Enantioselective Hydrogenation of β-Disubstituted α-Acetamidoacrylates Catalyzed by Rhodium Complexes with TRAP Trans-Chelating Chiral Phosphine Ligands

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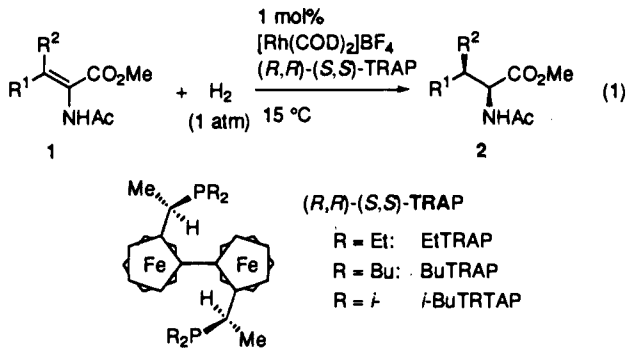
Regardless of extensive studies devoted to the development of the enantioselective catalytic hydrogenation of the carbon−carbon double bond,[2] enantioselective hydrogenation of tetrasubstituted olefins is yet to be accomplished in general.[3] We report here the use of TRAP trans-chelating chiral phosphine ligands[4−7] in the rhodium-catalyzed asymmetric hydrogenation of α-acetamidoacrylates.[8,9] High enantioselectivities were obtained in the hydrogenation of various β-disubstituted α-acetamidoacrylates, for which no highly enantioselective hydrogenation has so far been reported in spite of its potential wide applicability.

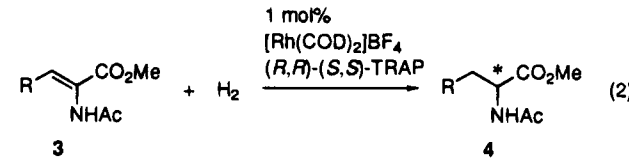
Hydrogenations of β-disubstituted α-acetamidoacrylates (**1**) were carried out at 15 °C and 1 atm of hydrogen pressure in the presence of rhodium catalysts prepared *in situ* from [Rh(COD)$_2$]BF$_4$ and (*R*,*R*)-(*S*,*S*)-TRAPs (1:1.1) (eq 1). Representative results are summarized in Table 1. In the hydrogenation



of **1a** (entries 1−3), *N*-acetylvaline methyl ester (**2a**) with the *S* configuration was produced with high enantioselectivity when the TRAP ligands with linear alkyl *P*-substituents such as EtTRAP (83% ee) or BuTRAP (88% ee) were used as chiral ligands. On the other hand, no reaction took place with the ligand bearing *P*-alkyl groups branched at the β-position (*i*-BuTRAP). This *P*-alkyl group seems to be too bulky even though it is still a primary alkyl group.

Enantioselective hydrogenation of α-(*N*-acylamino)acrylates bearing two different β-substituents would provide an efficient method for the synthesis of optically active β-alkylated α-amino acids with vicinal stereogenic centers, which are an important class of compounds as unusual amino acids.[10,11] From (*Z*)- and (*E*)-**1** were obtained specifically *threo*-(2*S*,3*R*)- and *erythro*-(2*S*,3*S*)-**2**, respectively, as expected from the cis stereochemistry of hydrogenation. The configurations of *threo*-**2b**−**f** and *erythro*-**2b**−**e** at the α-carbons are the same as that of **2a**. The (*Z*)-olefins were generally hydrogenated in higher selectivities with EtTRAP than with BuTRAP [(*Z*)-**1e**; BuTRAP; CH_2Cl_2; 80% ee], while (*E*)-olefins (and **1a**) were hydrogenated in higher selectivities with BuTRAP [(*E*)-**1e**; EtTRAP; *i*-PrOH; 75% ee]. It is also an obvious trend that the hydrogenation of the (*Z*)-olefins is more selective than that of (*E*)-olefins. Various β-alkylated α-amino acid derivatives were obtained as shown in Table 1 (entries 4−12). Thus, the hydrogenation of (*Z*)-2-(*N*-acetylamino)-3-phenyl-2-butenoate [(*Z*)-**1b**] gave (2*S*,3*R*)-*N*-acetyl-β-methylphenylalanine methyl ester (**2b**) with 85% ee, and the ee value was little affected by ring substituents with different electronic demands [*p*-MeO (**2c**), *p*-F (**2d**)]. Similarly, β-ethylphenylalanine derivatives *threo*- and *erythro*-**2e** were obtained with 86% ee and 77% ee, respectively. It is of particular importance that the extremely bulky *tert*-butyl-substituted olefin (*Z*)-**1f** was hydrogenated smoothly to give (2*S*,3*R*)-**2f** with high enantiomeric excess (86% ee).

The present Rh−TRAP catalysts showed some remarkable features also in the hydrogenation of *usual* α-(*N*-acylamino)-acrylate substrates such as β-unsubstituted (**3a**) and β-monosubstituted (*Z*)-α-acetamidoacrylates (**3b**−**e**) (eq 2). Results are



summarized in Table 2. The enantioselectivity in the hydrogenation of these substrates was found to be strongly dependent on H_2 pressure, reaction temperature and solvent as well as the ligand *P*-substituent. In general, a decrease in the H_2 pressure and an increase in the reaction temperature favored the formation of **4** with the *R* configuration. The chiral sense of enantioselection is usually opposite to that for the reaction of β-disubstituted α-acetamidoacrylates (**1**). The highest selectivity [96% ee (*R*)] for the reaction of β-unsubstituted enamide **3a** was obtained when EtTRAP was used in $ClCH_2CH_2Cl$ at 60 °C and 0.5 atm of partial H_2 pressure (H_2:N_2 = 1:1), while only 70% ee was obtained at 1 atm of H_2 pressure (entries 1 and 2). The enantioselectivity decreased drastically with increasing steric demand of the ligand *P*-alkyl chain, BuTRAP and *i*-BuTRAP giving **4a** with 66% ee (*R*) and 8% ee (*S*), respectively (entries 3 and 4). The enantioselectivity in the hydrogenation of β-monosubstituted α-acetamidoacrylates **3b**−**e** decreased obviously with increasing bulkiness of the olefin β-substituents under

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Table 1. Asymmetric Hydrogenation of β-Disubstituted α-Acetamidoacrylates (**1**) Catalyzed by Rh−TRAP Complexes (Eq 1)[a]

entry	1	R^1	R^2	TRAP[b]	solvent	conv, %	2	ee, %[c]	config[d]
1	**1a**	Me	Me	EtTRAP	*i*-PrOH	100	**2a**	83	*S*
2	**1a**	Me	Me	BuTRAP	*i*-PrOH	100	**2a**	88	*S*
3	**1a**	Me	Me	*i*-BuTRAP	*i*-PrOH	0	**2a**		
4	(*Z*)-**1b**	Ph	Me	EtTRAP	CH_2Cl_2	100	*threo*-**2b**	85	(2*S*,3*R*)
5	(*Z*)-**1c**	*p*-MeO-C_6H_4	Me	EtTRAP	CH_2Cl_2	100	*threo*-**2c**	85	(2*S*,3*R*)
6	(*Z*)-**1d**	*p*-F-C_6H_4	Me	EtTRAP	CH_2Cl_2	100	*threo*-**2d**	83	(2*S*,3*R*)
7	(*Z*)-**1e**	Ph	Et	EtTRAP	CH_2Cl_2	100	*threo*-**2e**	86	(2*S*,3*R*)
8	(*Z*)-**1f**	*t*-Bu	Me	EtTRAP	CH_2Cl_2	100	*threo*-**2f**	86	(2*S*,3*R*)
9	(*E*)-**1b**	Me	Ph	BuTRAP	*i*-PrOH	100	*erythro*-**2b**	80	(2*S*,3*S*)
10	(*E*)-**1c**	Me	*p*-MeO-C_6H_4	BuTRAP	*i*-PrOH	84	*erythro*-**2c**	80	(2*S*,3*S*)
11	(*E*)-**1d**	Me	*p*-F-C_6H_4	BuTRAP	*i*-PrOH	100	*erythro*-**2d**	79	(2*S*,3*S*)
12	(*E*)-**1e**	Et	Ph	BuTRAP	*i*-PrOH	100	*erythro*-**2e**	77	(2*S*,3*S*)

[a] The reaction was carried out at 15 °C for 24 h. No byproduct was observed. **1** (0.5 mmol, 0.5 M):[$Rh(COD)_2$]BF_4:TRAP = 1:0.01:0.011. [b] (*R*,*R*)-(*S*,*S*)-TRAP was used. [c] Determined by HPLC analysis of **2** with a SUMICHIRAL OA-3000 chiral stationary phase column. [d] See supporting information for the determination of configuration.

Table 2. Asymmetric Hydrogenation of α-Acetamidoacrylates (**3**) Catalyzed by Rh−TRAP Complexes (Eq 2)[a]

					4	
entry	R (**3**)	TRAP[b]	P_{H_2}, atm	temp, °C	ee, %[c]	config[d]
1	H (**3a**)	EtTRAP	0.5	60	96	*R*
2	H (**3a**)	EtTRAP	1	60	70	*R*
3	H (**3a**)	BuTRAP	0.5	60	66	*R*
4	H (**3a**)	*i*-BuTRAP	0.5	60	8	*S*
5	Me (**3b**)	EtTRAP	0.5	60	92	*R*
6	*i*-Bu (**3c**)	EtTRAP	0.5	60	88	*R*
7	*i*-Pr (**3d**)	EtTRAP	0.5	60	57	*R*
8	Ph (**3e**)	EtTRAP	0.5	60	77	*R*
9[e]	Ph (**3e**)	*i*-BuTRAP	1	15	92	*S*

[a] The reaction was carried out in dichloroethane for 24 h unless otherwise noted. Complete conversion to **4** was observed. **3** (0.5 mmol, 0.5 M):[$Rh(COD)_2$]BF_4:TRAP = 1:0.01:0.011. [b] (*R*,*R*)-(*S*,*S*)-TRAP was used. [c] Determined by HPLC analysis of **4** with a SUMICHIRAL OA-3000 chiral stationary phase column. [d] See supporting information for the determination of configuration. [e] The reaction was carried out in CH_2Cl_2.

identical conditions: 92% ee, 88% ee, 77% ee, and 57% ee for **3b**, **3c**, **3e**, and **3d**, respectively (entries 5−8). The effect of the ligand *P*-substituent was found to be much more dramatic for substrate **3e** than for **3a**. Thus, the *i*-BuTRAP ligand showed a chiral sense of enantioselection opposite to that with EtTRAP, producing (*S*)-**4e** with the enantiomeric excess as high as 92% (1 atm, CH_2Cl_2, 15 °C, entry 9).

These results suggest that these reactions may proceed via two competitive reaction pathways: one involves the coordination of the olefin to a TRAP−Rh(I) complex followed by the oxidative addition of hydrogen, leading to the preferential formation of (*R*)-product (favorable under low hydrogen pressure, path A); the other involves the oxidative addition of hydrogen prior to the coordination of olefin, which favors the formation of (*S*)-product (favorable under high hydrogen pressure, path B).[12,13] Increases in the steric demands of both the substrate and the ligand *P*-alkyl group would disfavor olefin binding, leading to the preferential formation of the (*S*)-products through path B. This path seems to be dominant in the hydrogenation of sterically demanding β-disubstituted α-acetamidoacrylates (**1**).[14,15]

In summary, high selectivities were achieved in the rhodium-catalyzed enantioselective hydrogenation of various β-disubstituted α-acetamidoacrylates by using the trans-chelating chiral phosphine ligands EtTRAP [for (*Z*)-olefins] and BuTRAP [for (*E*)-olefins and dehydrovaline derivative **1a**]. It is suggested that H_2 oxidative addition may occur prior to olefin coordination for this class of substrates. The present reaction provides, in principle, a useful method for the preparation of optically active β-alkylated α-amino acids. Further studies to improve the catalyst efficiency and to elucidate the reaction mechanism are now in progress.

Supporting Information Available: Listing of ^1H and ^{13}C NMR spectral data of **2b**−**f** and **4c** and the experimental procedures for the preparation of **1** and the determination of the absolute configurations of products (8 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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