ORGANIC LETTERS

2010
Vol. 12, No. 14
3238−3241

In Situ Measurement of the Enantiomeric Excess of Alcohols and Amines under Asymmetric Reduction Reaction by ^{1}H NMR

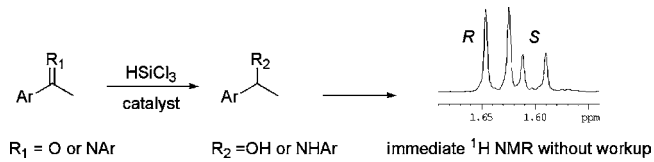
Xiaoxia Ye,[†,‡] Xinxiang Lei,[*,†,§] Zhenfei Chen,[†] Lixue Zhang,[†] and Anjiang Zhang[*,†,||]

College of Chemistry & Materials Engineering, Wenzhou University, Wenzhou 325035, People's Republic of China, Department of Chemistry, Wenzhou Medical College, Wenzhou 325035, People's Republic of China, Chengdu Institute of Biology, Chinese Academy of Sciences, Chengdu 610041, People's Republic of China, and Ningbo Institute of Material Technology and Engineering, Chinese Academy of Sciences, Ningbo 315201, People's Republic of China

anjiangzhang@gmail.com; xinxianglei@gmail.com

Received May 24, 2010

ABSTRACT



^{1}H NMR, in situ, determines the enantiomeric excess of reduced chiral alcohols or amines without adding any auxiliary and workup. The percent ee data determined by this method agree well with those given by HPLC. This approach may be potentially applicable to many asymmetric reductions.

Asymmetric catalysis of organic reactions to provide enantiomerically enriched products is a central goal in contemporary synthetic and pharmaceutical chemistry.[1] Understanding catalytic process development and enantiodifferentation scaleup helps to explore efficiently asymmetric catalysts.[2] However, enantioselective analysis often remains the bottleneck in these processes because it usually entails laborious and time-consuming chromatographic techniques. There have been recent advances in the development of methods potential for real time or in situ analysis of reaction conversion and enantiomeric purity, which include ingenious methods based on colorimetry,[3] UV absorption,[4] fluorescence spectroscopy,[5] circular dichroism,[6] and ^{2}H- or ^{13}C-isotopically labeled NMR analysis.[7] Ideally, the optimal method can be applied directly to analyze the percent ee of the

[†] Wenzhou University.
[‡] Wenzhou Medical College.
[§] Chengdu Institute of Biology.
[||] Ningbo Institute of Material Technology and Engineering.

(1) (a) Federsel, H. T. *Nat. Rev. Drug Discovery* **2005**, *4*, 285. (b) MacMillan, D. W. C. *Nature* **2008**, *455*, 304. (c) Breuer, M.; Ditrich, K.; Habicher, T.; Hauer, B.; Stúrmer, M. K. R.; Zelinski, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 788.

(2) (a) Blackmond, D. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 4302. (b) Ma, S.; Busacca, C. A.; Frandrick, K. R.; Bartholomeyzik, T.; Haddad, N.; Shen, S.; Lee, H.; Saha, A.; Yee, N.; Senanayake, C.; Grinberg, N. *Org. Lett.* DOI: 10.1021/ol100734t. Published Online: May 20, 2010.

(3) (a) Kubo, Y.; Maeda, S.; Tokita, S.; Kubo, M. *Nature* **1996**, *382*, 522. (b) Eelkema, R.; van Delden, R. A.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 5013.

(4) Reetz, M. T.; Zonta, A.; Schimossek, K.; Liebeton, K.; Jaeger, K. E. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2830.

(5) (a) Zhao, J.; Fyles, T. M.; James, T. D. *Angew. Chem., Int. Ed.* **2004**, *43*, 3461. (b) Tumambac, G. E.; Wolf, C. *Org. Lett.* **2005**, *7*, 4045. (c) Liu, H.-L.; Hou, X.-L.; Pu, L. *Angew. Chem., Int. Ed.* **2009**, *48*, 382. (d) Liu, H.-L.; Peng, Q.; Wu, Y. D.; Chen, D.; Hou, X. L.; Sabat, M.; Pu, L. *Angew. Chem., Int. Ed.* **2010**, *49*, 602.

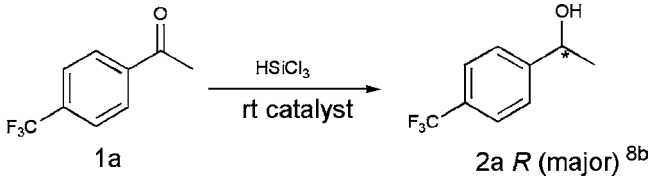
(6) (a) Ding, K.; Shii, A.; Mikami, K. *Angew. Chem., Int. Ed.* **1999**, *38*, 497. (b) Arai, T.; Watanade, M.; Fujiwara, A.; Yokoyama, N.; Yanagisawa, A. *Angew. Chem., Int. Ed.* **2006**, *45*, 5978.

10.1021/ol1011899
Published on Web 06/14/2010

product of an asymmetric reaction without any auxiliary. Here we wish to report, by ^{1}H NMR, the first direct observation of well-separated signals from a pair of enantiomers during an asymmetric reaction. Our in situ percent ee determination results, which were done without the necessity of any workup or further purification, agree well with traditional HPLC analysis.

Quite recently several groups reported the organocatalytic enantioselective reduction of ketones and imines with trichlorosilane ($HSiCl_3$).[8] Although they proposed different mechanisms, detailed structural and mechanistic studies remain to be further carried out. As we began to explore the hydrosilylation of ketones, with the goal of capturing the intermediates, we selected the catalyst **C** with medium enantioselectivity in hopes of capturing higher concentrations of the two proposed intermediates. However, we were disappointed that the NMR sample of the crude reaction product (Scheme 1) showed no relevant information in the

Scheme 1. Asymmetric Reduction of Ketone **1a**



^{29}Si NMR, only a broad peak. Unexpectedly, we discovered that the ^{1}H NMR of the reaction mixtures exhibited two well-separated doublets at δ 1.6−1.7, where the methyl signal of the (*R* or *S*)-1-[4-(trifluoromethyl)phenyl]ethanol (**2a**) was usually considered unable to resolve and split into two doublets (Figure 1).[9] After the reaction was quenched,[10] the two well-separated doublets at δ 1.6−1.7 disappeared and displayed two peaks at δ 1.5 (Figure 1). We monitored the

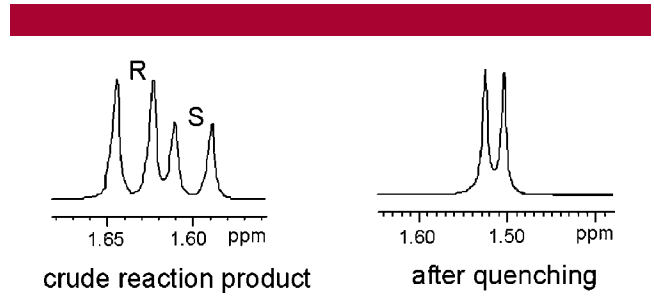


Figure 1. ^{1}H NMR of the methyl signal of **2a** from the crude reaction product in $CDCl_3$.

singlets every 2 h when the reaction occurred. We were delighted to discover that the relative intensities of the two different sets of integrals kept increasing as the reaction progressed. To observe whether the relative intensities of two different sets of doublets will change, a catalyst with good enantioselectivity was chosen and a series of data have been recorded as shown in Table 1.

Table 1. Reaction Progress Monitored by ^{1}H NMR (Catalysis **A**)

entry	time (h)	yield (%)	ee (%)	entry	time (h)	yield (%)	ee (%)
1	0.25	7.1	44	8	14	42	64
2	2	13	49	9	16	45	66
3	4	18	57	10	18	49	66
4	6	25	63	11	20	51	67
5	8	30	63	12	22	53	68
6	10	35	63	13	24	54	68
7	12	39	64				

Subsequently, we observed that comparison of the relative intensities of the two different sets of integrals could be used to accurately determine the percent ee of **2a** by ^{1}H NMR.

This method has been applied to examine five chiral Lewis base catalysts **A**−**E** (developed by Sun, see ref 8f) with 0−70% ee (Figure 2).[11] We confirmed that in situ ee determination by ^{1}H NMR corresponds well with the values obtained from chiral HPLC based on workup, isolation, and purification and is time-consuming (Table 2). As seen in Table 2, the direct ^{1}H NMR percent ee measurement provides a new, simple, and accurate method: average error, ±2.6% ee, maximum error, 4% ee. To investigate if the method retains good NMR resolution of methyl proton signals of different chiral alcohols, we selected **A** as catalyst to reduce a broad range of aromatic ketones (**1b**−**f**) with $HSiCl_3$. Delightfully, the crude reaction products displayed particularly good self-recognition, and the results corresponded well with ee values measured by more traditional and slower HPLC analysis, indicating quantitative measurements of

(7) (a) Evans, M. A.; Morken, J. P. *J. Am. Chem. Soc.* **2002**, *124*, 9020. (b) Jackman, H.; Marsden, S. P.; Shapland, P.; Barrett, S. *Org. Lett.* **2007**, *9*, 5179.

(8) (a) Wang, Z.; Wei, S.; Wang, C.; Sun, J. *Tetrahedron: Asymmetry* **2007**, *18*, 705. (b) Zhou, L.; Wang, Z.; Wei, S.; Sun, J. *Chem. Commun.* **2007**, 2977. (c) Pei, D.; Wang, Z.; Wei, S.; Zhang, Y.; Sun, J. *Org. Lett.* **2006**, *8*, 5913. (d) Wang, Z.; Cheng, M.; Wu, P.; Wei, S.; Sun, J. *Org. Lett.* **2006**, *8*, 3045. (e) Wang, Z.; Ye, X.; Wei, S.; Wu, P.; Zhang, A.; Sun, J. *Org. Lett.* **2006**, *8*, 999. (f) Sun, J.; Wang, Z. P. R. Chinese Patent 200510125694.2, 2006. (g) Malkov, A. V.; Figlus, M.; Stončius, S.; Kočý, P. *J. Org. Chem.* **2007**, *72*, 1315. (h) Malkov, A. V.; Liddon, A.; Ramírez-López, P.; Bendová, L.; Haigh, D.; Kočovský, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 1432. (i) Onomura, O.; Kouchi, Y.; Iwasaki, F.; Matsumura, Y. *Tetrahedron Lett.* **2006**, *47*, 3751. (j) Matsumura, Y.; Ogura, K.; Kouchi, Y.; Iwasaki, F.; Onomura, O. *Org. Lett.* **2006**, *8*, 3789. (k) Zheng, H.; Deng, J.; Lin, W.; Zhang, X. *Tetrahedron Lett.* **2007**, *48*, 7934. (l) Wang, C.; Wu, X. J.; Zhou, L.; Sun, J. *Chem.—Eur. J.* **2008**, *14*, 8789. (m) Malkov, A. V.; Vranková, K.; Stončius, S.; Kočovský, P. *J. Org. Chem.* **2009**, *74*, 5839.

(9) Trichlorosilane was added to a stirred solution of ketone (**1a**) and catalyst in $CDCl_3$, and the mixture was quickly transferred into a 5 mm NMR tube and ^{1}H NMR expeditiously recorded. A simple homonuclear decoupling experiment has been done to show that the two doublet resonances arise from the methyl group of **2a** split by the *R* proton and *S* proton on the adjacent carbon, respectively (see the Supporting Information).

(10) The reaction was quenched with a saturated aqueous solution of $NaHCO_3$. The silicon dioxide was removed by centrifugation of the reaction product.

(11) Trichlorosilane was added to a stirred solution of ketone and catalyst in $CDCl_3$ (or DCM-d_2). The mixture was stirred at room temperature for 16 h and then transferred, without the necessity of any workup or further purification, into a 5 mm NMR tube and ^{1}H NMR promptly recorded.

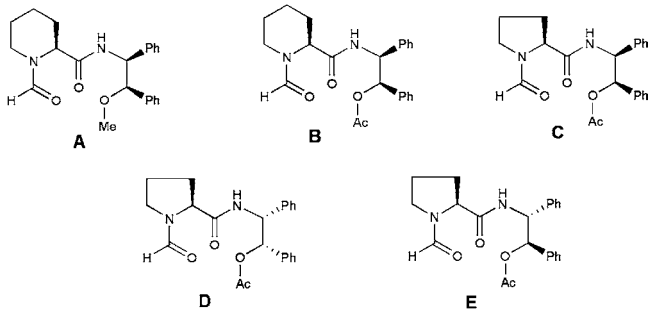


Figure 2. Chemical structures of catalyst **A**−**E**.

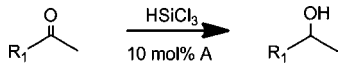
Table 2. NMR and HPLC ee (%) for Asymmetric Reduction of Ketone **1a** with Catalysts **A**−**E**[a]

entry	catalyst	NMR[b]	HPLC[c]	error
1	**A**	67	66	1
2	**B**	59	57	2
3	**C**	34	37	3
4	**D**	39	35	4
5[d]	**E**	7	4	3

[a] Unless specified otherwise, reactions were carried out with 10 mol % of catalysts and 2.0 equiv of $HSiCl_3$ on a 0.2 mmol scale in 1.0 mL of $CDCl_3$ for 16 h at room temperature. [b] The mixture was transferred into a 5 mm NMR tube and ee was directly recorded by ^1H NMR at 300 MHz. [c] Isolated product ee values were determined with use of a chiral OJ-H column. [d] The reaction was carried out in DCM-d_2.

percent ee within a precision of 3%, average error, ±1.4% ee (Table 3).

Table 3. NMR and HPLC ee (%) for Asymmetric Reduction of Ketones **1b**−**1f** with Catalyst **A**[a]



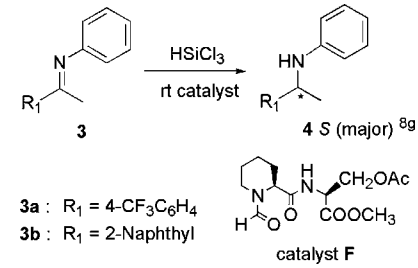
entry	ketone	R_1	NMR[b]	HPLC[c]	error
1	**1b**	4-$NO_2C_6H_4$	83 (*R*)	82 (*R*)	1
2	**1c**	4-ClC_6H_4	79 (*R*)	80 (*R*)	1
3	**1d**	4-BrC_6H_4	81 (*R*)	80 (*R*)	1
4	**1e**	3-BrC_6H_4	80 (*R*)	77 (*R*)	3
5	**1f**	2-naphthyl	73 (*R*)	72 (*R*)	1

[a] Unless specified otherwise, reactions were carried out with 10 mol % of catalysts and 2.0 equiv of $HSiCl_3$ on a 0.2 mmol scale in 1.0 mL of $CDCl_3$ for 16 h at −20 °C. [b] The mixture was transferred into a 5 mm NMR tube and ee was directly recorded by ^1H NMR at 300 MHz. [c] Isolated product ee values were determined with use of a chiral OJ-H or OD-H column.

The results presented above show that the in situ percent ee determination not only can be used for high-throughput screening of chiral Lewis bases which catalyze the reduction of ketones with $HSiCl_3$, but also immediately detects the substrate scope of the catalyst, which was generally laborious because HPLC techniques should be established by prepared racemic substrates prior to analysis.

To probe the generality of the method, ^1H NMR analysis was conducted to explore the reduction of ketimines with $HSiCl_3$ (Scheme 2). Perfectly, the methyl resonance of **4** from

Scheme 2. Asymmetric Reduction of Ketimines **3**



the crude reaction product can also be well resolved, showing an especially clear part of the ^1H NMR spectrum (two distinct resonances) in Figure 3. The integration of the resonances

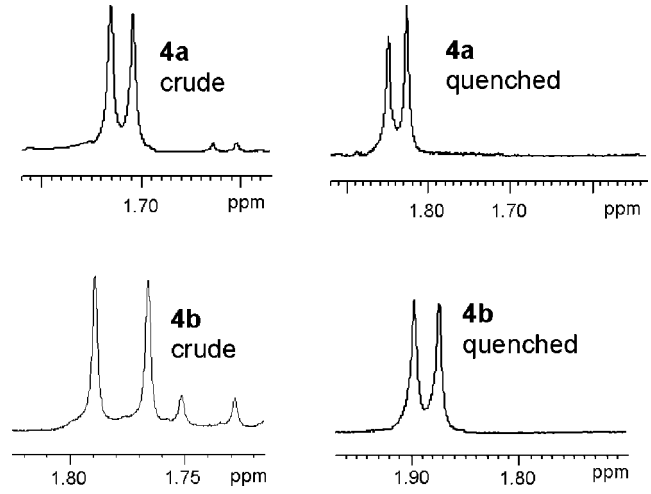


Figure 3. ^1H NMR of the methyl signal of **4** from the crude reaction product (**4a** in DCM-d_2, **4b** in $CDCl_3$).

can yield percent ee, for example, the ratio of the peaks of **4b** revealing 54% ee, which was in good agreement with the 60% ee determined by HPLC. This demonstrates that the method can be applicable to the asymmetric reduction of ketimines with $HSiCl_3$ as well.

The mechanism that has been explored is that the two proposed intermediates were formed during the asymmetric reaction (Figure 4),[8b] in which catalyst **A** functioned as a chiral solvating agent (CSA) that could resolve the enantiomeric signals directly, and a small amount of the CSA was enough for chiral discrimination in NMR.[12] When the reaction was quenched with a saturated aqueous solution of $NaHCO_3$, *R*- and *S*-alcohols were formed from the two

(12) Ema, T.; Tanida, D.; Sakai, T. *J. Am. Chem. Soc.* **2007**, *129*, 10591.

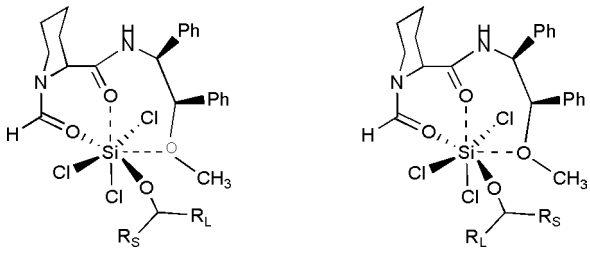


Figure 4. Chemical structures of the two proposed intermediates.

intermediates by hydrolysis. This is a very important phenomenon that substoichiometric amounts of organic activators displayed not only as catalysts, but also as chiral solvating agents (CSAs) in the enantioselective reduction.

A similar phenomenon where chiral catalysts that coordinate with enantiomers and $HSiCl_3$ possess self-discriminated properties in an asymmetric environment was also observed, which was supported by experimental data. The racemate (**2a**, 1 mmol),[13] excess $HSiCl_3$ (2 mmol), and catalyst **D** (0.1 mmol) were directly mixed in a 5 mm NMR tube. Two distinct doublets at δ 1.6−1.7, as shown in Figure 1, have been detected although the phenomenon was observed after 48 h, which appeared much later than that in the in situ reaction.[14]

In conclusion, to our knowledge, this is the first-reported example of the in situ determination of percent ee for the reaction complexes without any additive by ^{1}H NMR. The new method described here is promptly and conveniently performed since it requires no labor-intensive steps, and the large scale for the asymmetric reduction of compounds warrants its high potential as protocol for determining the enantiomeric excess. Notably, a reaction analysis was done in situ without quenching the catalytic reactions, which will intrigue investigators to discover self-enantiodiscrimination under asymmetric catalysis.

Acknowledgment. The work was supported in part by grants from NSFC 30900129, ZJNSFC Y2080331, Y406386, ZJST 2009C34014, and WZST H20080052.

Supporting Information Available: Experimental procedures along with copies of spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

OL1011899

(13) The racemate (**2a**) was prepared after **1a** was reduced by $NaBH_4$.

(14) We mixed the racemate (**2a**) with excess $HSiCl_3$, but the methyl signal of **2a** just showed a doublet. This means that no homo- or heterodimeric aggregates are formed.