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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

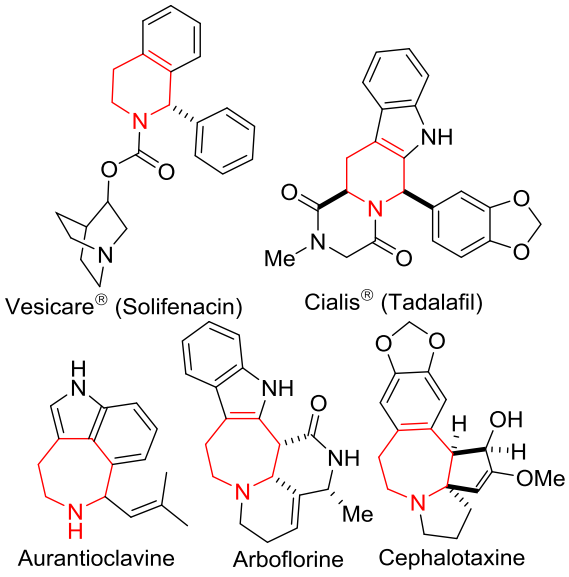

Fig. 1. Examples of bioactive piperidines and azepanes.

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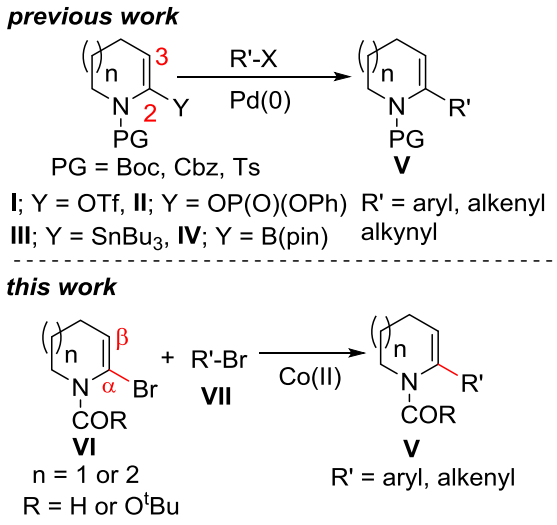


Fig. 2. C-2 functionalization strategies.

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).

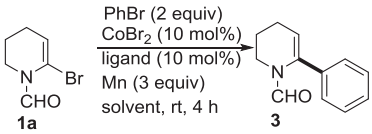
With satisfactory conditions in hand (Table 1, entry 4 or 14), the scope of the α-arylation with respect to the aryl bromide coupling partner was briefly explored (Scheme 1). Sterically demanding, electron-rich, electron-deficient, and π-deficient aryl bromides were surveyed. A highly electron-rich aryl 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.