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A Rapid ^{1}H NMR Assay for Enantiomeric Excess of α-Substituted Aldehydes

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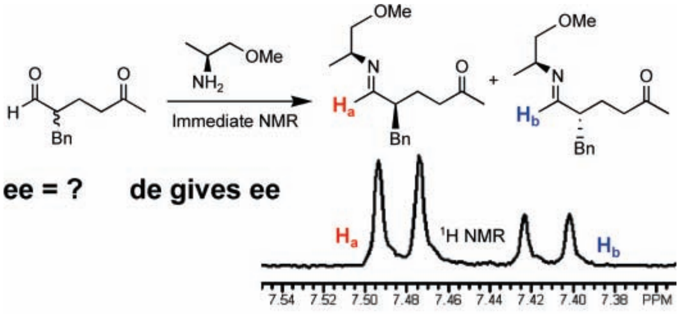
ABSTRACT



In situ derivatization of a variety of α-substituted aldehydes via reaction with chiral amines allows convenient and efficient determination of enantiomeric excess. ^{1}H NMR analysis of the imine diastereomer ratio can be conducted immediately after the aldehyde and amine have been mixed. The results correlate well with ee values determined by more traditional (and slower) methods. This approach may be broadly applicable to α-substituted aldehydes.

The development of asymmetric methods for synthesis of organic molecules is a central goal in contemporary chemistry. Discovery and optimization of such methods require efficient techniques for determining the enantiomeric excess (ee) of reaction products.[1] Ideally, the analytical method can be applied directly to the product of an asymmetric reaction. Purification or derivatization of the initial reaction product, although often necessary, is undesirable because such processes are time-consuming and can inadvertently obscure the ee of the reaction under consideration.

We are interested in the Michael addition of aldehydes to enones. The simple examples discussed here give rise to products that contain a single new chiral center, but analogous reactions of more elaborate substrates could generate up to three adjacent stereocenters. Melchiorre and Jørgensen have achieved significant enantioselectivity in aldehyde Michael additions carried out with chiral pyrrolidine catalysts (ee = 50−82%).[2] As we began to explore this reaction, with the goal of improving enantioselectivity, we recognized a need for a new approach to assessing the ee of the δ-keto-aldehyde products. Direct analysis of α-substituted aldehydes by chiral stationary phase GC can be problematic because the products can racemize at elevated temperatures.[3] This lability has led others to analyze aldehyde derivatives, such as acetals, alcohols, or carboxylic acids, with enhanced stability.[4] Such indirect methods, however, are time-consuming.

We report here that ee analysis of α-substituted aldehydes resulting from chiral pyrrolidine-catalyzed Michael additions (Scheme 1)[2] can be carried out expeditiously by simple addition of a commercially available chiral primary amine, in enantiomerically pure form, to an NMR sample of the "crude" reaction product (Scheme 2).[5] Imine protons from

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[1] For recent reviews on enantiomeric excess measurements, see: (a) Tsukamoto, M.; Kagan, H. B. *Adv. Synth. Catal.* **2002**, *344*, 453. (b) Reetz, M. T. *Angew. Chem., Int. Ed.* **2001**, *40*, 284. (c) Reetz, M. T. *Angew. Chem., Int. Ed.* **2002**, *41*, 1335.

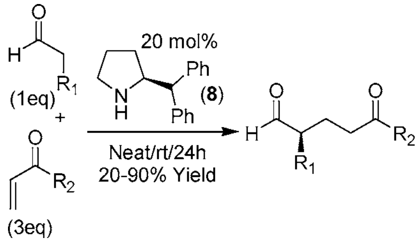
[2] Melchiorre, P.; Jørgensen, K. A. *J. Org. Chem.* **2003**, *68*, 4151.

[3] For examples of substrates epimerization at GC conditions, see: Trapp, O.; Schurig, V. *Chem. Eur. J.* **2001**, *7*, 1495.

[4] For examples, see: (a) Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 6798. (b) Pidathala, C.; Hoang, L.; Vignola, N.; List, B. *Angew. Chem., Int. Ed.* **2003**, *42*, 2785. (c) Hechavarria Fonseca, M. T.; List, B. *Angew. Chem., Ind. Ed.* **2004**, *43*, 3958. (d) List, B. *J. Am. Chem. Soc.* **2002**, *124*, 5656. (e) Betancort, J. M.; Barbas, C. F., III. *Org. Lett.* **2001**, *3*, 3737. (f) Cürdova, A.; Sunden, H.; Engqvist, M.; Ibrahem, I.; Casas, J. *J. Am. Chem. Soc.* **2004**, *126*, 8914. (g) Bolm, C.; Rantanen, I. S.; Zani, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 1758. (h) Marigo, M.; Wabnitz, T. C.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem., Int Ed.* **2005**, *44*, 794.

10.1021/ol051174u CCC: $30.25

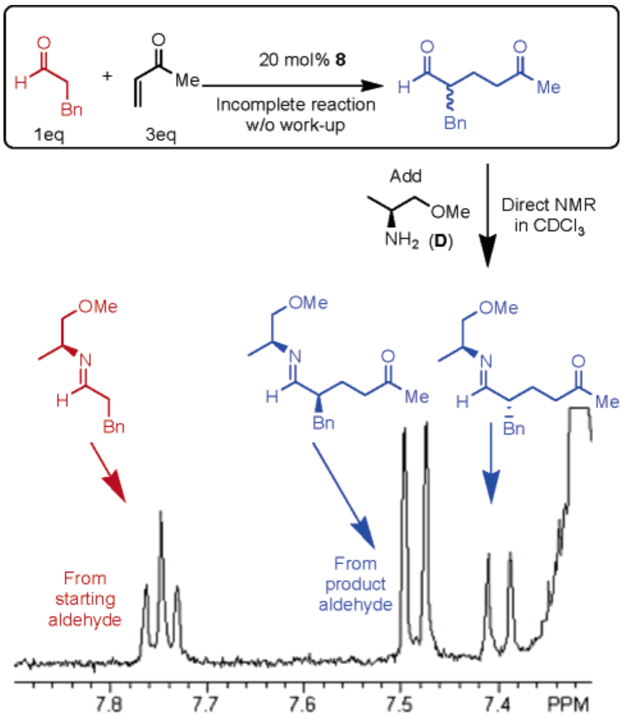
Scheme 1



	R_1	R_2
1	Et	Me
2	*n*-Pr	Me
3	*i*-Pr	Me
4	*n*-Hex	Me
5	Bn	Me
6	Et	Et
7	Bn	Et

the two enantiomers of the α-substituted δ-keto-aldehyde products are well resolved, and both are resolved from the imine derived from the starting aldehyde (Scheme 2). The evidence presented below was obtained mostly with aldehyde samples that were purified by column chromatography prior to analysis, so that our in situ ee determination method could be compared with more traditional techniques based on preparation, isolation, and chromatographic analysis of configurationally stable derivatives. However, the results of the NMR method do not change if the purification step is omitted. Once the NMR sample of the aldehyde has been prepared, analysis can be completed within 5 min.

Scheme 2



Our initial studies focused on the Michael addition of hydrocinnamaldehyde to methyl vinyl ketone to form α-substituted aldehyde **5**. Among the eight commercially available chiral amines examined (Figure 1), **A**/**A′**, **D**, and **E** formed diastereomeric imines that displayed particularly good NMR resolution of imine proton signals (Figure 2).

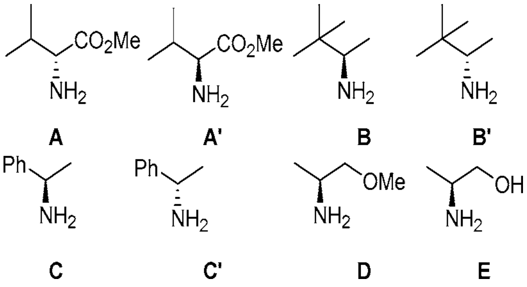


Figure 1. Chiral primary amines screened.

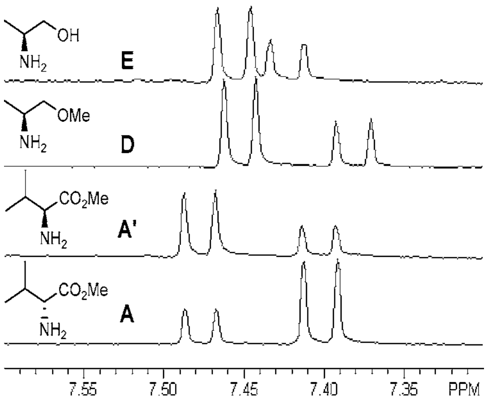


Figure 2. ^1H NMR of imine protons from **5** and four amines.

Apparently just one imine configuration is formed in each case; the imine configuration is assigned as *E* (across the C=N bond) on the basis of precedent.[6] Under the Michael addition conditions we used, the NMR method indicated an imine diastereomeric excess (de) of 33−38%, suggesting that the original aldehyde **5** was formed with 33−38% ee (the value varied slightly with the amine employed). The absolute configuration of the major enantiomer was assigned following Melchiorre and Jørgensen.[2] Measurements of de using enantiomeric amines **A′** or **A** gave comparable results, which shows that there is no kinetic resolution in the imine formation process. Complete conversion of the α-substituted aldehyde to imine is not necessary in order to obtain accurate ee values.

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(5) For an early review on NMR-based enantiomeric excess measurement, see: Parker, D. *Chem. Rev.* **1991**, *91*, 1441. For recent examples, see: (a) Reetz, M. T.; Eipper, A.; Tielmann, P.; Mynott, R. *Adv. Synth. Catal* **2002**, *344*, 1008. (b) Bohm, A.; Seebach, D. *Helv. Chim. Acta* **2000**, *83*, 3262. (c) Dignam, C. F.; Richards, C. J.; Zopf, J. J.; Wacker, L. S.; Wenzel, T. J. *Org. Lett.* **2005**, *7*, 1773.

(6) Imines from α-substituted aldehydes and substituted amines were present only as *E*-isomers. This *E* presence is well-known, see: (a) Berkessel, A.; Vennemann, M. R.; Lex, J. *Eur. J. Org. Chem.* **2002**, *16*, 2800. (b) Boyd, S. L.; Boyd, R. J.; *J. Phys. Chem. A.* **2001**, *105*, 7096. (c) Kosmrlj, J.; Weigel, L. O.; Evans, D. A.; Downey, C. W.; Wu, J. *J. Am. Chem. Soc.* **2003**, *125*, 3208.

The imines slowly epimerize upon standing in the NMR solvent, and the apparent de therefore gradually declines after the imines have formed. For the δ-keto-aldehydes discussed here, the drop in apparent de is <5% after 20 min. If the de is measured within 5 min of amine addition to the NMR sample, the results agree well with those obtained via other methods, as shown below.[7]

To determine whether the NMR method can be used for δ-keto-aldehydes with varying structure, especially varying α-substituents, we examined the products from several organocatalytic Michael additions described in Scheme 1. In each case the product ee was evaluated via the NMR method using amine **A′** or **D** (separate measurements), which gave comparable results for most aldehydes (the worst correlation was observed for **3**, 83% ee implied by reaction with **D** vs 77% ee implied by reaction with **A′**; entry 3, Table 1). As a further check on the NMR-based assay we used an alternative technique to evaluate the ee of each Michael addition product: each aldehyde was converted to a more configurationally stable derivative that was purified and evaluated via chiral stationary phase chromatography. δ-Keto-aldehydes **1**, **3**, and **6** were oxidized to the corresponding carboxylic acids,[8] which were then analyzed by chiral stationary phase GC [Supelco β-Dex 120 column]. δ-Keto-aldehyde **4** was converted to an enone via Wittig reaction,[4b,4c] and **5** and **7** were converted to monoacetals;[2] these derivatives were analyzed via chiral stationary phase HPLC [Chiracel OD column]. As indicated in Table 1, the ee values obtained from the configurationally stable derivatives were comparable to the ee values deduced via in situ imine formation followed by NMR analysis.

Table 1. NMR ee and Indirect GC or HPLC ee

entry	aldehyde	ee by **D** (%)	ee by **A′** (%)	indirect ee (%)
1	**1**	75	75	79
2	**2**	80	84	ND[a]
3	**3**	83	77	83
4	**4**	76	72	73
5	**5**	38	33	35
6	**6**	77	74	73
7	**7**	31	30	34

[a] Not determined.

We probed the accuracy of the NMR method over a wide range of ee values by comparison with results obtained with the configurationally stable carboxylic acids derived from **1** and **3**. Amine **D** was used with **1**, and amine **A′** was used with **3**. For each δ-keto-aldehyde, samples ranging between 0% ee and ~80% ee were prepared by mixing racemic material[9] with enantio-enriched material obtained from Michael addition catalyzed by chiral pyrrolidine **8** (Scheme 1). As shown in Figure 3, the results obtained via these two methods agree very well with one another for both δ-keto-aldehydes.

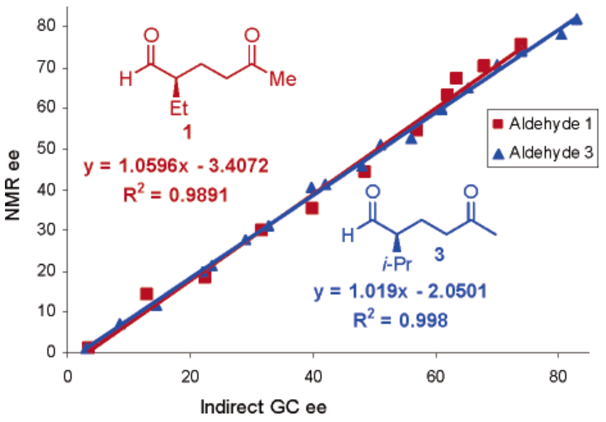
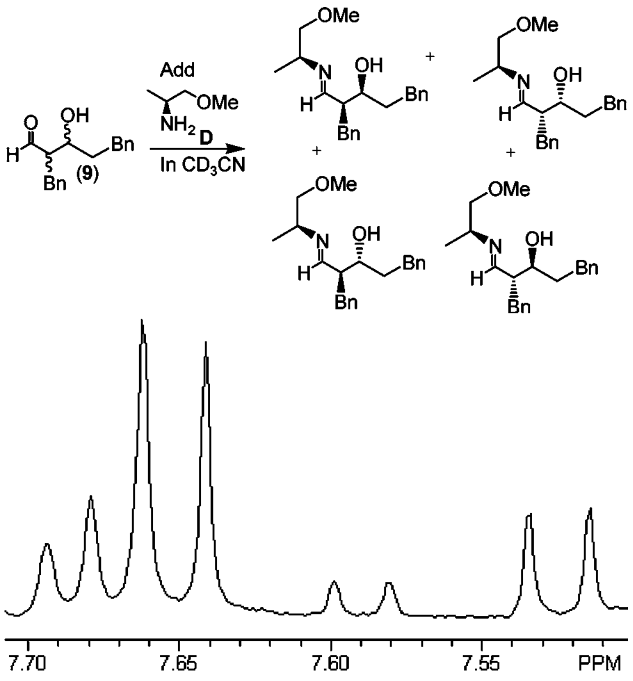


Figure 3. NMR ee vs indirect GC ee of aldehydes **1** and **3**.

We also examined two other types of α-substituted aldehyde using our approach. The four aldol product isomers (**9**) from the self-aldol condensation of hydrocinnamaldehyde can be resolved with chiral amine **D**, giving four distinct imine proton resonances (Scheme 3). The commercially available racemic α-substituted aldehyde (±)-2-methylbutyraldehyde (**10**) can also be resolved, albeit imperfectly, by chiral amine **D** (Scheme 4).

Scheme 3



We have examined only a small set of α-substituted aldehydes, but it seems likely that the simple strategy we

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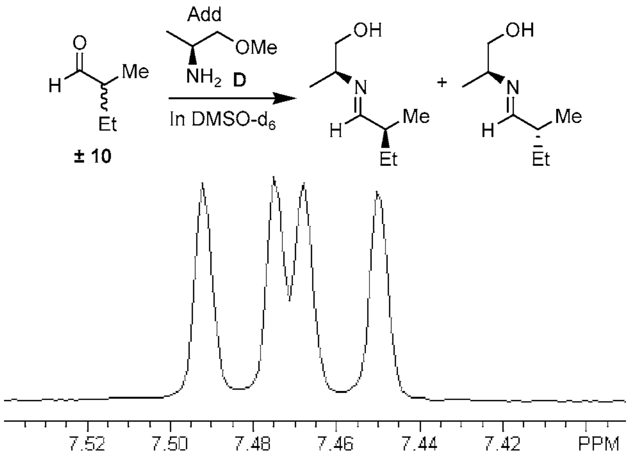
[7] No significant reaction between the primary amine and the ketone moiety of the α-substituted δ-keto-aldehyde was observed within 20 min.

[8] Rangaishenvi, M. V.; Singaram, B.; Brown, H. C. *J. Org. Chem.* **1991**, *56*, 3286.

[9] Obtained by using racemic proline as catalyst for the Michael addition.

Scheme 4



have employed will be applicable to other α-substituted aldehydes as well. Of course, it may be necessary to examine a larger range of chiral amines in order to achieve success with other aldehydes, but many chiral amines are readily available (e.g., α-amino alcohols and esters of α-amino acids). Incomplete reaction samples can be directly assayed without any workup. Analyzing incomplete reaction mixtures allows one to monitor ee as a function of reaction progress, which can be useful for enantioselective process optimization. Our method should be most useful in the early stage of discovery efforts aimed at identifying catalysts for asymmetric reactions that produce α-substituted aldehydes, because of the simplicity and rapidity of our assay.

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Supporting Information Available: Experimental details, selected NMR spectra, GC and HPLC data. This material is available free of charge via the Internet at http://pubs.acs.org.

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