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Asymmetric transfer hydrogenation of α-amino β-keto ester hydrochlorides through dynamic kinetic resolution

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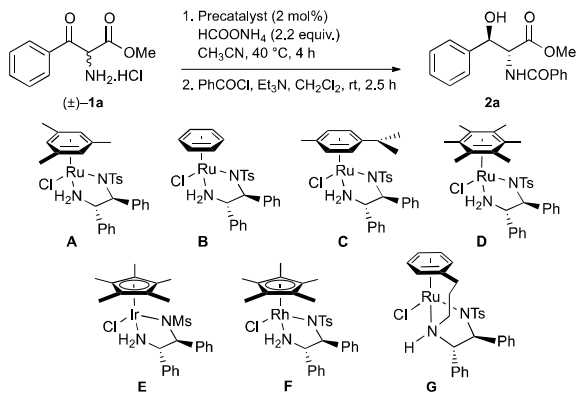
The development of Ru-catalyzed asymmetric transfer hydrogenation of α-amino β-keto ester hydrochlorides is described. The reaction proceeds through dynamic kinetic resolution to afford *anti* β-hydroxy α-amino esters with good diastereomeric ratios and high enantioselectivities.

Because optically active β-hydroxy α-amino acids and their corresponding vicinal amino alcohols are important building blocks in natural products and pharmaceuticals,[1] the search for efficient and atom-economical processes for the stereoselective synthesis of these compounds remains a challenge. An elegant approach to these subunits relies on ruthenium-mediated asymmetric hydrogenation via dynamic kinetic resolution (DKR),[2] which sets two contiguous stereogenic centers in a single operation. In this field, Noyori *et al.*[3] and one of our groups[4] have reported the *syn*-selective preparation of β-hydroxy α-amino esters whereas the production of the *anti* isomers was later described by the groups of Hamada,[5] Zhang[6] and one of us.[7] Although the DKR of α-amino β-keto ester hydrochlorides through transition metal-catalyzed asymmetric hydrogenation is now well established,[5,7,8] the related asymmetric transfer hydrogenation (ATH) of these compounds, to the best of our knowledge, has not been studied to date, and only ATH of *N*-protected α-amino β-keto esters has been described.[9] Asymmetric transfer hydrogenation[10] appears as one of the most powerful tools for the stereoselective reduction of prochiral ketones. Not only does it usually deliver high level of stereoselectivity, but the reaction also proceeds with operational simplicity, involving nonsensitive catalysts. Moreover a variety of hydrogen sources can be used. Accordingly, and as an extension of our previous work on the dynamic kinetic resolution of α-substituted β-keto esters,[11] we report herein the first example of Ru-catalyzed ATH of α-amino β-keto ester hydrochlorides.

We first investigated the ATH reaction of (±)-**1a** in the presence of the Ru, Ir or Rh complexes **A–G** (2 mol%) in acetonitrile at 40 °C utilizing ammonium formate as the hydrogen source (Table 1). The use of the ruthenium(II)/η^6-arene complexes **A–D** containing the *N*-tosyl-1,2-diphenylethylenediamine (TsDPEN) ligand failed to afford the expected product, and only unidentified degradation compounds were obtained (Table 1, entries 1–4).

Table 1 Survey of the ATH of **1a** with various precatalysts[a]



Entry	Precatalyst	Conv. (%)[b]	Yield (%)[c]	*dr*[d]	*er*[e]
1	**A**	—[f]	—	—	—
2	**B**	—[f]	—	—	—
3	**C**	—[f]	—	—	—
4	**D**	—[f]	—	—	—
5	**E**	100	50	86:14	58:42
6	**F**	100	61	97:3	50:50
7	**G**	100	76	83:17	99:1

[a] Reaction conditions: **1a** (0.44 mmol), precatalyst (2 mol%), HCO_2NH_4 (2.2 equiv.), CH_3CN (2 mL), 40 °C, 4 h. [b] Determined by ^{1}H NMR of the crude product after the ATH reaction. [c] Isolated yields for **2a**. [d] Determined by ^{1}H NMR of the crude product **2a**. [e] Determined for the *anti* isomer by SFC analysis. [f] Only by-products were obtained.

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Nevertheless, the *anti* β-hydroxy α-amino ester **2a** could be prepared in 50% yield (after conversion of the ATH product into the corresponding *N*-benzoyl amide for analytical purpose) using the iridium complex **E**. In this case, a good diastereomeric ratio was observed for the *anti* compound, which was formed with only poor enantioselectivity (Table 1, entry 5). Interestingly, the use of the related Rh complex **F** provided a very high level of diastereoselectivity but unfortunately the *anti* compound was obtained as a racemic mixture (Table 1, entry 6). Finally, the best results were obtained with the 'tethered' Ru-complex **G** developed by Wills and co-workers.[12] The reaction proceeded with good diastereoselectivity (*dr* 83:17) and excellent enantioselectivity (*er* 99:1) in 76% yield (Table 1, entry 7). The relative and absolute configuration of **2a** was unambiguously assigned by single X-ray analysis (Fig 1).[13] The *anti* diastereoselectivity of the ATH reaction of (±)**–1a** using the Ru-tethered complex **G** was the same as that observed for the related Ru-catalyzed asymmetric hydrogenation, while it was shown that the ATH of α-amido β-keto esters resulted in a reversal of diastereoselectivity[9c] from *syn* to *anti* as compared with the related asymmetric hydrogenation of these compounds. The enantiocontrol in the ATH reaction of (±)**–1a** probably arises from the well-established edge-to-face arene/aryl interaction between the η^6-arene, and the phenyl group on the ketone through a transition state in which this stabilizing CH/π interaction ensures a high enantiomeric excess (Fig 1).[14] On the other hand, the preferential formation of the *anti* isomer might be explained by a cyclic intermediate wherein a hydrogen bond exists between *N*-H and the carbonyl moiety (Fig 1).[9c]

Having established the Ru-tethered complex **G** as an efficient catalyst for the ATH of (±)**–1a**, we next turned our attention to a survey of the hydrogen donor source and to a screening of solvents under the previous reaction conditions (Table 2). First, a formic acid/triethylamine (5:2) azeotropic mixture was used as the hydrogen source. The reaction produced the expected *anti* amino alcohol **2a** in moderate yield and with a lower enantiomeric excess compared to the one obtained with ammonium formate, although a higher level of diastereoselectivity was observed (Table 2, compare entry 2 vs 1). Other formate salts were also examined. Sodium formate afforded comparable results as those obtained for ammonium formate in terms of yield and stereoselectivity (Table 2, entry 3), whereas no conversion was observed with calcium formate (Table 2, entry 4).

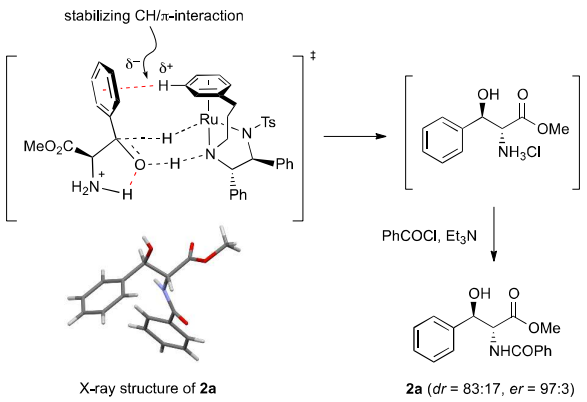
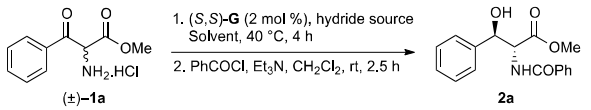


Fig. 1 Proposed model for the absolute stereochemistry in ATH of compound **1a**.

Table 2 Optimization of the reaction conditions for the ATH of **1a** with (*S,S*)**–G**[a]

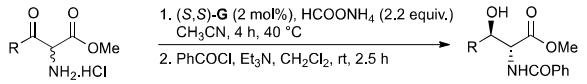


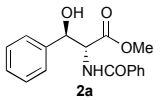
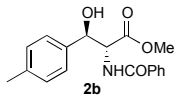
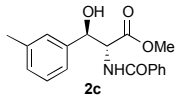
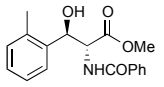
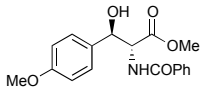
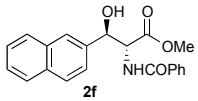
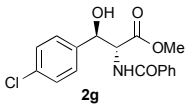
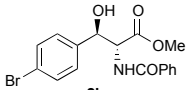
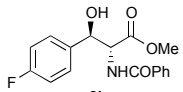
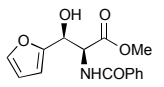
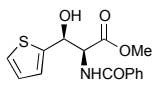
Entry	Hydride source (equiv.)	Solvent	Conv. (%)[b]	Yield (%)	*dr*[c]	*er*[d]
1	HCO_2NH_4 (2.2)	CH_3CN	100	76	83:17	99:1
2	HCO_2H/NEt_3 (5:2) (2.2)	CH_3CN	100	36	94:6	88:12
3	HCO_2Na (2.2)	CH_3CN	100	77	86:14	96:4
4	$(HCO_2)_2Ca$ (1.1)	CH_3CN	0	—	—	—
5[e]	*i*PrOH/KOH (1.3)	*i*PrOH	—[f]	—	—	—
6[g]	$NaH_2PO_2.H_2O$ (5)	H_2O	100	40	92:8	57:43
7[h]	HCO_2NH_4 (2.2)	MeOH	100[i]	—	—	—
8[h]	HCO_2NH_4 (2.2)	*i*PrOH	100	63[j]	84:16	99:1
9[h]	HCO_2NH_4 (2.2)	AcOEt	100	50[j]	81:19	96:4
10[h]	HCO_2NH_4 (2.2)	Et_2O	100	41[j]	85:15	97:3

[a] Reaction conditions: **1a** (0.44 mmol), (*S,S*)**–G** (2 mol%), hydride source, CH_3CN (2 mL), 40 °C, 4 h. [b] Determined by ^1H NMR of the crude product after the ATH reaction. [c] Determined by ^1H NMR of the crude product **2a**. [d] Determined for the *anti* isomer by SFC analysis. [e] Reaction conducted at rt for 3 h. [f] Incomplete conversions and unidentified by-products were obtained. [g] Reaction conducted at 50 °C for 96 h. [h] 1 mol% of complex was used. [i] Only the retroaldol product was observed. [j] The retroaldol product was also obtained alongside unidentified by-products.

In the case of the isopropanol/potassium hydroxide combination as the hydrogen donor source, only degradation products were produced (Table 2, entry 5). Finally, the ATH reaction was carried out with sodium hypophosphite monohydrate in water to give a moderate 40% yield with a good diastereoselectivity (*dr* 92:8) but with almost no enantioselectivity (*er* 57:43) (Table 2, entry 6). This short screening of hydrogen donor source prompted us to pursue the study with ammonium formate for which the *er* for **2a** was the highest (Table 2, entry 1). Other solvents were subsequently examined under the otherwise unmodified reaction conditions. Methanol proved to be an unsuitable solvent for this transformation, leading only to by-products, mainly arising from a competitive retroaldol reaction (Table 2, entry 7).[15] Although high *er* and good diastereoselectivities were obtained in isopropanol, ethyl acetate and diethyl ether, in these solvents lower yields were observed as the retroaldol compound was also formed alongside unidentified by-products (Table 2, entries 8–10).

Table 3. ATH of **1a-k** with (*S*,*S*)–**G**/$HCOONH_4$: scope and limitations.[a]



Entry	ATH product, **2**	Yield (%)[b]	*dr*[c]	*er* $_{(anti)}$[d]
1	 **2a**	76	83:17	99:1
2	 **2b**	90	79:21	94:6
3	 **2c**	77	80:20	99:1
4	 **2d**	0	—	—
5	 **2e**	69	79:21	97:3
6	 **2f**	90	78:22	96:4
7	 **2g**	82	76:24	93:7
8	 **2h**	66	74:26	95:5
9	 **2i**	82	76:24	93:7
10	 **2j**	66	41:59	>99:1[e]
11	 **2k**	79	32:68	>99:1[e]

[a] Reaction conditions: (1) **2** (0.42 mmol), (*S*,*S*)–**G** (2 mol%), $HCOONH_4$ (0.92 mmol), CH_3CN (2 mL), 40 °C, 4 h. (2) Crude hydroxyester hydrochloride (0.42 mmol), PhCOCl (0.46 mmol), Et_3N (1.26 mmol), CH_2Cl_2 (2 mL), rt, 2.5 h. [b] Isolated yields for **2a–k**. [c] Determined by ^1H NMR of the crude product after the ATH reaction. [d] Determined by SFC or HPLC analysis. The relative and absolute configurations of compounds **2b-k** were assigned by comparison with reported analytical data or by analogy. [e] *ee* of the *syn* isomer.

With the optimal reaction conditions in hand, we next examined the scope of the Ru-catalyzed ATH of α-amino β-keto ester hydrochlorides with a series of aromatic substrates **1a–k** (Table 3).[16] Accordingly, reactions were carried out in the presence of (*S*,*S*)-**G** (2 mol%) and ammonium formate (2.2 equiv.) in acetonitrile at 40 °C for 4 h, affording mainly the expected amino alcohols **2** in good yields with diastereomeric ratios up to 83:17 and enantiomeric excesses as high as 98% for the *anti* isomer. Introduction of a methyl group at the *para*– or *meta*–position on the phenyl ring had no influence on either the diastereo- or enantioselectivity of the reaction (Table 3, entries 1–3). However, compound **1d** having an *ortho*-substitution on the aryl ring proved to be too sterically hindered and failed to afford any conversion (Table 3, entry 4). The presence of a *para*-methoxy substituent on the aromatic ring had no consequence on the stereochemical outcome of the reaction (Table 3, entry 5) whereas the naphthyl derivative **1f** afforded likewise comparable results (Table 3, entry 6). With a halogen atom (chlorine, bromine or fluorine) in the *para*–position of the phenyl ring, the reaction proceeded with about 75:25 *dr*, whereas good *er* up to 94:6 were attained (Table 3, entries 7–9). A surprising reversal of diastereoselectivity whose cause is unclear at present was observed in the ATH of the furan and thiophene derivatives **1j** and **1k**. Indeed, these compounds delivered the corresponding amino alcohols **2j** and **2k** with moderate *dr* of 59:41 and 68:32, respectively, in favor of the *syn* isomers. In both cases, the reaction proceeded with a very high level of enantioselectivity for the *syn* product (Table 3, entries 10 and 11, *er* > 99:1). This moderate *syn* selectivity might be explained by a competitive six-membered cyclic intermediate wherein a hydrogen bond exists between *N*-H and the heteroatom of the furan or thiophene ring, instead of the five-membered cyclic intermediate leading to the *anti* compounds. Finally, α-amino β-keto ester hydrochlorides bearing R = cyclohexyl or *iso*propyl substituents showed no conversion under the standard reaction conditions.

Conclusions

In conclusion, the asymmetric transfer hydrogenation of α-amino β-keto ester hydrochlorides has been reported for the first time. We found that ruthenium 'tethered' complex **G** associated with ammonium formate as the hydrogen source, was effective for the ATH reduction of racemic α-amino β-keto ester hydrochlorides. The Ru/HCO_2NH_4 combination delivered the corresponding reduced *anti* products in good yields, diastereo- and enantioselectivities through a dynamic kinetic resolution process. The operational simplicity of this ATH was applied to various α-amino β-keto ester hydrochlorides bearing aromatic groups on the ketone function. The reaction usually afforded the corresponding *anti* compounds in good yields with good diastereomeric ratios and high enantiomeric purities (*er* of up to 99:1). Interestingly, heteroaromatic compounds gave predominantly the *syn* isomers with excellent enantioinductions albeit moderate diastereoselectivities.

Experimental Section

General procedure for the Ru-catalyzed ATH of compounds 1a-k:

A round-bottomed tube fitted with a rubber septum equipped with a balloon of argon was charged with α-amino β-keto ester hydrochloride **1** (0.42 mmol), [RuCl(benzene)((*S*,*S*)-teth-TsDPEN)] (0.0084 mmol, 2 mol%) and $HCOONH_4$ (0.92 mmol, 2.2 equiv.), and the solids were subjected to three vacuum/argon cycles before distilled acetonitrile (2 mL) was added, and another three vacuum/argon cycles were performed. The reaction mixture was stirred at 40 °C for 4 h and the solvent was removed under reduced pressure. The conversion was determined by ^{1}H NMR analysis of the crude product. To a solution of the previous β-hydroxy ester hydrochloride (0.42 mmol) in dry CH_2Cl_2 (2 mL) were added benzoyl chloride (0.46 mmol, 1.1 equiv.) and NEt_3 (1.26 mmol, 3 equiv.) at 0 °C. The reaction mixture was stirred at 0 °C for 1.5 h and 1 h at rt, then diluted with CH_2Cl_2, quenched with saturated aqueous NH_4Cl, extracted with CH_2Cl_2, and dried over $MgSO_4$. The crude protected product was purified by flash chromatography to afford **2**. The diastereomeric ratio was determined by ^{1}H NMR analysis of the crude product **2**, and the enantiomeric excess was determined by SFC or HPLC analysis of the purified product (using Chiralcel OD-H, Chiralpak IA, IC or AD-H columns).

Acknowledgements

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Notes and references

1 (*a*) C. Nájera, J. M. Sansano, *Chem. Rev*., 2007, **107**, 4584; (*b*) S. C. Bergmeier, *Tetrahedron*, 2000, **56**, 2561.

2 For selected reviews on dynamic kinetic resolution, see: (*a*) R. Noyori, M. Tokunaga, M. Kitamura, *Bull. Chem. Soc. Jpn*., 1995, **68**, 36; (*b*) R. S. Ward, *Tetrahedron: Asymmetry*, 1995, **6**, 1475; (*c*) T. Ohkuma, M. Kitamura, R. Noyori, *Catalytic Asymmetric Synthesis* 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; p. 1; (*d*) V. Ratovelomanana-Vidal, J.-P. Genet, *Can. J. Chem*., 2000, 846; (*e*) O. Pàmies, J.-E. Bäckvall, *Chem. Rev.*, 2003, **103**, 3247; (*f*) E. Vedejs, M. Jure, *Angew. Chem. Int. Ed.*, 2005, **44**, 3974; (*g*) H. Pellissier, *Tetrahedron*, 2008, **64**, 1563; (*h*) H. Pellissier, *Tetrahedron*, 2011, **67**, 3769; (*i*) H. Pellissier, *Adv. Synth. Catal.*, 2011, **353**, 659.

3 R. Noyori, T. Ikeda, T. Ohkuma, M. Widhalm, M. Kitamura, H. Takaya, S. Akutagawa, N. Sayo, T. Saito, T. Taketomi, Kumobayashi, *J. Am. Chem. Soc.*, 1989, **111**, 9134.

4 (*a*) J.-P. Genet, S. Mallart, S. Jugé, French Patent n° 8911159, August, 1989; (*b*) J.-P. Genet, C. Pinel, S. Mallart, S. Jugé, S. Thorimbert, J. A. Laffitte, *Tetrahedron: Asymmetry*, 1991, **2**, 555.

5 (*a*) K. Makino, T. Goto, Y. Hiroki, Y. Hamada, *Angew. Chem. Int. Ed.*, 2004, **43**, 882; (*b*) K. Makino, T. Goto, Y. Hiroki, Y. Hamada, *Tetrahedron: Asymmetry*, 2008, **19**, 2816.

6 A. Lei, S. Wu, M. He, X. Zhang, *J. Am. Chem. Soc.*, 2004, **126**, 1626.

7 (*a*) C. Mordant, P. Dünkelmann, V. Ratovelomanana-Vidal, J.-P. Genet, *Eur. J. Org. Chem.*, 2004, 3017; (*b*) C. Mordant, P. Dünkelmann, V. Ratovelomanana-Vidal, J.-P. Genet, *Chem. Commun.*, 2004, 1296.

8 (*a*) K. Makino, Y. Hiroki, Y. Hamada, *J. Am. Chem. Soc.*, 2005, **127**, 5784; (*b*) K. Makino, T. Fujii, Y. Hamada, *Tetrahedron: Asymmetry*, 2006, **17**, 481; (*c*) K. Makino, M. Iwasaki, Y. Hamada, *Org. Lett.*, 2006, **8**, 4573; (*d*) Y. Hamada, Y. Koseki, T. Fujii, T. Maeda, T. Hibino, K. Makino, *Chem. Commun.*, 2008, 6206; (*e*) K. Makino, T. Goto, Y. Hiroki, Y. Hamada, *Tetrahedron: Asymmetry*, 2008, **19**, 2816; (*f*) T. Maeda, K. Makino, M. Iwasaki, Y. Hamada, *Chem. Eur. J.*, 2010, **16**, 11954; (*g*) J. Ohtaka, A. Hamajima, T. Nemoto, Y. Hamada, *Chem. Pharm. Bull.*, 2013, **61**, 245.

9 (*a*) B. Mohar, A. Valleix, J.-R. Desmurs, M. Felemez, A. Wagner, C. Mioskowski, *Chem. Commun.*, 2001, 2572; (*b*) L. H. Bourdon, D. J. Fairfax, G. S. Martin, C. J. Mathison, P. Zhichkin, *Tetrahedron: Asymmetry*, 2004, **15**, 3485; (*c*) B. Seashore-Ludlow, P. Villo, C. Häcker, P. Somfai, *Org. Lett.*, 2010, **12**, 5274; (*d*) 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; (*e*) B. Seashore-Ludlow, P. Villo, P. Somfai, *Chem. Eur. J.*, 2012, **18**, 7219; (*f*) B. Seashore-Ludlow, F. Saint-Dizier, P. Somfai, *Org. Lett.*, 2012, **14**, 6334.

10 For comprehensive reviews on asymmetric transfer hydrogenation, see: (*a*) G. Zassinovich, G. Mestroni, S. Gladiali, *Chem. Rev*., 1992, **92**, 1051; (*b*) C. F. de Graauw, J. A. Peters, H. van Bekkum, J. Huskens, *Synthesis*, 1994, 1007; (*c*) R. Noyori, S. Hashiguchi, *Acc. Chem. Res.,* 1997, **30**, 97; (*d*) M. J. Palmer, M. Wills, *Tetrahedron: Asymmetry*, 1999, **10**, 2045; (*e*) O. Pàmies, J.-E. Bäckvall, *Chem. Eur. J.*, 2001, **7**, 5052. (*f*) K. Everaere, A. Mortreux, J.-F. Carpentier, *Adv. Synth. Catal*., 2003, **345**, 67; (*g*) S. Gladiali, E. Alberico, *Chem. Soc. Rev*., 2006, **35**, 226; (*h*) S. M. Joseph, J. S. Samec, J.-E. Bäckvall, P. G. Andersson, P. Brandt, *Chem. Soc. Rev*., 2006, **35**, 237; (*i*) T. Ikariya, A. J. Blacker, *Acc. Chem. Res*., 2007, **40**, 1300; (*j*) A. J. Blacker, in Handbook of Homogeneous Hydrogenation (Eds.: J. G. de Vries, C. J. Elsevier), Wiley-VCH, Weinheim, 2007, p. 1215; (*k*) C. Wang, X. Wu, J. Xiao, *Chem. Asian J.*, 2008, **3**, 1750; (*l*) T. Ikariya, *Bull. Chem. Soc. Jpn.*, 2011, **84**, 1.

11 (*a*) J.-P. Genet, X. Pfister, V. Ratovelomanana-Vidal, C. Pinel, J. A. Laffitte, *Tetrahedron Lett.,* 1994, **35**, 4559; (*b*) P. Phansavath, S. Duprat de Paule, Ratovelomanana-Vidal, J.-P. Genet, *Eur. J. Org. Chem*., 2000, 3903; (*c*) D. Lavergne, C. Mordant, V. Ratovelomanana-Vidal, J.-P. Genet, *Org. Lett*., 2001, **3**, 1909; (*d*) O. Labeeuw, P. Phansavath, J.-P. Genet, *Tetrahedron: Asymmetry,* 2004, **15**, 1899; (*e*) C. Mordant, S. Reymond, H. Tone, D. Lavergne, R. Touati, B. Ben Hassine, V. Ratovelomanana-Vidal, J.-P. Genet, *Tetrahedron,* 2007, **63**, 6115; (*f*) H. Tone, M. Buchotte, C. Mordant, E. Guittet, T. Ayad, V. Ratovelomanana-Vidal, *Org. Lett*., 2009, **11**, 1995; (*g*) S. Prévost, T. Ayad, P. Phansavath, V. Ratovelomanana-Vidal, *Adv. Synth. Catal.*, 2011, **353**, 3213; (*h*) S. Prévost, S. Gauthier, M. C. Cano de Andrade, C. Mordant, A. R. Touati, P. Lesot, P. Savignac, T. Ayad, P. Phansavath, V. Ratovelomanana-Vidal, J.-P. Genet, *Tetrahedron: Asymmetry*, 2010, **21**, 1436; (*i*) P.-G. Echeverria, S. Prévost, J. Cornil, J., C. Férard, S. Reymond, A. Guérinot, J. Cossy, V. Ratovelomanana-Vidal, P. Phansavath, *Org Lett*., 2014, **16**, 2390; (*j*) P.-G. Echeverria, C. Férard, J. Cornil, A. Guérinot, J. Cossy, P. Phansavath, V. Ratovelomanana-Vidal, *Synlett*, 2014, **25**, 2761.

12 (*a*) A. M. Hayes, D. J. Morris, G. J. Clarkson, M. Wills, *J. Am. Chem. Soc.*, 2005, **127**, 7318; (*b*) D. J. Morris, A. M. Hayes, M. Wills, *J. Org. Chem.*, 2006, **71**, 7035; (*c*) R. Soni, J.-M. Collinson, G. C. Clarkson, M. Wills, *Org. Lett.*, 2011, **13**, 4304; (*d*) K. E. Jolley, A. Zanotti-Gerosa, F. Hancock, A. Dyke, D. M. Grainger, J. A. Medlock, H. G. Nedden, J. J. M. Le Paih, S. J. Roseblade, A. Seger, V. Sivakumar, I. Prokes, D. J. Morris, M. Wills, *Adv. Synth. Catal.,* 2012, **354**, 2545; (*e*) Z. Fang, M. Wills, *J. Org. Chem*., 2013, **78**, 8594; (*f*) R. Soni, K. E. Jolley, G. J. Clarkson, M. Wills, *Org. Lett.*, 2013, **15**, 5110.

13 Crystallographic data for compound **2a** have been deposited with the accession number CCDC 1403819 and can be obtained free of charge from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44(1223)336033; E-mail: deposit@ccdc.cam.ac.uk; Web site: www.ccdc.cam.ac.uk/conts/retrieving.html.

14 (*a*) M. Yamakawa, I. Yamada, R. Noyori, *Angew. Chem. Int. Ed.*, 2001, **40**, 2818; (*b*) E. H. Krenske, K. N. Houk, *Acc. Chem. Res.*, 2013, **46**, 979.
15 After protection of the crude ATH product with benzoyl chloride, the retroaldol product has been isolated and characterized as methyl 2-benzamidoacetate.
16 Compounds **1a**-**1k** were synthesized according to literature protocols: (*a*) J. Singh, T. D. Gordon, W. G. Earley, B. A. Morgan, *Tetrahedron Lett.,* 1993, **34**, 211; (*b*) A. Pinter, G. Haberbauer, *Eur. J. Org. Chem.,* 2008, 2375; (*c*) F. M. Bravin, G. Busnelli, M. Colombo, F. Gatti, L. Manzoni, *Synthesis*, 2004, 353.