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Dynamic Kinetic Resolution: Asymmetric Transfer Hydrogenation of α-Alkyl-Substituted β-Ketoamides

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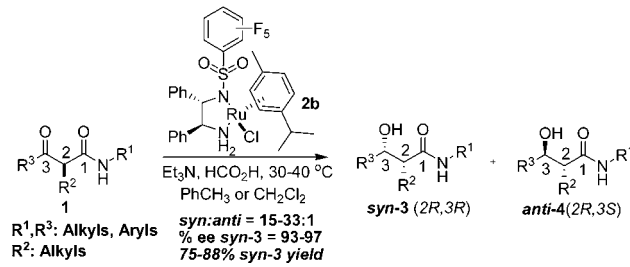
ABSTRACT



Dynamic kinetic resolution (deracemization) of various α-alkyl-substituted β-ketoamides 1 via asymmetric transfer hydrogenation proceeded efficiently to give the corresponding *syn*-β-hydroxy amides 3 in high diastereo- and enantioselectivities. Specifically, subjection of 1 to HCO_2H and Et_3N in the presence of 0.5−1 mol % of pentafluorobenzenesulfonyl-DPEN-Ru catalyst 2b at 30−40 °C in either $PhCH_3$ or CH_2Cl_2 generated the *syn*-hydroxy product 3 selectively in 15−33:1 dr, 93−97% ee, and 75−88% isolated yields.

The fields of dynamic kinetic resolution (DKR) and asymmetric transfer hydrogenation (ATH) have each sparked extensive interest and found numerous applications in both academic and industrial arenas. While DKR is a powerful method for converting a racemic starting material into an enantio- and/or diastereopure product in a quantitative theoretical yield,[1] ATH has proven to be a useful strategy for metal- or enzyme-catalyzed enantioselective reduction of prochiral ketones using suitable hydrogen donors (i.e., formic acid or 2-propanol) as a practical alternative to conventional molecular hydrogen.[2]

The demonstration of DKR in a metal-catalyzed asymmetric hydrogenation (AH) of α-substituted β-keto esters was initially reported by Noyori et al.[3] and later exploited by others.[4] While there have been several reports on DKR−ATH of chirally labile ketones, the scope of the substrate is generally limited to cyclic aliphatic β-ketoesters or α-heteroatom-substituted β-ketoesters.[5]

To the best of our knowledge, the concept of metal-catalyzed DKR−ATH has never been applied to α-*alkyl-substituted β-ketoamides* for the preparation of optically

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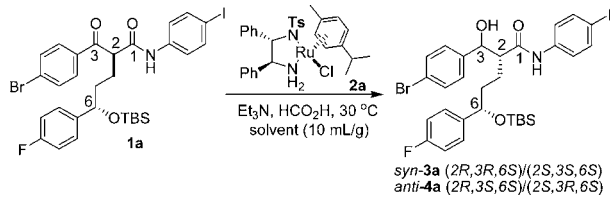
Table 1. Initial DKR−ATH Studies of **1a** with Catalyst **2a**[a]



entry	solvent	**2a** (mol %)[b]	time[c] (h)	Et_3N[d] (equiv)	HCO_2H[d] (equiv)	convn[e] (%)	**3a**:**4a**[f] (HPLC)	% ee[g] **3a**
1	CH_2Cl_2	2	20	5	5	99	91:9	84.7
2	EtOAc	2	48	5	5	97	80:20	74.2
3	MeCN	2	60	5	5	90	77:23	76.4
4	$PhCH_3$	2	20	5	5	98	89:11	81.0
5	CH_2Cl_2	2	20	2	2[h]	100	94:6	88.0
6	CH_2Cl_2	2	20	2[h]	2	99	94:6	87.1
7	CH_2Cl_2	2	20	2[i]	2[i]	98	94:6	88.5
8	CH_2Cl_2	0.5	21	2	2	100	94:6	87.3
9	**CH_2Cl_2**	**0.5**	**18**	**1**	**1.2**[j]	**100**	**95:5**	**92.7**
10	CH_2Cl_2	0.5	15[k]	1	1.2[j]	100	94:6	87.6
11	CH_2Cl_2	0.5	40[l]	1	1.2[j]	96	95:5	92.3

[a] [**1**] = 10 mL/g of solvent, 200 mg scale. [b] Isolated or in situ generated catalyst. [c] Required time to reach the conversion. [d] Unless noted otherwise, added all at once in the beginning of the reaction. [e] HPLC analysis. [f] Sum of *syn*-epimers:sum of *anti*-epimers in the crude reaction mixture as analyzed by HPLC and confirmed by NMR and X-ray single crystal structure, where the major *syn*-**3a** epimer has configuration of (2*R*,3*R*,6*S*) and the major *anti*-**4a** epimer (2*R*,3*S*,6*S*). [g] See ref 12. [h] Added over 2 h. [i] Added as a 1:1 mixture over 2 h. [j] Added over 8 h. [k] 40 °C. [l] 23 °C.

active β-hydroxyamides.[6] These types of products, as well as their 1,3-amino alcohol derivatives,[7] have been widely used as synthetic building blocks to access many natural products and advanced pharmaceutical intermediates, including various potent β-lactam (azetidinone) derivatives.[8] Herein, we wish to report the first enantio- and diastereoselective approach to α-alkyl-substituted *syn*-β-hydroxyamides via highly efficient catalytic DKR−ATH reactions from the corresponding racemic β-ketoamides.[9]

Using compound **1a** as a test substrate,[10] our DKR−ATH studies were initially performed with Noyori's *p*-cymene-TsDPEN ruthenium(II) chloride complex **2a**. Considering that optically active α-substituted β-ketoamides have been previously prepared via a chiral auxiliary methodology,[11] the rate of α-epimerization for our ketoamide substrate was unknown at the time. Gratifyingly, we found that subjection of **1a** to 2 mol % of **2a** and 5 mol equiv of each Et_3N and HCO_2H at 30 °C resulted in high conversions to give the corresponding alcohols in various solvents (entries 1−4, Table 1), with CH_2Cl_2 yielding the highest diastereoselectivity and enantioselectivity[12] for the *syn*-hydroxyamide (2*R*,3*R*,6*S*)-**3a**.[13] The observed high enantio- and diastereoselectivity for the *syn* epimers indicates that the α-epimerization event certainly takes place under these conditions. Upon reducing the amounts of base and hydride donor to 2 equiv each, higher de and ee were both observed, regardless of the order of addition (entries 5−7). Furthermore, performing the reaction with a reduced amount of catalyst (0.5 mol %) did not result in the erosion of de and ee (entry 8). Better results were obtained when performing

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(6) For an example of *enzymatic* DKR−ATH of 2-oxocyclopentanecarboxamides, see: Quirós, M.; Rebolledo, F.; Gotor, V. *Tetrahedron: Asymmetry* **1999**, *10*, 473.

(7) For reviews, see: (a) Knapp, S. *Chem. Rev.* **1995**, *95*, 1859. (b) Ohfune, H. *Acc. Chem. Res.* **1992**, *25*, 360.

(8) For *representative* examples, see: (a) Brandi, A.; Cicchi, S.; Cordero, F. M. *Chem. Rev.* **2008**, *108*, 3988. (b) Alcaide, B.; Almendros, P.; Aragoncillo, C. *Chem. Rev.* **2007**, *107*, 4437. (c) Thiruvengadam, T. K.; Sudhakar, A., R.; Wu, G. *Process Chemistry in the Pharmaceutical Industry*; Gadamasetti, K. G., Ed.; Marcel Dekker, Inc.: New York, NY, 1999; p 221. (d) Déziel, R.; Malenfant, E. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1437. (e) Clader, J. W.; Burnett, D. A.; Caplen, M. A.; Domalski, M. S.; Dugar, S.; Vaccaro, W.; Sher, R.; Browne, M. E.; Zhao, H.; Burrier, R. E.; Salisbury, B.; Davis, H. R. *J. Med. Chem.* **1996**, *39*, 3684. (f) Wild, H.; Kant, J.; Walker, D. G.; Ojima, I.; Ternansky, R. J.; Morin, J. M., Jr.; Georg, G. I.; Rabikumar, V. T. *The Organic Chemistry of β-Lactams*; Georg, G. I., Ed.; VCH: New York, 1993.

(9) For examples of *nonasymmetric*, but diastereoselective, reduction of *racemic* α-substituted β-ketoamides, see: (a) Bartoli, G.; Bosco, M.; Marcantoni, E.; Melchiorre, P.; Rinaldi, S.; Sambri, L. *Synlett* **2004**, *1*, 73. (b) Bartoli, G.; Bosco, M.; Dalpozzo, R.; Marcantoni, E.; Massaccesi, M.; Rinaldi, S.; Sambri, L. *Tetrahedron Lett.* **2001**, *42*, 8811. (c) Fujita, M.; Hiyama, T. *J. Am. Chem. Soc.* **1985**, *107*, 8294.

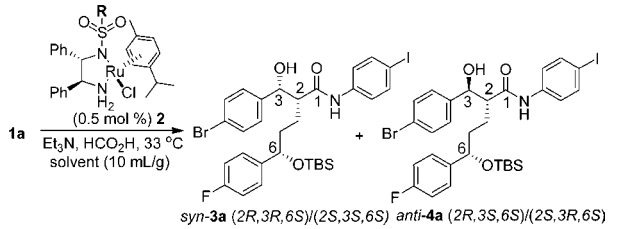
(10) See Supporting Information for the synthesis of this compound.

(11) Evans, D. A.; Ennis, M. D.; Le, T. *J. Am. Chem. Soc.* **1984**, *106*, 1154.

(12) For ease of discussion, the term "enantioselectivity" refers to the absolute configuration at carbon 2 and 3 of the *syn*-epimer **3a** while ignoring the fixed stereocenter at the benzylic carbon labeled 6 [i.e., (2*R*,3*R*,6*S*) vs (2*S*,3*S*,6*S*)].

(13) The absolute stereochemistry was confirmed by X-ray single-crystal structure (see Supporting Information). Additional information can be found at the Cambridge Crystallographic Data Centre (CCDC) with deposition code of CCDC 752316.

Table 2. DKR−ATH of **1** with Various Ru Catalysts **2**[a]



syn-**3a** (2*R*,3*R*,6*S*)/(2*S*,3*S*,6*S*) *anti*-**4a** (2*R*,3*S*,6*S*)/(2*S*,3*R*,6*S*)

entry	cat. **2**[b] **R**	solvent	time[c] (h)	convn[d] (% assay)	**3a**:**4a**[e] (HPLC)	% ee[f] **3a**
1	*p*-Tol (**2a**)	CH_2Cl_2	18	100 (88)	94.5:5.5	92.5
2	*p*-F-Ph (**2b**)	CH_2Cl_2	20	100	96.2:3.8	91.5
3	*p*-CF_3-Ph (**2c**)	CH_2Cl_2	20	100	96.2:3.8	94.2
4	CF_3 (**2d**)	CH_2Cl_2	21	100	95.5:4.4	90.9
5	**F_5-Ph (2e)**	**CH_2Cl_2**	**22**	**100 (95)**	**96.9:2.9**	**96.7**
6	F_5-Ph (**2e**)	iPAc	28	98	92.1:7.7	88.8
7	F_5-Ph (**2e**)	DME	48	99	90.7:9.2	88.9
8	F_5-Ph (**2e**)	iPA	72	89	85.7:14.3	88.6
9	F_5-Ph (**2e**)	**$PhCH_3$**	**23**	**100 (93)**	**96.8:3.0**	**93.6**

[a] [**1**] = 10 mL/g of solvent, 200 mg scale, 0.5 equiv of Et_3N, 1.1 equiv of HCO_2H added over 8 h. [b] Isolated catalyst or in situ generated from $[RuCl_2$-*p*-cymene$]_2$ and the chiral ligands. [c] Required time to reach the conversion. [d] HPLC analysis. [e] Sum of *syn*-epimers:sum of *anti*-epimers in the crude reaction mixture as analyzed by HPLC and confirmed by NMR, where the major *syn*-**3a** epimer has configuration of (2*R*,3*R*,6*S*) and the major *anti*-**4a** epimer (2*R*,3*S*,6*S*). [f] See ref 12.

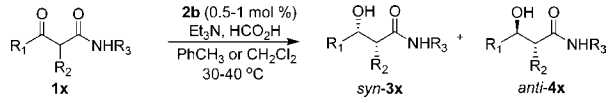
a slow addition of HCO_2H (1.2 equiv) over 8 h to a solution of **1**, Et_3N (1 equiv), and **2a** (0.5 mol %) in CH_2Cl_2 at 30 °C (entry 9). On the other hand, erosion of enantioselectivity was observed at higher temperature (entry 11), whereas long reaction time and lower conversions were obtained at lower temperature (entry 10).

To further optimize the transformation, other Ru catalysts, particularly those bearing electron-deficient aryl sulfonyl groups on the chiral ligands[5d] (**R** in **2**), were screened (Table 2). In general, high conversions were obtained using 0.5 mol % catalyst loading, 0.5 mol equiv of Et_3N, and 1.1 mol equiv of HCO_2H. As discovered previously, slow addition of HCO_2H over 8 h was found to be optimal for achieving the high conversion and selectivity. In CH_2Cl_2, excellent diastereo- and enantioselectivity of the *syn*-isomer were obtained for all catalysts (entries 1−5), with pentafluorobenzenesulfonyl-DPEN Ru catalyst **2e** affording the highest dr (97:3) and ee (96.7%). While performing the reactions in "greener" solvents, such as iPAc, DME, or iPA, afforded lower dr and ee with slightly lower conversions and longer reaction times (entries 6−8), similar results could be favorably obtained in toluene, in which the reaction could be completed in 23 h to afford 93% assay yield of the combined products in 96.8:3 dr and 93.6% ee for the *syn*-epimer (2*R*,3*R*)-**3a**. Upon scale-up (mol scales), the *syn*-product (2*R*,3*R*)-**3a** could be selectively crystallized from iPA:H_2O, affording the product in 90% yield, 98:2 dr, and 99.5% ee.

With optimized conditions in hand, the substrate scope and limitation was subsequently explored. The results from these studies (Table 3) indicate that the current conditions (0.5−1 mol % **2b**, Et_3N, HCO_2H, $PhCH_3$, or CH_2Cl_2, 30−40 °C) generally apply to other α-alkyl-substituted (R_2) aromatic *β*-ketoamides (**1b**−**h**), affording the corresponding *syn* *β*-hydroxide amides (**3b**−**h**) in high yields and good diastereo- and enantioselectivities (entries 2−8). In addition, the reaction could also be extended to include aliphatic ketones (entry 9) and aliphatic amides (entry 10), albeit with lower diastereoselectivities. Nonetheless, the product purity could be conveniently upgraded by crystallization to afford the *syn* diastereomers in high yields, enantio-, and diastereoselectivities.

As mentioned previously, *syn*-*β*-hydroxyamides can be readily transformed into synthetically useful *trans*-*β*-lactam (azetidinone) derivatives via either a Mitsunobu reaction[14] or intramolecular displacement of the preactivated alcohols with the corresponding amide anion.[15] In the present case,

Table 3. Substrate Scope[a]

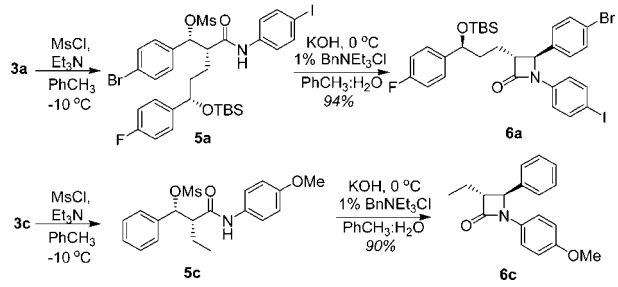


entry	x	R_1	R_2	R_3	**3x**:**4x**[b]	**3x**:**4x**[c]	% ee **3x**[d]	% yield **3x**[e]
1	**a**	*p*-BrPh	*p*-FPhCH-(*S*)-OTBS-Et−	*p*-IPh	97:3	98:2	99.5	90
2	**b**	Ph	Et	Ph	92:8	99:1	99.5	80
3	**c**	Ph	Et	*p*-OMePh	91:9	98:2	99	85
4	**d**	Ph	Bn	Ph	88:12	99:1	99	70
5	**e**	Ph	allyl	Ph	92:8	92:8	98	74
6	**f**	Ph	cinnamyl	Ph	93:7	97:3	95	77
7	**g**	*p*-BrPh	cinnamyl	*p*-IPh	93:7	94:6	98	90
8	**h**	*p*-AllylOPh	*p*-FPhCH-(*S*)-OTBS-Et−	*p*-FPh	93:7	99:1	92	90
9	**i**	*c*-Hex	cinnamyl	Ph	83:17	99:1	95	80
10	**j**	Ph	Ph−Pr−	Bn	80:20	99:1	99.5	75

[a] [**1**] = 10 mL/g of solvent, 1−50 g scale, 0.5 equiv of Et_3N, 1.1−2 equiv of HCO_2H added over 8 h, preformed/isolated catalyst **2b**. [b] HPLC ratio of the crude reaction mixture and confirmed by NMR spectroscopy. [c] HPLC ratio in the isolated material. [d] Chiral HPLC analysis (see Supporting Information). [e] Isolated by crystallization or SiO_2 gel column purification.

activation of the hydroxyl group in compounds *syn*-**3a** and *syn*-**3c** with MsCl and Et_3N at −10 °C in toluene cleanly afforded mesylates **5a** and **5c**, which were then subsequently subjected to 35 wt % aqueous KOH and a phase transfer catalyst, such as $BnNEt_3Cl$, to exclusively afford *trans*-β-lactam **6a** and **6c** in 94% and 90% isolated yield, respectively, in a one-pot, through process (Scheme 1).[16]

Scheme 1. Diastereoselective Synthesis of *trans*-β-Lactam



In summary, the first enantio- and diastereoselective synthesis of various *syn*-α-alkyl-substituted β-hydroxyamides via highly efficient Ru-catalyzed DKR−ATH of the corresponding β-ketoamides has been successfully demonstrated. Excellent dr and ee were observed when the transformation was performed in CH_2Cl_2 or toluene using Ru catalysts bearing an electron-deficient sulfonyl diamine ligand, such as **2b**. Various types of substrates, including aromatic and aliphatic α-substituted β-ketoamides **1**, were shown to selectively yield *syn*-β-hydroxyamides **3** in 80:20−97:3 diastereomeric ratio. Upon crystallization or purification by column chromatography, the desired *syn*-product **3** could be obtained in 75−90% isolated yield, 92−99.5% ee, and 92:8−99:1 dr.[17] An example of the potential utility of this class of compounds was demonstrated by the preparation of stereochemically pure, highly functionalized *trans*-β-lactams **6a** and **6c** in high yields.

Acknowledgment. We acknowledge the following Merck's analytical group: Mr. Bob Reamer and Ms. Lisa DiMichele for their assistance with NMR interpretations and structural assignments, Ms. Mirlinda Biba for her assistance with HPLC chiral assay method development, and Mr. Thomas Novak for the HRMS measurements. In addition, we would also like to thank Dr. Michael McNevin and Dr. Richard Ball from Merck's physical characterization group for generating crystallographic data.

Supporting Information Available: Experimental procedures and characterization of new substrates, including their NMR spectra and single-crystal X-ray structure of compound **3a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) For phase transfer catalyzed cyclization of O-phosphorylated or O-benzoylated substrates, see ref.8c For a nonphase transfer promoted process, see: Evans, D. A.; Sjogren, E. B. *Tetrahedron Lett.* **1986**, *27*, 3119.

(16) While executing the mesylation at higher temperatures (>5 °C) resulted in partial chloride displacement leading to *syn* β-lactams, performing the cyclization under homogenous conditions (KOtBu/THF or LiHMDS/THF) gave initially the *trans*-β-lactam **6**, which during the course of the reaction equilibrated rapidly to a 4:1 mixture of *trans:syn* β-lactams.

(17) **Typical Experimental Procedure:** To a solution of keto amide **1a** (5 g, 7.04 mmol, 1 equiv) in dry toluene (KF < 50 ppm, 50 mL) was added the ruthenium catalyst **2b** (25 mg, 0.035 mmol, 0.005 equiv) all at once as a solid at 20−25 °C. The resulting mixture was then purged several times with N_2. Neat triethylamine (0.49 mL, 3.52 mmol, 0.5 equiv) was then added, and the reaction mixture was warmed to 30−33 °C, at which neat formic acid (KF = <1.7 wt %, 0.325 mL, 7.74 mmol, 1.1 equiv) was charged at a uniform rate over 8 h via a syringe pump. The reaction mixture was then aged at 30−33 °C for an additional 12 h or until >99.5% conversion was obtained. Once the reaction was judged complete, the mixture was then concentrated and solvent switched completely to iPA to give a thin slurry at 7 mL/g (wrt SM) of final volume (35 mL). The batch was then warmed to 36−40 °C to give a homogenous solution and cooled to 25 °C, at which the product started to crystallize. After aging for 10 h at 20−25 °C, water (3 vol. wrt SM, 15 mL) was added as an antisolvent over 1 h. After cooling to 0−5 °C, the resulting slurry was aged for another 2 h and then filtered. The wetcake was washed with a cold mixture of 1:1 iPA: H2O (20 mL) and then dried at 40 °C in a vacuum oven. The β-hydroxy amide product **3a** was typically isolated in 98:2 dr (**3a:4a**), 99.5% ee, and 90% yield (4.5 g). The absolute stereochemistry of the product was confirmed by X-ray single crystal structure (see Supporting Information). Mp: 122−123 °C. $[\alpha]_D^{25}$ −67 (*c* 0.05 M, MeOH). ^{1}H NMR ($CDCl_3$) δ 7.60 (s + d, J = 8.7 Hz, 3H), 7.44 (d, J = 8.4 Hz, 2H), 7.23 (t, J = 8.4 Hz, 4H), 7.15 (m, 2H), 6.95 (t, J = 8.7 Hz, 2H), 5.08 (s, 1H), 4.57 (m, 1H), 3.42 (s, 1H), 2.50 (m, 1H), 1.66 (m, 4H), 0.82 (s, 9H), −0.04 (s, 3H), −0.20 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 173.1, 162.1 (d, *JCF* = 245.0 Hz), 141.2 (d, *JCF* = 3.0 Hz), 140.5, 138.2, 137.2, 131.7, 127.9, 127.4 (d, *JCF* = 7.9 Hz), 122.1, 121.8, 115.2 (d, *JCF* = 21.3 Hz), 88.1, 75.0, 73.6, 54.2, 38.7, 26.0, 25.9, 22.9, 18.3, −4.4, −4.8. ^{19}F NMR ($CDCl_3$) δ 115.51. Anal. Calcd for $C_{30}H_{36}BrFINO_3Si$: C, 50.57; H, 5.09; N, 1.97. Found: C, 50.72; H, 5.10; N, 1.86.