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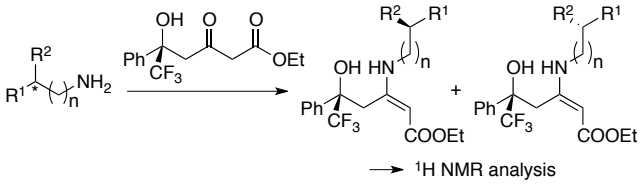

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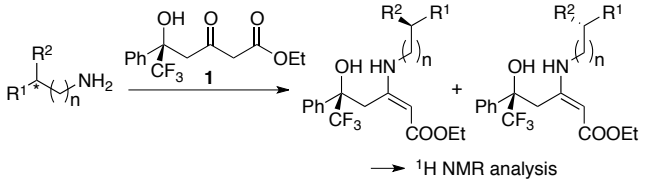
ABSTRACT

A ^{1}H NMR analysis method that detects enantiomers of molecules bearing a primary amino group has been developed. The method uses a β-keto ester-derived probe that forms enamines with the amines and is able to discriminate enantiomers of functionalized amines and amines that have chiral centers at positions remote from the amine group.

Chiral primary amines or chiral molecules bearing primary amine groups are found in pharmaceuticals, bioactives, probes, reaction catalysts, and other functional molecules and their building blocks.[1-4] Because functions, such as bioactivity, often differ between the enantiomers of a molecule, the ability to detect enantiomers of amines is of interest in areas ranging from asymmetric synthesis to drug discovery.[1-4] Here we report a ^{1}H NMR analysis method that uses β-keto ester-derived probe **1** to detect enantiomers of molecules with primary amines including those that have chiral centers at positions remote from the amine group (Scheme 1).



Scheme 1. Detection of amine enantiomers using the reaction with probe **1** by ^{1}H NMR analysis.

Enantiomers of amines are often detected by HPLC or GC analyses with chiral columns for the determination of enantiomeric excess (ee) or enantiomeric ratio (er) values directly or after derivatization.[1] Enantiomers of amines have also been detected by circular dichroism (CD), fluorescence, and NMR analyses after derivatization or with in situ reactions or interactions with probe molecules for the determination of the ee ~~or er~~ values, or for the determination of the absolute configurations.[2-4] Use of HPLC requires a search for suitable chiral columns and conditions including solvents and peak-detection methods. ^{1}H NMR analysis methods for the detection of enantiomers are often easy to use[2,3] and are useful for amines that do not have strong UV-active groups, which are often difficult to detect using a conventional UV-equipped HPLC.

Previously reported ^{1}H NMR methods to directly monitor amine enantiomers for the determination of ee or er include those that use the formation of imines with probes[2] and those that use the coordination to probes.[3] The previously reported direct ^{1}H NMR analysis methods that involve imine formation employ probes composed of two types of molecules, achiral enamine-forming aldehydes and chiral acids.[2] In these methods, the ratios of the amines and the probe components are important to obtain the results.[2] In the cases of the reported ^{1}H NMR methods that use coordination to metal-derived probes, concentrations and ratios of the amines and the probes are also critical;[3] chemical shifts of the amines depend on the concentrations and ratios of the amines and the probe molecules.[3] In addition, in these reported methods, most amines evaluated are those that have the chiral center at the amine-substituted carbon; only limited examples for the amines with the chiral centers distant from the amine-substituted carbon have been reported.[2,3] NMR methods involving derivatization of amines and then isolation of the products before analysis have also been reported,[4a] but direct analysis methods are more desirable than the methods requiring a purification step.

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We have recently reported DBU-catalyzed aldol reactions of ethyl 3-oxobutanoate with aryl trifluoromethyl ketones that afford the aldol products (such as **1**) as a result of the C-C bond formation at the γ-position of the β-keto ester.[5] Through resolution via the formation of enamines with enantiomerically pure 1-phenylethylamine (**2a**, Figure 1), enantiomerically pure forms (>99% ee) of the aldol products were obtained.[5] Based on these results, we sought ^{1}H NMR analysis methods for discriminating amine enantiomers. In our previous study, we have observed that the two diastereomers of the enamine generated from racemic aldol **1** and enantiopure 1-phenylethylamine (**2a**) have characteristic ^{1}H NMR chemical shifts and are distinguished each other at selected peaks.[5] These results suggested that enantiomers of 1-phenylethylamine are distinguished by ^{1}H NMR analyses with the use of enantiopure aldol **1** as a probe. We hypothesized that enantiomers of amines would be detected by ^{1}H NMR analyses with the use of the enantiopure form of aldol **1** as a probe. In particular, we sought to discriminate enantiomers of amines including those functionalized and those that have chiral centers located one or more atoms apart from the amine-substituted carbon.

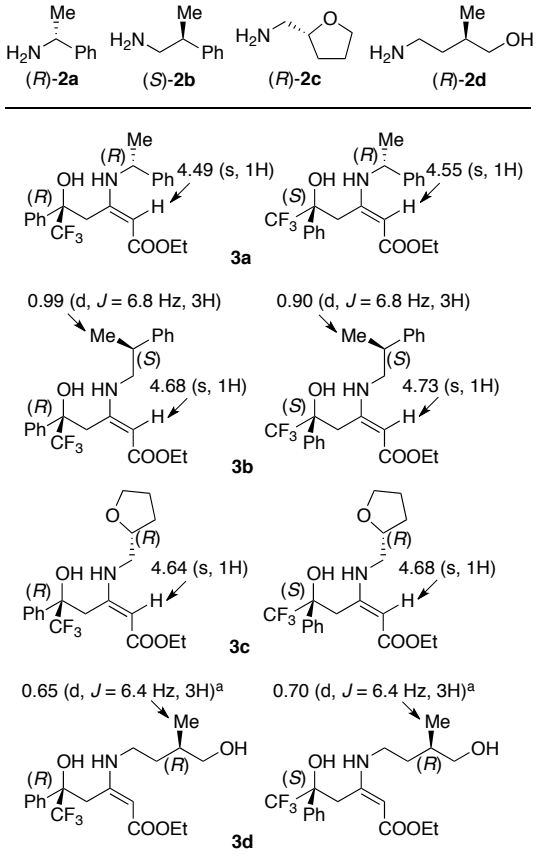

Figure 1. Amines **2** and the selected ^{1}H NMR chemical shifts of enamines **3** to detect the enantiomers of **2**; chemical shifts in $CDCl_3$ except where noted. [a] Chemical shifts in CD_3CN.

First, to estimate whether enantiomers of amines are discriminated using probe **1**, enantiopure amines **2** (>99% ee or >98% ee, Figure 1) were mixed with racemic aldol **1** and with enantiopure (*R*)-**1** (>99%), respectively, and the formed enamines were purified and characterized. As reported previously, the diastereomers of enamine **3a** generated from **1** with **2a** were isolated each other by usual silica gel flash column chromatography.[5] However, diastereomers of enamines **3b**, **3c**, and **3d** obtained from **2b**,[1g,3,4g,h] **2c**,[6] and **2d**,[4h] respectively, were not separated each other by silica gel flash column chromatography. During the formation of **3** using racemic aldol **1**, the diastereomers from the enantiomers of an amine were formed without notable rate differences.

The ^{1}H NMR spectra of the generated diastereomers of each amine were compared, and peaks to distinguish the diastereomers were identified. The identified ^{1}H NMR signals of **3** suitable for the detection of the amine enantiomer sets are shown in Figure 1. The chemical shifts shown in Figure 1 do not overlap with the ^{1}H NMR peaks of **2** and **1**, and thus can be used to detect the enantiomers even when the enamine formation reaction is not completed. ^{1}H NMR peaks that distinguish the amine enantiomers were found for all the amines tested, including amines with chiral centers at remote positions from the amine-substituted carbon and amines bearing functional groups such as ether moiety and hydroxy group. For each amine, the differences in the chemical shifts of **3** shown in Figure 1 between the diastereomers were in the range of 0.04-0.09 ppm. Peaks in addition to those shown in Figure 1 may also be used to distinguish the diastereomers.

Table 1. Ratio of diastereomers of **3** generated from **2** with probe (*R*)-**1**.[a]

entry	**2**	er of **2** (*R*):(*S*)[b]	**2**:(*R*)-**1**	**3**	time	conversion (%)[c]	dr of **3**[d]
1	**2b**	80:20	1:1	**3b**	75 min	12	82:18
2					2.5 h	22	80:20
3					14 h	65	81:19
4	**2b**	87:13	1:1	**3b**	3 h	17	87:13
5					14 h	60	87:13
6	**2d**	83:17	1:1	**3d**	16 h	46	82:18
7	**2d**	90:10	1:1	**3d**	15 h	32	89:11
8	**2d**	90:10	2:1	**3d**	12 h	28	90:10

[a] Conditions: Amine **2** (0.03 mmol) and **1** in $CDCl_3$ (0.5 mL) for entries 1-5 and in CD_3CN (0.5 mL) for entries 6-8 at room temperature (25 °C).

[b] Prepared by mixing stock solutions that were made based on weighing of enantiopure forms of **2b** or of (*R*)-**2c** and (±)-**2c**.

[c] For entries 1-5: Determined based on the ratio of **1** and **3** by ^{1}H NMR analysis. For entries 6-8: Determined based on the ratio of **2** and **3** by ^{1}H NMR analysis. For entry 8, the theoretical maximum conversion is 50%.

[d] (*R**,*R**)-isomer:(*R**,*S**)-isomer, determined by ^{1}H NMR analysis (400 MHz).

For a ^{1}H NMR method to be useful for the determination of ee or er values of the amines by the formation of the diastereomers, the diastereomers should be completely formed before the analysis or the diastereomer formation rates should be same for both the enantiomers to reflect the enantiomer ratio in the diastereomer ratio. Depending on the correlation between the er of the amine and the dr of the generated diastereomers, the timing of the NMR analysis to determine the ee or er values should be determined. Thus, next, enamine formation reactions of enantiopure amines **2b**, **2c**, and **2d** with racemic **1** were performed in $CDCl_3$, and the conversion and the dr values of the generated **3** were analyzed at various time points. The dr values of **3** were 1:1 at all the time points (see Supporting Information, page S4 and Table S1). Therefore, the enamine formation was analyzed using (*R*)-**1** (>99% ee) and the amines with pre-determined enantiopurity (Table 1). For these experiments, amine 0.03 mmol and the same or half equivalents of probe (*R*)-**1** were used.

The dr values of **3** were mostly consistent with the er values of the amines at all the stages of the enamine formation at times corresponding to 17% or greater conversion (entries 2-8). In addition, the ratio of the amine to probe **1** did not affect the detection of the enantiomers (entry 8). Note that chemical shifts of the diastereomers were the same at all the time points analyzed for each diastereomer.

The concentrations used in Table 1 experiments (amine 0.03 mmol/0.5 mL) were 8- to 10-fold lower than the concentrations used for the preparation of enamines **3** as the standards (Figure 1). The use of low concentrations of amines and probe **1** in Table 1 experiments resulted in slow formation of enamine **3**, but the amine enantiomers were detected as the corresponding enamine diastereomers as formed at the characteristic ppm on the NMR spectra. The chemical shifts of the diastereomers formed were consistent over the time and did not depend on the ratio of the amine to probe **1**.

In this method, the rate of the enamine formation of an enantiomer of an amine with probe **1** was the same as that of the other enantiomer of the amine, and the enamine diastereomers generated from the enantiomers of amines were distinguished by the ^{1}H NMR chemical shifts. The critical factors allowing such observations to lead the success of this NMR methods are: (1) The chiral center in probe **1** is located one methylene group apart from the enamine-forming carbonyl group. That is, the chiral center of **1** is not close enough to influence the rates of the enamine formation of amine enantiomers, and the enamine formation is not hindered by the tetra-substituted chiral carbon center of the probe. (2) Although the chiral center of probe **1** does not lead to different rates of the enamine formation between amine enantiomers, the chiral center provides sufficient differences to distinguish the diastereomers generated from amine enantiomers with probe **1** in ^{1}H NMR. (3) The β-keto ester group of probe **1** selectively forms an (*E*)-enamine,[7] and the enamine is stable because of the π-conjugation.

In previously reported direct NMR methods to discriminate amine enantiomers in which probes interact with amines noncovalently and/or through metal coordination, chemical shifts of the amines depend on the concentrations and/or on the ratios of amines and probe molecules regardless the NMR nucleus, and thus the samples to be analyzed must be accurately prepared.[3,4h] In our method, chemical shifts of the diastereomers generated from enantiomers of an amine with probe **1** do not depend on the concentrations of the amine and the probe or on the ratio of the amine to the probe; and thus, precise conditions that require accurate weighing of amines and of the probe are not necessary. The er values of the amines are observed as the ratio of the enamine diastereomers formed with the probe even when the enamine formation reaction is in progress or is not completed. In our method, the ^{1}H NMR analysis can be performed at the initial stage (~20% conversion) of the enamine formation using a small scale reaction mixture. In addition, our method uses a single component probe.

In summary, we have developed a concise ^{1}H NMR method that uses an enantiomer of γ-position aldol product of a β-keto ester as a probe for detecting amine enantiomers and for approximating the enantiomer ratios through the formation of the enamines on a small scale. The method was able to discriminate the enantiomers of amines including functionalized amines that have chiral centers at remote positions from the amine group.

Acknowledgments

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7. The (*E*)-enamine structure of (*R*,*R*)-**3a** was previously determined by the X-ray crystal structural analysis.[5]

Supplementary Material

Supporting Information is available. Experimental procedures, compound characterization, and NMR spectra. (pdf)