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Exploring the Scope of Asymmetric Synthesis of *β*-Hydroxy-*γ*-lactams via Noyori-type Reductions

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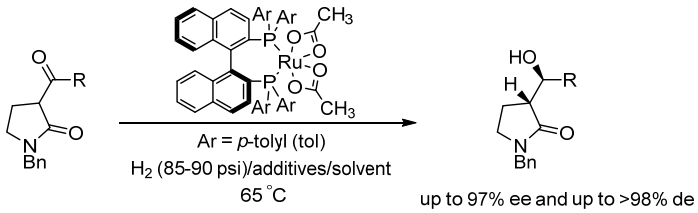
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ABSTRACT



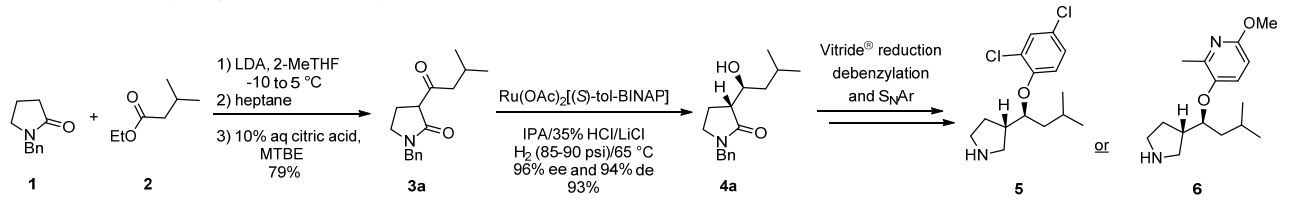
Enantio- and diastereoselective hydrogenation of *β*-keto-*γ*-lactams with a ruthenium–BINAP catalyst, involving a dynamic kinetic resolution (DKR), has been employed to provide a general, asymmetric approach to *β*-hydroxy-*γ*-lactams, a structural motif common to several bioactive compounds. Full conversion to the desired *β*-hydroxy-*γ*-lactams was achieved with high diastereoselectivity (up to >98% de) by addition of catalytic HCl and LiCl, while *β*-branching of the ketone substituent demonstrated a pronounced effect on the modest to excellent enantioselectivity (up to 97% ee) obtained.

The generation of contiguous stereogenic centres from racemic or achiral starting materials in a selective fashion is a standing ambition of asymmetric synthesis. Dynamic kinetic resolution (DKR) is a powerful methodology which enables the necessary two supplementary steps: racemisation together with a consecutive asymmetric transformation.[1] In pursuit of a synthetic approach for access to multigram quantities of two serotonin norepinephrine reuptake inhibitors (SNRIs) **5** and **6**, a route (Scheme 1) was developed by Magnus and coworkers at Lilly which employed a DKR involving the enantio- and diastereoselective hydrogenation of a *β*-

keto-γ-lactam **3a**,[2] based on the chemistry precedented by Takasago International Corporation.[3a] The optimised DKR-hydrogenation afforded the critical β-hydroxy-γ-lactam **4a** in high yield (93%) and with impressive stereocontrol (96% ee, 94% de).

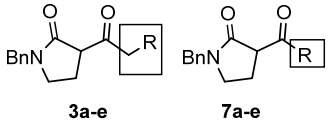
Given the remarkable success of this reaction, in furnishing a single product, in high yield and excellent enantiomeric and diastereomeric excess, and the paucity of known examples for similar substrates,[3a-c] we wished to explore the scope of the transformation, with the ultimate aim of establishing the route as a general pathway to optically pure β-hydroxy-γ-lactams. The β-hydroxy-γ-lactam structure provides a viable precursor to compounds containing a pyrrolidine moiety, an important pharmacophore in many biologically active molecules. The motif is present in compounds exhibiting diverse pharmacological effects, ranging from antimicrobial and antifungal activity[3] to serotonin norepinephrine reuptake inhibition,[4] making a general asymmetric approach to β-hydroxy-γ-lactams—and any pyrrolidine-containing compounds derived thereafter—a desirable objective in its own right.

Scheme 1. DKR-Hydrogenation-based Synthesis of SNRIs **5** and **6**



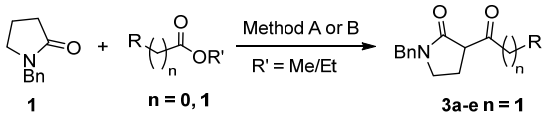
To evaluate substrate scope of the transformation, nine novel β-keto-γ-lactams **3b-e** and **7a-e** (Figure 1) were prepared for investigation, alongside the model compound **3a** used by Lilly. The substrates comprized 5 pairs, where each of the pair was differentiated by the presence or absence of a methylene functionality adjacent to the ketone. This enabled the importance of branching at the β-position to be comprehensively assessed, with respect to both substrate conversion and stereochemical outcome.

Figure 1. β-Keto-γ-Lactams for Substrate Study



All β-keto-γ-lactams **3a-e** and **7a-e** were prepared via Claisen-type condensations, using *N*-benzyl-γ-lactam **1** and the appropriate ester (Table 1). In most cases, cryogenic conditions (–75 °C) were employed, though a modified protocol, used for preparation of the original substrate **3a**,[2] could also be implemented for synthesis of β-keto-γ-lactams **3e** and **7c**. The latter procedure allowed the reactions to be run at –10 to 5 °C and took advantage of the insolubility of the intermediate enolate, which was isolated from the reaction mixture by filtration prior to acidic workup, and rendered subsequent chromatographic purification a trivial endeavour. The reduced yield of compound **7c** (Table 1, entry 6) was due to inefficient enolate precipitation, however, as sufficient material for this study was recovered, the reaction was neither repeated nor optimized.

Table 1. Claisen-type Synthesis of β-Keto-γ-Lactams **1**

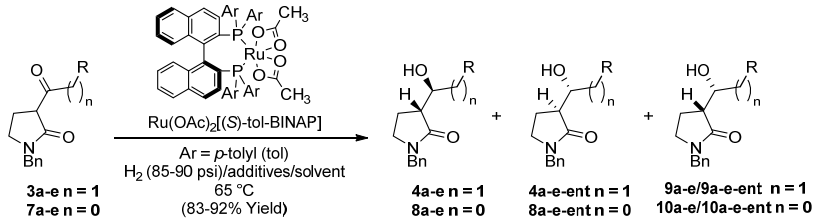


entry	n	R	method[a]	product (% yield)[b]
1	1	*i*-propyl	A	**3a** (65)
2	0	*i*-propyl	B	**7a** (68)
3	1	cyclopropyl	B	**3b** (63)
4	0	cyclopropyl	B	**7b** (66)
5	1	cyclohexyl	B	**3c** (41)
6	0	cyclohexyl	A	**7c** (34)
7	1	phenyl	B	**3d** (69)
8	0	phenyl	B	**7d** (48)
9	1	*t*-butyl	A	**3e** (66)
10	0	*t*-butyl	B	**7e** (61)

[a]Method A involved addition of a mixture of γ-lactam **1** and the ester to a solution of LDA in 2-MeTHF at –10 to 5 °C with subsequent addition of heptane to precipitate the intermediate enolate of β-keto-γ-lactam **3**, the precipitate was collected, suspended in MTBE, and worked-up with 10% aq citric acid; Method B involved pre-generation of the enolate of γ-lactam **1**, as a solution in THF at –75 °C, to which the ester was added slowly. [b]Isolated yield after chromatography on silica gel.

Each of the substrates **3a-e** and **7a-e** was then subjected to the key Noyori-type reduction, under conditions previously optimized for **3a**, to investigate if the methodology developed for **3a** could be generally applied. Ruthenium-catalyzed hydrogenations were conducted using methanol, ethanol or IPA as solvent, and in the presence of catalytic HCl and LiCl as additives (Table 2).

Table 2. DKR-Hydrogenation Substrate Screen



				n = 1				n = 0			
entry[a]	R	LiCl[b]	solvent	substrate (product)	Time (%[c])	% ee[d]	% de[d]	substrate (product)	Time (%[c])	% ee[d]	% de[d]
1	*i*-propyl	0	MeOH	**3a (4a)**	16 h	93.6	90.2	**7a (8a)**	16 h	78.7	>98.0
2	cyclohexyl	0	MeOH	**3c (4c)**	16 h	94.5	96.5	-	-	-	-
3	*t*-butyl	0	MeOH	**3e (4e)**	16 h (<2.0)	39.0	NA[e]	-	-	-	-
4	*i*-propyl	0	EtOH	**3a (4a)**	16 h	94.3	94.4	**7a (8a)**	16 h	74.6	88.7
5	cyclopropyl	0	EtOH	**3b (4b)**	16 h	84.2	97.5	**7b (8b)**	16 h	96.8	95.8
6	cyclohexyl	0	EtOH	**3c (4c)**	16 h	95.0	94.7	**7c (8c)**	16 h	35.5	>98.0
7	phenyl	0	EtOH	**3d (4d)**	16 h	84.7	91.6	**7d (8d)**	16 h	18.2	>98.0
8	*t*-butyl	0	EtOH	**3e (4e)**	16 h (<2.0)	63.9	NA[e]	**7e (8e)**	16 h (<2.0)	NA[e]	NA[e]
9	*t*-butyl	1	EtOH	**3e (4e)**	16 h (<2.0)	NA[e]	NA[e]	**7e (8e)**	16 h (<2.0)	NA[e]	NA[e]
10	*t*-butyl	0	CF_3CH_2OH	**3e (4e)**	16 h (<2.0)	42.1	NA[e]	-	-	-	-
11	*i*-propyl	0	IPA[f]	-	-	-	-	**7a (8a)**	16 h	72.1	>98.0
12	*i*-propyl	1	IPA[f]	**3a (4a)**	16 h (63.5)	-	-	**7a (8a)**	16 h	67.1	93.4
					36 h[g]	96.5	95.6				
13	cyclopropyl	1	IPA[f]	**3b (4b)**	16 h	86.1	>98.0	**7b (8b)**	16 h	94.9	92.6
14	cyclohexyl	1	IPA[f]	**3c (4c)**	16 h (95.4)	-	-	**7c (8c)**	16 h	38.5	>98.0
					32 h[g]	97.4	96.2				
15	phenyl	1	IPA[f]	**3d (4d)**	16 h (75.1)	-	-	**7d (8d)**	16 h	15.3[h]	>98.0
					36 h[g]	87.5	97.0				

[a]Screening reactions run with *β*-keto-*γ*-lactam **3** or **7** (1 g), diacetato[(*S*)-(−)-2,2′-bis(di-*p*-tolylphosphino)-1,1′-binaphthyl]ruthenium(II) ($Ru(OAc)_2$[(*S*)-tol-BINAP)])[5] (substrate to catalyst mole ratio (S/C): 280), HCl (6 mol%), and solvent (55 mL) at 65 °C under 85–90 psi of H_2. [b]Mole percent relative to substrate **3** or **7**. [c]Extent of reaction as determined by ^{1}H NMR analysis. [d]Determined by chiral HPLC (see SI). [e]Not applicable (too small to accurately measure). [f]Reactions in IPA were run at a concentration of 88 mg/mL (4.4 g of substrate **3** or **7**) as a dilution effect caused ineffective hydrogenation at the lower concentration employed when using other solvents. [g]Second charge of catalyst (S/C: 280) was added after 16 h. [h]This reaction was repeated with a value of 8.3% ee recorded.

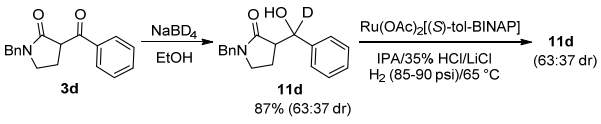
While the use of HCl in Noyori-type reductions is heavily precedented,[6] use of LiCl as an additive had also been established as a critical component of the catalyst system for hydrogenations performed in IPA; its presence was found to be essential for reliable conversion of **3a** to the corresponding *β*-hydroxy-*γ*-lactams (±)-**4/9a**.[2] LiCl has previously been shown to enhance the reactivity of ruthenium–BINAP catalytic systems.[7] Thus, with a view to generalizing the reaction, LiCl was included as an additive for each substrate undergoing hydrogenation in IPA, though in some instances it is not necessarily required—as indicated by the complete conversion of the isopropyl substrate **7a** in its absence. Effective stereoselective hydrogenation of most of the substrates **3a-e** and **7a-e** was achieved, as summarised in Table 2, with the corresponding products obtained in good isolated yields (83–92%). While reactions were slightly slower on going from methanol/ethanol to IPA, overall, the enantioselectivity was in general slightly higher for reactions conducted in IPA.

The presence of a bulky *t*-butyl group, adjacent to the site of hydrogenation in substrates **3e** and **7e**, essentially blocked reduction of these compounds (Table 2, entries 3, 8, 9 and 10). Interestingly, variation of the steric (MeOH *cf.* EtOH) and electronic properties (trifluoroethanol, pK_a 12.4 *cf.* EtOH, pK_a 15.9)[8] of the solvent had virtually no impact on the extent of hydrogenation observed in these challenging substrates. Hydrogenation of **3e** and **7e** in IPA was not attempted, as hydrogenation in this solvent is more challenging across all susbtrates, often requiring a second charge of catalyst and prolonged reaction times. The use of LiCl as an additive in reactions of **3e** and **7e** in ethanol was also ineffective (Table 2, entry 9), and so was deemed unlikely to have an impact with IPA.

While diastereocontrol was excellent across both series of substrates **3** and **7**, the presence of *β*-branching in substrates **3** was found to have a profound impact on the enantioselectivity of the reactions. Thus, hydrogenation of substrates **3**, which possessed a methylene linker, resulted in higher enantioselectivities (>85% ee, other than for **3e** with *t*-butyl, where the extent of reaction was negligible) than the analogous substrates **7** (15–97% ee).

Given the unusually low enantioselectivity observed in the case of the phenyl substrate **7d** (Table 2, entries 7 and 15), it seemed prudent to investigate if racemization of the product might occur during the reaction, although the retention of excellent levels of diastereocontrol suggested otherwise. Formation of a benzylic carbocation (under the acidic reaction conditions employed), or, alternatively, a reversible hydride transfer from the ruthenium catalyst could potentially be envisaged. When an enantioenriched sample of (±)-**8/10d** (15.2% ee), from the initial reduction of **7d** in IPA, was re-subjected to the hydrogenation conditions for a further 72 h, only a minor decrease in the enantiopurity of the material (11.7% ee) was observed, suggesting the decreased enantioselectivity of the process is not related to stereochemical scrambling in the reaction mixture. Also, the corresponding deuterated *β*-hydroxy-*γ*-lactam **11d** was prepared and similarly underwent the hydrogenation conditions in IPA for 72 h (Scheme 2), without any evidence for deuterium–hydrogen exchange, or a change in diastereomeric ratio of the material. Accordingly, it appears that the intrinsic enantiocontrol in the reduction of the phenyl substrate **7d** is genuinely significantly lower than that of most other substrates explored.

Scheme 2. Preparation and hydrogenation of Deuterated *β*-Hydroxy-*γ*-Lactam **11d**



In line with precedent,[2] the stereochemistry of **4c** and **4d** was determined unambiguously to be 3-*R*, 1′-*S* by single crystal X-ray diffraction using Cu Kα radiation. The individual crystals used for X-ray diffraction were grown from enantioenriched samples of **4c** and **4d** (Table 2, entries 6 and 15), with the stereochemical identity of each crystal subsequently confirmed by chiral HPLC analysis following the crystallographic work. The stereochemistry of the other *β*-hydroxy-*γ*-lactam derivatives was assigned by inference from these results, with the major enantiomer in all cases displaying the characteristic features of the appropriate (*R*, S**) diastereomer in their ^{1}H NMR spectra. The appearance of the C-3H signal as a characteristic triplet or triplet of doublets at ca. 2.80 ppm was the key distinguishing feature of this diastereomer, with the C-3H signal of the (*R*, R**) diastereomer appearing as an apparent quartet at ca. 2.50 ppm.

In summary, the asymmetric DKR-hydrogenation strategy to generate *β*-hydroxy-*γ*-lactams was found to be generally applicable across a range of substrates, other than those with the sterically demanding *t*-butyl group close to the site of hydrogenation. The stereochemical outcome, in terms of enantiocontrol, is moderately dependent on the solvent employed, while strongly substrate dependent, with the best results generally seen for *β*-branched substrates **3**. Excellent diastereocontrol was seen in almost all instances.

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Supporting Information Available: Experimental procedures, characterizations for all new compounds, chiral HPLC analysis, and crystallographic data (CIF files for compounds **4c**, CCDC 1505406 and **4d**, CCDC 1505405). This material is available free of charge via the Internet at http://pubs.acs.org.

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