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Direct access to functionalized benzotropones, azepanes, and piperidines by reductive cross-coupling of α-bromo enones with α-bromo enamides†

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The synthesis of functionalized azepenes and piperidines bearing an α-cycloheptenone or benzotropone derivative has been accomplished through direct reductive cross-coupling of α-bromo eneformamides or enecarbamates with highly versatile α-bromo benzotropone derivatives, under cobalt catalysis. The coupling products have been further elaborated to other synthetically useful aza-heterocyclic frameworks.

Functionalized benzotropones, cycloheptenones, azacycloheptanes (*i.e.*, azepanes), and azacyclohexanes (*i.e.*, piperidines) are ubiquitous structural motifs in bioactive natural products and pharmaceuticals including perovskatone A (from *Perovskia atriplicifolia*, Fig. 1),[1] colchicine (from *Colchicum automnale*),[2] longeracinphyllin B (from *Daphniphyllum yunnanense*),[3] stenine (from *Stemona tuberosa*), and nominine (from *Aconitum sanyoense*).[4]

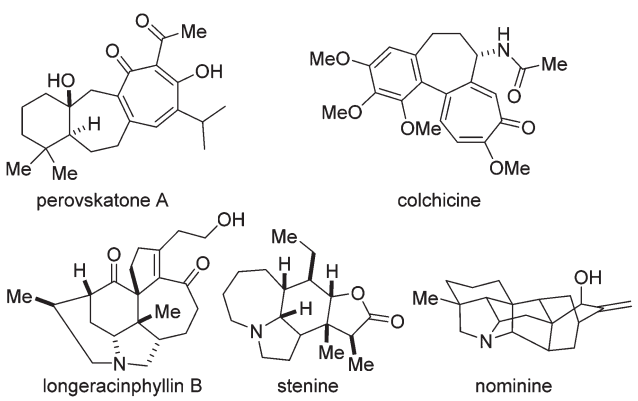

Fig. 1 Examples of functionalized tropone, cycloheptenone, azepane, and piperidine alkaloids and pharmaceuticals.

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Fittingly, key features such as structural diversity and biological relevance continue to inspire researchers toward developing increasingly more efficient strategies for the construction and functionalization. of (benzo)tropone,[5] cycloheptenone,[6] azepane,[7–9] and piperidine[9–13] derivatives. If two or more of the aforementioned motifs are coupled together, it is recognized that the structural space for the discovery of novel scaffolds with medicinal value would be greatly expanded. The conventional cross-coupling of nucleophilic coupling partners such as vinyl stannanes and aryl boronic acids (see **I**, Fig. 2A) with α-halo enones such as **II** has previously been accomplished under forcing conditions.[14] Given the now established reactivity series of α-halo enones relative to the unsubstituted counterpart (Fig. 2B),[15] conventional cross-coupling strategies featuring the latter, under less forcing conditions, have subsequently emerged.[16] Our interest in functionalized azaheterocycles[11,12,17,18] led us to the discovery that α-halo eneformamides such as **IV** may be satisfactorily coupled with aryl, alkenyl, and alkynyl nucleophiles.[7,18] Very recently, we have disclosed that cyclic α-bromo eneformamides and enecarbamates are amenable to cobalt-catalyzed reductive cross-coupling with aryl or vinyl bromides (Fig. 2C).[19] In this umpolung process, the catalyst (rather than the substrate) is reduced, thus, obviating the need for the pregeneration of difficult-to-handle, expensive, or toxic organometallic reagents. Seeking an efficient strategy that would provide access to functionalized azaheterocycles bearing a benzotropone derivative (Fig. 2D) or a β-amino substituent (Fig. 2E), we reasoned that direct reductive cross-coupling of two readily available, stable, and easy to handle electrophilic organic bromides, under transition metal-catalysis, offered an attractive approach.[20] Communicated herein, are our current efforts toward the realization of the proposed plan.

Our studies on the reductive cross-coupling of α-bromo enones (examples of which are depicted in Fig. 3) with α-bromo eneformamides and enecarbamates commenced with the search for the best phosphine-based ligand and transition metal catalyst.

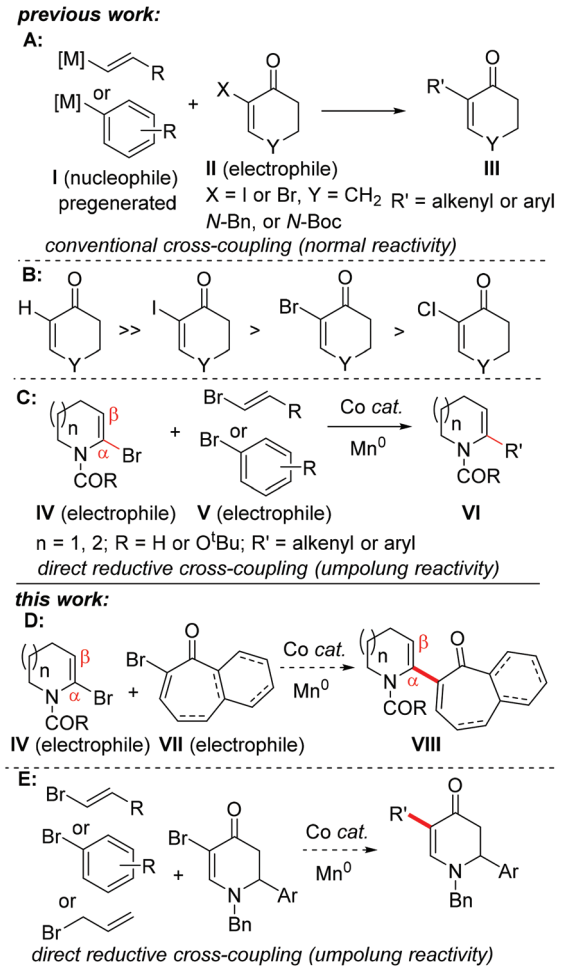


Fig. 2 Proposed plan for accessing functionalized azaheterocycles containing at least one cycloheptenone derivative.

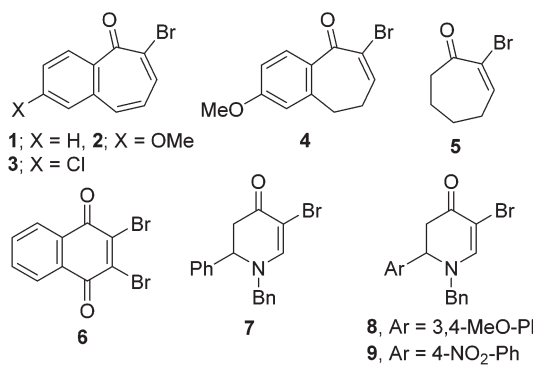
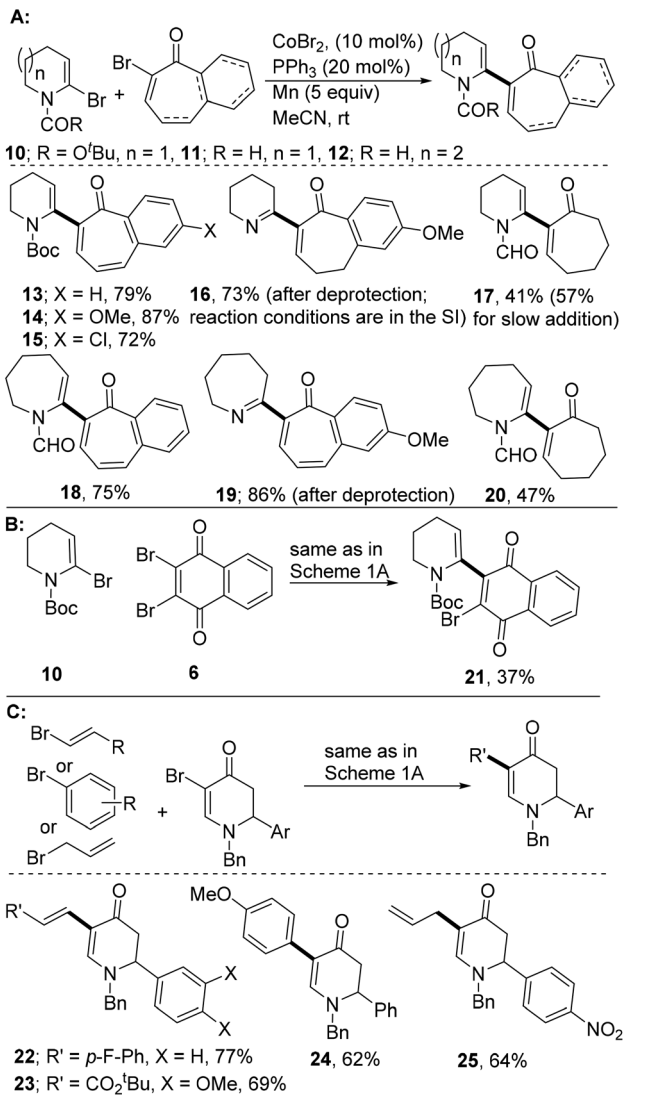


Fig. 3 Selected enone derivatives employed in these studies.

Cognizant of the high tolerance for carbonyl-containing functional groups in reductive cross-couplings and hoping to apply some of the lessons learned from our recent report on Co-catalyzed cross-coupling of bromo enamides with bromoarenes[19] to the current scenario, we were pleased to find that the coupling of bromo enecarbamate **10** with bromo enone **1** proceeds efficiently at room temperature using the conditions described in Scheme 1A (see **13**). As a testament to the generality of the transformation, methoxy-bearing bromo enone **2** and chlorine-containing enone **3** both furnish the α-vinylated adducts in good yield (see **14** & **15**). This is noteworthy, since either substituent (*i.e.*, the methoxy or chlorine substituent) could serve as a place-holder or functional handle for late-stage diversification. The marginal increase in the efficacy and rate of coupling of **2** with **10** suggests that electron-rich bromo enones have a beneficial effect on the transformation. This is somewhat understandable given the general reactivity of α-halo enones (see Fig. 2B). Encouragingly, despite being less stable and enolizable, bromo enone **4** still couples

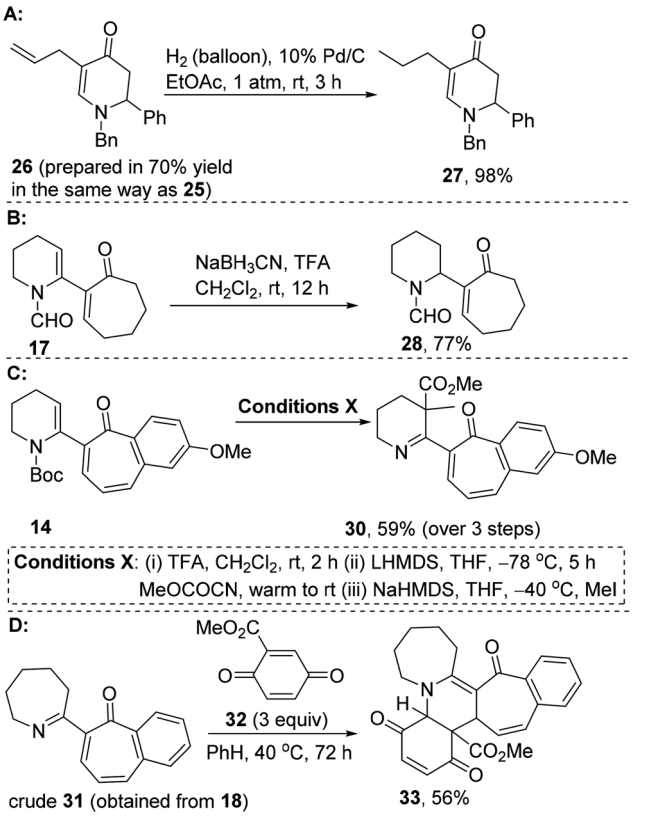


Scheme 1 Co-catalyzed reductive cross-coupling of α-bromo enones with organic bromides.

with bromo enecarbamate **10**, affording imino diene **16** in acceptable yield, following acid-mediated cleavage of the Boc-group. The importance of having a benzannulated bromo enone (which aids to slow down reactivity, thus, mitigating undesirable homocoupling) is supported by the observation that the reaction of α-bromocycloheptenone **5** with bromo enecarbamate **10** affords mostly the homocoupling product, even when the former is introduced slowly over the course of an hour. Consistent with our previous findings on the superiority of bromo eneformamide **11** (relative to bromo enecarbamate **10**) as a coupling partner in reductive cross-couplings,[19] we find that it couples modestly with **5** (see **17**).

As further illustrated in Scheme 1A, azepane-derived bromo eneformamide **12** is also amenable to Co-catalyzed reductive cross-coupling with α-bromo enones (see **18–20**). Understandably (especially from a stability standpoint), dibromonaphthoquinone **6** couples inefficiently with **10** under the identified conditions (Scheme 1B). These studies have also revealed that highly versatile α-bromo enaminones such as **7**, **8**, or **9** undergo satisfactory co-catalyzed cross-electrophile-coupling with bromo styrenes, bromo acrylates, bromoarenes, and allylic bromides (Scheme 1C). The latter example (*i.e.*, formation of **25**) features net regioselective β-allylation of an enaminone. This is noteworthy since the presence of an allyl moiety on a piperidine skeleton offers several advantages for the synthesis of piperidine alkaloids and pharmaceuticals. For example, as has been demonstrated for 2-allyl piperidine derivatives, the double bond on the allyl moiety can be reduced,[11,21] oxidized,[11,22] engaged in metathesis reactions,[13] or carbolithiated.[23]

Desiring to broaden the synthetic utility of the reductive coupling methodology described herein, we have shown that further elaboration of the coupling products depicted in Scheme 1 to other synthetically important molecular architectures is possible. For example, chemoselective reduction of the double bond resident in the allyl moiety of allylated enaminone **26** (prepared in the same way as **25**, see Scheme 1C) affords β-alkylated derivative **27** in high yield, without any complications arising from benzonolysis, conjugate, or 1,2-reduction of the enaminone motif (Scheme 2A). Additionally, *N*-acyl iminium reduction of *N*-formyl amino diene **17** affords piperidine derivative **28** (Scheme 2B). Furthermore, cleavage of the Boc-group in **14** quantitatively furnishes α-functionalized cyclic imine **29** (not shown), which upon subjection to sequential α-acylation and α-methylation of the corresponding azaenolate, affords 3,3-difunctionalized 1,2-dehydropiperidine **30** in 59% overall yield (Scheme 2C). In another significant outcome, we have found that electronically frustrated imino dienes such as **31** (obtained from **18**, see Scheme 1A) are amenable to a [4 + 2] cycloaddition with activated dienophiles such as ester quinone **32**. For example, treatment of **31** with **32** under thermal conditions affords highly functionalized pentacycle **33** (Scheme 2D). Primarily due to challenges associated with stability, the relative configuration of **33** hasn't been unambiguously established at this point.



Scheme 2 Elaboration of reductive coupling products to other functionalized azaheterocycles.

Conclusions

In summary, the cobalt-catalyzed reductive cross-coupling of versatile α-bromo enones with cyclic α-bromo enamides has been accomplished under mild conditions. The 2-substituted benzotropone and cycloheptenone derivatives are amenable to further functionalization under different modes of reactivity, including chemoselective catalytic hydrogenation, *N*-acyl iminium reduction, [4 + 2]-cycloaddition, and α-acylation/methylation. These short synthetic sequences set the stage for the synthesis of functionalized piperidine or azepane alkaloids and pharmaceuticals bearing a benzotropone derivative, details of which will be disclosed later.

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