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Dynamic Kinetic Asymmetric Reductive Amination: Synthesis of Chiral Primary β-amino Lactams

Yazhou Lou[a], Yutao Hu[a], Jiaxiang Lu[a], Fanfu Guan[a], Gelin Gong[a], Qin Yin*[a,b], Xumu Zhang*[a]

Abstract: A highly efficient Ru-catalyzed asymmetric reductive amination (ARA) of racemic β-keto lactams with molecular hydrogen and ammonium salts has been disclosed for the synthesis of enantiomerically pure primary amino lactams *via* dynamic kinetic resolution (DKR). Using this approach, a range of *syn*-primary β-amino lactams are obtained in high yields and high chemo-, enantio- and diastereo-selectivities (up to 98% yield, 99% *ee*, >20:1 d.r., *syn*-products). The utility of the products has been demonstrated by a quick access to a key synthetic intermediate towards biologically active drug molecules. Meanwhile, mechanistic studies and control experiments indicate that the recation may proceed through a process of hydrogenation of an iminium intermediate.

Chiral amines are very common structural units in natural products, pharmaceuticals and agrochemicals.[1] Transition metal-catalyzed ARA of carbonyl compounds with transition metal hydrides has emerged as a powerful and useful tool for the construction of chiral C-N bonds.[2] Due to competitive reduction between ketone and imine intermediates in the presence of transition metal hydrides and product inhibition of amines to transition-metal catalysts, up to now, this field remains underdeveloped.[3] Arylamines[4] or benzyl amines[5] are generally considered as the amine sources in reductive amination and chiral secondary amines are thus obtained. An additional deprotection step is necessary to achieve more valuable primary amines. Compared to well-established methodologies toward chiral secondary amines, limited reports are available regarding the direct construction of chiral primary amines by ARA. Considering the step efficiency and atom economy, the direct preparation of unprotected amines in one step by ARA would be highly desirable. In 2003, Kadyrov and co-workers reported a Rh-catalyzed hydrogen-transfer ARA of ketones with ammonium formate to construct primary amines.[6] Subsequently, more efficient hydrogenation processes capable of constructing chiral primary β-amino ester with ammonium salts were developed by the scientists in Lanxess and Takasago, respectively.[7] And shortly after, this approach was applied to prepare top-selling drugs sitagliptin and ezetimibe.[8] Very recently, Schaub and our group independently reported Ru-catalyzed ARA of simple aryl ketones employing ammonia or ammonium salts, respectively.[9] Despite these promising results, ARA of racemic ketones with ammonium salts or ammonia to access continuous chiral stereocenters containing a primary amino fragment *via* DKR has not been systematically explored and remains a great challenge. To our knowledge, only two catalytic examples of cyclic ketones were recorded, yielding mainly *anti* amino acid derivatives with moderate to good enantio- and diastereoselectivity.[10] Herein, we report a highly efficient asymmetric synthesis of *syn* primary β-amino lactams *via* ARA of racemic β-keto lactams with up to 98% yield, 99% *ee* and >20:1 d.r. (*syn*-products as major products).

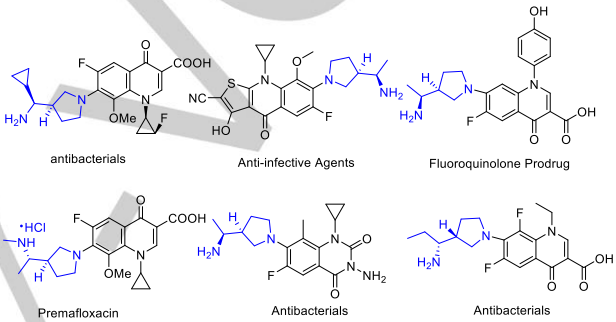

Figure 1. Selected biologically active compounds containing a chiral γ-aminopyrrolidine moiety

Chiral unprotected β-amino lactams are pivotal precursors to access primary γ-aminopyrrolidine and γ-aminopiperidine,[9b] which are very common fragments in biologically active compounds including antibacterial agents,[11,12] anti-infective agents,[13] antitumor agents[14] and fluoroquinolone prodrugs[15] (Figure 1). However, multi-steps synthetic routes are generally required to access these versatile chiral amine building blocks[12,16] and catalytic asymmetric approaches remain unknown. Transition-metal-catalyzed ARA of racemic β-ketone lactams with ammonia or its equivalents by DKR would be a facile and ideal way to achieve this goal.

Continuing our interest in ARA,[9b] we started our research with racemic α-acetyl γ-lactam **1a** as the model substrate, hydrogen as the reducing reagent and ammonium benzoate as the amine source (Table 1). We evaluated the performance of various diphosphine ligands in combination with a Ru precursor. Gratifyingly, all reactions proceeded smoothly to give the desired product, though under some conditions trace amounts of secondary alcohols resulting from competitive ketone reduction were detected (entries 1-9). The simple (*S*)-SegPhos gave the best results in terms of enantio- and diastereoselectivities (93% *ee*, >20:1 d.r., entry 2) while our previous reported C_3-TunePhos yielded comparable enantiocontrol (90% ee, entry 5). Besides, the reaction could also work well with a Rh precursor albeit with a decreased ee (entry 9).

Table 1. Ligand screening of Ru-catalyzed ARA of β-keto lactams[a]

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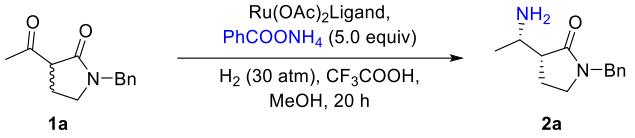
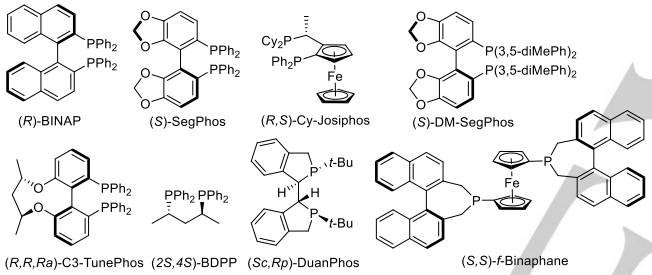


1a **2a**

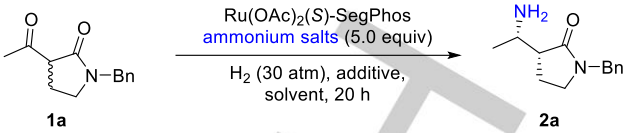
Entry	Ligand	Conv. (%)[b]	d.r.[c]	*ee* (%)[d]
1	(*S*)-BINAP	>99	>20:1	82
2	(*S*)-SegPhos	>99	>20:1	93
3[e]	(*R,S*)-Cy-JosiPhos	>99	>20:1	-57
4	(*S*)-DM-SegPhos	>99	>20:1	92
5	(*R,R,Ra*)-C$_3$-TunePhos	>99	>20:1	-90
6[e]	(*Sc,Rp*)-DuanPhos	>99	19:1	44
7[e]	(*2S,4S*)-BDPP	>99	>20:1	race
8[e]	(*S,S*)-*f*-Binaphane	>99	54:46	-30
9[f]	(*S*)-SegPhos	>99	>20:1	89

[a] The reactions were performed with **1a** (0.2 mmol), $PhCOONH_4$ (5.0 equiv), $Ru(OAc)_2$Ligand (2.0 mol%) and TFA (0.2 mmol) in 2.0 mL MeOH at 80 °C for 20 h. [b] determined by crude ^1H NMR. [c] determined with chiral HPLC or ^1H NMR. [d] determined with chiral HPLC after acylation. [e] Prepared in situ by mixing $Ru(COD)(methylallyl)_2$ (2 mol%) , Ligand (2 mol%) and MeCOOH (4 mol%) in MeOH for 30 min before using. [f] $[Rh(COD)Cl]_2$, instead of $Ru(OAc)_2$, was used. TFA = trifluoroacetic acid.



Then we systematically screened the reaction conditions, including the evaluations of ammonium salts, additives, solvents, temperature and hydrogen pressure (Table 2, also see Supporting Information for details). Ammonium salts such as NH_4F and NH_4OAc could be used as nitrogen donors to smoothly give the chiral primary amine product with great stereo control, but NH_4Cl, NH_4Br and NH_4HSO_4 failed.[17] An attempt using ammonia (NH_3) as the amino source did not provide any conversion (entry 4). Investigation of acid additives revealed that all tested acid had a positive effect on the outcome and acetic acid proved to be the best choice, yielding *syn* product **2a** as the major product with 97% *ee* and >20:1 d.r. without formation of any alcohol byproduct (<1%) (entry 6). Acid additives are necessary to improve the reaction activities and suppress the inhibitory effect of the free amines toward the catalysts.[8a] Without any acid additive, the reaction proceeded with decreased reactivity (95% conv.) and alcohol byproduct was thereby found (8% selectivity) (entry 8). Screening of solvents disclosed that the desired products could be obtained in various solvents except THF, and methanol was found to be the best solvent. Additionally, reaction temperature, H_2 pressure and catalyst loading were also evaluated (see Supporting Information for details). To be noted, secondary amine product formed by double reductive aminations was not observed throughout the study. Considering both the yield and stereoselectivity of **2a**, the combination of 1.0 mol% $Ru(OAc)_2$(*S*)-SegPhos as catalyst, 2.5 equiv NH_4OAc as amine source, 1.0 equiv AcOH as additive, 30 atm of H_2 at 80 °C in 2.0 mL MeOH is the optimal choice.

Table 2. Further optimization of reaction conditions[a]

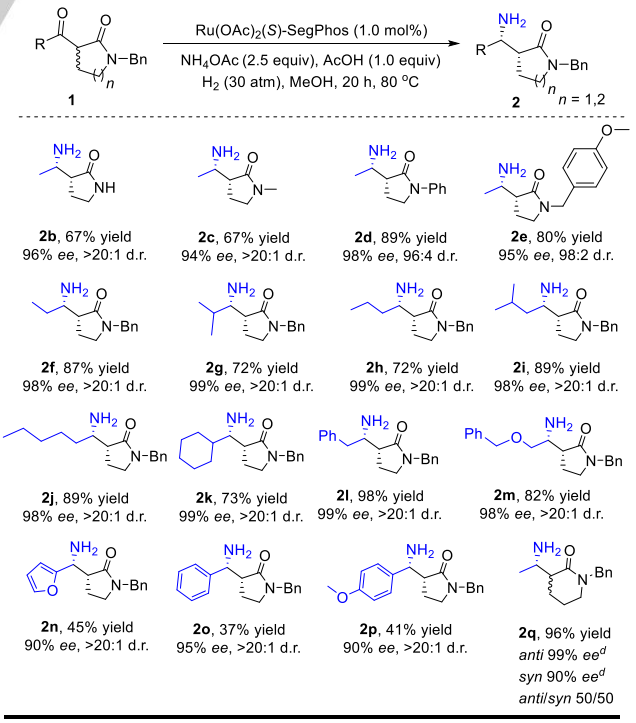


1a **2a**

Entry	Amine source[b]	Additive[b]	Solvent[b]	Conv.(%)[c]	d.r.[c]	*ee*(%)[d]
1	NH_4F	TFA	MeOH	>99	>20:1	95
2	NH_4OAc	TFA	MeOH	>99	>20:1	96
3	NH_4Cl	TFA	MeOH	>99	n.d.	n.d.
4[e]	NH_3	TFA	MeOH	n.r.	n.d.	n.d.
5	NH_4OAc	TsOH	MeOH	>99	>20:1	96
6	NH_4OAc	AcOH	MeOH	>99	>20:1	97
7	NH_4OAc	PhCOOH	MeOH	>99	>20:1	95
8[f]	NH_4OAc	–	MeOH	95(76)	>20:1	96
9	NH_4OAc	AcOH	DCE	78	>20:1	97
10	NH_4OAc	AcOH	*i*-PrOH	72	>20:1	97
11	NH_4OAc	AcOH	Toluene	44	>20:1	97
12	NH_4OAc	AcOH	THF	trace	n.d.	n.d.
13[g]	NH_4OAc	AcOH	MeOH	>99(85)	>20:1	97

[a] Unless otherwise mention, the reaction was performed with **1a** (0.2 mmol), NH_4X (5.0 equiv), $Ru(OAc)_2$(*S*)-SegPhos(**L2**) (2.0 mol%) and additive (0.2 mmol) in 2.0 mL solvent at 80 °C for 20 h. [b] See SI for detail. [c] Determined by crude ^1H NMR, isolated yield of **2a** in parentheses. [d] determined with chiral HPLC after acylation. [e] 7 atm NH_3 and 30 atm H_2 were used. [f] no additive was used and 8% of alcohol was obseverd. [g] 2.5 equiv NH_4OAc was used. DCE = 1,2-dichloroetnane. THF = tetrahydrofuran

Table 3. Substrate scope.[a,b,c]



[a]The reaction was performed with **1** (0.2 mmol), NH_4OAc (2.5 equiv), $Ru(OAc)_2$(*S*)-Segphos (1.0 mol%) and AcOH (0.2 mmol) in 2.0 mL MeOH at

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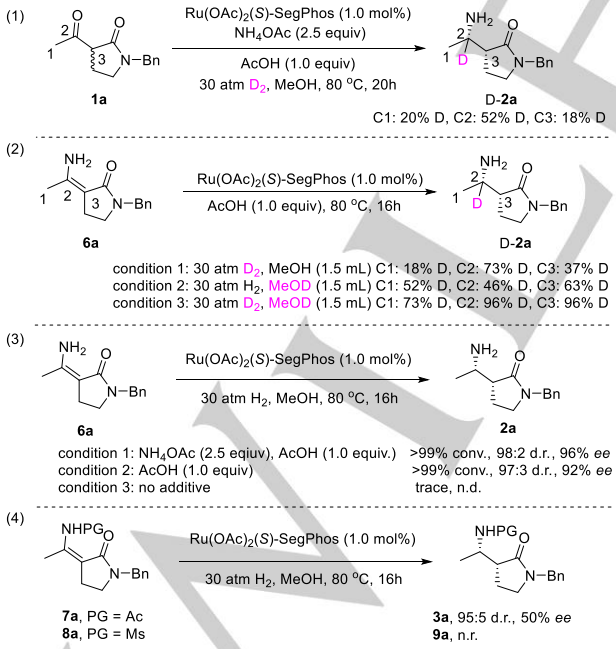
80 °C for 20 h. [b] Isolated yields. [c] ee values were determined by HPLC after acylation; d.r. values were determined by HPLC or ^{1}H NMR analysis. [d] The two diastereoisomers could be separated by chromatographic purification of their corresponding acylation products (see Supporting Information).

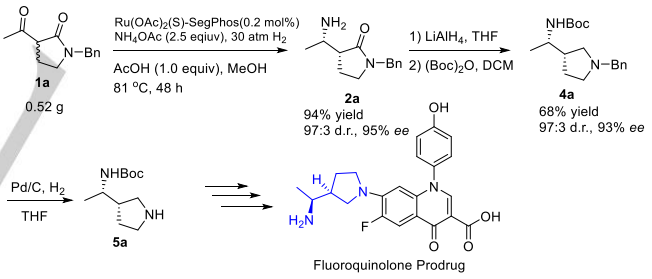
A range of racemic α-acyl-substituted γ-lactams were synthesized and tested under the optimal conditions, and the results are summarized in Table 3. Overall, all tested substrates proceeded smoothly to give the corresponding primary β-amino lactams in moderate to excellent yields with generally excellent enantioselectivity (**2a**-**2p**, 90-99% *ee*) and diastereoselectivity (>20:1 d.r., *syn*-products as major products). When nonprotected lactam **1b** was used, the reaction worked smoothly to yield the NH free primary amine **2b** with 96% *ee* and >20:1 d.r.. Replacing the N-protecting group of lactam substrates with a methyl-, phenyl- or *p*-MeO-benzyl group has little effect on the enantio- and diastereocontrol (**2c**, **2d, 2e**). Various alkyl substituted β-keto lactams were well tolerated, providing the corresponding primary amines in good yields and excellent stereocontrol (**2f**-**2m**, 98-99% *ee*). Substrate **1n** with a heteroaryl group was tolerant in this reaction with modest yield albeit high stereoselectivity (**2n**). Unfortunately, substrates **1o** or **1p** with a benzoyl group provided the desired products **2o** or **2p** in only low yields due to lower reactivity. The β-keto δ-lactams can also be hydrogenated to the corresponding β-amino δ-lactams in good yields (96%) with excellent enantioselectivities (90-99% *ee*) (**2q**). However, the diastereoselectivity-control is problematic, which may be due to the configuration effect of the six-membered ring. Nevertheless, the two diastereoisomers could be separated by chromatographic purification of their corresponding Ac-protected derivatives. The extension of this DKR process to acyclic β-keto amides proved to be inefficient at this stage. The stereo configuration of generated β-amino γ-lactams was assigned to be *syn*-(*S,R*) by X-ray crystallographic analysis of 4-NO_2Ts-**2g** (see SI). [18]



Scheme 1. Isotopic labelling experiments with D_2 and control experiments.

In this reaction, the stereo-induction can be achieved through the process of hydrogenation of the iminium or enamine intermediate and both of them could be hydrogenated to yield the final products. However, related research on this topic is still undefined.[19] To gain some insights into the reaction pathway, we conducted several isotopic labelling experiments and control experiments (Scheme 1). From ^{1}H NMR analysis, for either **1a** or independently prepared unprotected enamine **6a**, deuterium incorporation at the C1, C2 and C3 position was observed with different ratios when using D_2 gas,[20] indicating the complexity of this reaction and the difficulty of getting a conclusion of the reaction pathway with only isotopic labeling experiments (Eqs 1-2). In the presence of AcOH, **6a** was smoothly transformed to the desired *syn* **2a** with remarkable stereocontrol, whilst only trace amounts of conversion was observed without the acid additive (Eq 3), implying the importance of acid to promote the transformation from an enamine to iminium. Moreover, decreased stereocontrol was observed in the case of Ac-protected enamine **7a** while Ms-protected enamine **8a** did not work in the present reaction at all. Based on these experimental results and literature precedences,[21] we tentatively speculate that the final products are likely accessed through hydrogenation of an iminium intermediate rather than an enamine intermediate.

To demonstrate the utility of this efficient approach, a scale-up (0.52 g) preparation of β-amino lactams were performed, giving **2a** in 94% yield with 95% *ee* and 97:3 d.r.. **2a** was subsequently applied to synthesize chiral pyrrolidine **5a**, which is the key intermediate to many antibacterial agents, *anti*-infective agents and fluoroquinolone prodrug (see Figure 1). After the reduction of **2a** with $LiAlH_4$, the resulting primary amine was protected with $(Boc)_2O$ and subsequent removal of the benzyl group with Pd/C under hydrogenation condition yielded the desired chiral intermediate **5a** in 58% overall yield, without loss of the optical purity.



Scheme 2. Gram-scale synthesis and synthetic utility of the product **2a**.

In summary, we have developed an atom- and step economical methodology for the construction of enantiomerically enriched primary β-amino lactams *via* DKR. A series of racemic β-ketone γ- and δ-lactams could be hydrogenated to the corresponding primary β-amino γ- and δ-lactams in good yield with generally high stereoselectivity. The reaction pathway of this reaction was also studied and likely involved hydrogenation of the iminium intermediates instead of the enamine intermediates. In addition, with this method, synthetically useful enantioenriched β-aminopyrrolidines could be facilely obtained in an efficient manner.

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Keywords: asymmetric catalysis • asymmetric hydrogenation • chiral lactams • primary amines • reductive amination

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[17] For NH_4Br, NH_4Cl and NH_4HSO_4, the direct condensation with ketone **1a** (**1a**/ammonium = 1/5) proved to be unsuccessful after 20 h in MeOH at 75 °C, with the starting material untouched. This result is partly due to the poor solubility of strong acid's ammonium salts in MeOH, and also the fact that they are hard to release the free NH_3. In contrast, after condensation with **1a** for 2 h in MeOH at 75 °C, the enamine intermediates of other tested ammonium salts were observed from crude ^{1}H NMR analysis (46% for $PhCOONH_4$, 18% for NH_4PF_6, 38% for NH_4F, 67% for $HCOONH_4$, 67% for NH_4OAc and 94% for $(NH4)_2CO_3$.

[18]CCDC 1842282 (*syn*-(*S,R*)-4-NO_2Ts-**2g**) contains the supplementary crystallographic data for this paper. This data could be obtained free of charge from the Cambridge Crystallographic Data Centre via https://www.ccdc.cam.ac.uk/structures/.

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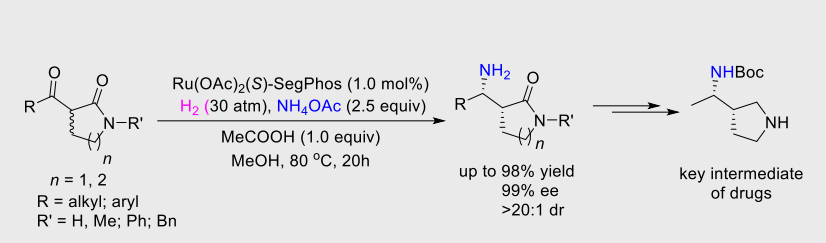

A dynamic kinetic Ru-catalyzed ARA of racemic β-keto lactams with molecular hydrogen and ammonium salts for the synthesis of enantioenriched primary amino lactams in high yields and high chemo-, stereoselectivities (up to 98% yield. 99% ee. >20:1 d.r.) has been achieved.

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Dynamic Kinetic Asymmetric Reductive Amination: Synthesis of Chiral Primary β-amino Lactams

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