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Hydrogenation of β-*N*-substituted enaminoesters in the presence of ruthenium catalysts

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ABSTRACT

β-Aminoesters were prepared in two simple steps from β-ketoesters derivatives and primary amines under mild conditions. Their hydrogenation was performed at 50 °C in the presence of several organometallic catalysts under acidic conditions. The new β-*N*-substituted aminoesters were isolated in moderate to good yields.

1. Introduction

Hydrogenation of enamides and imines is a reaction of substantial industrial interest and is widely used in the production of several chemicals in the agricultural, pharmaceutical and fine chemical industries [1–7]. However, imines and related C=N functional groups have some chemical peculiarities that make their reduction more complex than that of carbonyl derivatives and olefins. The C=N compounds are often sensitive to hydrolysis and the presence of *syn*/*anti* isomers as well as enamine tautomers can create problems as demonstrated for the hydrogenation of imines and oximes [8]. The nature of the *N*-substituents of the C=N functionality has more influence on the properties (basicity, reduction potential, etc.) than the nature of the substituents at the carbon atom. For example, it was found that the Ti-ebthi catalyst (ebthi = ethylenebis(tetrahydroindenyl)) can hydrogenate only *N*-alkylimines but not *N*-arylimines [9]. On the other hand, iridium catalysts have recently shown high enantioselectivity in hydrogenation of quinoxalines and *N*-arylimines, but only low ee were obtained with *N*-alkylimines [10]. Oximes and other C=N–X compounds show even a more pronounced variations in their reactivity [11].

Among the amine-containing compounds, β-amino acids are important targets in pharmaceutical industry as they are useful functional building blocks for the synthesis of β-lactams, β-peptides, antibiotics and drugs [12]. One of the most promising methods for a large scale preparation of optically pure β-amino-acids appears to be the catalytic asymmetric hydrogenation of β-acetamidoacrylates, which involves clean atom economical reactions and offers the preparation of both (*R*) and (*S*)-enantiomers [13], but suffers from the ultimate deprotection step. With β-*N*-substituted enaminoesters, the same observations, than those reported for imines, were also done. With acetyl substituent on the nitrogen atom, the hydrogenation reactions occurred within 1 h under low pressure of hydrogen in the presence of rhodium catalysts, whereas with *N*-alkyl substituent no reaction was observed (*vide infra*). Then, usually, the preparation of chiral β-amino esters from prochiral β-keto esters was associated with the hydrogenation of β-acetamidoacrylates using late transition metal catalysts bearing chiral bidentate or monodentate phosphine ligands.

In our ongoing work on hydrogenation of β-acetamidoacrylates catalyzed by chiral rhodium complexes [14], and on hydrogenation of β-*N*-substituted and β-*N*,*N*-disubstituted enaminoesters catalyzed by iridium(I) complexes [15], we report here the preparation of β-aminoesters based on hydrogenation of β-*N*-substituted enaminoesters catalyzed by ruthenium(II) species in acidic medium.

In a first set of reactions, methyl-3-*N*-benzylaminobut-2-enoate **1a** was selected as a model substrate for the hydrogenation of β-*N*-substituted enaminoesters. Whatever the reaction conditions (rhodium complexes such as [Rh(diphosphine)(COD)]BF_4 or ruthenium complexes, such as [Ru(*p*-cymene)(diphosphine)Cl]Cl and CpRu(diphosphine)Cl as precatalysts, hydrogen pressure, solvent...),

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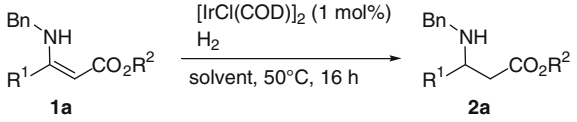
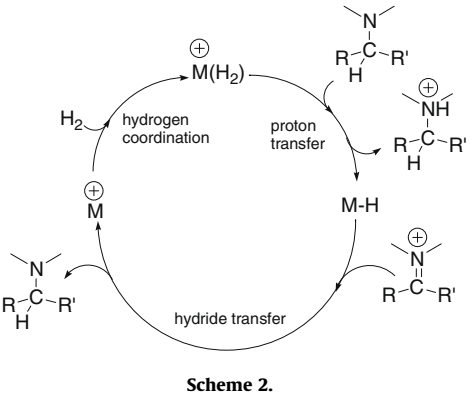
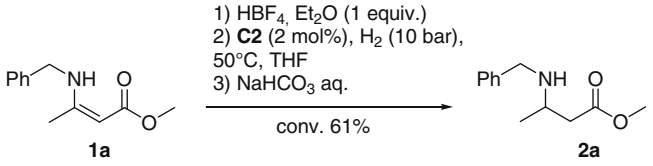


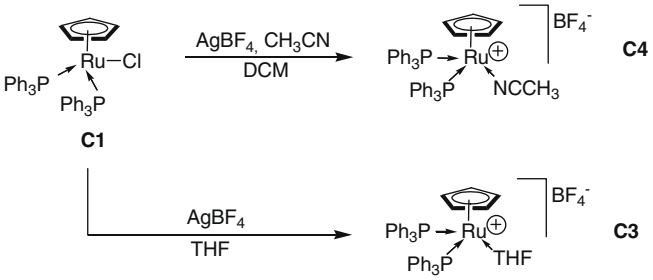
Scheme 1.



Scheme 2.



Scheme 3.



Scheme 4.

no reaction occurred. These results were in sharp contrast with those obtained in the presence of the commercially available iridium(I) dimer $[Ir(COD)Cl]_2$ (Scheme 1) [15].

Recently, Norton reported the hydrogenation of iminium cations in the presence of CpRu(diphosphine)H complexes under low pressure of hydrogen [16]. Following the proposed mechanism, the ruthenium hydride may reduce the iminium via an hydride transfer and liberate the amine. Dihydrogen might then coordinate to the cationic ruthenium species to furnish the $[Ru(H_2)]^+$ intermediate. A deprotonation step might regenerate the catalyst and liberate the ammonium salt (Scheme 2).

Based on this work, we hypothesized that, in acidic medium, the β-*N*-substituted enaminoesters might be isomerized and protonated to the corresponding iminium salts (Fig. 1), and then be reduced in the presence of a ruthenium hydride catalyst. A similar isomerization/hydrogenation was also proposed by the Merck group during their studies on the hydrogenation of non protected β-enaminoesters in the presence of rhodium complexes [6].

To validate this approach, we prepared a ruthenium hydride complex and the iminium salt. Following the procedure described by Demerseman et al., the complex $[CpRu(PPh_3)_2H]$ **C2** was obtained in 96% yield from $[CpRu(PPh_3)_2Cl]$ **C1** in refluxing methanol in the presence of 1.1 equiv. of K_2CO_3 [17]. The iminium salt was generated *in situ* by adding 1 equiv. of $HBF_4{\cdot}OEt_2$ to an ethereal solution of methyl 3-*N*-benzylaminobut-2-enoate **1a**. Then, in the presence of 2 mol% of the ruthenium complex **C2**, in THF at 50 °C for 50 h under 15 bar of hydrogen, we were pleased to observe the reduction of **1a** and the compound **2a** was obtained in a moderate but encouraging conversion (61%, Scheme 3). Without the addition of the acid, no hydrogenation occurred. The use of basic conditions also did not provide any reaction. In a protic solvent, such as methanol, the hydrogenation of the iminium salt led to the corresponding *N*-substituted aminoester but the deprotected methyl 3-aminobutanoate resulting from hydrogenolysis of the *N*-benzyl group was also formed.

As proposed by Norton in Scheme 2, a cationic intermediate might be involved in the catalytic cycle. These cationic ruthenium complexes would be more stable and easier to handle than the corresponding hydride species. Then, in order to improve the practical aspect of this process, we synthesized two cationic ruthenium complexes (**C3** and **C4**) bearing either a THF or an acetonitrile ligand in nearly quantitative yields by halide abstraction in the presence of 1 equiv. of silver tetrafluoroborate at room temperature in THF or a mixture dichloromethane/acetonitrile, respectively

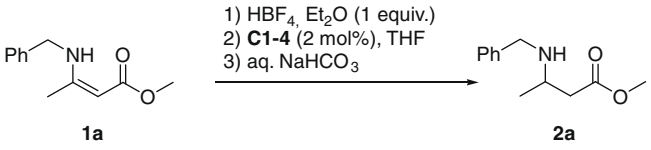


Table 1
Hydrogenation of methyl β-benzylaminoacrylate **1a**.[a]

Entry	Catalyst	*t* (h)	Conv. (%)[b]
1	**C2**	50	61
2	**C3**	16	42
3	**C4**	50	2
4[c]	**C1**	2	50[f]
5[d]	**C1**	2	50
6[d]	**C1**	4	65
7[e]	**C1**	2	80
8	**C1**	2	76

[a] The hydrogenation reactions were carried out with 0.5 mmol of enaminoester **1a**, 0.5 mmol of HBF_4 and 2% of ruthenium precatalyst **C1–4** in 5 mL of THF under 10 bar of hydrogen at 50 °C.
[b] As determined by ^1H NMR spectroscopy.
[c] 1 mol% of catalyst in methanol.
[d] 2 mol% of catalyst in methanol.
[e] 1 mol% of catalyst in methanol under 20 bar of H_2.
[f] Debenzylation was observed.

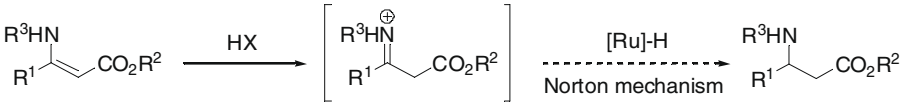


Fig. 1. Work hypothesis for the hydrogenation of β-*N*-substituted enaminoesters.

(Scheme 4). Complexes **C3** and **C4** were isolated in 93% and 97%, respectively.

As shown in Table 1, when the complex **C3** was used in the reduction of the *in situ* generated iminium salt, an improved conversion was noticed (42% within 16 h with **C3** vs. 61% within 50 h with **C2**). On the other hand, using complex **C4**, almost no conversion was observed after 50 h of reaction time. The lack of reactivity might be explained by the strong coordination of the acetonitrile ligand to the ruthenium center avoiding coordination of hydrogen and generation of hydride species. Our initial hypothesis based on reduction of an iminium salt was validated by these results. However, despite the greater reactivity of **C3**, this complex was not very stable and not easy to handle, and we finally tested **C1** as stable precursor of complexes **C2–4,** as precatalyst. We were pleased to observe the formation of the β-aminoester **2a** in various solvents such as methanol or THF, but sometimes accompanied by the debenzylated derivative when the hydrogenation was carried out in methanol (Table 1). It is worth noting that the hydrogenation rate in the presence of $[CpRu(PPh_3)_2Cl]$ **C1** was higher than in the presence of catalysts **C2–4,** and that **C1** was completely air stable and moisture insensitive.

We then explored the catalytic activity of various ruthenium precursors in this hydrogenation reaction (Table 2). Ruthenium(arene) precursors are well-known precatalysts for the reduction of carbonyl functions [18]; they might then be also active in the hydrogenation of iminium derivatives [16]. The first attempt with ruthenium bidentate bipyridine complex [RuCl(bipyridine)(*p*-cymene)]Cl **C5** in THF at 50 °C under 10 bar of hydrogen gave no conversion. However, the use of complexes bearing phosphine ligands provided better results (Table 2, entries 2–10). Under the same reaction conditions, moderate conversions (up to 39%) were obtained with bidentate dppe, dppp and dppb as ligands. The use of monodentate PMe_3 or $P(OMe)_3$ as ligand improved this procedure and conversions of 58% and 48%, respectively, were obtained (Table 2, entries 6–7). Finally, the neutral complex **C11** containing the monophosphine PPh_3 led to the best results as the hydrogenation of **1a** in the presence of this precursor provided the aminoester **2a** in 78% conversion within 2 h (Table 2, entry

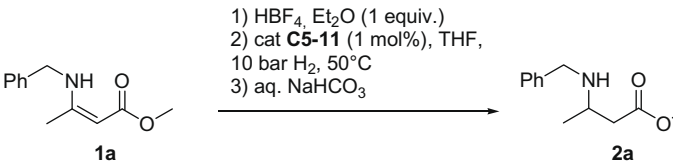


Table 2
Hydrogenation of methyl β-benzylaminoacrylate **1a** with various ruthenium precatalyst.[a]

Entry	Catalyst	*t* (h)	Conv. (%)[b]
1	[RuCl(bipy)(*p*-cymene)]Cl **C5**	16	0
2	[RuCl(dppe)(*p*-cymene)]Cl **C6**	2	22
3	[RuCl(dppe)(*p*-cymene)]Cl **C6**	4	33
4[c]	[RuCl(dppp)(*p*-cymene)]Cl **C7**	2	32
5[c]	[RuCl(dppb)(*p*-cymene)]Cl **C8**	2	39
6	$RuCl_2(PMe_3)$(*p*-cymene) **C9**	4	58
7	$RuCl_2(P(OMe)_3)$(*p*-cymene) **C10**	4	48
8	$RuCl_2(PPh_3)$(*p*-cymene) **C11**	2	78
9	$RuCl_2(PPh_3)$(*p*-cymene) **C11**	4	85
10	$RuCl_2(PPh_3)$(*p*-cymene) **C11**	6	96

[a] The hydrogenation reactions were carried out with 0.5 mmol of enaminoester **1a,** 0.5 mmol of HBF_4 and 1% of ruthenium precatalyst **C5–11** in 5 mL of THF under 10 bar of hydrogen at 50 °C.
[b] As determined by ^1H NMR spectroscopy.
[c] Only one phosphine was coordinated to the ruthenium center.

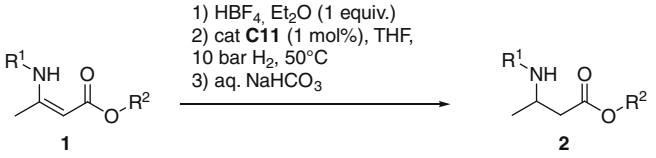


Table 3
Hydrogenation of alkyl β-*N*-substituted aminoacrylate **1**.[a]

Entry	R^1	R^2	Aminoester **2**	*t* (h)	Yield (%)[b]
1	Bn	Me	**2a**	6	96
2	Bn	Et	**2b**		70
3	Ph	Me	**2c**	16	98
4[c]	Ph	Me	**2c**	16	100
5[c]	Ph	Et	**2d**	16	100
6[c]	Ph	*t*-Bu	**2f**	16	100
7	Bu	Me	**2d**	16	95
8	*i*-Pr	Me	**2e**	12	90

[a] The hydrogenation reactions were carried out with 0.5 mmol of enaminoester **1**, 0.5 mmol of HBF_4 and 1% of ruthenium precatalyst **C11** in 5 mL of THF under 10 bar of hydrogen at 50 °C.
[b] Isolated yield after purification on silica gel.
[c] In a 2:1 mixture of CH_2Cl_2:THF.

8). Increasing the reaction time to 6 h enhanced the conversion and the aminoester **2a** was obtained in almost quantitative yield (Table 2, entry 10).

With this optimized catalytic system in hand, we explored the scope of the hydrogenation reaction by using a variety of β-*N*-substituted-enaminoesters (Table 3). In all reactions, whatever the *N*-alkyl or *N*-aryl substituent, the conversions were complete and isolated yields were excellent. The hydrogenation occurred usually within 16 h. As compared to our previous studies in iridium-catalyzed hydrogenation under neutral conditions, there is no difference of reactivity between the *N*-aryl and *N*-alkyl substituted enaminoesters in terms of yields and reaction rate.

In conclusion, we have found a new general procedure for the synthesis of a range of β-*N*-substituted aminoesters via catalytic hydrogenation of β-*N*-substituted enaminoesters in acidic conditions in the presence of ruthenium complexes. Further efforts are now devoted to the asymmetric version of this transformation.

2. Experimental section

2.1. General

Purifications by column chromatography were performed with 70–230 mesh silica gel. TLC analysis were carried out on alumina sheets precoated with silica gel (60 F254) and visualized with UV light; NMR spectra were recorded with a Bruker Avance DRX 500 FT spectrometer [200.13 MHz (^1H) and 50.33 MHz (^{13}C)] or a Bruker AH 300 FT spectrometer [300.13 MHz (^1H) and 75.45 MHz (^{13}C)]. Chemical shifts are expressed in ppm downfield from TMS. High-resolution mass spectra were obtained with a Varian Mat 311 double focussing instrument at the CRMPO "Centre de Mesures Physiques de l'Ouest" with a source temperature of 170 °C. An ion accelerating potential of 3 kV and ionising electrons of 70 eV were used. All commercially available reagents were used as supplied. Solvents were freshly distilled and kept under argon flush.

2.2. General procedure for the preparation of β-aminoesters

In a 25 mL stainless steel autoclave were placed under an argon atmosphere, the *N*-substituted β-amino acrylates (0.5 mmol,

1 equiv.), the ruthenium precatalyst (0.005 mmol, 1% mol). The mixture was degassed by three vacuum-filling with argon cycles before adding 5 mL of degassed and distilled CH_2Cl_2. Then, the autoclave was purged three times by hydrogen and the vessel was pressurized to 10 bar of hydrogen. At the end of the reaction (see text) at 50 °C, the autoclave was carefully opened; the solvent was removed under reduced pressure. Conversion was determined by ^{1}H NMR analysis of the crude mixture. Subsequently, the residue was purified by purification on silica gel, eluted with a 1:1 mixture of heptane and AcOEt.

2.3. Methyl 3-(benzylamino)-butanoate (**2a**)

^{1}H NMR (300.13 MHz, $CDCl_3$), δ ppm: 1.15 (d, J = 6 Hz, 3H), 2.44 (ABX, J_{AB} = 15 Hz, J_{AX} = 6 Hz, J_{BX} = 6 Hz, 2H), 3.16 (m, 1H), 3.66 (s, 3H), 3.79 (AB, J_{AB} = 12 Hz, 2H), 7.20-7.34 (m, 5H). ^{13}C NMR (75.03 MHz, $CDCl_3$), δ ppm: 20.5, 41.4, 49.7, 51.2, 51.5, 126.9, 128.1, 128.4, 140.4, 172.8. HRMS Calc. for $C_{11}H_{14}NO_2$ $[M-CH_3]^+$: 192.1024. Found: 192.1013.

2.4. Ethyl 3-(benzylamino)-butanoate (**2b**)

^{1}H NMR (300.13 MHz, $CDCl_3$), δ ppm: 1.15 (d, J = 6 Hz, 3H), 1.24 (t, J = 7.5, 3H), 2.42 (ABX, J_{AB} = 15 Hz, J_{AX} = 6 Hz, J_{BX} = 6 Hz, 2H), 3.16 (m, 1H), 3.79 (AB, J_{AB} = 12 Hz, 2H), 4.12 (q, J = 7 Hz, 2H), 7.20–7.35 (m, 5H). ^{13}C NMR (75.03 MHz, $CDCl_3$), δ ppm: 14.2, 20.5, 41.7, 49.7, 51.2, 60.3, 126.9, 128.1, 128.4, 140.4, 172.3. HRMS Calc. for $C_{12}H_{16}NO_2$ $[M-CH_3]^+$: 206.1181. Found: 206.1196.

2.5. Methyl 3-(phenylamino)-butanoate (**2c**)

^{1}H NMR (300.13 MHz, $CDCl_3$), δ ppm: 1.30 (d, J = 6 Hz, 3H), 2.56 (ABX, J_{AB} = 15 Hz, J_{AX} = 6 Hz, J_{BX} = 6 Hz, 2H), 3.70 (s, 3H), 3.97 (m, 1H), 6.64–6.76 (m, 3H), 7.09-7.37 (m, 2H). ^{13}C NMR (75.03 MHz, $CDCl_3$), δ ppm: 20.7, 40.8, 46.0, 51.6, 113.6, 117.7, 129.4, 146.8, 172.3. HRMS Calc. for $C_{11}H_{15}NO_2$: 193.1103. Found: 193.1096.

2.6. Ethyl 3-(phenylamino)butanoate (**2d**)

^{1}H-NMR (300.13 MHz, $CDCl_3$), δ ppm: 1.26(d, J = 6 Hz, 3H), 1.30 (t, J = 4.5 Hz, 3H), 2.54 (ABX, J_{AB} = 15 Hz, J_{AX} = 6 Hz, J_{BX} = 6 Hz, 2H), 3.96 (m, 1H), 4.16 (q, J = 7 Hz, 2H), 6.62–6.75 (m, 3H), 7.15–7.23 (m, 2H). ^{13}C NMR (75.03 MHz, $CDCl_3$), δ ppm: 14.3, 20.6, 41.1, 46.0, 60.5, 113.6, 117.6, 129.4, 146.9, 171.8.

HRMS Calc. for $C_{12}H_{17}NO_2$: 207,1259. Found: 207.1276.

2.7. Tert-butyl 3-(phenylamino)butanoate (**2e**)

^{1}H NMR (300.13 MHz, $CDCl_3$), δ ppm: 1.29 (d, J = 6 Hz, 3H), 1.47 (s, 9H), 2.46 (ABX, J_{AB} = 15 Hz, J_{AX} = 6 Hz, J_{BX} = 6 Hz, 2H), 3.92 (m, 1H), 6.61–6.75 (m, 3H), 7.16–7.23 (m, 2H). ^{13}C NMR (75.03 MHz, $CDCl_3$), δ ppm: 20.5, 28.1, 42.3, 46.2, 80.7, 113.5, 117.5, 129.3, 147.0, 171.2.

HRMS Calc. for $C_{10}H_{13}NO_2$ $[M-C_4H_8]^+$: 179.0946. Found : 179.0958.

2.8. Methyl 3-(butylamino)-butanoate (**2f**)

^{1}H-NMR (300.13 MHz, $CDCl_3$), δ ppm: 0.89 (t, J = 7,5 Hz, 3H), 1.09 (d, J = 6 Hz, 3H), 1.32 (m, 2H), 1.42 (m, 2H), 2.38 (ABX, J_{AB} = 15 Hz, J_{AX} = 6 Hz, J_{BX} = 6 Hz, 2H), 2.57 (m, 2H), 3.07 (m,1H), 3.66 (s, 3H). ^{13}C NMR (75.03 MHz, $CDCl_3$), δ ppm: 14.0, 20.5, 20.6, 32.4, 41.3, 46.8, 50.2, 51.4, 172.9. HRMS Calc. for $C_9H_{19}NO_2$: 173.1416. Found: 173,1423.

2.9. Methyl 3-(iso-propylamin)-butanoate (**2g**)

^{1}H NMR (300.13 MHz, $CDCl_3$), δ ppm: 0.98 (dd, J = 6 Hz, 12 Hz, 6H), 1.04 (d, J = 6 Hz, 3H), 2.32 (ABX, J_{AB} = 15 Hz, J_{AX} = 7.5 Hz, J_{BX} = 9 Hz, 2H), 2.83 (m, 1H), 3.12 (m, 1H), 3.61 (s, 3H). ^{13}C NMR (75.03 MHz, $CDCl_3$), δ ppm: 20.9, 22.9, 23.5, 41.7, 45.2, 47.1, 51.3, 172.7. HRMS Calc. for $C_8H_{17}NO_2$: 159.1259. Found: 159.1271.

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