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Ru-Catalyzed Highly Enantioselective Hydrogenation of β-Alkyl-Substituted β-(Acylamino)acrylates

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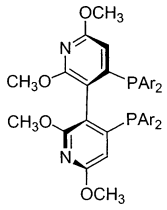
Abstract: Highly enantioselective hydrogenation of β-alkyl-substituted (*E*)-β-(acylamino)-acrylates catalyzed by Ru((*R*)-Xyl-P-Phos)(C_6H_6)Cl_2 complex (**cat. 1c**) was achieved in up to 99.7% ee. Moderate to good enantioselectivities in the hydrogenation of corresponding (*Z*)-isomers in the presence of [Rh((*R*)-Xyl-P-Phos)(COD)]BF_4 (**cat. 2c**) were also obtained. The results demonstrated that the electronic and steric properties of the dipyridylphosphine ligands as well as the different transition metal ions have significant influences on the catalytic properties in the hydrogenation of β-(acylamino)acrylates.

The homogeneous asymmetric hydrogenation of prochiral olefins catalyzed by chiral phosphine-transition metal complexes is one of the most important advancements in modern organic synthesis.[1] In the past three decades, tremendous success has been achieved in the Rh-catalyzed enantioselective hydrogenation of α-amidoacrylic acids and their esters, which has been developed to be a standard procedure for the synthesis of α-amino acids with high enantioselectivities.[1,2] In contrast, the asymmetric hydrogenation of β-(acylamino)acrylates is much less mature, although enantiomerically pure β-amino acids and their derivatives are very attractive targets for the asymmetric synthesis in view of their structural properties,[3] pharmacological activities,[4] and usefulness as building blocks for the synthesis of numerous biologically active compounds such as β-lactams and β-peptides.[4,5] Good to excellent optical yields of β-alkyl-substituted β-amino acids have been obtained by employing some chiral diphosphine−rhodium complexes (such as Rh complexes of BICP,[6a] DuPhos,[6a,b] MiniPhos,[6c] BDPMI,[6d] and TangPhos[6e]) in the catalytic asymmetric hydrogenation of the corresponding prochiral substrates. However, the application of ruthenium complexes as catalysts in the asymmetric hydrogenation of β-(acylamino)acrylates is rather limited. More recently, Zhang[7a] reported the first highly enantioselective hydrogenation of β-aryl-substituted β-(acylamino)acrylates catalyzed by Ru complexes with a new family of ortho-substituted BINAPO ligands. As for the Ru-catalyzed asymmetric hydrogenation of β-alkyl-substituted (acylamino)acrylates, Noyori and co-workers[7b] have studied a few substrates based on the Ru$(OCOCH_3)_2$(BINAP) catalyst system and the optical yields of most products obtained from (*E*)-isomers of substrates were about 90%, the highest ee being 96%.

SCHEME 1



(*R*)-**1a**, Ar = C_6H_5, (*R*)-P-Phos
(*R*)-**1b**, Ar = 4-$CH_3C_6H_4$, (*R*)-Tol-P-Phos
(*R*)-**1c**, Ar = 3,5-$(CH_3)_2C_6H_3$, (*R*)-Xyl-P-Phos

We have previously demonstrated the effectiveness of a class of chiral dipyridylphosphine ligands (Scheme 1) P-Phos (**1a**, P-Phos = 2,2′,6,6′-tetramethoxy-4,4′-bis-(diphenylphosphino)-3,3′-bipyridine),[8a,8b] Tol-P-Phos (**1b**, Tol-P-Phos = 2,2′,6,6′-tetramethoxy-4,4′-bis[di(*p*-tolyl)-phosphino]-3,3′-bipyridine),[8c] and Xyl-P-Phos (**1c**, Xyl-P-Phos = 2,2′,6,6′-tetramethoxy-4,4′-bis[di(3,5-dimethylphenyl)phosphino]-3,3′-bipyridine)[8d] in the enantioselective Ru-catalyzed hydrogenation of β-ketoesters,[8b−d] 2-(6′-methoxy-2′-naphthyl)propenoic acid,[8a,b] and aromatic ketones.[8e]

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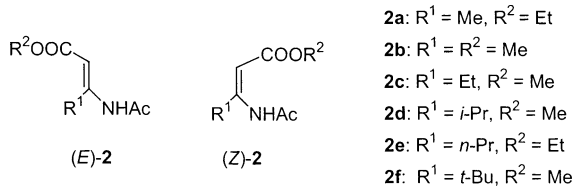
SCHEME 2



Herein, we present a highly enantioselective hydrogenation system for a variety of β-akyl-substituted (*E*)-β-(acylamino)acrylates ((*E*)-**2a**−**f**, Scheme 2) by using Ru-((*R*)-Xyl-P-Phos)(C_6H_6)Cl_2 (**cat. 1c**) as a catalyst precursor. The hydrogenation of the corresponding (*Z*)-isomers of **2** catalyzed by the Ru- or Rh-Xyl-P-Phos complex was studied as well.

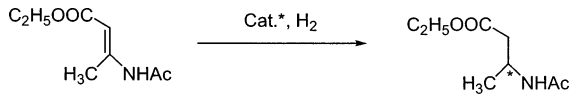
According to the reported procedures,[6a,d,7b] substrates **2a**−**f** were conveniently obtained in the form of the mixture of (*E*)-/(*Z*)-isomers with the exception of **2f**, which only existed as the (*E*)-isomer. The (*E*)- and (*Z*)-isomers can be separated by silica gel column chromatography. Ruthenium complexes, RuL*(C_6H_6)Cl_2 [L* = (*R*)-P-Phos (**cat. 1a**), (*R*)-Tol-P-Phos (**cat. 1b**),[8c] (*R*)-Xyl-P-Phos (**cat. 1c**)[8d]], were prepared by mixing [$RuCl_2$ (C_6H_6)]$_2$ with the corresponding dipyridylphosphine ligands in an 8:1 mixture of ethanol−benzene at 50−60 °C for 1 h according to Mashima et al.'s method.[9] The rhodium complexes, RhL*(COD)BF_4 [L* = (*R*)-P-Phos (**cat. 2a**), (*R*)-Tol-P-Phos (**cat. 2b**), (*R*)-Xyl-P-Phos (**cat. 2c**)], were prepared in situ by mixing Rh(COD)$_2BF_4$ with 1.05 equiv of the corresponding dipyridylphosphine ligand in dichloromethane under a nitrogen atmosphere.

In the preliminary study, a number of experiments were performed using (*E*)-ethyl 3-acetamino-2-butenoate ((*E*)-**2a**) as a model substrate and Ru-Xyl-P-Phos (**cat. 1c**) as a catalyst to find the optimal conditions for the asymmetric hydrogenation reaction (Table 1). The conversion yields and enantioselectivities were largely dependent on the solvent. **Cat. 1c** showed lower or almost no catalytic activity in aprotic solvents such as acetone, CH_2Cl_2, toluene, or THF (entries 1−4). Protic solvents such as methanol and ethanol led to dramatic improvements in the activity and enantioselectivity, and methanol appeared to be the best choice (entries 5 and 6). A study of the effect of the hydrogen pressure indicated that a lower H_2 pressure gave a slightly higher product ee (entries 6 and 7 vs entries 8 and 9). Further investigations demonstrated that the reaction proceeded smoothly in methanol at ambient temperature with 4 atm of an initial hydrogen pressure for 6 h to give a quantitative yield of the product with 97.4% ee (entry 11). A lower reaction temperature gave a higher enantioselectivity at the expense of the reaction rate. For instance, when the reaction was carried out at 0 °C for 20 h, the desirable product (*S*)-**3a** was obtained in 95% yield with 97.9% ee (entry 12).

Under the preferred reaction conditions, the metal and ligand effects on the hydrogenation reaction were examined (Table 1, entry 11 and entries 13−17) and Ru-Xyl-P-Phos complex (**cat. 1c**) was found to be the most effective catalyst. Under otherwise identical conditions, Ru complexes (**cat. 1a**−**c**) exhibited far superior activity and enantioselectivity to Rh complexes (**cat. 2a**−**c**) irrespective of the ligand used (entries 11, 13, and 14 vs entries 15−17). In addition, these ligands (**1a**−**c**) exhibited different catalytic properties and trends when different transition metal ions were used in the asymmetric hydrogenation. In the Ru catalyst system, the steric hindrance effect of the ligand enhanced the rate and enantioselectivity of the reaction. For example, at ambient temperature and under 4 atm of initial hydrogen pressure, the reaction was completed in 6 h with 97.4% ee when Ru-Xyl-P-Phos (**cat. 1c**) was employed (entry 11), whereas in the case of Ru-P-Phos (**cat. 1a**), the catalytic activity and enantioselectivity were substantially lower (84.8% conversion after 24 h, 89.4% ee, entry 13). In the Rh catalyst system, the steric hindrance effect of the ligand on the stereoselectivity was completely opposite to the corresponding Ru-catalyzed hydrogenations. Interestingly, the hydrogenation products catalyzed by Rh and Ru complexes with the same chiral ligand were found to be of opposite configurations (entries 11, 13, and 14 vs entries 15−17).

The asymmetric hydrogenation of a variety of β-alkyl-substituted (*E*)-β-(acylamino)acrylates ((*E*)-**2b**−**f**) catalyzed by **cat. 1c** was studied, and consistently high enantioselectivities were obtained in all cases (Table 2). Substrate (*E*)-**2f** with a bulky alkyl substituent gave the best ee (up to 99.7%, Table 2, entry 10). To the best of our knowledge, the results summarized in Table 2 represent the highest enantioselectivities obtained by

TABLE 1. Asymmetric Hydrogenation of (*E*)-Ethyl-3-acetamido-2-butenoate ((*E*)-2a)[a]



(*E*)-**2a** → **3a**

entry	catalyst	solvent	p_{H_2} (atm)	temp (°C)	time (h)	conversion (%)[b]	ee (%)[b]
1	(*R*)-**cat. 1c**	acetone	4	rt	24	11.8	13.4 (*S*)
2	(*R*)-**cat. 1c**	CH_2Cl_2	4	rt	24	5.4	c
3	(*R*)-**cat. 1c**	toluene	4	rt	24	<1	c
4	(*R*)-**cat. 1c**	THF	4	rt	24	33.2	40.3 (*S*)
5	(*R*)-**cat. 1c**	EtOH	4	rt	24	99.7	96.6 (*S*)
6	(*R*)-**cat. 1c**	MeOH	4	rt	12	>99.9	97.3 (*S*)
7	(*R*)-**cat. 1c**	MeOH	1	rt	12	99.4	97.3 (*S*)
8	(*R*)-**cat. 1c**	MeOH	18	rt	12	>99.9	96.7 (*S*)
9	(*R*)-**cat. 1c**	MeOH	35	rt	12	>99.9	96.0 (*S*)
10	(*R*)-**cat. 1c**	MeOH	4	rt	4	87.3	97.2 (*S*)
11	(*R*)-**cat. 1c**	MeOH	4	rt	6	>99.9	97.4 (*S*)
12	(*R*)-**cat. 1c**	MeOH	4	0	20	95.2	97.9 (*S*)
13	(*R*)-**cat. 1a**	MeOH	4	rt	24	84.8	89.4 (*S*)
14	(*R*)-**cat. 1b**	MeOH	4	rt	6	>99.9	93.8 (*S*)
15	(*R*)-**cat. 2a**	MeOH	4	rt	24	55.9	41.0 (*R*)
16	(*R*)-**cat. 2b**	MeOH	4	rt	24	66.4	38.2 (*R*)
17	(*R*)-**cat. 2c**	MeOH	4	rt	24	72.2	28.9 (*R*)

[a] Reaction conditions: 3.4 mg of substrate; substrate/catalyst = 100 (M/M); substrate concentration = 0.05−0.09 M. [b] Conversions were determined by NMR and GC analysis. Ee values were determined by chiral GC with a 25 m × 0.25 mm Chrompack Chirasil-DEX CB column. The absolute configuration was determined by comparing the retention time with that from the literature (ref 6). [c] Ee value could not be determined accurately due to the low conversion.

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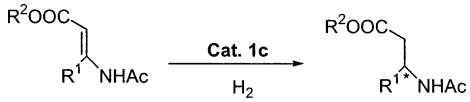
TABLE 2. Ru-Catalyzed Asymmetric Hydrogenation of (*E*)-*β*-(Acylamino)acrylates

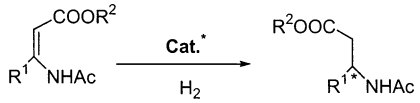


(*E*)-**2** 3

entry	substrate	R^1	R^2	p_{H_2} (atm)	temp (°C)	time (h)	conversion (%)[b]	ee (%)[b]
1	(*E*)-**2b**	Me	Me	4	rt	6	>99.9	97.3 (*S*)
2	(*E*)-**2b**	Me	Me	8	0	30	99.3	98.1 (*S*)
3	(*E*)-**2c**	Et	Me	4	rt	6	>99.9	97.3 (*S*)
4	(*E*)-**2c**	Et	Me	8	0	30	>99.9	98.2 (*S*)
5	(*E*)-**2d**	*i*-Pr	Me	4	rt	6	>99.9	97.4 (*R*)
6	(*E*)-**2d**	*i*-Pr	Me	8	0	30	>99.9	98.3 (*R*)
7	(*E*)-**2e**	*n*-Pr	Et	4	rt	6	99.4	97.6 (*S*)
8	(*E*)-**2e**	*n*-Pr	Et	8	0	30	98.3	98.5 (*S*)
9	(*E*)-**2f**	*t*-Bu	Me	4	rt	6	>99.9	99.4 (*R*)
10	(*E*)-**2f**	*t*-Bu	Me	8	0	30	>99.9	99.7 (*R*)

[a] Reaction conditions: 3−4 mg of substrate; substrate concentration = 0.05−0.09 M in MeOH; substrate/catalyst = 100 (M/M). [b] Conversions were determined by NMR and GC analysis. Ee values were determined by chiral GC with a 25 m × 0.25 mm Chirasil-DEX CB column or 30 m × 0.25 mm *γ*-DEX-225 column. The absolute configuration was determined by comparing the retention time or the sign of optical rotation with those reported in the literature (ref 6).

TABLE 3. Rh-Catalyzed Asymmetric Hydrogenation of (*Z*)-*β*-(Acylamino)acrylates[a]



(*Z*)-**2** 3

entry	substrate	catalyst	solvent	p_{H_2} (atm)	time (h)	conversion (%)	ee (%)[b]
1	(*Z*)-**2a**	(*R*)-**cat. 1c**	MeOH	4	6	>99.9	37.5 (*R*)
2	(*Z*)-**2a**	(*R*)-**cat. 1c**	CH_2Cl_2	8	12	5.8	7.8 (*S*)
3	(*Z*)-**2a**	(*R*)-**cat. 1c**	THF	8	12	2.5	10.7 (*S*)
4	(*Z*)-**2a**	(*R*)-**cat. 2c**	MeOH	4	6	70.7	11.5 (*S*)
5	(*Z*)-**2a**	(*R*)-**cat. 2c**	CH_2Cl_2	8	12	31.9	59.3 (*R*)
6	(*Z*)-**2a**	(*R*)-**cat. 2c**	Toluene	8	12	33.6	67.2 (*R*)
7	(*Z*)-**2a**	(*R*)-**cat. 2c**	THF	8	12	74.0	66.7 (*R*)
8	(*E*)-**2a**	(*R*)-**cat. 2c**	THF	8	6	66.7	61.0 (*R*)
9	(*Z*)-**2a**	(*R*)-**cat. 2c**	THF	8	30	99.4	68.3 (*R*)
10	(*Z*)-**2a**	(*R*)-**cat. 2c**	THF	1	48	83.8	57.8 (*R*)
11	(*Z*)-**2a**	(*R*)-**cat. 2c**	THF	35	24	>99.9	68.3 (*R*)
12	(*Z*)-**2a**	(*R*)-**cat. 2a**	THF	8	12	40.1	55.8 (*R*)
13	(*Z*)-**2a**	(*R*)-**cat. 2b**	THF	8	30	96.9	57.7 (*R*)
14	(*Z*)-**2b**	(*R*)-**cat. 2c**	THF	8	30	>99.9	71.9 (*R*)
15	(*Z*)-**2c**	(*R*)-**cat. 2c**	THF	8	30	>99.9	79.7 (*R*)
16	(*Z*)-**2d**	(*R*)-**cat. 2c**	THF	8	30	>99.9	82.3 (*S*)
17	(*Z*)-**2e**	(*R*)-**cat. 2c**	THF	8	30	99.4	78.5 (*R*)

[a] Reaction conditions: 3−4 mg of substrate; substrate concentration = 0.05−0.09 M; substrate/catalyst = 100 (M/M). [b] Conversions were determined by NMR and GC analysis. Ee values were determined by chiral GC with a 25 m × 0.25 mm Chirasil-DEX CB column or 30 m × 0.25 mm *γ*-DEX-225 column. The absolute configuration was determined by comparing the retention time or the sign of optical rotation with those reported in the literature (ref 6).

using the chiral Ru catalyst in the hydrogenation of alkyl-substituted (*E*)-*β*-(acylamino)acrylates.

On account of the fact that the catalytic properties highly rely on the (*E*)- or (*Z*)-isomers of *β*-(acylamino)-acrylates, **cat. 1c** was then employed in the hydrogenation of (*Z*)-**2a** to investigate its catalytic behavior. When the reaction was conducted in methanol, under the identical hydrogenation conditions for (*E*)-**2a**, an opposite enantiomer (*R*)-**3a** was obtained in only 37.5% ee (Table 3, entry 1). With CH_2Cl_2 or THF as a solvent, **cat. 1c** showed much lower activity and enantioselectivity and provided **3a** in an (*S*)-enantiomer (entries 2 and 3). The effects of the conventional cationic rhodium complexes [Rh(COD)((*R*)-P-Phos)]BF_4 (**cat. 2c**) in the hydrogenation of (*Z*)-**2a** were also studied and compared favorably with those of Ru-Xyl-P-Phos (**cat. 1c**). The asymmetric hydrogenation could be carried out in a variety of common organic solvents (entries 4−7), and the aprotic solvent THF was found to be the best one (entry 7). Unlike the Ru-catalyzed (**cat. 1c**) asymmetric hydrogenation of **3a**, the Rh-catalyzed (**cat. 2c**) hydrogenation of **3a** showed to be insensitive to the olefin geometry (entry 8 vs entry 7) and a higher initial H_2 pressure led to increases in the enantioselectivity and reaction rate (entries 9 and 11 vs entry 10). In contrast to the Rh-catalyzed hydrogenation of (*E*)-**2a** (Table 1, entries 15−17), sterically encumbered ligands favor higher enantioselectivities in the case of Rh-catalyzed hydrogenation of (*Z*)-**2a** (Table 3, entry 9 vs entries 12 and 13). Further studies confirmed that **cat. 2c** was also effective for hydrogenating other *β*-alkyl-substituted (*Z*)-*β*-(acylamino)acrylates ((*Z*)-**2b**−**e**) leading to moderate to good enantioselectivities (71.9−82.3%, entries 14−17).

In conclusion, highly enantioselective hydrogenation of the (*E*)-isomers of *β*-alkyl-substituted *β*-(acylamino)-acrylates with Ru-Xyl-P-Phos (**cat. 1c**) as a catalyst was observed in this study. Moderate to good enantioselectivities in the hydrogenation of (*Z*)-isomers in the presence of Rh-Xyl-P-Phos catalyst (**cat. 2c**) were also achieved. In addition, the results demonstrated that the electronic and steric properties of the dipyridylphosphine ligands (**1a**−**c**) as well as the different transition metal ions have significant influences on the catalytic properties in the hydrogenation of *β*-(acylamino)acrylates.

Experimental Section

General and Materials. All manipulations involving air-sensitive reagents were carried out under a dry nitrogen atmosphere. The hydrogenation reactions were performed in a 50 mL stainless steel autoclave. Commercial reagents were used as received without further purification unless otherwise stated. All solvents used were dried using standard, published methods and were distilled before use. Optically pure P-Phos (**1a**), Tol-P-Phos (**1b**), and Xyl-P-Phos (**1c**) as well as their Ru complexes were synthesized according to our previously reported procedures.[8a−d] Substrates (Scheme 2) were prepared according to methods previously reported.[6a,d,7b]

Preparation of a Stock Solution of [Rh((*R*)-1a)(COD)]-BF_4, Cat. 2a. Under a nitrogen atmosphere, $[Rh(COD)_2]BF_4$ (4.1 mg, 0.01 mmol) was dissolved in CH_2Cl_2 (0.5 mL). A solution of (*R*)-**1a** (6.8 mg, 0.0105 mmol) in CH_2Cl_2 (0.5 mL) was added dropwise to the above solution with stirring. The reaction mixture was stirred overnight to give a solution of [Rh((*R*)-**1**)-(COD)]BF_4 (**cat. 2a**, 0.01 M).

Preparation of a Stock Solution of [Rh((*R*)-1b)(COD)]-BF_4, Cat. 2b. A stock solution of **cat. 2b** was prepared in a similar fashion as that for the preparation of **cat. 2a**.

Preparation of a Stock Solution of [Rh((*R*)-1c)(COD)]-BF_4, Cat. 2c. A stock solution of **cat. 2c** was prepared in a similar fashion as that for the preparation of **cat. 2a**.

Typical Procedure for the Asymmetric Hydrogenation. A solution of 1.94×10^{-3} M **cat. 1c** in methanol (103 μL, 2.0×10^{-4} mmol), (*E*)-ethyl 3-acetamino-2-butenoate ((*E*)-**2a**, 3.4

mg, 0.02 mmol), and methanol (150 μL) were charged to a 50 mL autoclave equipped with a magnetic stirring bar under a nitrogen atmosphere. Hydrogen was initially introduced into the autoclave at a pressure of 8 atm before being reduced to 1 atm by carefully releasing the stop valve. After this procedure was repeated for three times, the vessel was pressurized to 4 atm. The reaction mixture was stirred at room temperature for 6 h before releasing the H_2. The conversion and the enantiomeric excess of the product (*S*)-ethyl 3-acetamidobutanoate ((*S*)-**3a**) were determined by NMR and chiral GC analysis to be >99.9% and 97.4%, respectively (column, Chirasil-DEX CB; 25 m × 0.25 mm, carrier gas = N_2).

Ethyl 3-Acetamidobutanoate (3a). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.20 (d, J = 7.0 Hz, 3H), 1.25 (t, J = 7.2 Hz, 3H), 1.95 (s, 3H), 2.42−2.53 (m, 2H), 4.13 (q, J = 6.7 Hz, 2H), 4.30−4.35 (m, 1H), 6.28 (br, 1H). Capillary GC, Chirasil-DEX CB column, 140 °C, isothermal. (*S*) t_1 = 11.84 min, (*R*) t_2 = 12.78 min.

Methyl 3-Acetamidobutanoate (3b). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 1.22 (d, J = 6.5 Hz, 3H), 1.96 (s, 3H), 2.48−2.57 (m, 2H), 3.69 (s, 3H), 4.32−4.37 (m, 1H), 6.14 (br, 1H). Capillary GC, Chirasil-DEX CB column, 135 °C, isothermal. (*S*) t_1 = 11.19 min, (*R*) t_2 = 11.98 min.

Methyl 3-Acetamidopentanoate (3c). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.91 (t, J = 7.5 Hz, 3H), 1.52−1.59 (m, 2H), 1.99 (s, 3H), 2.53 (d, J = 5.5 Hz, 2H), 3.68 (s, 3H), 4.02−4.05 (m, 1H), 6.04 (br, 1H). Capillary GC, Chirasil-DEX CB column, 140 °C, isothermal. (*S*) t_1 = 20.48 min, (*R*) t_2 = 21.27 min.

Methyl 4-Methyl-3-acetamidopentanoate (3d). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.91 (q, J = 7.0 Hz, 6H), 1.78−1.86 (m, 1H), 1.99 (s, 3H), 2.53−2.58 (m, 2H), 3.67 (s, 3H), 4.11−4.17 (m, 1H), 6.22 (br, 1H). Capillary GC, γ-DEX-225 column, 142 °C, isothermal. (*S*) t_1 = 44.69 min, (*R*) t_2 = 45.66 min.

Ethyl 3-Acetamidohexanoate (3e). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.89 (t, J = 7.0 Hz, 3H), 1.25 (t, J = 7.25 Hz, 3H), 1.27−1.37 (m, 2H), 1.42−1.54 (m, 2H), 1.96 (s, 3H), 2.45−2.55 (m, 2H), 4.09−4.16 (m, 2H), 4.20−4.25 (m, 1H), 6.19 (br, 1H). Capillary GC, γ-DEX-225 column, 135 °C, isothermal. (*S*) t_1 = 43.13 min, (*R*) t_2 = 44.38 min.

Methyl 4,4-Dimethyl-3-acetamidopentanoate (3f). ^{1}H NMR ($CDCl_3$, 500 MHz): δ 0.92 (s, 9H), 2.02 (s, 3H), 2.24−2.61 (m, 2H), 3.66 (s, 3H), 4.21−4.25 (m, 1H), 5.96 (br, 1H). Capillary GC, γ-DEX-225 column, 145 °C, isothermal. (*S*) t_1 = 22.07 min, (*R*) t_2 = 23.27 min.

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