ORGANIC LETTERS

2000
Vol. 2, No. 4
547−549

Diastereoselective Allylation of Aldehydes with an Enantiopure 2-Sulfinylallyl Halide under Environmentally Friendly Barbier-Type Conditions

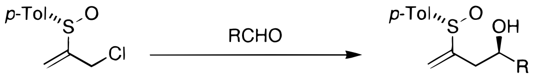
Francesc Márquez,[†,‡] Amadeu Llebaria,[‡] and Antonio Delgado*,[†]

Facultat de Farmàcia, Unitat de Química Farmacèutica, Universitat de Barcelona, Avgda. Joan XXIII, s/n, 08028 Barcelona, Spain, and Departament de Química Orgànica Biològica, Institut d'Investigacions Químiques i Ambientals de Barcelona (IIQAB-C.S.I.C), Jordi Girona 18-26, 08034 Barcelona, Spain

adcqob@cid.csic.es

Received December 31, 1999

ABSTRACT



(S_S)-**1**

3

A simple, efficient, and diastereoselective zinc-promoted allylation of aldehydes with enantiopure (S_S)-3-chloro-2-(*p*-tolylsulfinyl)-1-propene [(S_S)-1] under aqueous Barbier conditions is described. The observed diastereoselectivity can be explained via an acyclic antiperiplanar transition state model.

The allylation of carbonyl derivatives to afford homoallylic alcohols is a useful synthetic transformation that has attracted considerable attention over the past few years.[1] Recently, much effort has been devoted to the development of new methods for enantioselective carbonyl allylation by means of either enantiopure allylmetal derivatives[2] or asymmetric Lewis acid catalysis.[3] However, reports on enantioselective carbonyl allylations in aqueous medium are limited,[4] despite the increasing demand for clean and environmentally safe chemical technologies and the availability of well-precedented methodology enabling the combination of water with different organometallic systems.[5]

Our interest in the development of new building blocks based on the use of sulfoxides as chiral auxiliaries[6] prompted us to focus on enantiopure (*S*)-3-chloro-2-(*p*-tolylsulfinyl)-

---

[†] Universitat de Barcelona.

[‡] Institut d'Investigacions Químiques i Ambientals de Barcelona.

(1) For reviews, see: (a) Roush, W. R. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: Oxford, 1991; Vol. 2; pp 1−53. (b) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207−2293.

(2) Allylboronates: (a) Roush, W. R.; Hoong, L. K.; Palmer, M. A.; Park, J. C. *J. Org. Chem.* **1990**, *55*, 4109−4117. (b) Roush, W. R.; Ando, K.; Powers, D. B.; Palkowitz, A. D.; Halterman, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 6339−6348. (c) Roush, W. R.; Hoong, L. K.; Palmer, M. A.; Straub, J. A.; Palkowitz, A. D. *J. Org. Chem.* **1990**, *55*, 4117−4126. Allylstannanes: (d) Boldrini, G. P.; Tagliavini, E.; Trombini, C.; Umanironchi, A. *J. Chem. Soc., Chem. Commun.* **1986**, 685−686. (e) Costa, A. L.; Piazza, M. G.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *J. Am. Chem. Soc.* **1993**, *115*, 7001−7002. Allylzinc: (f) Cozzi, P. G.; Orioli, P.; Tagliavini, E.; Umanironchi, A. *Tetrahedron Lett.* **1997**, *38*, 145−148. Allylchromium: (g) Sugimoto, K.; Aoyagi, S.; Kibayashi, C. *J. Org. Chem.* **1997**, *62*, 2322−2323. Allyl titanates: (h) Riediker, M.; Duthaler, R. *Angew. Chem., Int. Ed. Engl.* **1989**, 494−495. (i) Hafner, A.; Duthaler, R.; Marti, R.; Rihs, G.; Rothestreit, P.; Schwarzenbach, F. *J. Am. Chem. Soc.* **1992**, *114*, 2321−2336.

(3) (a) Keck, G. E.; Tarbet, K. H.; Geraci, L. S. *J. Am. Chem. Soc.* **1993**, *115*, 8467−8468. (b) Bedeschi, P.; Casolari, S.; Costa, A. L.; Tagliavini, E.; Umanironchi, A. *Tetrahedron Lett.* **1995**, *36*, 7897−7900. (c) Cozzi, P. G.; Tagliavini, E.; Umanironchi, A. *Gazz. Chim. Ital.* **1997**, *127*, 247−254. (d) Marshall, J. A.; Palovich, M. R. *J. Org. Chem.* **1998**, *63*, 4381−4384.

(4) Loh, T. P.; Zhou, J. R. *Tetrahedron Lett.* **1999**, *40*, 9115−9118.

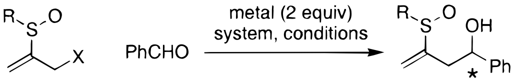
(5) (a) Lubineau, A.; Augé, J.; Queneau, Y. *Synthesis* **1994**, 741−760. (b) Lubineau, A. *Chem. Ind.* **1996**, *4*, 123−126. (c) Li, C. J. *Tetrahedron* **1996**, *52*, 5643−5668. (d) Li, C.-J.; Chan, T.-H. *Organic Reactions in Aqueous Media*; John Wiley & Sons: New York, 1997.

10.1021/ol991412j CCC: $19.00

1-propene ((S_S)-**1**)[7] and to study its application to the diastereoselective synthesis of 2-sulfinyl-2-propenylmethanols **3** using environmentally friendly protocols. The versatility of this strategy relies on both the diversity of commercially available starting aldehydes and the synthetic potential of the vinylsulfinyl moiety.[8]

Preliminary studies were carried out with benzaldehyde and racemic 3-halo-2-(phenylsulfinyl)-1-propenes **(±)-4a**[9] or **(±)-4b**[10] and under In- or Zn-promoted Barbier-type allylations in different solvent systems (Table 1).[11]

Table 1. Allylation of Benzaldehyde with 2-Arylsulfinyl-3-halo-1-propenes



(±)-4a: X=Cl; R=Ph
(±)-4b: X=I; R=Ph
(S_S)-1: X=Cl; R=p-Tol

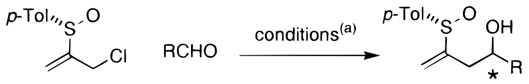
3a: R=p-Tol
5a: R=Ph

entry	halide	metal	system[a]	cond[b]	dr[c]	yield[d,e]
1	(±)-**4a**	In	A	72; rt	3:1	59[d]
2	(±)-**4a**	In	B	24; rt	4:1	74[d]
3	(±)-**4a**	In	C	15; rt	5:1	60[e]
4	(±)-**4a**	Zn	D	4; rt	4:1	89[d]
5	(±)-**4b**	Zn	D	1; rt	6:1	40[d]
6	(±)-**4a**	Zn	E	18; rt	5:1	82[d]
7	(S_s)−**1**	Zn	D	16; rt	3:1	85[e]
8	(S_s)−**1**	Zn	D	24; 0	4:1	83[d]
9	(S_s)-**1**	Zn	E	24; 0	6:1	80[d]

[a] Solvent system: A, THF; B, THF−H_2O (1:1); C, H_2O; D, saturaed aqueous NH_4Cl/THF (6:1); E, NaI (3 equiv.), 1.6 N aqueous NH_4I/THF (6:1). [b] Conditions: reaction time (h); temperature (°C). [c] Diastereomeric ratio calculated by ^1H NMR. [d] Isolated. [e] Calculated by ^1H NMR in the presence of dimethyl terephthalate as an external standard.

Indium-promoted allylations with (±)-**4a** took place in a variety of H_2O−THF mixtures in moderate yields and diastereoselectivities (entries 1−3).[12,13] The use of Zn turned out to be more efficient in terms of diastereoselectivity, overall yields, and reaction rates.[13] Allylation with (±)-**4a** and Zn in 6/1 saturated aqueous NH_4Cl/THF afforded homoallylic alcohol **5a** in high yield and moderate diastereoselectivity (entry 4). The use of iodide (±)-**4b** increased the diastereoselectivity, at the expense of the reaction yield (entry 5). This moderate yield can be attributed, in part, to the unstability of the starting iodide under the reaction conditions. Interestingly, both yield and diastereoselectivity could be optimized using (±)-**4a** in the presence of an excess of iodide (entry 6). It is conceivable that iodide (±)-**4b**, or a related species, can be formed in situ under the above conditions. Enantiomerically pure 2-sulfinylallyl chloride (S_S)-**1** behaved similarly to (±)-**4a**, giving **3a** (3:1 diastereomeric mixture) in high yield (entry 7). It is noteworthy that the diastereoselectivity of this process could be further increased up to 6:1 by carrying out the reaction at 0 °C in the presence of excess iodide (entry 9). These conditions were further applied to a range of aldehydes **2a−g** as shown in Table 2.[14]

Table 2. Allylation of Aldehydes with (S_S)-**1**



(S_S)-1 **2a-g** **3a-g**

entry		R	dr[b]	yield[c]
1	**a**	Ph	6:1	80[d]
2	**b**	cyclohexyl	5:1	60
3	**c**	n-Bu	3:1	67
4	**d**	t-Bu	5:1	60
5	**e**	p-$(OCH)_3Ph$	5:1	70
6	**f**	2-furyl	4:1	60
7	**g**	$BnOCH_2$−	2:1	75

[a] Zn (2 equiv)/NaI (3 equiv)/1.6 N aqueous NH_4I/THF (6:1); 0 °C. For a detailed experimental procedure, see ref 14. [b] Calculated by ^1H NMR. [c] Calculated by ^1H NMR in the presence of dimethyl terephthalate as an external standard. [d] Isolated yield.

The configuration of the new stereogenic center in the major diastereomer of homoallylic alcohols **3a**,**b** was assigned as R from ozonolysis[15] to the corresponding enantiopure β-hydroxyacid and comparison with reported litera-

---

(6) (a) Villar, J. M.; Delgado, A.; Llebaria, A.; Moreto, J. M. *Tetrahedron: Asymmetry* **1995**, *6*, 665−668. (b) Villar, J. M.; Delgado, A.; Llebaria, A.; Moretó, J. M.; Molins, E.; Miravitlles, C. *Tetrahedron* **1996**, *52*, 10525−10546. (c) Henrich, M. L.; Delgado, A.; Molins, E.; Roig, A.; Llebaria, A. *Tetrahedron Lett.* **1999**, *40*, 4259−4262. For a review on applications of sulfoxides to asymmetric synthesis, see: Carreño, M. C. *Chem. Rev.* **1995**, *95*, 1717−1760.

(7) Prepared as follows: A solution of (S_S)-2-(p-tolylsulfinyl)-1-propen-1-ol[20] (1.1 g, 5.6 mmol) in anhydrous DMF (8 mL) under argon is treated at 0 °C with Et_3N (63 mg, 6.2 mmol) and methanesulfonyl chloride (705 mg, 6.2 mmol). The reaction mixture is allowed to warm to room temperature and monitored by TLC (CH_2Cl_2/MeOH 97:3) untilthe starting alcohol is not detected. The mixture is next diluted with additional anhydrous DMF (10 mL), and LiCl (952 mg, 22.4 mmol) is added portionwise. Stirring at room temperature is continued until TLC monitoring indicates total consumption of the intermediate mesylate. The reaction mixture is then evaporated to dryness, and the oily residue is taken up in ether and washed with brine. Drying of the organic phase (anhydrous Na_2SO_4) and evaporation afforded a crude that was flash-chromatographed (hexanes−EtOAc 85:15) to afford allylic chloride (S_S)-**1** in 65% yield: $[\alpha]^{25}_D$ +128 (c, 0.68 MeOH); ^1H NMR ($CDCl_3$) 2.38 (3H), 3.79 (1H, J = 14.5; J' = 1.2; J'' = 0.9), 4.10 (1H, J = 14.5; J' = 1.6; J'' = 1.0), 5.99 (1H), 6.22 (1H), 7.29 (2H), 7.49 (2H); ^{13}C NMR ($CDCl_3$) 150.7, 142.4, 138.3, 130.2, 125.1, 120.5, 39.0, 21.4.

(8) For synthetic applications of closely related (±)-3-halo-2-sulfonyl-1-propenes, see: (a) Knochel, P.; Normant, J. F. *Tetrahedron Lett.* **1985**, *26*, 425−428. (b) Auvray, P.; Knochel, P.; Normant, J. F. *Tetrahedron Lett.* **1985**, *26*, 4455−4458. (c) Knochel, P.; Normant, J. F. *J. Organomet. Chem.* **1986**, *309*, 1−23. (d) Auvray, P.; Knochel, P.; Normant, J. F. *Tetrahedron Lett.* **1986**, 5095−5098. (e) Auvray, P.; Knochel, P.; Normant, J. F. *Tetrahedron* **1988**, *44*, 6095−6106. (f) Auvray, P.; Knochel, P.; Normant, J. F. *Tetrahedron* **1988**, *44*, 4509−4519.

(9) Anzeveno, P. B.; Matthews, D. P.; Barney, C. L.; Barbuch, R. J. *J. Org. Chem.* **1984**, *49*, 3134−3138.

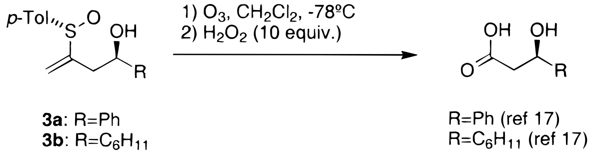
(10) Prepared from (±)-**4a** by reaction with excess NaI in refluxing acetone.

(11) For carbonyl allylations of related 2-sulfonyl-substituted allylic halides under *nonaqueous* conditions, see: (a) Auvray, P.; Knochel, P.; Normant, J. F. *Tetrahedron Lett.* **1985**, *26*, 2329−2332. (b) Auvray, P.; Knochel, P.; Normant, J. F. *Tetrahedron Lett.* **1986**, 5091−5094. (c) Auvray, P.; Knochel, P.; Normant, J. F. *Tetrahedron* **1988**, *44*, 4495−4508.

(12) Iodide (±)-**4b** afforded similar results.

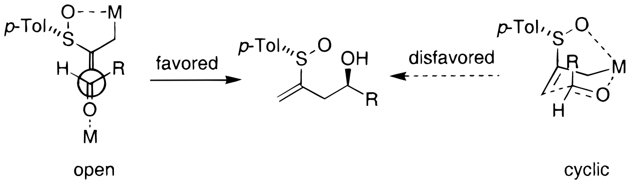
ture data.[16] Thus, β-hydroxy acids of opposite optical rotation to that described in the literature for the corresponding *S* enantiomers were obtained (Scheme 1).[17]

Scheme 1



From a mechanistic standpoint, a highly energetic 1,3-diaxial interaction between R and the sulfoxide moiety would be required if the currently accepted six-membered cyclic transition state for the metal-mediated coupling of allylic halides with aldehydes in aqueous media were operative.[5c,d] For this reason, the observed diastereoselectivity can be better explained by an open antiperiplanar transition state model,[18] in which the above interactions are avoided (Scheme 2).[19]

Scheme 2



In conclusion, we have developed a simple, efficient, and environmentally friendly protocol for the diastereoselective allylation of aldehydes with enantiopure 2-sulfinylallyl chloride (S_S)-**1**. Further studies addressing the use of the synthetic potential of the resulting 2-sulfinyl-2-propenylmethanols **3** are currently underway and will be reported in due course.

Acknowledgment. Financial support from Dirección General de Enseñanza Superior, Ministerio de Educación y Cultura (PB97-1171), and Comissionat per a Universitats i Recerca, Generalitat de Catalunya (Projects 1997SGR00140 and SGR00187), is gratefully acknowledged. F.M. is also grateful to Ministerio de Educación y Cultura for a predoctoral fellowship.

OL991412J

---

(13) Experiments with Yb(OTf)$_3$, a water-compatible Lewis acid, did not significantly improve either the yields or the diastereoselectivities in In and Zn-promoted allylations, although reaction rates were generally higher; for the use of lanthanides as Lewis acids in the allylation of aldehydes in aqueous medium, see: (a) Diana, S. C. H.; Sim, K. Y.; Loh, T. P. *Synlett* **1996**, 263. (b) Kobayashi, S.; Wakabayashi, T.; Oyamada, H. *Chem. Lett.* **1997**, 831−832. (c) Loh, T. P.; Cao, G. Q.; Pei, J. *Tetrahedron Lett.* **1998**, *39*, 1453−1456.

(14) Allylations with sulfinyl halide (S_S)-**1**: A solution of (S_S)-**1** (1 mmol) in THF (1.0 mL) is treated with NaI (450 mg, 3 mmol) and stirred at room temperature. After 5 min, 9 mL of 1.6 N aqueous NH$_4$I is added dropwise, followed by a solution of the aldehyde **2a**−**g** (1 mmol) in THF (0.5 mL). The mixture is cooled to 0 °C (ice bath), and Zn dust (130 mg, 2 mmol) is added portionwise. The reaction mixture is stirred at 0 °C until consumption of the starting halide (TLC monitoring) and diluted with EtOAc. The organic extracts are separated, dried (MgSO$_4$), and concentrated to give **3a**−**g** as a mixture of diastereomers, which can be separated by careful flash chromatography on hexanes−EtOAc (8:2 or 7:3).

(15) For ozonolysis of vinyl sulfoxides, see: Griesbaum, K.; Kim, W. S. *Erdoel Ergdgas Kohle* **1995**, *111*, 485−486 (*Chem. Abstr.* **1996**, *124*, 55322).

(16) Since olefinic protons in sulfinyl homoallylic alcohols **3a**−**g** showed an almost superimposable ^{1}H NMR pattern, an identical diastereochemical induction was assumed in all cases.

(17) Wang, Z.; Zhao, C.; Pierce, M. E.; Fortunak, J. M. *Tetrahedron: Asymmetry* **1999**, *10*, 225−228.

(18) Yamamoto, Y. *Acc. Chem. Res.* **1987**, *20*, 243−249.

(19) The observed stereochemical outcome is also in agreement with an intermolecular chelated acyclic model postulated for the allylation of aldehydes with a sulfinylallylstannane under Lewis acid catalysis in nonaqueous medium (Mortlock, S. V.; Thomas, E. J. *Tetrahedron* **1998**, *54*, 4663−4672).

(20) Hayes, P.; Maignan, C. *Synthesis* **1999**, 783−786.