Enantioselective hydrogenation of α-aminomethylacrylates containing a free N—H group for the synthesis of β-amino acid derivatives

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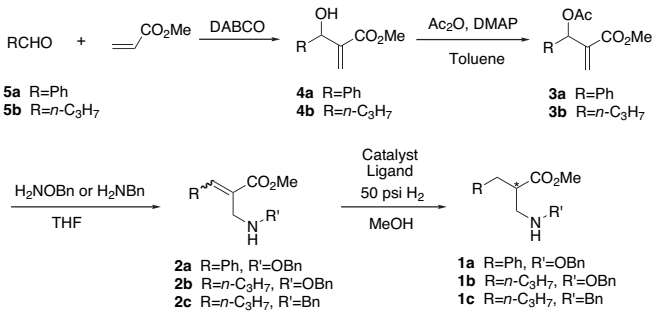
We describe highly enantioselective synthesis of β-amino acid derivatives (1a-c) using asymmetric hydrogenation of α-aminomethylacrylates (2a-c), which contain a free basic N—H group, as the key step. The α-aminomethylacrylates (2a-c) were prepared using the Baylis–Hillman reaction of an appropriate aldehyde with methyl acrylate followed by acetylation of the resulting allylic alcohols (4a-b) and S_N2'-type amination of the allylic acetates (3a-b).

asymmetric catalysis | Baylis–Hillman reaction

In recent years, β-amino acids have received increasing attention as constituents of molecules with interesting biological and pharmacological activities (1–5) such as hypoglycemic and ketogenic activities. They are key moieties of a number of bioactive molecules, such as in taxol and in peptidic natural products with various enzyme inhibiting activities. Nonpeptidic β-amino acids are found in well known β-lactams. Considering their importance, asymmetric synthesis of enantiomerically pure β-amino acids has become an important challenge for organic chemists. The synthesis of enantiopure β-amino acids has been extensively studied (6–9). However, the known methods are mostly for the synthesis of β-substituted β-amino acids, and their preparation still suffers from a long synthetic sequence, low product yields, and laborious execution (10–14). For example, a recently reported synthesis of **1a** involved nine steps from 3-phenylpropanoic acid (15–18). Peptide deformylase (PDF, EC 3.5.1.31), a metallopeptidase found in prokaryotic organisms, is essentially required for bacterial growth (19–21). Certain *N*-formyl hydroxylamine compounds were recently revealed to have good antibacterial function by means of their PDF-inhibiting capabilities. Chiral compounds **1**, α-substituted β-amino acid derivatives, are key intermediates in the synthesis of this kind of compounds (15–18, 22). Their prochiral dehydroprecursors **2** could be prepared in high yields via a synthetic process shown in Scheme 1. Asymmetric hydrogenation of these substrates **2** is the simplest and most direct route to synthesize **1** because of its inherent efficiency and atom economy. In contrast to the great progress in the synthesis of β-substituted β-amino acids and derivatives via enantioselective hydrogenations (23–38), reports on the synthesis of α-substituted β-amino acids with this protocol are very limited. To the best of our knowledge, only one exceptional example has been given, very recently by Zheng and coworkers (38), using Rh-monophosphorus catalyst system for the hydrogenation of β-phthalimide acrylates. However, the activity of the catalyst was not high, and only *E*-isomers of substituted β-phthalimide acrylates were investigated. In fact, compounds **2** were a mixture of *E*- and *Z*-isomers formed in the synthesis, and they were not always easy to separate into single isomers. Generally, it is also difficult to achieve high activity and enantioselectivity for the system containing both isomers (23–33). In light of the successful development and preparation of α-aminomethyl acrylates **2**, herein we report a highly enantioselective synthesis of β-amino acid derivatives by Rh-catalyzed asymmetric hydrogenation of α-aminomethylacrylates



Scheme 1. Synthesis of α-aminomethylacrylates and the asymmetric hydrogenation process.

(**2a-c**), which contain a free basic N—H group, as the key step. To the best of our knowledge, such an asymmetric hydrogenation of α-aminomethyl acrylates to *N*-unprotected amino acid derivatives has not been reported in the literature.

Results and Discussion

Synthesis of α-Aminomethylacrylates 2a-c. The success of our asymmetric hydrogenation approach depended on the development of an efficient synthesis of α-aminomethylacrylates **2a-c** (Scheme 1). We rationalized that **2a-c** will be easily accessible by a Baylis–Hillman reaction (39–50) of methyl acrylate with an appropriate aldehyde, followed by acetylation (51, 52) of the resulting allylic alcohols **4a-b** and S_N2'-type amination of the resulting acetates **3a-b**. The acetates were obtained in >90% yield and were used in the next step without further purification. The final S_N2'-type displacement reaction of the acetates with *O*-benzylhydroxylamine or benzylamine was achieved with excess amounts of these amines in THF (53–55). The reaction required 2 days at room temperature with *O*-benzylhydroxylamine and only 2 h with benzylamine. A mixture of *E*- and *Z*-isomers (**2a-c**) was formed, which could be detected by HPLC and NMR analysis. The crude products were purified by flash chromatography to remove the excess amine. However, it was not necessary to separate the *E*- and *Z*-isomers for the asymmetric hydrogenation step (23–33).

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Table 1. Asymmetric hydrogenation of α-aminomethylacrylates

Entry*	Sub	Catalyst/ligand, mol%	S/C	Solvent	T, °C	P, psi	Time, h	Product	Isolated yield, %	ee, % (config.)
1	*E*-2a	[Ru((*S*)-BINAP)(C_6H_6)Cl]Cl	100	MeOH	RT	1000	20	1a	15†	45 (*R*)
2	*E*-2a	[Ru((*S*)-BINAP)(C_6H_6)Cl]Cl	100	EtOH	RT	1000	20	1a	0†	—
3	*E*-2a	[Ru((*S*)-BINAP)(C_6H_6)Cl]Cl	100	*i*PrOH	RT	1000	20	1a	0†	—
4	*E*-2a	[Ru((*S*)-BINAP)(C_6H_6)Cl]Cl	100	THF	RT	1000	20	1a	0†	—
5	*E*-2a	[Ru((*S*)-BINAP)(C_6H_6)Cl]Cl	100	DCM	RT	1000	20	1a	0†	—
6	*E*-2a	[Ru((*S*)-BINAP)(C_6H_6)Cl]Cl	100	Toluene	RT	1000	20	1a	0†	—
7	*E*-2a	[Ru((*S*)-BINAP)(C_6H_6)Cl]Cl	100	MeOH	50	1000	24	1a	39†	44 (*R*)
8	*E*-2a	[Ru((*RSS*)-Bu-PQPhos)(C_6H_6)Cl]Cl	100	MeOH	RT	1000	24	1a	4†	ND
9	*E*-2a	$Rh(COD)_2BF_4$-((*R*)-Monophos)	100	DCM	RT	1000	48	1a	7†	62 (*S*)
10	*E*-2a	(2*R*,5*R*)-[(COD)Rh(Me-Duphos)]$^+CF_3SO_3^-$ (15%)	7	MeOH	RT	50	48	1a	99	95 (*S*)
11	*E*-2a	$[Rh(NBD)_2]BF_4$ (2.0%) (1*R*,1′*R*,2*S*,2′*S*)-Tangphos (2.2%)	50	MeOH	RT	50	48	1a	97	91 (*R*)
12	*E*-2a	[Rh((*R*,*R*)-Me-Duphos)(COD)]BF_4	100	MeOH	RT	700	42	1a	89†	68 (*S*)
13	*E*-2a	[Rh((*R*,*R*)-Et-Duphos)(COD)]BF_4	100	MeOH	RT	1000	24	1a	>99†	92 (*S*)
14	*E*-2a	[Rh((*S*,*S*)-*i*Pr-Duphos)(COD)]BF_4	100	MeOH	RT	1000	97	1a	20†	72 (*R*)
15	*E*-2a	[Rh((*R*,*R*)-Et-Duphos)(COD)]BF_4	100	DCM	RT	1000	90	1a	58†	94 (*S*)
16	*E*-2a	[Rh((*R*,*R*)-Et-Duphos)(COD)]BF_4	100	*i*PrOH	RT	1000	24	1a	>99†	99 (*S*)
17	*E*-2a	[Rh((*S*,*S*)-Et-Duphos)(COD)]BF_4	100	*i*PrOH	RT	50	20 min	1a	>99†	99 (*R*)
18	*E*-2a	[Rh((*S*,*S*)-Et-Duphos)(COD)]BF_4	100	THF	RT	50	20 min	1a	>99†	99 (*R*)
19	*E*-2a	[Rh((*S*,*S*)-Et-Duphos)(COD)]BF_4	1000	iPrOH	RT	50	10	1a	>98	99 (*R*)
20	*E*-2a	[Rh((*S*,*S*)-Et-Duphos)(COD)]BF_4	1000	THF	RT	50	10	1a	>98	99 (*R*)
21	*E*-2a	[Rh((*S*,*S*)-Et-Duphos)(COD)]BF_4	10000	*i*PrOH	RT	50	78	1a	>98	99 (*R*)
22	*E*-2a	[Rh((*S*,*S*)-Et-Duphos)(COD)]BF_4	10000	THF	RT	50	44	1a	24†	99 (*R*)
23	*Z*-2a	[Rh((*S*,*S*)-Et-Duphos)(COD)]BF_4	100	*i*PrOH	RT	50	20 min	1a	>99†	92 (*R*)
24	*Z*-2a	[Rh((*S*,*S*)-Et-Duphos)(COD)]BF_4	1000	*i*PrOH	RT	50	10	1a	>98	92 (*R*)
25	*E*/*Z*-2a‡	[Rh((*S*,*S*)-Et-Duphos)(COD)]BF_4	10000	*i*PrOH	RT	50	78	1a	>98	98 (*R*)
26	2b	[Rh((*S*,*S*)-Et-Duphos)(COD)]BF_4	100	*i*PrOH	RT	50	20 min	1b	>99†	>99.5 (*R*)
27	2b	[Rh((*S*,*S*)-Et-Duphos)(COD)]BF_4	100	THF	RT	50	20 min	1b	>99†	>99.5 (*R*)
28	2b	[Rh((*S*,*S*)-Et-Duphos)(COD)]BF_4	1000	*i*PrOH	RT	50	10	1b	30†	>99.5 (*R*)
29	2b	[Rh((*S*,*S*)-Et-Duphos)(COD)]BF_4	1000	THF	RT	50	10	1b	23†	>99.5 (*R*)
30	2b	[Rh((*S*,*S*)-Et-Duphos)(COD)]BF_4	500	*i*PrOH	RT	500	17	1b	85†	>99.5 (*R*)
31	2b	[Rh((*S*,*S*)-Et-Duphos)(COD)]BF_4	500	*i*PrOH	RT	50	17	1b	86†	>99.5 (*R*)
32	2b	[Rh((*S*,*S*)-Et-Duphos)(COD)]BF_4	500	*i*PrOH	RT	50	24	1b	>98	>99.5 (*R*)
33	2b	[Rh((*S*,*S*)-Et-Duphos)(COD)]BF_4	500	THF	RT	50	24	1b	>98	>99.5 (*R*)
34	2b	[Rh((*S*,*S*)-Et-Duphos)(COD)]BF_4	1000	*i*PrOH	50	50	7	1b	>98	>99.5 (*R*)
35	2b	[Rh((*S*,*S*)-Et-Duphos)(COD)]BF_4	1000	*i*PrOH	70	50	5	1b	>98	>99.5 (*R*)
36	2b	[Rh((*S*,*S*)-Et-Duphos)(COD)]BF_4	1000	*i*PrOH	90	50	5	1b	>98	>99.5 (*R*)

Asymmetric Hydrogenation of α-Aminomethylacrylates. With α-aminomethylacrylates **2a-c** in hand, we next focused our attention on the key enantioselective hydrogenation step. Ru and Rh were selected as the catalysts and phosphanes such as 2,2′-bis(diphenylphosphino-1,1′-binaphthyl (BINAP), (*R*)-[6,6′-(2*S*,3*S*-butadioxy)]-(2,2′)-bis(diphenylphosphino)-(1,1′)-biphenyl (Bu-PQ-Phos), 2,2′-*O*,*O*′-(1,1′-binaphthyl)-*O*,*O*′-dioxo-*N*,*N*-dimethylphospholidine (Monophos), 1,2-bis(phospholano)benzene (Duphos), 1,1′-di-*tert*-butyl-[2,2′]-diphospholanyl (Tangphos), etc., were screened as ligands (56–65). The detailed data are listed in Table 1.

Because the reported synthesis of **1a** was lengthy (15–18) and pure ***E*-2a** as a major isomer (***E*-2a**/***Z*-2a** = 80/20) could be acquired by column chromatography and recrystalization, we first studied the asymmetric hydrogenation of (*E*)-**2a** with several chiral catalyst systems. The results of using Ru-BINAP (56, 57), Bu-PQ-Phos (35, 36), and Rh-Monophos (24) complexes as catalysts were rather disappointing, showing poor reactivities and enantioselectivities (Table 1, entries 1–9). Good improvement occurred by employing Rh-(Me-Duphos) (58) or Rh-Tangphos (59) complex in this reaction. Product **1a** was isolated in almost quantitative yield with excellent enantioselectivity. The enantiopurity of **1a** was determined by chiral HPLC using a Daicel Chiralcel OD-H column and hexane/2-propanol (95/5) as the mobile phase. For example, complete hydrogenation of ***E*-2a** was achieved in 48 h with 15 mol% of (2*R*,5*R*)-[(COD)Rh(Me-Duphos)]$^+CF_3SO_3^-$ (Table 1, entry 10), giving the corresponding product **1a** with 95% ee. A similar result was obtained with 5.0 mol% $[Rh(NBD)_2]BF_4$ and 5.5 mol% (1*R*,1′*R*,2*S*,2′*S*)-Tangphos (Table 1, entry 11), but the enantioselectivity was somewhat lower (91% ee). As observed for ***E*-2a**, the (2*R*,5*R*)-Duphos afforded mostly the (*S*)-enantiomer, whereas the (1*R*,1′*R*,2*S*,2′*S*)-Tangphos gave mostly the (*R*)-enantiomer. Product **1a** from each reaction was converted to the hydrochloride salt with HCl gas in isopropyl acetate, and the absolute configuration was determined based on reported optical rotation (15–18). Anions of the Rh complexes also showed significant influence on the enantioselectivity of **1a**. Ee values decreased from 91% to 68% when $CF_3SO_3^-$ was replaced by BF_4^- (Table 1, entry 10 vs. entry 12). When we switched to the use of Rh-(Et-Duphos) for this reaction, an interesting phenomenon was noted: Et-Duphos was significantly better than Me-Duphos and *i*Pr-Duphos (Table 1, entries 12–14, 92% vs. 68% and 72% ee, respectively). This finding implied that the substituent effect of the ligands was significant, which influenced not only the reactivity but also the enantioselectivity. The enantioselectivites were further improved to 99% using *i*PrOH and THF as solvents instead of MeOH and dichloromethane. Latter experiments demonstrated that the catalyst was more active in *i*PrOH than in THF (Table 1, entries 21, 22, 28, and 29). The

Table 1. (continued)

Entry*	Sub	Catalyst/ligand, mol%	S/C	Solvent	T, °C	P, psi	Time, h	Product	Isolated yield, %	ee, % (config.)
37	2b	(*S*,*S*,*S*,*S*)-[(COD)Rh(Et-FerroTANE)]$^+BF_4^-$ (13.6%)	7	MeOH	RT	50	72	1b	—	no rxn
38	2b	$[Rh(NBD)_2]BF_4$ (1.0%) (*R*)-(*S*)-Josiphos (1.1%)	100	MeOH	RT	50	24	1b	97	10 (*S*)
39	2b	(2*R*,5*R*)-[(COD)Rh(Me-Duphos)]$^+CF_3SO_3^-$ (15%) (almost no rxn with 1%)	7	MeOH	RT	50	24	1b	95	>96 (*S*)
40	2b	(2*S*,5*S*)-[(COD)Rh(Me-Duphos)]$^+CF_3SO_3^-$ (15%)	7	MeOH	RT	50	24	1b	98	98 (*R*)
41	2b	$[Rh(NBD)_2]BF_4$ (1.0%) (1*S*,1′*S*,2*R*,2′*R*)-Tangphos (1.1%)	100	MeOH	RT	50	24	1b	94	>96 (*S*)
42	2b	$[Rh(NBD)_2]BF_4$ (1.0%) (1*R*,1′*R*,2*S*,2′*S*)-Tangphos (1.1%)	100	MeOH	RT	50	24	1b	96	97 (*R*)
43	2c	(2*R*,5*R*)-[(COD)Rh(Me-Duphos)]$^+CF_3SO_3^-$ (15%)	7	MeOH	RT	50	96	1c	98	85 (*S*)
44	2c	$[Rh(NBD)_2]BF_4$ (1.0%) (1*S*,1′*S*,2*R*,2′*R*)-Tangphos (1.1%)	100	MeOH	RT	50	72	1c	—	no rxn
45	2c	$[Rh(NBD)_2]BF_4$ (5.0%) (1*S*,1′*S*,2*R*,2′*R*)-Tangphos (5.5%)	20	MeOH	RT	50	48	1c	94	86 (*S*)
46	2c	$[Rh(NBD)_2]BF_4$ (5.0%) (1*R*,1′*R*,2*S*,2′*S*)-Tangphos (5.5%)	20	MeOH	RT	50	48	1c	97	89 (*R*)
47	6a	(2*R*,5*R*)-[(COD)Rh(Me-Duphos)]$^+CF_3SO_3^-$ (15%)	7	MeOH	RT	50	72	7a	20†	ND
48	6a	$[Rh(NBD)_2]BF_4$ (5.0%) (1*S*,1′*S*,2*R*,2′*R*)-Tangphos (5.5%)	20	MeOH	RT	50	72	7a	35†	ND
49	6b	(2*R*,5*R*)-[(COD)Rh(Me-Duphos)]$^+CF_3SO_3^-$ (15%)	7	MeOH	RT	50	120	7b	97	<1 (*S*)
50	6b	$[Rh(NBD)_2]BF_4$ (3.0%) (1*S*,1′*S*,2*R*,2′*R*)-Tangphos (3.3%)	33	MeOH	RT	50	72	7b	98	7 (*R*)
51	6c	(2*R*,5*R*)-[(COD)Rh(Me-Duphos)]$^+CF_3SO_3^-$ (15%) (no rxn with 1%)	7	MeOH	RT	50	120	7c	75†	19 (*S*)
52	6c	$[Rh(NBD)_2]BF_4$ (5.0%) (1*S*,1′*S*,2*R*,2′*R*)-Tangphos (5.5%)	20	MeOH	RT	50	120	7c	50†	15 (*S*)

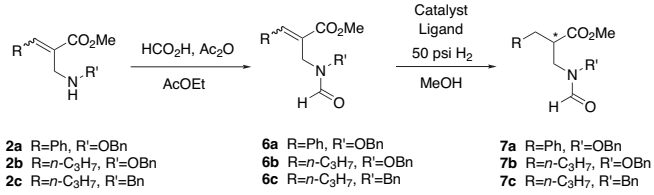
ND, not determined; RT, room temperature.

*Entries 1–9, 12–18, and 23: substrate = 0.01 mmol, solvent volume = 0.7 ml; entries 10, 11, and 37–52: substrate = 1 mmol, solvent volume = 6 ml; entries 19, 20, 24, 28, 29, and 34–36: substrate = 0.1 mmol, solvent volume = 1.5 ml; entries 26 and 27: substrate = 0.02 mmol, solvent = 0.7 ml; entries 21, 22, and 25: substrate = 1 mmol, solvent volume = 4 ml; entries 30–33: substrate = 0.05 mmol, solvent volume = 1 ml.

†Reported as conversion based on ^1H NMR spectroscopy.

‡*E*-2a/*Z*-2a = 80/20.

reaction was very fast, it proceeded completely within 20 min at a substrate/catalyst (S/C) ratio of 100, even when the hydrogen pressure was decreased to 50 psi. It was further observed in the following cases that the hydrogen pressure of the catalyst system had little effect on the reactivity and enantioselectivity of this kind of reaction (Table 1, entries 30 and 31). This was very different from the asymmetric hydrogenation process of the *E*/*Z* mixture of β-substituted β-acylamino acrylates, in which remarkable pressure dependence was reported (23). As S/C was increased to 1,000, the reaction was completed within 10 h. Furthermore, it gave full conversion and the same high ee in *i*PrOH by prolonging the reaction time to 78 h even with a S/C ratio of up to 10,000. Consequentially, the hydrogenation of pure ***Z*-2a** and ***E*/*Z*-2a** mixtures were also tested. Rh-(Et-Duphos) as the catalyst was still effective for this reaction with very high reactivity. Although ee values decreased slightly to 92% in the hydrogenation of ***Z*-2a** (minor isomer), the hydrogenation of ***E*/*Z*-2a** mixture gave **1a** with 98% ee (Table 1, entries 23–25). The chirality of product **1a** was determined by the ligand's configuration regardless of the double bond configuration in substrate **2a**. This means that the costly separation of the isomers can be avoided. After the success in the asymmetric hydrogenation of **2a**, we put our effort to alkyl-substituted substrate **2b** (1:1 mixture of (*E*) and (*Z*)-isomers; Table 1, entries 26–42). The result was also satisfactory by using [Rh-(Et-Duphos)(COD)]BF_4 catalyst although the activity decreased a little in comparison with **2a** (Table 1, entries 26–33). At room temperature and under 50 psi of H_2, the reaction was complete within 24 h in *i*PrOH and THF with S/C up to 500, giving **1b** in >98% yield and with >99.5% ee (Table 1, entries 32 and 33). The configuration of the major enantiomer was determined by further converting **1b** to an advanced intermediate in our synthesis with known configuration and comparing the retention time of *R* and *S* enantiomers. The reaction rate increased as the reaction temperature was raised. Interestingly, no decrease of enantioselectivity for product **2b** was found (Table 1, entries 34–36). The S/C ratio could be further increased to 1,000 at 50°C. The reaction was complete in 7 h under these conditions. Full conversions were achieved within 5 h at 70°C. The reaction rates were not further optimized. In contrast to the use of [Rh(Et-Duphos)(COD)]BF_4 catalyst, no hydrogenation was observed with 1.0 mol% of $[Rh(NBD)_2]BF_4$ and 1.1 mol% of (*S*)-C4-Tunaphos (61), (*S*)-f-Binaphane (62), or (2*S*,4*S*)-Me-Ketalphos (63) in methanol for as long as 72 h. There was also no reaction with 1.0 mol% of (2*R*,5*R*)-[(COD)Rh(Me-DPEphos)]$^+CF_3SO_3^-$ or 13.6 mol% of (*S*,*S*,*S*,*S*)-[(COD)Rh(Et-FerroTANE)]$^+BF_4^-$ (64) (entry 37) as catalyst. The hydrogenation was complete with 1.0 mol% of $[Rh(NBD)_2]BF_4$ and 1.1 mol% of



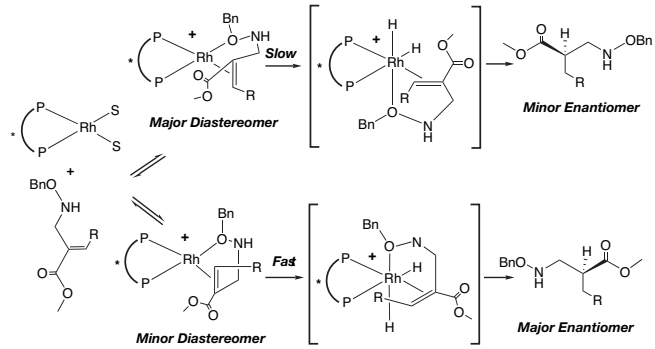
Scheme 2. Synthesis of *N*-formylated derivates **6a-c** and the hydrogenation process.

(*R*)-(*S*)-Josiphos (65) in 24 h, however, the enantioselectivity was extremely poor (10% ee; Table 1, entry 38). The asymmetric hydrogenation was very slow with 1 mol% of (2*R*,5*R*)-[(COD)Rh(Me-Duphos)]$^+CF_3SO_3^-$, but it was complete in 24 h with ee >96% when the catalyst loading was increased to 15 mol% (Table 1, entry 39). As expected, the hydrogenation of **2b** with (2*S*,5*S*)-Me-Duphos yielded **1b** with 98% ee (Table 1, entry 40), but Tangphos had higher activity. The hydrogenation of **2b** was complete in 24 h with only 1.0 mol% of $[Rh(NBD)_2]BF_4$ and 1.1 mol% of (1*S*,1′*S*,2*R*,2′*R*)-Tangphos, affording **1b** in 94% isolated yield and >96% ee (Table 1, entry 41). Again as expected, the ligand with opposite chirality, (1*R*,1′*R*,2*S*,2′*S*)-Tangphos, afforded **1b** with 97% ee (Table 1, entry 42). Overall [Rh-(Et-Duphos)(COD)]BF_4 was the best catalyst in our studies of the asymmetric hydrogenation of **2b**.

To study the role of the oxygen atom in the $NHOCH_2Ph$ group, we next examined the asymmetric hydrogenation of α-*N*-benzylaminomethyl-substituted acrylate **2c**, which lacked the oxygen atom. The complete hydrogenation of **2c** with 15 mol% of (2*R*,5*R*)-[(COD)Rh(Me-Duphos)]$^+CF_3SO_3^-$ required 96 h compared with the requirement of 24 h for **2b**. The enantioselectivity was also slightly lower (85% ee vs. >96% ee; see Table 1, entry 43 vs. 39). Similar results were obtained with Tangphos. In contrast to **2b**, almost no reaction was observed for **2c** with 1 mol% of catalyst and 1.1 mol% of ligand in 72 h (Table 1, entry 41 vs. 44). An increase in the loading of the catalyst to 5 mol% and the ligand to 5.5 mol% led to a completion of the reaction in 48 h (Table 1, entries 45 and 46). The enantiopurities of the product were also slightly lower than those from **2b**. Thus, the presence of the oxygen atom in the $NHOCH_2Ph$ group has a positive effect on the reaction rates.

Because the *N*-acetyl group has been reported to coordinate to the catalyst during the synthesis of α-amino acids (66), it was of interest to study the hydrogenation of the *N*-acylated substrates. Thus, we synthesized *N*-formylated derivates **6a-c** by reacting **2a-c** with the mixed anhydride prepared from an excess of formic acid and acetic anhydride (Scheme 2). Surprisingly, the hydrogenation of **6b** was very slow, and it required 120 h for the completion of the reaction even with 15 mol% of (2*R*,5*R*)-[(COD)Rh(Me-Duphos)]$^+CF_3SO_3^-$ (Table 1, entry 49) and 72 h with 3.0 mol% $[Rh(NBD)_2]BF_4$ and 3.3 mol% (1*S*,1′*S*,2*R*,2′*R*)-Tangphos (Table 1, entry 50). Enantioselectivity was almost absent in both cases. Similarly, the hydrogenation of *N*-formylated substrate **6a** also proceeded much slower. Only 20% and 35% conversions were observed with 15 mol% of Duphos and 5 mol% of Tangphos, respectively (Table 1, entries 47 and 48). The hydrogenation of **6c** required 120 h with 15 mol% of Duphos or 5 mol% of Tangphos to achieve 75% and 50% conversion, respectively (Table 1, entries 51 and 52). The enantioselectivities were poor in both cases. These results were consistent with those reported for the hydrogenation of α-phthalimidomethyl-β-methylacrylate, which gave only 10% ee (67).

The mechanism of the Rh(I)-catalyzed asymmetric hydrogenation has been widely studied. The work by Halpern *et al.* (68), Brown *et al.* (69) and Landis *et al.* (70) concluded that the predominant enantiomer was derived from the minor (less stable) catalyst-substrate adduct due to its higher reactivity toward H_2. Burk *et al.*



Scheme 3. Proposed mechanism for Rh-catalyzed asymmetric hydrogenation.

(66) also suggested that Rh-Duphos catalysts behaved in a similar fashion. The Rh-catalyzed hydrogenation described in this paper is expected to follow the same mechanistic pathway involving a coordination of the metal with oxygen atom in the $NHOCH_2Ph$ group (Scheme 3). The configuration of the catalyst determined the product configuration and not the *E*/*Z* configuration the alkene. The higher efficiency observed for Tangphos was ascribed to its rigid backbone (59). The dramatic slow reaction rates and poor enantioselectivities with *N*-formylated compounds **6a-c** suggested a possible different binding fashion of these substrates to the catalysts, perhaps via oxygen atom of the N—CHO group. The high enantioselectivities obtained with the free basic amine derivatives are especially interesting as this avoids the need for protection and deprotection of the nitrogen in the synthesis.

Conclusions

We have developed a highly enantioselective method for the synthesis of β-amino acid derivatives (**1a-c**), in which Rh-catalyzed asymmetric hydrogenation of the *E*/*Z* mixtures α-aminomethylacrylates (**2a-c**) containing a free basic NH group was used as the key step. The α-aminomethylacrylates (**2a-c**) were prepared using the Baylis–Hillman reaction of an appropriate aldehyde with methyl acrylate followed by acetylation of the resulting allylic alcohols (**4a-b**) and S_N2'-type amination of the allylic acetates (**3a-b**). The easy approach and high S/C ratio provide a practical route for the practical preparation of β-amino acids and their derivatives via asymmetric hydrogenation under mild reaction conditions.

Materials and Methods

All of the reagents were purchased from commercial suppliers and used without further purification. (*S*)-C4-Tunaphos, (*S*)-f-Binaphane, (2*S*,4*S*)-Me-Ketalphos, (1*S*,1′*S*,2*R*,2′*R*) and (1*R*,1′*R*,2*S*,2′*S*)-Tangphos were obtained from Chiral Quest (Monmouth Junction, NJ). BINAP, Monophos, *i*Pr-Duphos, Me-Duphos, $[Rh(COD)_2]BF_4$, (2*R*,5*R*)-[(COD)Rh(Me-Duphos)]$^+CF_3SO_3^-$, (2*S*,5*S*)-[(COD)Rh(Me-Duphos)]$^+CF_3SO_3^-$, [Rh((*S*,*S*)-Et-Duphos)(COD)]BF_4 and [Rh((*R*,*R*)-Et-Duphos)(COD)]BF_4 were purchased from Strem Chemicals (Newburyport, MA). $[Rh(NBD)_2]BF_4$ was obtained from Johnson Matthey (London, U.K.). ^1H and ^{13}C NMR spectra were recorded on a Bruker FT-NMR spectrometer at 300 and 75 MHz or a Varian 500 spectrometer at 500 and 125 MHz, respectively. High-resolution mass spectroscopy (HRMS) was carried out on a ThermoFinnigan MAT-900 (Finnigan MAT, Bremen, Germany) in electrospray mode. Other mass spectra were obtained on a Micromass LCT in electrospray mode. Optical rotations were recorded on a PerkinElmer 341 (Manchester, U.K.) polarimeter in a 10-cm cell. Melting points were measured on a Büchi 533 melting point apparatus (Flawil, Switzerland). The enantiopurities of **1a-c** were determined by chiral HPLC on a Rainin Dynamax (Woburn, MA) system or an Agilent 1100 series using Daicel Chiralcel OD-H

column (4.6 × 250 mm) and a mixture of hexane/2-propanol (95/5) as the mobile phase (isocratic at a flow rate of 0.5 ml/min and UV detector at 220 nm). The retention times of (*R*)-**1a** and (*S*)-**1a** (free base) were 21.9 and 24.3 min, respectively. The retention time of (*R*)-**1b** and (*S*)-**1b** was 11.4 and 13.0 min, respectively. The retention time of (*R*)-**1c** and (*S*)-**1c** was 11.2 and 11.8 min, respectively. The enantiopurities of **7b** and **7c** were determined by *N*-deformylating them to **1b** and **1c** with HCl and analysis by chiral HPLC. 3-Hydroxy-3-phenyl-2-methylenepropanoic acid methyl ester (**4a**) and 3-hydroxy-2-methylenehexanoic acid methyl ester (**4b**) are known compounds and were prepared by reacting methyl acrylate with butanal, benzal, and pentanaldehyde, respectively, for 7 days at room temperature in the presence of catalytic DABCO (39–46, 51, 52).

(*E*/*Z*)-2-[(Benzyloxyamino)methyl]-3-Phenylacrylic Acid Methyl Ester (2a). A mixture of 3-acetoxy-3-phenyl-2-methylenepropanoic acid methyl ester (3a) (35.14 g, 150 mmol) and *O*-benzylhydroxylamine (55.42 g, 450 mmol) in THF (100 ml) was allowed to stir at room temperature under N_2 for 2 days. The reaction mixture was concentrated under reduced pressure (20 mbar) until no further solvent distilled. The residue was dissolved in ethyl acetate (500 ml) and washed with saturated aqueous sodium bicarbonate (250 ml). The ethyl acetate layer was concentrated under reduced pressure (20 mbar) until no further solvent distilled to afford a colorless liquid (87.4 g). The crude material was purified by column chromatography (silica gel, 5% ethyl acetate in heptane) to afford an ≈80:20 mixture of (*E*) and (*Z*)-(**2a**) (39.72 g, 89%) as a semisolid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.64 (s, 0.2 × 3H), 3.80 (s, 0.8 × 3H), 3.83 (bs, 0.2 × 2H), 3.96 (bs, 0.8 × 2H), 4.71 (s, 0.2 × 2H), 4.72 (s, 0.8 × 2H), 6.08 (bs, 0.8 × 1H), 6.86 (bs, 0.2 × 1H), 7.25–7.4 (m, 8H), 7.45–7.55 (m, 2H), 7.87 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 49.05, 52.09, 52.55, 57.04, 76.36, 76.68, 127.84, 128.19, 128.24, 128.42, 128.58, 128.70, 128.77, 128.83, 128.87, 128.92, 129.45, 130.02, 130.68, 135.23, 135.91, 137.98, 138.23, 138.45, 144.26, 168.63, 169.61; MS(ESI) 298.15 (MH^+). The semisolid can be recrystallized from heptane to afford (*E*)-(**2a**) as a white solid (30.34 g, 68%): mp 47–49°C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.80 (s, 3H), 3.96 (d, 2H, J = 5.7 Hz), 4.72 (s, 2H), 6.08 (bs, 1H), 7.25–7.4 (m, 8H), 7.45–7.55 (m, 2H), 7.87 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 49.05, 52.55, 76.36, 127.84, 128.19, 128.77, 128.83, 128.92, 129.45, 130.02, 135.23, 138.45, 144.26, 168.63; MS(ESI) 298.15 (MH^+). The residual part in the mother liquid was concentrated and purified again by column chromatography to give oily (*Z*)-(**2a**). ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.66 (s, 3H), 3.84 (s, 2H), 4.72 (s, 2H), 6.88 (s, 1H), 7.25–7.38 (m, 11H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 51.67, 56.58, 76.24, 127.81, 128.13, 128.26, 128.33, 128.42, 128.47, 130.18, 135.45, 137.61, 137.76, 169.18; MS(ESI) 298.15 (MH^+).

(*E*/*Z*)-2-[(Benzyloxyamino)methyl]-2-Hexenoic Acid Methyl Ester (2b). A mixture of 3-acetoxy-2-methylenehexanoic acid methyl ester (3b) (4.00 g, 20 mmol) and *O*-benzylhydroxylamine (7.39 g, 60 mmol) in THF (30 ml) was allowed to stir at room temperature under N_2 for 2 days. The reaction mixture was concentrated under reduced pressure (20 mbar) until no further solvent distilled. The residue was dissolved in ethyl acetate (75 ml) and washed with saturated aqueous sodium bicarbonate (50 ml). The ethyl acetate layer was concentrated under reduced pressure (20 mbar) until no further solvent distilled to afford a colorless liquid (11.2 g). The crude material was purified by column chromatography (silica gel, 5% ethyl acetate in heptane) to afford an ≈1:1 mixture of (*E*) and (*Z*)-(**2b**) (4.01 g, 76%) as a colorless liquid: ^{1}H NMR (300 MHz, $CDCl_3$) (≈1:1 mixture of *E*/*Z* isomers) δ 0.89–0.96 (m, 3H), 1.38–1.53 (m, 2H), 2.19 (m, 0.5 × 2H), 2.48 (m, 0.5 × 2H), 3.65 (s, 0.5 × 2H), 3.71 (s, 0.5 × 3H), 3.72 (s, 0.5 × 3H), 3.74 (s, 0.5 × 2H), 4.67 (s, 0.5 × 2H), 4.68 (s, 0.5 × 2H), 5.88 (bs, 1H), 6.14 (t, 0.5 × 1H, J = 7.4 Hz), 6.95 (t, 0.5 × 1H, J = 7.6 Hz), 7.25–7.29 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.21, 14.26, 22.41, 22.82, 31.02, 32.05, 48.04, 51.70, 52.13, 56.31, 76.29, 76.30, 127.89, 127.96, 128.13, 128.69, 128.77, 128.86, 138.35, 138.41, 147.97, 148.06, 168.03, 168.22; HRMS(ESI) 264.1554 (MH^+, exact mass calculated for $C_{15}H_{22}NO_3$ 264.1600).

(*E*/*Z*)-2-[(Benzylamino)methyl]-2-Hexenoic Acid Methyl Ester (2c). A mixture of 3-acetoxy-2-methylenehexanoic acid methyl ester (3b) (10.01 g, 50 mmol) and benzylamine (21.43 g, 80 mmol) in THF (75 ml) was allowed to stir at room temperature under N_2 for 2 h. The resulting suspension was concentrated under reduced pressure (20 mbar) until no further solvent distilled. To the residue was added ethyl acetate (200 ml) and saturated aqueous sodium bicarbonate (50 ml) to afford a biphasic solution. The ethyl acetate layer was separated and washed with water (50 ml). The organic layer was concentrated under reduced pressure (20 mbar) until no further solvent distilled to afford a colorless liquid (23.1 g). The crude material was purified by column chromatography (silica gel, 20% ethyl acetate in heptane) to afford an ≈65:35 mixture of (*E*) and (*Z*)-(**2c**) (8.01 g, 65%) as a colorless liquid: ^{1}H NMR (300 MHz, $CDCl_3$) (≈65:35 mixture of *E*/*Z* isomers) δ 0.85–0.97 (m, 3H), 1.37–1.52 (m, 2H), 1.79 (bs, 1H), 2.05–2.15 (m, 0.65 × 2H), 2.4–2.5 (m, 0.35 × 2H), 3.40 (s, 0.35 × 2H), 3.45 (s, 0.65 × 2H), 3.7–3.8 (m, 5H), 6.06 (t, 0.35 × 1H, J = 7.4 Hz), 6.90 (t, 0.65 × 1H, J = 7.6 Hz), 7.2–7.4 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.86, 14.13, 22.12, 22.58, 22.70, 30.48, 31.52, 44.27, 51.23, 51.66, 52.42, 52.86, 126.86, 128.06, 128.14, 128.30, 128.33, 129.79, 130.14, 140.27, 140.32, 144.85, 145.57, 167.93, 168.04; MS(ESI) 248.2 (MH^+).

General Procedure for the Asymmetric Hydrogenation. The appropriate catalyst prepared *in situ* or purchased from commercial suppliers was added to a solution of the substrate **2a-c** or **6a-c** and degassed solvent in a Parr bottle or a glass-lined stainless steel autoclave under nitrogen purge. After four vacuum/H_2 cycles, the reaction mixture was pressurized to 50 psig H_2 and maintained constantly under this pressure during the course of hydrogenation. The reaction was allowed to continue at room temperature for the time specified in Table 1. The completion of the reaction was monitored by HPLC. The reaction mixture was concentrated under reduced pressure (20 mbar) until no further solvent distilled. The residue was filtered through a short SiO_2 column (≈1 g) with ethyl acetate/heptane (50/50, 10 ml) to remove the catalyst. The filtrate was concentrated under reduced pressure (20 mbar) until no further solvent distilled. The enantiomeric purity was determined by chiral HPLC.

(*R*)-2-[(Benzyloxyamino)methyl]-3-Phenylpropionic Acid Methyl Ester (1a). Aymmetric hydrogenation of (*E*)-2-[(benzyloxyamino)methyl]-3-phenylacrylic acid methyl ester (**2a**) was carried out with bis(norbornadiene)rhodium(I) tetrafluoroborate (2.0 mol%) and (1*R*,1′*R*,2*S*,2′*S*)-Tangphos (2.2 mol%) at 50 psig H_2 for 48 h at room temperature to afford (*R*)-2-[(benzyloxyamino)methyl]-3-phenylpropionic acid methyl ester (**1a**) (97%) as a colorless oil. The free base was added into a solution of 1 M HCl gas in isopropyl acetate (3 equiv) at room temperature to form a suspension. The solid was filtered, washed with isopropyl acetate, and dried to afford (*R*)-(**1a**) hydrochloride salt (94%) as a white solid: mp 145–147°C; ee = 91% (*R*); $[\alpha]_D^{25}$ +26.9 (*c* 1.0, EtOH); spectroscopic data were in agreement with published data (15–18).

(*S*)-2-[(Benzyloxyamino)methyl]-3-phenyl-propionic acid methyl ester (*S*)-**1a** was also obtained by using (2*R*,5*R*)-[(COD)Rh(Me-Duphos)]$^+CF_3SO_3^-$ (15 mol%) as catalyst in 48 h at room temperature [99%, ee = 95% (*S*)].

(*R*)-2-[(Benzyloxyamino)methyl] Hexanoic Acid Methyl Ester (1b). Asymmetric hydrogenation of an ≈1:1 mixture of (*E*) and (*Z*)-2-[(benzyloxyamino)methyl]-2-hexanoic acid methyl ester (**2b**) was carried out with [Rh((*S*,*S*)Et-Duphos)(COD)]BF_4 as the catalyst (S/C = 500) at 50 psig H_2 for 24 h at room temperature to afford (*R*)-(**1c**) (>98% yield): oil; ee >99.5% (*R*); $[\alpha]_D^{25}$–11.8 (*c* 1.0,

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EtOH); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 0.90 (t, 3H, J = 7.0 Hz), 1.21–1.34 (m, 4H), 1.47–1.63 (m, 2H), 2.73–2.80 (m, 1H), 3.02–3.07 (m, 1H), 3.17–3.22 (m, 1H), 3.67 (s, 3H), 4.72 (d, 2H, J = 3.5 Hz), 5.25 (bs, 1H), 7.2–7.4 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.79, 22.47, 29.30, 29.97, 43.72, 51.42, 53.74, 76.13, 127.72, 128.24, 128.37, 137.66, 175.79; HRMS(ESI): calcd for C15H24NO3 (MH^+) 266.1756, found 266.1757.

(*R*)-2-[(Benzylamino)methyl]hexanoic Acid Methyl Ester (1c). Asymmetric hydrogenation of an ≈65:35 mixture of (*E*) and (*Z*)-2-[(benzylamino)methyl]-2-hexenoic acid methyl ester (**2c**) was carried out with bis(norbornadiene)rhodium(I) tetrafluoroborate (5.0 mol%) and (1*R*,1′*R*,2*S*,2′*S*)-Tangphos (5.5 mol%) at 50 psig H_2 for 48 h at room temperature to afford (*R*)-(**1c**) (97%): oil; ee = 89% (*R*); $[\alpha]_D^{25}$ −10.9 (*c* 1.0, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.87 (t, 3H, J = 7.0 Hz), 1.15–1.35 (m, 4H), 1.4–1.7 (m, 3H), 2.52–2.64 (m, 1H), 2.64–2.74 (m, 1H), 2.8–2.9 (m, 1H), 3.67 (s, 3H), 3.77 (d, 2H, J = 2.6 Hz), 7.18–7.34 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.91, 22.61, 29.54, 30.08, 46.13, 50.81, 51.48, 53.72, 126.89, 128.01, 128.34, 140.30, 176.07; MS(ESI) 250.17 (MH^+); anal. calcd. for $C_{15}H_{23}NO_2$: C, 72.25; H, 9.30; N, 5.62; found: C, 72.38; H, 9.45; N, 5.65.

(*S*)-2-[(Benzylamino)methyl]hexanoic acid methyl ester (*S*)-**1c** was prepared by using (1*S*,1′*S*,2*R*,2′*R*)-Tangphos [94%, ee = 86% (*S*)] or (2*R*,5*R*)-[(COD)Rh(Me-Duphos)]$^+CF_3SO_3^-$ [98%, ee = 85% (*S*)] as catalyst.

The synthesis of substrates **3a-b** and **6a-c** and the spectra of **3a-b**, **6a-c**, and **7a-c** are provided in supporting information (SI) *Text*.

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