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Communication

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A Modular and Diastereoselective 5+1 Cyclization Approach to *N*-(Hetero)Aryl Piperidines

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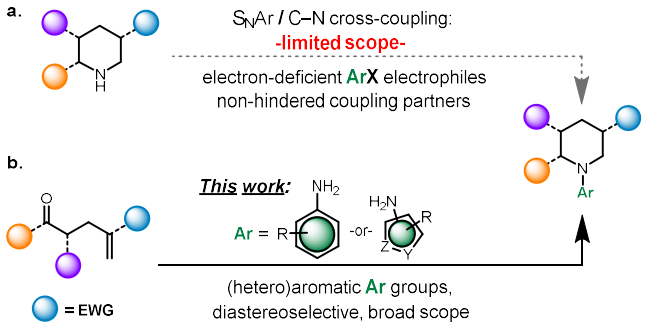
Supporting Information Placeholder

ABSTRACT: A new general *de novo* synthesis of pharmaceutically important *N*-(hetero)aryl piperidines is reported. This protocol uses a robustly diastereoselective reductive amination/aza-Michael reaction sequence to achieve rapid construction of complex polysubstituted ring systems starting from widely available heterocyclic amine nucleophiles and carbonyl electrophiles. Notably, the diastereoselectivity of this process is enhanced by the presence of water, and DFT calculations support a stereochemical model involving a facially selective protonation of a water-coordinated enol intermediate.

Piperidine is the most common nitrogen heterocycle in FDA-approved pharmaceuticals and thus represents a key structure in drug discovery.[1] The importance of this motif has motivated the development of numerous methods for stereoselective construction or elaboration of piperidine ring systems.[2] Separate from these efforts, *N*-arylation and *N*-(hetero)arylation of piperidines have emerged as essential tactics for the preparation of a wide variety of prospective drug molecules.[3] Traditional approaches to these C(sp_2)–N bond constructions rely on S_NAr reactions[4] or transition metal-catalyzed cross-coupling methods[5] (Scheme 1a), and although these strategies are widely implemented, they are also notably limited in scope. S_NAr reactions depend on the intrinsic electron-deficiency of aromatic electrophiles, and thus, electron-rich aromatics, including five-membered heterocycles, are notoriously problematic substrates. Advances in C–N cross-coupling technology have overcome some of these limitations, but the coupling of piperidines[6] with 5-membered heteroaromatics continues to be exceptionally challenging with current methodologies.[7] These shortcomings are exacerbated when either coupling partner contains steric bulk proximal to the reaction site. Further, Pd-catalyzed C–N coupling can result in loss of stereochemical integrity due to off-cycle β-hydride elimination[8] or deprotonation pathways.

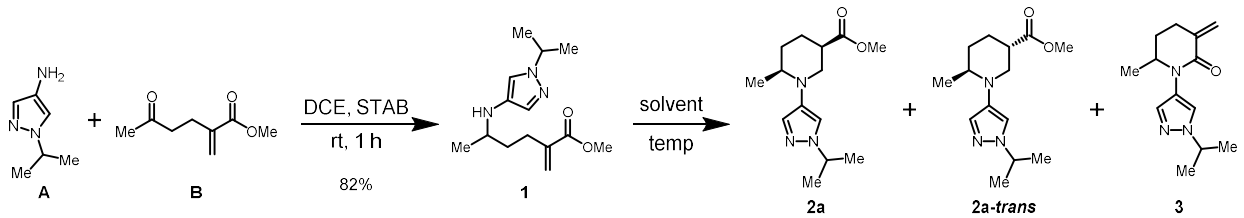
We were motivated by these methodological limitations to survey alternative bond disconnections for the preparation of *N*-(hetero)aryl piperidines. Ultimately, we chose to pursue methods involving *de novo* synthesis of the piperidine ring as these have the potential to be modular and convergent, providing access to products with substitution at any point of the ring system from relatively simple precursors. While several cyclization strategies for piperidine synthesis have been reported, these often exhibit poor generality, suffer from low regio- or stereochemical control, or require protecting group manipulations or multi-step substrate syntheses.[2f] Herein, we present a reliably diastereoselective reductive amination/aza-Michael synthesis of functionalized *N*-(hetero)aryl piperidines starting from widely available heterocyclic amine nucleophiles (Scheme 1b); we further show that this transformation is highly tolerant of steric hinderance and readily furnishes products that would be very difficult to generate using traditional *N*-(hetero)arylation methodology.

Scheme 1. Synthetic approaches to *N*-aryl piperidines



Our optimization studies began with substrates **A** and **B** because the resulting product (**2a**) represents a desirable, yet synthetically challenging class of compounds to access (Table 1). We reasoned that the reductive amination step would be relatively straightforward, and indeed the linear intermediate (**1**) formed rapidly in the presence of sodium triacetoxyborohydride (STAB) in 1,2-dichloroethane (DCE) and was isolable in good yield.[9] We next explored the impact of solvent and temperature on the efficiency and selectivity of the subsequent aza-Michael cyclization. Heating **1** at 60 ºC in trifluoroethanol (TFE), a solvent known to be well-suited for aza-Michael reactions,[10] resulted in quantitative conversion to the desired product with a diastereomeric ratio (dr) of 8:1 (favoring the *cis* isomer, **2a**, Entry 1). The undesired lactam (**3**) was not detected. The reaction profile in EtOH was significantly more complex than that of TFE, which impeded dr measurement (Entry 2), whereas in MeOH, the desired reaction oc-

Table 1. Effects of solvent and temperature on diastereoselectivity[a]



Entry	Solvent (**60 °C**)	dr (NMR)	Entry	Solvent (**30 °C**)	dr (NMR)
1	TFE	8:1	7	TFE/H_2O	18:1
2	EtOH	N.D.	8	EtOH/H_2O	14:1
3	MeOH	11:1	9	IPA/H_2O	11:1
4	TFE/H_2O	14:1	10	HFIPA/H_2O	13:1
5	EtOH/H_2O	9:1	11	MeOH/H_2O	20:1
6	MeOH/H_2O	14:1	12	THF/H_2O	9:1
			13	MeCN/H_2O	9:1

[a]Reactions were conducted on a 0.2 mmol scale. Solvent and water mixtures are 50% v/v. Analysis by ^{1}H NMR spectroscopy was conducted on the crude reaction mixtures to determine dr (*cis*:*trans*)

curred in quantitative yield (Entry 3) and with improved diastereoselectivity (11:1 *cis*:*trans*). Unexpectedly, the inclusion of water (50% v/v) in alcohol solvents resulted in a significant enhancement in both the rate and diastereoselectivity (Entries 4–6, see SI), and further improvement in the dr was obtained upon lowering the temperature to 30 ºC. The optimal solvent combination identified was MeOH/H_2O (Entry 11), which yielded **2a** with 20:1 dr, although TFE/H_2O also provided good results (Entry 7). Finally, we found that we could streamline our protocol by omitting the isolation of **1**; simply quenching excess STAB with NaOH after the reductive amination step and performing a solvent-swap to MeOH/H_2O afforded **2a** in a more convenient procedure with no deterioration in yield or selectivity (Table 2).

Having established an optimal set of reaction conditions, we next explored the scope of ketones tolerated in the reaction with pyrazole **A**. In general, the ketone electrophiles were readily prepared in one or two steps (see SI).[11] Aliphatic ketones were well tolerated (**2a**, **b**; Table 2). Acetophenone derivatives with varying electronic properties were also competent in the reaction (**2c–e**) but gave lower yields due to a more challenging reductive amination step. A cyclic ketone provided access to the all-*cis* decahydroquinoline (**2f**) as the major product. In addition to α,β-unsaturated esters, cyanoalkenes (**2g**), nitroalkenes (**2h, j**), and 2-vinylpyridines (**2i**) all serve as suitable Michael acceptors, permitting variation of the C5 substituent and providing functional handles for further elaboration. Notably, the high reactivity of the nitroalkene acceptor enabled formation of the exceptionally hindered 2,5,6-trisubstituted piperidine **2j**, in which N1 is flanked on either side by phenyl and methyl groups. Variation in tether-length within the unsaturated ester series (Examples **2k** and **2l**) revealed that the desired general reactivity is specific to formation of six-membered rings: a truncated ketone, which would have led to a pyrrolidine product in the normal pathway, instead exclusively formed lactam **2k**, in accordance with Baldwin's Rules.[12] Additionally, attempts to generate azepane **2l** via the homologated ketone yielded only the uncyclized reductive amination product.

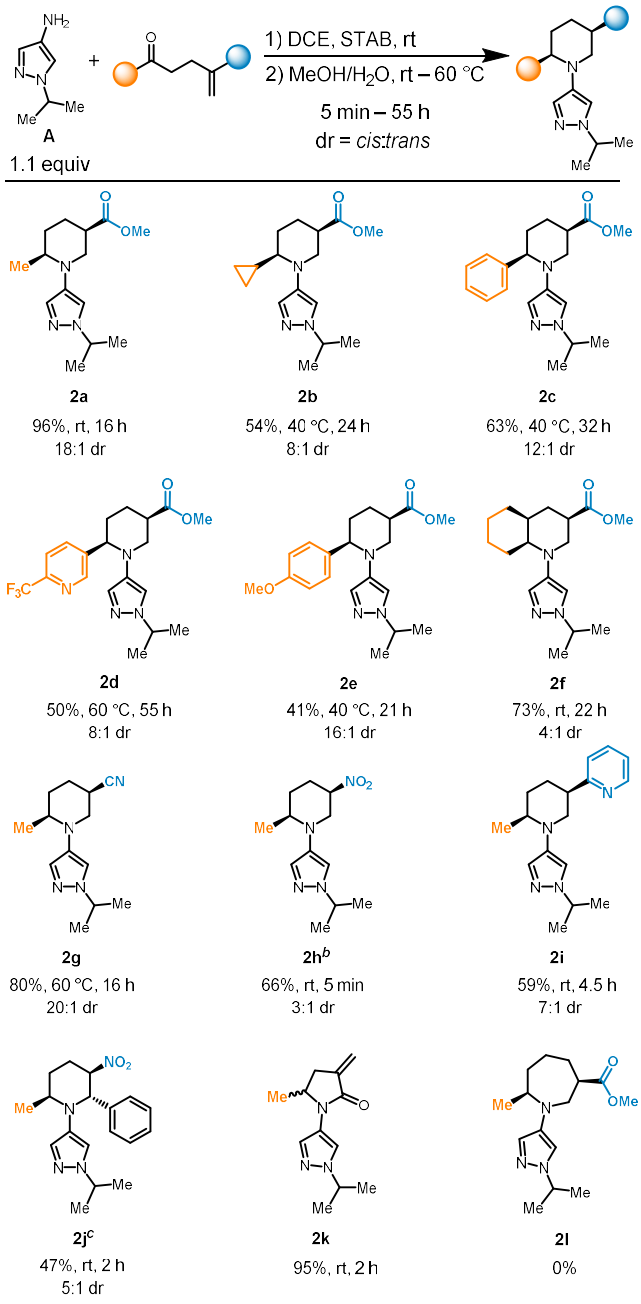
Extension of this approach to aldehyde-containing electrophiles, which were generally available in a single step via enamine-catalyzed α-alkylation chemistry,[13] enabled the diastereoselective preparation of 3,5-disubstituted piperidines (Table 3). Due to the facile nature of the reductive amination with these substrates, that step could be performed in methanol, which eliminated the need for solvent swapping; consequently, the reaction sequence could be conducted in a single pot by simply adding water to effect cyclization. Thus, 3,5-disubstituted piperidine products **4a–f** were formed in moderate to good yield and with high diastereoselectivity, although formation of lactam products analogous to **3** (Table 1) was competitive with the desired pathway in some cases. Cyclization reactions of aldehyde substrates were similarly functional-group tolerant as their ketone counterparts, yet interestingly generated *trans*- rather than *cis*-disubstituted piperidines as the major diastereomers (*vide infra*).

Following our investigation of electrophilic coupling partners, we next explored the nucleophile scope. Taking keto-acrylate **B** as our standard electrophile, we found that the amination/cyclization sequence was compatible with a wide assortment of aryl- and (hetero)arylamine nucleophiles (Table 4). In the course of these studies, we observed that substrates less electron-rich than **A** undergo sluggish aza-Michael cyclizations in MeOH/H_2O. However, using TFE/H_2O led to significantly higher rates of cyclization, therefore we employed the later solvent system in our survey of nucleophiles (See SI).

Aniline derivatives were competent nucleophiles, affording the *cis*-2,5-disubstituted piperidines in good yield and diastereoselectivity (Table 4, examples **5a**–**5f**); however, *ortho* substitution required higher reaction temperatures to achieve complete conversion and resulted in lower diastereoselectivity (**5c** compared to **5d**). Electron-donor-substituted 3-aminopyridines formed the corresponding piperidines (**5g, h**) in useful yields and with comparable diastereomeric ratios to those obtained with other anilines. As example **5h** demonstrates, application of this protocol to electronically differentiated bis(amino)heterocycle substrates selectively generates *N*-(hetero)aryl piperidines with the opposite regiochemical outcome one would obtain in an S_NAr or C–N cross-coupling reaction of the corresponding dihaloheterocycle. Additionally, functionalized or hindered 5-membered heteroaromatic amines gave good yields of the *cis*-disubstituted piperidines (examples **5i–r**), although elevated temperatures and elongated reaction time were sometimes required for efficient cyclization (**5n–p, r, s**).

The routinely high diastereoselectivities achieved via the reductive amination/aza-Michael cyclization protocol is an important advantage of this synthetic approach, yet the mechanistic basis for

Table 2. Scope of the ketone-containing electrophiles[a]

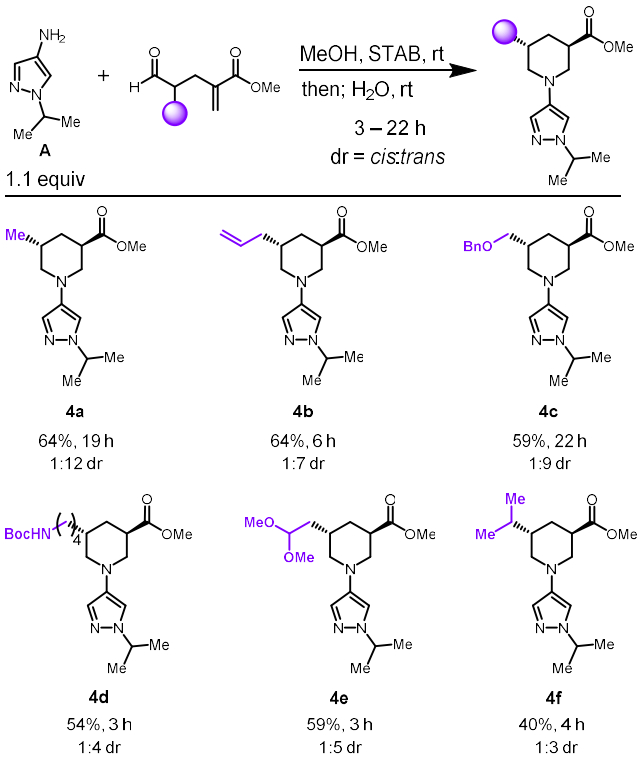


[a]Reactions conducted on a 1.0 mmol scale. Isolated yields are reported as an average of two runs. Products isolated as a single diastereomer unless otherwise noted. Analysis by ^{1}H NMR spectroscopy of the crude mixture was conducted to determine the dr (*cis*:*trans*). [b]Isolated as a 2.5:1 mixture of diastereomers. Reductive amination/aza-Michael cyclization conducted in MeOH. [c]Isolated as a 4:1 mixture of diastereomers.

this selectivity was not readily intuitable, nor was the origin of the opposing sense of diastereoselectivity obtained with 2,5- versus 3,5-disubstituted products. To address this, we undertook a computational study to better understand the influence of both reactant structure and reaction medium on the stereochemical outcome. DFT geometry optimizations at the M06-2X/6-31G**-SMD(water) level[14] indicated that the two possible diastereomers (**5a** and **5a-*trans***) were similar in energy, suggesting that diastereoselection occurs under kinetic control. Corroborating this result, equilibrating **5a** under basic conditions resulted in an erosion of stereochemistry and a 1.4:1 (*cis*:*trans*) diastereomeric mixture was observed (see SI).

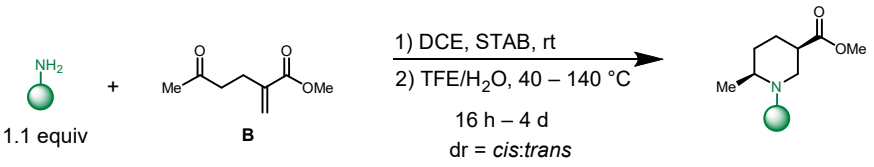
In related, cyclohexane-based systems, Zimmerman has rationalized the observed stereochemical distribution of products by invoking irreversible kinetic protonation of a six-membered exocyclic enol intermediate at the more accessible *exo* face of its thermodynamically favored chair-conformer.[15] Accordingly, we computationally analyzed the conformations of exocyclic enol intermediates **8** and **9** (Scheme 2a, b), which arise from aza-Michael reactions of **Int-5a** and **Int-6a**, respectively. In the absence of explicit solvation, our calculations predicted a favored conformer for **8** that, upon protonation, would yield the opposite diastereomer than that experimentally obtained (see SI), while for **9** the diastereoselectivity would be underestimated. It is known, however, that implicit continuum solvation models do not satisfactorily treat specific solvent–solute interactions, which are important for accurate description of the solvation of amines in protic solvents.[16] Indeed, when one or two explicit water (or MeOH) molecules were included to account for hydrogen bonding with solvent, the lowest-energy conformers of **8** and **9** (Scheme 2a, b), would now lead to the experimentally observed diastereomers **5a** and **6a** upon protonation from the *exo* faces. This computational model predicts diastereomeric ratios that are in good agreement with the experimental values. Furthermore, alternative models invoking an axial protonation of the unsolvated enol chair conformers were unable to consistently account for the observed stereochemical outcome (see SI).

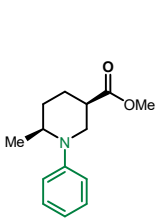
Table 3. Scope of the aldehyde-containing electrophiles[a]



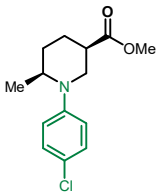
[a]Reactions conducted on a 1.0 mmol scale. Isolated yields are reported as an average of two runs. Products isolated as a single diastereomer. Analysis by ^{1}H NMR spectroscopy of the crude mixture was conducted to determine the dr (*cis*:*trans*).

Table 4. Reaction scope of keto-acrylate B with various nucleophiles[a]

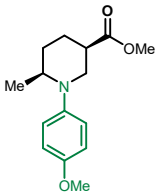




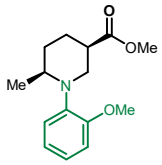
5a
82%, 40 °C, 24 h
17:1 dr



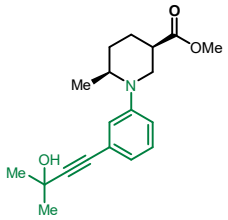
5b
71%, 60 °C, 24 h
15:1 dr



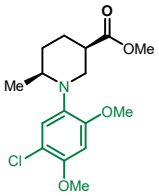
5c
82%, 40 °C, 24 h
17:1 dr



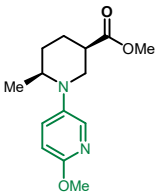
5d[b]
54%, 60 °C, 24 h
4.8:1 dr



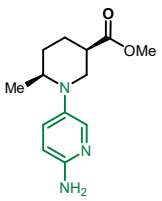
5e[c]
77%, 80 °C, 22 h
13:1 dr



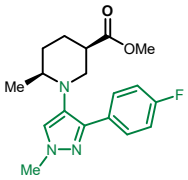
5f
54%, 60 °C, 27 h
6:1 dr



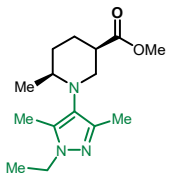
5g[d]
82%, 60 °C, 23 h
17:1 dr



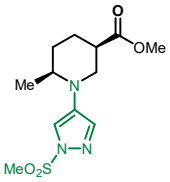
5h[d]
24%, 60 °C, 24 h
16:1 dr



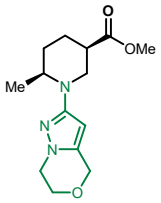
5i[e]
99%, 60 °C, 24 h
13:1 dr



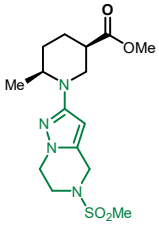
5j[f]
72%, 60 °C, 19 h
7:1 dr



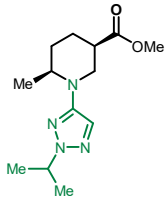
5k[e]
83%, 80 °C, 4 d
13:1 dr



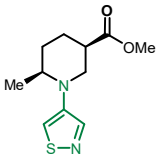
5l[g]
72%, 80 °C, 16 h
10:1 dr



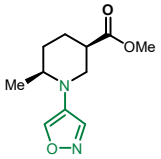
5m[c]
60%, 80 °C, 30 h
12:1 dr



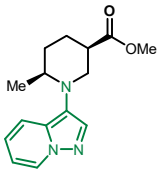
5n
58%, 80 °C, 5 d
10:1 dr



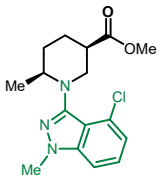
5o[h]
84%, 80 °C, 51 h
14:1 dr



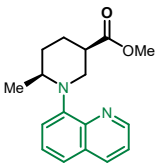
5p[i]
33%, 80 °C, 53 h
10:1 dr



5q[d]
91%, 40 °C, 24 h
17:1 dr



5r[j]
35%, 140 °C, 4 d
5:1 dr



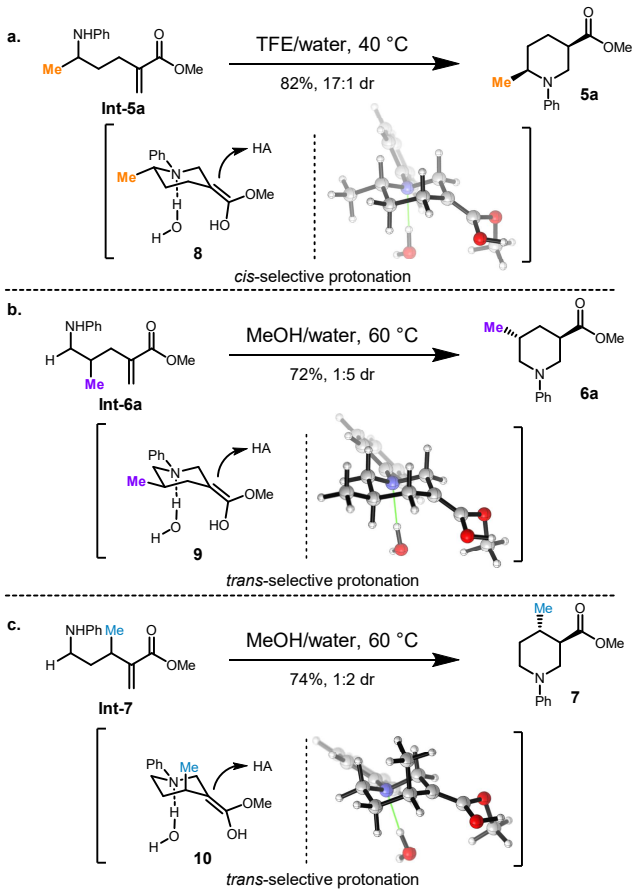
5s
35%, 80 °C, 53 h
4:1 dr

[a]Reactions conducted on a 1.0 mmol scale. Products isolated as a single diastereomer unless otherwise stated. Analysis by ^{1}H NMR spectroscopy of the crude mixture was conducted to determine the diastereoselectivity (*cis*:*trans*). [b]Isolated dr of 4.4:1. [c]Isolated dr of 9:1. [d]Isolated dr of 17:1. [e]Isolated dr of 12:1. [f]Isolated dr of 7:1. [g]Isolated dr of >20:1. [h]Isolated dr of 13:1. [i]Isolated dr of 15:1. [j]Isolated dr of 3:1.

Extending our synthetic method further, we considered the reaction of a β-alkyl aldehyde with aniline to form a 4,5-disubstituted piperidine (**7**, Scheme 2c). For the lowest-energy conformers of **8** and **9**, the methyl group sits in an equatorial position; however, for **10**, an equatorial-methyl conformation results in $A_{1,3}$ strain with the exocyclic alkylidene substituent. This unfavorable interaction places the methyl group in an axial position for the lowest-energy conformer of **10**. Preferential protonation at the exo-face of **10**, as generally required by our model, would lead to **7**, though we expected selectivity to be moderate due to the orientation of the methyl group. Consistent with this reasoning, we found that **Int-7** underwent cyclization in good yield to give the trans diastereomer as the major product (*cis*:*trans* = 1:2) and with minimal selectivity.

In summary, we have developed a reductive amination/aza-Michael reaction sequence that furnishes a wide variety of *N*-aryl and *N*-(heteroaryl)piperidines with robust and predictable diastereoselectivity starting from simple precursors. This method easily furnishes numerous medicinally relevant product chemotypes that remain inaccessible through current state-of-the-art *N*-(hetero)arylation reactions and thus represents an important and practical complement to those methods; it is additionally modular and highly functional-group tolerant, and we therefore expect that it will be a broadly useful synthetic tool. It emerged in the course of our investigations that the rate and diastereoselectivity of this transformation were strongly dependent on the nature of the protic solvent mixture, and, with the support of DFT computational studies, we have put forward a stereochemical model for the cyclization step predicated on stereodetermining protonation of a water-coordinated enol intermediate; this model successfully accounts for both the observed solvent effect and the differing stereochemical outcomes observed for the 2,5- and 3,5-disubstituted piperidine product classes. We are currently exploring strategies for developing asymmetric variants of this general transformation.

Scheme 2. Computational model predicting observed diastereoselectivities[a]



[a]Reactions conducted on a 1.0 mmol scale. Analysis by ^{1}H NMR spectroscopy of the crude mixture was conducted to determine the diastereoselectivity (*cis*:*trans*). a) Predictive DFT model for the *cis* selective protonation of **8** to form **5a**. b) Predictive DFT model for the *trans* selective protonation of **9** to form **6a**. c) Predictive DFT model for the *trans* selective protonation of **10** to form **7**.

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures and characterization data (PDF). Computational methods, energies and Cartesian coordinates of all optimized structures. (PDF)

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Notes

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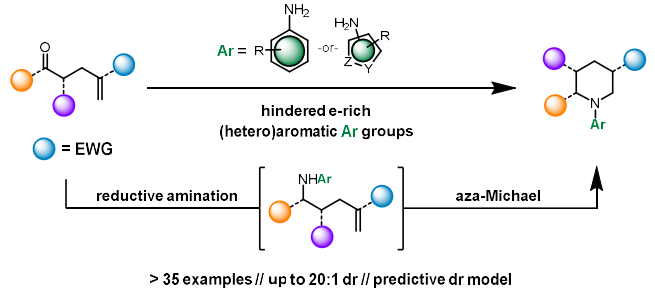
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