Deracemization via Highly Enantioselective Enolate Protonation Using a Chiral Aniline as the "Acid"

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Enol or enolate protonation by a chiral acid is potentially capable of deracemizing a variety of carbonyl compounds,[1-5] but only a few isolated experiments have encountered promising levels of enantioselectivity in the range of 90–91% enantiomeric excess (ee).[3] There are cases where crystallization techniques can be employed to upgrade partly deracemized carbonyl compounds from 77–84% ee to practical levels of 95% ee or better but at some cost in efficient recovery of the major enantiomer.[4,5] The most highly enantioselective protonation of an *achiral* enol derivative reported to date uses a catalytic antibody for the hydrolysis of an enol ether ((*E*)- or (*Z*)-1-methoxy-2-methyl-3-phenylpropene) to give 2-methyl-3-phenylpropanal with 93–96% ee.[6] Higher enantioselectivities have been reported only in examples where the proton-transfer step involves an enol or enolate derivative that is covalently bound to a chiral auxiliary[7a,b] or to a (chiral) enzyme.[7c] In the latter examples, selectivity depends on diastereomer (not enantiomer) excess, and the outcome is determined by cooperation between a chiral acid and a chiral substrate (double stereodifferentiation).[7]

We can now report a simple chemical technique that achieves practical enantioselectivity levels in the protonation of a series of β,γ-unsaturated amide enolates using the commercially available diamine **1** as the chiral "acid".[8] The results (Table 1) are the best ever seen with achiral enolate substrates in terms of enantioselectivity and tolerance of structural modifications. Like other nonenzymatic protonation methods, this procedure requires a stoichiometric amount of **1**, but the process is catalytic in the sense that **1** is recovered unchanged after the experiment by simple acid–base extraction.

Amides **2a–h**[5,9] were converted into lithium enolates **3** at –78 °C (ca. 0.15 M in THF) using 1.75 equiv of *sec*-BuLi to ensure complete deprotonation. After 10 min, 2 equiv of **1** was added. The solution was kept at –78 °C for 30 min and was then warmed to the workup temperature listed in Table 1. Basic species were quenched with NH_4Cl–H_2O, and conventional acid extraction was used to separate the diamine **1** (>90% recovery) from the enantiomerically enriched amide **4**. Isolated yields of **4** exceeded

Chart 1

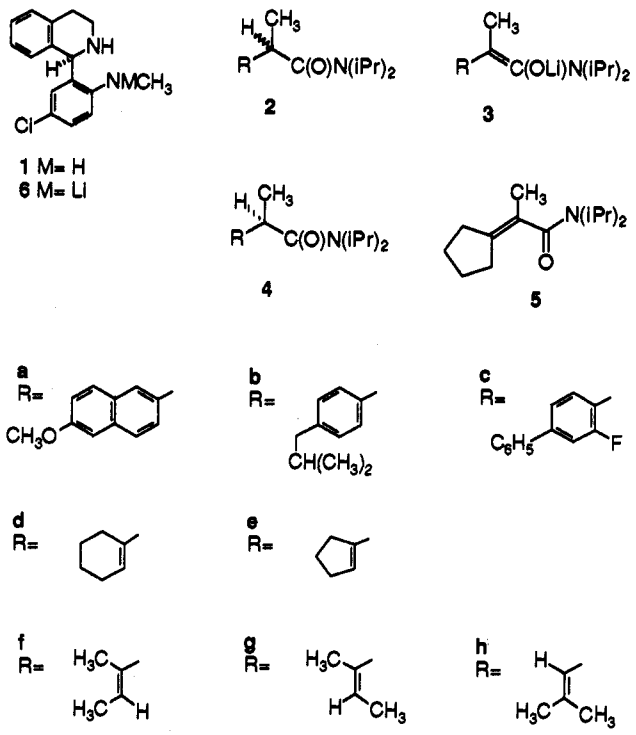

Table 1. Quenching of Amide Enolates with **1**[a]

amide	workup temperature (°C)	ee[b] (%)
4a	0	97
4b	0	97
4c	–25	95
4d	0	97
4e	0	95[c]
4f	0	97
4g	0	95[d]
4h	0	53

[a] Amides were obtained with >90% recovery of **4** and **1** unless otherwise noted. [b] HPLC analysis, chiral stationary phase at base line resolution. [c] The isomer **5** was the major product, 66% yield; 18% of **4e** was obtained. [d] The product of γ-protonation was isolated in 30% yield in addition to **4g** (60%).

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(8) (a) Diamine **1**: mp 100–101 °C (ether/hexane); lit.[8b] mp 98–99 °C; α^{20}_D +51° (*c* = 0.37, $CHCl_3$); absolute configuration by X-ray anomalous dispersion; **1** was obtained from recrystallized 1-[5-chloro-2-(methylamino)-phenyl]-1,2,3,4-tetrahydroisoquinoline tartrate (Aldrich), mp 199–200 °C dec (methanol). See supplementary material: possible labeling errors by Aldrich. (b) Ott, H.; Hardtmann, G.; Denzer, M.; Frey, A. J.; Gogerty, J. H.; Leslie, G. H.; Trapold, J. H. *J. Med. Chem.* **1968**, *11*, 777.

(9) Amides **2a–c** were prepared from commercially available acids (see supplementary material); amides **2d**, **2e**, and **2h** were obtained from the known acids. (a) **2d**: Kon, G. A. R.; Nargund, K. S. *J. Chem. Soc. C* **1932**, 2461. (b) **2e**: Black, T. H.; Eisenbeis, S. A.; McDermott, T. S.; Maluleka, S. L. *Tetrahedron* **1990**, *46*, 2307. (c) **2h**: Henin, F.; Mortezaei, R.; Muzart, J.; Pete, J.-P.; Piva, O. *Tetrahedron* **1989**, *45*, 6171. (d) Amides **2f** and **2g** were made from (*E*)- or (*Z*)-2-bromo-2-butenes and α-lithio *N,N*-diisopropylpropionamide by analogy to the procedure of Millard and Rathke: Millard, A. A.; Rathke, M. W. *J. Am. Chem. Soc.* **1977**, *99*, 4833.

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90% in all cases except with enolates **3e** and **3g**. In the case of **3e**, the major product after chromatography was the α,β-unsaturated amide **5** (66%) derived from γ-protonation of the enolate, while **4e** was obtained in 18% yield. Significant γ-protonation was also seen with **3g**, resulting in formation of the corresponding α,β-unsaturated isomer (30%) in addition to **4g** (60%). The (*R*) configuration was established for **4a–c** by HPLC comparison with authentic (*S*)-amides prepared from the parent (*S*)-acids. The same configuration is assumed for **4d–h** on the basis of structural analogy and consistent HPLC retention behavior on a chiral stationary phase.[10]

In contrast to many of the previously described enolate protonation methods,[1-5] enantioselectivity with **1** is not very sensitive to stoichiometry, order of mixing, or the details of aqueous quenching. However, the temperature profile up to the aqueous quenching step can be important. An early experiment with enolate **3c** (fluorbiprofen series) was performed by slowly warming the mixture of **3c** + **1** from −78 °C to 20 °C followed by the usual addition of aqueous NH_4Cl. Similar experiments with **3a** (20 °C quench) gave **4a** with 92–94% ee, but the result from **3c** was the formation of nearly racemic amide (16% ee). Workup with H_2O/NH_4Cl at lower temperature greatly improved enantiomeric purity: warming from −78 °C to 0 °C and quench, 85% ee; warming to −25 °C and quench, 95% ee. In a control experiment, **4c** (95% ee) was treated with the same ratio of diamine **1** + lithioamide **6** that would be present after enolate protonation in THF prior to workup. After 10 min at 0 °C, the mixture was allowed to warm to 20 °C and was then quenched in the usual way to give **4c** with 31% ee. The temperature effect with **3c** can therefore be explained by assuming reversible deprotonation of **4c** (eq 1) at 0 °C or above. In the context of eq 1, racemization is possible if k_{-1} becomes significant relative to k_1. This is more likely for **4c** than for **4a** because of the acidifying effect of the electron-withdrawing fluorine substituent.

$$1 + 3 \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} 6 + 4/2 \qquad (1)$$

According to the argument presented above, enolate quenching occurs by direct proton transfer from **1** to the enolates **3** and is *not* the result of internal proton return during workup.[1b] This was proved by monitoring the orange-red mixture of enolate **3a** + **1** in THF-d_8 at −78 °C using ^1H NMR. Detection limits were no better than 10% due to line broadening, but signals of **4a** were evident a few minutes after the addition of **1**, and at least 85% of **3a** was protonated after 30 min at −78 °C. Significant fading of the enolate color occurred over the same time scale. When the mixture was quenched by workup at −78 °C, **4a** was recovered with 70–80% ee due to incomplete proton transfer. Warming of the mixture of **3a** + **1** is essential for complete enolate protonation, and quenching at 0 °C gives the maximum value of ee (97%).

The ee values of Table 1 are comparable to enzymatic enol protonation results and also to the best diastereoselectivities reported for protonation of chiral enolates.[7] The detailed mechanism for the reactions of **1** + **3** is not established, and it is too early to rationalize decreased selectivity with the β-unbranched enolate **3h** or to comment on the intriguing α vs γ selectivity patterns (**3e** vs **3g**). However, one of the variables responsible for exceptional enantioselectivity can be identified with some confidence. We believe that **1** has nearly ideal relative acidity compared to the amides **2**. Diamine **1** must be a stronger "acid" by at least 2 orders of magnitude in THF (k_1 > ca. 100 k_{-1}, assuming the simple stoichiometry of eq 1). Otherwise, >95% ee in the enolate protonations would not be possible because of incomplete proton transfer and competing product racemization, as seen with **2c** at 0 °C or above. However, proton transfers between strong bases and increasingly strong acids become increasingly rapid and exothermic.[11] Thus, enantioselectivity may decrease as the ratio of k_1:k_{-1} increases much past the minimally acceptable 2 or 3 orders of magnitude. A good match between the effective acidities of the proton donor (**1**) and the carbonyl compound (**4**) is necessary for high enantioselectivity according to this argument, presumably to maintain significant N···H as well as C···H bonding in the transition state for enolate protonation. Studies are under way to examine more highly acidic analogs of **1** and to explore deracemization of other enolate families.

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Supplementary Material Available: Characterization data of key products and representative experimental procedures (5 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(10) The major enantiomer was slower to elute on CHIRALCEL-OD for **2b–h**; see supplementary material.

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