Regiocontrolled synthesis of (hetero)aryl and alkenyl dehydropyrrolidines, dehydropiperidines and azepenes by Ru-catalyzed, heteroatom-directed α-C-H activation/cross-coupling of cyclic enamides with boronic acids

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Regiocontrolled synthesis of (hetero)aryl and alkenyl dehydropyrrolidines, dehydropiperidines and azepenes by Ru-catalyzed, heteroatom-directed α-C-H activation/cross-coupling of cyclic enamides with boronic acids

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The synthesis of α-aryl and alkenyl pyrrolidine-, piperidine-, and azepane derivatives, through the intermediacy of cyclic enamides is described. The desired outcome is achieved through ruthenium-catalyzed, site-selective sp^2 C-H activation/cross-coupling with aryl boronic acids. The regioselectivity (α-sp^2 *vs* α-sp^3 *vs* β-sp^2 C-H functionalization) is governed by the rate differences between sp^2 and sp^3 C-H activation and the necessity for chelation between the ruthenium metal and the carbonyl directing group.

The pyrrolidine, piperidine, and azepane structural motifs are found in a wide variety of pharmaceuticals that span over thirty therapeutic areas including antidepressants, antipsychotics, and analgesics.[1] For example, α-arylated pyrrolidines, piperidines and azepanes constitute the core of bioactive molecules such as SIB-1508Y,[2-4] crispine,[5-8] Vesicare®,[9] maackiamine,[10] and aurantioclavine[11] (Fig. 1).

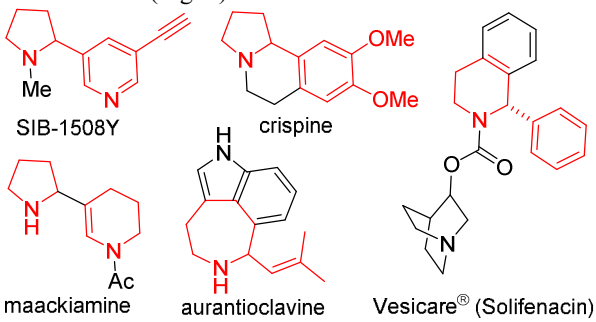


Fig. 1 Examples of bioactive pyrrolidines, piperidine and azepanes

One of the most direct, atom-ecomonical, and divergent strategies for accessing functionalized pyrrolidine, piperidine and azepane derivatives is to employ a cyclic enamide or enecarbamate since they serve as versatile intermediates for a diverse range of transformations. For example, they may be engaged in hydrogenation,[12] cyclopropanation,[13] halogenation,[14] amination,[15] hexannelations,[16] aminoxylation,[17] or allylic functionalization protocols.[18] As detailed in many previous reports, C-2 functionalization of azaheterocycles is achievable when *preactivated* cyclic enamide precursors such as halides,[19] triflates,[20-22] or phosphates[23] are engaged in Suzuki cross-coupling reactions (Fig. 2A). Additionally, we have demonstrated that such requisite group-bearing enamides are suitable substrates for Co-catalyzed reductive cross-couplings with cheap feedstock chemicals such as organic bromides (Fig. 2B).[24, 25] Although understandable, it is quite unfortunate that most existing tactics for α-functionalization of *unactivated enamides* such as **V** are plagued by regioselectivity and double-bond isomerization issues (Fig. 3C).[26]

Following pioneering work by Murai and coworkers[27] on ruthenium-catalyzed α-functionalization of saturated cyclic amines (see **X–XII**, Fig. 2D) with unactivated olefins, Sames[28] and Maes[29, 30] subsequently disclosed that α-arylation of such *N*-heterocycles using aryl boronic esters as coupling partners is possible. In Sames' report, it was eloquently articulated that a carbamate- (*e.g.*, Boc-) or an amide- (*e.g.*, pivaloyl-) directing group rendered a pyrrolidine substrate unreactive toward α-arylation.[28] As a result, the 2-pyridinyl group is more frequently employed in this mode of reactivity.[27, 29-32] However, we questioned whether such a powerful directing group could be *over activating* toward α-C-H activation of enamine-type substrates such that the regioselectivity between α- and α'-functionalization (*i.e.*, sp^2 *vs* sp^3 C-H activation) becomes compromised. Our pessimism was heightened by a previous disclosure that an unsymmetrical substrate such as tetrahydroisoquinoline **XII** unexpectedly underwent nonselective (*i.e.*, benzylic *vs* non benzylic) α-arylation.[30]

Continuing our quest for expedient-, practical- and complementary- methods for accessing functionalized

azaheterocycles,[24, 25, 33-43] and cognizant of the *inherently high reactivity* of unfunctionalized cyclic enamides such as **V** (relative to the corresponding saturated cyclic amine), it was surmised that regioselective sp^2 α-C-H functionalization/cross-coupling of the latter with boronic acids, under ruthenium catalysis, offered an attractive approach (Fig 2E). While transition metal-catalyzed β-arylation[44-46] of cyclic enamides of type **V** have previously been reported, we anticipate that in this case, β-functionalization would be abrogated due to the necessity for chelation of the metal to the carbonyl oxygen of the directing group (Fig. 2F). Herein, efforts toward the *Ru-catalyzed sp^2 α-C-H activation and concomitant arylation of cyclic enamides* are described.

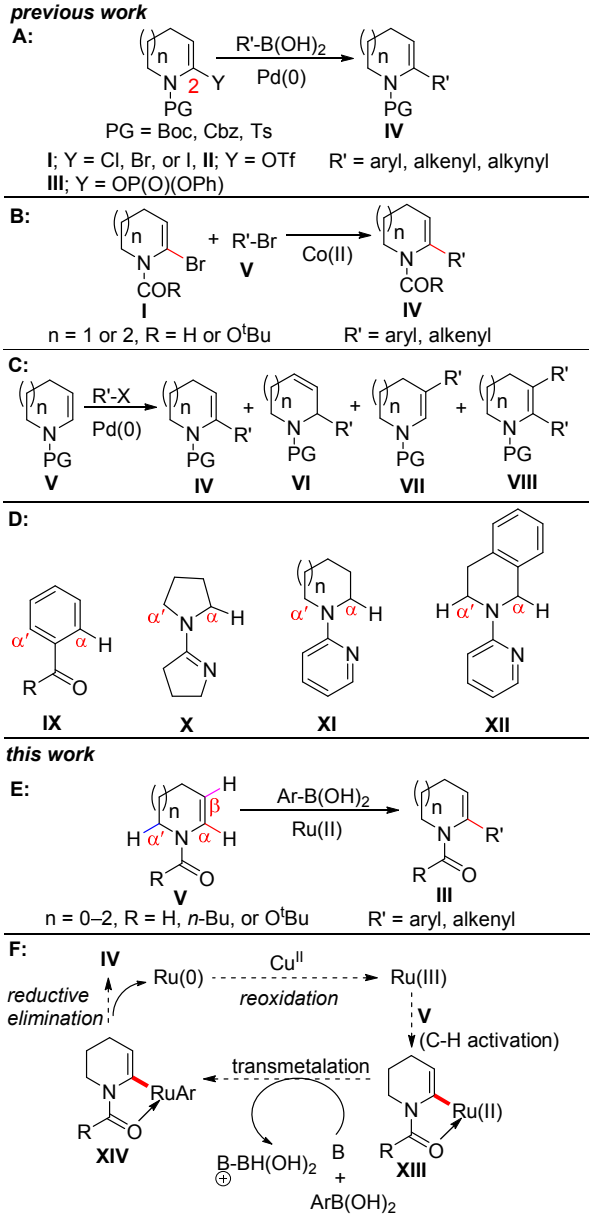
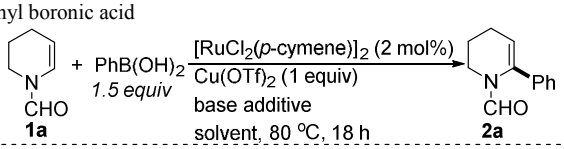


Fig. 2. Proposed plan for accessing α-functionalized azaheterocycles and mechanistic hypothesis

Studies on Ru-catalyzed C-H activation[47]/cross-coupling of cyclic enamides with aryl boronic acids commenced with the search for an appropriate ruthenium precatalyst, reoxidant, base additive, and solvent. Toward this end, eneformamide **1a** and phenyl boronic acid were coupled in the presence of a ruthenium precatalyst[48] (*i.e.*, $[RuCl_2(p\text{-cymene})]_2$), a reoxidant (*i.e.*, $Cu(OTf)_2$), and a base additive. Using Cs_2CO_3 as the base and after performing the reaction using the conditions described in Table 1, 1,4-dioxane emerged as the most suitable solvent (see entries 1 to 3). The exclusive formation of **2a**[24] indicates a preference for functionalization of the α-sp^2 C-H bond over both the α'-sp^3 C-H bond and the distal β-sp^2 C-H bond, thereby lending credence to our mechanistic hypothesis. Next, a small number of bases were evaluated (entries 4–6). Fortuitously, resounding success was achieved when Ag_2O[49] was employed (entry 4). The coupling proceeds inefficiently in the absence of a base (entry 7). When the Ru-precatalyst is omitted, no coupling is observed (entry 8). The efficiency of the arylation unsurprisingly improves when the catalyst loading is increased (entry 10) but the cost-effectiveness is somewhat questionable. In a mechanistically intuitive result, we find that a stoichiometric amount of the reoxidant (*i.e.*, $Cu(OTf)_2$) is desirable (entry 11). Of note, the use of more costly boron reagents such as phenyl boronic ester leads only to a marginal increase in the efficacy of the phenylation. In passing, attempts at effecting the arylation with the frequently employed trinuclear cluster $[Ru_3(CO)_{12}]$[30] (see conditions X) failed to yield satisfactory results.

Table 1 Optimization of the Ru-catalyzed coupling of eneformamide **1a** with phenyl boronic acid



Entry	base additive	Solvent	% yield (by GC)
1	Cs_2CO_3	DMA	45
2	Cs_2CO_3	dioxane	53
3	Cs_2CO_3	THF	0
4	Ag_2O	dioxane	80
5	Ag_2CO_3	dioxane	33
6	CuTFA	dioxane	14
7	none	dioxane	12
8[a]	Ag_2O	dioxane	0
9[b]	Ag_2O	dioxane	57
10[c]	Ag_2O	dioxane	88
11[d]	Ag_2O	dioxane	<10%
12[e]	Ag_2O	dioxane	85%

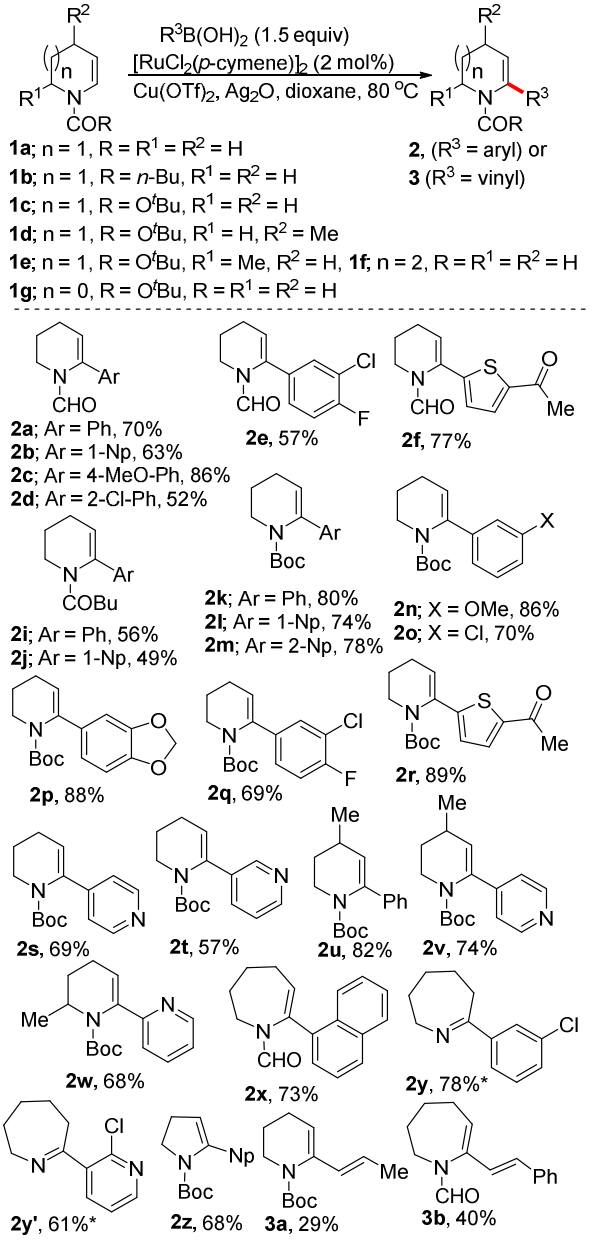
(a) in the absence of [Ru], (b) using 1 mol% of Ru-precatalyst
(c) using 8 mol% of [Ru], (d) 20 mol% $Cu(OTf)_2$ + balloon O_2
(e) using PhB(pin) (1.5 equiv)

conditions X: Ph-B(pin) (1.5 equiv), $[Ru_3(CO)_{12}]$ (5 mol%) Et_3COH (1 equiv), reflux, 3 h; yield = 16%

With satisfactory α-arylation conditions in hand, the scope of the reaction with respect to the boronic acid coupling partner was next explored. Sterically demanding-, electron-rich-, electron-deficient-, π-excessive hetero- and π-deficient hetero- aryl boronic acids were surveyed. In general, electron-rich aryl boronic acids undergo faster and more efficient coupling compared to the electron-neutral or electron-deficient boronic acids (**2k** *vs* **2n** *vs* **2o**). Of note, ortho substitution is tolerated on the boronic acid (see **2d**). Enecarbamates such as **1d/e**, which bear γ or α'-substituents, couple readily with aryl boronic acids to afford 2,4- or 2,6-dehydropiperidines, respectively (see **2u/v** and **2w**). These studies have also revealed that enecarbamate substrates are more suitable coupling partners than the

corresponding eneformamide substrates (*e.g.*, **2k/l** *vs.* **2a/b**), which is probably a reflection of the well-recognized dipole-stabilizing ability of the Boc-group. Not surprisingly, *N*-alkyl and benzyl variants of **1** (which lack the ability to chelate to ruthenium) do not undergo arylation under these identified conditions.

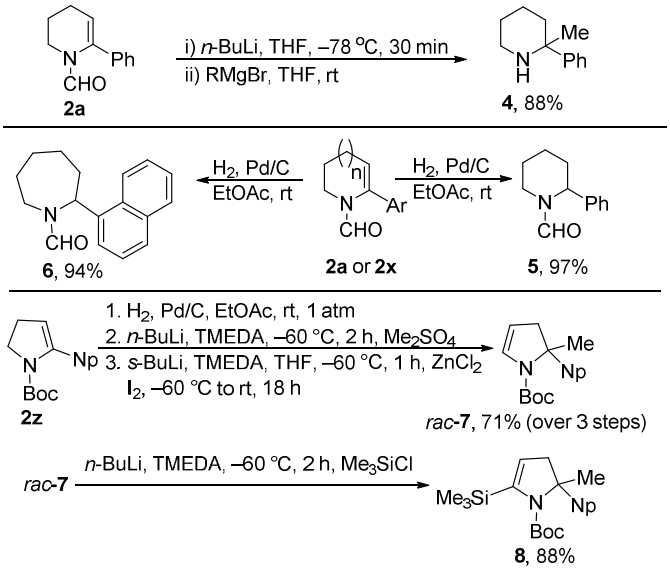
The Ru-catalyzed C-H activation/cross coupling strategy is not limited to the piperidine heterocycle. This assertion is supported by observations that azepane eneformamide **1f** undergoes efficient (hetero)arylation to afford α-aryl azepenes or their imine tautomers (see **2x–y'**). Furthermore, coupling of dehydropyrrolidine **1g** with 1-naphthylboronic acid proceeds satisfactorily and furnishes arylated dihydropyrrole **2z**. The generality of this transformation is commendable since it is now common knowledge to the synthesis community that extrapolating reactivity trends from one *N*-heterocycle to another can sometimes be quite daunting.



Scheme 1. α-arylation and vinylation of enamides and enecarbamates

Ruthenium-catalyzed α-alkenylation of **1** has also been explored. Disappointingly, we find that piperidine enecarbamate **1c** reacts inefficiently with 1-propenylboronic acid under similar reaction conditions to afford diene **3a** in low yield. Additionally, eneformamide **1f** couples regio- and stereoselectively with a β-styrenylboronic acid to afford *N*-formyl amino diene **3b**, with a marginal increase in the efficacy of the transformation. Efforts toward fine-tuning the alkenylation conditions to attain satisfactory efficiency levels are underway. This is all the more necessary since vinylated adducts of azepenes and dehydropiperidines are highly sought after given that they serve as valuable dienes in hexannelation protocols.[50]

We have amply demonstrated that the products prepared herein may be elaborated to other functionalized cyclic amine derivatives. For example, base-mediated cleavage of the formyl group resident in eneformamide **2a** and concomitant addition of methyl magnesium bromide to the resulting imine affords quaternary cyclic amine **4** (Scheme 2). Additionally, catalytic hydrogenation of dehydropiperidine **2a** furnishes tertiary benzylic amine **5**. Naphthyl-bearing azepene **2x** also undergoes unceremonious catalytic hydrogenation to afford α-naphthyl azepane **6**. Furthermore, reduction of **2z** followed by three sequential directed lithiations (*i.e.*, benzylic lithiation[41, 51, 52]/methylation, α'-lithiation[34]/transmetalation[41]/iodination/elimination[53] and vinyl lithiation/silylation) affords prospective Hiyama coupling partner **8**, *via* chiral racemic dehydropyrrolidine **7**.



Scheme 2. Further elaboration of arylated enamides/enecarbamates

Conclusions

In summary, α-arylation and alkenylation of cyclic enamides by heteroatom-directed, ruthenium catalyzed sp^2 α-C-H activation/cross-coupling with aryl and vinyl boronic acids has been accomplished on the piperidine, azepane, and pyrrolidine heterocycles. The cost-effectiveness of this ruthenium-catalyzed process, functional group tolerance and its applicability to a diverse

range of *N*-heterocycles are some of the merits offered by the current approach. The 2-substituted enamides have been further elaborated to other functionalized variants, including cyclic ketimines and α,α-saturated cyclic amines. These short synthetic sequences have set the stage for accessing libraries of potentially bioactive piperidine, azepane, and pyrrolidine derivatives bearing α-amino quaternary stereocenters. Efforts toward extending the methodology to large ring *N*-heterocycles and to render the alkenylation protocol synthetically more attractive are ongoing and will be disclosed in due course.

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Notes and references

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Electronic Supplementary Information (ESI) available: Experimental procedures and spectroscopic data. See DOI: 10.1039/c000000x/

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