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Enantioselective Intramolecular Alkene Hydroaminations Catalyzed by Yttrium Complexes of Axially Chiral Bis(thiolate) Ligands

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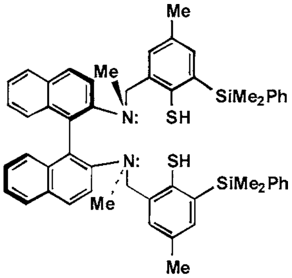
ABSTRACT



7c

A yttrium(III) complex derived from proligand 7c has been shown to be a superior catalyst for enantioselective intramolecular alkene hydroaminations that provide cyclic amines with ee's ranging from 69% to 89%.

The intramolecular hydroamination of alkenes remains a transformation of fundamental importance to small molecule synthesis.[1] Recently, nonmetallocene complexes of the group 3 metals have been shown to nicely complement their traditional metallocene counterparts as catalysts for this important reaction.[2a,b] Despite the increased scrutiny this reaction has attracted, there remains a paucity of reports describing effective enantioselective variations. Aside from the seminal contribution of Marks involving chiral menthyl and neomenthyl Cp complexes,[3a] only bis(oxazolinato),[3b] chiral bis(phenolate),[4] and amido complexes[5] have proven marginally useful in this context. We recently disclosed that chelating bis(thiophosphinic amidate) and bis(thioenamide) complexes of the group 3 metals (particularly Y) are unusually efficient catalysts for intramolecular alkene hydroamination that easily surpass those derived from the corresponding oxygen containing ligands in this capacity.[6] In this paper, we report that yttrium complexes derived from axially chiral bis(thiolate) ligands provide superior enantioselectivities as catalysts for this reaction.

A modular synthetic approach to the axially chiral dithiol proligands **7a**−**c** utilized in this study was devised as follows. Dilithiation of *p*-toluenethiol (**1**) (*n*-BuLi/TMEDA)[7] followed by silylation using the appropriate silyl chloride (**2a**−**c**) provided the corresponding 2-silyl derivatives **3a**−**c** in 76−82% isolated yield. Subsequent dilithiation of **3a**−**c** followed

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[1] (a) Pohilki, F.; Doye, S. *Chem. Soc. Rev.* **2003**, *32*, 104. (b) Muller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675.

[2] (a) Kim, Y. K.; Livinghouse, T.; Bercaw, J. E. *Tetrahedron Lett.* **2001**, *42*, 2933. (b) Kim, Y. K.; Livinghouse, T. *Angew. Chem., Int. Ed.* **2002**, *114*, 3797.

[3] (a) Giardello, M. A.; Conticello, V. P.; Brard, L.; Gagné, M. R.; Marks, T. J. *J. Am. Chem. Soc.* **1994**, *116*, 10241. (b) Hong, S.; Tian, S.; Metz, M.; Marks, T. J. *J. Am. Chem. Soc.* **2003**, *125*, 14768.

[4] (a) Gribkov, D. V.; Hultzsch, K. C.; Hampal, F. *Chem. Eur. J.* **2003**, *9*, 4796. (b) Gribkov, D. V.; Hultzsch, K. C. *J. Chem. Soc., Chem. Commun.* **2004**, 730. (c) O'Shaughnessy, P. N.; Knight, P. D.; Morton, C.; Gillespie, K. M.; Scott, P. *J. Chem. Soc., Chem. Commun.* **2003**, 1770.

[5] (a) O'Shaughnessy, P. N.; Scott, P. *Tetrahedron: Asymmetry* **2003**, 1979. (b) Collin, J.; Daran, J. C.; Schultz, E.; Trifonov, A. *J. Chem. Soc., Chem. Commun.* **2003**, 3048.

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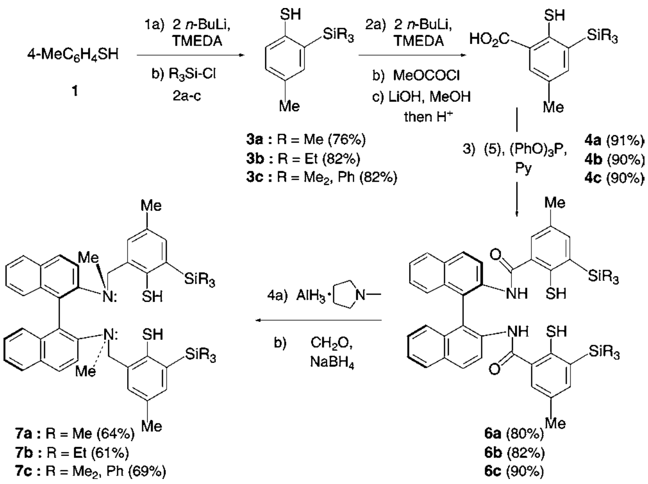
10.1021/ol050294z CCC: $30.25

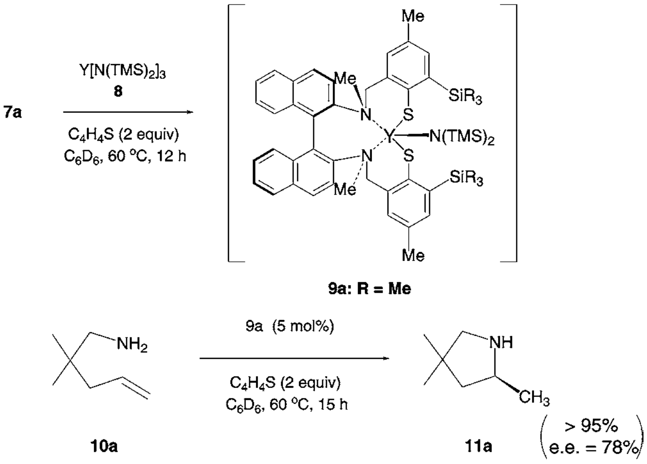
by addition to methyl chloroformate (5 equiv) and final hydrolysis [(a) LiOH, MeOH; (b) HCl_{aq}] furnished the carboxylic acids **4a**−**c** in ≥90% yield. Condensation of **4a**−**c** (2 equiv) with (*R*)-2,2′-diamino-1,1′-dinaphthyl (**5**) [$(PhO)_3P$, Py)[8] gave the bis(amides) **6a**−**c** (80−90%) which upon reduction (AlH_3·*N*-methylpyrrolidine)[9] and reductive methylation ($NaBH_4$, CH_2O) delivered the desired proligands **7a**−**c** (61−70%, Scheme 1).

Scheme 1



The preparation of both metallocene and nonmetallocene complexes of the group 3 metals has frequently been achieved via amine elimination using $Ln[N(SiMe_2H)_2]_3$·$(THF)_2$ by virtue of the enhanced *kinetic* basicity[10] of these amides relative to commercially available reagents such as $Y[N(TMS)_2]_3$ (**8**).[11] Invariably, the use of the former class of amides leads to the presence of THF as a complexing agent in the reaction medium. The possibility that auxiliary ligands [e.g., THF, 4-DMAP, $(n\text{-Bu})_3P$, Et_2S, and thiophene) might influence the rates of complexation of **8** and hydroamination by **9a** as well as alter the enantioselectivity of C−N bond formation was gauged by the addition of these ligands (2 equiv/equiv **8** and **7a**) prior to amine elimination. *Of these auxiliary ligands, the addition of THF led to both suppression of the rate of hydroamination and ee. In contrast, the presence of thiophene increased the efficiency of proligand metalation to generate the putative yttrium chelate, presently formulated as* ***9a****, but does not affect the rate of hydroamination or the observed ee.* In a typical set of experiments, complexation of **7a** with $Y[N(TMS)_2]_3$ (**8**) and subsequent cyclization of amine **10a** was conducted both in the presence and absence of thiophene. Whereas chelate formation between **7a** and **8** alone required 24 h at 120 °C (C_6D_6), the same reaction occurred in only 12 h at 60 °C when conducted in the presence of thiophene (2 equiv). In the latter case, the cyclization of **10a** took place in 15 h at 60 °C in the presence of 5 mol % of **9a** (>95% conversion)[12] to provide **11a** in 78% ee (Scheme 2).[13] *Significantly, the cyclization of* ***10a*** *at 30 °C [****9a*** *(5 mol %), C_4H_4S (10 mol %), 23 d] provided* ***11a*** *in 89% ee and >95% conversion.* These are, to our knowledge, the highest ee's obtained for the intramolecular hydroamination of **10a** achieved to date. The cyclization of several other aminoalkenes (e.g., **10b**−**e**) catalyzed by chelates generated from **7a**−**c** and **8** in the presence of thiophene were then conducted. These results are summarized in Table 1.[14] It is significant that asymmetric hydroaminations could readily be achieved on a preparative scale. In this context, cyclization of aminoalkenes **10a** and **10d** on a 3 mmol scale in the presence of the yttrium chelate

Scheme 2



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[8] Adolfson, H.; Moberg, C. *Tetrahedron: Asymmetry* **1995**, *6*, 2023.

[9] Martlett, E. M.; Park, W. S. *J. Org. Chem.* **1990**, *55*, 2968.

[10] Eppinger, J.; Spiegler, M.; Hieringer, W.; Herrmann, W. A.; Anwander, R. *J. Am. Chem. Soc.* **2000**, *122*, 3080.

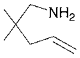
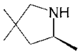
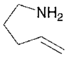
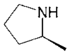
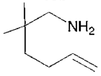
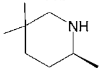
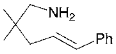
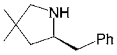
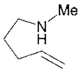
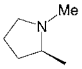
[11] Available from Gelest, Inc., 612 William Leigh Drive, Tullytown, PA 19007-6308.

[12] Conversions were based on ^1H NMR integration relative to *p*-xylene as the internal standard.

[13] Enantiomeric excesses and absolute configurations of the products were determined by ^1H NMR after conversion to the diastereomeric (−)-*O*-acetylmandelate[15] or Mosher's acid[16] derivatives following quantitative vacuum transfer from the catalyst.

[14] **General Procedure for Asymmetric Aminoalkene Hydroaminations.** In an argon-filled glovebox, $Y[N(TMS)_2]_3$ (**8**) (9.1 mg, 0.016 mmol), the appropriate bis(thiol) proligand **7** (0.016 mmol), C_6D_6 (0.7 mL), and thiophene (2.7 mg, 2.6 μL, 0.032 mmol) were introduced sequentially into a J. Young NMR tube equipped with Teflon screw cap. The homogeneous reaction mixture was maintained at 60 or 75 °C, respectively, in a constant temperature oil bath until ligand attachment was judged complete by the disappearance of the $Y[N(TMS)_2]_3$ resonance in the ^1H NMR spectrum, with concomitant production of $(TMS)_2NH$. To the resulting complex was added the appropriate aminoalkene **10** (0.32 mmol) and the reaction mixture was subsequently heated at 30 or 60 °C in an oil bath to achieve hydroamination. ^1H NMR spectroscopy using a pulse delay of 10 s to avoid signal saturation was employed to monitor reaction progress. The cyclic amines so produced were vacuum transferred along with the C_6D_6 at 10^{-3} Torr to a 5 mL round-bottomed flask containing (*R*)-(−)-O-acetylmandelic acid[15] [or (*R*)-(+)-2-methoxy-2-(trifluoromethyl)phenylacetic acid[16] in the case of **11e**] (0.32 mmol) at −78 °C. This transfer was quantitated by washing the NMR tube with a small amount of $CDCl_3$. The resulting mixture was stirred at 22 °C for 2 h, and the volatile components were removed in vacuo. The resulting diastereomeric salt was then dissolved in $CDCl_3$ and the enantiomeric excesses were determined by ^1H NMR spectroscopy. Procedures for representative asymmetric hydroaminations conducted on a preparative (3 mmol) scale are provided in the Supporting Information.

Table 1. Asymmetric Hydroaminations Catalyzed by Yttrium(III) Bis(thiolato) Complexes

	substrate	product[a]	7a (ee %) conditions[b]	7b (ee %) conditions[b]	7c (ee %) conditions[b]
a	 **10a**	 **11a**	(78%) 60 °C, 15 h	(83%) 60 °C, 12 h	(87%) 60 °C, 9 h
b	 **10b**	 **11b**	(69%) 60 °C, 10 h	(73%) 60 °C, 5 h	(81%) 60 °C, 8 h
c	 **10c**	 **11c**	(65%) 60 °C, 18 h	(75%) 60 °C, 10 h	(80%) 75 °C, 3 h
d	 **10d**	 **11d**	(73%) 60 °C, 8 h	(80%) 60 °C, 9 h	(82%) 60 °C, 3 h
e	 **10e**	 **11e**	(60%) 60 °C, 36 h	(63%) 60 °C, 38 h	(69%) 60 °C, 30 h

[a] Stereochemistry of the major enantiomer. [b] Conversion >95% (^{1}H NMR) based on *p*-xylene as the internal standard.

derived from **7c** followed by separation of the products from the catalyst by vacuum transfer and protonation (HCl–MeOH) furnished **11a** and **11d** as the corresponding hydrochloride salts in 100% and 98% yield, respectively.

The results presented in Table 1 reveal that an excellent correlation exists between the enantioselectivity observed for hydroamination and the size of the thiol-buttressing silyl substituent adjacent to the metal binding cavity. In addition, although the ee's obtained for the cyclization of the secondary aminoalkene **10e** are lower than those secured for the corresponding primary amine **10b**, the highest value (e.g., 69% achieved with the complex derived from **7c**) is superior to the best result obtained previously with this substrate.[16] As an additional example that reflects the temperature dependency of enantioselection, cyclization of **10d** in the presence of the yttrium chelate derived from **7c** (5 mol %, 30 °C, 3 d, >95% conversion) gave **11d** in 86% ee.

In conclusion, we have shown that axially chiral bis(thiolato) complexes of yttrium(III) are excellent catalysts for the asymmetric intramolecular hydroamination of representative aminoalkenes. These results, coupled with the high activities and diastereoselectivities previously observed for bis(thiophosphinic amidate) and bis(thioenamide) complexes in aminoalkene cyclizations,[6] provide compelling evidence that anionic sulfur-based motifs can serve as superior ligand environments for oxophilic early metals.

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

OL050294Z

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(16) Knight, P. D.; Munslow, I.; O'Shaughnessy, P. N.; Scott, P. *J. Chem. Soc., Chem. Commun.* **2004**, 894.