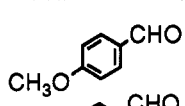
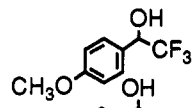
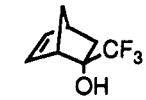
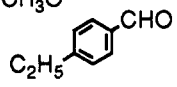
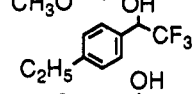
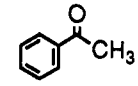
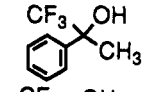
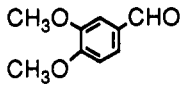
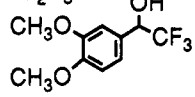
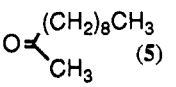
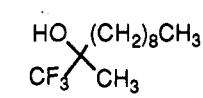
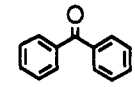
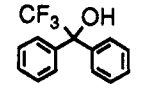
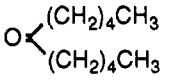
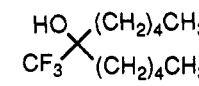
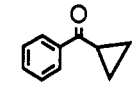
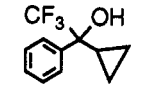
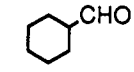
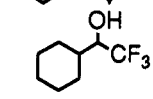
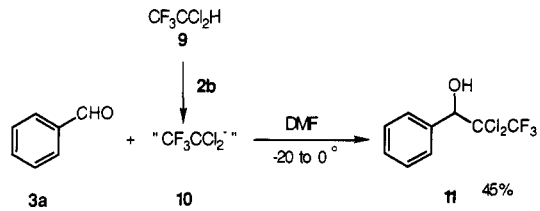
Table II. Trifluoromethylation of Aldehydes and Ketones

run	carbonyl compound	method[a]	product	yield,[b] %	run	carbonyl compound	method[a]	product	yield,[b] %
1		A		(4b) 92	7		B		65
2		A		(4c) 60	8		A		trace
3		A		(4d) 78	9		B		60
4		A		(6) 36	10		B		84
5	(5)	B		(6) 83					
6		B		71	11		B		73
					12		B		23

[a] All reactions were performed in DMF, using 3 equiv (based on carbonyl compound) of **2b**. Method A: no HMDS present. Method B: 6 equiv of HMDS present in the reaction mixture. [b] Isolated yield of pure compound.

Scheme IV



moting the trifluoromethylation of other ketones (runs 6–11).

It seems reasonable to assume that HMDS promoted the reaction by silylating the intermediate **7**, formed by the reaction of **5** with the trifluoromethyl anion equivalent (Scheme III). Silyl ether **8** was, in fact, detected in the reaction mixture.

We also found that the introduction of **2b** into a mixture of **3a** and trifluorodichloroethane (**9**) in DMF led to the formation of alcohol **11**[19] in fair yield (Scheme IV). This result was interesting because the formation of **11** indicated the involvement of an intermediate chemically equivalent to anion **10**, in which the negative charge is localized on the carbon atom α to the trifluoromethyl group. An anion of this type is highly unstable,[20-21] and hence reports of its nucleophilic addition to carbonyl compounds are rare.

Why the electrogenerated base was so effective in promoting the formation and subsequent reaction of the trifluoromethyl anion equivalent is not clear. However, it seems reasonable to assume that two factors—the use of a tetraalkylammonium counterion and the use of a highly aprotic reaction medium—were, at least in part, responsible for the observed stability of the trifluoromethyl anion equivalent.

(19) Fujita, M.; Morita, T.; Hiyama, T. *Tetrahedron Lett.* **1986**, *27*, 2135.
(20) Yokozawa, T.; Nakai, T.; Ishikawa, N. *Tetrahedron Lett.* **1984**, *26*, 3987.
(21) Fuchigami, T.; Nakagawa, Y. *J. Org. Chem.* **1987**, *52*, 5276.

Stereoselective Addition Reactions of Chiral *N*-Benzylidene-*p*-toluenesulfinamides. Asymmetric Syntheses of β- and γ-Amino Acids

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Received October 15, 1990

Summary: Chiral *N*-benzylidene-*p*-toluenesulfinamides **2** were prepared by the reaction of benzonitrile with alkyllithium in ether followed by (−)-*l*-menthyl (*S*)-*p*-tolylsulfinate. Treatment of **2** with allylmagnesium bromide in ether at 0 °C gave the adducts (*R*)-**7** with excellent stereoselectivity. Pure chiral sulfinamides **7** were converted into chiral β- and γ-amino acids in four and five steps, respectively.

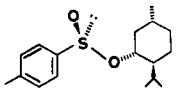
Racemic *N*-alkylidenearenesulfinamides were first reported by Davis[2] and Burger.[3] The optically active versions were prepared in 15–70% yields by Cinquini et al.[4] by the reaction of Grignard reagents with benzonitrile followed by (−)-*l*-menthyl (*S*)-*p*-toluenesulfinate (**1S**). As part of our continuing studies in the enantioselective addition reactions of α-sulfinyl ketimines,[5] the chemistry of

† Fellow of the Alfred P. Sloan Foundation, 1989–1991.

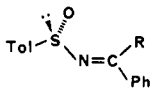
(1) Ono Pharmaceutical Co., Osaka 618, Japan.
(2) (a) Davis, F. A.; Friedman, A. J.; Kluger, E. W. *J. Am. Chem. Soc.* **1974**, *96*, 5000. (b) Davis, F. A.; Friedman, A. J. *J. Org. Chem.* **1976**, *41*, 898. (c) Davis, F. A.; Kluger, E. W. *J. Am. Chem. Soc.* **1976**, *98*, 302. (d) Davis, F. A.; Friedman, A. J.; Nadir, U. K. *J. Am. Chem. Soc.* **1978**, *100*, 2844.
(3) Burger, K.; Albanbauer, J.; Kafig, F.; Penninger, S. *Liebigs Ann. Chem.* **1977**, 624.
(4) (a) Cinquini, M.; Cozzi, F. *J. Chem. Soc. Chem. Commun.* **1977**, 502. (b) *Ibid.* **1977**, 723. (c) Annunziata, R.; Cinquini, M.; Cozzi, F. *J. Chem. Soc., Perkin Trans. 1* **1982**, 339–43.

0022-3263/91/1956-0004$02.50/0

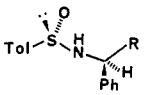
chiral *N*-alkylidene-*p*-toluenesulfinamides was investigated. Herein, we report the synthesis of chiral *N*-benzylidene-*p*-toluenesulfinamides **2**, stereoselective addition reactions of **2**, and conversions of the adducts to 100% optically pure β- and γ-amino acids.



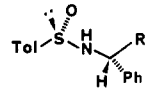
1S



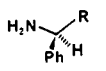
2a : R = Me
2b : R = *n*-Bu



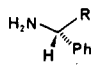
3a : R = Me
3b : R = *n*-Bu



4a : R = Me
4b : R = *n*-Bu



5a : R = Me
5b : R = *n*-Bu

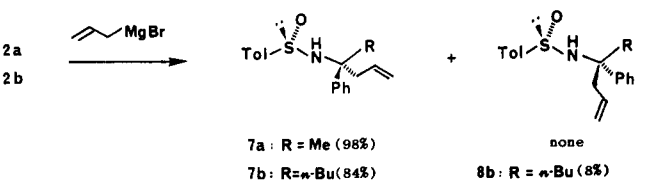


6a : R = Me
6b : R = *n*-Bu

Higher yields of chiral *N*-benzylidene-*p*-toluenesulfinamides have now been realized by treating benzonitrile with alkyllithium (CH_3Li or *n*-BuLi) in ether at 0 °C for 1 h followed by the addition of **1S** at 0 °C. Sulfinamides **2** [**2a**, 50% yield (and 10% recovery of **1S**)[6] and **2b**, 75% yield (and 5% of **1S**)] were thus prepared. The *E* stereochemistry of **2a** was shown by single-crystal X-ray analysis.[7] Sulfinamides **2** can be stereoselectively reduced with diisobutylaluminum hydride (DIBAL)[8] in THF at −30 °C for 1 h to provide mainly sulfinamides **3**. From **2a**, a 92% yield of **3a** and **4a** was formed in a ratio of 96:4, and from **2b**, a 96% yield of **3b** and **4b** (94:6) was obtained. Sulfinamides **3** were separated on a silica gel column using a hexane–ether mixture as eluant and then hydrolyzed with 2 equiv of CF_3CO_2H in methanol[9] at 25 °C for 3 h to give 100% optically pure (*S*)-amines **5** (~92% yields). The minor isomers, **4**, contain a small amount of **3**. Amines **6** can be prepared by the same procedure starting with (+)-*d*-menthyl (*R*)-*p*-toluenesulfinate (**1R**).

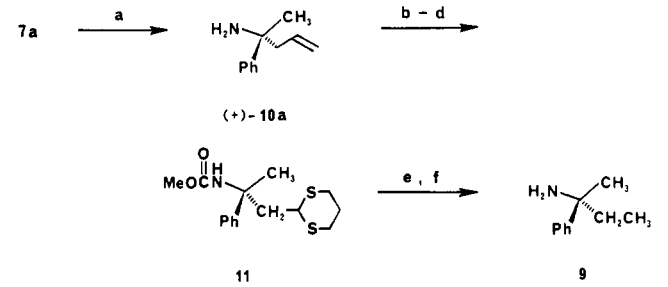
Remarkably, sulfinamides **2** also underwent stereoselective addition reaction with allylmagnesium bromide in ether at 0 °C for 2.5 h to produce (*R*)-**7**. From **2a**, a 98% yield of a single diastereomer (*R*)-**7a** {$[\alpha]^{22}_D$ = +43.2° (*c* 1.05, $CHCl_3$)} was obtained while from **2b**, a 92% yield of **7b** {$[\alpha]^{22}_D$ = +59.2° (*c* 3.25, $CHCl_3$)} and **8b** {$[\alpha]^{22}_D$ = +1.1° (*c* 2.05, $CHCl_3$)} (91:9) was realized (Scheme I). Diastereomers **7b** and **8b** were readily separated by silica gel column chromatography employing a mixture of hexane and ether as eluant. The absolute configuration of the newly formed chiral center of **7** was determined by converting sulfinamide **7a** into the known amine, (+)-(*R*)-2-phenyl-2-butylamine (**9**)[10] as outlined in Scheme II. Hydrolysis of **7a** with 2 equiv of CF_3CO_2H in MeOH at 25 °C gave a 97% yield of (+)-**10a**. Carbamoylation of (+)-**10a** with methyl chloroformate followed by ozonolysis in CH_2Cl_2 at −78 °C and treatment with 1,3-propanedithiol produced a 67% overall yield of dithiane **11**. Desulfurization of **11** with Raney nickel in ethanol at 25 °C followed by removal of the carbamate group with KOH–H_2O–diethylene glycol at 100 °C[11] furnished a 67% yield of (+)-(*R*)-**9**; $[\alpha]^{22}_D$ = +18° (*c* 0.8, $CHCl_3$) (lit.[10] +15.8°; *R* configuration).

Scheme I



7a : R = Me (98%)
7b : R = *n*-Bu (84%)
none
8b : R = *n*-Bu (8%)

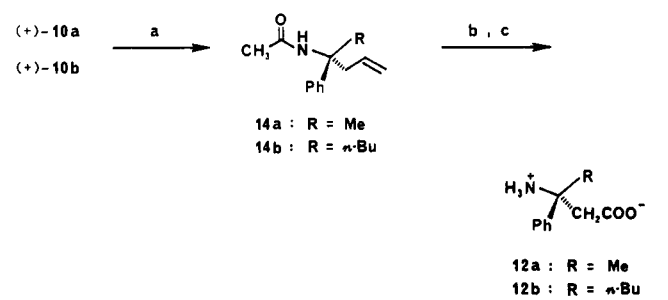
Scheme II[a]



11
9

[a] (a) 2 equiv of CF_3COOH, MeOH, 25 °C, 3 h; 97% yield; (b) 1.5 equiv of $ClCO_2Me$, 3 equiv of pyridine, ether, 25 °C, 5 h; 80% yield; (c) O_3, CH_2Cl_2, −78 °C; CH_3SCH_3; 92% yield; (d) 1 equiv of $HSCH_2CH_2CH_2SH$, CH_2Cl, 0.4 equiv of BF_3-ether, 25 °C, 3 h; 90% yield; (e) Raney Ni, EtOH, 25 °C, 4 h; 70% yield; (f) KOH, H_2O, $HOCH_2CH_2OCH_2CH_2OH$, 100 °C, 3 h; 95% yield.

Scheme III[a]



14a : R = Me
14b : R = *n*-Bu

12a : R = Me
12b : R = *n*-Bu

[a] (a) Ac_2O, Et_3N, ether, 0 °C, 1 h (R = CH_3, 95% yield; R = *n*-Bu, 93% yield); (b) (i) O_3, CH_2Cl_2, −78 °C; (ii) $AgNO_3$, KOH, EtOH, 0 °C (R = CH_3, 70% yield; R = *n*-Bu, 69% yield); (c) (i) 1 N HCl, H_2O, 100 °C, 12 h; (ii) NH_4OH; Rexyn-101 (H^+) (R = CH_3, 80% yield; R = *n*-Bu, 87% yield).

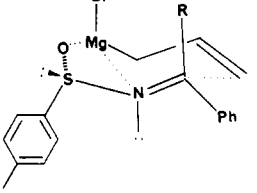


Figure 1.

A six-membered-ring transition state for this addition reaction is proposed (Figure 1). The magnesium chelates with both N and O atoms of sulfinamides **2**; therefore, approach of the allyl Grignard reagents occurs from the *re* face[12] of the sulfinamides. The suggestion of a six-

(5) (a) Hua, D. H.; Bharathi, S. N.; Takusagawa, F.; Tsujimoto, A.; Panangadan, J.; Hung, M. H.; Bravo, A. A.; Erpelding, A. M. *J. Org. Chem.* **1989**, *54*, 5659. (b) Hua, D. H.; Bharathi, S. N.; Robinson, P. D.; Tsujimoto, A. *J. Org. Chem.* **1990**, *55*, 2128.

(6) With methylmagnesium bromide[4] only 15% yield of **2a** was realized.

(7) Robinson, P. D.; Hua, D. H.; Chen, J. S.; Saha, S. *Acta Crystallogr.*, in press. The stereochemistry at sulfur **2a** has previously been established.[4] The geometry of **2b** is assumed by analogy to **2a**.

(8) The reductions[4] of sulfinamide **2a** with $NaBH_4$, $LiAlH_4$, or lithium alkoxyaluminum hydrides gave lower optical yields.

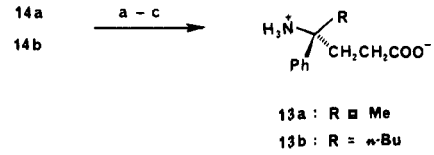
(9) Kikolajczyk, M.; Drabowicz, J.; Bujnicki, B. *J. Chem. Soc., Chem. Commun.* **1976**, 568.

(10) (a) Cram, D. J.; Bradshaw, J. S. *J. Am. Chem. Soc.* **1963**, *85*, 1108. (b) Kopecky, K. R.; Mojelsky, T. W.; Gillan, T.; Barry, J. A.; Lopez Sastre, J. A. *Can. J. Chem.* **1977**, *55*, 1001.

(11) Wenkert, E.; Hudlicky, T.; Hollis Showalter, H. D. *J. Am. Chem. Soc.* **1978**, *100*, 4893.

(12) The Izumi–Tai nomenclature is employed: Izumi, I.; Tai, A. *Stereodifferentiating Reactions*; Kodansha Ltd.: Tokyo; Academic Press: New York, 1977; pp 68–69.

Scheme IV[a]



[a] (a) (i) BH_3·THF, 0 °C, 3 h; (ii) NaOH, 30% H_2O_2 (R = CH_3, 55% yield; R = *n*-Bu, 60% yield); (b) (i) pyridinium chlorochromate, CH_2Cl_2, 25 °C; (ii) $AgNO_3$, KOH, EtOH, 0 °C (R = CH_3, 65% yield; R = *n*-Bu, 80% yield); (c) (i) 1 N HCl, H_2O, 100 °C, 12 h; (ii) NH_4OH; Rexyn-101 (H^+) (R = CH_3, 81% yield; R = *n*-Bu, 85% yield).

membered-ring transition state is in accord with that proposed for the reactions of allylmagnesium bromide with aldehydes[13] and allylboranes with imines;[14] it is also supported by the addition reaction of (3-methyl-2-butenyl)-magnesium bromide[13b] with **2a** which provided the γ-adduct, *N*-(1,2,2-trimethyl-1-phenyl-3-butenyl)-*p*-toluenesulfinamide {83% yield; a single isomer: $[\alpha]^{22}_D$ = +19.4° (*c* 1.2, $CHCl_3$)}. The reactivity of sulfinamides **2** described here differs from that of ketimines in that the sulfinamides did not undergo addition reactions with *n*-BuLi or vinylmagnesium bromide, but underwent deprotonation at the α-imino carbon instead.

The optical purity of (+)-**10a** was also determined by treating (+)-**10a** with Mosher's acid chloride,[15] (+)-(*R*)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride in pyridine at 50 °C, to give the corresponding amide whose ^1H and ^{13}C NMR (400 and 100 MHz) spectra indicated a single diastereomer.[16]

Chiral β-[17] and γ-amino acids[18] are important intermediates in organic synthesis and biological studies, and amines (+)-**10** were readily converted into β- and γ-amino acids (−)-**12** and (+)-**13** (Scheme III and IV). Acetylation of (+)-**10** with acetic anhydride and triethylamine in ether, ozonolysis of the resulting amides (+)-**14** with O_3 in CH_2Cl_2 at −78 °C, and subsequent oxidation with $AgNO_3$–KOH[19] in ethanol at 0 °C, and deacetylation of the resulting acids with 1 N HCl in refluxing H_2O[20] provided β-amino acids (−)-**12** {(−)-**12a**, $[\alpha]^{22}_D$ = −10.2° (*c* 0.78, CH_3OH); (−)-**12b**, $[\alpha]^{22}_D$ = −13.1° (*c* 0.38, CH_3OH)}. Hydroboration of (+)-**14** with BH_3·THF followed by oxidation and then hydrolysis with 1 N HCl furnished γ-amino acids (+)-**13** {(+)-**13a**, $[\alpha]^{22}_D$ = +2.3° (*c* 0.75, MeOH); (+)-**13b**, $[\alpha]^{22}_D$ = +25.3° (*c* 0.3, MeOH)}. Since (+)-**7a** and **7b** are single diastereomers, amino acids (−)-**12** and (+)-**13** can be assumed to be 100% optically pure.

The highly efficient stereoselective addition reaction of chiral *N*-benzylidene-*p*-toluenesulfinamides with allylmagnesium bromide provided optically pure amines, β- and γ-amino acids. Related asymmetrically induced reactions of chiral conjugated *N*-alkylidene-*p*-toluenesulfinamides with substituted allyl Grignard reagents and other organometallic species will be reported in due course.

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Supplementary Material Available: Optical rotations, ^1H and ^{13}C (400 and 100 MHz) NMR and mass spectral data, and elemental analyses for compounds **2**–**14** and ^1H and ^{13}C NMR data for Mosher's derivatives of (+)-**10a** and (−)-**10a** (11 pages). Ordering information is given on any current masthead page.

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