Catalytic Asymmetric Protonation of Amide Enolates: Optimization of Kinetic Acidity in the Catalytic Cycle

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Received November 25, 1997

Several highly enantioselective techniques for protonation of prochiral enolates have been reported using stoichiometric amounts of a chiral proton donor.[1] In most cases, simple aqueous workup allows efficient recovery and reuse of the chiral auxiliary, but there are clear advantages if smaller quantities of the chiral proton source would be sufficient.[2,3] In the first practical demonstration of the concept, Fehr et al. achieved remarkable selectivities in the range of 94−98% ee using 20 mol % of a chiral catalyst together with an achiral stoichiometric proton donor and 90% ee in one case using 5 mol % chiral catalyst.[2] Related publications by Fehr have noted the importance of pK_a matching between the chiral proton donor and the substrate,[1] and this issue has also been discussed in a report from our laboratory.[4] Optimum enantioselectivity in the protonation of amide enolates related to **2** was observed with **3** (pK_a(DMSO) 27.7) to give *(R)*-**1** (pK_a(DMSO) ca. 31). Irreversible quenching of the enolate was possible with Δ pK_a ca. 3, and the reaction was slow enough to be highly enantioselective. Substrate vs chiral acid pK_a matching must be equally important in catalytic asymmetric protonation, but in this case product enantiomer excess also depends on the relative rates of eqs 1−3, Scheme 1. Catalytic turnover of **3** requires that an achiral acid A−H must react faster with **4** than with the enolate **2**. Furthermore, the rate of eq 1 must be large compared to that of eq 3 to avoid formation of racemic product. The current study was undertaken to determine whether acceptable selectivity in a catalytic cycle can be achieved with amide enolates and to explore qualitative pK_a matching of the chiral and achiral acids as a means to guide optimization of the crucial kinetic acidity terms in eqs 1−3.

In the initial experiments, several achiral acids were surveyed to identify promising structural types and pK_a trends. Treatment of amide **1** with 1.5 equiv of *s*-BuLi at −78 °C produced the enolate **2** (THF solution). Catalyst **3** (10 mol %)[4,5] was introduced, followed by slow addition of the achiral proton donor (2 equiv). The solution was then warmed to −20 °C and quenched (NH_4Cl−H_2O), resulting in >90% recovery of nonracemic amide **1** (Table 1).

Hydroxylic agents (entries 1 and 2) quenched the dark orange enolate at −78 °C, but they produced nearly racemic amide **1**. Evidently, the catalytic cycle cannot compete with eq 3 in these experiments. Racemic **1** was also obtained when acetonitrile was tested as the potential proton source, but the enolate color was not discharged and ca. 85% of the enolate **2** was not protonated prior to aqueous workup according to deuterium-labeling studies.[6] Phenylacetonitrile did quench the enolate, and **1** was obtained with modest ee (entry 4). However, the more acidic 1-phenyl-2-propanone (the optimal achiral proton source in Fehr's study of thiol ester enolates)[2] gave nearly racemic product (entry 5). These findings stimulated the investigation of carbon acids having relatively high pK_a values, and ethyl acetate (entry 6) was found to give **1** with much improved 85% ee. However, simple alterations of the ethyl acetate core (entries 7−9) drastically reduced ee. In the case of *tert*-butyl acetate as the achiral acid (entry 7), a deuterium-quenching experiment (DOAc) revealed that only ca. 50% of **2** had been protonated using the standard conditions. On the other hand, ethyl phenylacetate afforded *(R)*-**1** with 92% ee (entry 10), and the corresponding *tert*-butyl ester (entry 11; 94% ee) gave the best results in this series.

The above evidence is consistent with a "proton shuttle" mechanism that is controlled by the relative rates of eqs 1−3. The initial enolate solution contains 0.5 equiv of excess *sec*-butyllithium, sufficient to convert the added chiral amine **3** (0.1 equiv) to the lithiated catalyst **4**. Subsequent syringe pump addition of the achiral acid A−H (2 equiv) destroys the remaining *sec*-butyllithium and in the best experiments (entries 10 and 11) effects rapid protonation of **4** to **3**. As **3** accumulates, some of the enolate **2** is quenched in eq 1 to give *(R)*-**1** and the lithiated catalyst **4**. However, if the kinetic acidity of the achiral acid is too low, then the proton

Scheme 1

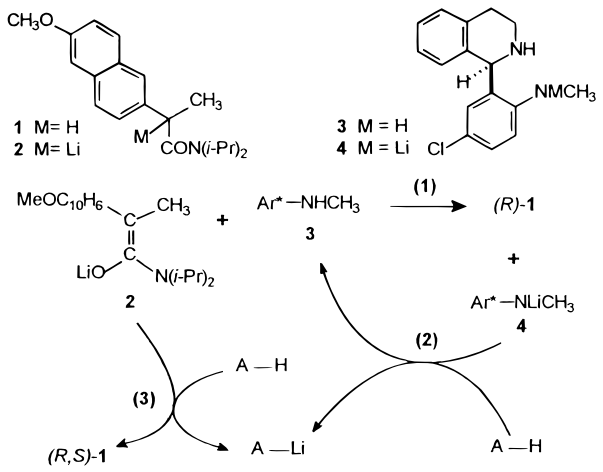

Table 1. Catalytic Asymmetric Protonation of 2 Using 10 Mol % 3[a]

entry	achiral acid (A−H)	pK_a[b]	ee[c] (%)
1	*t*-BuOH	32	0
2	H_2O	31	5
3	CH_3CN	31	0
4	$PhCH_2CN$	22	40
5	$PhCH_2COCH_3$	20	6
6	CH_3CO_2Et	27.5;[d] ∼30[b]	85
7	CH_3CO_2tBu	∼30[e]	35
8	$CH_3CH_2CO_2Et$		19
9	$(CH_3)_2CHCO_2Et$		0
10	$PhCH_2CO_2Et$	22.7	92
11	$PhCH_2CO_2tBu$	23.6[e]	94

[a] 1 equiv of **2**, 1.5 equiv of *s*-BuLi; 2 equiv of A−H added over 1 h at −78 °C. [b] DMSO pK_a of chiral acid; ref 7a unless noted. [c] HPLC analysis on chiral support, Pirkle (*S*,*S*) Beta-gem 1. [d] Reference 7b. [e] Reference 7d.

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(2) Fehr, C.; Galindo, J. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1888.

(3) (a) Enolate protonation using 10 mol % catalyst, 90% ee: Yanagisawa, A.; Kikuchi, T.; Watanabe, T.; Kuribayashi, T.; Yamamoto, H. *Synlett* **1995**, 372. (b) Ketene trapping and enolate protonation with 93% ee (55% yield) using 15 mol % of catalyst: Nakamura, Y.; Takeuchi, S.; Ohira, A.; Ohgo, Y. *Tetrahedron Lett.* **1996**, *37*, 2805. (c) Enol silane + MeLi/LiBr; 20 mol % catalyst, 83% ee: Riviere, P.; Koga, K. *Tetrahedron Lett.* **1997**, *38*, 7589. (d) *β*-Keto acid decarboxylation with 30 mol % chiral amino alcohol, >99% ee (86% yield): Muzart, J.; Henin, F.; Aboulhoda, S. J. *Tetrahedron: Asymmetry* **1997**, *8*, 381.

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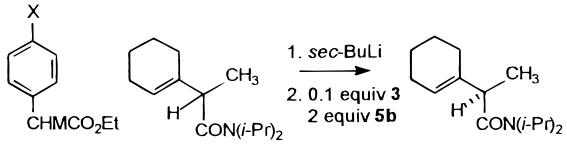
(5) Vedejs, E.; Lee, N. *J. Am. Chem. Soc.* **1991**, *113*, 5483.

(6) The standard experiment using 1.5 equiv of *s*-BuLi, 10 mol % of **3**, and 2 equiv of acetonitrile as the achiral "acid" was performed, but final quenching was done with DOAc to give **1** with 83% deuterium incorporation.

S0022-3263(97)02147-6 CCC: $15.00
Published on Web 04/08/1998

Table 2. Catalytic Asymmetric Protonation; *p*-$XC_6H_4CH_2CO_2C_2H_5$ (5) as Achiral Acid using 5 mol % 3[a]



5 M= H
6 M= Li
7

entry	X	σp^b	ee[c] (%)
a	Cl	0.23	40
b	H	0.00	77
c	CH_3	−0.17	85
d	CH_3O	−0.27	87
e	$(CH_3)_2N$	−0.83	92

[a] 1 equiv of **2**, 1.5 equiv of *s*-BuLi; 2 equiv of A−H added over 1 h at −78 °C. [b] Reference 11. [c] HPLC analysis on chiral support, Pirkle (*S*,*S*) Beta-gem 1; ee for (*R*)-**1**.

shuttle fails because eq 2 is too slow to generate an adequate concentration of **3** for protonation of the enolate. This situation was encountered in entry 3 and to some extent in entry 7 according to the DOAc quenching experiments[6] and probably also for entries 8 and 9 where the kinetic acidity of the achiral acids would be decreased by the presence of α-substituents. Alternatively, the catalytic cycle might fail if the kinetic acidity of A−H is too high. Under these circumstances, eq 3 could be dominant over eq 1, resulting in low ee (entries 1, 2, and 5). For the ideal case, eq 3 would be totally suppressed, and the catalyzed reaction would afford (*R*)-**1** with the same 97% ee observed in the stoichiometric reaction. In the best experiments (entries 10 and 11), this goal was nearly realized.

It is instructive to consider the selectivity behavior of the carbon acids of Table 1 in the context of the pK_a(DMSO) values.[7] Achiral acids having the lowest pK_a values tend to give poor ee in **1**, probably because eq 3 is too fast. For the least acidic carbon acids (highest pK_a(DMSO)) product ee can be low because the rate of eq 2 is too small to sustain the catalytic cycle on a convenient time scale. This results in varying degrees of nonselective enolate protonation in the workup step, depending on the time allowed for proton shuttling. However, there is a striking transition to promising ee for achiral acids at both ends of the pK_a scale (below pK_a(DMSO) ca. 30, ethyl acetate, entry 6; above pK_a(DMSO) ca. 22, ethyl phenylacetate, entry 10). To better understand the trends near these threshold pK_a values, we investigated an isostructural series of achiral proton donors *p*-$XC_6H_4CH_2CO_2Et$ (**5a**−**e**, Table 2) that were expected to span the pK_a(DMSO) range from ca. 22−28.[7c] These experiments were conducted under more demanding conditions using 5 mol % of the catalyst to help establish the practical limits for efficient catalyst turnover.

The enantioselectivities in Table 2 improved as the electron-releasing ability of the **X** substituent in **5** increased. The least acidic *p*-(dimethylamino)phenylacetate ester **5e** afforded *(R)*-**1** with 92% ee, the highest value observed to date for the overall sequence of enolization, catalytic asymmetric protonation using 5 mol % of a chiral proton donor. The exceptional ee was obtained by following the procedure optimized for the ethyl phenylacetate example (Table 2, entry b) on a 0.15 mmol scale, and 92% ee for entry e was confirmed on a 3 mmol scale using a similar procedure (see the Supporting Information). Relatively little decrease in ee was found in the intermediate pK_a range from **5e** to **5d** to **5c**. However, increased achiral proton donor acidity from **5c** to **5b** to **5a** resulted in a progressively larger decline in product ee, and the 40% ee for **5a** (Table 2, entry 1) corresponds to the behavior of Table 1 (entries 4 and 5) where the transition to nonselective behavior was initially noted. Thus, competition by eq 3 becomes serious below a threshold pK_a(DMSO) = ca. 22. This change in achiral acid behavior reflects the inability of **5** to discriminate between the carbon base (enolate **2**) and the heteroatom base (lithiated aniline **4**) when the difference in pK_a's (**5** vs **1**) becomes sufficiently large (Δ pK_a(DMSO) >ca. 8).[8] On the other hand, there is large window of opportunity for acceptable discrimination toward the upper end of the pK_a scale. The requirements for pK_a matching between the stoichiometric achiral acid **5** and the protonated enolate **1** are considerably less demanding than for **1** vs the chiral proton donor **3**.[4]

It is interesting that the best enantioselectivities were obtained using an achiral acid **5e** that may have a pK_a value near that of **3** (pK_a(DMSO) 27.7).[4] The rate of proton transfer between the nitrogen base **4** and the carbon acid **5e** is sufficient to maintain the catalytic cycle, but the proton transfer from **5e** to the carbon base **2** is at a minimum. This behavior corresponds to the generalization that proton transfer between a heteroatom base and a carbon acid is inherently much faster than transfer involving a carbon acid and a carbon base.[9] In principle, the catalytic cycle could be maintained even if **5e** is a weaker acid compared to the aniline **3**, resulting in an "uphill" proton transfer between **4** and **5** to give **3** and **6** in an unfavorable equilibrium. It is possible that an example of this behavior was encountered in Table 1, entry 6. High ee was obtained using ethyl acetate as the achiral acid, even though the corresponding pK_a(DMSO) = 27.5−30[7a,b] may be higher than that (27.7)[4] of **3**. However, the pK_a values in THF are not known in either example, and ion-pairing effects could change the relative acidities in the ether solvent.[7a]

In summary, catalytic asymmetric protonation has been extended to the amide enolate family. Slow addition of an achiral proton donor **5** as the stoichiometric proton source allows the use of the more expensive chiral acid **3** in catalytic amounts of 5 mol % or 10 mol % to give **1** with 92 or 94% ee, respectively.[10] The optimal pK_a value for the achiral carbon acid should be near that of the chiral acid to maximize the rate of eq 1 vs eq 3, but satisfactory results can be obtained over a surprisingly broad range (ΔpK_a(DMSO) ca. 8, **5** vs **1**). Initial experiments exploring the scope of the catalytic process are promising. Deracemization of the β,γ-unsaturated amide **7** using the standard procedure with $PhCH_2CO_2$-*t*-Bu as the achiral proton donor and 10% of the chiral catalyst **3** gave recovered *(R)*-**7** with 89% ee and >95% yield. Other applications of the catalytic method are under investigation.

Acknowledgment. This work was supported by the National Institutes of Health (GM44724).

Supporting Information Available: Detailed procedure for deracemization of **1** using 5 mol % **3** and **5e** and HPLC assay conditions (1 page).

JO972147N

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(10) To 967 mg of racemic **1** (3.1 mmol) in 20 mL of THF was added *s*-BuLi (3.56 mL, 1.3 M in cyclohexane), and the solution was stirred for 1 h. Catalyst **3** (42 mg, 0.15 mmol) was added in 2 × 1.0 mL of THF at −78 °C. After 15 min, a solution of ethyl 4-(dimethylamino)phenylacetate (10 mL of a 0.62 M solution in THF, 6.2 mmol) was added over 1.5 h using a syringe pump (−78 °C, N_2 atmosphere throughout). After 20 min, the solution was warmed to −20 °C over 20 min and quenched with 10 mL of saturated NH_4Cl. Drying and solvent removal gave 907 mg (94%) of **1** (92% ee) as an oil that solidified on standing. The product can be upgraded to >99% ee by crystallization.[4].

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