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Synthesis of β-Substituted α-Amino Acids with Use of Iridium-Catalyzed Asymmetric Allylic Substitution

Takatoshi Kanayama, Kazumasa Yoshida, Hideto Miyabe, Tetsutaro Kimachi, and Yoshiji Takemoto*

Graduate School of Pharmaceutical Sciences, Kyoto University, Sakyo-ku, Kyoto 606-8501, Japan, and Faculty of Pharmaceutical Sciences, Mukogawa Women's University, 11-68 Koshien Kyuban-cho, Nishinomiya 663-8179, Japan

takemoto@pharm.kyoto-u.ac.jp

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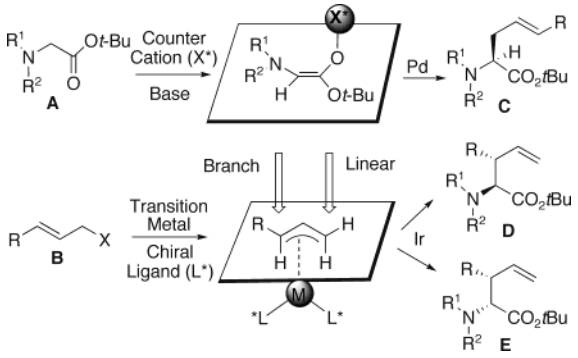
The asymmetric synthesis of β-substituted α-amino acids with use of iridium-catalyzed allylic substitution was described. The Ir-catalyzed allylic substitution of diphenylimino glycinate with allylic phosphates proceeded smoothly even at 0 °C and gave branch products with high enantioselectivity (up to 97% ee), when chiral bidentate phosphite bearing the 2-ethylthioethyl group was employed. In addition, both diastereomers of the branch products were synthesized stereoselectively by simply switching the base employed. These methods were also applied to the asymmetric synthesis of quaternary α-amino acids.

Introduction

The transition metal-catalyzed asymmetric allylic substitution is a useful reaction in organic synthesis.[1] Since the allylic alkylation with dialkyl malonates has been intensively studied, good yields and high enantioselectivities can now be obtained with a proper combination of a transition metal and a chiral ligand.[2−5] In contrast to the symmetric C-nucleophiles, the same reaction of 3-substituted allylic alcohol derivatives **B** with unsymmetrical C-nucleophiles **A** is a tough and challenging task, because both regio- and diastereoselectivities as well as enantioselectivity should be controlled to give the desired stereoisomers (Scheme 1). Over the past few years, research has been focused on finding catalysts and chiral ligands, which favor the formation of branched chiral products **D** and **E** in the allylic substitution of α-amino esters **A** with **B**.[6,7] We have already reported the Pd-mediated asymmetric allylic alkylation of diphenylimino glycinate **1** with several allylic acetates in the presence of the chiral phase transfer catalyst (PTC) **11**

SCHEME 1. Transition Metal-Mediated Asymmetric Allylic Substitution



* Corresponding author. Fax: 81-075-753-4569.

(1) Recent reviews: (a) Trost, B. M. *Chem. Pharm. Bull.* **2002**, *50*, 1. (b) Trost, B. M.; Lee, C. B. In *Catalytic Asymmetric Synthesis II*; Ojima, I., Ed.; Wiley-VCH: Weinheim, Germany, 2000; p 593. (c) Hayashi, T. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: Weinheim, Germany, 2000; p 193. (d) Pfaltz, A.; Lautens, M. *Compr. Asymmetric Catal. I−III* **1999**, *2*, 833−884.

(2) (a) Matsushima, Y.; Onitsuka, K.; Kondo, T.; Mitsudo, T.; Takahashi, S. *J. Am. Chem. Soc.* **2001**, *123*, 10405. (b) You, S.-L.; Zhu, X.-Z.; Luo, Y.-M.; Hou, X.-L.; Dai, L.-X. *J. Am. Chem. Soc.* **2001**, *123*, 7471. (c) Helmchen, G.; Pfaltz, A. *Acc. Chem. Res.* **2000**, *33*, 336. (d) Blacker, A. J.; Clarke, M. L.; Loft, M. S.; Mahon, M. F.; Humphries, M. E.; Williams, J. M. J. *Chem. Eur. J.* **2000**, *6*, 353. (e) Hayashi, T. *J. Organomet. Chem.* **1999**, *576*, 195. (f) Prétôt, R.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 323. (g) Williams, J. M. J. *Synlett* **1996**, 705.

(3) (a) Fuji, K.; Kinoshita, N.; Tanaka, K.; Kawabata, T. *Chem. Commun.* **1999**, 2289. (b) Bartels, B.; Helmchen, G. *Chem. Commun.* **1999**, 741. (c) Janssen, J. P.; Helmchen, G. *Tetrahedron Lett.* **1997**, *38*, 8025.

(4) (a) Trost, B. M.; Dogra, K.; Hachiya, I.; Emura, T.; Hughes, D. L.; Krska, S.; Reamer, R. A.; Palucki, M.; Yasuda, N.; Reider, P. J. *Angew. Chem., Int. Ed.* **2002**, *41*, 1929. (b) Glorius, F.; Neuburger, M.; Pfaltz, A. *Helv. Chim. Acta* **2001**, *84*, 3178. (c) Kaiser, N.-F.; Bremberg, U.; Larhed, M.; Hallberg, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3596. (d) Trost, B. M.; Hildbrand, S.; Dogra, K. *J. Am. Chem. Soc.* **1999**, *121*, 10416.

(5) (a) Lloyd-Jones, G. C.; Pfaltz, A. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 462. (b) Lehmann, J.; Lloyd-Jones, G. C. *Tetrahedron* **1995**, *51*, 8863.

(6) (a) Nakoji, M.; Kanayama, T.; Okino, T.; Takemoto, Y. *Org. Lett.* **2001**, *3*, 3329. (b) Chen, G.; Deng, Y.; Gong, L.; Mi, A.; Cui, X.; Jiang, Y.; Choi, M. C. K.; Chan, A. S. C. *Tetrahedron: Asymmetry* **2001**, *12*, 1567. (c) You, S.-L.; Hou, X.-L.; Dai, L.-X.; Cao, B.-X.; Sun, J. *Chem. Commun.* **2000**, 1933. (d) Trost, B. M.; Ariza, X. *J. Am. Chem. Soc.* **1999**, *121*, 10727. (e) Kuwano, R.: Ito, Y *J. Am. Chem. Soc.* **1999**, *121*, 3236. (f) Hiroi, K.; Hidaka, A.; Sezaki, R.; Imamura, Y. *Chem. Pharm. Bull.* **1997**, *45*, 769. (g) Genet, J.-P.; Juge, S.; Achi, S.; Mallart, S.; Montes, J. R.; Levif, G. *Tetrahedron* **1988**, *44*, 5263.

(7) (a) Nakoji, M.; Kanayama, T.; Okino, T.; Takemoto, Y. *J. Org. Chem.* **2002**, *67*, 7418. (b) Weiss, T. D.; Helmchen, G.; Kazmaier, U. *Chem. Commun.* **2002**, 1270. (c) Kazmaier, U.; Zumpe, F. L. *Eur. J. Org. Chem.* **2001**, 4067. (d) Kazmaier, U.; Zumpe, F. L. *Angew. Chem., Int. Ed.* **2000**, *39*, 802. (e) Kazmaier, U.; Zumpe, F. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 1468. (f) Trost, B. M.; Ariza, X. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2635. (g) Baldwin, I. C.; Williams, J. M. J.; Beckett, R. P. *Tetrahedron: Asymmetry* **1995**, *6*, 1515.

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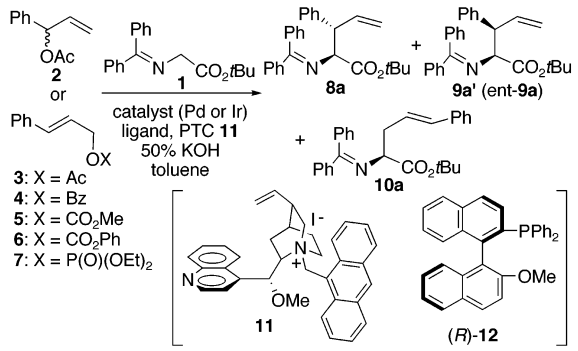
TABLE 1. Asymmetric Allylic Alkylation of 2−7 with 1 in the Presence of Chiral PTC 11



entry	substrate	conditions	yield, % 8a + 9a′	yield, % 10a	ratio 8a:9a′	ee, % 8a	ee, % 9a′
1	**2**	**A**[a]	13	71	5:95	*c*	85
2	**3**	**B**[b]	31	0	77:23	49	*c*
3	**4**	**B**[b]	40	0	75:25	46	*c*
4	**5**	**B**[b]	15	0	80:20	29	*c*
5	**6**	**B**[b]	23	0	83:17	57	*c*
6	**7**	**B**[b]	47	0	83:17	26	*c*

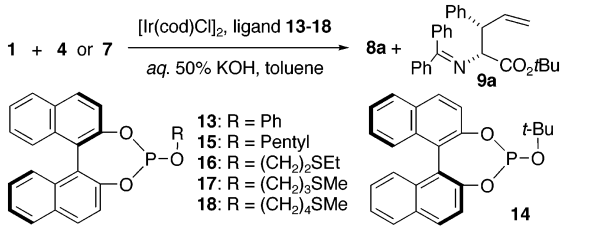
[a] $Pd_2(dba)_3$·$CHCl_3$ (3 mol %), chiral ligand **12** (9 mol %), 0 °C. [b] $[Ir(cod)Cl]_2$ (10 mol %), $(PhO)_3P$ (40 mol %), room temperature. [c] Not determined.

(Table 1), giving the chiral products **C** with high enantioselectivity (up to 96% ee).[6a] Unlike the palladium catalyst, some transition metals such as Ir,[3] Mo,[4] and W[5] promote the allylic alkylation at the more substituted terminus of the allylic substrate. Trost et al. recently reported that the Mo-catalyzed asymmetric allylic alkylation with azlactones occurs at the more substituted terminus with high regio-, diastereo-, and enantioselectivity.[8] However, there are no reports concerning the asymmetric synthesis of both diastereomers **D** and **E** as a major product with use of the same starting materials and the same chiral ligand. In this article, we detail the enantioselective Ir-catalyzed allylic substitutions of **1** in the presence of various chiral phosphites, and the significant effect of bases on diastereoselectivity of the obtained branch products **8** and **9** as well as application of the reaction to asymmetric synthesis of quaternary amino acids.[9]

Results and Discussion

Asymmetric Allylic Alkylation of Allylic Alcohol Derivatives 2−7 with 1 in the Presence of Chiral PTC 11 and Chiral Phosphites 13−24. Our previous work[7a] prompted us to examine PTC **11** as a chiral catalyst in transition metal-catalyzed allylic substitutions of diphenylimino glycinate **1** (Table 1). We first carried out the Pd-catalyzed reaction of **1** and acetate **2** in the presence of **11** and chiral ligand **12** (entry 1). Although the branch product **9a′** was obtained with good diastereo- and enantioselectivity, the regioselectivity of **9a′** to **10a** was low. Then we examined the Ir-catalyzed allylic substitutions of **1** and several allylic alcohol derivatives **3**−**7** under the phase-transfer conditions (50% KOH, $[Ir(cod)Cl]_2$, and $(PhO)_3P$) (entries 2−6). In all cases with the iridium catalyst, the regioselectivity was almost perfect and **10a** could not be observed. Furthermore, the other diastereomer **8a** among the branch products was obtained as a major product with moderate enantioselectivity. The absolute configuration of the C-2 stereogenic center of the products **8a** and **9a′** was assumed to be *S*, because the alkylation[10] and Pd-mediated allylic alkylation[7a] of **1** with the chiral PTC **11** generally produce (2*S*)-amino acid derivatives. Unfortunately, the chemical yield and ee of **8a** could not be improved by simply changing the leaving groups of the substrates. To overcome this situation, we next investigated the effect of chiral Ir-ligands **13**−**18**[11] in place of the chiral PTC **11** on the enantioselectivity (Table 2). The reaction of **1** with benzoate **4** was carried out in the presence of 50% KOH (3 equiv), $[Ir(cod)Cl]_2$ (10mol %), and chiral phosphite (20mol %). Indeed, it was revealed that the enantioselectivity, but not the diastereoselectivity, was dramatically affected by the substituent (R) of the ligands **13**−**18**.

TABLE 2. Ir-Catalyzed Allylic Alkylation of 4 and 7 with 1 in the Presence of Chiral ligands 13−18



entry	substrate	ligand, conditions	yield, % 8a + 9a	ratio 8a:9a	ee, % 8a	ee, % 9a
1	**4**	**13**, rt	29	69:31	*a*	23[a]
2	**4**	**14**, rt	7	86:14	68[a]	*b*
3	**4**	**15**, rt	6	67:33	95	46
4	**4**	**16**, rt	11	73:27	93	25
5	**7**	**16**, 0 °C	82	82:18	97	66
6	**7**	**15**, 0 °C	0			
7	**7**	**17**, 0 °C	43	65:35	29	39
8	**7**	**18**, 0 °C	4	75:25	41	53

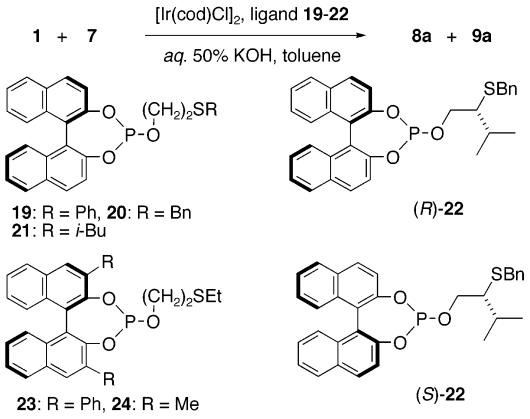
[a] The enantiomers of **8a** and **9a** were obatined as a major product. [b] Not determined.

Whereas addition of the known chiral phosphites **13**[3a] and **14**[11f] in place of $(PhO)_3P$ gave the same product **8a** as a major product with moderate enantioselectivity, that of new ligands **15** and **16** afforded **8a** in 95% and 93% ee yield at the expense of the chemical yield, respectively (entries 1−4). These results suggest that phosphite ligands comprised of a BINOL and a primary alcohol are more effective to enhance the enantioselectivity of the product. As hydrolysis of **4** to cinnamyl alcohol occurred

(8) Trost, B. M.; Dogra, K. *J. Am. Chem. Soc.* **2002**, *124*, 7256.
(9) Kanayama, T.; Yoshida, K.; Miyabe, H.; Takemoto, Y. *Angew. Chem., Int. Ed.* **2003**, *42*, 2054−2056.

(10) (a) O'Donnell, M. J. *Aldrichim. Acta* **2001**, *34*, 3. (b) Corey, E. J.; Xu, E.; Noe, M. C. *J. Am. Chem. Soc.* **1997**, *119*, 12414. (c) Lygo, B.; Crosby, J.; Peterson, J. A. *Tetrahedron Lett.* **1999**, *40*, 8671−8674. (d) Okino, T.; Takemoto, Y. *Org. Lett.* **2001**, *3*, 1515.
(11) (a) Ansell, J.; Wills, M. *Chem. Soc. Rev.* **2002**, *31*, 259. (b) Reetz, M. T.; Mehler, G. *Angew. Chem., Int. Ed.* **2000**, *39*, 3889. (c) Deerenberg, S.; Schrekker, H. S.; van Strijdonck, G. P. F.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Fraanje, J.; Goubitz, K. *J. Org. Chem.* **2000**, *65*, 4810. (d) Arena, C. G.; Drommi, D.; Faraone, F. *Tetrahedron: Asymmetry* **2000**, *11*, 2765. (e) Selvakumar, K.; Valentini, M.; Pregosin, P. S.; Albinati, A. *Organometallics* **1999**, *18*, 4591. (f) Ovchinnikov, V. V.; Cherkasova, O. A.; Verizhnikov, L. V. *Zh. Obshch. Khim.* **1982**, *52*, 707.

TABLE 3. Ir-Catalyzed Allylic Alkylation of 7 with 1 in the Presence of Chiral Ligands 19−24



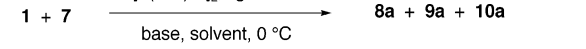
entry	ligand	yield, % 8a + 9a	ratio 8a:9a	ee, % 8a	ee, % 9a
1	(*R*)-**19**	17	71:29	82	52
2	(*R*)-**20**	62	71:29	97	42
3	(*R*)-**21**	67	75:25	96	*a*
4	(*R*)-**22**	37	81:19	95	*a*
5	(*S*)-**22**	52	79:21	68[b]	25[b]

[a] Not determined. [b] The enantiomers of **8a** and **9a** were obatined as a major product.

predominantly under these conditions, phosphate **7** was employed as an allylic substrate, which should be resistant to the hydrolysis. After several experiments, it was revealed that the best result (82% yield, **8a**:**9a** = 82:18, 97% ee) was obtained when the reaction was performed at 0 °C with **7** in the presence of chiral ligand **16** (entry 5). On the other hand, carbon-analogue **15** did not promote the reaction efficiently (entry 6). In addition, the choice of the chiral phosphite bearing the sulfur atom in the proper position on the alkyl group was essential to improve both the chemical yield and stereoselectivity of **8a** (entries 7 and 8). The acceleration of the reaction rate with **16** is attributed to the formation of six-membered chelation with **16**, which enhances nucleophilicity of the Ir catalyst. To clarify the reason for the excellent performance of phosphite **16**, we synthesized various phosphites and reexamined their potential (Table 3). Although replacement of the EtS group in **16** by a PhS group retarded the reaction, that by other alkyl groups such as BnS and *i*-BuS gave similar results in terms of stereoselectivity (entries 1−3). From the results of the allylic substitution with (*R*)-**22** and (*S*)-**22** as a chiral ligand, the chirality of BINOL affected the enantioselectivity more strongly than that of sulfide (entries 4 and 5). Unfortunately, phosphites **23**−**24**, introducing the substituents (Ph, Me) on the 3- and 3′-position of BINOL, did not promote the reaction and no desired products were afforded due to the severe steric hindrance.

Diastereoselective Synthesis of Both Stereoisomers 8 and 9 by Switching a Base. Having established higher levels of enantioselectivity of **8a**, our attention was focused on the diastereoselectivity (**8a**/**9a**). Since the diastereoselectivity of **8a**/**9a** was marginally affected by chiral ligands such as PTC and phosphites, we explored the effect of the countercations of the resulting enolate by the reaction of **1** with various bases, and the results are shown in Table 4. Noteworthy is that the counter-

TABLE 4. Ir-Catalyzed Allylic Substitution of 1 and 7 with Various Reaction Conditions



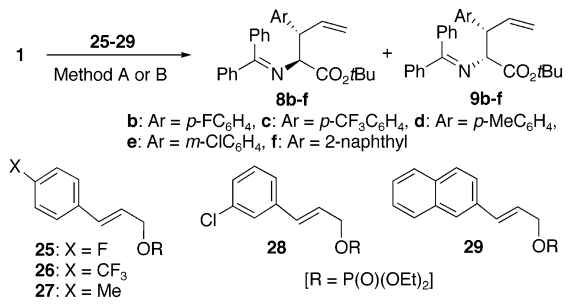
entry	reaction conditions	yield, % 8a:9a	yield, % 10a	ratio 8a:9a	ee, % 8a	ee, % 9a
1	**11**, 50%KOH, Tol.	30	0	83:17	95	87
2	PTC,[a] 50%KOH, Tol.	41	0	51:49	95	60
3	solid KOH, Tol.	71	0	70:30	97	*b*
4	$KN(SiMe_3)_2$, THF	28	0	79:21	48	72
5	$CsOH·H_2O$, Tol.	43	0	70:30	95	59
6	NaH, THF	29	0	62:38	91	73
7	LiBr, DBU, THF	20	23	30:70	44	63
8	LDA, THF	56	3	11:89	*b*	96
9	$LiN(SiMe_3)_2$, THF	82	<1	12:88	56	92

[a] PTC: $[CH_3(CH_2)_{15}N(CH_3)_3]Br$. [b] Not determined.

cations had a more significant influence on the diastereoselectivity (**8a**/**9a**) than on the enantioselectivity of **8a**. At first, we expected that the diastereoselectivity should be improved by the dual asymmetric induction, if chiral PTC **11** can form a chiral complex with the resulting enolate. Then, we carried out the substitution of **1** and **7** in the presence of either chiral PTC **11** or achiral PTC $[CH_3(CH_2)_{15}NMe_3]Br$ using 50% KOH as a base (entries 1 and 2). However, the diastereoselectivity of **8a** was almost the same or decreased compared with the result without PTC's, while high ee values were still maintained. Other bases such as solid KOH, $KN(SiMe_3)_2$, $CsOH·H_2O$, and NaH had a marginal effect on the stereoselectivity except entry 4, producing the same isomer **8a** as a major product (entries 3−6). On the other hand, use of bases such as LiBr/DBU, LDA, and LHMDS, which would generate the lithium enolate, affected the diastereoselectivity, producing the other isomer **9a** as a major product (entries 7−9). In terms of chemical yield and stereoselectivity, 50% KOH in toluene [method A] and LHMDS in THF [method B] are the best conditions for diastereoselectively preparing **8a** and **9a**, respectively. In this manner, these two methods allow us to synthesize both diastereomers **8a** and **9a** with high enantioselectivity.

Adopting the two protocols (methods A and B) as our standard, various allylic substrates **25**−**29** were examined (Table 5). Although the requisite phosphates **25**−**29** were synthesized from the corresponding allylic alcohols, phosphate **27** was used without purification for the allylic substitution due to its lability to column chromatography. In general, the Ir-catalyzed allylic substitution was not affected by the para and meta substituent of the aromatic ring of **25**−**28**. Furthermore, phosphate **29**, bearing a naphthyl group, could be employed as an allylic substrate, giving the desired products **8f** and **9f** in comparable yields. Thus, with method A, the corresponding branch products **8b**−**f** were obtained diastereoselectively (**8**/**9** = 71/29 to 79/21) with excellent enantioselectivity (>90% ee). Similarly, with method B, other branch products **9b**−**f** could be synthesized stereoselectively (**8**/**9** = 13/87 to 10/90, >88% ee). As described above, these two protocols were applicable to several allylic substrates and were demonstrated to be a versatile tool for asymmetric synthesis of both diastereomers **8a**−**f** and **9a**−**f**.

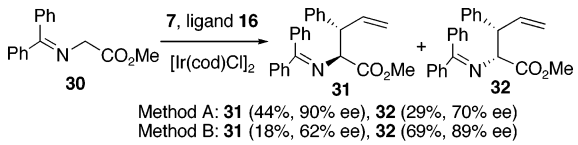
TABLE 5. Ir-Catalyzed Allylic Substitution of 1 with Various Substrates 25−29



entry	substrate	method[a]	yield, % 8 + 9	ratio 8:9	ee, % 8	ee, % 9
1	**25**	A	77	78:22	97	63
2	**26**	A	78	71:29	98	61
3	**27**[b]	A	86	79:21	90	70
4	**28**	A	79	76:24	97	74
5	**29**	A	97	77:23	94	69
6	**25**	B	81	10:90	62	88
7	**26**	B	78	10:90	93	94
8	**27**[b]	B	70	13:87	46	90
9	**28**	B	81	10:90	73	94
10	**29**	B	84	11:89	67	96

[a] Method A: In toluene at 0 °C. The ratio of **1**:**25**−**29**:50% KOH:[Ir(cod)Cl]$_2$:(*R*)-**16** was 100:100:300:10:20. Method B: In THF at 0 °C. The ratio of **1**:**25**−**29**:LiN(SiMe$_3$)$_2$:[Ir(cod)Cl]$_2$:(*R*)-**16** was 150:100:150:10:20. [b] The crude phosphate **27** was used without purification.

SCHEME 2. Ir-Catalyzed Allylic Alkylation of Methyl Ester 30 with 7



We next applied these methods to the methyl ester **30** to identify the importance of the *tert*-butyl group of **1** for stereoselectivity (Scheme 2). Treatment of **30** by method A gave the same diastereomer **31** as a major product in good enantioselectivity (90% ee), but the diastereoselectivity decreased significantly (73% combined yield, **31**:**32** = 60:40). Similarly, subjection of **30** to method B gave the other diastereomer **32** with good enantioselectivity (89% ee) but with moderate diastereoselectivity (87% combined yield, **31**:**32** = 21:79). These results suggest that (1) the *tert*-butyl group of **1** would be essential for good diastereoselectivity but not for enantioselectivity and (2) stereodifferentiation of the enantiotopic faces of the allyl−metal complex coordinated by chiral ligand **16** is highly independent of the nucleophiles employed.

Application of 8 and 9 to Asymmetric Synthesis of the Conformationally Constrained Amino Acids and Determination of their Absolute and Relative Configurations. As described in Scheme 3, two obtained diastereomers **8a** and **9a** were transformed into pipecolic acid derivatives **34** and **36** in 4 and 6 steps, respectively, by using the intramolecular olefin metathesis reaction as a key step. Furthermore, the hydrogenation of **36** gave rise to the product **37**,[12a] which is known as a useful conformationally constrained amino acid.[12] By comparison of their spectra (**37** and antipode of **37**), the relative

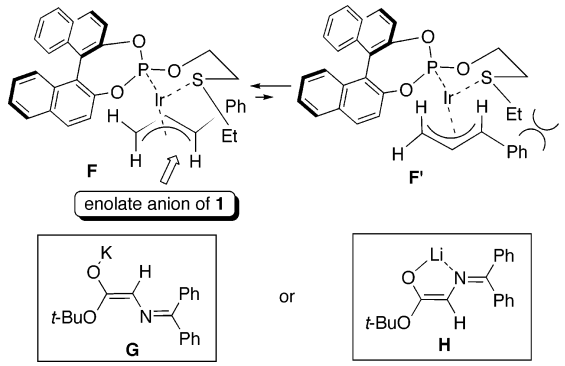
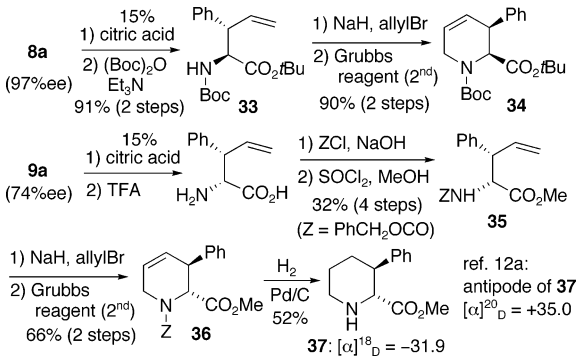


FIGURE 1. The plausible allyl−Ir(III) complex F and F′.

SCHEME 3. Determination of Configuration of 8a and 9a and Their Synthetic Application to Chiral Heterocyclic Compounds



and absolute configurations of products **8a** and **9a** were revealed to be correct as depicted in Scheme 3.[7a] The configurations of **8b**−**f** and **9b**−**f** were then assumed by analogy. From the results described above, the stereochemical course of the reaction can be explained as follows (Figure 1). Initially, two π-allyl complexes **F** and **F′** (σ-allyl complexes could not be denied) would be formed predominantly by attack of the iridium(I)−ligand **16** complex on the allylic substrate **7**.[13] However, the complex **F′** should be disfavored due to the steric interaction between the ethylthio group of the ligand and the phenyl group of **7**. Therefore, the nucleophilic attack of the enolate of **1** at the allylic carbon trans to the phosphorus atom would give the chiral products **8** and **9** with high enantioselectivity. Although we cannot explain the different behavior of the bases at this stage, it might be attributed to the geometry of the enolate of **1**. Namely, it was assumed that the use of KOH as a base would give the *E*-enolate **G** predominantly, but, in contrast, the *Z*-enolate **H** would be formed with use of LiN(SiMe$_3$)$_2$ as a base.[14]

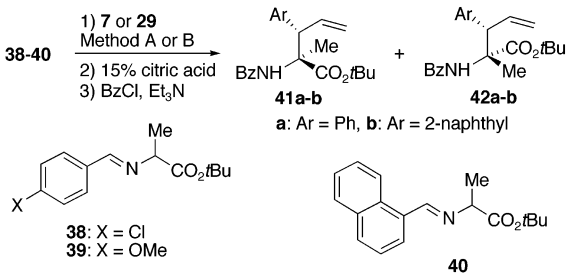
Asymmetric Allylic Alkylation of Allylic Phosphates 7 and 29 with Various Imino Alaninates 38−40 in the Presence of Chiral Phosphite 16. Since we succeeded in the enantioselective synthesis of the branch products **8a**−**f** and **9a**−**f**, we finally investigated the asymmetric synthesis of quaternary amino acids using

(12) (a) Liu, D.-G.; Gao, Y.; Wang, X.; Kelley, J. A.; Burke, T. R., Jr. *J. Org. Chem*. **2002**, *67*, 1448. (b) Liu, D.-G.; Wang, X.-Z.; Gao, Y.; Li, B.; Yang, D.; Burke, T. R., Jr. *Tetrahedron* **2002**, *58*, 10423.

(13) O'Donnell, M. J.; Wu, S. *Tetrahedron*: *Asymmetry* **1992**, *3*, 591.

(14) Lipkowitz, K. B.; Cavanaugh, M. W.; Baker, B.; O'Donnell, M. J. *J. Org. Chem*. **1991**, *56*, 5181.

TABLE 6. Ir-Catalyzed Allylic Substitution of Variuous Imino Alaninate 38−40 with 7 and 29



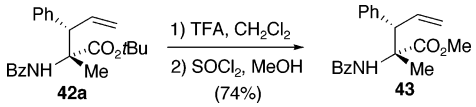
entry	substrate	method[a]	yield, % 41 + 42	ratio 41:42	ee, % 41	ee, % 42
1	**38** + **7**	A	18	50:50	92	30
2	**38** + **29**	A	22	50:50	91	35
3	**40** + **29**	A + **11**[b]	17	65:35	91	46
4	**40** + **29**	A + PTC[c]	49	55:45	93	66
5	**38** + **29**	B	59	17:83	84	82
6	**39** + **29**	B	47	19:81	82	75
7	**40** + **29**	B	64	25:75	87	83

[a] Method A: In toluene at 0 °C. The ratio of **38**−**40**:**7**−**29**:50% KOH:[Ir(cod)Cl]$_2$:(*R*)-**16** was 100:100:300:10:20, Method B: In THF at 0 °C. The ratio of **38**−**40**:**29**:LiN(SiMe$_3$)$_2$:[Ir(cod)Cl]$_2$:(*R*)-**16** was 150:100:150:10:20. [b] **11** (10 mol %). [c] PTC: [CH$_3$(CH$_2$)$_{15}$N(CH$_3$)$_3$]Br (10 mol %).

the Ir-catalyzed allylic alkylation of various alaninates **38**−**40**[15] (Table 6). The adoption of method A to phosphate **7** and alaninate **38** gave **41a** and **42a** as a 1/1 mixture in low yield (entry 1). The reaction of **29** and **38** also proceeded slowly and gave a similar result (entry 2).

It is noteworthy that the enantioselectivity of the products **41a**,**b** was high, but that of **42a**,**b** was low. Although chiral and achiral PTC's were added to the reaction mixture to improve the chemical yield (entries 3 and 4), the chemical yield and diastereoselectivity of **41b** are only somewhat increased. In contrast to method A, the adoption of method B to phosphate **29** and alaninate **38** afforded **42b** as a major product (**41b**:**42b** = 17:83) in 59% yield (entry 5). In this case, both diastereo- and enantioselectivity were acceptable. A similar reaction of **29** with other alaninates **39** and **40** gave no efficient enhancement in terms of stereoselectivity (entries 6−8). In contrast to method A (entries 1 and 2), it should be noted that the enantioselectivities of both products **41b** and **42b** were good to high (75−87% ee). The configuration of **42a** was determined by chemical transformation of **42a** into the known compound **43**[8] as described in Scheme 4. Furthermore, the configuration of **41a**,**b** and **42b** was assumed by analogy to the allylic alkylation of **1** and **7**, giving **8a** and **9a**. The above results suggest that chiral quaternary amino acids could be synthesized by using the Ir-catalyzed allylic alkylation of alaninate **38** and allylic phosphate with acceptable yield and stereoselectivity.

SCHEME 4. Determination of Configuration of 42a



Conclusion

We have developed the first enantioselective Ir-catalyzed allylic substitutions of diphenylimino glycinate **1** by using chiral bidentate ligand **16** (up to 98% ee), and also succeeded in the diastereoselective asymmetric synthesis of both diastereomers **8** and **9** by simply switching the base employed. In addition, these methods could be applied to the asymmetric synthesis of chiral quaternary amino acids starting from imino alaninate **38** and phosphates **7** and **29**.

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Supporting Information Available: Experimental details and characterization of **8a**−**f**, **9a**−**f**, **16**, **37**, **41a**,**b**, and **42a**,**b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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