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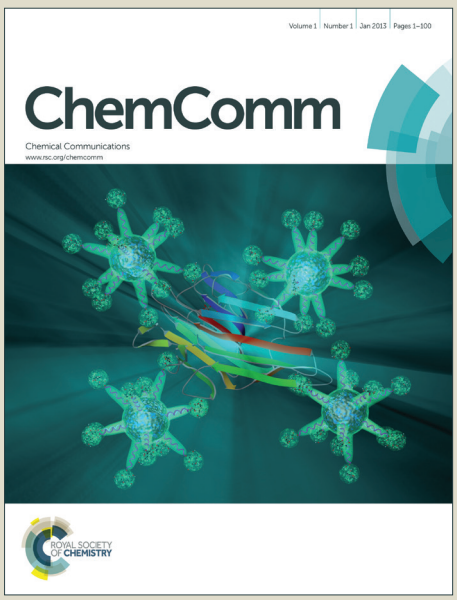

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C–H Functionalization of Cyclic Amines: Redox-Annulations with α,β-Unsaturated Carbonyl Compounds

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

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Cyclic amines such as pyrrolidine and 1,2,3,4-tetrahydroisoquinoline undergo redox-annulations with α,β-unsaturated aldehydes and ketones. Carboxylic acid promoted generation of a conjugated azomethine ylide is followed by 6π-electrocylization, and, in some cases, tautomerization. The resulting ring-fused pyrrolines are readily oxidized to the corresponding pyrroles or reduced to pyrrolidines.

Electrocyclic ring-closures of conjugated azomethine ylides enable efficient access to 5- and 7-membered azacycles.[1,2] A number of mechanistically distinct methods for the generation of the required dipolar intermediates have been developed, the most common of which involve decarboxylation or the deprotonation of a preformed iminium salt.[1,2] In contrast, the direct generation of conjugated azomethine ylides via redox-neutral amine α-C–H functionalization[3,4] as an avenue for 1,5- and 1,7-electrocyclizations has been explored to only a limited extent.[1] Previous examples include the reaction of enamines or related compounds with dimethyl acetylenedicarboxylate (DMAD) (e.g., eq 1)[5] or intramolecular rearrangements of dienamines bearing multiple electron-withdrawing groups (e.g., eq 2).[6] Oxidative C–H functionalization methods for the generation of conjugated azomethine ylides have also emerged.[7–9] Here we report a carboxylic acid facilitated method for the in situ generation of conjugated azomethine ylides and their subsequent 1,5-electrocyclizations. Simple cyclic amines such as pyrrolidine or 1,2,3,4-tetrahydroisoquinoline (THIQ) and α,β-unsaturated aldehydes/ketones serve as the starting materials in these cascade reactions (eq 3).

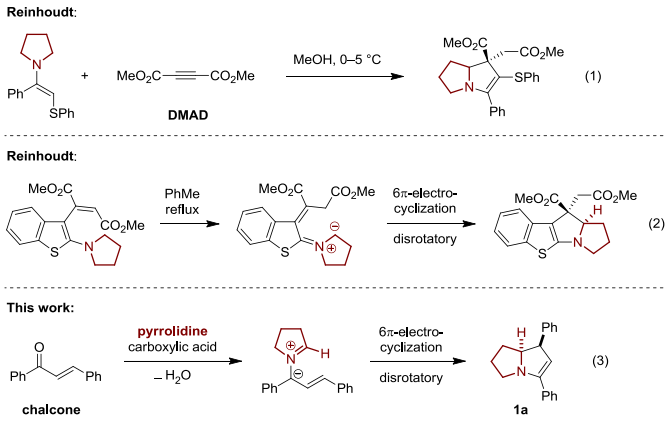
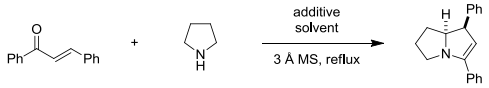


Table 1. Evaluation of Reaction Conditions.



entry	X	solvent (M)	additive (equiv)	time [h]	yield (%)
1	5	PhMe (0.25)	-	15	trace
2	5	PhMe (0.25)	BzOH (0.5)	5	65
3[a]	5	PhMe (0.25)	BzOH (0.5)	5	58
4	5	PhMe (0.1)	BzOH (0.5)	5	74
5	5	PhMe (0.1)	AcOH (0.5)	5	65
6	5	PhMe (0.1)	2-EHA (0.5)	5	69
7	5	PhMe (0.1)	HCO_2H (0.5)	5	trace
8	5	PhMe (0.1)	BzOH (0.2)	6	68
9	5	PhMe (0.1)	BzOH (1.0)	3	77
10	5	*n*-BuOH (0.1)	BzOH (1.0)	5	23
11	5	1,2-DCE (0.1)	BzOH (1.0)	12	trace
12	3	PhMe (0.1)	BzOH (1.0)	3	62
13	2	PhMe (0.1)	BzOH (1.0)	15	64

[a] Without molecular sieves. 2-EHA = 2-ethylhexanoic acid.

Our group has recently advanced a general amine α-C–H bond functionalization concept to access reactive azomethine ylide intermediates via the condensation of a secondary amine with an aldehyde or a ketone.[3u, 10] This enabled the development of a range

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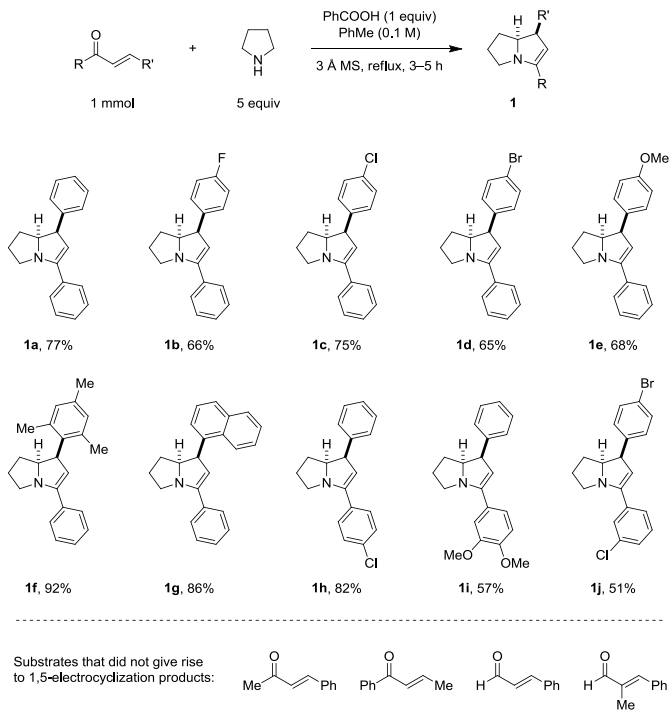
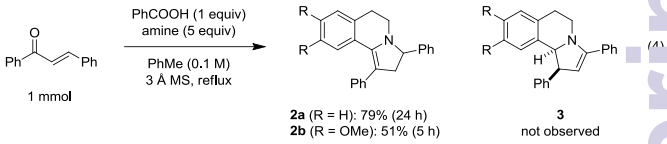
Electronic Supplementary Information (ESI) available: Experimental procedures and characterization data. See DOI: 10.1039/x0xx00000x

of new reactions in which azomethine ylides are transformed in non-pericyclic ways.[11,12] Carboxylic acids were found to be essential additives in many of these processes as they substantially lower the barriers for azomethine ylide formation. In addition, carboxylic acids serve to readily protonate azomethine ylides to form iminium ions or related *N*,*O*-acetal intermediates that undergo further transformations. Thus, the presence of a carboxylic acid, while required to access azomethine ylides, appears to be incompatible with well-established pericyclic azomethine ylide chemistry. However, we could recently show that azomethine ylides, accessed via a benzoic acid catalyzed process, readily undergo intramolecular [3+2]-cycloadditions.[13] To test whether this strategy is compatible with other types of pericyclic reactions, we decided to explore 1,5-electrocyclizations using pyrrolidine and chalcone as model substrates.

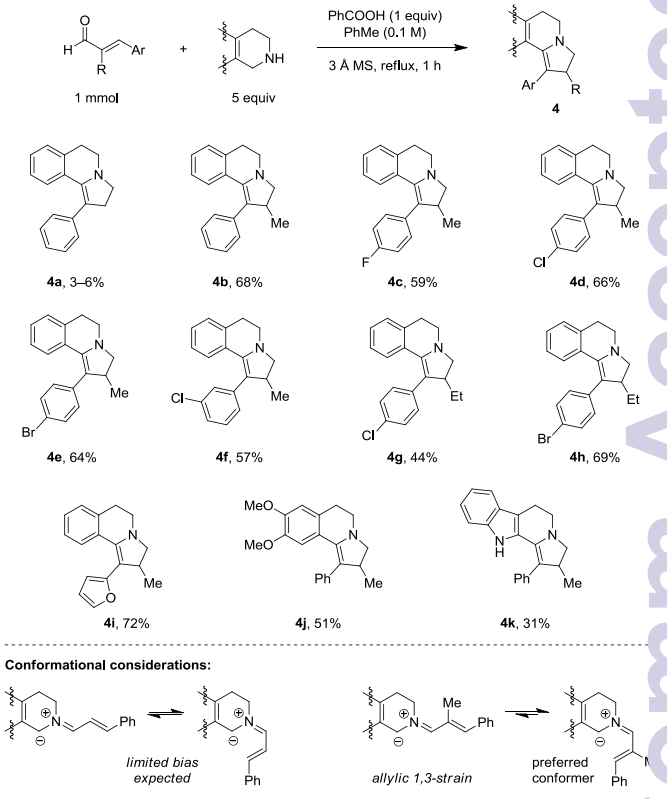
As summarized in Table 1, reactions between pyrrolidine and chalcone proceeded under a range of conditions. No formation of **1a** was observed in the absence of a carboxylic acid additive (entry 1). Instead, analysis of the crude reaction mixture by ^{1}H-NMR indicated the presence of the conjugate addition product (not shown) in addition to unmodified chalcone.[14] Addition of benzoic acid (0.5 equiv) under otherwise identical conditions led to the formation of **1a** as a single diastereomer in 65% yield (entry 2). The presence of molecular sieves was not essential, but slightly diminished yields were obtained in their absence (entry 3). Improved results were obtained upon lowering the reaction molarity from 0.25 M to 0.1 M (entry 4). Carboxylic acid additives other than benzoic acid were less effective (entries 5–7). While a reduction in benzoic acid loading was tolerated (entry 8), the best results were obtained with one equivalent of this additive (entry 9). Solvents other than toluene were explored briefly but provided inferior results (entries 10, 11). Finally, while the amount of pyrrolidine could be reduced, this led to longer reaction times and slightly diminished yields (entries 12, 13).



Scheme 1. Scope of the reaction with pyrrolidine.



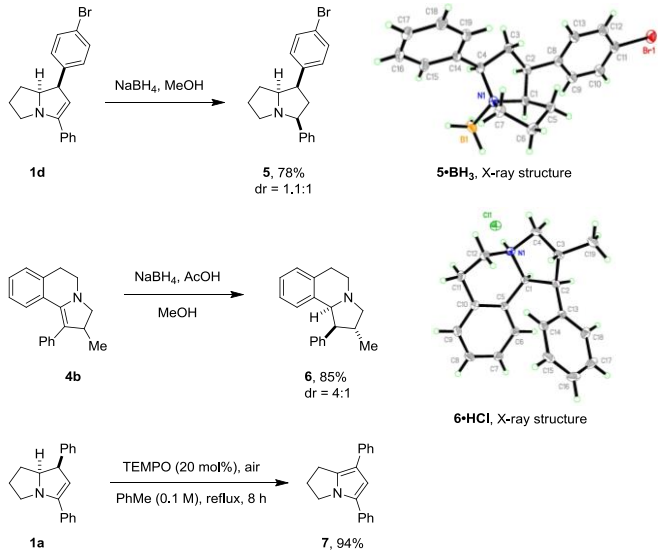
A range of diversely substituted chalcones readily underwent reactions with pyrrolidine under the optimized conditions, providing the corresponding pyrrolizidine-type annulation products in moderate to good yields (Scheme 1).[15] Substitution of either of chalcone's phenyl groups for a methyl substituent was not tolerated; no 1,5-electrocyclization products could be isolated. Similarly, reactions of pyrrolidine with cinnamaldehyde or α-methyl-cinnamaldehyde led to complex reaction mixtures and no appreciable formation of the desired annulation products. The scope of the reaction was easily extended to THIQ's (eq. 4). However, the expected products **3** were not observed. Rather, tautomeric products **2** were obtained, indicating that isomerization to the thermodynamically more stable enamines is rapid under the reaction conditions.



Scheme 2. Scope of the reaction with cinnamaldehydes.

In contrast to pyrrolidine, THIQ's and tryptoline readily underwent annulation reactions with cinnamaldehydes (Scheme 2). Parent cinnamaldehyde itself was a poor substrate, resulting in complex product mixtures out of which product **4a** could be isolated in only 3–6% yield. However, α-substituted cinnamaldehydes gave rise to fast reactions and moderate to good yields of annulation products. This is consistent with what would be expected based on a simple conformational analysis. The presence of an α-substituent should

result in an increased amount of the requisite conformer for the 6π-electrocyclization, as this avoids an unfavorable allylic 1,3-interaction present in the non-productive conformer (Scheme 2).[16] The amine annulation products could be reduced to the corresponding pyrrolidine ring-systems (Scheme 3). Reduction of **1d** with sodium borohydride led to the formation of **5** as a nearly 1:1 mixture of readily separable diastereomers. The BH_3 complex of the major diastereomer, which was found to be stable to chromatographic purification, was analyzed by X-ray crystallography. A moderately selective reduction was achieved with **4b**, allowing for the isolation of **6** in a 4:1 ratio of easily separable diastereomers. X-ray quality crystals of the HCl salt of the major diastereomer could be obtained which served to establish its relative configuration. Finally, **1a** could be readily oxidized to ring-fused pyrrole **7** under aerobic conditions.[17]



Scheme 3. Product transformation.

In summary, we have developed a simple method for the redox-neutral C–H annulation of amines with α,β-unsaturated aldehydes and ketones, providing easy access to alkaloid-like structures from simple starting materials. This study further establishes that the generation of azomethine ylides via a carboxylic acid promoted process is compatible with the subsequent pericyclic transformation of these dipolar species. This concept, which was applied here for the first time to 6π-electrocyclizations, is expected to find widespread use in related transformations.

Acknowledgements

Financial support from the NIH–NIGMS (R01GM101389) is gratefully acknowledged. We thank Dr. Tom Emge (Rutgers University) for crystallographic analysis.

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