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Improved Protocol for Asymmetric, Intramolecular Heteroatom Michael Addition Using Organocatalysis: Enantioselective Syntheses of Homoproline, Pelletierine, and Homopipecolic Acid

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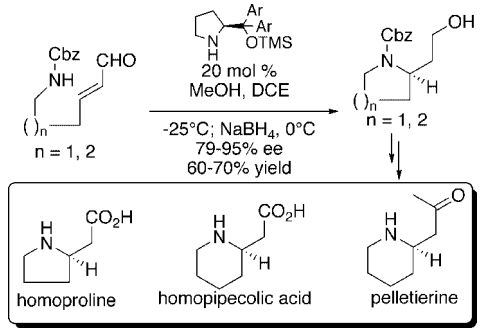

An improved protocol for the construction of enantioenriched pyrrolidine, indoline, and piperidine rings using an organocatalyzed, intramolecular heteroatom Michael addition is described. Application to the enantioselective synthesis of homoproline, homopipecolic acid, and pelletierine has been accomplished.

Pyrrolidine- and piperidine-based ring systems are ubiquitous in natural products. Consequently, construction of these heterocyclic rings systems in an enantioenriched fashion has been a subject of considerable synthetic attention. For example, the elegant work by Beak,[1] Hoppe,[2] and others[3] has showcased the ability to asymmetrically deprotonate N-protected pyrrolidines and piperidines. Alternatively, Comins has developed an asymmetric pyridinium salt reaction using *trans*-2-(α)-cumylcyclohexanol chloroformate for the synthesis of enantioenriched piperidines.[4] Dipolar cycloadditions[5] have also been exploited for the construction of these heterocyclic ring systems. Interestingly, despite the wealth of research directed toward piperidine- and pyrrolidine-based alkaloids, we are aware of only limited examples for the construction of pyrrolidine and pyrrolidine rings using organocatalysis.[5d,e,6,7] Recently, Fustero and coworkers reported the development of an organocatalyzed protocol for facilitating enantioselective, intramolecular heteroatom Michael additions.[8] While this protocol was effective on a range of substrates with generally high levels of enantioselectivity, it is not without its shortcomings. Specifically, the reaction temperatures for these transformations are low (typically starting at −50 °C) and usually require a slow warming of the reaction over a long period of time (e.g., "warming the resulting solution from −50°C until −30°C over a period of 48 hours").[8] Additionally, their protocol requires the addition of benzoic acid for the reaction to proceed at a suitable rate. This additive may not be advantageous for acid-sensitive substrates. Independently to this work, our own laboratory had begun developing conditions for enantioselective, intramolecular heteroatom Michael additions using organocatalysis which proceeded at more modest temperatures and did not require the use of any acid additives. Herein, we disclose an improved protocol for facilitating enantioselective, intramolecular heteroatom Michael addition reaction using a diaryl TMS-prolinol catalyst to construct pyrrolidine, indoline, and piperidine ring systems and its application to the total synthesis of homoproline, homopipecolic acid, and pelletierine.

We first chose to explore the cyclization of the piperidine precursor **3** (Table 1). This known enal **3**[8] can be readily prepared by cross-metathesis of the monosubstituted alkene **1** with crotonaldehyde (**2**) using second generation Grubbs catalyst. We found that use of alternate catalysts, such first generation Grubbs catalyst or second-generation Grubbs−Hoveyda catalyst, gave vastly inferior results. It is also worth noting that crotonaldehyde gave consistently higher yields than acrolein. As the product from the cyclization **4** proved unstable on the chiral HPLC column, we reduced the aldehyde at the end of each reaction with $NaBH_4$ to provide the alcohol **5**. The major advance in enantioselectivity came when the TMS diphenylprolinol catalyst **7** was used instead of proline (**6**)—leading to

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(2) Hoppe, D.; Hense, T. *Angew. Chem., Int. Ed.* **1997**, *36*, 2282–316.

(3) (a) Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 2206–25. (b) McGrath, M. J.; Bilke, J. L.; O'Brien, P. *Chem. Commun.* **2006**, 2607–09, and references cited within. (c) Dieter, R. K.; Topping, C. M.; Kishan, R. C.; Lu, K. *J. Am. Chem. Soc.* **2001**, *123*, 5132–5133.

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(6) Takasu, K.; Maiti, S.; Ihara, M. *Heterocycles* **2003**, *59*, 51–55.

(7) Metal-catalyzed: (a) Myers, J. K.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1999**, *121*, 8959–60. (b) Taylor, M. S.; Zalatan, D.; Lerchner, A. M.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2005**, *127*, 1313–17. (c) Gandelman, M.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2005**, *44*, 2393–97Organocatalyzed: (d) Horstmann, T. E.; Guerin, D. J,; Miller, S. J. *Angew. Chem., Int. Ed.* **2000**, *39*, 3635–38. (e) Chen, Y. K.; Yoshida, M.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 9328–29. (f) Ibrahem, I.; Rios, R.; Vesely, J.; Zhao, G.-L.; Córdova, A. *Chem. Commun.* **2007**, 849–51. (g) Vesely, J.; Ibrahem, I.; Rios, R.; Zhao, G.-L.; Xu, Y.; Córdova, A. *Tetrahedron Lett.* **2007**, *48*, 2193. (h) Dinér, P.; Nielsen, M.; Marigo, M.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 1983–87. (i) Li, H.; Wang, J.; Xie, H.; Zu, L.; Jiang, W.; Duesler, E. N.; Wang, W. *Org. Lett.* **2007**, *9*, 965–68. (j) Wang, J.; Zu, L.; Xie, H.; Wang, W. *Synthesis* **2007**, 2576–80. (k) Gerasyuto, A. I.; Hsung, R. P.; Sydorenko, N.; Slafer, B. *J. Org. Chem.* **2007**, *70*, 4248–56. (l) Vicario, J. L.; Badía, D.; Carrillo, L. *Synthesis* **2007**, 2065–92.

(8) Fustero, S.; Jiménez, D.; Moscardó, J.; Catalán, S.; del Pozo, C. *Org. Lett.* **2007**, *9*, 5283–86.

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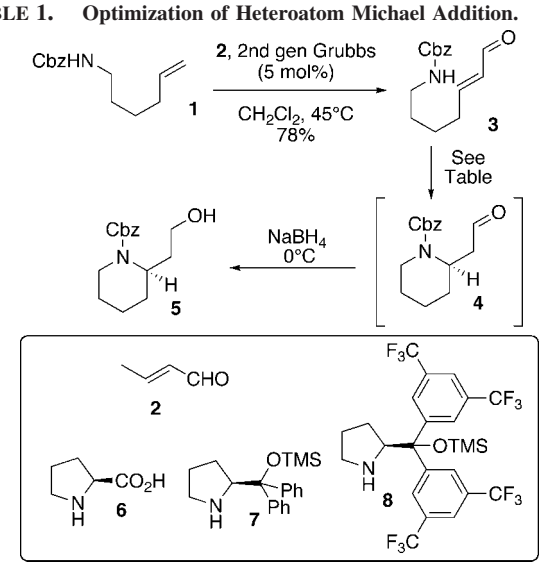
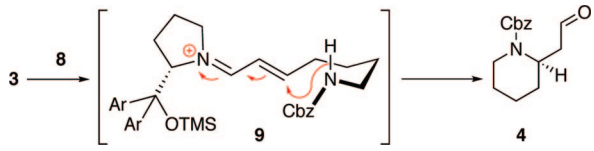
TABLE 1. Optimization of Heteroatom Michael Addition.



entry	catalyst	conditions	% ee[a] (% yield)
1	**6** (20 mol %)	EtOH, rt 48 h	9 (40)
2	**7** (20 mol %)	EtOH, rt 48 h	59 (41)
3	**8** (20 mol %)	EtOH, rt 48 h	71 (29)
4	**8** (20 mol %)	EtOH/$CHCl_3$ (1:1), rt, 48 h	80 (62)
5	**8** (20 mol %)	EtOH/DCE (1:1), rt, 48 h	78 (80)
6	**8** (20 mol %)	MeOH/DCE (1:1), rt, 24 h	83 (78)
7	***8*** (20 mol %)	*MeOH/DCE (1:1), −25 °C, 3 d*	*95 (70)*

[a] The enantiomeric excess (ee) was determined by chiral HPLC chiral HPLC (Daicel OD 10 μm, 4.6 mm × 250 mm column) of alcohol.

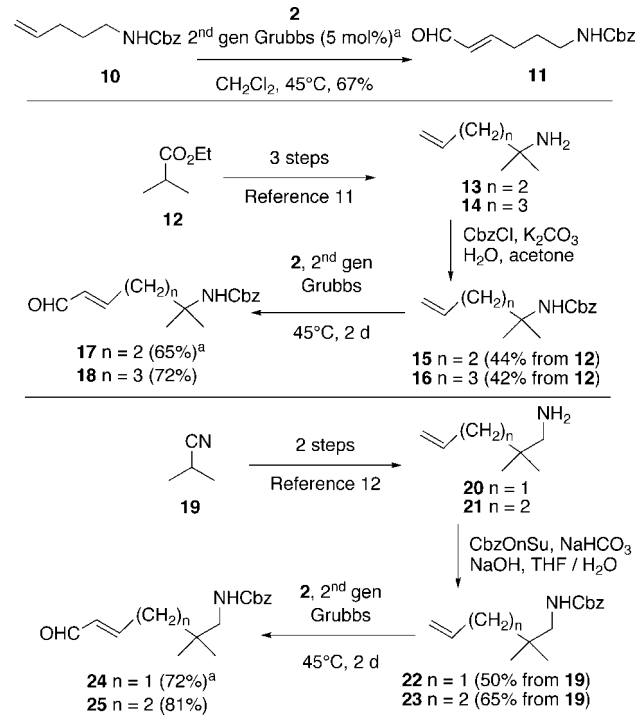
SCHEME 1. Possible Mechanistic Model for Observed Stereochemical Outcome



a 59% ee (entry 2). Further optimization with Jørgensen's trifluoromethyl derivative **8**[9] led to an additional improvement in enantioselectivity (entry 3). The use of chloroform or 1,2-dichloroethane (DCE) led to a significant improvement in yield (entries 5 and 6).[10] The optimized conditions required the reaction to be cooled to −25 °C (typically by placing the flask unstirred in the freezer until complete by TLC) to yield the product **5** in 70% yield and excellent enantioselectivity (95% ee) (entry 7). A possible mechanistic model to address the stereochemical outcome of the reaction is put forth in Scheme 1.

With a working catalyst system, we next began to explore the scope of the transformation (Scheme 2). We set out to study the effects of ring size (five versus six) as well as the effect of substitution. The first of these two variants to be explored was substrate **11** for producing the five-membered product **26**. Interestingly, use of the previously discussed second-generation Grubbs conditions (crotonaldehyde, CH_2Cl_2, 45 °C) on the five-membered series gave inconsistent results—depending solely on the bottle of Grubbs catalyst that was used. With older bottles,

SCHEME 2. Synthesis of Additional Cyclization Precursors[a]



[a] This enal substrate was formed using "aged" second-generation Grubbs catalyst which had been left in a container open to the air for a period of 3 d.

clean conversion was observed to the enal **11**. Interestingly, with newer bottles of Grubbs catalyst, a complex mixture of compounds was observed in the metathesis reaction. After considerable experimentation, it was discovered that an "aging" of the commercial catalyst was required to obtain reproducible results. The catalyst was removed from the sealed bottle and allowed to sit on the benchtop (or in a desiccator) exposed to air for a period of 3 days. This "aging" process has proven critical to the success of any cross-metathesis where the Cbz nitrogen is located five atoms away from the internal alkene carbon (alkenes **10**, **15** and **22**). We are unsure as to the exact nature of this "aging" process; however, careful inspection the aged second-generation Grubbs catalyst ^{1}H NMR spectrum reveals some subtle changes in the splitting pattern in the aromatic region. It should be noted that a somewhat related observation has been recently reported by Blechert.[11] Substitution in the α position (relative to the Cbz nitrogen) was accomplished by a Curtius rearrangement following known procedures.[12] The β-substituted enals **24** and **25** were constructed from alkylation with the nitrile **19**.[13]

With the required precursors in hand, we next studied their reactivity (Scheme 3). The parent pyrrolidine **26** was constructed from enal **11** in 67% yield with 90% ee. Substitution on the carbon backbone yielded some interesting results. In general, dimethyl substitution in the α position led to a reduced reactivity (presumably on steric grounds). The α-dimethyl pyrrolidine **27** required extended reaction time to proceed to completion and

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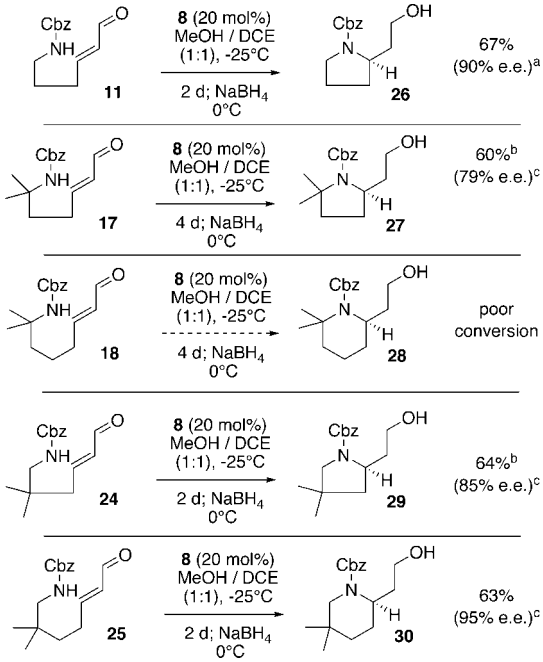
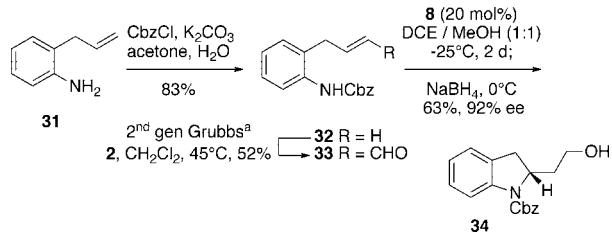
SCHEME 3. Exploration of Scope for Organocatalyzed, Intramolecular Heteroatom Michel Addition



[a] The enantiomeric excess (ee) was determined by chiral HPLC chiral HPLC (Daicel OD 10 μm, 4.6 mm × 250 mm column) of alcohol. [b] This alcohol contained a minor impurity that could be readily removed after hydrogenation of the Cbz protecting group (87−90%). [c] The enantiomeric excess (ee) was determined by chiral HPLC (Daicel OD 10 μm, 4.6 mm×250 mm column) of (*S*) Mosher ester.

SCHEME 4. Enantioselective Construction of Indoline Ring Systems[a]

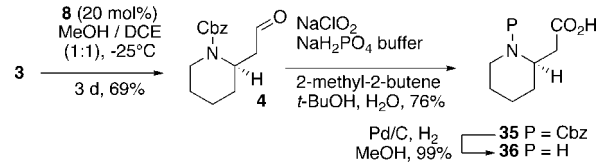


[a] Enal **33** was formed using "aged" second-generation Grubbs catalyst which had been left in a container open to the air for a period of 3 d.

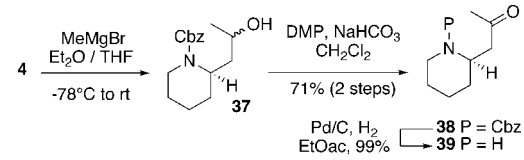
led to a reduced level of enantioselectivity. Formation of the piperidine analogue **28** was not reliable even under extended reaction times and increased amounts of catalyst. Conversely, dimethyl substitution β to the amino group yielded increased reactivity with good levels of enantiomeric excess. The increased reaction rate is likely due to the reduced level of conformational flexibility for the backbone—in accord with Thorpe and Ingold's observations.[14]

We were also interested in exploring the possibility of accessing the indoline ring system **34** in an enantioselective manner (Scheme 4). This precursor **33** was accessed from its corresponding known *o*-allyl aniline **31**.[15] Cbz protection gave aniline **32**.[16] Next, Grubbs cross-metathesis using the "aged"

SCHEME 5. Synthesis of Homopipecolic Acid



SCHEME 6. Synthesis of Pelletierine



catalyst provided the enal **33**. Not surprisingly, compound **33** proved unstable and had to be immediately submitted to the cyclization reaction upon its formation. Despite this instability, the level of enantioselectivity in the cyclization to form indoline **34** was still quite good (92% ee) with a reasonable yield (63%).

With a working methodology developed for synthesizing pyrrolidine, indoline and piperidine ring systems, we next sought to demonstrate the utility of this route for the construction of selected alkaloids and cyclic β-amino acid derivates. The cyclic β-amino acid **36**[17] was selected as an initial target for application of this methodology (Scheme 5). Oxidation of the β-amino aldehyde **4** to the acid **35** (76%) followed by Cbz deprotection (99%) yielded the desired material **36**. Comparison of observed optical rotation for synthetic **36** {$[\alpha]_D = -23.6$ ($c = 0.11$, H_2O)}with the literature value {(*S*)-isomer lit.[18] $[\alpha]_D = +24$ ($c = 0.87$, H_2O)} allowed us to establish the *R* absolute configuration of piperidine **36**.

Next, we set out to synthesize pelletierine (**39**)—an alkaloid with a storied history in natural products (Scheme 6). Piperidine **39** was isolated by Tanret in 1878;[19] however, debate swirled in the chemical community for years as to the exact structure of this natural product—in part due to chemists' inability to synthesize it.[20] Gilman and Marion finally resolved the issue through NMR studies 83 years later.[21] Further confirmation came through synthesis by Beyerman and Maat in 1963.[22,23] This natural product was synthesized starting from the aldehyde **4**. Grignard addition yielded the secondary alcohol **37** as an inconsequential 3:1 ratio of diastereomers which was oxidized

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(22) (a) Beyerman, H. C.; Maat, L. *Recl. Trav. Chim. Pays-Bas* **1963**, *82*, 1033–39. (b) Beyerman, H. C.; Maat, L. *Recl. Trav. Chim. Pays-Bas* **1965**, *84*, 385–88. (c) Beyerman, H. C.; Maat, L.; van Veen, A.; Zweistra, A. *Recl. Trav. Chim. Pays-Bas* **1965**, *84*, 1367–79.
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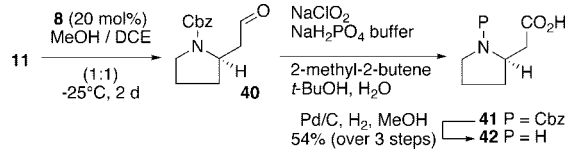
SCHEME 7. Synthesis of Homoproline



using Dess−Martin's periodinane to give ketone **38** in 71% yield over two steps. Finally, hydrogenation of the Cbz protecting group revealed (−)-pelletierine (**39**)[24] in 99% yield.

Finally, homoproline (**42**) has attracted considerable attention for its use in medicinal chemistry as well as organocatalysis (Scheme 7).[25] Our organocatalyzed heteroatom Michael additions should provide a rapid synthesis of this compound. Following a similar sequence as was used for the construction of homopipecolic acid, sodium chlorite oxidation followed by Cbz deprotection yielded the target **42**[18]in 54% yield over the three steps. It should be noted that the oxidation of the aldehyde **40** needed to be conducted immediately after its formation; use of purified aldehyde **40** led to a considerable erosion in enantioselectivity.

In conclusion, an improved organocatalyzed, intramolecular heteroatom Michael addition protocol has been developed for the asymmetric synthesis of pyrrolidine, indoline and piperidine derivatives. The scope of this transformation has been explored on a series of enal precursors. Application to the synthesis of homopipecolic acid, pelletierine and homoproline has been demonstrated. Further utilization of this methodology in alkaloid synthesis will be disclosed in due course.

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Experimental Section

General Procedure of Organocatalyzed Heteroatom Michael Addition with in Situ $NaBH_4$ Reduction. To a solution of aldehyde (1 equiv) and MeOH (0.2 M) was added a solution of the catalyst **8** (20 mol %) in DCE (0.04 M in catalyst **8**) via syringe at −25 °C. The reaction was placed in the freezer (−25 °C). After being judged complete by TLC, the solution was warmed to 0 °C and $NaBH_4$ (3 equiv) was added. The solution was then allowed to warm to rt. After 2 h, the reaction was quenched with HCl (2 mL per mmol of aldehyde, 10% aq), diluted with H_2O (50 mL per mmol aldehyde), and extracted with Et_2O (3 × 100 mL per mmol aldehyde). The combined organic layers were washed with satd aq NaCl (300 mL per mmol aldehyde), and the dried extract ($MgSO_4$) was concentrated in vacuo. The crude product was purified by chromatography over silica gel, eluting with EtOAc/hexanes to give the alcohol (60−71%).

Alcohol (*R*)-5. Purified by chromatography over silica gel, eluting with 10−30% EtOAc/hexanes to give the known alcohol **5**[8] (17.7 mg, 0.067 mmol, 70%) as a pale yellow oil. Enantiomeric excess was determined by chiral HPLC [4.6 × 250 mm Diacel OD column, 95:5 hexanes/iPrOH, retention times 16.87 (minor) and 18.69 min (major)] to be 95% ee: $[\alpha]_D$ +14.2 (c = 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.42 (m, 5H), 5.17 (s, 2H), 4.50−4.60 (m, 1H), 4.05−4.12 (m, 1H), 3.55−3.65 (m, 1H), 3.35−3.50 (m, 1H), 2.79 (t, J = 12.8 Hz, 1H), 1.98 (t, J = 13.6 Hz, 1H), 1.52−1.70 (m, 5H), 1.40−1.52 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8, 136.7, 128.6, 128.1, 127.9, 67.4, 58.7, 47.0, 39.5, 32.6, 29.2, 25.5, 19.1; HRMS (EI^+) calcd for $C_{15}H_{21}NO_3$ (M^+) 263.1522, found 263.1522.

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Supporting Information Available: Complete experimental procedures are provided, including ^{1}H and ^{13}C spectra, of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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