



HAL
open science

Rhodium-Mediated Asymmetric Transfer Hydrogenation: a Diastereo-and Enantioselective Synthesis of syn- -Amido -Hydroxy Esters

Long-Sheng Zheng, Charlène Férard, Phannarath Phansavath, Virginie Ratovelomanana- Vidal

► **To cite this version:**

Long-Sheng Zheng, Charlène Férard, Phannarath Phansavath, Virginie Ratovelomanana- Vidal. Rhodium-Mediated Asymmetric Transfer Hydrogenation: a Diastereo-and Enantioselective Synthesis of syn- -Amido -Hydroxy Esters. *Journal of the Chemical Society, Chemical Communications*, 2017, 10.1039/x0xx00000x . hal-04353245

HAL Id: hal-04353245

<https://hal.science/hal-04353245>

Submitted on 19 Dec 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Rhodium-Mediated Asymmetric Transfer Hydrogenation: a Diastereo- and Enantioselective Synthesis of *syn*- α -Amido β -Hydroxy Esters

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

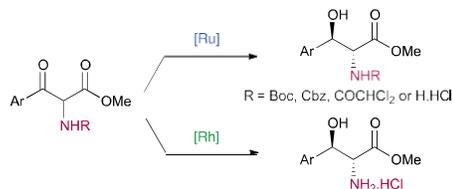
Long-Sheng Zheng, Charlène Férard, Phannarath Phansavath* and Virginie Ratovelomanana-Vidal*

The preparation of *syn* α -benzoylamido β -hydroxy esters through asymmetric transfer hydrogenation (ATH) with a tethered Rh(III)-DPEN complex via dynamic kinetic resolution (DKR) has been developed for the first time starting from α -benzoylamido β -keto esters. A variety of α -benzoylamido β -keto esters were converted under mild conditions into the corresponding *syn* α -benzoylamino β -hydroxy esters with high yields (up to 98%) and diastereomeric ratios (up to >99:1 dr) as well as excellent enantioselectivities (up to >99% ee).

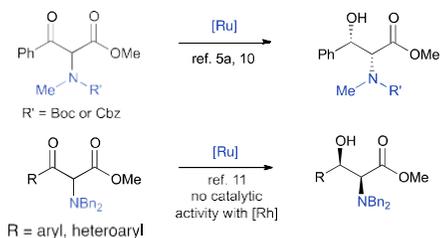
Because enantiomerically pure β -amino alcohols bearing two contiguous stereocenters are valuable building blocks in natural products and pharmaceuticals, and because they can be used as ligands in asymmetric catalysis, an efficient synthesis of these scaffolds is highly desirable. A straightforward and atom-economical access to such compounds involves the dynamic kinetic resolution (DKR) of racemic α -amino β -keto ester derivatives that can be performed through either asymmetric hydrogenation (AH) or asymmetric transfer hydrogenation (ATH), to obtain the *syn* or *anti* reduced products.¹ However, although the DKR of α -amido β -keto esters through asymmetric hydrogenation is now well established, the asymmetric transfer hydrogenation of these compounds is much less documented. Previous work in this field only focused on β -keto esters that were substituted with carbamate, 2,2-dichloro *N*-acetamido or amino hydrochloride functional groups in the α -position to access the *anti* amino alcohol derivatives using either ruthenium²⁻⁸ or rhodium⁹ complexes (Scheme 1, previous work). On the other hand, scarce examples of the production of the *syn* compounds through Ru-catalyzed ATH have been described so far for *N*-diprotected compounds.^{5a,10,11} We have previously observed this reversal of diastereoselectivity from *anti* to *syn*

Previous work:

- ATH-DKR of monoprotected aryl α -amino β -keto esters



- ATH-DKR of diprotected aryl α -amino β -keto esters



This work:

- ATH-DKR of monoprotected aryl α -amino β -keto esters: access to *syn* products



Scheme 1 ATH of α -amino β -keto ester derivatives

in the Ru⁷ or Rh-mediated⁹ ATH of α -amino β -keto ester hydrochlorides, bearing thienyl or furyl substituents on the ketone functional group. These results clearly indicate that the stereochemical outcome of the ATH of these α -amino β -keto ester derivatives is highly dependent on the nature of the amino group as well as on the ketone substituent. As part of an ongoing program aimed at developing efficient methods for the asymmetric reduction of functionalized ketones,¹² we report herein an unprecedented *syn* diastereoselectivity obtained in the Rh-catalyzed DKR/ATH of *N*-monoprotected α -amino β -keto esters, in this case, α -benzoylamino β -keto esters (Scheme 1, this work). The novelty of this study resides

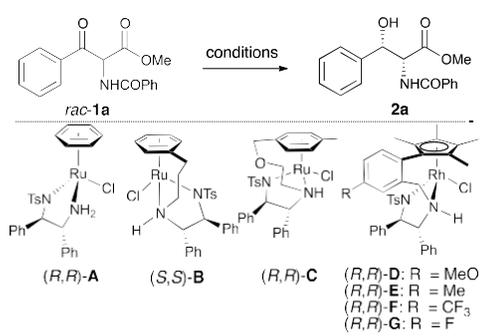
PSL Research University, Chimie ParisTech - CNRS, Institut de Recherche de Chimie Paris, 75005 Paris, France
E-mail: phannarath.phansavath@chimie-paristech.fr; virginie.vidal@chimie-paristech.fr

Electronic Supplementary Information (ESI) available: CCDC 1581420, CCDC 1581421 and CCDC 1581422. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/x0xx00000x

in the use of a rhodium complex for the ATH-DKR of *N*-monoprotected α -amino β -keto esters to access the corresponding syn products, as opposed to the work described by Wang and coworkers,¹¹ which involved the Ru-catalyzed ATH of *N*-diprotected compounds and for which rhodium and iridium complexes were inefficient.

We started our study with the racemic methyl 2-benzoylamino-3-oxo-3-phenylpropanoate **1a** as the standard substrate (Table 1). The initial asymmetric transfer hydrogenation experiments were carried out in CH₂Cl₂ at 30 °C using ruthenium complexes (*R,R*)-**A**, (*S,S*)-**B** and (*R,R*)-**C** in the presence of a 5:2 HCO₂H/Et₃N azeotropic mixture as the hydrogen source, and afforded the corresponding anti amino alcohol derivatives as the major isomers albeit with low enantiomeric excesses (Table 1, entries 1–3). The sense of diastereoselectivity observed here was in agreement with the results reported previously for the ruthenium-catalyzed ATH of the parent α -*N*-Boc or α -*N*-Cbz β -keto ester compounds. To our surprise however, we found that with the tethered rhodium complex (*R,R*)-**D**,^{13,14} the reaction proceeded smoothly within 5 h to deliver the reduced syn product (*R,S*)-**2a** in 90% yield with a good 86:14 dr and an excellent enantiomeric excess of >99% for the syn isomer (Table 1, entry 4). The absolute configuration of the reduced product **2a** was assigned as (2*R*,3*S*) by converting the diastereomerically pure syn **2a** into the known (1*S*,2*S*)-2-benzoylamino-1-phenylpropane-1,3-diol and comparing the optical rotation value with the reported data ($[\alpha]^{20} = +80.1$ (c 1.0, EtOH), lit.:¹⁵ $[\alpha] +94.6$ (c 1.0, EtOH)).¹⁶ To our knowledge, this reversal of diastereoselectivity from anti to syn provided by the use of a Rh complex has never been reported to date for the ATH of *N*-monoprotected α -amino β -keto esters. The use of other solvents under otherwise identical conditions afforded similar results in terms of yields and stereoselectivities although the reaction time was longer in THF and *i*-PrOH (Table 1, entries 5–7). The neat reaction also led to an 86:14 dr and >99% ee (Table 1, entry 8). The stereochemical outcome of the transfer

Table 1 Catalyst and solvent screening^a

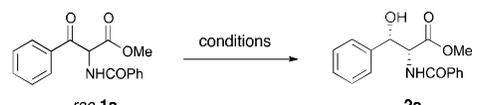


entry	catalyst	solvent	time (h)	yield (%)	dr (syn/anti) ^b	ee _{syn} (%) ^c
1	A	CH ₂ Cl ₂	96	96	15:85	28 ^d
2	B	CH ₂ Cl ₂ ^e	7	95	10:90	36 ^d
3	C	CH ₂ Cl ₂ ^e	9	94	8:92	25 ^d
4	D	CH ₂ Cl ₂	5	90	86:14	>99
5	D	CH ₃ CN	4.5	86	87:13	>99
6	D	THF	23	89	87:13	>99
7	D	<i>i</i> -PrOH	28	88	83:17	>99
8 ^f	D	–	4	87	86:14	>99
9	E	CH ₂ Cl ₂	7	89	86:14	>99
10	F	CH ₂ Cl ₂	7	88	86:14	>99
11 ^f	G	–	20	93	84:16	>99

^a Conditions: 0.8 mmol of **1a**, 0.5 mol% of precatalyst, 134 μ L of HCO₂H/Et₃N (5:2) in 4 mL of solvent at 30 °C. Complete conversions in all cases. ^b Determined by ¹H NMR of the crude product. ^c Determined by SFC analysis. ^d ee of the anti compound. ^e 1.6 mL of solvent was used. ^f Neat reaction.

hydrogenation reaction was not altered by switching from (*R,R*)-**D** to (*R,R*)-**E**, (*R,R*)-**F** or (*R,R*)-**G**¹⁷ bearing respectively, methyl, trifluoromethyl or fluoro groups on the aryl ring, even though the reactions required more time (Table 1, entries 9–11). Accordingly, we selected complex (*R,R*)-**D** as the pre-catalyst and CH₂Cl₂ as the solvent for further studies (Table 2).

Table 2 Catalyst loading and temperature screening^a



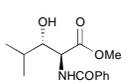
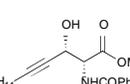
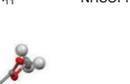
entry	catalyst (mol %)	c ^b	temp (°C)	time (h)	yield (%)	dr (syn/anti) ^c	ee _{syn} (%) ^d
1	0.5	0.2	30	5	90	86:14	>99
2	0.1	0.2	30	23	91	86:14	>99
3 ^e	0.5	0.2	30	24	61 ^f	86:14	>99
4	0.5	0.2	18	22	87	89:11	>99
5	0.5	0.2	0	47	93	92:8	>99
6	0.2	0.2	0	94	73	92:8	>99
7	0.5	0.4	0	34	94	92:8	>99
8	0.5	0.5	0	28	93	92:8	>99

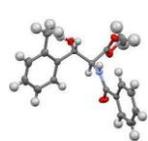
^a Conditions: 0.8 mmol of **1a**, respective mol% of (*R,R*)-**D**, 134 μ L of HCO₂H/Et₃N (5:2) in 1.6–4.0 mL of CH₂Cl₂. Complete conversions except where indicated. ^b Initial concentration of α -amido β -keto ester. ^c Determined by ¹H NMR of the crude product. ^d Determined by SFC analysis. ^e 1:1 mixture of HCO₂H/Et₃N used. ^f 64% conversion obtained under these conditions.

Performing the reaction at 30 °C with a catalyst loading of 0.1 mol% instead of 0.5 mol% resulted only in an extended reaction time without any noticeable effect on either the yield or stereoselectivity (Table 2, entries 1–2), whereas using a 1:1 HCO₂H/Et₃N azeotropic mixture rather than the 5:2 system led to incomplete conversion after 24 h of reaction (Table 2, entry 3). The temperature effect was then investigated, and the reaction was run at 18 °C, affording a slightly higher diastereomeric ratio of 89:11 (Table 2, entry 4). A satisfying 92:8 dr was attained at a temperature of 0 °C after either 47 h (Table 2, entry 5) or 94 h with a catalyst loading of 0.2 mol% (Table 2, entry 6). Finally, maintaining a 0.5 mol% catalyst loading, a variation of the initial concentration of α -amido β -keto ester from 0.2 to 0.4 and 0.5 M showed a decrease of the reaction time from 47 h to 34 h and 28 h, respectively (Table 2, entries 5 and 7–8). Accordingly, the optimized reaction conditions were set as follows: 0.5 mol% of (*R,R*)-**D**, a 5:2 HCO₂H/Et₃N azeotropic mixture as the hydrogen source, CH₂Cl₂ as the solvent (0.5 M), and a reaction temperature of 0 °C. With these conditions in hand, we next investigated the scope of the reaction and a series of variously substituted α -benzoylamino β -keto esters were subjected to the ATH. Compounds bearing substituted phenyl groups on the ketone functional group generally gave the corresponding reduced syn products in high yields with high diastereoselections and excellent enantioselectivities irrespective of the electron-donating or electron-withdrawing character of the substituents (Table 3, entries 1–9). An exception to this trend was observed for **1j** having a sterically hindered ortho-tolyl substituent on the ketone, which delivered in moderate yield the anti compound as the major isomer (syn/anti 13:87) albeit with a low enantiomeric excess (52% ee), whereas the syn isomer was produced in >99% ee (Table 3, entry 10). On the other hand, heteroaryl ketones afforded excellent levels of diastereo- and enantioinductions and the reduced compounds were obtained in very good yields with the exception of compound **1l**, which produced **2l** in 87:13 dr and 96% ee (Table 3, entries 11–15). Furthermore, for the amido ester **1o** bearing a thienyl substituent on the ketone, no temperature effect was observed because the reaction could be carried out at 30 °C within only 1 h without any alteration of the dr or ee (Table 3, entries 15–16). In addition, the reduction of **1o** was efficiently performed on gram-scale demonstrating the usefulness of this method. The substrate scope was then expanded to α -amido β -keto esters containing an alkyl ketone. For these compounds, the reduced syn products were obtained with lower diastereomeric ratios while the ee remained >99% (Table 3, entries 17–18). As for the sterically demanding substrate **1j**, a reversal of diastereoselectivity was observed as well, with the amido ester **1r** having an isopropyl substituent on the ketone. This time the anti isomer was formed with a very high level of diastereo- and enantioinductions albeit after a prolonged reaction time of 10 days (Table 3, entry 19), which could be reduced to 92 h by working at 30 °C with no loss of stereoselectivity (Table 3, entry 20). Finally, the Rh-catalyzed ATH of substrate **1s** having an alkyne residue proceeded with near-perfect diastereo- and enantioselectivities in either

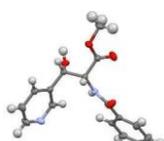
Table 3 Substrate scope^a

entry/ATH product 2	time (h)	yield (%)	dr (syn/anti) ^b	ee _{syn} (%) ^c	
1a-1s					
1/2a		28	93	92:8	>99
2/2b		48	98	93:7	>99
3/2c		70	96	93:7	>99
4/2d		48	96	94:6	>99
5/2e		64	96	92:8	>99
6/2f		45	86	91:9	>99
7/2g		23	98	92:8	>99
8/2h		23	95	93:7	>99
9/2i		25	98	94:6	>99
10/2j		72	70	13:87	>99 52 _{anti}
11/2k		22	96	97:3	>99
12/2l		42	63	87:13	96
13/2m		15	93	98:2	>99
14/2n		24	96	>99:1	99
15/2o		34	98	>99:1	>99
16/2o		1 ^d	96	>99:1	>99
17/2p		46	97	80:20	>99
18/2q		24	98	75:25	>99

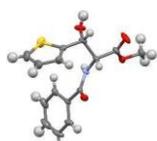
19/2r		10d	72	2:98	>99
20/2r ^d		92	74	3:97	99
21/2s		10d	86	>99:1	>99
22/2s ^d		24	80	>99:1	>99



2j (CCDC 1581420)



2l (CCDC 1581421)



2o (CCDC 1581422)

^aConditions: 0.8 mmol of **1**, 0.5 mol% of (*R,R*)-**D**, 134 μ L of HCO₂H/Et₃N (5:2) in 1.6 mL of CH₂Cl₂ at 0 °C. Complete conversions except for compounds **1j** and **1r** for which 73–82% conv. were obtained. ^bDetermined by ¹H NMR of the crude product. ^cDetermined by SFC or HPLC analysis. ^dReaction carried out at 30 °C.

10 days at 0 °C (Table 3, entry 21) or in only 24 h at 30 °C (Table 3, entry 22).

In summary, the rhodium-catalyzed asymmetric transfer hydrogenation of α -amido β -keto esters via DKR appears to be an efficient tool for the synthesis of syn α -benzoylamido β -hydroxy esters, which until now were not directly attainable through ATH. The reaction proceeded under mild conditions using a low catalyst loading with tolerance for a diverse set of functional groups, delivering the reduced compounds in good yields, high diastereomeric ratios, and excellent enantioselectivities for a wide range of substrates. Furthermore, the usefulness of this method was demonstrated by the efficient gram-scale reduction of **1o**.

This work was supported by the Ministère de l'Éducation Nationale, de l'Enseignement Supérieur et de la Recherche (MENESR) and the Centre National de la Recherche Scientifique (CNRS). We gratefully acknowledge the China Scholarship Council (CSC) for a grant to L.-S. Z. We would like to thank L.-M. Chamoreau and G. Gontard for the X-ray analysis. This manuscript is dedicated to Prof. Miguel Yus on the occasion of his 70th birthday.

Conflicts of interest

There are no conflicts to declare.

Notes and references

- For selected reviews on DKR through AH/ATH, see: (a) R. Nozori, M. Tokunaga, M. Kitamura, *Bull. Chem. Soc. Jpn. Rev.*, 1995, **68**, 36; (b) S. Caddick, K. Jenkins, *Chem. Soc. Rev.*, 1996, **25**, 447; (c) R. S. Ward, *Tetrahedron: Asymmetry*, 1995, **6**, 1475; (d) V. Ratovelomanana-Vidal, J.-P. Genêt, *Can. J. Chem.*, 2000, **78**, 846; (e) F. F. Huerta, A. B. E. Minidis, J.-E. Bäckvall, *Chem. Soc. Rev.*, 2001, **30**, 321; (f) O. Pàmies, J.-E. Bäckvall, *Chem. Rev.*, 2003, **103**, 3247; (g) H. Pellissier, *Tetrahedron*, 2003, **59**, 8291; (h) H. Pellissier, *Tetrahedron*, 2008, **64**, 1563; (i) H. Pellissier, *Tetrahedron*, 2011, **67**, 3769;
- (j) Y. Hamada, *Chem. Rec.*, 2014, **14**, 235; (k) F. Foubelo, C. Nájera, M. Yus, *Tetrahedron: Asymmetry*, 2015, **26**, 769; (l) P.-G. Echeverria, T. Ayad, P. Phansavath, V. Ratovelomanana-Vidal, *Synthesis*, 2016, **48**, 2523.
- M. Perez, P.-G. Echeverria, E. Martinez-Arripe, M. Ez Zoubir, R. Touati, Z. Zhang, J.-P. Genêt, P. Phansavath, T. Ayad, V. Ratovelomanana-Vidal, *Eur. J. Org. Chem.*, 2015, 5949.
- X. Wang, L. Xu, L. Yan, H. Wang, S. Han, Y. Wu, F. Chen, *Tetrahedron*, 2016, **72**, 1787.
- L. H. Bourdon, D. J. Fairfax, G. S. Martin, C. J. Mathison, P. Zhichkin, *Tetrahedron: Asymmetry*, 2004, **15**, 3485.
- (a) B. Seashore-Ludlow, P. Villo, C. Häcker, P. Somfai, *Org. Lett.*, 2010, **12**, 5274; (b) B. Seashore-Ludlow, F. Saint-Dizier, P. Somfai, *Org. Lett.*, 2012, **14**, 6334; (c) B. Seashore-Ludlow, P. Villo, P. Somfai, *Chem. Eur. J.*, 2012, **18**, 7219.
- Z. Liu, C. S. Shultz, C. A. Sherwood, S. Krska, P. G. Dormer, R. Desmond, C. Lee, E. C. Sherer, J. Shpungin, J. Cuff, F. Xu, *Tetrahedron Lett.*, 2011, **52**, 1685.
- P.-G. Echeverria, J. Cornil, C. Féraud, A. Guérinot, J. Cossy, P. Phansavath, V. Ratovelomanana-Vidal, *RSC Adv.*, 2015, **5**, 56815.
- X. Wang, L. Xu, F. Xiong, Y. Wu, F. Chen, *RSC Adv.*, 2016, **6**, 37701.
- Q. Llopis, C. Féraud, G. Guillaumot, P. Phansavath, V. Ratovelomanana-Vidal, *Synthesis*, 2016, **48**, 3357.
- B. Mohar, A. Valleix, J. Desmurs, M. Felemez, C. Mioskowski, *Chem. Commun.*, 2001, 2572.
- G. Sun, Z. Zhou, Z. Luo, H. Wang, L. Chen, Y. Xu, S. Li, W. Jian, J. Zeng, B. Hu, X. Han, Y. Lin, Z. Wang, *Org. Lett.*, 2017, **19**, 4339.
- (a) Z. Wu, T. Ayad, V. Ratovelomanana-Vidal, *Org. Lett.*, 2011, **13**, 3782; (b) F. Berhal, Z. Wu, Z. Zhang, T. Ayad, V. Ratovelomanana-Vidal, *Org. Lett.*, 2012, **14**, 3308; (c) D. Cartigny, F. Berhal, T. Nagano, P. Phansavath, T. Ayad, J.-P. Genêt, T. Ohshima, K. Mashima, V. Ratovelomanana-Vidal, *J. Org. Chem.*, 2012, **77**, 4544; (d) Z. Wu, M. Perez, M. Scalone, T. Ayad, V. Ratovelomanana-Vidal, *Angew. Chem. Int. Ed.*, 2013, **52**, 4925; (e) L. Monneré, D. Cartigny, M. Scalone, T. Ayad, V. Ratovelomanana-Vidal, *Chem. Eur. J.*, 2015, **21**, 11799; (f) T. Ayad, P. Phansavath, V. Ratovelomanana-Vidal, *Chem. Rec.*, 2016, **16**, 2750.
- (a) P.-G. Echeverria, C. Féraud, P. Phansavath, V. Ratovelomanana-Vidal, *Catal. Commun.*, 2015, **62**, 95; (b) D. S. Matharu, D. J. Morris, A. M. Kawamoto, G. J. Clarkson, M. Wills, *Org. Lett.*, 2005, **7**, 5489; (c) D. S. Matharu, J. E. D. Martins, M. Wills, *Chem. Asian J.*, 2008, **3**, 1374; (d) J. Dimroth, U. Schedler, J. Keilitz, R. Haag, R. Schomäcker, *Adv. Synth. Catal.*, 2011, **353**, 1335; (e) J. Dimroth, J. Keilitz, U. Schedler, R. Schomäcker, R. Haag, *Adv. Synth. Catal.*, 2010, **352**, 2497.
- The Rh-catalyzed ATH of the corresponding *N*-dibenzyl compound, using 10 mol% of complex (*R,R*)-**D**, resulted in no conversion, even at 40 °C. This result confirmed what Wang and co-workers observed with Cp*RhTFDPEN in ref. 11.
- X.-M. Zhang, H.-L. Zhang, W.-Q. Lin, L.-Z. Gong, A.-Q. Mi, X. Cui, Y.-Z. Jiang, K.-B. Yu, *J. Org. Chem.*, 2003, **68**, 4322.
- The absolute configuration of **2a** was further confirmed by comparison with authentic samples of compounds (2*R*,3*S*)-**2a** and (2*S*,3*R*)-**2a** (prepared by ruthenium-catalyzed AH of *rac*-**1a** with [RuCl(*R*)-SYNPHOS]₂(μ-Cl)₂[MeNH]₂⁺ and [RuCl(*S*)-SYNPHOS]₂(μ-Cl)₂[Me₂NH]₂⁺, respectively) using HPLC analysis. The absolute configurations of **2e** and **2g** were assigned by using the same method.
- L.-S. Zheng, Q. Llopis, P.-G. Echeverria, C. Féraud, G. Guillaumot, P. Phansavath, V. Ratovelomanana-Vidal, *J. Org. Chem.*, 2017, **82**, 5607.