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Asymmetric induction in the inter- and intramolecular radical carbon–carbon bond forming reactions of *N*-arylsulfonyl-α-bromocarboxamides with chiral ligands: the use of chiral sulfoxide ligands in radical chemistry

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Abstract

Inter- and intramolecular asymmetric radical carbon–carbon bond-forming reactions of sulfonamides were successfully achieved using chiral ligands in the presence of Lewis acids. The use of chiral sulfoxides as chiral ligands in the radical reactions of sulfonamides provided higher enantioselectivity, proceeding through a diastereomerically more favorable intermediate, presumably by enantiotopically selective coordination of one of the two oxygen atoms of the sulfonamides. © 2000 Elsevier Science Ltd. All rights reserved.

Free radical carbon–carbon bond-forming reactions have received much attention in recent years for the stereoselective construction of cyclic compounds, especially five-membered carbocycles[1] and heterocycles.[2] Over the last decade, rapid progress in radical chemistry has provided a new strategic dimension for the synthesis of complex molecules such as natural products.[3] Increasing interest has been focused on the stereoselectivity of free radical reactions.[4] Currently, in particular, our attention is focused on asymmetric synthesis by radical reactions; however, there have appeared only a limited number of reports related to this asymmetric synthesis,[5] including those employing chiral sulfoxides as reaction substrates.[6] We wish to communicate herein asymmetric induction in inter- and intramolecular radical carbon–carbon bond-forming reactions with chiral ligands. Few reports have been published so far concerning radical asymmetric reactions with chiral ligands.[7] This paper presents the first example of asymmetric synthesis via radicals using chiral sulfoxides as chiral ligands.

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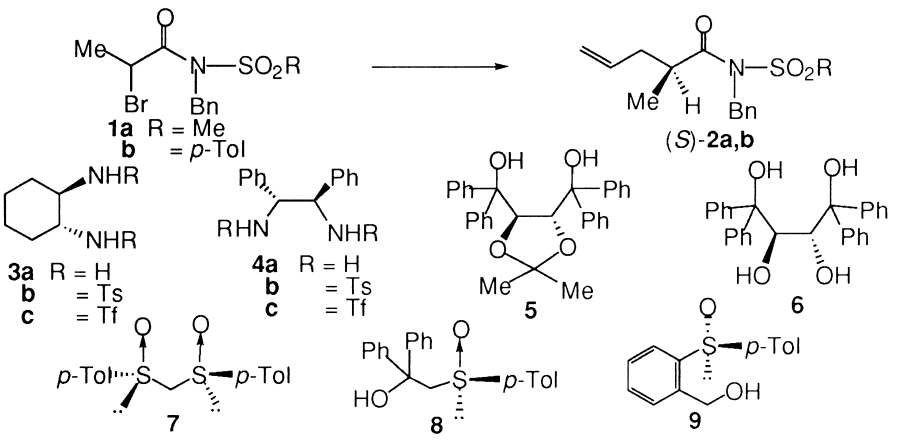
Intermolecular radical allylation reactions of sulfonamides **1a,b** were studied under the mediation of Lewis acids using chiral ligands such as chiral diamine derivatives **3a–c** and **4a–c**, chiral diols **5** and **6**, and chiral sulfoxides **7–9**. The reactions of **1a,b** with allyl (tri-*n*-butyl)stannane (2.0 equiv.) were carried out in dichloromethane at –78°C for 3 h in the presence of chiral ligands **3–9** (1.0 equiv.), triethylborane (3.0 equiv.), and Lewis acids (1.0 equiv.) such as $Ti(O\textit{i}\text{-}Pr)_4$, Et_3Al, or $Mg(OTf)_2$ to give (*S*)-**2a,b** in good yields. The ee of the products **2a,b** was determined by HPLC analysis with Chiralpak AS. The absolute configuration of the products (*S*)-**2a,b** was determined by chemical correlation to (*S*)-(+)-2-methyl-4-pentenoic acid of known absolute configuration (Scheme 1).[8]



Scheme 1.

As shown in Table 1, the steric bulk of substituents in sulfonamides plays an important role in achieving the radical allylation with high enantioselectivity; the allylation of a methanesulfonamide **1a** using **5** as a chiral ligand provided (*S*)-**2a** in good yield (83%) with very poor ee (5%), whereas that of a sulfonamide **1b** bearing a more bulky group (*p*-tolyl) resulted in formation of (*S*)-**2b** with higher ee (50%).

Table 1
Asymmetric radical allylation of sulfonamides **1a,b** with chiral ligands **3–9**[a)]

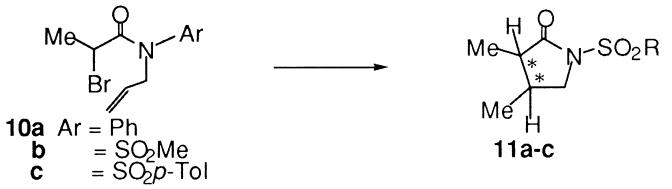
Substrates	Ligand	Lewis acid	Yield (%) of **2a,b**	e.e.% of (*S*)-**2a,b**[b)]
1a	**5**	$Ti(O\textit{i}\text{-}Pr)_4$	83 (**2a**)	5
1b	**3a**	Et_3Al	72 (**2b**)	53
1b	**3b**	Et_3Al	68 (**2b**)	60
1b	**3c**	Et_3Al	83 (**2b**)	58
1b	**4a**	Et_3Al	88 (**2b**)	53
1b	**4b**	Et_3Al	80 (**2b**)	64
1b	**4c**	Et_3Al	83 (**2b**)	63
1b	**5**	$Ti(O\textit{i}\text{-}Pr)_4$	44 (**2b**)	50
1b	**6**	$Ti(O\textit{i}\text{-}Pr)_4$	52 (**2b**)	52
1b	**7**	$Mg(OTf)_2$	65 (**2b**)	52
1b	**8**	$Mg(OTf)_2$	41 (**2b**)	83
1b	**9**	$Mg(OTf)_2$	64 (**2b**)	50

a) The reactions of **1a,b** with allyl(tri-*n*-butyl)stannane (2.0 equiv.) were carried out in CH_2Cl_2 at -78 °C for 3 h in the presence of chiral ligand **3-9** (1.0 equiv.), Lewis acid (1.0 equiv.) and triethylborane (3.0 equiv.).

b) The enantiomeric excess (e.e.) of **2a,b** was determined by HPLC analysis with CHIRALPAK AS.

The reactions of **1b** mediated by Et_3Al using chiral diamines **3a** and **4a**, or disulfonamides **3b,c** and **4b,c** as chiral ligands furnished (*S*)-**2b** in good yields with moderate ee (53–64%). The reactions of **1b** mediated by Ti(O*i*-Pr)$_4$ using chiral diols **5** and **6** as chiral ligands gave (*S*)-**2b** with 50 and 52% ee, respectively. The use of chiral sulfoxides **7**–**9** in the allylation of **1b** provided (*S*)-**2b** with 52, 83, and 50% ee, respectively. Thus, a chiral sulfoxide **8** was definitely demonstrated to be the most effective among the ligands examined.

The intramolecular radical reactions of **10a**–**c** were carried out in dichloromethane at –78°C for 3 h using tri-*n*-butyltin hydride (2.0 equiv.) as a radical initiator in the presence of chiral ligands **3**–**8** (1.0 equiv.), triethylborane (3.0 equiv.), and Lewis acids (1.0 equiv.) described before to give **11a**–**c**. The relative configuration of **11a**–**c** was determined as *trans* between the two methyl groups by the NOE in the NMR spectral analysis. The ee of **11a**–**c** was determined by HPLC analysis with Chiralpak AS (Scheme 2).



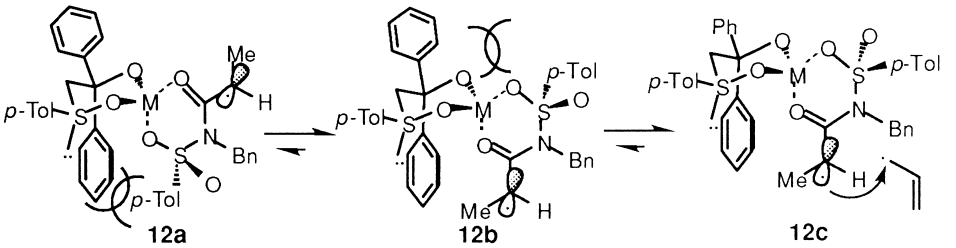
Scheme 2.

Similarly to the intermolecular reactions, the degree of asymmetric induction in the intramolecular reactions was also largely dependent upon the *N*-substituents in the starting amides. Radical cyclizations of **10a**–**c** with tri-*n*-butyltin hydride (2.0 equiv.) mediated by Ti(O*i*-Pr)$_4$ (1.0 equiv.) using a chiral diol **5** (1.0 equiv.) as a chiral ligand in CH_2Cl_2 at –78°C for 3 h gave **11a**–**c** with 5, 4, and 47% ee, respectively. Thus, it might be assumed that the steric bulk of *N*-substituents in the amides plays a crucial role in achieving high enantioselectivity. However, too bulky *N*-substituents such as the 2,4,6-triisopropylphenyl- and 1-naphthalenesulfonyl groups provided no cyclization product, recovering the starting materials, along with the corresponding reduction products.

The intramolecular radical cyclization of **10c** with **3a,b**, **4a,b** (Et_3Al), **7** or **8** ($Mg(OTf)_2$) as ligand under similar reaction conditions mentioned above exhibited much lower enantioselectivity (11, 12, 15, 15, 3, or 5% ee, respectively). However, the use of the chiral ligand **6** in the Ti(O*i*-Pr)$_4$-mediated reaction of **10c** afforded **11c** in 53% yield with considerably high ee (77%). The ee of **11a–c** was determined by HPLC analysis with Chiralpak AS.

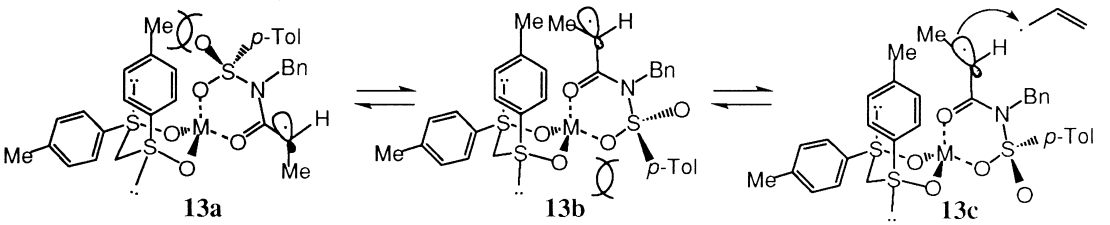
The plausible mechanism of these Lewis acid-mediated radical reactions with chiral ligands is proposed as follows. The reaction of a sulfonamide **1b** with Lewis acid ($Mg(OTf)_2$) and chiral β-hydroxyethyl sulfoxide **8** would result in the initial formation of a six–six-membered chelate **12** of the magnesium ion, in which one of the two oxygen atoms of the sulfonamide would enantiotopically selectively coordinate to generate a diastereomerically more favorable intermediate. In the conformational equilibrium of the chelate **12**, **12c** would be favorably formed in preference to **12a,b**, since **12a** and **12b** have rather severe steric interference between a phenyl ring and a *p*-tolyl group of the sulfonamide (the s-*cis* conformation of the methyl group at the α-carbon of the carboxamide is preferred to the s-*trans* one becausee of the severe $A^{1,3}$ strain between the *N*-benzyl substituent and the methyl group in the s-*trans* form). Thus, the allyl radical attacks the reactive α site of the carboxamide from the back side of the bulky group (*p*-tolyl) of the sulfonamide in **12c** to give (*S*)-**2b** (Scheme 3).

The allylation of **1b** with **7** is rationalized in a similar way. The magnesium chelate **13c** is favorably formed in preference to **13a,b** due to steric interference between the *p*-toluenesulfonyl and *p*-tolyl groups in **13a,b**. Allyl radical attacks the reactive site from the back side of the tolyl group in the sulfonamide portion of **13c** to furnish (*S*)-**2b** (Scheme 4).



Scheme 3.

The above explanations are essentially based on a new chirality induced on the sulfur atom of the sulfonamide. This is firmly supported also by the fact that amide substrates having rather smaller *N*-substituents such as a phenyl group and a methanesulfonyl substituent provided extremely poor enantioselectivity, as mentioned before.



Scheme 4.

Thus, the inter- and intramolecular asymmetric radical carbon–carbon bond-forming ractions of sulfonamides were successfully achieved by employing chiral ligands, particularly chiral sulfoxide ligands.

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