3$ and then with brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to give the crude product as an oil.

Grignard addition. To the crude imine dissolved in freshly distilled THF (5 mL), was slowly added allyl magnesium bromide (0.5 mL, 1.0 M solution in Et_2O, 2 equiv) under nitrogen at 0 °C. The mixture was stirred for 10 min at 0 °C, then warmed slowly to room temperature. After complete consumption of the imine (as indicated by TLC and LC-MS, ~12 h), the mixture was cooled to 0 °C, diluted with Et_2O. Water was then added slowly and the layers were separated. The aqueous layer was extracted twice with Et_2O and the combined organic layers were dried over Na_2SO_4 for 30 min, filtered, and concentrated under reduced pressure to give the desired product. Purification: Flash chromatography on silica (pretreated with 1% Et_3N) eluting with Hexane/EtOAc (1:2). Yield = 52.3 mg; 84%. ^{1}H NMR (400 MHz, C_6D_6) δ 7.63 (1H), 7.27 to 6.87 (3H), 5.42 to 5.20 (1H), 4.75 to 4.71 (2H), 2.63 to 2.57 (1H), 2.29 to 2.06 (2H), 1.84 to 0.75 (10H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 151.1, 134.3, 134.0, 129.2,

127.0, 126.0, 124.9, 118.2, 61.6, 48.1, 42.9, 41.3, 33.2, 30.2, 22.7. HRMS calc for $C_{15}H_{20}ClN$ 249.1284, found 249.1289.

*Compound **30***

Prepared in the same way as **29** starting from diene **12** (57 mg, 0.25 mmol). Purification: Flash chromatography on silica (pre-treated with 1% Et_3N) eluting with Hexane/EtOAc (20:80). Yield = 46.5 mg; 77%. ^1H NMR (400 MHz, $CDCl_3$) δ 7.46 to 7.04 (5H), 5.83 to 5.55 (1H), 5.19 to 4.91 (2H), 3.38 to 1.21 (15H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.06, 136.19, 128.95, 128.47, 127.48, 126.44, 116.78, 48.63, 43.14, 40.87, 40.72, 39.64, 27.35, 25.93, 22.77. . HRMS calc for $C_{17}H_{23}N$ 241.1830, found 241.1827.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jorganchem.2015.01.001.

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