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Communication

# One-shot access to α,β-difunctionalized azepenes and dehydropiperidines by reductive cross-coupling of α-selenonyl-β-selenyl enamides with organic bromides

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**The synthesis of α- and α,β-functionalized azepenes and dehydropiperidines from readily prepared α-selenonyl eneformamides or enecarbamates has been achieved through Fe-catalyzed α-substitutive deselenonation, β-regioselective lithiation/trapping, and Co-catalyzed reductive cross-coupling protocols.**

Functionalized piperidines and azepanes (examples of which are depicted in Fig. 1) constitute the core of several bioactive molecules, including alkaloid natural products and pharmaceuticals.[1] Fittingly, the architectural complexity and biological significance of these privileged *N*-heterocyclic motifs continue to inspire the synthesis community toward developing increasingly more efficient strategies for their construction, peripheral functionalization, and evaluation of structure-activity relationships (*i.e.*, SAR).

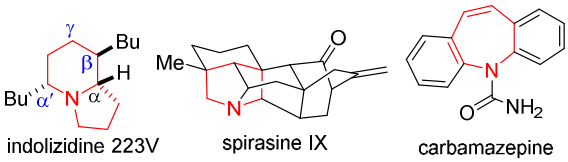



**Fig. 1** Selected examples of functionalized piperidine- and azepane-alkaloids and pharmaceuticals

For example, some of the well-heeled strategies for accessing piperidines (and in some cases azepanes) include those employed by Bode[2, 3] (using SnAP reagents), Cossy[4, 5] (using a ring expansion tactic), Bosch[6] (using bicyclic lactams), Charette[7] (using pyridinium salts), Comins[8, 9]/Georg[10, 11] (using dihydropyridones), Liebeskind[12] (using organometallic scaffolding), Beak[13, 14]/Gawley[15-19]/O'Brien[20, 21]/Coldham[22, 23]/Meyers[24]/Clayden[25] (using directed lithiation/trapping protocols), McMillan[26-29] (using photoredox catalysis), Maes[30, 31] (using Ru-catalyzed C-H activation), Danheiser[32]/Garg and Houk[33] (using azacyclohexynes), Coudert[34]/Occhiato[35, 36]/Comins[37]/Speckamp[38] (using lactam-derived phosphates or triflates), and Dake[39-41]/Gillaizeau[42, 43]/others[44] (using enamides or enecarbamates). Recognizing the merits of cyclic enamides or enecarbamates as starting substrates for differential functionalization (e.g., in hydrogenation,[45] cyclopropanation,[46] halogenation,[47] amination,[48] hexannelation,[49] aminoxylation,[50] or allylic functionalization[51] manifolds), we joined the fray and found that cyclic α-halo eneformamides and enecarbamates are amenable to Pd-catalyzed arylation, alkenylation, or alkynylation,[52, 53] and Ru-catalyzed β-sulfonation.[54] Additionally, we have recently disclosed that cyclic α-bromo eneformamides and enecarbamates are amenable to cobalt-catalyzed reductive cross-coupling with cheap feedstock chemicals such as organic bromides or α-bromo enones.[55] In this electrophile-electrophile coupling mode,[56-60] traditionally difficult functional groups (e.g., ester, ketone, nitrile, or alcohol groups) are impressively tolerated and the need for pregeneration of expensive or difficult-to-handle organometallic reagents (e.g., boronic esters) is obviated.[61-63]

Seeking *complementary* and *unifying* strategies for accessing *differentially-substituted* azaheterocycles, especially those bearing *vicinal disubstitution*, it was surmised that α-selenonyl eneformamides or enecarbamates such as **1** (Fig. 2), bearing traceless functionality at C-2 (*i.e.*, the selenonyl group) offered a succinct approach. Specifically, it was envisioned that Denmark-motivated[57] cross-coupling reactions of **1** using the selenonyl group as a functional handle, would give rise to α-carbofunctionalized products such as **2**. Importantly, the electron-withdrawing nature of the α-selenonyl group could aid in rendering the β-position acidic *enough* to allow for Comins-style[9] directed lithiation/trapping with electrophiles (see **3**). In this mode of reactivity, the installation of a second traceless group at the β-position (e.g., a selenyl group) would set the stage for accessing carbo-difunctionalized products such as **4**, via a Gosmini-inspired[63] one-pot reductive cross-coupling protocol. Given the propensity for vinyl selenones to participate

in conjugate additions,[64] it is theorized that **1** would serve as a (hetero) Michael acceptor, thereby allowing for the introduction of nucleophiles at the β-position (see **5**). Herein, synthetic efforts toward the realization of these ideals are described.

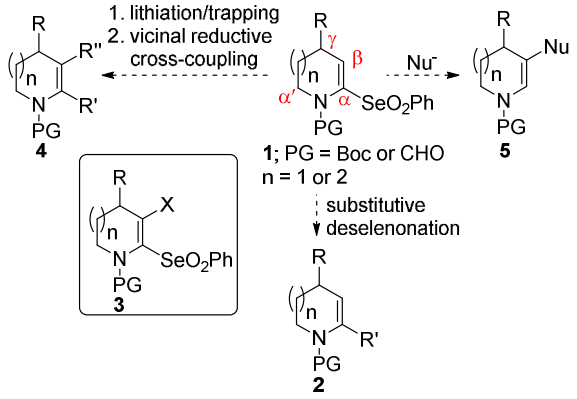
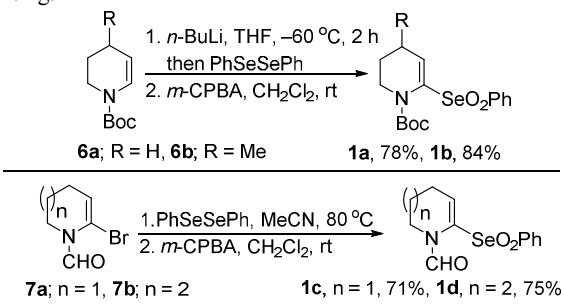


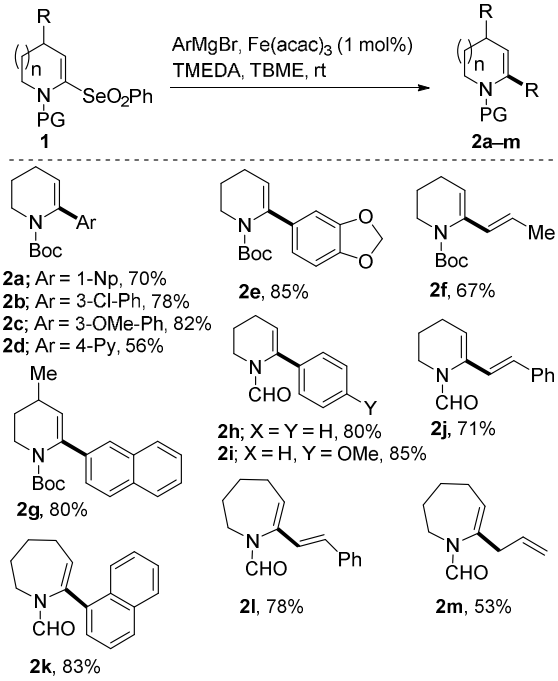

**Fig. 2.** Proposed plan for the synthesis of functionalized azepenes and dehydropiperidines using α-selenonyl enamides

Studies toward the functionalization of enecarbamates or eneformamides bearing a pendant leaving group at C-2 commenced with the preparation of α-selenonyl precursors capable of undergoing alkylative deselenonation. In the event, we were pleased to find that readily available piperidine enecarbamates **6a/b**,[65] undergo satisfactory vinyl lithiation[66]/selenation and subsequent *m*-CPBA-induced oxidation of the crude selenide to the desired α-selenonyl piperidine enecarbamates (Scheme 1, see **1a/b**). Encouragingly, bromo eneformamide **7a** (available in one step from δ-valerolactam[55]) affords selenone **1c** in reasonable yield, following selenation and oxidation. Furthermore, the identified conditions are applicable to α-bromo azepene **7b**[52] (see **1d**). This is noteworthy since it is now common knowledge to the synthesis community that extrapolating reactivity trends from one *N*-heterocycle to another can be daunting.



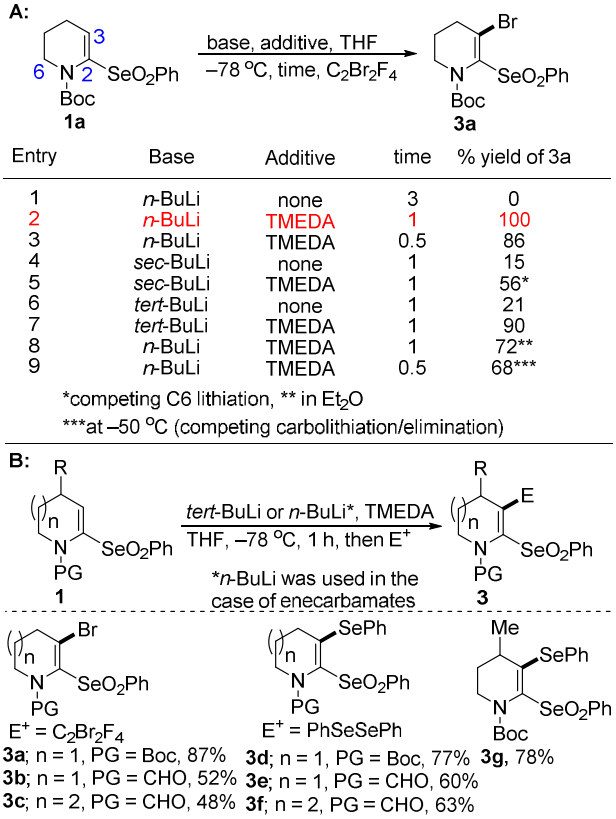

**Scheme 1.** Preparation of α-selenonyl enecarbamates or eneformamides

With α-selenonyl enecarbamates and eneformamides in hand, their amenability to alkylative deselenonation was next explored. Gratifyingly, starting with α-selenonyl dehydropiperidines and using Fe-catalyzed conditions analogous to those developed by Denmark and Cresswell,[57] the resulting carbo-functionalized products depicted in Scheme 2 were obtained in satistisfactory yields. As a testament to the generality of this deselenonative coupling mode of reactivity, aryl and heteroaryl, alkenyl, and allyl Grignard reagents are well tolerated.




**Scheme 2.** Synthesis of α-carbo-functionalized azaheterocycles

Intrinsic to our design of selecting an α-selenonyl group was the prospect of utilizing it as a requisite group for α-functionalization protocols (as discussed thus far) and as an activating group toward regioselective β-functionalization via Comins-style[9] directed lithiation/trapping with electrophiles.

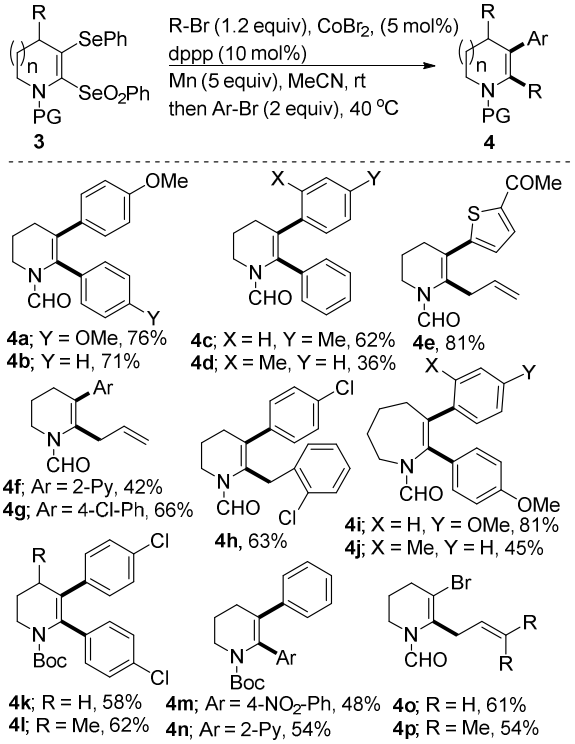



| Entry | Base | Additive | time | % yield of 3a |
|---|---|---|---|---|
| 1 | *n*-BuLi | none | 3 | 0 |
| 2 | *n*-BuLi | TMEDA | 1 | 100 |
| 3 | *n*-BuLi | TMEDA | 0.5 | 86 |
| 4 | *sec*-BuLi | none | 1 | 15 |
| 5 | *sec*-BuLi | TMEDA | 1 | 56* |
| 6 | *tert*-BuLi | none | 1 | 21 |
| 7 | *tert*-BuLi | TMEDA | 1 | 90 |
| 8 | *n*-BuLi | TMEDA | 1 | 72** |
| 9 | *n*-BuLi | TMEDA | 0.5 | 68*** |

*competing C6 lithiation, ** in $Et_2O$
***at –50 °C (competing carbolithiation/elimination)

**Scheme 3.** Directed lithiation/trapping of α-selenonyl eneformamides and enecarbamates

Detailed investigations (Scheme3A) into the latter scenario have led us to the discovery that TMEDA-mediated lithiation/trapping of selenones such as **1** with hetero electrophiles affords the desired products under the conditions described in Scheme 3B (see **3a–g)**. Of note, the deprotonating base, temperature, and reaction time are key adjustable parameters for mitigating deformylation (where applicable), α'-, allylic-, aryl-, or reductive- lithiation. The improved efficiency of lithiation of the enecarbamate substrates (relative to the eneformamides) is probably a reflection of the robustness and/or superior directing ability of the Boc-group in such directed lithiations.[9] The importance of the α-selenonyl group in this reaction manifold is highlighted by the observation that α-carbo-functionalized enecarbamates such as **2a/b/d** (see Scheme 2) fail to react under the specified conditions. Instructively, while conditions for lithiation/trapping with carbon electrophiles are currently being fine-tuned, central among our objectives in the current study was the goal of preparing substrates bearing two pendant leaving groups, in view of utilizing them in one-pot vicinal carbo-functionalization protocols. Having noticed that the Fe-catalyzed conditions employed in Scheme 2 for substitutive deselenonation were non discriminative when two-pronged electrophiles such as **3b/e** were utilized, and cognizant of the high tolerance for a diverse range of functional groups in reductive cross-couplings,[63] we sought efficient conditions for vicinal reductive cross-coupling of **3** with cheap feedstock chemicals such as organic bromides. As noted earlier, in our previous vicinal difunctionalization strategy,[67] we were not able to achieve β-arylation nor α-alkylation of dehydropiperidines. Thus, the current reaction scope was slightly tailored toward our needs. Fortuitously, *bis*-electrophilic coupling partners such as **3d-g** are amenable to one-pot-, temperature-, and reagent-controlled regioselective coupling with aryl bromides under cobalt-catalysis (Scheme 4, see **4a–n)**. Although we could tell (based on HMBC analysis) that α-deselenonative functionalization preceded β-deselenative arylation, it was quite reassuring when we found that β-unsubstituted selenone **1c** (see Scheme 1) coupled readily with *p*-bromoanisole to afford arylated eneformamide **2i** under identical Co-catalyzed conditions. This vicinal coupling strategy presumably takes advantage of the reactivity differences between the α-selenonyl and β-selenyl requisite groups. Indeed, the second coupling event leading to the installation of the β-substituent requires warming to 40 °C, during which we begin to see evidence of homocoupling of the aryl bromide coupling partner. A highly electron-rich aryl bromide undergoes faster and more efficient coupling compared to an electron-neutral aryl bromide (**4b** *vs* **4c**). Ortho-substituted aryl bromides are barely tolerated during deselenative arylation (**4c** *vs* **4d**). While π-excessive heteroaryl bromides (e.g., thiophenes) couple in good yield (see **4e**), π-deficient heteroaryl bromides are less competent coupling partners and afford the desired products in low yield (see **4f**). The ability to append an α-allyl group under the identified conditions (see **4e–g**) is noteworthy since the allyl motif is a well-recognized pyrrolidine surrogate.[68] Congruous with our previous disclosure on the inertness of aryl chlorides under these reaction conditions,[55] we find that o-chlorobenzyl bromide selectively affords the benzylated product over the arylated product (see **4h**). Intriguingly, when enecarbamate precursors are employed, α-deselenonative arylation is competitive with β-deselenative arylation, prompting us to employ identical aryl bromides (see **4k/l**). Only in the case of slowly reactive electrophilic aryl bromides are we able to achieve selective coupling (see **4m/n**) since they do not participate in β-arylation. Presumably, the sterically-encumbered Boc-group slows down reactivity at the α-position; consistent with our previous findings on the superiority of α-bromo eneformamides (over α-bromo enecarbamates) as coupling partners under these reductive cross-coupling conditions.[55, 69] Of note, α-selenonyl-β-bromo eneformamides such as **3b** appear to be recalcitrant coupling partners under the conditions described in Scheme 4. For example, **3b** readily affords allylated eneformamides **4o** and **4p**, but the latter fail to furnish the desired carbo-difunctionalized dehydropiperidines, following treatment with bromobenzene. Nevertheless, we are not that disheartened by this outcome since intermediates such as **4o**/**p** may serve as a Heck-donor[9] in a late-stage diversification strategy.




**Scheme 4.** Difunctionalization of **3d–g** and monofunctionalization of **3b**

## Conclusions

In summary, the regioselective functionalization of readily prepared α-selenonyl enecarbamates and eneformamides has led to expedient syntheses of α,β-carbo-difunctionalized piperidine- and azepane- derivatives. Key to the successful implementation of the current tactic are the excellent departing- and electron-withdrawing-abilities of the selenonyl group. It is anticipated that these operationally simple manipulations will endow the current strategy with a practical advantage as well as complement existing approaches for accessing vicinally functionalized azaheterocycles. Efforts to expand the scope of the directed lithiation/trapping protocol to carbon electrophiles (see **4**), install nucleophiles at the β-position of α-selenonyl enamides (see **5**), and to perform stereocontrolled reductions of the unsaturated azaheterocycles prepared herein are ongoing.

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## Notes and references

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