Lewis Acid Catalyzed Formation of Tetrahydroquinolines via an Intramolecular Redox Process

Sandip Murarka, Chen Zhang, Marlena D. Konieczynska, and Daniel Seidel*

Department of Chemistry and Chemical Biology, Rutgers, The State University of New Jersey, Piscataway, New Jersey 08854

seidel@rutchem.rutgers.edu

Received October 30, 2008

 $\begin{array}{c} \text{ABSTRACT} \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & &$

Polycyclic tetrahydroquinolines were prepared by an efficient Lewis acid catalyzed 1,5-hydride shift, ring closure sequence. Gadolinium triflate was identified as a catalyst that is superior to scandium triflate as well as other Lewis acids. An approach toward a catalytic enantioselective variant is also described.

Tetrahydroquinolines have attracted considerable attention due to their diverse array of biological activities.¹ Common methods for the synthesis of tetrahydroquinolines¹ include the Povarov reaction² and various reductions of quinolines.³ An underutilized approach to polycyclic tetrahydroquinolines, not readily available by other means, is outlined in Scheme 1. Tertiary anilines **1** with an appropriate acceptor group in the *ortho* position rearrange to tetrahydroquinolines **2** under thermal conditions. In this process, a C–H bond α to the tertiary amine nitrogen is replaced by a C–C bond that becomes part of the newly formed tetrahydroquinoline ring system.⁴ Harsh reaction conditions are typically required for this transformation, therefore resulting in limited synthetic

Scheme 1. Tetrahydroquinoline Synthesis via Redox Neutral C-H Bond Functionalization



use. Here we report an efficient Lewis acid catalyzed approach that readily proceeds at room temperature and significantly enhances the applicability of this rearrangement.

The thermal rearrangement of 1 (Z = Z' = CN) was originally reported in 1984 by Reinhoudt et al.,⁵ and variants

⁽¹⁾ For a comprehensive review, see: Katritzky, A. R.; Rachwal, S.; Rachwal, B. *Tetrahedron* **1996**, *52*, 15031–15070.

⁽²⁾ For a recent review on the Povarov reaction, see: Glushkov, V. A.; Tolstikov, A. G. *Russ. Chem. Rev.* **2008**, *77*, 137–159.

⁽³⁾ For recent examples, see: (a) Rueping, M.; Antonchick, A. P.; Theissmann, T. Angew. Chem., Int. Ed. 2006, 45, 3683–3686. (b) Zhou, Y.-G. Acc. Chem. Res. 2007, 40, 1357–1366. (c) Chan, S. H.; Lam, K. H.; Li, Y.-M.; Xu, L.; Tang, W.; Lam, F. L.; Lo, W. H.; Yu, W. Y.; Fan, Q.; Chan, A. S. C. Tetrahedron: Asymmetry 2007, 18, 2625–2631. (d) Guo, Q.-S.; Du, D.-M.; Xu, J. Angew. Chem., Int. Ed. 2008, 47, 759–762. (e) Mrsic, N.; Lefort, L.; Boogers, J. A. F.; Minnaard, A. J.; Feringa, B. L.; de Vries, J. G. Adv. Synth. Catal. 2008, 350, 1081–1089. (f) Wang, X.-B.; Zhou, Y.-G. J. Org. Chem. 2008, 73, 5640–5642, and references cited therein.

⁽⁴⁾ Due to this unusual reactivity, reactions of this type have been described by the term "*tert*-amino effect." For reviews, see: (a) Meth-Cohn, O.; Suschitzky, H. *Adv. Heterocycl. Chem.* **1972**, *14*, 211–278. (b) Verboom, W.; Reinhoudt, D. N. *Recl. Trav. Chim. Pays-Bas* **1990**, *109*, 311–324. (c) Meth-Cohn, O. *Adv. Heterocycl. Chem.* **1996**, *65*, 1–37. (d) Quintela, J. M. *Recent Res. Devel. Org. Chem.* **2003**, *7*, 259–278. (e) Matyus, P.; Elias, O.; Tapolcsanyi, P.; Polonka-Balint, A.; Halasz-Dajka, B. Synthesis **2006**, 2625–2639.

of this reaction have been reported.⁶ In some examples, the benzene ring has been replaced by different heterocycles,⁷ and one of the acceptors (Z) can also be a heterocycle.⁸

While microwave acceleration of the thermal rearrangement has been reported,⁹ surprisingly little effort has focused on using Lewis acids to accelerate this reaction.¹⁰ Lewis acids such as zinc chloride and boron trifluoride—diethyl ether have been used in stoichiometric amounts, with heating still being required to induce the rearrangement.¹⁰

As part of a program to develop intramolecular redox reactions of broad synthetic applicability,¹¹ we decided to explore the use of Lewis acids for the rearrangement of **1a** to **2a** (Scheme 2).¹² We speculated that alkylidene malonates represent ideal acceptor moieties that are susceptible to activation by a Lewis acid catalyst capable of chelation to the malonate subunit. This interaction is expected to increase the hydride acceptor capability of the conjugated double bond. The dipolar intermediate resulting from hydride transfer is expected to readily undergo ring closure to form **2a**.

(7) (a) Verboom, W.; Verboom, C.; Eissink, I. M.; Lammerink, B. H. M.; Reinhoudt, D. N. *Recl. Trav. Chim. Pays-Bas* **1990**, *109*, 481–484. (b) Ojea, V.; Peinador, C.; Quintela, J. M. *Synthesis* **1992**, 798–802. (c) Ojea, V.; Peinador, C.; Vilar, J.; Quintela, J. M. *Synthesis* **1993**, 152–157. (d) Ojea, V.; Maestro, M. A.; Quintela, J. M. *Tetrahedron* **1993**, *49*, 2691–2700. (e) Matyus, P.; Fuji, K.; Tanaka, K. *Heterocycles* **1994**, *37*, 171–174. (f) Ojea, V.; Muinelo, I.; Figueroa, M. C.; Ruiz, M.; Quintela, J. M. *Syntett* **1995**, 622–624. (g) Wamhoff, H.; Kramer-Hoss, V. *Liebigs Ann./Recueil* **1997**, 1619–1625. (h) Ojea, V.; Muinelo, I.; Quintela, J. M. *Tetrahedron* **1998**, *54*, 927–934. (i) Devi, I.; Baruah, B.; Bhuyan, P. J. *Synlett* **2006**, 2593– 2596. (j) Dajka-Halasz, B.; Foldi, A. A.; Ludanyi, K.; Matyus, P. *ARKIVOC* **2008**, 102–126. (k) Ivanov, I. C.; Glasnov, T. N.; Belaj, F. *J. Heterocycl. Chem.* **2008**, *45*, 177–180.

(8) (a) Tverdokhlebov, A. V.; Gorulya, A. P.; Tolmachev, A. A.; Kostyuk, A. N.; Chernega, A. N.; Rusanov, E. B. *Synthesis* **2005**, 2161– 2170. (b) Ryabukhin, S. V.; Plaskon, A. S.; Volochnyuk, D. M.; Shivanyuk, A. N.; Tolmachev, A. A. *Synthesis* **2007**, 2872–2886.

(9) (a) Kaval, N.; Dehaen, W.; Matyus, P.; Van der Eycken, E. *Green Chem.* **2004**, *6*, 125–127. (b) Kaval, N.; Halasz-Dajka, B.; Vo-Thanh, G.; Dehaen, W.; Van der Eycken, J.; Matyus, P.; Loupy, A.; Van der Eycken, E. *Tetrahedron* **2005**, *61*, 9052–9057.

(10) (a) Noguchi, M.; Yamada, H.; Sunagawa, T. J. Chem. Soc., Perkin Trans. 1 **1998**, 3327–3329. (b) Prajapati, D.; Borah, K. J. Beilstein J. Org. Chem. **2007**, *3*, No. 43.

(11) (a) Zhang, C.; De, C. K.; Mal, R.; Seidel, D. J. Am. Chem. Soc. **2008**, *130*, 416–417. (b) Zhang, C.; Murarka, S.; Seidel, D. J. Org. Chem. **2009**, *74*, 419–422.

(12) Lewis acid catalysis has been applied to other intramolecular redox reactions: (a) Woelfling, J.; Frank, E.; Schneider, G.; Tietze, L. F. *Eur. J. Org. Chem.* **2004**, 90–100. (b) Pastine, S. J.; McQuaid, K. M.; Sames, D. *J. Am. Chem. Soc.* **2005**, *127*, 12180–12181. (c) Pastine, S. J.; Sames, D. *Org. Lett.* **2005**, *7*, 5429–5431.





Indeed, catalytic amounts of various Lewis acids facilitate rearrangement of **1a** to **2a** at room temperature (Table 1).

Table 1. Evaluation of Potential Catalysts^a

Ia MeO ₂ C CO ₂ Me	catalyst	C 2a	CO ₂ Me CO ₂ Me	
catalyst	mol %	solvent	time	yield (%)
Mg(OTf) ₂	20	CH_2Cl_2	24 h	20^b
$Mg(ClO_4)_2$	20	$\mathrm{CH}_2\mathrm{Cl}_2$	20 h	83
Mg(ClO ₄) ₂ •6H ₂ O	20	CH_2Cl_2	$24 \mathrm{h}$	trace
$InCl_3$	20	$\mathrm{CH}_2\mathrm{Cl}_2$	$24 \mathrm{h}$	66^b
$Zn(OTf)_2$	20	$\mathrm{CH}_2\mathrm{Cl}_2$	24 h	72^b
Cu(OTf) ₂	20	$\mathrm{CH}_2\mathrm{Cl}_2$	$24 \mathrm{h}$	55
$Ni(ClO_4)_2 \cdot 6H_2O$	20	$\mathrm{CH}_2\mathrm{Cl}_2$	$24 \mathrm{h}$	28^b
FeCl ₃ •6H ₂ O	20	$\mathrm{CH}_2\mathrm{Cl}_2$	$24 \mathrm{h}$	trace
Yb(OTf) ₃	20	$\mathrm{CH}_2\mathrm{Cl}_2$	$2.5 \ h$	84
Sc(OTf) ₃	20	$\mathrm{CH}_2\mathrm{Cl}_2$	$30 \min$	86
$Sc(OTf)_3$	20	MeCN	1 h	93
$Sc(OTf)_3$	10	MeCN	4 h	93
Sc(OTf) ₃	5	MeCN	22 h	83
La(OTf) ₃	10	MeCN	$45 \min$	86
Gd(OTf) ₃	10	MeCN	$15 \min$	93
Gd(OTf)3	5	MeCN	$15 \min$	90
$Gd(OTf)_3 \\$	5	$\mathrm{CH}_2\mathrm{Cl}_2$	$50 \min$	75
	$\begin{array}{c} & & \\ & & \\ & & \\ \hline \\ & & \\ & & \\ \hline \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & & \\ & &$	$\begin{array}{c c} & catalyst & catalyst \\ \hline \\ & solvent, rt \\ & solvent, rt \\ \hline \\ & solvent, rt \\ & solvent$	$\begin{array}{c c} catalyst \\ meO_2C \\ co_2Me \\ \hline \\ catalyst \\ mol \% \\ solvent, rt \\ \hline \\ solvent, rt \\ \hline \\ catalyst \\ mol \% \\ solvent \\ \hline \\ rec \\ re$	$\begin{array}{c c} \begin{array}{c} \begin{array}{c} catalyst \\ solvent, rt \\ \hline \\ solvent, rt \\ \hline \\ catalyst \\ \hline \\ meO_2C \\ \hline \\ cO_2Me \\ \hline \\ column{2}{c} \\ cO_2Me \\ \hline \\ column{2}{c} \\ cO_2Me \\ \hline \\ solvent, rt \\ \hline \\ column{2}{c} \\ cO_2Me \\ \hline \\ column{2}{c} \\ column{2}{c} \\ cO_2Me \\ \hline \\ column{2}{c} \\$

^{*a*} Reactions were performed in a given solvent (0.1 M) on a 0.25 mmol scale and were run to full conversion as judged by TLC analysis. ^{*b*} Conversion by ¹H NMR.

Scandium triflate readily catalyzes this transformation.^{12b,c} Albeit less efficiently, several main group and transition metals also catalyze this rearrangement. Remarkably, gadolinium triflate showed a striking rate acceleration as compared to scandium triflate. The use of 5 mol % of scandium triflate in acetonitrile required 22 h for full conversion of **1a** to **2a**, whereas the identical reaction with gadolinium triflate was completed in 15 min (entries 13 and 16). Ultimately, gadolinium triflate was selected as the optimum catalyst for

⁽⁵⁾ Verboom, W.; Reinhoudt, D. N.; Visser, R.; Harkema, S. J. Org. Chem. 1984, 49, 269–276.

^{(6) (}a) Nijhuis, W. H. N.; Verboom, W.; Reinhoudt, D. N.; Harkema, S. J. Am. Chem. Soc. 1987, 109, 3136-3138. (b) Nijhuis, W. H. N.; Verboom, W.; Reinhoudt, D. N. Synthesis 1987, 641-645. (c) Groenen, L. C.; Verboom, W.; Nijhuis, W. H. N.; Reinhoudt, D. N.; Van Hummel, G. J.; Feil, D. Tetrahedron 1988, 44, 4637-4644. (d) Nijhuis, W. H. N.; Verboom, W.; Abu El-Fadl, A.; Harkema, S.; Reinhoudt, D. N. J. Org. Chem. 1989, 54, 199-209. (e) Nijhuis, W. H. N.; Verboom, W.; Abu El-Fadl, A.; Van Hummel, G. J.; Reinhoudt, D. N. J. Org. Chem. 1989, 54, 209-216. (f) Nijhuis, W. H. N.; Leus, G. R. B.; Egberink, R. J. M.; Verboom, W.; Reinhoudt, D. N. Recl. Trav. Chim. Pays-Bas 1989, 108, 172-178. (g) Kelderman, E.; Noorlander-Bunt, H. G.; Van Eerden, J.; Verboom, W.; Reinhoudt, D. N. Recl. Trav. Chim. Pays-Bas 1991, 110, 115-123. (h) Tverdokhlebov, A. V.; Gorulya, A. P.; Tolmachev, A. A.; Kostyuk, A. N.; Chernega, A. N.; Rusanov, E. B. *Tetrahedron* **2006**, *62*, 9146–9152. (i) Rabong, C.; Hametner, C.; Mereiter, K.; Kartsev, V. G.; Jordis, U. Heterocycles 2008, 75, 799-838. (j) Ryabukhin, S. V.; Plaskon, A. S.; Volochnyuk, D. M.; Pipko, S. E.; Tolmachev, A. A. Synth. Commun. 2008, 38, 3032-3043.

this study. Acetonitrile was found to be superior to a number of other solvents such as toluene, ethyl acetate, tetrahydrofuran and methanol (results not shown). The use of acetonitrile in combination with a concentration of 0.1 M was found to provide the best results in terms of reaction rate and yield.

The scope of the reaction with regard to the acceptor moiety is summarized in Table 2. Different malonate esters participate in this reaction, giving rise to products in good yields after relatively short reaction times (entries 1-4). An



^{*a*} Reactions were performed at room temperature on a 1 mmol scale in MeCN (0.1 M) and were run to full conversion as judged by TLC analysis. ^{*b*} dr = 64:36, major diastereomer not determined. ^{*c*} No reaction.





^{*a*} Reactions were performed at room temperature on a 1 mmol scale in MeCN (0.1 M) and were run to full conversion as judged by TLC analysis. ^{*b*} Reaction was performed at 40 °C.

exception is the benzylester 1e, which rearranged to product 2e in lower yield, while requiring a longer reaction time (entry 5). The β -ketoester derived starting material 1f (*E*/*Z* ratio = 53:47) rearranged to product 2f, which was isolated as a 64:36 mixture of diastereomers (entry 6). Diketones 1g and 1h also rearranged efficiently to products 2g and 2h, respectively (entries 7 and 8). These substrates required slightly longer reaction times as compared to the corresponding malonate compounds. As anticipated, due to the limited propensity of the dinitrile substrate 1i to engage into chelating interactions with the catalyst, no rearrangement of this

compound was observed after 24 h under standard conditions (entry 9). Further heating of the reaction mixture at 40 $^{\circ}$ C for an additional 24 h gave only trace quantities of product **2i**.

The scope of this rearrangement was explored further by evaluating a number of different amine donors (Table 3). The piperidine derived compound 1j required a longer reaction time as compared to the pyrrolidine compound 1a (entry 1). The related morpholine compound 1k did not efficiently rearrange at room temperature but reaction at 40 °C for 12 h led to full consumption of 1k, with product 2k being isolated in 78% yield (entry 2). The corresponding seven- and eight-membered amine starting materials 11 and 1m rearranged readily to the corresponding products (entries 3 and 4). Presumably due to the enhanced hydride donor capabilities of benzylic C-H bonds, the tetrahydroisoquinoline 1n rapidly rearranged to 2n upon exposure to gadolinium triflate (entry 5). The 2-methylpyrrolidine-derived starting material 10 gave rise to a single regioisomer (20) upon rearrangement (entry 6). This finding likely reflects the increased hydride donor capability of a tertiary over a secondary C-H bond. Starting materials that incorporate noncyclic amines also rearranged to the expected products (entries 7 and 8). Although structurally closely related, 1p required heating at 40 °C for 24 h to reach full conversion to form 2p, while 1q completely rearranged into 2q after just 2 h at room temperature. This significant rate difference is likely due to unfavorable steric interactions in the course of the reaction. Only a single regioisomer of **2q** was isolated, which can be attributed to the superior hydride donor capability of benzylic over primary C-H bonds.

In preliminary experiments, we have found that the use of various chiral ligands in combination with scandium or gadolinium triflate does not lead to significant enantioenrichment in product **2a**. Gratifyingly, a chiral magnesium bisoxazoline catalyst is effective in catalyzing the rearrangement of **1a** to **2a** (Scheme 3).¹³ In this instance, product **2a** was isolated in 74% yield and 30% ee, illustrating for the first time that such a reaction is amendable to enantioselective catalysis.

In summary, we have demonstrated that intramolecular, redox neutral C-H bond functionalizations can be signifi-



cantly accelerated by gadolinium triflate catalysis, providing efficient access to polycyclic tetrahydroquinolines. Current efforts are focused on identifying more highly enantioselective variants of this and related reactions.

Acknowledgment. Is made to the donors of the American Chemical Society Petroleum Research Fund for support of this research. Financial support from Rutgers, The State University of New Jersey is gratefully acknowledged. We thank Dr. Jacob M. Janey (Merck & Co.) for a generous donation of 1,2-*cis*-aminoindanol. Dr. Tom Emge (Rutgers University) is acknowledged for crystallographic analysis. M.D.K. acknowledges fellowship support from the Aresty Research Center for Undergraduates.

Supporting Information Available: Experimental procedures and characterization data for all new compounds including the X-ray structure of **2p**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL802519R

⁽¹³⁾ For selected examples of chiral magnesium complexes in asymmetric catalysis, see: (a) Corey, E. J.; Ishihara, K. *Tetrahedron Lett.* **1992**, *33*, 6807–6810. (b) Sibi, M. P.; Ji, J.; Wu, J. H.; Guertler, S.; Porter, N. A. J. Am. Chem. Soc. **1996**, *118*, 9200–9201. (c) Evans, D. A.; Nelson, S. G. J. Am. Chem. Soc. **1996**, *119*, 6452–6453. (d) Kanemasa, S.; Kanai, T. J. Am. Chem. Soc. **2000**, *122*, 10710–10711. (e) Yoon, T. P.; MacMillan, D. W. C. J. Am. Chem. Soc. **2001**, *123*, 2911–2912. (f) Barnes, D. M.; Ji, J.; Fickes, M. G.; Fitzgerald, M. A.; King, S. A.; Morton, H. E.; Plagge, F. A.; Preskill, M.; Wagaw, S. H.; Wittenberger, S. J.; Zhang, J. J. Am. Chem. Soc. **2002**, *124*, 13097–13105. (g) Trost, B. M.; Hisaindee, S. Org. Lett. **2006**, *8*, 6003–6005. (h) Cutting, G. A.; Stainforth, N. E.; John, M. P.; Kociok-Koehn, G.; Willis, M. C. J. Am. Chem. Soc. **2007**, *129*, 10632–10633.