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Synthesis of chiral γ-sultams through intramolecular reductive amination with sulfonylcarbamate as *N*-source

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ABSTRACT

An efficient and enantioselective palladium-catalyzed intramolecular asymmetric reductive amination with sulfonylcarbamates as *N*-sources was reported, providing a facile and general access to the chiral γ-sultam derivatives with up to 97% of enantioselectivity. This tandem process avoids additional deprotection manipulation and arduous isolation of the *N*-sulfonyl-imine intermediates.

Asymmetric reductive amination (ARA) represents one of the most practical methods to enantioenriched amines.[1] Over the past decades, significant advances have been made in development of highly effective catalyst systems.[1] Generally, electron-rich amines including ammonia, simple alkyl- and arylamine sources are predominant as *N*-nucleophiles,[2] and examples involving carbamates,[3] hydrazides[4] and Ellman's sulfinamides[5] as less electron-rich *N*-nucleophiles have also been reported. In sharp contrast, sulfonamides have been rarely used as *N*-nucleophiles in ARA. Several factors have impeded the development of efficient ARA with sulfonamides as the *N*-nucleophiles. (a) The intrinsically low nucleophilicity leads to the sluggish formation of *N*-sulfonylimine intermediates. (b) Strong Brønsted acids are required to accelerate the formation of *N*-sulfonylimines, and molecular sieves may also be needed to remove the equivalent water byproduct to promote the equilibrium for reaction of the carbonyls with sulfonamides toward the formation of unfavorable *N*-sulfonylimines.[6] (c) The side reaction of ketone direct reduction poses an issue of chemoselectivity.[7] (d) High levels of chemo- and stereocontrol are not easily fulfilled because most asymmetric hydrogenation systems are not compatible to moisture and strong acidic conditions.[8]

In order to overcome these problems and in continuation of our efforts in exploring catalytic asymmetric synthesis of chiral sultams,[6,9] we have successfully developed a palladium-catalyzed intramolecular reductive amination of ketones with *N*-*tert*-butyl protected sulfonamides as *N*-nucleophiles in the presence of Brønsted acid, providing a wide range of chiral γ-, δ-, and ε-sultams (Scheme 1).[10] The tolerable palladium catalysis system to water and Brønsted acid laid the foundation of success for the tandem sequence of deprotection and subsequent intramolecular asymmetric reductive amination. The addition of Brønsted acid lead to easy removal of the protective group (*t*-Bu) and formation of sulfonylimine or enamine intermediates, the palladium catalyst facilitated high levels of chemo- and stereoselective control. Considering the simplicity of synthesis of *tert*-butyl keto sulfonylcarbamates from simple starting marterials.[6,9d] and ready removal of Boc protective group by Brønsted acid,[11] we wondered the feasibility that the combination of palladium catalysis and Brønsted acid could promote the intramolecular asymmetric reductive amination of *tert*-butyl keto sulfonylcarbamates. Herein, we report the palladium-catalyzed intramolecular asymmetric reductive amination using sulfonylcarbamates as *N*-sources, providing a concise and efficient access to the chiral γ-sultam derivatives (Scheme 1).

To evaluate the proposed transformation, *tert*-butyl 3-*oxo*-3-phenylpropylsulfonylcarbamate (**1a**), which could be conveniently synthesized from *tert*-butyl (methylsulfonyl) carbamate according to literature procedures,[6,9d] was selected as the model substrate to assay reaction conditions. $Pd(OCOCF_3)_2$/(*S*,*S*)-f-Binaphane complex was used as hydrogenation catalyst to begin the investigation. Considering that stoichiometric amount of Brønsted acid, which was compatible with palladium catalysis system, was required to remove Boc protecting group in prior, we first examined the effect of Brønsted acids on reactivity and enantioselectivity. It was found

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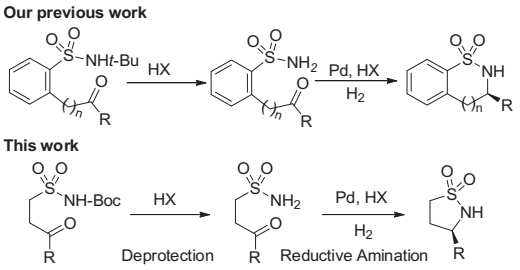


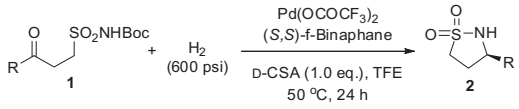
Scheme 1. Intramolecular Asymmetric Reductive Amination (ARA) with Sulfonamide as *N*-Nucleophile.

that the use of stoichiometric amount of weak di-*p*-toluoyl-d-tartaric acid (d-DTTA) or benzoic acid did not yield a detectable amount of the desired product (Table 1, entries 1–2). Fortunately, in the presence of more acidic l-camphorsulfonic acid (l-CSA), γ-sultam **2a** could be obtained in 95% yield and 94% ee besides trace amount of carbonyl reduction product (entry 3). This observation illustrated that this catalytic system could chemoselectively distinguish carbonyl group and *N*-sulfonylimines, the chiral palladium catalyst was well-compatible to moisture, water and acidic condition. This tandem process involves deprotection of *N*-Boc protective group and one-pot intramolecular reductive amination of ketones and sulfonamides. The enantioselectivity was further improved to 97% by employing d-camphorsulfonic acid (d-CSA) as acid additive, which might ascribe to match of chiral ligand and camphorsulfonic acid. Next, different solvents were examined and trifluoroethanol (TFE) proved to be optimal (entries 6–9). Upon further optimization of some commercially available bisphosphine ligands, (*S*,*S*)-f-Binaphane still emerged as the most favorable one. Thus, the optimized reaction conditions were established: Pd$(OCOCF_3)_2$/(*S*,*S*)-f-Binaphane/d-CSA/TFE/H_2 (600 psi)/50 °C.

With the optimal reaction conditions in hand, a range of keto sulfonylcarbamates **1** were explored, and the results were summarized in Table 2. Intramolecular reductive amination of substrates bearing alkyl and aryl substituents was successfully conducted, providing the desired chiral γ-sultam derivatives in excellent yields and enantioselectivities. In general, the substrates with simple aryl substituents gave slightly higher ee than the alkyl substituents (entries 1–5). For the benzyloxymethyl substituted substrate **1f**, moderate 82% of enantioselectivity was observed (entry 6, Table 2). For the aryloxymethyl substituted substrates, high yields and enantioselectivities were obtained regardless of positions and electronic properties of substituents of aryl (entries 7–10).

In summary, we have developed a facile method for the rapid synthesis of diverse enantiomerically enriched γ-sultams *via* palladium-catalyzed intramolecular asymmetric reductive amination

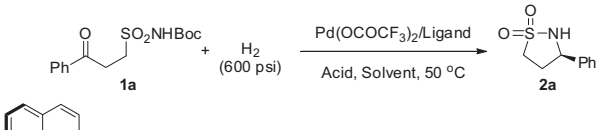
Table 2
Substrate Scope for Keto Sulfonylcarbamates.[a]

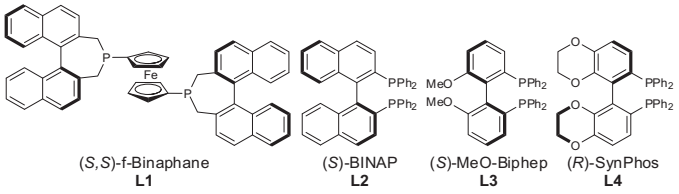


Entry	R	Yield (%)[b]	Ee (%)[c]
1	Ph	95 (**2a**)	97 (*R*)
2	4-FC_6H_4	95 (**2b**)	95 (*R*)
3	Me	85 (**2c**)	90 (*S*)
4	*n*-Bu	91 (**2d**)	94 (*S*)
5	*n*-C_6H_{13}	95 (**2e**)	94 (*S*)
6	$BnOCH_2$	81 (**2f**)	82 (*R*)
7	$C_6H_5OCH_2$	96 (**2g**)	94 (*R*)
8	2-$MeC_6H_4OCH_2$	98 (**2h**)	94 (*R*)
9	4-$MeC_6H_4OCH_2$	88 (**2i**)	94 (*R*)
10	2-Napthyl-OCH_2	96 (**2j**)	94 (*R*)

[a] Reaction conditions: **1** (0.2 mmol), Pd$(OCOCF_3)_2$ (3.0 mol%), (*S*,*S*)-f-Binaphane (3.3 mol%), d-CSA (100 mol%), H_2 (600 psi), TFE (3.0 mL), 50 °C, 24 h.
[b] Isolated yields.
[c] Determined by HPLC.

Table 1
Examination of Reaction Parameters.[a]





Entry	Solvent	Acid	Ligand	Yield (%)[b]	Ee (%)[c]
1	TFE	PhCOOH	**L1**	<5	ND
2	TFE	d-DDTA	**L1**	<5	ND
3	TFE	l-CSA	**L1**	95	94 (*R*)
4	TFE	TFA	**L1**	77	87 (*R*)
5	TFE	$TsOH{\cdot}H_2O$	**L1**	90	96 (*R*)
6	TFE	d-CSA	**L1**	95	97 (*R*)
7	DCM	d-CSA	**L1**	92	95 (*R*)
8	Toluene	d-CSA	**L1**	87	94 (*R*)
9	THF	d-CSA	**L1**	<5	ND
10	TFE	d-CSA	**L2**	92	34 (*R*)
11	TFE	d-CSA	**L3**	90	67 (*R*)
12	TFE	d-CSA	**L4**	46	63 (*S*)

[a] Reaction conditions: **1a** (0.2 mmol), Pd$(OCOCF_3)_2$ (3.0 mol%), ligand (3.3 mol%), acid (100 mol%), H_2 (600 psi), solvent (3.0 mL), 50 °C, 24 h.
[b] Isolated yields.
[c] Determined by HPLC.

using *N*-Boc protected sulfonamides as *N*-source in the presence of Brønsted acid with up to 97% ee. This tandem process avoids additional deprotection manipulation and arduous isolation of *N*-sulfonylimine intermediates. The cheap starting materials, simple operation, wide substrate scope and high enantioselectivity make this methodology practical for synthesis of chiral γ-sultam derivatives. Further investigation on its complementary intermolecular alternatives is currently underway.

Acknowledgments

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A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2017.03.012.

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