Enantioselective Enolate Protonation with Chiral Anilines: Scope, Structural Requirements, and Mechanistic Implications

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Abstract: High enantioselectivity has been demonstrated in the protonation of *N,N*-diisopropyl amides (Table 1, entries 1−4, 7, and 10−13) derived from certain β,γ unsaturated acids. Depending on double bond geometry and the degree of substitution at the γ-carbon, γ-protonation can be a competing reaction in the case of the aliphatic substrates **12**, **14b**, **14d**, and **18**. The evidence is most consistent with a mechanism that involves proton transfer from **1a** to a mixed aggregate consisting of enolate **4a** and the lithiated amide **5**, but direct proton transfer from **1a** to the enolate is not ruled out.

Some years ago, we reported that the commercially available chiral aniline **1a** can be used for the enantioselective protonation of hindered amide enolates **4**.[1] Subsequent work has established that the process can be carried out under catalytic as well as stoichiometric conditions,[2] and that there is a qualitative relationship between the optimum pK_a value of the "chiral acid" and the pK_a of the carbonyl substrate.[3] Thus, **1a** is superior to more acidic (**1c**) or less acidic (**1b**) analogues for the enantioselective protonation of the strongly basic enolate **4**. Only one enantiomer of **1a** is sold, but Noyori hydrogenation can be used to prepare a quasi-enantiomeric diamine **2a** that reacts with complementary enantioselectivity.[4] These chiral "acids" protonate the enolates of hindered amides **3** with enantioselectivities in the range of 90% ee or better. A variety of other chiral proton donors are now known that can be used with certain prochiral ketone enolates,[5] and some of the best results have been reported using a specific β,γ-unsaturated ester enolate as the substrate.[6] Many of these studies have reached excellent levels of enantioselectivity above 95% ee, but usually the range of substrates is limited, and the relationship between enantioselectivity and reaction variables is complex. The current report summarizes our efforts to address related issues in the protonation of amide enolates. One goal of the studies was to define the essential structural features of the chiral acids and the enolate substrates required for high enantioselectivity. Another goal was to gain insight into the mechanistic aspects of the process. The clarification of transition state preferences has proved to be difficult, but some progress has been made as described below.

Results

Most of the detailed optimization experiments have been performed using the naproxen amide *rac*-**3a** as the substrate. The hindered amide requires somewhat forcing enolization conditions to ensure >98% conversion to the enolate **4**, but treatment with *s*-BuLi at −78 °C is sufficient, and the process is easily reproducible if 1.75 equiv of the base is used. When the resulting enolate **4** is quenched with TMSCl, careful removal of solvent followed by NMR assay affords a 24:1 ratio of enol silane isomers in the best experiments. According to NOE evidence,[7] the major enol silane is derived from enolate **4-*Z***, so this is the isomer that is largely responsible for the enantioselective protonation.

In the first experiments, the enolate solution from *rac*-**3a** was treated with 2 equiv of **1a** at −78 °C, followed by quenching at the same temperature after 30 min. Similar results were obtained using a Lewis acid (BF_3/Et_2O) or a Brønsted acid (CF_3CO_2D) to quench the enolate, and the product (*R*)-**3a** was obtained with 85% ee in both experiments. In the latter case, the level of deuterium incorporation was less than 20% by NMR assay, suggesting that the α-proton in *(R)*-**3a** comes from **1a** rather than from the quenching agent, but the issue was not probed beyond the qualitative level at this stage of work.

Initially, the BF_3 quenching procedure was used for comparison with an alternative enolate protonation method that relies on BF_3 complexation of chiral amine ligands to force internal proton return (ipr).[7] The ipr method is very sensitive to stoichiometry and order of mixing, and requires a mixed aggregate intermediate derived from 1 equiv of a chiral amine as well as 1 equiv of the corresponding lithium amide per equivalent of the enolate for optimum enantioselectivity.[7] However, the reaction of **4a** with **1a** proved to be relatively fast, and proton transfer was >80% complete before the

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

entry	amide	ee, %	entry	amide	ee, %
1	**3a**	97	10	**10**	97
2	**3b**	97[b]	11	**12**	95[e]
3	**3c**	97	12	**14a**	97
4	**3d**	95[c]	13	**14b**	95[f]
5	**6a**	79	14	**14c**	53
6	**6b**	73	15	**17a**	40[g]
7	**7**	95[d]	16	**17b**	32[g]
8	**9a**	71	17	**18**	73[g]
9	**9b**	60			

[a] Enolate generation in THF using *s*-BuLi at −78 °C; >90% recovery after NH_4Cl quench, 0 °C unless noted; assay by hplc analysis, chiral stationary phase; *(R)*-configuration major unless noted. [b] The ee value was determined after conversion to *(R)*-**11**. [c] Quench at −25 °C. [d] Recovery: 83% after chromatography. [e] The isomer **13** was the major product, 66% yield; 18% of **12** was obtained. [f] The product of γ-protonation (**15b**) was isolated in 30% yield in addition to **14b** (60%). [g] Absolute configuration not assigned.

quenching agent was added (NMR assay).[7] The issue of stoichiometry was therefore addressed, and it was found that there is no specific requirement for the use of 2 equiv of the chiral amine or a substantial excess of base. A careful experiment using 1.1 equiv of *sec*-butyllithium and 1.0 equiv of **1a** followed by quenching with BF_3/Et_2O at −78 °C gave nearly the same result (81% ee for (*R*)-**3a**) as in the previous experiments. More recently, the corresponding conversion has been performed under catalytic conditions using as little as 5 mol % of **1a** together with excess *sec*-butyllithium and an achiral proton source ($PhCH_2CO_2Et$), resulting in (*R*)-**3a** with >90% ee.[2] These observations have a number of ramifications to be discussed later, but they prove that the protonation of **4a** involves direct proton transfer from **1a**, and not the ipr process. On the other hand, the results were more easily reproducible if excess *s*-BuLi (1.75 equiv) was used with 2 equiv of **1a** for enolate quenching, so this procedure was adopted in subsequent experiments.

Further optimization work established that the proton-transfer process does not go to completion unless the mixture of **1a** + **4a** is warmed prior to quenching. In the case of *rac*-**3a** as the substrate, warming to 0 °C followed by NH_4Cl/H_2O quench gave ee values near 90%. The final improvement was realized when the commercial material (the tartrate salt of **1a**) was recrystallized prior to neutralization with aqueous NaOH, and the resulting **1a** was recrystallized twice. With maximum precautions taken, the reaction of **4a** with **1a** gave *(R)*-**3a** in >95% yield and with 97% ee. If desired, **1a** could be recovered by simple acid/base extraction, recrystallized, and reused in subsequent enolate protonation experiments.

When the same conditions were used with structurally related amides *rac*-**3b** or *rac*-**3c**, essentially identical results were obtained (Table 1, see entries 1−4). However, the flurbiprofen amide *rac*-**3d** behaved differently, and gave (*R*)-**3d** with only 16% ee. The problem was traced to partial equilibrium between the relatively acidic **3d** and the corresponding enolate **4d** in the presence of lithiated aniline **5**, and this was confirmed by a control experiment.[8] Fortunately, the resulting racemization of **3d** could be suppressed by lowering the quenching temperature from 0 to −20 °C. This adjustment in the usual procedure gave (*R*)-**3d** with 95% ee.

Variation of the α-alkyl substituent resulted in decreased enantioselectivity. Thus **6a** and **6b** were obtained with 79% ee and 73% ee, respectively, from the corresponding enolates. The sense of enantioselection was confirmed by synthesis of (*R*)-**6a,b** from the known acids, but attempts to cleave the amides by hydrolysis encountered partial racemization. To avoid this complication, a derivative of the α-arylpropionamide family was sought that could be prepared with high enantioselectivity from the enolate by protonation with **1a**, and that could also be cleaved to the corresponding acid with retention of stereochemistry. A solution to the problem was found with the hydrazide **7**, available from *N,N*-dimethyl-*N′*-isopropylhydrazine and the acid chloride from **8a** and oxaloyl chloride. The hydrazide **7** is isostructural with **3b**, and the corresponding enolate reacts with **1a** with nearly the same enantioselectivity (95% ee). Subsequent hydrolytic cleavage was possible under oxidative conditions using ceric ammonium nitrate (CAN) in HOAc/MeCN/water,[9] and afforded the acid **8a** in 64% yield. Conversion to the ester **8b** with $Me_3SiCH{=}N_2$[10] occurred smoothly in methanol and subsequent hplc assay and comparison with authentic material confirmed the (*R*) configuration with 93% ee. Thus, it is possible to carry out the enantioselective enolate protonation using a substrate that is readily cleaved to the carboxylic acid with minimal loss of enantiomeric excess.[11] This result was not unexpected, but the similarity in ee for the hydrazide **7** vs the corresponding amide **3b** (Table 1, entry 2) is significant in the context of transition state characteristics. Presumably, the presence of an additional nitrogen in the enolate corresponding to **7** could influence enolate stability and geometry because there are additional options for lithium complexation. Since no change in enantioselectivity was observed, it appears that the steric similarity between **3b** and **7** may be the dominant factor. Certainly, the *N,N*-diisopropyl substituents in **3b** are important. This is apparent in the lower enantioselectivity seen with the corresponding *N,N*-dimethyl amides **9a** and **9b** in the usual experiment (Table 1, entries 8 and 9, 71% ee and 60% ee, respectively).

To gain further insight regarding geometric factors that influence enantioselectivity, a number of β,γ-unsaturated amide enolates were compared as substrates for the asymmetric protonation (Scheme 2). The cyclohexenyl analogue **10**[13] was expected to mimic **3b** in terms of geometry, and the expected high enantioselectivity (97% ee) was confirmed (Table 1, entry 10). The reaction proceeded in excellent yield, sufficient to allow the use of the resulting (*R*)-**10** as the starting material for the synthesis of chiral butenolides via diastereoselective osmylation and intramolecular acyl transfer.[14] To confirm the absolute configuration of (*R*)-**10**, a chemical correlation was performed with **3b**. This sequence was based on the Birch reduction of **3b** to **11**, followed by partial hydrogenation using the Wilkinson

(8) In a control experiment, *(R)*-**3d** (95% ee) was treated with the same ratio of diamine **1a** + lithioamide **5** 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, indicating partial racemization.

(9) De Oliveira Baptista, M. J. V.; Barrett A. G. M.; Barton, D. H. R.; Girijavallubhan, M.; Jennings, R. C.; Kelly, J.; Papadimitriou, V. J.; Turner, J. V.; Usher, N. A. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1477.

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(11) A hydrazide corresponding to **7**, but derived *from N,N′*-diisopropylhydrazine could also be deracemized. Because of the presence of an N−H subunit, a temporary blocking procedure was used as follows: N−H lithiation with 1 equiv of *n*-BuLi; N-silylation with TMSCl (1 equiv) at −78 °C; enolate formation with 2 equiv of *n*-BuLi; protonation with **1a**, and quenching as usual. The recovered hydrazide after aqueous workup was formed with 69−72% ee.

(12) Prepared from the known carboxylic acids (ref 13) via the acid chloride and diisopropylamine; see the Experimental Section.

(13) (a) **10**: Kon, G. A. R.; Nargund, K. S. *J. Chem. Soc. C* **1932**, 2461. (b) **12**: Black, T. H.; Eisenbeis, S. A.; McDermott, T. S.; Maluleka, S. L.; *Tetrahedron* **1990**, *46*, 2307. (c) **14c**: Henin, F.; Mortezaei, R.; Muzart, J.; Pete, J. P.; Piva, O. *Tetrahedron* **1989**, *45*, 6171. (d) Pirkle, W. H.; Welch, C. J. *J. Liq. Chromatogr.* **1991**, *14*, 3387.

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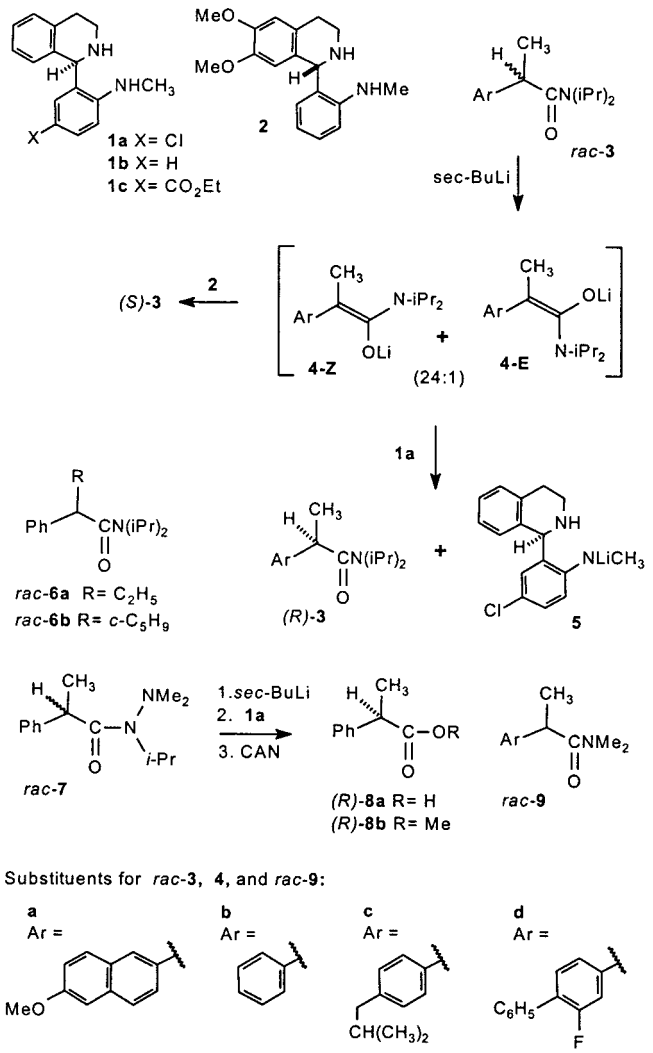
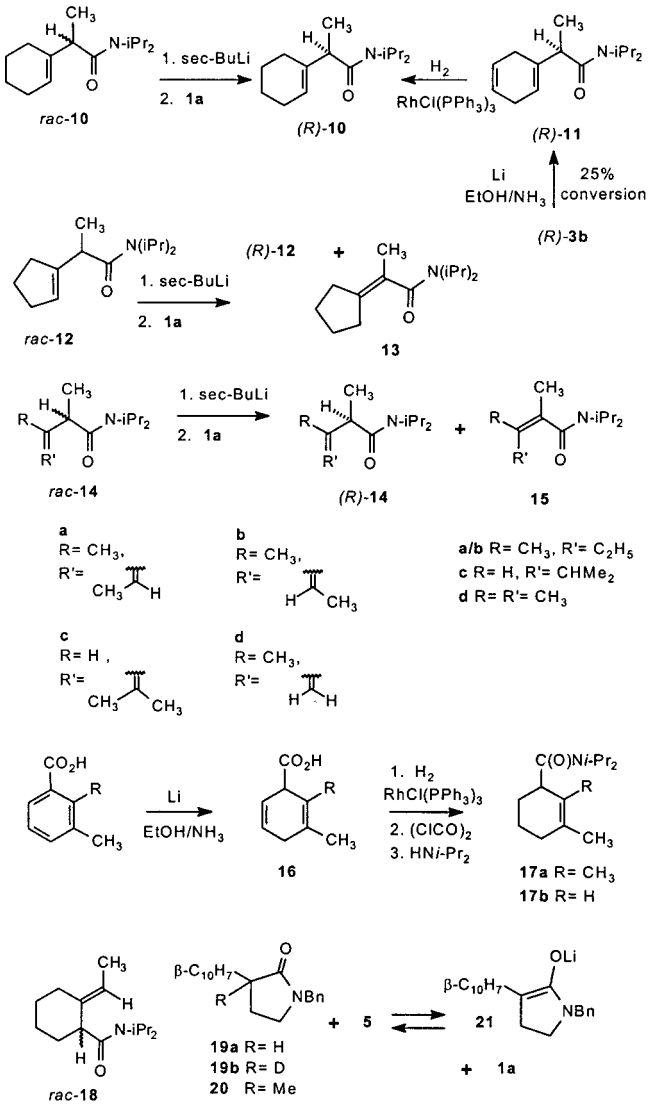
Scheme 1



Scheme 2



catalyst. It proved very difficult to separate unreacted **3b** and **11** from **10**, but sufficient material was obtained from the best chromatography fractions to confirm that the absolute configuration of (*R*)-**3b** is the same as in the enolate protonation experiment to form *rac*-**10**.

A cyclopentenyl analogue **12** was investigated next, and an unexpected result was obtained. Enolate generation with *s*-BuLi proceeded normally, and enolate quenching with NH_4Cl/H_2O returned the starting *rac*-**12**. However, the corresponding experiment using **1a** to quench the enolate resulted in **13** as the major product (79%) together with *(R)*-**12** (18%; 95% ee). In other respects, the reaction was typical in that the bright yellow color of the enolate was discharged upon the addition of **1a** at −78 °C, and was replaced by the pink-orange color that is characteristic of the *N*-lithiated derivative **5**.

Similar regiochemical results were encountered with certain other β,γ-unsaturated amides, depending on the details of substitution at the γ-carbon. Thus, **14a**[15] reacted normally upon treatment with *s*-BuLi followed by **1a** to give *(R)*-**14**, 97% ee,[16] with nearly quantitative recovery. No definitive evidence was found for the isomeric amide **15a** that would be formed by γ-protonation of the conjugated enolate, although traces of **14b** were detected due to contamination in the starting material **14a**. In contrast, the same experiment starting from the *Z*-trisubstituted alkene isomer *rac*-**14b** afforded a substantial amount (30%) of **15b** (*Z*-isomer) in addition to (*R*)-**14b**, (95% ee), while *rac*-**14d** gave **15d** with >10:1 selectivity. The corresponding reaction of the γ,γ-dimethyl amide *rac*-**14c** produced only the desired amide, but the enantiomeric purity was significantly lower (50% ee). Presumably, the absence of a branch point at the β-carbon in **14c** is the reason for the modest enantioselectivity compared to **14b**.

Partially constrained amide analogues of **14** were explored in an attempt to clarify transition state preferences. Thus, **17a** and **17b** were prepared from the known acids.[17] The corresponding dienolates would be able to adopt *E* or *Z* geometries with respect to the exocyclic enolate double bond, but the cyclohexenyl ring enforces a transoid conjugated dienolate geometry. On the other hand, the amide **18**[18] (exocyclic ethylidene derivative) can adopt *E* or *Z* geometries in a cisoid conjugated enolate. Enolate formation and protonation with **1a** proceeded smoothly with **17a,b**, and no products of γ-protonation were detected, but **17a** and **17b** were recovered with

(15) Prepared from the lithium enolate of *N*,*N*-diisopropylpropionamide and *E*-2-bromo-2-butene (for **14a**) or *Z*-2-bromo-2-butene (for **14b**) in the presence of $NiBr_2$ by analogy to the following: Millard, A. A.; Rathke, M. W. *J. Am. Chem. Soc.* **1977**, *99*, 4833.

(16) The absolute configuration is assigned by analogy to *(R)*-**10**.

(17) Van Bekkum, H.; Van den Bosch, C. B.; Van Minnen-Pathuis, G.; De Mos, J. C.; Van Wijk, A. M. *Recl. Trav. Chim. Pays-Bas* **1971,** *90*, 137.

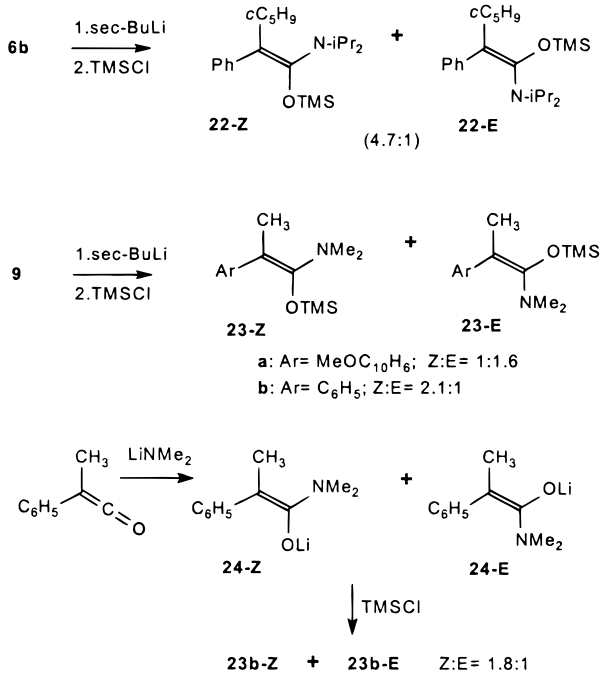
(18) Whitesell, J. K.; Helbling, A. M. *J. Org. Chem.* **1980**, *45*, 4135.

modest ee (40% ee and 32% ee, respectively).[19] These selectivities resemble the 50% ee value observed in the asymmetric protonation to afford **14c**, a case where the dienolate is likely to prefer a transoid geometry to minimize nonbonded interactions. A higher ee value (73% ee) was obtained with the constrained cisoid amide **18**, but this system gave substantial amounts of a second product (1.25:1 ratio) that could be the conjugated isomer. Isomer separation failed and the NMR characteristics of the new isomer were largely obscured by signals due to **18**.

One additional example of a constrained amide was explored (**19a**). This substrate is constrained to have a *Z*-enolate geometry, similar to **4-*Z*** (Scheme 1), but with the enolate carbons as well as the nitrogen substituents constrained to a nearly planar arrangement within the five-membered ring. The dark red enolate **21** was formed in the usual way, and addition of **1a** caused a color change to an intense orange. When this solution was warmed to 0 °C and quenched with NH_4Cl/H_2O, the resulting **19a** was completely racemic according to hplc assay. Because of the unusual color behavior, it was suspected that the enolate may not be completely protonated by **1a** due to the expected decrease in the ion pair pK_a of **19a**, resulting from the cyclic structure.[20] To test this possibility, the experiment was repeated to the stage of the intensely orange solution (**19a** + 2 equiv of *s*-BuLi at −78 °C, followed by 2.5 equiv of **1a**; warmed to −50 °C), and excess iodomethane was added. This caused the color to fade as the temperature was allowed to reach 0 °C. After aqueous quench, the experiment returned less than 3% of **19a**, and NMR signals were observed consistent with the formation of **20**. Evidently, the enolate **21** is in equilibrium with **19a**, the amine **1a**, and the corresponding *N*-lithio derivative **5**, and *C*-methylation of **21** can take place. For final confirmation, a similar experiment was performed where **21** was generated, combined with **1a** as before, and the resulting mixture was quenched with CF_3CO_2D. This returned a ca. 6:1 mixture of **19a**:**19b**, suggesting that a minimum of ca. 15% of enolate **21** is present in the equilibrium mixture. This 15% is a lower limit for the presence of enolate because CF_3CO_2D is likely to induce substantial internal proton return involving the N−H protons of **1a** in an enolate−diamine complex.[21] Thus, the cyclic lactam enolate **21** is not basic enough for complete and irreversible protonation by **1a**, as required in an asymmetric protonation experiment. An attempt to protonate **21** with the more acidic **1c** also gave racemic **20a**, so this series of experiments was not pursued.

An effort to clarify the importance of enolate geometry in the flexible substrates **3a**, **6**, and **9** was initiated in the hope that enantioselectivity in the asymmetric protonation might be optimized by optimizing the enolate *Z*:*E* ratio. As already mentioned, the usual *s*-BuLi conditions converted **3a** into **4a-*Z*** and **4a-*E*** in a ratio of 24:1 according to a highly optimized assay based on conversion to the enol silane. This isomer ratio is qualitatively consistent with the 97% ee if the minor enolate isomer affords mostly the minor product enantiomer. However, numerous attempts to test this idea by preparing enolate mixtures enriched in the *E*-enolate failed because the same dominant *Z*-isomer **4a-*Z*** was formed using a variety of deprotonation conditions. Apparent support for the importance of enolate geometry in the asymmetric protonation was obtained when it was found that the α-cyclopentyl analogue **6b** produces a 4.7:1

Scheme 3



Z:*E* ratio of **22-*Z***:**22-*E*** (Scheme 3). This ratio corresponds qualitatively to the enantiomer ratio (6.3:1) for the asymmetric protonation of **6b** (73% ee) with **1a**. Presumably, the lower enolate *Z*:*E* ratio from **6b** reflects a steric effect (cyclopentyl vs phenyl) on the population of amide rotamers in the transition state for deprotonation, so the effect of decreasing the size of amide *N*-alkyl substituents was probed using **9b** as the substrate. This proved difficult because the corresponding enol silanes **23b-*Z*** and **23b-*E*** were exceptionally sensitive to hydrolytic cleavage back to the starting **9b**. The highest ratio (2.1:1) was seen under conditions where hydrolytic cleavage was minimal (<5%), so the 2.1:1 ratio probably corresponds to the enolate ratio. If this is correct, then enolate geometry cannot be a dominant factor in the case of **9b** because the enantioselectivity (71% ee) indicates an enantiomer ratio that is considerably higher (5.9:1).

Evaluation of enantioselectivity for the individual enolate isomers would require access to the same enolate, but with a substantially different *Z*:*E* ratio. To this end, an independent method for generation of the enolate **24** was investigated following an analogy for making ester enolates from ketenes.[22] Thus, distilled methyl phenyl ketene was added to $LiNMe_2$ in THF at −78 °C, and the resulting **24** was converted to **23b** with TMSCl. The isomer ratio was ca. 1.8:1 **23b-*Z***:**23b-*E*** in the best experiment, nearly the same as in the deprotonation experiments starting from **9a**, so this approach was not investigated further. However, the result was useful in that it supports the assignment of enolate geometry for **23b**. Originally, this was based on chemical shift analogies,[23] but the assignment is also consistent with least hindered attack by $LiNMe_2$ in the ketene trapping experiment.

(19) Absolute configuration not assigned.

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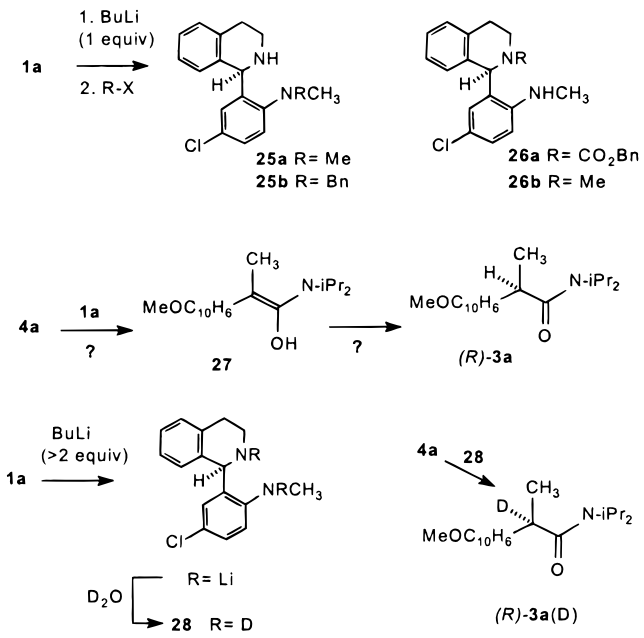
(21) Seebach, D.; Boes, M.; Naef, R.; Schweizer, W. B. *J. Am. Chem. Soc.* **1983**, *105*, 5390. Hogeveen, H.; Zwart, L. *Tetrahedron Lett.* **1982**, *23*, 105.

(22) Baigrie, L. M.; Seiklay, H. R.; Tidwell, T. T. *J. Am. Chem. Soc.* **1985**, *107*, 5391. Kresz, G.; Runge, E.; Ruch, E. *Justus Liebigs Ann. Chem.* **1972**, 756, 112.

(23) Preliminary assignment of the *Z*-enol silane geometry was made based on chemical shift precedents fom ref 22 (the *Z*-enol silane $SiMe_3$ signal upfield relative to the *E*-isomer). The assignment was confirmed in the case of the enol silanes derived from **4a** by an NOE experiment. In contrast to the major enol silanes derived from **4a** and from **9b**, the major enol silane isomer from **9a** has a downfield chemical shift (δ 0.253 ppm, major, vs −0.122 ppm, minor), suggesting that this may be the *E*-enol silane **23a-*E***. A definitive assignment could not be made using NOE methods.

Scheme 4



Attention was turned to the evaluation of the structural features of **1a** that are important for its use as an effective chiral proton donor (Scheme 4). From the experimentally determined DMSO pK_a value of 27.7,[24] it appeared likely that the aniline proton is involved in enolate protonation. To test this supposition, **25a** was prepared from **1a** via the lithiated diamine **5a** by *N*-alkylation with iodomethane. As expected, **25a** was not effective in the asymmetric protonation of **4a**. In fact, the minimal 4% ee in the product **3a** favored the (*S*)-enantiomer, in contrast to the behavior of **1a**. It was less clear whether the piperidine N−H would be important, so two derivatives **26a** (from **1a** and $ClCO_2Bu$) and **26b** (from **25b** via reductive methylation and hydrogenolysis over Pd/C) were compared, but neither was effective (<5% ee with **4a**). Thus, both of the N−H subunits of **1a** are essential for the enantioselective protonation of amide enolates, presumably because both nitrogens participate in complexation of lithium in the enolate.[25] The result is consistent with transfer of the aniline N−H proton to the enolate carbon, either directly (one-step mechanism) or via the enol **27** and subsequent intramolecular proton transfer (two-step mechanism). The latter pathway could be mediated by the neutral diamine **1a** (present in excess) or by the *N*-lithio derivative **5** (two-step mechanism) acting as proton-transfer agents. A third possibility is that proton transfer occurs during aqueous workup and that the proton comes from the quenching agent. To choose among these options, the deuterated diamine **28** was prepared by dilithiation of **1a** with excess *s*-BuLi, followed by quenching with D_2O. Best results were obtained by minimal handling of **28**, so the unpurified diamine was used in the standard enantioselective protonation experiment with **4a**. The resulting *(R)*-**3a**(D) was found to be >80% deuterated at the α-carbon by NMR integration, and the product was obtained with 92% ee. Attempts to purify the diamine **28** resulted in a lower percent deuterium incorporation. A second experiment was performed using the standard conditions for the reaction of **4a** with **1a**, but the aqueous quench procedure was carried out with NH_4Cl in D_2O. This gave no deuterium incorporation within the limits of NMR detection, and *(R)*-**3a** was isolated with 93% ee. These tests prove that the α-proton in *(R)*-**3a** is derived from **1a**.

The next series of experiments was designed to probe the details of enantioselective proton transfer from chiral aniline diamines to the enolate **4a**. The initial purpose was to learn whether the conversion from **4a** to (*R*)-**3a** occurs in a single step (direct H transfer to the amide α-carbon) or whether the reaction occurs via an enol intermediate **27**. Direct H-transfer provides a clear role for the chiral diamine **1a** in the enantioselectivity determining step, and some of the evidence points to such a scenario. For example, the qualitative correlation of chiral acid pK_a with enantioselectivity (maximum ee when the pK_a of the chiral aniline is ca. 3 units lower than the pK_a of **3**)[3] is easy to understand in this situation. More strongly acidic derivatives of **1** would react faster and less selectively, and this is the empirical result. On the other hand, the apparent correlation with aniline pK_a values might be accidental. If the enol **27** is the kinetic product, as in the case of ketone enolate protonation with a variety of acids,[26] then diamine **1a** or the lithiated **5** might serve as chiral proton carriers that mediate the conversion from enol to carbonyl. A similar process occurs in the enantioselective ketonization of dienols,[5c] and a correlation betwen aniline pK_a and the ability of the aniline to act as a proton transfer agent is plausible. Ketone enols having similar, bulky substituents can be relatively long-lived,[27a] but we could find no data directly relevant to the lifetimes of amide-derived enols. Accordingly, the reaction of **4a** with **1a** was studied at low temperatures using the REACT-IR system to monitor the process vs time and temperature. Conversion from **3a** to **4a** could be followed by the disappearance of amide carbonyl signals at 1644 cm^{-1} and the appearance of a new absorption at 1548 cm^{-1}, tentatively assigned to the enolate C═C (OLi) double bond. The latter signal vanished upon addition of **1a**, and the signals of **3a** reappeared. However, no OH absorptions of a possible enol intermediate **27** were detected, nor was there any other indication of a transient intermediate other than **4a** over the range of temperatures from −78 to 0 °C. This evidence argues against a long-lived enol intermediate, but the negative result is not decisive.

An alternative approach was considered for testing the possible involvement of the enol **27** in the enantioselectivity-determining step. If **27** is an intermediate, then a chiral environment must be maintained until **27** has been converted to *(R)*-**3a**. This is possible if **5** or unreacted **1a** participates in the proton transfer. A second possibility is that the enol **27** itself may be chiral due to restricted rotation.[27b] If it is generated with a >98% preference for one enantiomer in the protonation step, then **27** might be converted into *(R)*-**3a** without further participation by **1a**. The latter possibility is suspect for several reasons, but it can be discounted according to the evidence described below.

A qualitative test to probe the possible involvement of **5** or **1a** in proton delivery at the enolate α-carbon was performed using an analogue **29** designed to serve as a "suicide acid" in the reaction with **4a** (Scheme 5). Conversion to the *N*-lithiated **30** must occur if the enol **27** is formed in this experiment.

(24) This value was determined by Bordwell and Satish; see ref 7.

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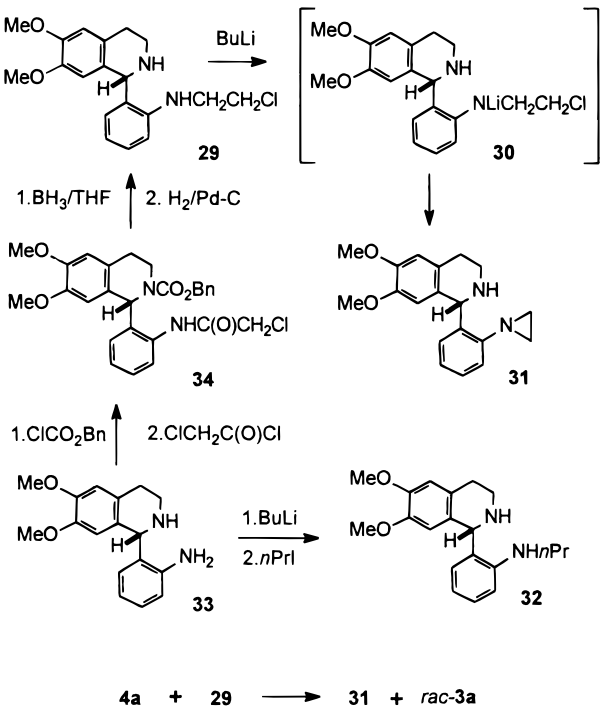
Scheme 5



However, **30** should cyclize to an aziridine **31**. If **27** is formed in a chiral geometry that is converted into *(R)*-**3a**, then the formation of **31** should be irrelevant, and the ee of the process should be comparable to that using an isostructural proton donor **32**. The latter was prepared from **33**[4] via lithiation (*n*-BuLi) and alkylation with *n*-PrI, and was shown to serve as an effective chiral acid for the protonation of **3a**, 78% ee for (*S*)-**3a** (**32** is quasienantiomeric compared to **1a**). The synthesis of **29** was challenging due to the reactivity of the "suicide" chloroethylamino side chain, but a successful route was realized by sequential *N*′-protection and *N*-chloroacetylation of **33** to give **34**, followed by borane reduction and deprotection under hydrogenolysis conditions. The resulting **29** was stable enough for rapid chromatographic purification, and treatment with *s*-BuLi at −78 °C gave the suicide product, the aziridine **31** as required to use **29** as a mechanistic probe in the enantioselective protonation. The key experiment was carried out in the usual way by adding **29** to preformed **4a** at −78 °C, followed by aqueous NH_4Cl quench at 0 °C. Aziridine **31** was formed as expected, and **3a** was isolated from the neutral products in good yield. According to hplc assay, the product was completely racemic. One added control experiment was necessary to show that the LiCl byproduct of aziridine formation would not interfere with the usual enantioselective protonation process. The control was performed with the highly selective reaction of **1a** with **4a**, and the product *(R)*-**3a** was obtained with 96% ee in the presence of an equivalent of LiCl, generated in situ under anhydrous conditions by reaction of TMSCl with *s*-BuLi. Thus, formation of **27** in a chiral conformation that determines enantioselectivity in a subsequent proton transfer is unlikely. Furthermore, the experiment suggests that the chiral proton donor or its *N*-lithiated derivative must be present in the transition state for enantioselective protonation of the enolate **4a** for high selectivity

Summary

Excellent enantioselectivity has been demonstrated in the protonation of *N*,*N*-diisopropyl amides (Table 1, entries 1−4, 7, and 10−13) derived from certain β,γ-unsaturated acids. A flexible, cisoid dienolate geometry appears necessary for the highest selectivity, as indicated by the low selectivities with the constrained transoid dienolates from **17a** or **17b**. Enolate geometry may be important for the hindered *N*,*N*-diisopropyl amides, but enantioselectivity with the *N*,*N*-dimethyl analogues **9a** or **9b** (Table 1, entries 8 and 9) is higher than expected if each enolate isomer reacts with high and opposite enantiospecificity. Depending on double bond geometry and the degree of substitution at the γ-carbon, γ-protonation can be a competing reaction in the case of the aliphatic substrates **12**, **14b**, **14d**, and **18**. The undesired protonation pathway is dominant in the case of **12** and **14d**, and results in the formation of the α,β-unsaturated amides **13** and **15b**, respectively. Fehr and Galindo have reported analogous observations regarding the regioselectivity of protonation in their study of cyclogeranate ester dienolates.[6c]

The proton-transfer step is not sensitive to the presence of lithium halide, in contrast to some of the other enantioselective enolate protonation techniques, and the stoichiometry is not critical if sufficient base is used for complete conversion to the enolate. Most of the mechanistic evidence is consistent with direct proton transfer from the aniline nitrogen of **1a** to the enolate carbon. This would account for the labeling results using **28**, as well as the qualitative pK_a trends. However, there is one data point that argues against the simplest version of a direct proton-transfer process. The experiment where **4a** is treated with **29** to give racemic **3** cannot easily be understood if the transition state for enantioselective protonation involves only the chiral diamine and **4a**. Formal rejection of this mechanistic possibility is not warranted because the test experiment produces a "negative" result. On the other hand, **29** is the only derivative of **1** or **2** to give racemic **3a** among many analogues that were tested containing an alkyl group as well as a proton at aniline nitrogen. We regard the formation of racemic **3a** as mechanistically significant, partly because of the analogies (for example, **32** + **4a** to give *(S)*-**3a**, 78% ee), but mainly because there is a mechanism that is consistent with all of the evidence. This mechanism involves proton transfer from **1a** to a mixed aggregate consisting of **4a** and the lithiated amide **5**. If this is correct, then the protonation as well as the formation of the aggregate must be fast compared to the direct proton transfer from **1a** to **4a** to explain the high enantioselectivity under catalytic as well as stoichiometric conditions. However, all three components are present by the nature of the experiment, and their involvement in the selectivity-determining step cannot be ruled out. Fehr et al. have reached similar conclusions.[6] The complexity of the components in such a mechanism precludes discussion of transition state models for the enantioselective proton-transfer process, so one of the goals stated at the outset cannot be addressed pending further study. However, the scope of the enantioselective protonation of amide enolates is now clear, and the reaction with **1a** is successful with a relatively broad range of enolate substrates. Further studies will be needed to address the remaining mechanistic questions.

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

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