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Intramolecular Pyridine Activation−Dearomatization Reaction: Highly Stereoselective Synthesis of Polysubstituted Indolizidines and Quinolizidines

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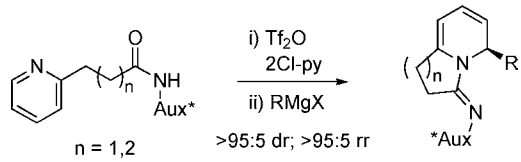
ABSTRACT



An unprecedented intramolecular pyridine activation−asymmetric dearomatization reaction is described. This process produces 5-substituted indolizidines and 6-substituted quinolizidines in excellent yields and in a highly regio- and diastereoselective fashion. Formal syntheses of *trans*-indolizidine alkaloids are presented along with some preliminary results in the formation of C-5 quaternary centers.

Extracts from the skin of amphibians provide a large array of structurally unique[1] and pharmacologically active alkaloids.[2] Particularly, indolizidine and quinolizidine alkaloids represent privileged motifs, and accordingly, their chemical syntheses have benefited from a worldwide interest.[3]

Despite immense efforts, a more general and expedient approach to synthetically flexible polysubstituted indolizidines and quinolizidines remains highly desirable.[4] Herein, we report on the stereoselective synthesis of 5(6)-substituted indolizidines (quinolizidines) through an unprecedented intramolecular pyridine activation−asymmetric dearomatization reaction.

Over the past decades, pyridine dearomatization has emerged as an attractive and cost-effective approach to the asymmetric synthesis of polysubstituted piperidines.[5,6] Recognizing the unique directing ability of nitrogen-containing

(1) Daly, J. W.; Spande, T. F.; Garraffo, H. M. *J. Nat. Prod.* **2005**, *68*, 1556.

(2) For a review of the biological significance of indolizidine alkaloids, see: Daly, J. W.; Garraffo, H. M.; Spande, T. F. In *Alkaloids: Chemical and Biological Perspectives*; Pelletier, S. W., Ed.; Pergamon: New York, 1999; Vol. 13, pp 1−161.

(3) Michael, J. P. *Nat. Prod. Rep.* **2008**, *25*, 139. and other reviews in these series.

(4) For recent approaches, see: (a) Yu, R. T.; Lee, E. E.; Malik, G.; Rovis, T. *Angew. Chem., Int. Ed.* **2009**, *48*, 2379. (b) Liu, P.; Hong, S.; Weinreb, S. M. *J. Am. Chem. Soc.* **2008**, *130*, 7562. (c) Yu, R. T.; Rovis, T. *J. Am. Chem. Soc.* **2006**, *128*, 12370. (d) Turunen, B. J.; Georg, G. I. *J. Am. Chem. Soc.* **2006**, *128*, 8702.

(5) For chiral auxiliary-based strategies, see: (a) Mehmandoust, M.; Marazano, C.; Das, B. C. *J. Chem. Soc., Chem. Commun.* **1989**, 1185. (b) Comins, D. L.; Goehring, R. R.; Sajan, J. P.; O'Connor, S. *J. Org. Chem.* **1990**, *55*, 2574. (c) Comins, D. L.; Hong, H. *J. Am. Chem. Soc.* **1991**, *113*, 6672. (d) Sreith, J.; Boiron, A.; Sifferlen, T.; Strehler, C.; Tschamber, T. *Tetrahedron Lett.* **1994**, *35*, 3927. (e) Comins, D. L.; Josef, S. P.; Goehring, R. R. *J. Am. Chem. Soc.* **1994**, *116*, 4719. (f) Charette, A. B.; Grenon, M.; Lemire, A.; Pourashraf, M.; Martel, J. *J. Am. Chem. Soc.* **2001**, *123*, 11829. (g) Hoesl, C. E.; Pabel, J.; Polborn, K.; Wanner, K. T. *Heterocycles* **2002**, *58*, 383. (h) Legault, C.; Charette, A. B. *J. Am. Chem. Soc.* **2003**, *125*, 6360. (i) Comins, D. L.; Sahn, J. J. *Org. Lett.* **2005**, *7*, 5227.

(6) For catalysis-based strategies, see: (a) Ichikawa, E.; Suzuki, M.; Yabu, K.; Albert, M.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 11808. (b) Legault, C.; Charette, A. B. *J. Am. Chem. Soc.* **2005**, *127*, 8966. (c) Sun, Z.; Yu, S.; Ding, Z.; Ma, D. *J. Am. Chem. Soc.* **2007**, *129*, 9300. (d) Rueping, M.; Antonchick, A. P. *Angew. Chem., Int. Ed.* **2007**, *46*, 4562. (e) Black, D. A.; Beveridge, R. E.; Arndtsen, B. A. *J. Org. Chem.* **2008**, *73*, 1906.

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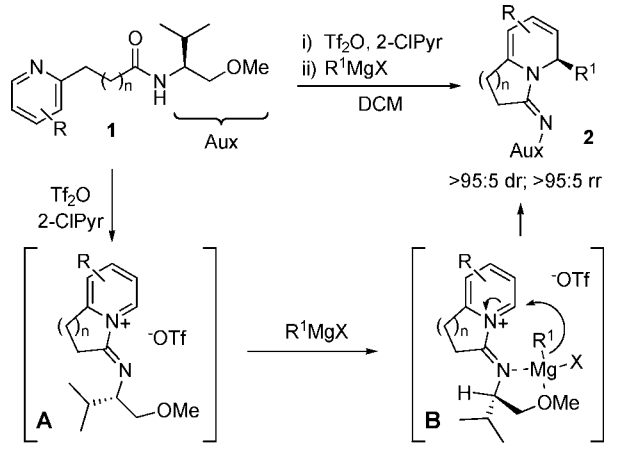
functionalities,[7] our group disclosed a highly regio- and stereoselective dearomatization of unsubstituted pyridine.[5f] In an effort to find a general entry into the indolizidine and quinolizidine scaffold, we hypothesized that treating a chiral-auxiliary derived pyridinium salt such as **A** with Grignard reagents could undergo an amidine-directed addition (**B**) at the 5(6)-position selectively (Scheme 1).[8] In the event,

Scheme 1. Intramolecular Pyridine Activation Strategy



diastereoenriched unsaturated compounds **2** would be generated, allowing for further derivatization along the rings. Pyridinium salt **A** would in return come from a new intramolecular pyridine activation reaction. More precisely, we reasoned that treating amides **1** with trifluoromethanesulfonic anhydride (Tf_2O) would result in the formation of a highly reactive iminium species[9] capable of triggering a base-mediated cyclization with the pyridine ring.[10]

To begin our study, we developed short multigram scale syntheses of **1** and elected to use **1a** for reaction development.[11] After extensive optimization, we found that treating pyridine **1a** with Tf_2O in the presence of 2-chloropyridine (2-ClPyr) smoothly produced pyridinium salt **A** as a transient intermediate (Table 1, entry 9).[12] The use of 2-ClPyr as a non-nucleophilic and slightly basic additive was found crucial for efficient intramolecular pyridine activation.[13]

Most importantly, it ensured the stability of the base-sensitive pyridinium **A** (entries 4−6). These results led us to anticipate deprotonation issues when treating **A** with strongly basic Grignard reagents. Gratifyingly, addition of MeMgBr to pyridinium salt **A** at −78 °C cleanly resulted in

(7) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307.
(8) For examples of amidine-directed transformations, see: (a) Shawe, T. T.; Meyers, A. I. *J. Org. Chem.* **1991**, *56*, 2751. (b) Pastine, S. J.; Gribkov, D. V.; Sames, D. *J. Am. Chem. Soc.* **2006**, *128*, 14220.
(9) Barbe, G.; Charette, A. B. *J. Am. Chem. Soc.* **2008**, *130*, 18, and references cited therein.
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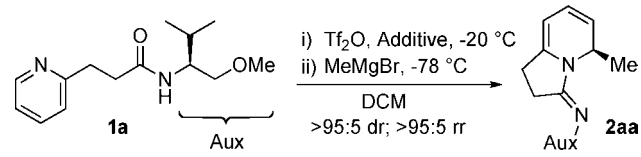
(12) Myers, A. G.; Tom, N. J.; Fraley, M. E.; Cohen, S. B.; Madar, D. J. *J. Am. Chem. Soc.* **1997**, *119*, 6072.
(13) (a) Movassaghi, M.; Hill, M. D. *J. Am. Chem. Soc.* **2006**, *128*, 14254. (b) Medley, J. W.; Movassaghi, M. *J. Org. Chem.* **2009**, *74*, 1341, and references cited therein.

Table 1. Pyridine Activation−Grignard Addition Optimization



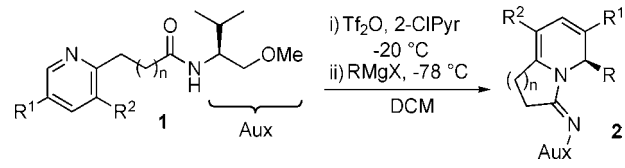
entry	additive	equiv	[**1a**] (M)	yield[a] (%)
1	none	2.00	0.05	39
2	K_2CO_3	2.00	0.05	44
3	MgO	2.00	0.05	53
4	Et_3N	2.00	0.05	0
5	DIPEA	2.00	0.05	0
6	pyridine	2.00	0.05	11
7	2,6-lutidine	2.00	0.05	60
8	2-chloropyridine	2.00	0.05	78
9	2-chloropyridine	1.50	0.05	92
10	2-chloropyridine	1.25	0.05	84
11	2-chloropyridine	1.50	0.10	89
12	2-chloropyridine	1.50	0.01	87

[a] Determined by ^{1}H NMR vs Ph_3CH as an internal standard.

the formation of the unsaturated indolizidine **2aa** in 92% NMR yield as a single regio- and diastereomer (entry 9).

The stereoinduction is believed to originate from a precomplexation of the *E*-imidate lone pair to the Grignard reagent, thereby directing the nucleophilic addition at the proximal 5(6)-position of the pyridinium ring (intermediate

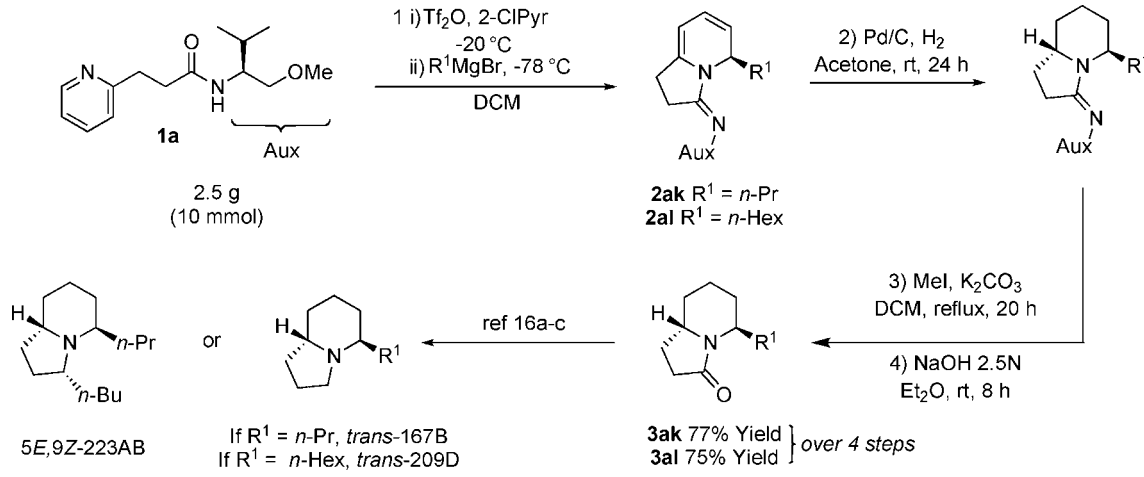
Table 2. Synthesis of Polysubstituted Indolizidines and Quinolizidines[a]



entry	*n*	R^1:R^2	RMgX	**2**	yield (%)[b]
1	1	H:H	MeMgBr	**2aa**	94
2	1	H:H	*n*-pentylMgCl	**2ab**	91
3	1	H:H	*i*-PrMgCl[c]	**2ac**	89
4	1	H:H	*c*-hexylMgBr	**2ad**	89
5	1	H:H	*t*-BuMgCl[c]	**2ae**	83
6	1	H:H	vinylMgBr	**2af**	85
7	1	H:H	2-furylMgBr[d]	**2ag**	84
8	1	H:H	2-thiophenylMgBr[e]	**2ah**	86
9	1	H:H	*N*-Me-2-indolylMgBr[d]	**2ai**	84
10	1	H:H	1-hexynylMgBr[f]	**2aj**	85
11	2	H:H	vinylMgBr	**2bf**	83
12	2	H:H	2-thiophenylMgBr[e]	**2bh**	86
13	2	H:H	1-hexynylMgBr[f]	**2bj**	88
14	1	H:Me	MeMgBr[c]	**2ca**	87
15	1	Me:H	MeMgBr[c]	**2da**	93

[a] All reactions performed on 1 mmol of **1**. [b] Isolated yield of a single regio- and diastereomer. [c] Grignard addition at −20 °C. [d] Prepared from the heteroaryl, *n*-BuLi, and $MgBr_2$-Et_2O. [e] Prepared from 2-bromothiophene and Mg turnings. [f] Prepared from the terminal alkyne and EtMgBr.

Scheme 2. Stereoselective Synthesis of *trans*-Indolizidines



B, Scheme 1). Coordination to the magnesium by the ether functionality ensures a high degree of organization at the transition state. By minimizing the 1,3-allylic strain with the chiral auxiliary, this chelation shifts the Grignard reagent toward the β-face of the pyridinium ring resulting in the observed diastereomer.[14]

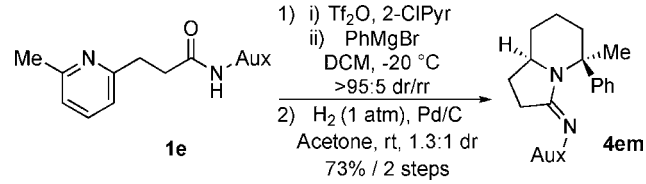
With our optimal conditions in hand, we evaluated the scope of the reaction. As shown in Table 2, sp^3 (entries 1−5), sp^2 (entries 6−9, 11, and 12), and sp (entries 10 and 13) hybridized carbon nucleophiles react smoothly with the pyridinium intermediates **A**, producing indolizidines **2a** and quinolizidines **2b** with excellent yields, regio-, and diastereoselectivities.[15]

A demonstration of the synthetic relevance of this methodology is shown in Scheme 2. Starting from 10 mmol of the amide **1a**, our standard conditions using *n*-PrMgCl and *n*-HexMgBr as nucleophiles afforded dihydropyridines **2ak** and **2al**, respectively. Subsequently, diastereoselective hydrogenation of the alkenes using Pd/C in acetone gave the corresponding saturated cycles. These amidines were then regioselectively hydrolyzed via the formation of an amidinium salt using MeI as the alkylating reagent followed by a basic treatment of the amidinium salt in aqueous NaOH. This two-step process led to the isolation of the corresponding *trans*-indolizidinones **3ak** and **3al** in over 75% yield overall for the four steps. These *trans*-indolizidinones are known in the literature[16] to be intermediates in the asymmetric syntheses of indolizidines *trans*-167B,[16a] *trans*-209D,[16b] and 5*E*,9*Z*-223AB,[16c] and they allowed us to confirm the absolute configuration of indolizidines **2a**.

Finally, we evaluated the effect of pyridine substitution on the outcome of the activation−dearomatization process. By substituting positions 3 and 5, the excellent yields, regio- and diastereoselectivities were maintained producing 5,8-(entry 14) and 5,6-disubstituted indolizidines (entry 15), respectively.

These results contrast with literature precedents[5h,17] and prompted us to further explore the directing ability of the auxiliary for the formation of quaternary centers. To our delight, using **1e** and PhMgBr as reagents, the C-5 quaternary center was formed as a single regio- and diastereomer.[15] After hydrogenation of the remaining alkenes, a good yield of the 5,5-disubstituted indolizidine **4em** was obtained (eq 1, Scheme 3).[18] To our knowledge, this represents the first

Scheme 3. Quaternary Center Formation



asymmetric quaternary center formation via a pyridine dearomatization reaction. In addition, this features unusually mild conditions for the activation of 2,6-disubstituted pyridine.

In conclusion, a highly stereoselective synthesis of 5(6)-substituted indolizidines (quinolizidines) has been described.

(14) This is supported by NOE experiments performed on compound **2aa**. See Supporting Information for more details.

(15) All entries in this paper showed >20:1 rr and >20:1 dr by ^{1}H NMR of the crude mixture, with the exception of *t*-Bu (entry 5, Table 2) which showed a ratio of 14:1 rr and >20:1 dr.

(16) (a) Toyooka, N.; Nemoto, H. *Heterocycles* **2005**, *66*, 549. (b) Alegret, C.; Riera, A. *J. Org. Chem.* **2008**, *73*, 8661. (c) Hart, D. J.; Tsai, Y. *J. Org. Chem.* **1982**, *47*, 4403.

(17) (a) Comins, D. L.; Abdullah, A. H. *J. Org. Chem.* **1982**, *47*, 4315. (b) Yamaguchi, R.; Nakazono, Y.; Kawanisi, M. *Tetrahedron Lett.* **1983**, *24*, 1801. (c) Lemire, A.; Grenon, M.; Pourashraf, M.; Charette, A. B. *Org. Lett.* **2004**, *6*, 3517, and references cited therein.

(18) Hydrogenation of the diene was found necessary to ensure complete stability of the indolizidine. Although still under investigation, evidence points toward the formation of ring-opened products resulting from a 6π-electron electrocyclic ring-opening process. For recent calculations, see: Walker, M. J.; Hietbrink, B. N.; Thomas IV, B. E.; Nakamura, K.; Kallel, E. A.; Houk, K. N. *J. Org. Chem.* **2001**, *66*, 6669.

This strategy highlights an unprecedented intramolecular pyridine activation−asymmetric dearomatization reaction. Applications of this methodology to the total synthesis of natural products along with a complete survey of the quaternary center formation are under investigation. The results will be reported in due course.

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Supporting Information Available: Experimental details and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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