phenylphosphine (526 mg, 20 mmol), and anhydrous toluene (25 mL) which was previously purged with argon and heated for 45 min at 80–81.5 °C. Aliquots were taken at the intervals indicated in Table II. Each aliquot was quenched by being poured into a mixture of 3 mL of solution A (0.77 g of 1-chloronaphthalene in 100 mL of pentane) and 2 mL of solution B (HCl, 1.2 N) and shaken for 30 s. The organic layers were washed and dried and analyzed by GLC to give the results indicated in Table II. A blank experiment was performed without palladium acetylacetonate and triphenylphosphine. After 24 h *cis*-**2g** remained unchanged.

***cis*-3-Methylcyclohexanol Acetate (10).** A shaken mixture of *cis*-**2g** (2.92 g, 20 mmol), a catalytic amount of Ra–Ni W2, and ethanol (50 mL) was hydrogenated at atmospheric pressure for 2 h until no more uptake of hydrogen was observed. The mixture was filtered through a short column of Celite and the solvent was fractionally distilled. The residue afforded 2.06 g (66%) of **10**: bp 69 °C/10 mmHg; IR ($CHCl_3$) 1725 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.53–2.10 (m, 9 H), 0.93 (d, J = 5.3 Hz, 3 H), 2.02 (s, 3 H), 4.46–4.91 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 20.78, 21.81, 23.61, 30.98, 31.16, 37.72, 40.21, 72.67, 169.66.

Acknowledgment. Financial support from CAICYT (Ministerio de Educación y Ciencia of Spain) through Grant no. 2014/83 is gratefully acknowledged.

Registry No. 1, 675-10-5; **2a**, 21040-45-9; **2b**, 7204-29-7; **2c**, 6737-11-7; **2d**, 31001-80-6; **2e**, 14447-34-8; **2f**, 116504-03-1; *cis*-**2g**, 61221-47-4; *trans*-**2g**, 61221-48-5; **3a**, 115580-35-3; (*E*)-**3b**, 115580-47-7; (*Z*)-**3b**, 115580-49-9; **3c**, 115580-46-6; **3d**, 115580-36-4; **3e**, 115580-37-5; **3f**, 16266-64-1; *cis*-**3g**, 116503-95-8; *trans*-**3g**, 116503-96-9; **3h**, 116503-97-0; **3i**, 116503-98-1; **3j**, 16266-65-2; **4a**, 116503-99-2; **4b**, 115580-48-8; **4f**, 16266-55-0; **5a**, 116504-04-2; **6a**, 115580-42-2; **6b**, 39849-74-6; **6c**, 116504-00-8; **6d**, 115580-43-3; **6e**, 115580-44-4; *cis*-**6g**, 116504-01-9; *trans*-**6g**, 116504-02-0; **7**, 115580-45-5; *cis*-**8a**, 22049-46-3; *trans*-**8a**, 22031-97-6; *cis*-**10**, 116531-33-0; *trans*-**10**, 66922-08-5; (*E*)-$H_3CCH{=}CHCH_2OH$, 504-61-0; (*E*)-$HOCH_2CH{=}CHPh$, 4407-36-7; $H_3CCH(OH)CH{=}CH_2$, 598-32-3; (*E*)-$H_3CCH(OH)CH{=}CHCH_3$, 3899-34-1; palladium acetylacetonate, 14024-61-4; 2-cyclohexen-1-ol, 822-67-3; 3-methyl-2-buten-1-ol, 556-82-1; 4-nitrobenzoyl chloride, 122-04-3; *cis*-5-methylcyclohex-2-en-1-ol 4-nitrobenzoate, 52393-62-1.

Use of Carboxylic Acids as Chiral Solvating Agents for the Determination of Optical Purity of Chiral Amines by NMR Spectroscopy

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Optically pure mandelic acid, Mosher's acid, and *N*-(3,5-dinitrobenzoyl)phenylglycine have been used as chiral solvating agents to induce nonequivalence in the ^1H NMR spectra of several diamines, amino acid esters, amino alcohols, and other amines. The identity of the chiral solvating agent and the stoichiometry of the solvation complexes that yield the greatest nonequivalence varies with the nature of the substrate.

The increasing number of efforts devoted to the design of chiral ligands for metal-promoted reactions in organic synthesis have necessitated the development of methods for measuring the optical purity of both the ligands and the reaction products. The use of specific rotations to determine optical purity can be problematic since rotations vary significantly with the conditions of the measurement, particularly for polar molecules.[1] We were recently faced with the problem of determining the optical purity of several amino acid esters, β-amino alcohols and vicinal diamines of general structures **1–5** for use as potential chiral ligands in the asymmetric osmium tetroxide oxidation of olefins to vicinal diols.[2] Our initial efforts using the chiral shift reagent $Eu(tfc)_3$ were abandoned due to the immediate onset of severe line broadening when the shift reagent was added, even in trace amounts.[3] We subsequently found that mandelic acid and other readily available, optically pure carboxylic acids (**6–8**) can be successfully utilized as chiral solvating agents (CSA's) with ^1H NMR spectroscopy.[4] Nonequivalence in the ^1H NMR spectrum suitable for integration was achieved under ambient conditions, enabling the measurement of the optical purity.

Results and Discussion

Induced Nonequivalence. Nonequivalence[5] was observed in the ^1H NMR spectra of the racemic substrate amines **1–5**, usually in the signals of the protons adjacent to the amino group, with mandelic acid (**6**),[6] Mosher's acid

(1) For some specific examples: (a) Horn, D. H. S.; Pretorius, Y. Y. *J. Chem. Soc.* **1954**, 1460. (b) Horeau, A. *Tetrahedron Lett.* **1969**, 3121. (c) Kumata, Y.; Furukawa, J.; Fueno, T. *Bull. Chem. Soc. Jpn.* **1970**, *43*, 3920. (d) Meyers, A. I.; Roth, G. P.; Hoyer, D.; Barner, B. A.; Laucher, D. *J. Am. Chem. Soc.* **1988**, *110*, 4611.

(2) (a) Tokles, M.; Snyder, J. K. *Tetrahedron Lett.* **1986**, *27*, 3951. (b) Tokles, M.; Snyder, J. K., accepted for publication in *J. Org. Chem.*

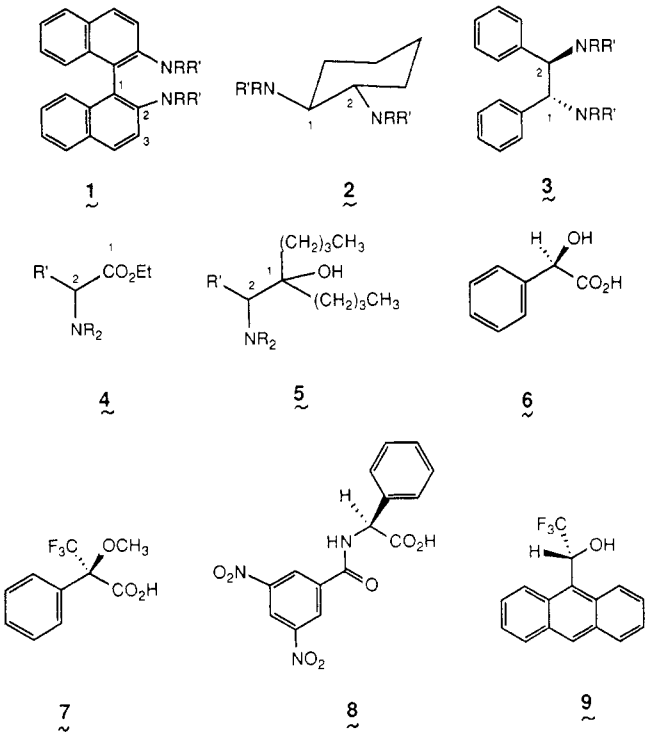
(3) For a similar example of peak broadening in binaphthyl derivatives in the presence of a lanthanide shift reagent: (a) Brown, K. J.; Berry, M. S.; Waterman, K. C.; Lingenfelter, D.; Murdoch, J. R. *J. Am. Chem. Soc.* **1984**, *106*, 4717. A recent report suggests the use of polar NMR solvents such as acetonitrile-d_3 to avoid this broadening: (b) Sweeting, L. M.; Crans, D. C.; Whitesides, G. M. *J. Org. Chem.* **1987**, *52*, 2273.

(4) For a review of the use of NMR in determining optical purity: Rinaldi, P. L. *Prog. Nucl. Magn. Reson. Spectrosc.* **1982**, *15*, 291. For recent reviews of chiral solvating agents: (a) Pirkle, W. H.; Hoover, D. J. *Top. Stereochem.* **1982**, *13*, 263. (b) Weisman, G. R. in *Asymmetric Synthesis*; Morrison, J. D., Ed., Academic: New York 1983; Vol. 1, pp 153–172. For a recent report with an excellent reference list: (c) Sweeting, L. M.; Anet, F. A. *Org. Magn. Reson.* **1984**, *22*, 539. For recent reports on the determination of the enantiomeric purity of primary monoamines using chiral derivatizing agents: (d) Johnson, C. R.; Elliott, R. C.; Penning, T. D. *J. Am. Chem. Soc.* **1984**, *106*, 5019. (e) Terunuma, D.; Kato, M.; Kamei, M.; Uchida, H.; Nohira, H. *Chem. Lett.* **1985**, 13. (f) Feringa, B. L.; Strijtveen, B.; Kellogg, R. M. *J. Org. Chem.* **1986**, *51*, 5484. (g) Nabeya, A.; Endo, T. *J. Org. Chem.* **1988**, *53*, 3358.

(5) The degree of nonequivalence, $\Delta\delta$, is the separation in ppm between the signals experiencing the nonequivalence induced by the CSA.

(6) Previous use of **6** as a chiral solvating agent for amines: (a) Dyllick-Brenzinger, R.; Roberts, J. D. *J. Am. Chem. Soc.* **1980**, *102*, 1166. (b) Zingg, S. P.; Arnett, E. M.; McPhail, A. T.; Bothner-By, A. A.; Gilkerson, W. R. *J. Am. Chem. Soc.* **1988**, *110*, 1565.

0022-3263/88/1953-5335$01.50/0



(7),[7] or *N*-(3,5-dinitrobenzoyl)phenylglycine (8)[8] as chiral solvating agents in $CDCl_3$ and other common NMR solvents (Table I).[9] While the $\Delta\delta$ values could be enhanced by careful adjustment of solvent ratio in a binary or ternary solvent system, in most cases this was not necessary to achieve base-line resolution to monitor optical purity. Nonetheless, the $\Delta\delta$ values were sensitive to the solvent composition, and nonequivalence was only observed with **7** in benzene-d_6 for **1a**, **2a**, and **2e**. For some substrates, the induced nonequivalence had insufficient resolution for accurate optical purity determination by integration. The only substrate in which we were unable to observe nonequivalence with any CSA was **2c**. As expected, the most convenient optical purity determinations were those of the *N*-methylamino substrates wherein nonequivalence was induced in the methyl singlets. Attempts to utilize (*R*,*R*)-(+)-tartaric acid, (*R*,*R*)-2,3-di-*O*-benzoyltartaric acid,[10] and (1*R*)-(−)-10-camphorsulfonic acid as chiral solvating agents with several diamines were unsuccessful. The relatively expensive (*R*)-(−)-2,2,2-trifluoro-1-(9-anthryl)-ethanol (**9**)[11] succeeded in inducing nonequivalence for some but not all of the few substrates examined, (Table I; **1c**, **2b**, **2d**, and **3a**).

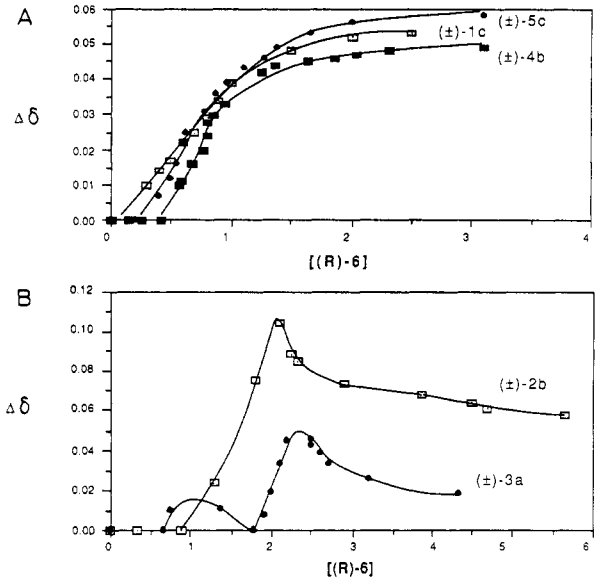


Figure 1. Dependence of the $\Delta\delta$ induced in ^1H NMR spectra of (A) (±)-**1c**, (±)-**4b**, and (±)-**5c** and (B) (±)-**2b** and (±)-**3a**, both in $CDCl_3$ on [(*R*)-**6**]. The $\Delta\delta$ values are in units of ppm, the [(*R*)-**6**] is in units of mole equivalents relative to the substrates.

Mandelic acid, **6**, induced excellent, base line resolved nonequivalence in the *N*-methyl signals of the binaphthyldiamines **1b** and **1c**. Mosher's acid, **7**, however, was better than **6** for achieving nonequivalence in the cyclohexanediamines, **2a**, **2d**, and **2e**. Both **6** and **8** were effective for inducing nonequivalence in the amino acid esters **4** and the amino alcohols **5**. Only Mosher's acid succeeded for **1a**, wherein nonequivalence was observed in the H-3 proton of the aromatic ring. In some cases, nonequivalence was optimized only with the addition of a drop or two of acetone-d_6 or methanol-d_4, which also improved the solubility of the diastereomeric salts.

Stoichiometry. The dependence of the nonequivalence induced by mandelic acid, **6**, on the [CSA]/[substrate] ratio was investigated by using racemic **1c**, **2b**, **3a**, **4b**, and **5c** as models for each class of substrate (Figure 1). Addition of **6** caused downfield shifts in the resonances of concern for both enantiomers of **1c**, **4b**, and **5c**. Nonequivalence induced in the *N*-methyl resonances of the binaphthyldiamine **1c** and the monoamine **5c**, and in the α-proton resonance of the monoamine **4b**, increased as 1–1.5 equivalents of **6** were added (Figure 1A). Further addition of **6** increased $\Delta\delta$ only marginally. Furthermore, the $\Delta\delta$ values for **1c** observed with 1 equiv of **6** were invariant to dilution within the concentration range of 0.007–0.029 M of the diastereomeric salt. These results emphasize an advantage in using carboxylic acids (e.g. **6**) over more weakly interacting CSA's (such as **9**) for enantiomeric purity determination of amines: complete formation of diastereomeric salts with maximal nonequivalence may be achieved at high dilution (small amounts of sample) without a large excess of the CSA.

The limited solubility of **6** in $CDCl_3$, which prevented the measurement of $\Delta\delta$ in the presence of a large excess of **6**,[12] was overcome by the addition of 2 or 3 drops of

(7) Previous use of **7** as a chiral solvating agent for amines, ref 6, also: (a) Baxter, C. A. R.; Richards, H. C. *Tetrahedron Lett.* **1972**, 3357. (b) Maryanoff, B. E.; McComsey, D. F. *J. Heterocycl. Chem.* **1985**, *22*, 911. (c) Villani, F. J.; Costanzo, M. J.; Inners, R. R.; Mutter, M. S.; McClure, D. E. *J. Org. Chem.* **1986**, *51*, 3715.

(8) *N*-(3,5-Dinitrobenzoyl)amino acids and their derivatives have been used as chiral bonded phase for chiral HPLC columns. For their use as chiral solvating agents: (a) Pirkle, W. H.; Tsipouras, A. *Tetrahedron Lett.* **1985**, *26*, 2989. (b) Pirkle, W. H.; Pochapsky, T. C. *J. Am. Chem. Soc.* **1986**, *108*, 5627.

(9) For racemic substrates, it is critical not to confuse nonequivalence induced by a CSA and the nonequivalence of enantiotopic ligands adjacent to a chiral center. The enantiotopic *N*-methyl resonances of the racemic as well as the optically pure amino alcohols **5** are base line separated singlets, presumably due to slow inversion of the nitrogen caused by intramolecular hydrogen bonding. Upon formation of the hydrogen chloride salt, the methyl resonances appear as doublets coupled to the NH proton. In the presence of **6**, the ^1H spectrum of optically pure **5** reveals one singlet (6 H) for the *N*-methyl groups. In contrast, racemic **5** yields two singlets (3 H each) in the presence of **6**. Addition of optically pure amine to this racemic sample in the presence of **6** led to an increase in the intensity of one of the two nonequivalent signals, confirming the nonequivalence due to the formation of diastereomeric salts. For enantiomerically enriched substrates, integration alone would suffice to establish that the observed nonequivalence is due to diastereomeric solvation complexes.

(10) Mannschreck, A.; Jonas, V.; Kolb, B. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 583.

(11) (a) Pirkle, W. H.; Sikkenga, D. L.; Pavlin, M. S. *J. Org. Chem.* **1977**, *42*, 384. (b) Pirkle, W. H.; Sikkenga, D. L. *J. Org. Chem.* **1977**, *42*, 1370. (c) Strekowski, L.; Visnick, M.; Battiste, M. A. *J. Org. Chem.* **1986**, *51*, 4836.

acetone-d_6. In comparison to the nonequivalence observed in the absence of acetone-d_6, the observed $\Delta\delta$ values for **1c** upon the initial addition of **6** were smaller. Far greater amounts of **6** could be added in the presence of acetone-d_6, however, ultimately leading to nonequivalence comparable to that observed in the absence of acetone-d_6 ([**6**]/[**1c**] = 9.8, $\Delta\delta$ = 0.052).

The (±)-cyclohexanediamine **2b**, with two strongly basic amino groups, showed an initial downfield shift of the *N*-methyl resonances as the CSA was added, but without the induction of nonequivalence when the [**6**]/[**2b**] ratio was less than 1. Increasing addition of **6** produced overall shielding of the *N*-methyl groups, and nonequivalence was observed in these signals. The nonequivalence increased as the CSA/diamine ratio approached 2 (Figure 1B). In the presence of acetone-d_6 nonequivalence was observed at an earlier stage of the titration with **6**, but a smaller $\Delta\delta_{max}$ was achieved even with a large excess of **6**. The maximum $\Delta\delta$ was observed with 2.0 molar equiv of **6** in the absence of acetone-d_6 and 1.5 molar equiv in the presence of 2 drops of acetone-d_6 per molar equiv of **2b**.

The nonequivalence induced in the α-protons of (±)-**3a** was dependent on the concentration of **6**, analogous to **2b**. With **3a**, however, nonequivalence was observed with a lower concentration of **6**, (<1 equiv). This initially induced nonequivalence disappeared with increasing amounts of **6** as the sense of nonequivalence inverted; the α-proton resonance of the diastereomeric salts which appeared at higher field when the [**6**]/[**3a**] ratio was less than 1 became the lower field α-resonance when [**6**]/[**3a**] was greater than 1.

These results can be interpreted as follows. For monoamines **4b** and **5c**, and the weakly basic binaphthyldiamine **1c**, addition of (*R*)-**6** resulted in the formation of diastereomeric, 1:1 salts, for example (+)-**1c**:(*R*)-**6** and (−)-**1c**:(*R*)-**6**, producing a downfield shift and induced nonequivalence in the resonances of the α-protons (NCH_3 or NCH) in the ^1H NMR spectra. Formation of the 1:1 diastereomeric salts was thus sufficient to measure the optical purity of these amines with NMR spectroscopy. The continued downfield shift and increasing nonequivalence of the α-protons as the amount of **6** increased beyond 1 molar equiv apparently was due to formation of increasingly complex interactions and aggregate formation, which reinforced the nonequivalence in the ^1H NMR spectra of the diastereomeric salts.[13]

For diamines **2b** and **3a**, the 1:1 diastereomeric salts with **6** which dominate at low [**6**], showed nonequivalence only for **3a**, not **2b**, in $CDCl_3$. With increasing amounts of **6**, a second molecule of **6** interacted with the diastereomeric salts. In this 1:2 complex, strong shielding of the *N*-methyl signals of the **2b**:**6** diastereomeric salts occurred, in contrast to the downfield shifts observed for the *N*-methyl signals of **1c** and **5c**, and the α-proton of **4b**. Thus, the *N*-methyl resonances of **2b** actually shift upfield despite the acid–base interaction with the second molecule of **6**. Nonequivalence was observed due to the formation of these diastereomeric complexes of **2b** (**2b**:2·**6**), and the $\Delta\delta$ increased as the 1:2 complex increased its contribution to the overall chemical shift of the **2b** resonances.

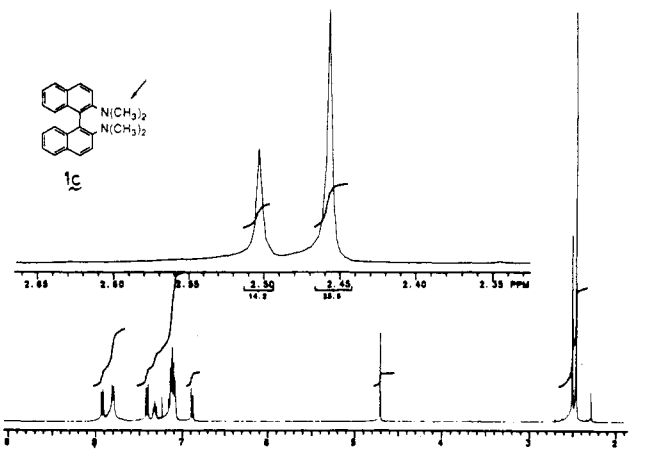


Figure 2. Nonequivalence (0.046 ppm) induced in the ^1H NMR spectrum of **1c** enriched in *S* enantiomer (29% ee) with (*R*)-**6** (1.6 mol equiv of $CDCl_3$) for determination of optical purity while monitoring resolution.

Nonequivalence was observed in the 1:1 diastereomeric salts of **3a** and **6**, but interaction of a second molecule of **6** with these salts to form the 1:2 complexes reversed the relative positions of the nonequivalent α-proton resonances in the NMR spectrum. The nonequivalence observed in the 1:2 complexes of **3a** was greater than that observed in the 1:1 diastereomeric salts (Figure 1B). When the amount of **6** exceeded 2 equiv, higher aggregates formed and the nonequivalence decreased. A similar effect was also noted for **2b** (Figure 1B). In contrast to **1c**, **4b**, and **5c**, increasing the relative concentration of **6** (greater than 2 mol equiv) reduced the nonequivalence for **2b** and **3a**.

The importance of the 1:2 complexation state of **2b** for observing nonequivalence was illustrated by the following experiment. A solution of **2b** and **6** in $CDCl_3$ at a 1:1 molar ratio did not show nonequivalence (Figure 1B). When 1 equiv or less of TFA, HCO_2H, CH_3CO_2H or even acetone-d_6 was added, nonequivalence was induced as the 1:2 complexation state became populated. Thus, only one of the two interacting carboxylic acids in the 1:2 complex need be the CSA for nonequivalence to be induced. Indeed, acetone-d_6 sufficed to induce nonequivalence.

Conclusion

As illustrated in Figure 2, nonequivalence can be induced in the NMR spectra of chiral amines sufficient for the determination of optical purity using mandelic acid as an inexpensive, readily available chiral additive. Mandelic acid also proved useful as a CSA for monitoring the optical purity of Johnson's ketone resolving agent **11** and the precursor **10**.[14] The nonequivalences, which can be large (e.g. 0.112 ppm for **2b**, Table I), allow for the routine monitoring of optical purity for amines of general structure **1**–**5**, at 93.94 kG (400 MHz for ^1H). For some amines, however, nonequivalence was only observed with Mosher's acid as the chiral additive in benzene-d_6. In general, benzene-d_6 was the best solvent to use with Mosher's acid, while $CDCl_3$ seemed to be best with **6**. More polar solvents such as acetone-d_6 were not applicable, presumably due to increased dissociation of the diastereomeric salts.

The important observation that emerges is the critical way in which the experimental conditions for observing suitable nonequivalence for enantiomeric purity deter-

(12) In the absence of a substrate amine, **6** was only slightly soluble in $CDCl_3$, 2.8 mg/mL.

(13) For a discussion of the equilibria that contribute to nonequivalence in diastereomeric salts, see ref 6b, also: (a) Guette, J. P.; Lacombe, L.; Horeau, A. *C. R. Acad. Sci.* **1968**, *267*, 166. (b) Mikolajczyk, M.; Ejchart, A.; Jurczak, J. *Bull. Acad. Pol. Sci.* **1971**, *19*, 721. (c) Ejchart, A.; Jurczak, J. *Bull. Acad. Pol. Sci.* **1971**, *19*, 725. (d) Ejchart, A.; Jurczak, J.; Bankowski, K. *Bull. Acad. Pol. Sci.* **1971**, *19*, 731. (e) Pirkle, W. H.; Sikkenga, D. L. *J. Org. Chem.* **1975**, *40*, 3430. (f) Mikolajczyk, M.; Omelanczuk, J.; Leitloff, M.; Drabowicz, J.; Ejchart, A.; Jurczak, J. *J. Am. Chem. Soc.* **1978**, *100*, 7003.

(14) (a) Johnson, C. R.; Schroeck, C. W.; Shanklin, J. R. *J. Am. Chem. Soc.* **1973**, *95*, 7424. (b) Johnson, C. R.; Zeller, J. R. *J. Am. Chem. Soc.* **1982**, *104*, 4021.

Table I. Conditions for Inducing Nonequivalence To Monitor Optical Purity[a]

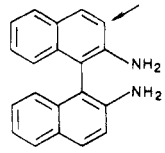
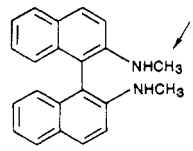
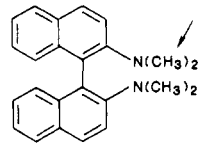
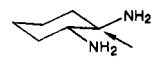
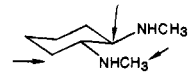
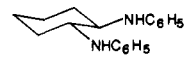
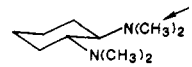
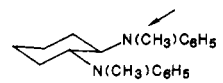
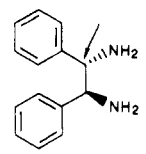
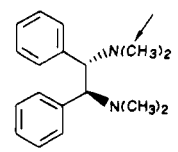
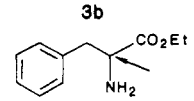
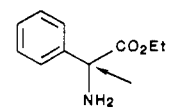
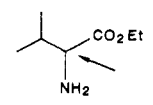
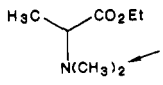
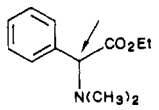
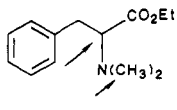
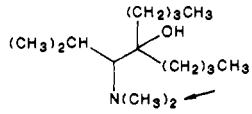
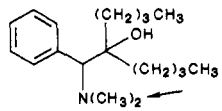
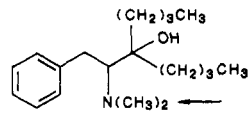
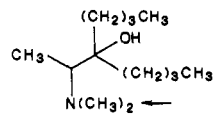
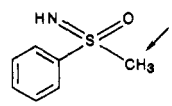
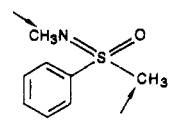
substrate	CSA (equiv)	$\Delta\delta$[b]	proton	solvent
 1a	**6** **7** (2.8) **8**	0 0.014* 0	H-3	C_6D_6
 1b	**6** (3.0)	0.040	NCH_3	$CDCl_3$
 1c	**6** (3.0) **9** (12, 20)	0.056 0	NCH_3	$CDCl_3$ $CDCl_3$
 2a	**6** **7** (0.3) **8**	0 0.005* 0	H-1,2	C_6D_6
 2b	**6** (2.0) **6** (2.0) **6** (2.0) **9** (2.5, 3.5, 15.5)	0.112 0.050 0.050 0	NCH_3 H-1,2 H-3,6 eq	$CDCl_3$ $CDCl_3$ $CDCl_3$ $CDCl_3$
 2c	**6**, **7**, **8**	0		
 2d	**6** (1.5) **7** (1.5) **8** (1.6) **9** (0.6)	0.008* 0.013 0.008* 0.025	NCH_3 NCH_3 NCH_3 NCH_3	$CDCl_3$ + C_6D_6 (2 drops) + acetone-d_6 (2 drops) C_6D_6 $CDCl_3$ $CDCl_3$
 2e	**6** (1.2) **7** (0.8)	0.004* 0.005*	NCH_3 NCH_3	$CDCl_3$ + C_6D_6 (6 drops) + acetone-d_6 (2 drops) C_6D_6
 3a	**6** (2.0) **9** (0.4)	0.046 0.025	H-1,2 H-1,2	$CDCl_3$ $CDCl_3$
 3b	**6** (1.9)	0.043	NCH_3	$CDCl_3$
 4a	**6** (1.0)	0.068	H-2	$CDCl_3$ + acetone-d_6 (2 drops)
 4b	**6** (2.0)	0.045	H-2	$CDCl_3$
 4c	**6** (4.0)	0.034	H-2	$CDCl_3$ + CD_3OD (2 drops)

Table I (Continued)

substrate	CSA (equiv)	$\Delta\delta^b$	proton	solvent
 4d	6 (3.0)	0.004*	2-CH_3	$CDCl_3$ + acetone-d_6 (2 drops)
	8	0		
 4e	6 (3.0)	0.006*	NCH_3	$CDCl_3$ + CD_3OD (2 drops)
	6 (3.0)	0.009	H-2	$CDCl_3$ + CD_3OD (2 drops)
	8 (1.0)	0.011	NCH_3	$CDCl_3$ + C_6D_6 (4 drops)
	8 (1.0)	0.014	H-2	$CDCl_3$ + C_6D_6 (4 drops)
 4f	6 (2.0)	0.006*	NCH_3	$CDCl_3$ + acetone-d_6 (2 drops)
	6 (2.0)	0.008*	H-2	$CDCl_3$ + acetone-d_6 (2 drops)
	8 (1.0)	0.006*	NCH_3	$CDCl_3$ + C_6D_6 (4 drops)
	8 (1.0)	0.009	H-2	$CDCl_3$ + C_6D_6 (4 drops)
 5a	6 (1.5)	0.056	NCH_3	$CDCl_3$
	8 (0.75)	0.050	NCH_3	$CDCl_3$ + CD_3OD (2 drops)
 5b	8 (1.0)	0.015	NCH_3	C_6D_6
 5c	8 (1.0)	0.046	NCH_3	$CDCl_3$ + CD_3OD (2 drops)
	6 (3.0)	0.058	NCH_3	$CDCl_3$
 5d	6 (1.0)	0.046	NCH_3	$CDCl_3$
 10	6 (0.25)	0.020	SCH_3	$CDCl_3$
 11	6 (0.25)	0.033	SCH_3	$CDCl_3$
	6 (0.25)	0.010	NCH_3	$CDCl_3$

[a] All spectra were recorded at ambient temperature. Arrows indicate sites of induced nonequivalence. [b] Nonequivalence not suitable for integration (base-line resolution) are indicated by an asterisk (*). In general, $\Delta\delta$ = 0.009 (3.6 Hz) was sufficient for base-line resolution of singlets.

mination vary with the nature of the substrate. Thus nonequivalence is sensitive to solvent, the concentrations of the substrate and CSA, and the concentration ratio of substrate/CSA. In general, substrates with two strongly basic sites such as the alkyldiamines require two molecules of CSA in order to maximize nonequivalence. The much less basic aryl diamines and monoamines, however, only require a single molecule of interacting CSA. For some amines, too much of the carboxylic acid CSA's can actually lead to a reduction in the nonequivalence. Such behavior has not been reported in the weaker CSA–solute interactions with CSA's such as **9**. Finally, the inversion of the sense of nonequivalence in the resonances of the diastereomeric salts of **3a** with increasing amounts of **6** as the chiral additive illustrates the extreme difficulty in predicting absolute configuration from the sense of nonequivalence.[15]

Experimental Section

General Procedures. All NMR spectra were recorded on a Varian XL-400 (93.94 kG, 400 MHz for ^1H) at ambient temperature. For solvent conditions, see Table I. The detection limits for optical purity determinations using the CSA nonequivalence method is <2%. Samples were prepared by dissolving the appropriate amounts of substrate and CSA in the NMR solvent. For the titrations (Figure 1), stock solutions of the substrates, which contained 4–5 mg/0.4 mL (typical concentrations used for NMR spectra), were prepared to enable an identical starting point (δ) since the chemical shifts of all substrates were sensitive to

(15) The importance of a good working model for the solvation complexes when predicting absolute stereochemistry has been stressed, (a) Pirkle, W. H. *J. Chem. Soc., Chem. Commun.* **1970**, 1525. (b) Stipanovic, R. D.; McCormick, J. P.; Schlemper, E. O.; Hamper, B. C.; Shinmyozu, T.; Pirkle, W. H. *J. Org. Chem.* **1986**, *51*, 2500. (c) Pirkle, W. H.; Pochapsky, T. C.; Mahler, G. S.; Corey, D. E.; Reno, D. S.; Alessi, D. M. *J. Org. Chem.* **1986**, *51*, 4991.

concentration. All CSA's could be recovered without detectable loss of optical purity. Multiplicity assignments for the ^{13}C NMR spectra were accomplished by using the DEPT and APT pulse sequences.

Materials. Chiral solvating agents: (+)-(*S*)- and (-)-(*R*)-mandelic acids, **6** (Fluka), were used without further purification after confirming optical purity by optical rotation. (-)-(*S*)- and (+)-(*R*)-Mosher's acid, **7**,[16] and (+)-(*S*)- and (-)-(*R*)-*N*-(3,5-dinitrobenzoyl)phenylglycine, **8**,[17] were prepared according to literature procedures. (-)-(*S*)-**7**: $[\alpha]_D$ -69.5° (*c* 1.2 g/100 mL, MeOH) [lit.[16] $[\alpha]_D$ -71.8° (*c* 3.28, MeOH)]. (-)-(*R*)-**8**: $[\alpha]_D$ -83.7° (*c* 0.20 g/100 mL, THF) [lit.[17] $[\alpha]_D$ -90.0° (*c* = 0.92, THF)].

Substrate Amines (Table I). Binaphthyldiamines: **1a** was prepared[18] and resolved[19] according to the literature; **1b** and **1c** were prepared from **1a** as indicated below.[2b] Cyclohexanediamines: **2a**, commercially available (Aldrich) and distilled prior to use, was resolved according to the literature;[20] **2b** and **2d** were prepared from **2a** as indicated below; **2c** was prepared according to the literature;[21] **2e** was prepared from **2c** as described below. 1,2-Diphenylethanediamines: **3a** was prepared[22] and resolved[23] according to the literature; **3b** was prepared from **3a** as indicated below. Amino acid esters, **4a–c** were prepared by the esterification of the corresponding amino acids.[24] *N,N*-Dimethylamino acid esters: **4d–f** were prepared from the corresponding amino acid esters by reductive formylation, as indicated below. The *N,N*-dimethylamino alcohols, **5a–d**, were prepared from the corresponding amino acid esters as described below. Sulfoximines **10** and **11** were prepared according to the literature.[14a] Spectroscopic data (NMR, IR, MS) for all compounds were consistent with their assigned structures, in accord with literature reports. All new compounds (**2e**, **5a**, **5b**, **5c**, and **5d**) yielded satisfactory analysis of molecular formula by FAB-HRMS and were shown to be >98% pure by ^1H NMR (control spectra of representative compounds indicated as little as 0.05% impurity could be detected).

General Procedure for the Monomethylation of Primary Amino Groups: Preparation of 1b and 2b.[25] To a solution of diamine **1a** or **2a** (1.77 mmol) in benzene (10 mL) and pyridine (1.3 mL) under N_2, cooled to 0 °C, was added a solution of ethyl chloroformate (4.42 mmol, 0.42 mL) in benzene (1 mL) dropwise over 15 min. The reaction mixture was warmed to room temperature and stirred for 2 h. The reaction was subsequently quenched by addition of 2 N KOH (10 mL), the organic layer was separated, and the aqueous layer was extracted with benzene (3 × 20 mL). The organic layers were combined and washed with brine, dried (Na_2SO_4), and the solvent removed by rotary evaporation. The residue was chromatographed [flash SiO_2], giving the corresponding dicarbamates; yields >95%.

To a stirred suspension of $LiAlH_4$ (0.403 g, 10.6 mmol) in THF (10 mL) under N_2, cooled to 0 °C, the dicarbamate (1.70 mmol) in THF solution (5 mL) was slowly added via addition funnel. The reaction mixture was subsequently warmed and refluxed for 3 h. After the reaction mixture was cooled to room temperature, excess $LiAlH_4$ was quenched with water (0.4 mL), and then NaOH solution (15%, 0.4 mL) and water (0.12 mL) were added: the gray precipitate was filtered and washed with ethyl ether (20 mL). The filtrate and washings were combined, and the solvent was reduced by rotary evaporation. The residues were chromatographed [flash SiO_2] to give the known *N,N'*-dimethyldiamines **1b**[25a] and **2b**;[25b] yields >85%.

General Procedure for the Permethylation of Amino Groups via the Eschweiler–Clarke Reaction: Preparation of 1c, 2d, and 3b.[26] A solution of the amine or diamine (1 mmol), formaldehyde (37% aqueous solution, 2.5-fold excess based on the number of methyl groups produced), and formic acid (10 mmol) was heated overnight on a steam bath. The reaction mixture was cooled, concentrated by rotary evaporation, made basic with NaOH (2 N solution), and extracted with $CHCl_3$ (3 × 20 mL). The combined organic layers were washed with brine and dried (Na_2SO_4). Evaporation yielded the *N,N,N',N'*-tetramethyldiamines, which were purified by recrystallization (anhydrous EtOH/benzene, 1:1), giving the known **1c**[27] (mp 216–218 °C), or chromatography (flash, SiO_2), giving the known **2d**[20b,28] and **3b**;[26c] yields >85%.

(±)-*N,N,N',N'*-Tetramethyl-1,1'-binaphthyl-2,2'-diamine (1c): ^1H NMR ($CDCl_3$) δ 7.86 (d, *J* = 8.8 Hz), 7.81 (d, *J* = 7.8 Hz), 7.46 (d, *J* = 8.8 Hz), 7.27 (br t), 7.14 (m, 2 H), 2.46 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 149.74 (s, 2 C), 134.66 (s, 2 C), 129.67 (s, 2 C), 128.40 (d, 2 C), 127.69 (d, 2 C), 126.27 (s, 2 C), 126.06 (d, 2 C), 125.86 (d, 2 C), 123.31 (d, 2 C), 120.59 (d, 2 C), 43.44 (q, 4 C).

General Procedure for the Methylation of Amino Groups via Reductive Formylation: Preparation of 2e and 4d–f.[29] A solution of the amine or diamine (10 mmol), formaldehyde (37% aqueous solution, 4-fold excess based on the number of methyl groups produced), and Pd–C (2 g) in 95% EtOH (40 mL) was shaken for 4 h in a Parr hydrogenator (50 lbs/in.^{2}). After filtration, the reaction mixture was concentrated by rotary evaporation, made basic with NaOH (2 N solution), and extracted with $CHCl_3$ (3 × 20 mL). The combined organic layers were washed with brine and dried (Na_2SO_4). Evaporation yielded the permethylated amines, which were purified by chromatography (flash SiO_2); yields >95%. Known compounds: **4d**,[29] **4e**,[26a] and **4f**.[29]

***trans*-*N,N'*-Dimethyl-*N,N'*-diphenylcyclohexane-1,2-diamine (2e):** colorless oil; ^1H NMR ($CDCl_3$) δ 7.20 (dd, *J* = 8.8, 7.2 Hz, 4 H), 6.69 (d, *J* = 8.8 Hz, 4 H), 6.68 (t, *J* = 7.2 Hz, 2 H), 3.78 (m, 2 H), 2.52 (s, 6 H), 1.85–1.95 (m, 4 H), 1.5–1.6 (m, 2 H), 1.40 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 149.94 (s, 2 C), 129.06 (d, 4 C), 116.05 (d, 2 C), 112.63 (d, 4 C), 59.83 (d, 2 C), 30.97 (t, 2 C), 29.20 (q, 2 C), 25.49 (t, 2 C); HRMS, $[M + 1]^+$, calcd for $C_{20}H_{27}N_2$ 295.2174, found (*m/z*) 295.2174.

General Procedure for the Preparation of 5a–d. To a solution of the *N,N*-dimethylamino acid ester (10 mmol) in anhydrous ethyl ether (50 mL) under N_2, cooled to 0 °C, was added dropwise *n*-BuLi (3.3 equiv in hexane) with stirring. The reaction mixture was stirred for 6 h at room temperature, and then the excess *n*-BuLi was quenched with water. Additional water (20 mL) was added, and the layers were separated. The aqueous layer was extracted with ethyl ether (4 × 10 mL), and the combined organic layers were washed with brine and dried (Na_2SO_4). The solvent was removed by rotary evaporation and purified by chromatography (flash SiO_2); yields >95%.

5a: colorless oil; ^1H NMR ($CDCl_3$) δ 5.22 (br, O*H*), 2.54 (s, 6 H), 2.27 (d, *J* = 10.2 Hz), 2.02 (m), 1.68 (m), 1.52 (m), 1.2–1.4 (10 H), 1.03 (t, *J* 6.6, 6 H), 0.92 (t, *J* = 7, 6 H); ^{13}C NMR ($CDCl_3$) δ 73.49 (s), 72.92 (d), 43.65 (br d, 2 C), 37.27 (t), 36.87 (t), 28.46 (d), 26.12 (t), 25.63 (t), 23.84 (t), 23.50 (t), 23.50 (q), 22.25 (q), 14.26 (q, 2 C); HRMS, $[M + 1]^+$, calcd for $C_{15}H_{34}NO$ 244.26404, found (*m/z*) 244.26403.

5b: colorless oil; ^1H NMR ($CDCl_3$) δ 7.36 (d, *J* = 8 Hz, 2 H), 7.3 (m, 3 H), 3.30 (s), 2.22 (s, 6 H), 1.7 (m, 2 H), 1.2–1.4 (m, 7 H), 1.1 (m, 3 H), 0.91 (t, *J* = 7 Hz, 3 H), 0.75 (t, *J* = 7 Hz, 3 H), O*H* too broad to be observed under ambient conditions at 400 MHz; ^{13}C NMR ($CDCl_3$) δ 135.09 (s), 131.29 (d, 2 C), 127.46 (d, 2 C), 126.97 (d), 78.18 (s), 74.09 (d), 44.39 (q, 2 C), 36.44 (t), 36.05 (t),

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(25) (a) Miyano, S.; Nawa, M.; Mori, A.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2171. (b) Kashiwabara, K.; Hanaki, K.; Fujita, J. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 2275.
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(27) Mislow, K.; Glass, M. A. W.; O'Brien, R. E.; Rutkin, P.; Steinberg, D. H.; Weiss, J.; Djerassi, C. *J. Am. Chem. Soc.* **1962**, *84*, 1455.
(28) Madgzinski, L. J.; Pillay, K. S.; Richard, H.; Chow, Y. L. *Can. J. Chem.* **1978**, *56*, 1657.
(29) Bowman, R. E.; Stroud, H. H. *J. Chem. Soc.* **1950**, 1342.

26.17 (t), 25.61 (t), 23.67 (t), 23.15 (t), 14.19 (q), 13.91 (q); HRMS, $[M + 1]^+$, calcd for $C_{18}H_{32}NO$ 278.24839, found (m/z) 278.25068.

5c: colorless oil; ^1H NMR ($CDCl_3$) δ 7.3 (m, 5 H), 3.03 (dd, J = 10, 4 Hz), 2.87 (dd, J_{AB} = 14.4 Hz, J = 10 Hz), 2.75 (dd, J_{AB} = 14.4 Hz, J = 8 Hz), 2.32 (s, 6 H), 1.65 (m), 1.4–1.5 (m, 4 H), 1.2–1.4 (m, 7 H), 0.93 (t, J = 7 Hz, 3 H), 0.91 (t, J = 7 Hz, 3 H), O*H* too broad to be observed under ambient conditions at 400 MHz; ^{13}C NMR ($CDCl_3$) δ 141.04 (s), 129.05 (d, 2 C), 128.27 (d, 2 C), 125.93 (d), 74.50 (s), 70.11 (t), 44.11 (q, 2 C), 36.62 (t), 35.96 (t), 25.68 (t), 25.55 (t), 23.71 (t), 23.42 (t), 14.14 (q, 2 C); HRMS, $[M + 1]^+$, calcd for $C_{19}H_{34}NO$ 292.26404, found (m/z) 292.26310.

5d: ^1H NMR ($CDCl_3$) δ 3.8 (br, O*H*), 2.52 (q, J = 7.2 Hz), 2.27 (s, 6 H), 1.55 (m), 1.2–1.4 (m, 11 H), 0.91 (d, J = 7.5 Hz, 3 H), 0.87 (t, J = 7.2 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 75.98 (s), 69.02 (d), 36.94 (t), 34.93 (t), 25.43 (t), 25.16 (t), 23.04 (t), 22.87 (t), 14.04 (q), 13.97 (q), 9.11 (q), $N(CH_3)_2$'s were severely broadened (δ 43 and 45) under ambient conditions at 100 MHz; HRMS, $[M + 1]^+$, calcd for $C_{13}H_{30}NO$ 216.23274, found (m/z) 216.23404.

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Notes

A Novel Ring System: 6a-Aminofuro[2,3-*b*]furans

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Although a fair amount of work has been published on heterocycles containing two fused five-membered rings, less is known about compounds in which furan rings are involved.[1,2] The parent furo[2,3-*b*]furan system and substituted derivatives are apparently unknown.

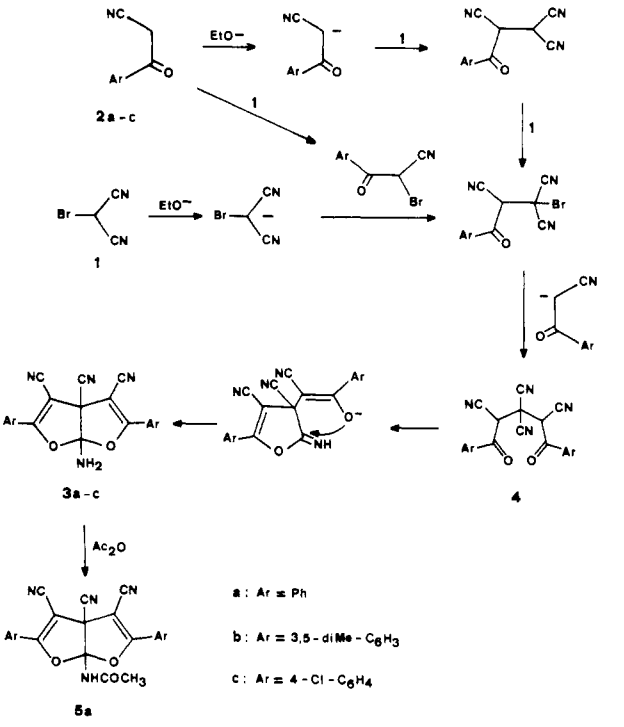
We report in this paper the reaction of bromomalonitrile (1) with ω-cyanoacetophenone (**2a**) in the presence of alkoxide from which a furo[2,3-*b*]furan results in a single step (Scheme I).

The reaction is easily performed in ethanol at room temperature by stirring a mixture of **2a** and bromomalononitrile (1). A crystalline solid is obtained in moderate yield (30%). The microanalytical and mass spectral data correspond to two units of ω-cyanoacetophenone per unit of malononitrile.

An unambiguous structural assignment could not be achieved from the analytical and the deceptively simple spectral data alone, and X-ray crystallographic analysis was therefore performed. Compound **3a** was found to be a novel furo[2,3-*b*]furan heterocyclic system, containing a most unusual functional grouping at carbon 6a (–O–C(NH_2)–O–), a primary amide acetal.

A perspective drawing of **3a** is shown in Figure 1, with the atomic labeling. The molecule presents a pseudo mirror plane. Each half is nearly situated in a plane, the dihedral angle being about 119.5°. Both five-membered rings are planar. Rings I and II and the C_{16}–N_{17} nitrile group are nearly planar. On the contrary, rings III and IV and the C_{20}–N_{17} nitrile group are farther from planarity

Scheme I



(see paragraph at the end of the paper about supplementary material). This nonsymmetrical molecular geometry in the solid state is probably a requirement of the molecular arrangement in the crystal; the NMR spectra suggest a perfect symmetry in solution, however.

The reaction can also be applied to substituted ω-cyanoacetophenones. The corresponding compounds **3** can be very easily isolated by simple filtration in moderate yields. The presence of electron-donating groups (e.g., methoxy) in the para position of the ω-cyanoacetophenones seems to prevent this reaction.

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