Enantioselective Organo-SOMO Cycloadditions: A Catalytic Approach to Complex Pyrrolidines from Olefins and Aldehydes

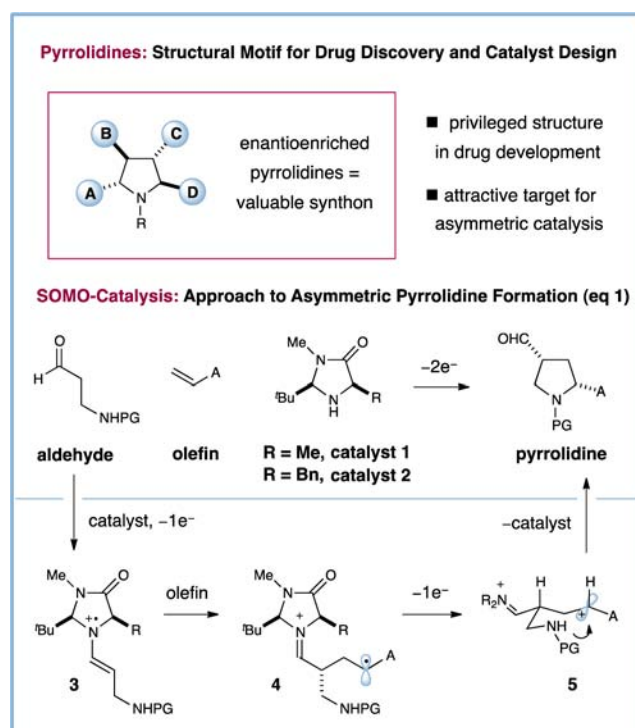Nathan T. Jui, Jeffrey A. O. Garber, Fernanda Gadini Finelli, and David W. C. MacMillan*

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Ⓢ *Supporting Information*

ABSTRACT: A new method to rapidly generate pyrrolidines via a SOMO-activated enantioselective (3 + 2) coupling of aldehydes and conjugated olefins has been accomplished. A radical-polar crossover mechanism is proposed wherein olefin addition to a transient enamine radical cation and oxidation of the resulting radical furnish a cationic intermediate which is vulnerable to nucleophilic addition of a tethered amine group. A range of olefins, including styrenes and dienes, are shown to provide stereochemically complex pyrrolidine products with high chemical efficiency and enantiocontrol.

The pyrrolidine ring system is central to a broad range of bioactive natural products,[1] is increasingly present in pharmaceutical agents,[2] and recently has become ubiquitous in catalysis, finding use as organocatalysts as well as ligands for a wide range of metal-mediated enantioselective protocols.[3] Not surprisingly, this high value heterocyclic framework has become an attractive target for new reaction invention,[4] with (3 + 2) cycloadditions[5] and the aza-Cope Mannich rearrangement[6] providing elegant solutions to access stereochemically complex variants. Recently, we sought to develop a new catalytic approach to pyrrolidines via the modular combination of β-amino aldehydes and simple olefins using an enantioselective SOMO-activation/cycloaddition mechanism. Herein we describe the successful execution of these ideals and demonstrate a simple yet powerful pyrrolidine forming reaction that we hope will be of significant utility to practitioners of medicinal agent synthesis and asymmetric catalysis.

Design Plan. Within the past few years, our laboratory has introduced a new mode of activation termed SOMO-catalysis that has enabled the direct enantioselective allylic alkylation,[7] enolation,[8] vinylation,[9] nitro-alkylation,[10] and carbo-oxidation[11] of aldehydes, as well as a new (4 + 2) cycloaddition to generate complex cyclohexyl rings.[12] Recently, we questioned if this radical-polar crossover mechanism might be employed to design a (3 + 2) cycloaddition to enantioselectively build complex pyrrolidine rings.[13,14] As outlined in eq 1, we hypothesized that exposure of β-amino aldehydes to SOMO-activation using imidazolidinone catalyst **1** and an oxidant would transiently form the radical cation **3**, which should rapidly engage an olefinic substrate in an enantioselective coupling to deliver the alkyl radical **4**. Oxidative radical-polar crossover would then furnish a carbocation that should trigger a stereoselective nitrogen addition—ring closure to deliver a complex pyrrolidine motif. In accord with previous SOMO-
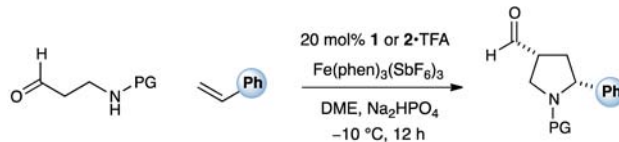
activation studies,[7−12] we presumed that high levels of enantiocontrol would be achieved on the basis of 3π-electron geometry control in catalyst−substrate adduct **3** and selective benzyl group shielding of the radical cation *Si*-face on the same system. As an important design criterion, we recognized that this new pyrrolidine forming reaction should be possible using readily accessible starting materials, such as simple olefins and β-amino aldehydes.

Results. As revealed in Table 1, the proposed design plan was rendered successful via the exposure of a variety of N-protected β-amino aldehydes to styrene and 2 equiv of iron(III)trisphenanthroline in the presence of amine catalysts **1** and **2**. Notably, high levels of enantiocontrol could be achieved using various protecting groups on the aldehydic nitrogen; however, the degree of diastereocontrol ranged from poor with Cbz to synthetically useful with nosyl (Table 1, entries 1−5, 62−86% yield, 1.2−6:1 dr, 82−90% ee). Interestingly, the more electron-withdrawing amine substituents (Cbz < Ts < Ns) clearly provide increased diastereocon-

Table 1. Effect of Amine Protecting Group and Catalyst Structure
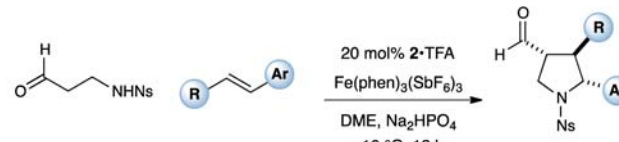
entry	PG	equiv. ald.	cat. (R)	% yield[a]	dr[b]	% ee[c]
1	Cbz	3.0	**1** (Me)	66	1.2:1	82
2	Boc	3.0	**1** (Me)	62	1.4:1	86
3	Ts	3.0	**1** (Me)	86	4:1	90
4	Ns	3.0	**1** (Me)	79	6:1	90
5	Ns	1.5	**1** (Me)	75	6:1	90
6	Ns	1.5	**2** (Bn)	77	9:1	92

[a]Isolated yield. [b]Determined by ^{1}H NMR analysis of crude reaction or isolated mixture. [c]Determined by chiral HPLC or SFC analysis of corresponding alcohol; absolute stereochemistry assigned by X-ray crystal structure or by analogy. Boc = *t*-butoxycarbonyl, Cbz = carboxybenzyl, Ts = 4-toluenesulfonyl, Ns = 4-nitrophenylsulfonyl.

trol, suggesting a more ordered (later) transition state with less nucleophilic tethered amines. Finally, changing the methyl group of the catalyst **1** to the more traditional benzyl-substituted imidazolidinone **2** further increased the relative stereoselectivities (Table 1, entry 6, 92% ee, 9:1 dr), a significant outcome given the propensity of five-membered ring cyclizations to be less diastereoselective than their six- and seven-membered counterparts.[15]

With the optimized conditions in hand, we next examined the scope of the olefinic component. As shown in Table 2, a range of electron-rich (entries 2, 4, and 6, 71–75% yield, 7–10:1 dr, 89–92% ee) and electron-poor (entries 7 and 8, 61–81% yield, 5–8:1 dr, 89–91% ee) styrenes are viable in this new cycloaddition reaction. Moreover, the enantioselectivity and efficiency are maintained for the *o*-, *m*-, and *p*-bromostyrenes (entries 1, 3, and 5, 72–76% yield, 93–94% ee), all useful substrates for further diversification in metal-catalyzed cross-coupling protocols. To our delight, varying the olefin substitution pattern is readily achieved. For example, the use of α-methyl styrene provides tertiary amino substituted pyrrolidines with excellent enantiocontrol (entry 9, 92% ee) and in 3:1 diastereocontrol (presumably due to the decreased preference for a pseudoequatorial phenyl group in the cyclization transition state). The diastereoselectivity improves significantly, to >20:1, when using *trans*-β-methyl styrene to stereoselectively build the pyrrolidine framework with three contiguous stereocenters (entry 10, 50% yield, 96% ee).
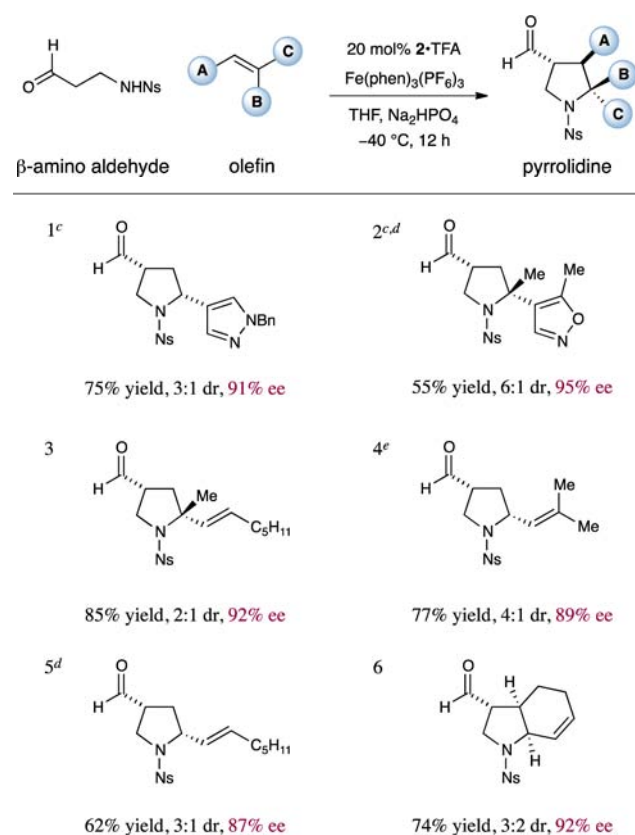
Given the importance of heteroaryl-substituted pyrrolidines in medicinal chemistry, we recognized an attractive prospect might be the replacement of styrene with vinyl heteroaromatics in this protocol (Table 3). As representative examples, both benzyl pyrazole (entry 1, 75% yield, 3:1 dr, 91% ee) and isoxazole (entry 2, 55% yield, 6:1 dr, 95% ee) were successfully incorporated in this manner. Importantly, this process is not limited to vinyl arenes. A full range of electron-neutral dienes were also competent in this transformation (entries 3–6, 62–85% yield, 1.5–4:1 dr, 87–92% ee), forming both bicyclic structures and fully substituted carbon stereocenters. Enantio-selectivities and yields remained high in all cases; however, diasterocontrol was observed to be moderate relative to other olefinic substrates.

Table 2. Enantioselective SOMO-Cycloaddition: Styrene Scope[a,b]

1. 72% yield, 9:1 dr, 93% ee
2. 71% yield, 7:1 dr, 91% ee
3. 76% yield, 8:1 dr, 93% ee
4. 73% yield, 8:1 dr, 92% ee
5. 76% yield, 3:1 dr, 94% ee
6. 75% yield, 10:1 dr, 89% ee
7. 61% yield, 5:1 dr, 89% ee
8. 81% yield, 8:1 dr, 91% ee
9[c]. 67% yield, 3:1 dr, 92% ee
10[c]. 50% yield, >20:1 dr, 96% ee

[a]Results listed as product, yield, diastereomeric ratio (dr), enantiomeric excess (% ee). [b]Diastereomeric ratio, % ee determined as in Table 1. [c]Reaction conducted at −20 °C using THF and Fe(phen)$_3$(PF$_6$)$_3$.

Finally, the use of indene as the π-coupling partner (eq 2) allows the production of unique tricyclic pyrrolidines in high yield and diastereoselectivity (75% yield, 9:1 dr, 85% ee). Perhaps even more notable, the use of optically active β-methyl β-amino aldehydes has enabled the construction of all four carbon stereocenters on the pyrrolidine ring while achieving excellent levels of diastereocontrol (eqs 3 and 4, 65–66% yield, ≥99% ee, 5–19:1 dr). Importantly, in these cases catalyst control appears to dominate for the formation of the formyl-bearing stereocenter, as well as the amine−carbocation cyclization event. As a result, various pyrrolidine isomers can be formed enantioselectively via the judicious choice of substrate and catalyst antipodes.

Table 3. Enantioselective Cascade Cycloaddition: Olefin Scope[a,b]

1[c]
75% yield, 3:1 dr, 91% ee

2[c,d]
55% yield, 6:1 dr, 95% ee

3
85% yield, 2:1 dr, 92% ee

4[e]
77% yield, 4:1 dr, 89% ee

5[d]
62% yield, 3:1 dr, 87% ee

6
74% yield, 3:2 dr, 92% ee

[a]Results listed as product, yield, diastereomeric ratio (dr), enantiomeric excess (% ee). [b]Diastereomeric ratio, % ee determined as in Table 1. [c]Reaction conducted with DME as solvent. [d]Reaction conducted at −20 °C. [e]Reaction conducted at −30 °C.

Tricyclic and Tetrasubstituted Pyrrolidine Products via (3 + 2) (eqs. 2−4)

(2) 75% yield, 9:1 dr, 85% ee

(3) 65% yield, 99% ee, 19:1 dr

(4) 66% yield, 99% ee, 5:1 dr
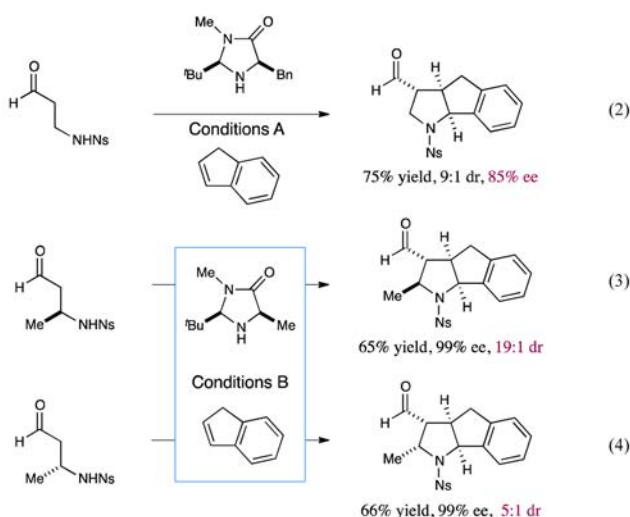
Conditions A: 20 mol% catalyst, Fe(phen)$_3$(PF$_6$)$_3$, Na$_2$HPO$_4$, THF, −40 °C, 12 h. Conditions B: 20 mol% catalyst, Fe(phen)$_3$(PF$_6$)$_3$, Na$_2$HPO$_4$, DME, −20 °C, 12 h.

In summary, a new protocol to rapidly construct enantioenriched pyrrolidines using β-amino aldehydes and π-nucleophilic olefins has been achieved using organo-SOMO catalysis in a formal cycloaddition cascade. As a critical design feature, the starting materials and catalysts are commercial materials or easily prepared, allowing rapid and modular production of a variety of pyrrolidine cores. We anticipate that this transformation will be valuable for catalyst development, natural product synthesis, and in the identification of new medicinal agents. Given this conceptual advance, future work will focus on the development of alternative oxidants of lower molecular weight for this protocol.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures, structural proofs, and spectral data for all new compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes
The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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