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Isotopically Chiral Probes for in Situ High-Throughput Asymmetric Reaction Analysis

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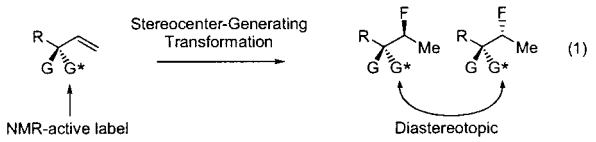
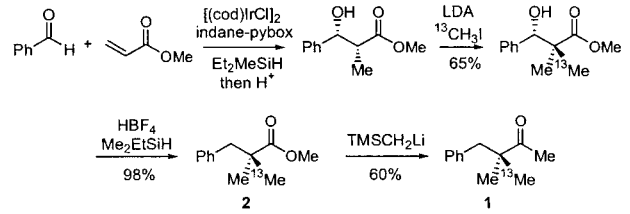
Recent advances in high-throughput reaction analysis have increased the rapidity with which new catalytic transformations can be developed.[1] Toward this end impressive new technologies involving doped liquid crystals,[2] fluorescence imaging of reaction microarrays,[3] mass spectrometry with pseudoenantiomers,[4] infrared thermography,[5] kinetic resolution/mass spectrometry,[6] circular dichroism,[7] enzymatic techniques,[8] antibody detection,[9] and arrayed chiral capillary electrophoresis[10] have improved upon the throughput that chiral GC and HPLC offer to asymmetric reaction analysis. In this research report, we describe an NMR-based complement to the above techniques that is readily accessible, high-throughput, and provides in situ enantioselection and conversion information in a simple single operation. On the basis of the fact that enantiotopic groups are rendered diastereotopic and therefore anisochronous when a neighboring prochiral center undergoes a chirality-generating reaction, suitably designed isotopically chiral materials can be used to probe enantioselection in asymmetric transformations.[11] As shown in eq 1, if an enantioenriched isotopically chiral substrate is used and kinetic isotope effects are minimal, then the ratio of isotope at each of the diastereotopic positions directly reflects enantioselectivity of the asymmetric transformation. Simple integration of the isotope resonances for the starting material and product diastereomers will suffice for determination of reaction conversion and enantiomeric excess.

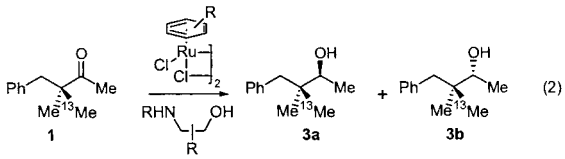


Our initial studies have employed ^{13}C NMR spectroscopy due to its high sensitivity and due to the low natural abundance of the NMR-active isotope. In addition, carbon NMR offers narrow line widths and high chemical shift dispersion, thereby facilitating analysis. We have targeted **1** (Scheme 1) as one prototypical substrate for reaction analysis since it contains the requisite enantiotopic groups attached to a configurationally stable stereocenter and since its low volatility eases experimental manipulation. In addition, **1** is readily available in gram-scale quantity through the short synthesis sequence outlined in Scheme 1 and with ^{13}C-labeled methyl iodide used as the source of NMR-active label. Preparation of **1** through an enantioselective reductive aldol reaction,[12] Fráter alkylation[13] and ionic hydrogenation provided the isotopically chiral ester **2** in 69% enantiomeric excess.

Scheme 1



Compound **2** was directly converted to ketone **1** by addition of $TMSCH_2Li$.[14]



To explore the utility of the NMR assay, we have examined the amino alcohol−ruthenium arene-catalyzed asymmetric transfer hydrogenation[15] of **1** to give diastereomers **3a** and **3b** (eq 2). While transfer reduction of aromatic ketones is highly selective with simple amino alcohol-derived catalysts, more complex ligand structures have been required for highly selective reduction of dialkyl ketones.[16] Along these lines, we surveyed an array of 30 metal−ligand combinations with each experiment composed of 10 mg of substrate **1** in 0.5 mL of degassed nondeuterated 2-propanol, 2 mol % of a 2:1 ligand:metal complex, and 10 mol % KOH. After shimming on the first sample, subsequent reactions were analyzed by single-pulse, unlocked, unshimmed, nonspinning ^{13}C NMR at timepoints of 2.5, 4.5, 8.5 h, and 5 days and required about 15 s per datapoint. By employing inverse gated ^{1}H decoupling and a single FT pulse, meaningful integration is not complicated by differential $^{1}H-^{13}C$ nOe enhancements or differential relaxation times for the diastereomeric reaction products. An example of the quality of data that is obtained by the assay is shown in Figure 1. Notably, *reaction analysis was done in situ without quenching the catalytic reactions*.

Table 1 shows the conversion and enantioselection data at the 5-day timepoint for all samples in the library assay. While erosion of enantioselection has been noted over prolonged reaction periods in some transfer hydrogenation experiments, we observed only small variation in enantioselection for all samples from 2.5 h to 5 days. To ascertain the accuracy with which the NMR assay can be used to determine enantioselection, a number of the reaction samples were analyzed by chiral GC chromatography. The comparison of GC- and NMR-determined isomer ratios is depicted in Table 2 and indicates an average error of about ±3 in the %ee value. Notably,

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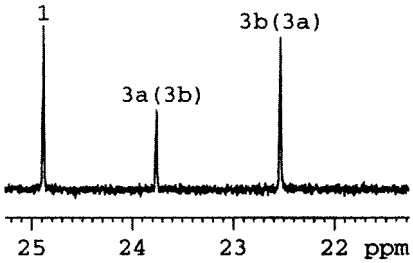
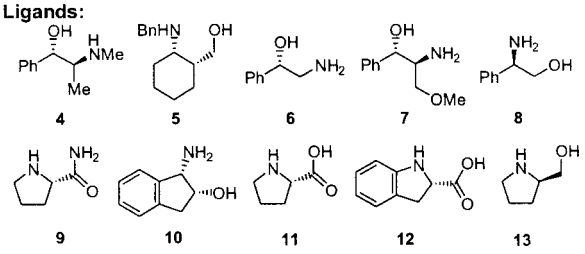


Figure 1. Single-pulse unlocked, unshimmed, nonspinning ^{13}C NMR of reaction in eq 2 with catalyst **A-13** at 5 days.

Table 1. Arrayed Evaluation Using Isotopically Chiral Probe **1**[a]

Ligands:



Metals:

A [(benzene)$RuCl_2$]$_2$ **B** [(*p*-cymene)$RuCl_2$]$_2$ **C** [(Me_6-benzene)$RuCl_2$]$_2$

	4	5	6	7	8	9	10	11	12	13
A %conv	100	14	97	100	100	100	100	28	8	62
%ee	11	22	20	27	−48	−12	8	−7	−15	−50
B	100	15	100	100	100	93	96	46	17	26
	20	7	16	19	−37	1	9	−2	−4	0
C	96	50	98	96	98	55	87	36	80	66
	48	−1	70	76	−81	−3	−75	1	−7	−17

[a] Note: %ee corrected for enantiomeric excess of probe substrate.

Table 2. Comparison of GC- and NMR-Determined %ee[a]

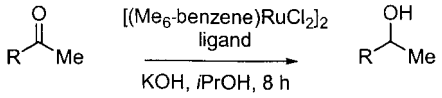
precatalyst	% ee by ^{13}C NMR[b]	% ee by chiral GC
A8	−47	−44
A13	−48	−44
B7	13	16
B8	−38	−38
B12	−1	−3
C6	70	66
C7	73	70
C8	−79	−78
C10	−71	−66
C13	−20	−18

[a] Determined after 20 days of reaction. [b] Using 8 FT pulses and a 25 s relaxation delay.

in addition to ee analysis one can also gain insight into reaction rates and catalyst lifetime by integrating product relative to starting material.

As expected in the reaction assay, the highest levels of enantioselection were achieved with hexamethylbenzene−ruthenium complexes, although it is surprising, in light of prior art, that simple primary amino alcohols such as phenyl glycinol (**8**) provided product with highest levels of enantiocontrol.[17] A brief examination of the utility of ligands **6** and **8** with acetophenone and 3-methyl-2-butanone (Table 3) indicates that 1-substituted ethanolamines may be a promising starting point for development of simple catalysts for reduction of dialkyl ketones.

Table 3. Transfer Hydrogenation Catalyzed by **C-6** and **C-8**[a]



entry	ketone	ligand	%conv	%ee	config.
1	acetophenone	**(*S*)-6**	96	64	*S*
2	acetophenone	**(*R*)-8**	97	22	*R*
3	3-methyl-2-butanone	**(*S*)-6**	92	30	*R*
4	3-methyl-2-butanone	**(*R*)-8**	98	55	*S*

[a] %Conv and %ee determined by GC analysis on β-dex 120 column.

In conclusion, we have reported a simple method for high-throughput asymmetric reaction analysis that uses standard instrumentation. We expect that this approach may be useful for the study of a number of asymmetric transformations since **2** may be readily converted to a range of functionalized probe substrates.

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Supporting Information Available: Characterization data and experimental procedures (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) For a comprehensive recent review, see: Dahmen, S.; Brase, S. *Synthesis* **2001**, 1431.
(2) van Delden, R. A.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2001**, *40*, 3198.
(3) Korbel, G. A.; Lalic, G.; Shair, M. D. *J. Am. Chem. Soc.* **2001**, *123*, 361.
(4) Reetz, M. T.; Becker, M. H.; Klein, H.-W.; Stockigt, D. *Angew. Chem., Int. Ed.* **1999**, *38*, 1758.
(5) Reetz, M. T.; Becker, M. H.; Kuhling, K. M.; Holzwarth, A. *Angew. Chem., Int. Ed.* **1998**, *37*, 2647.
(6) Guo, J.; Wu, J.; Siuzdak, G.; Finn, M. G. *Angew. Chem., Int.* **1999**, *38*, 1755.
(7) Ding, K.; Ishii, A.; Mikami, K. *Angew. Chem., Int. Ed.* **1999**, *38*, 497.
(8) Abato, P.; Seto, C. T. *J. Am. Chem. Soc.* **2001**, *123*, 9206.
(9) Taran, F.; Gauchet, C.; Mohar, B.; Meunier, S.; Valleix, A.; Renard, P. Y.; Cremion, C.; Grassi, J.; Wagner, A.; Mioskowski, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 124.
(10) Reetz, M. T.; Kuhling, K. M.; Deege, A.; Hinrichs, H.; Belder, D. *Angew. Chem., Int. Ed.* **2000**, *39*, 3891.
(11) For a conceptually related example of the use of isotopically chiral compounds to study the absolute facial selectivity of olefin insertion reactions, see: Gilchrist, J. H.; Bercaw, J. E. *J. Am. Chem. Soc.* **1996**, *118*, 12021.
(12) Taylor, S. J.; Duffey, M. O.; Morken, J. P. *J. Am. Chem. Soc.* **2000**, *122*, 4528. Zhao, C.-X.; Duffey, M. O.; Taylor, S. J.; Morken, J. P. *Org. Lett.* **2001**, *3*, 1829.
(13) Fráter, G.; Müller, U.; Günther, W. *Tetrahedron* **1984**, *40*, 1269.
(14) Mulzer, J.; Mantoulidis, A.; Ohler, E. *J. Org. Chem.* **2000**, *65*, 7456.
(15) For reviews, see: Noyori, R.; Hashiguchi, S. *Acc. Chem. Res.* **1997**, *30*, 30. Palmer, M. J.; Wills, M. *Tetrahedron: Asymmetry* **1999**, *10*, 2045.
(16) Phosphine−oxazolines: Arikawa, Y.; Ueoka, M.; Matoba, K.; Nishibayashi, Y.; Hidai, M.; Uemura, S. *J. Organomet. Chem.* **1999**, *572*, 163. Bis(oxazolinyl)phosphine: Jiang, Y.; Jiang, Q.; Zhu, G.; Zhang, X. *Tetrahedron Lett.* **1997**, *38*, 215.
(17) Takehara, J.; Hashiguchi, S.; Fujii, A.; Inoue, S. Ikariya, T.; Noyori, R. *J. Chem. Soc., Chem. Commun.* **1996**, 233.

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