Tetrahedron Letters 55 (2014) 1090–1092

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Remote induction of stereoselective 1,2-addition of aryl Grignard reagents to β-sulfinyl enones ☆

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ARTICLE INFO

Article history:
Received 29 October 2013
Revised 20 December 2013
Accepted 25 December 2013
Available online 3 January 2014

Keywords:
Chiral sulfoxide
Diastereoselectivity
Arylation
Grignard reagent

ABSTRACT

Optically active *tert*-allylic alcohols constitute important and often challenging targets in organic synthesis. In this work, we employed a β-sulfinyl moiety as a remote chiral auxiliary to effect asymmetric 1,2-addition of aryl Grignard reagents to enones to form a variety of optically active *tert*-allylic alcohols. The absolute configuration of a representative alcohol product was determined by X-ray crystallography.
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Tertiary alcohol motifs are known to exert a broad gamut of biological activities and are found in the structures of numerous natural products and pharmaceuticals, such as various prostaglandin derivatives, (+)-sydonol tetrodotoxicin, etc.[1] Given that many bioactive compounds feature a chiral quaternary carbon within a tertiary alcohol moiety, the development of new and/or improved methods for accessing enantiopure tertiary alcohols constitutes an important challenge in synthetic organic chemistry. The strategies that have been considered thus far in this regard include stereoselective nucleophilic addition to ketones,[2] rearrangements,[3] stereospecific insertion of carbenes into secondary alcohols,[4] and asymmetric oxidation.[5]

Stereoselective transformations facilitated by a chiral sulfoxide auxiliary have proven useful in a variety of synthetic applications and the ability to prepare such compounds with high enantiomeric excess offers significant practical benefit. In particular, optically active sulfinyl aldehydes, sulfinyl ketones, and sulfinyl enones have been employed to effect a range of asymmetric reduction transformations,[6] Diels–Alder reactions,[7] 1,2-additions,[8] and aldol reactions.[9] We have previously reported on a highly stereoselective reduction of α-sulfinyl enones using $NaBH_4$ with $YbCl_3$ in methanol (Luche reduction),[10] an asymmetric 2,3-sigmatropic rearrangement of α-sulfinyl enones under mild conditions,[11] and a remote stereocontrolled reduction of β-sulfinyl enones using $NaBH_4$ or DIBAL (diisobutylaluminum hydride) with $LaCl_3$.[12]

To date, numerous examples of asymmetric transformations of α-sulfinyl ketones and α-sulfinyl enones have been reported. In these reactions, the formation of a six-membered ring via interaction of the sulfoxide's oxygen atom and the carbonyl's oxygen atom with a Lewis-acidic metal ion has been invoked as a key transition state. However, only a few examples of remotely induced asymmetric reactions of β-sulfinyl ketones and β-sulfinyl enones have been documented. Herein, we describe the use of a remote β-sulfinyl chiral auxiliary in stereoselective 1,2-addition of aryl Grignard reagents to β-sulfinyl enones to afford optically pure tertiary and secondary chiral allylic alcohols.

Optically active (*Z*)-β-sulfinyl enones **1** were readily prepared from *l*-menthyl-(−)-(*S*)-toluenesulfinate in four steps.[12] Table 1 summarizes the results of 1,2-addition of different Grignard reagents to enone (*Ss*)-**1a** in the presence or absence of a Lewis acid. An analogous 1,2-addition of PhMgI to (*Ss*)-**1a** was considered as well. Combining **1a** with 1.0 equiv of PhMgI at −78 °C produced no reaction and led to the complete recovery of the starting material **1a** (entry 1). However, employing 2 equiv of the Grignard reagent under otherwise identical conditions afforded, after workup, the corresponding tertiary alcohol **2a** in a moderate yield with a high stereoselectivity (entry 2). Encouraged by this observation, we increased the amount of PhMgI used to 5 equiv, which afforded **2a** in a good yield while maintaining the high stereoselectivity of the

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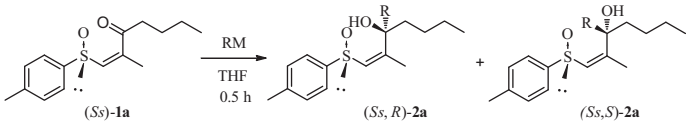
http://dx.doi.org/10.1016/j.tetlet.2013.12.108

Table 1
1,2-Addition of (*Z*)-β-sulfinyl enone **1a**



Entry[a]	RM	Temp	Lewis acid	D.r. (*R*:*S*)[b]	Yield[c] (%)
1	PhMgI (1.0 equiv)	−78 °C			0
2	PhMgI (2.0 equiv)	−78 °C		99.5:0.5	59
3	PhMgI (5.0 equiv)	−78 °C		99.1:0.9	88
4	PhMgI (5.0 equiv)	rt		98.0:2.0	81
5	PhMgBr (5.0 equiv)	−78 °C		98.5:1.5	85
6	PhMgI (5.0 equiv)	−78 °C	$LaCl_3$	98.3:1.7	27
7	PhMgI (5.0 equiv)	−78 °C	$YbCl_3$	97.2:2.8	37
8	PhLi (5.0 equiv)	−78 °C		99.5:0.5	6
9	MeMgI (5.0 equiv)	−78 °C		23:77	86
10	*i*-PrMgBr (5.0 equiv)	−78 °C		49:51	71

[a] Reactions were carried out on a 50 mg scale at 0.19 mmol of (*Ss*)-**1a**.
[b] The diastereoisomeric ratio was determined by ^{1}H NMR of the crude product.
[c] The yield was determined by ^{1}H NMR analysis of the crude product using CH_2Br_2 as an internal standard.

reaction (entry 3). Conducting the reaction at room temperature or using the bromide- instead of iodide-containing Grignard reagent caused a slight decrease in the stereoselectivity of the addition (entries 4 and 5). The presence of a Lewis acid in the reaction mixture had a critically detrimental effect on the yield of the alcohol product (entries 6 and 7). Finally, employing 5 equiv of PhLi instead of PhMgI afforded **2a** with an excellent diastereomeric ratio but in a

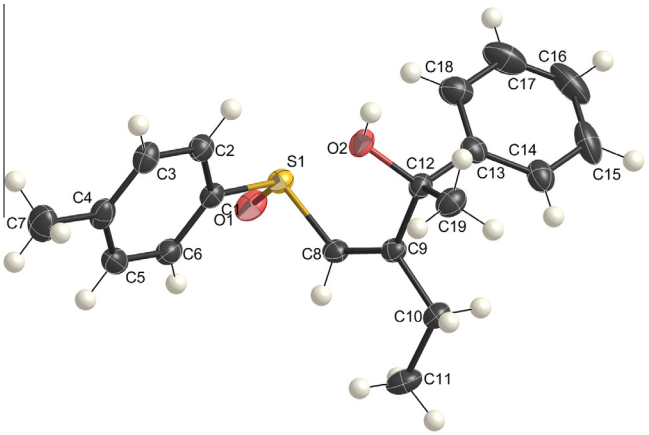
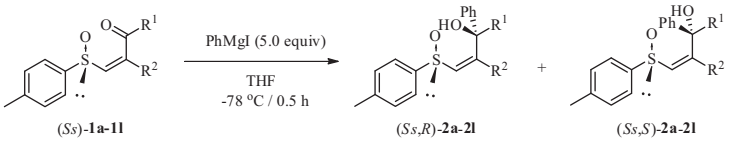


Figure 1. X-ray crystal structure of **2g**.

poor yield (entry 8). Interestingly, attempts to use alkyl Grignard reagents, namely MeMgI and *i*PrMgBr, gave good yields of **2a** but were accompanied by inversion or essentially complete loss of the diastereoselectivity of the addition (entries 9 and 10). The above observations provide some mechanistic hints regarding the interaction of **1a** with PhMgI. It is reasonable to postulate that the phenyl ring of PhMgI may engage in noncovalent π–π interaction with the *para*-tolyl moiety by approaching **1a** from the side opposite to sulfur's lone pair. The magnesium atom is then chelated by sulfoxide's oxygen and carbonyl's oxygen atoms, which facilitates the insertion of the C=O moiety into the aryl–Mg bond.

We further investigated the scope of this reaction by considering variously substituted substrates **1** and the results of the series of experiments are given in Table 2. Enones **1b–l** were synthesized following the general protocol developed for the preparation of **1a**.[12] The 1,2-addition of PhMgI proved to be almost completely stereoselective in all cases and provided good yields of the corresponding alcohols with the exception of entry 10 in Table 2. Compound **1j** features a phenyl group at the R^2 position in its structure. This phenyl ring may compete with the *para*-tolyl moiety of **1j** for

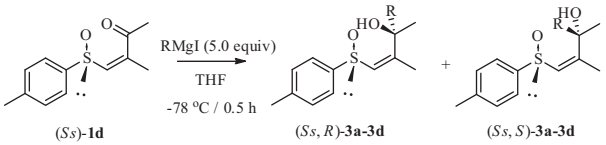
Table 2
Diastereoselective 1,2-addition reactions of (*Ss*)-**1a–1l**



Entry	Substrate			Product		
		R^1	R^2		D.r. (*R*:*S*)[a]	Yield[b] (%)
1	**1a**	*n*-Bu	Me	**2a**	99.1:0.9	85
2	**1b**	H	*i*-Pr	**2b**	91.0:9.0	74
3	**1c**	H	*n*-Bu	**2c**	91.0:9.0	70
4	**1d**	Me	Me	**2d**	100:0	84
5	**1e**	Me	*i*-Pr	**2e**	100:0	80
6	**1f**	Me	*n*-Bu	**2f**	99.7:0.3	76
7	**1g**	Me	Et	**2g**	99.4:0.6	86
8	**1h**	*n*-Bu	Et	**2h**	99.0:1.0	76
9	**1i**	*n*-Bu	*i*-Pr	**2i**	99.8:0.2	66
10	**1j**	*n*-Bu	Ph	**2j**	100:0	33
11	**1k**	*n*-Bu	*n*-Bu	**2k**	99.3:0.7	63
12	**1l**	*i*-Bu	*n*-Bu	**2l**	99.0:1.0	71

[a] The diastereoisomeric ratio was determined by ^{1}H NMR analysis of the crude product.
[b] Isolated yield, average of two runs.

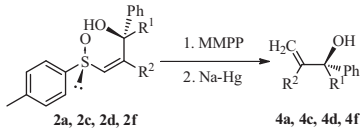
Table 3
Diastereoselective 1,2-addition reactions of (*Ss*)-**1d**



Entry	R	D.r. (*R*:*S*)[a]	Product	Yield[b] (%)
1	4-$H_3COC_6H_4$	93:7	**3a**	69
2	4-ClC_6H_4	98:2	**3b**	77
3	4-$H_3CC_6H_4$	92:8	**3c**	80
4	3-$H_3CC_6H_4$	93:7	**3d**	69

[a] The diastereoisomeric ratio determined by ^{1}H NMR analysis of the crude product.
[b] Isolated yield, average of two runs.

Table 4
Removal of sulfoxide moiety



Entry	Substrate (d.r.)	R^1	R^2	2 Steps yield[a] (%)	E.r. (*S*:*R*)[b]
1	**2a** (99.1:0.9)	*n*-Bu	Me	76	97:3
2	**2c** (91.0:9.0)	H	*n*-Bu	81	86:14
3	**2d** (100:0)	Me	Me	65	96:4
4	**2h** (99.0:1.0)	*n*-Bu	Et	78	92:8

[a] Isolated yield.
[b] The enantiomeric ratio determined by HPLC analysis of the isolated product.

the π–π interaction with PhMgI, furthermore **1j** is styrene-shaped so that the reactivity was different from the other enones, thereby decreasing the yield of alcohol **2j**.

The (*R*)-absolute configuration of the stereogenic center in the major diastereomer of products **2** was unambiguously established via single-crystal X-ray crystallographic analysis of the tertiary allylic alcohol (*Ss*,*R*)-**2g** (Fig. 1).

We explored the influence of *para*-substitution in the aryl ring of the Grignard reagent on the diastereoselectivity outcome of its addition to (*Ss*)-**1d**. The results of these experiments are summarized in Table 3. The incorporation of either electron-donating or electron-withdrawing groups in the *para*-position of the Grignard reagent's aromatic ring led to somewhat decreased diastereoisomeric ratios for the products **3a**–**3d** under identical reaction conditions. Nevertheless, the chiral sulfoxide auxiliary was still quite effective in controlling the stereoselectivity of 1,2-addition to β-sulfinyl enones thereby providing a new useful method for the synthesis of tertiary allylic alcohols.

Finally, we attempted to cleave a sulfoxide moiety from sulfinyl allylic alcohols **2** in order to gain the optically active allylic alcohols. These results are shown in Table 4. Variously substituted substrates **2** were treated with magnesium mono perphthalate (MMPP) followed by desulfurization from sodium amalgam (Na–Hg), and the corresponding optically active tertiary allylic alcohols were obtained in good yield. When the oxidation reaction was carried out using MCPBA as a oxidation reagent, the quaternary carbon was somewhat racemized and afforded the allylic alcohol with slightly decreased enantiomeric ratio (*S*:*R* = 80:20; data not shown).

In conclusion, we have developed the highly stereoselective 1,2-addition of aryl Grignard reagents to β-sulfinyl enones to afford the corresponding chiral tertiary alcohols in excellent diastereomeric purity. The reaction is considered to be facilitated by the π–π interaction between the *para*-tolyl substituent of the sulfinyl enone with the aryl moiety of the Grignard reagent and to involve formation of the seven-membered Mg-chelate ring. These results provide a new useful synthetic strategy that can be applied to the preparation of various natural products and other bioactive compounds containing chiral alcohol building blocks.

Acknowledgments

The authors thank the Analytical Center of the School of Pharmacy, Nihon University and the Center for Analytical Instrumentation, Chiba University for the X-ray crystallographic assistance.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.12.108.

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