Enantioselective Allylation

Enantio- and Diastereoselective Ir-Catalyzed Allylic Substitutions for Asymmetric Synthesis of Amino Acid Derivatives**

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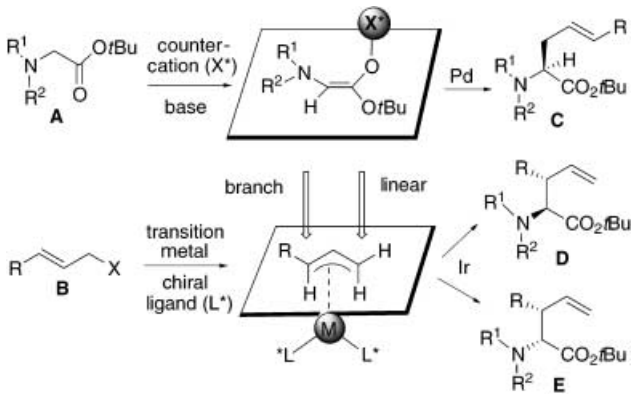
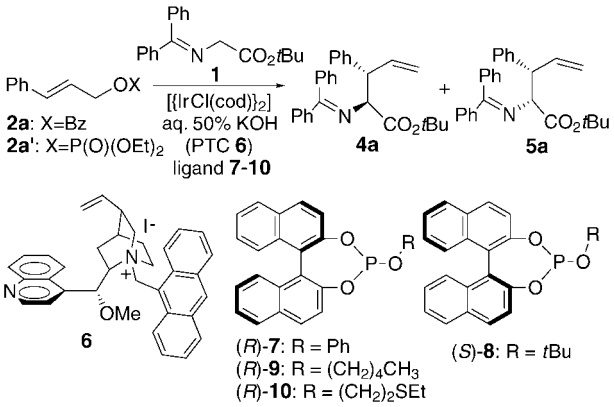
Transition-metal-catalyzed asymmetric allylic substitution is a useful reaction in organic synthesis.[1] In the reaction with symmetric C nucleophiles such as dialkyl malonates, good yields and high enantioselectivities can now be obtained with an appropriate combination of a transition metal and a chiral ligand.[2–5] In contrast to the symmetric C nucleophiles, allylic substitution of 3-substituted allylic alcohols **B** with unsymmetrical C nucleophiles **A** is a tough and challenging task, because regio-, diastereo-, and enantioselectivities must be controlled (Scheme 1). In the last few years, research has



Scheme 1. Transition-metal-mediated asymmetric allylic substitution.

focused on finding catalysts and chiral ligands that 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 Pd-mediated asymmetric allylic alkylation of diphenylimino glycinate **1** with several allylic acetates in the presence of the chiral phase-transfer catalyst (PTC) **6** to give the chiral products **C** with high enantioselectivity (up to 97% *ee*).[6a] In contrast to the palladium catalyst, some transition metals, such as Ir,[3] Mo,[4] and W,[5] promote allylic alkylation at the more highly substituted terminus of the allylic substrate. Trost et al. recently reported that 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 major products from the same starting materials and the same chiral ligand. We report here the first enantioselective allylic substitutions of **1** catalyzed by an iridium complex of chiral phosphite **10**, and the diastereoselective synthesis of the products **4** and **5** by simply switching the base employed (Scheme 2).



Scheme 2. Ir-catalyzed asymmetric allylic substitution of **1** with **2a,a′**.

Our previous work prompted us to examine PTC **6** as a chiral catalyst in Ir-catalyzed allylic substitutions (Table 1). We first carried out the Ir-catalyzed reaction of **1** and benzoate **2a** in the presence of the chiral PTC **6**, 50% KOH, [{IrCl(cod)}$_2$] (cod = cyclooctadiene), and $(PhO)_3P$ (entry 1). The reaction was complete after 8 h at room temperature and gave the branched products **4a** and **5a** as major products (40% yield, **4a**:**5a** = 75:25) but with low enantioselectivity (46% *ee*). We next examined the effect of chiral ligands **7**–**10**[9] in place of chiral PTC **6** on the enantioselectivity. The reaction of **1** with **2a** was carried out in the presence of 50% KOH (3 equiv), [{IrCl(cod)}$_2$] (10 mol%), and chiral phosphites (20–40 mol%). In all cases, no linear product could be detected. Indeed, the

Table 1: Ir-catalyzed asymmetric allylic substitution of **1** and **2a,a′** with chiral PTC **6** or various chiral ligands **7**–**10**.[a]

Entry	Substrate	Ligand (mol%)	Yield [%][b] (**4**:**5**)	*ee* of **4** [%][c]
1	**2a**	**6** (10), $(PhO)_3P$ (40)	40 (75:25)	46
2	**2a**	(*R*)-**7** (20)	29 (69:31)	32[d]
3	**2a**	(*S*)-**8** (40)	7 (86:14)	68[d]
4	**2a**	(*R*)-**9** (20)	6 (67:33)	95
5	**2a**	(*R*)-**10** (20)	11 (73:27)	93
6[e]	**2a′**	(*R*)-**9** (20)	0	–
7[e]	**2a′**	(*R*)-**10** (20)	82 (82:18)	97

[a] All reactions were carried out in toluene. The ratio of **1**:**2**:50% KOH:[{IrCl(cod)}$_2$] was 100:100:300:10 unless otherwise noted. [b] Yields of isolated products. [c] Determined by HPLC analysis with Daicel Chiral Pack OD-H column. [d] The enantiomer of **4** was obtained. [e] The reaction was carried out at 0°C.

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enantioselectivity was dramatically affected by the substituent R of the ligands. Whereas addition of the known chiral phosphites **7**[3a] and **8**[9f] in place of $(PhO)_3P$ gave the branched product **4a** as a major product with moderate enantioselectivity, the new ligands **9** and **10** gave **4a** in 95 and 93% *ee*, respectively, albeit at the expense of chemical yield (entries 2–5). However, hydrolysis of **2a** to cinnamyl alcohol predominantly occurred under these conditions. We next used phosphate **2a′** as an allylic substrate which should be resistant to hydrolysis. After several experiments, it was revealed that the best result (82% yield, **4a**:**5a** = 82:18, 97% *ee*) was obtained when the reaction was performed at 0°C with phosphate **2a′** (entries 6 and 7). Furthermore, use of the bidentate chiral ligand **10**, which promoted the reaction at 0°C, was essential to improve both the chemical yield and stereoselectivity of **4**.

Having established higher enantioselectivity, we explored the effect of the countercations of the enolate with **2a′** and **10**, and the results are shown in Table 2. It is noteworthy that the countercations had a more significant influence on the diastereoselectivity (**4a**/**5a**) than on the enantioselectivity for **4a**. In addition, for diastereoselective synthesis of **4a**, the reaction of **1** and **2a′** with 50% KOH in toluene (method A) was superior to reactions involving $KN(SiMe_3)_2$, CsOH, and NaH (entries 1–4), whereas these bases gave **4a** as a major product with more than 90% *ee*. On the other hand, use of lithium bases tends to produce the other diastereomer **5a** as a major product (entries 5–7). Among them, $LiN(SiMe_3)_2$ was the best base in terms of chemical yield and stereoselectivity (82% yield, **4a**:**5a** = 12:88, 92% *ee*; method B). These two methods allow us to synthesize both diastereomers **4a** and **5a** with high enantioselectivity.

Table 2: Ir-catalyzed allylic substitution of **1** and **2a′** under various reaction conditions.[a]

Entry	Reaction conditions	Yield [%][b] branched	linear	Ratio (**4**:**5**)	*ee* [%][c] **4**	**5**
1	$CsOH{\cdot}H_2O$, toluene	43	0	70:30	95	59
2	50% KOH, toluene	82	0	82:18	97	66
3	$KN(SiMe_3)_2$, THF	28	0	79:21	48	72
4	NaH, THF	29	0	62:38	91	73
5	LiBr, DBU[d], THF	20	23	30:70	44	63
6	LDA, THF	56	3	11:89	—[e]	96
7	$LiN(SiMe_3)_2$, THF	82	<1	12:88	56	92

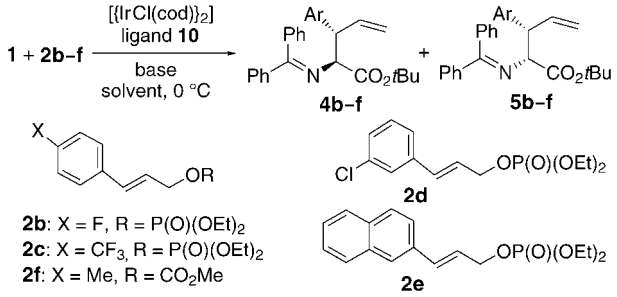
[a] All reactions were carried out at 0°C in the presence of $[\{IrCl(cod)\}_2]$ (10 mol%) and (*R*)-**10** (20 mol%). [b] Yields of isolated products. [c] Determined by HPLC analysis with Daicel Chiral Pack OD-H column. [d] DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene. [e] The *ee* was not determined.

Methods A and B were examined for various allylic substrates **2b–f** (Table 3, Scheme 3). Since the phosphate of *p*-methylcinnamyl alcohol could not be prepared, we employed methyl carbonate **2f** as substrate. In general, the Ir-catalyzed allylic substitution was not affected by the *para* and *meta* substituents of the aromatic ring of **2b–e**. Thus, method A gave the corresponding branched products **4b–e** diastereoselectively (**4**:**5** = 68:32–78:22) with excellent enantioselectivity

Table 3: Ir-catalyzed allylic substitution of **1** with various substrates **2b–f**.

Entry	Substrate **2**	Method[a]	Yield [%][b] branched	linear	Ratio (**4**:**5**)	*ee* [%][c] **4**	**5**
1	**2b**	A	77	0	78:22	97	63
2	**2c**	A	77	0	68:32	97	68
3	**2d**	A	79	0	76:24	97	74
4	**2e**	A	97	0	77:23	94	69
5[d]	**2f**	A	63	0	83:17	91	74
6	**2b**	B	82	0	13:87	59	85
7	**2c**	B	78	0	10:90	93	94
8	**2d**	B	81	<1	10:90	73	94
9	**2e**	B	84	<1	11:89	67	96
10	**2f**	B	88	1.1	34:66	51	70

[a] Method A: In toluene at 0°C unless otherwise noted. The ratio of **1**:**2**:50% KOH:$[\{IrCl(cod)\}_2]$:(*R*)-**10** was 100:100:300:10:20. Method B: In THF at 0°C. The ratio of **1**:**2**:$LiN(SiMe_3)_2$:$[\{IrCl(cod)\}_2]$:(*R*)-**10** was 150:100:150:10:20. [b] Yields of isolated products. [c] Determined by HPLC analysis with a Daicel Chiral Pack OD-H column. [d] The reaction was carried out at room temperature.



Scheme 3. Ir-catalyzed reaction of **1** with various allylic substrates **2b–f**.

(>94% *ee*). Similarly, by using method B, other branched products **5b–e** could be synthesized stereoselectively (**4**:**5** = 13:87–10:90, 85–96% *ee*). In contrast, due to lower reactivity of the methyl carbonate, the Ir-catalyzed allylic substitution of **2f** required prolonged reaction time and elevated temperature. As a result, the yield and stereoselectivity of the branched products **4f** and **5f** become somewhat lower than those of **4a–e** and **5a–e**. In any event, these two protocols are applicable to several allylic substrates and are demonstrated to be a versatile tool for asymmetric synthesis of both diastereomers **4a–f** and **5a–f**.

The relative and absolute configurations of products **4a** and **5a** were determined by comparison with the known compounds.[7a] The configurations of **4b–f** and **5b–f** were then assumed by analogy. From the results described above, the stereochemical course of the reaction can be explained as follows. Initially, the π- or σ-allyl complex **F** is formed by attack of the iridium(I) complex of the ligand on the allylic substrate **2**. The nucleophilic attack of the enolate of **1** at the allylic carbon atom *trans* to the phosphorus atom would give the chiral products **4** and **5** with high enantioselectivity. Although we cannot explain the different behavior of the bases at this stage, it might be attributable to the geometry of the enolate of **1**. It was assumed that the use of KOH as a base would give predominantly the *E* enolate **G**, whereas the *Z*

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enolate **H** would be formed with $LiN(SiMe_3)_2$ as base (Figure 1).[10]

In conclusion, we have developed the first enantioselective Ir-catalyzed allylic substitutions of diphenylimino glycinate **1** by using chiral bidentate ligand **10** (up to 97% *ee*), and also succeeded in the diastereoselective asymmetric synthesis of both diastereomers **4** and **5** by simply switching the base employed. The influence of the base on diastereoselectivity and further applications of this asymmetric allylic substitution are currently under investigation.

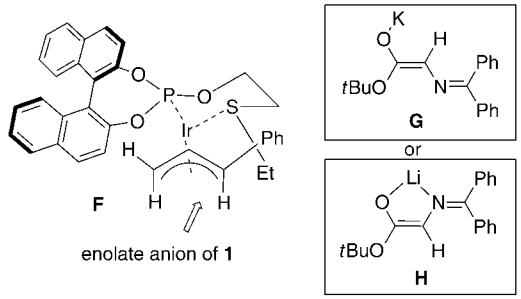

Figure 1. The plausible allyl Ir^{III} complex **F**.

Experimental Section

General procedure for asymmetric allylic substitution: Method A: A 50% KOH solution (38 μL, 0.51 mmol) was added to a stirred solution of *tert*-butyl glycinate benzophenone imine (**1**; 50 mg, 0.17 mmol), diethyl phosphate **2a′** (46 mg, 0.17 mmol), $[\{IrCl(cod)\}_2]$ (11 mg, 0.017 mmol), and (*R*)-**10** (14 mg, 0.034 mmol) in dry toluene (1.4 mL) at 0°C under an argon atmosphere, and the resulting mixture was stirred vigorously at 0°C for 20 h. The suspension was diluted with diethyl ether (15 mL), and the organic phase was washed with a saturated aqueous soltion of $NaHCO_3$ (2 mL) and brine (2 mL) and then dried over Na_2SO_4. After evaporation of the solvent, the crude product was purified by column chromatography (basic silica gel, AcOEt/hexane 1/500) to give the desired products **4a** (46 mg, 67%) and **5a** (11 mg, 15%) as a colorless oil.

Method B: A solution of **1** (75 mg, 0.25 mmol) in dry THF (1 mL) was added to a stirred solution of $LiN(SiMe_3)_2$ (0.25 mmol) in THF (0.16 mL) at −78°C. After being stirred for 30 min, the mixture was slowly added to a stirred solution of **2a′** (46 mg, 0.17 mmol), $[\{IrCl(cod)\}_2]$ (11 mg, 0.017 mmol), and (*R*)-**10** (14 mg, 0.034 mmol) in dry THF (0.4 mL) at 0°C under an argon atmosphere. After completion of the addition (30 min), the resulting mixture was quenched with water (2 mL) and diethyl ether (40 mL). The organic phase was washed with brine (2 mL) and then dried over Na_2SO_4. After evaporation of the solvent, the crude product was purified by column chromatography (basic silica gel, AcOEt/hexane 1/500) to give **4a** (7.0 mg, 10%) and **5a** (50 mg, 72%).

The enantioselectivity was determined by chiral HPLC (Daicel Chiralpak OD-H, *i*PrOH/hexanes 0.6/99.4, flow rate 0.3 mL min^{-1}, $\lambda = 254$ nm, retention times: **4a** (major) 26.5 min, (minor) 23.8 min, **5a** (major) 27.4 min, (minor) 25.7 min).

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