Pergamon

SCIENCE DIRECT®

Tetrahedron: *Asymmetry* 14 (2003) 2875–2878

TETRAHEDRON:
ASYMMETRY

Asymmetric radical carbon–carbon bond forming reactions in chiral amides and imides under sulfonyl groups stereocontrol

Kunio Hiroi,* Masamitsu Kaneko, Mikiyo Ishii and Fumiko Kato

Tohoku Pharmaceutical University, 4-4-1 Komatsushima, Aoba-ku, Sendai, Miyagi 98l-8558, Japan

Received 28 April 2003; accepted 13 June 2003

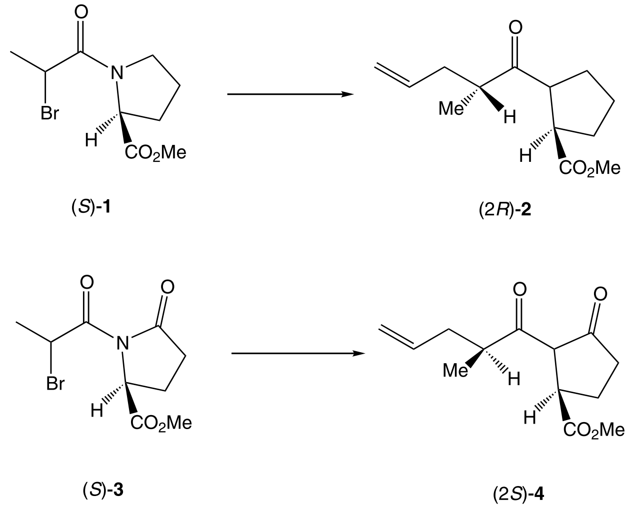
Abstract—Asymmetric radical carbon–carbon bond formation was achieved in chiral amide and imide systems under sulfonyl group stereocontrol, providing high diastereoselectivity. The stereochemistry of the products was determined and the mechanism of the stereochemical pathways is rationalized by the formation of chelates of Lewis acid metals between oxygens of acetyl, amide, and imide carbonyls, or sulfonyl groups.

There have been numerous methods reported for the asymmetric synthesis of biologically active chiral compounds,[1] on which much interest has been placed for the development of new drugs in the pharmaceutical area. Of these, asymmetric radical reactions have received much attention in recent years,[2] particularly for creating carbon–carbon bonds enantioselectively.[3] However, there are only a few reports of enantioselective radical reactions using a stoichiometric[4] or catalytic amounts[5] of Lewis acids as chiral catalysts. For instance, currently we have been developing a new asymmetric radical reaction with Lewis acids coordinated by chiral sulfoxide ligands.[6]

Use of Lewis acids in radical reactions is of importance[7] for increasing the reactivity and the stereoselectivity in some cases, owing to the stereocontrol of the conformation of the reaction substrates by the coordination to Lewis acids employed.

We wish to communicate herein a diastereoselective radical carbon–carbon bond forming reaction in chiral amides and imides, and demonstrate the high diastereomeric efficiency resulting from the stereocontrol by coordination of oxygens of ketone, amide, and imide carbonyls or sulfonyl functions involved to Lewis acids.

The radical allylation of 2-bromopropionic acid (*S*)-proline methyl ester amide, (*S*)-**1**, with allyltri-*n*-butylstannane was carried out at −78°C in CH_2Cl_2 for 3 h in the presence of $MgBr_2·OEt_2$ (3 equiv.) and triethylborane (10 equiv.) to give (2*R*)-**2** in 97% yield with 38.8% d.e. The allylation of an imide (*S*)-**3** under similar reaction conditions (−78°C, for 3 h) provided slightly higher diastereoselectivity of (2*S*)-**4** ($ZnCl_2·OEt_2$: 45.5% d.e., 91% yield and $MgBr_2·OEt_2$: 61.8% d.e., 91% yield). No reaction occurred without Lewis acids or with methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD) as a Lewis acid in the above reaction of (*S*)-**1** and (*S*)-**3** (Scheme 1).



Scheme 1.

---

* Corresponding author. E-mail: khiroi@tohoku-pharm.ac.jp

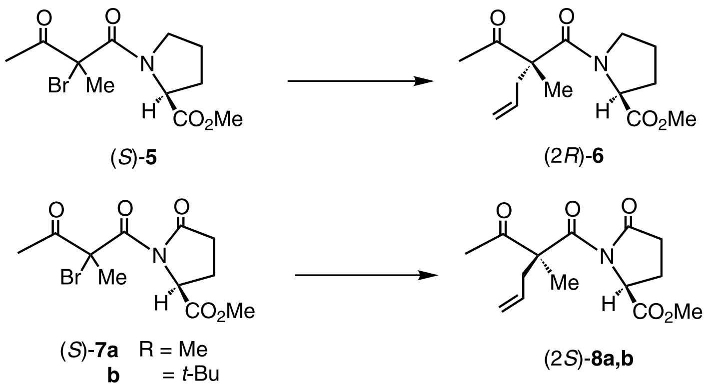
0957-4166/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/S0957-4166(03)00534-2

The stereocontrol by the β-keto carbonyl groups was observed in the radical allylation of the corresponding α-acetoacetic amide **5** or imide **7**. The radical reactions of an amide **5** with allyl-tri-*n*-butylstannane were carried out at −78°C in CH_2Cl_2 for 3 h under the same reaction conditions as mentioned above to give (2*R*)-**6** with 39.1% d.e. ($ZnCl_2 \cdot OEt_2$, 48% yield) and 38.5% d.e. ($MgBr_2 \cdot OEt_2$, 51% yield). The reaction of an imide **7a** was conducted under similar reaction conditions to provide (2*S*)-**8a** with 32.8% d.e. ($ZnCl_2 \cdot OEt_2$, 81% yield) and 54.2% d.e. ($MgBr_2 \cdot OEt_2$, 82% yield). Replacement of the methyl ester in **7a** with *t*-butyl ester **7b** provided excellent diastereoselectivity: 89.2% d.e. ($MgBr_2OEt_2$, at −78°C, 91% yield) and 82.1% d.e. ($MgBr_2 \cdot OEt_2$, at 0°C, 87% yield). The absolute configurations of newly created asymmetric carbon centers in the products **2**, **4**, **6**, and **8a**,**b** were determined by chemical correlation to (*S*)-2-methyl-4-pentenoic acid[8] and (*S*)-(−)-2-acetyl-2-methyl-4-pentenoic acid[9] of known absolute configuration (Scheme 2).

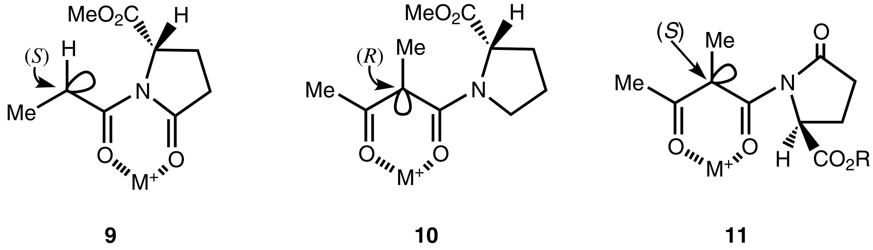
These stereochemical results can be rationalized by stereocontrol with coordination of the functional groups involved to Lewis acids. A six-membered chelate **9** would be formed by coordination of the two carbonyl oxygens of the imide in (*S*)-**3** to Lewis acids. The allylstannane attacks the reactive site in **9** from the back side of the ester group at the stereogenic center to give (2*S*)-**4**. In the case of an α-acetoacetamide **5** and an imide **7**, however, participation of the β-keto group for chelation would be preferred to give conformationally favored six-membered chelates **10** and **11**, due to the effects of the dipole–dipole repulsion betweeen the ester and the amide carbonyl groups or two imide-carbonyl groups, respectively. The attack of the allylstannane would occur, as shown in **10** and **11**, from the back side of the ester groups at the stereogenic centers to afford (2*R*)-**6**, and (2*S*)-**8**, respectively (Scheme 3).

Introduction of sulfonyl functions into reactive sites improved the reactivity of the radicals generated with unusually higher stereoselectivity. The reactivity of α-sulfonyl radicals depends on the Lewis acids used. Radical allylations of 3-bromo-3-*p*-toluenesulfonyl-2-butanone with allyltri-*n*-butylstannane were studied in CH_2Cl_2 at −78°C in the presence of triethylborane (3.0 equiv.) using various Lewis acids (1.0 equiv.). Use of $ZnCl_2 \cdot OEt_2$, $Zn(OTf)_2$, $MgBr_2 \cdot OEt_2$, $Mg(OTf)_2$, or $Ti(Oi\text{-}Pr)_4$ as a Lewis acid provided an allylated ketone, 3-methyl-3-*p*-toluenesulfonyl-5-hexen-2-one, in moderate chemical yields. An aluminum Lewis acid, MAD, was found to be the most effective for increasing the reactivity of the radical resulted, providing an excellent chemical yield (81%).

The allylations of α-sulfonyl imides (*S*)-**12a**,**b** with allyl-tri-*n*-butylstannane were studied in CH_2Cl_2 at −78°C for 5 h in the presence of triethylborane (2.0 equiv.) and various Lewis acids (1.0 equiv.) such as $ZnCl_2 \cdot OEt_2$, $Zn(OTf)_2$, $MgBr_2 \cdot OEt_2$, $Mg(OTf)_2$, $Ti(Oi\text{-}Pr)_4$, or MAD. The results obtained are listed in Table 1. The reactions without a Lewis acid provided lower chemical yields with extremely poor d.e. Use of Lewis acids in the above reaction resulted in smooth conversion of (*S*)-**12a**,**b** into (2*R*)-**13a**,**b** with moderate d.e. Surprisingly, however, use of an aluminum Lewis acid, MAD, provided excellent chemical yields and extremely high diastereoselectivity, as listed in Table 1. Contrary to



Scheme 2.



9 10 11

Scheme 3.

Table 1. Asymmetric induction in radical carbon–carbon bond forming reactions of (*S*)-**12a**,**b**[a]

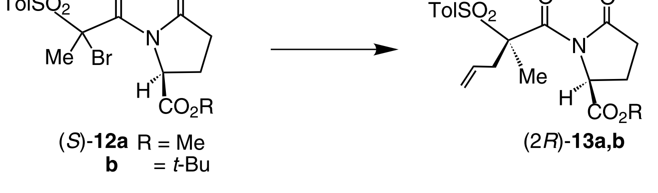
Substrate	Lewis acid	Reaction time (h)	Reaction temp. (°C)	Yield (%) of **13a**,**b**	D.e. (%) of (*R*)-**13a**,**b**[b]
12a	None	10	−78	27	4
	$ZnCl_2{\cdot}OEt_2$	5	0	73	20
	$Zn(OTf)_2$	5	−78	63	8
	$MgBr_2{\cdot}OEt_2$	5	−78	76	24
	$Mg(OTf)_2$	5	−78	86	27
	$Ti(O\textit{i}\text{-}Pr)_4$	5	−78	72	46
	MAD	5	−78	78	81
12b	None	10	−78	33	3
	$ZnCl_2{\cdot}OEt_2$	5	0	52	25
	$Zn(OTf)_2$	5	−78	58	32
	$MgBr_2{\cdot}OEt_2$	5	−78	52	25
	$Mg(OTf)_2$	5	−78	47	64
	MAD	5	−78	77	83

[a] The reactions of (*S*)-**12a**,**b** with allyltri-*n*-butylstannane (2.0 equiv.) were carried out in CH_2Cl_2 at −78°C in the presense of Lewis acids (1.0 equiv.) and triethylborane (2.0 equiv.).

[b] The diastereomeric excess (d.e.) of **13a**,**b** was determined by HPLC analysis with ODS.

our expectation, the steric bulk of the ester groups was not effective in achieving high stereoselectivity.

The absolute configuration of a newly created stereogenic carbon centers in **13a**,**b** was determined by chemical correlation to (*S*)-(−)-2-methyl-2-*p*-toluenesulfonyl-4-pentenoic acid[10] of known absolute configuration (Scheme 4).

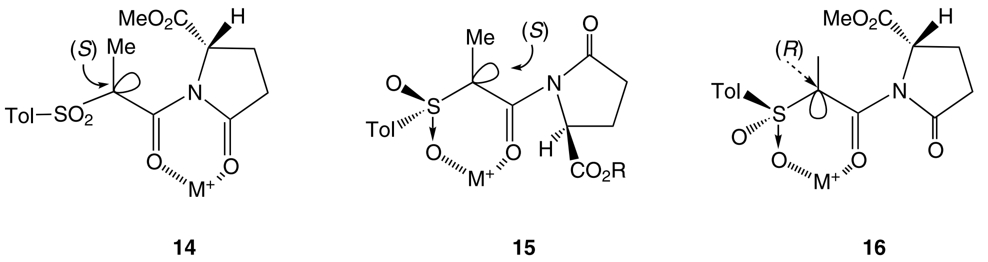


Scheme 4.

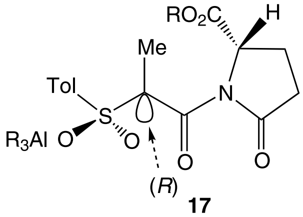
The rationalization of the stereochemical results obtained is as follows. The preferred formation of a chelate **14** between the two oxygens of the imide carbonyl group, followed by the radical allylation from the backside of the ester group, provides (2*S*)-**13**, which is not coincident with the experimental result. The formation of a chelate **15** betweeen the oxygens of the imide carbonyl and the sulfonyl group would be due to the dipole–dipole repulsion between the two imide-carbonyls, generating a new stereogenic sulfur atom by selecting one of the sulfonyl oxygens with the steric effect of the ester group. The allylation from the back side of a bulky tolyl group on the newly created stereogenic sulfur atom provides (2*S*)-**13**, which is not coincident with the results obtained above. So, finally it is certainly rationalized by the formation of a chelate **16** between one of the imide carbonyl and an oxygen of the sulfonyl group, owing to the dipole–dipole repulsion between one of the imide carbonyl and the ester group, in which one of the two oxygens of the sulfonyl group is sterically preferred to generate a stereogenic sulfur atom by the effect of the original stereogenic center with the ester group. The allylatannane attacks the reactive site from the less crowded sulfur-oxygen side in **16** by circumventing the steric interference of the *p*-tolyl group on a newly generated stereogenic sulfur atom, affording (2*R*)-**13** (Scheme 5).

In the case of a monodentate Lewis acid (MAD), coordination of one of the two oxygens of the sulfonyl group to an aluminum atom of MAD, as shown in **17**, would be crucial for achieving high diastereoselectivity. A new stereogenic sulfur atom generated by the effect of the original stereogenic center affected asymmetric induction in the radical allylation to give (2*R*)-**13** with high diastereoselectivity by the attack of the allylstannane from the less crowded sulfur-oxygen side (Scheme 6).

Thus, an α-sulfonyl radical provided high reactivity and diastereoselectivity on the use of an aluminum Lewis acid (MAD), presumably by formation of an aluminum



Scheme 5.



17

Scheme 6.

chelate between the amide carbonyl and the sulfonyl oxygens, in which one of the oxygens would be sterically selected by the effect of the original stereogenic center with an ester group to create a stereogenic sulfonyl sulfur atom, providing high diastereoselectivity by the effect of the new chirality.

References

1. (a) *Catalytic Asymmetric Synthesis*; Ojima, I. Ed.; VCH Publishers: New York, 1993; (b) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; John Wiley: New York, 1994.
2. (a) Porter, N. A.; Giese, B.; Curran, D. P. *Acc. Chem. Res.* **1991**, *24*, 294–304; (b) Curran, D. P.; Porter, N. A.; Giese, B. *Stereochemistry of Radical Reactions*; VCH: New York, 1996.
3. (a) Ruck, K.; Kunz, H. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 694–696; (b) Giese, B.; Hofmann, U.; Roth, M.; Velt, A.; Wyss, C.; Zehnder, M.; Zipse, H. *Tetrahedron Lett.* **1993**, *34*, 2445–2448; (c) Hanessian, S.; Yang, H.; Schaum, R. *J. Am. Chem. Soc.* **1996**, *118*, 2507–2508; (d) Wu, M.-J.; Fu, C.-L.; Duh, T.-H.; Yeh, J.-Y. *Synthesis* **1996**, 462–464; (e) Sibi, M. P.; Ji, J. *J. Am. Chem. Soc.* **1996**, *118*, 3063–3064; (f) Sibi, M. P.; Ji, J. *J. Org. Chem.* **1996**, *61*, 6090–6091; (g) Garner, P.; Leslie, R.; Anderson, J. T. *J. Org. Chem.* **1996**, *61*, 6754–6755; (h) Mase, N.; Watanabe, Y.; Toru, T. *J. Org. Chem.* **1998**, *63*, 3899–3904; (i) Giraud, L.; Renaud, P. *J. Org. Chem.* **1998**, *63*, 9162–9163; (j) Sibi, M. P.; Chen, J.; Rheault, T. R. *Org. Lett.* **2001**, *3*, 3679–3681; (k) Friestad, G. K.; Qin, J. *J. Am. Chem. Soc.* **2001**, *123*, 9922–9923.
4. (a) Wu, J. H.; Radinov, R.; Porter, N. A. *J. Am. Chem. Soc.* **1995**, *117*, 11029–11030; (b) Fhal, A.-R.; Renaud, P. *Tetrahedron Lett.* **1997**, *38*, 2661–2664; (c) Murakata, M.; Jono, T.; Hoshino, O. *Tetrahedron: Asymmetry* **1998**, *9*, 2087–2092; (d) Sibi, M. P.; Chen, J. *J. Am. Chem. Soc.* **2001**, *123*, 9472–9473; (e) Kurihara, M.; Hayashi, T.; Miyata, N. *Chem. Lett.* **2001**, 1324–1325.
5. (a) Sibi, M. P.; Ji, J. *J. Am. Chem. Soc.* **1996**, *118*, 9200–9201; (b) Yang, D.; Gu, S.; Yan, Y.-L.; Zhu, N.-Y.; Cheng, K.-K. *J. Am. Chem. Soc.* **2001**, *123*, 8612–8613.
6. Hiroi, K.; Ishii, M. *Tetrahedron Lett.* **2000**, *41*, 7071–7074.
7. (a) Guindon, Y.; Rancourt, J. *J. Org. Chem.* **1998**, *63*, 6554–6565; (b) Renard, P.; Gerster, M. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2562–2579.
8. (a) Lin, N.-H.; Overman, L. E.; Ravinowity, M. H.; Robinson, L. A.; Sharp, M. J.; Zablocki, J. *J. Am. Chem. Soc.* **1996**, *118*, 9062–9072; (b) Ghosh, A. K.; Cho, H.; Onishi, M. *Tetrahedron: Asymmetry* **1997**, *8*, 821–827.
9. (a) Frater, G. *Helv. Chim. Acta* **1979**, *62*, 2825–2828; (b) Tomioka, K.; Ando, K.; Takemasa, Y.; Koga, K. *J. Am. Chem. Soc.* **1984**, *106*, 2718–2719.
10. Hiroi, K.; Maezuru, K.; Kimura, M.; Ito, N. *Chem. Lett.* **1989**, 1751–1754.