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Synthesis of Chiral Sultams *via* Palladium-Catalyzed Intramolecular Asymmetric Reductive Amination

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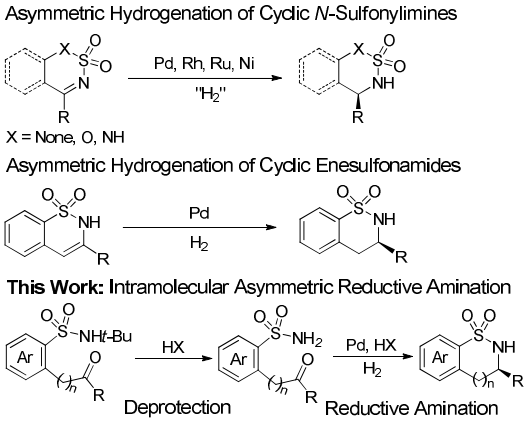
***A novel palladium-catalyzed intramolecular reductive amination of ketones with the low nucleophilic sulfonamides has been developed in the presence of Brønsted acid, giving a wide range of chiral γ-, δ-, and ε-sultams* in high yields and up to 99% of enantioselectivity.**

Chiral sultams are found in a large number of biologically active molecules and serve as versatile synthetic intermediates en route to many related architectures.[1] In light of the growing demand for chiral sultam-based therapeutics, considerable interests have been spurred on the development of efficient synthetic protocols. Consequently, several metal-catalyzed asymmetric cyclization[2] and various enantioselective addition of cyclic *N*-sulfonyl imines[3] have been developed and qualified to be efficient and reliable methodologies. Furthermore, metal-catalyzed asymmetric hydrogenation has also contributed to be powerful methods to construct chiral sultams, significantly enlarging their spectrum.[4-5] Since pioneering work by Oppolzer, sequential studies in transition-metal-catalyzed asymmetric hydrogenation or transfer hydrogenation of cyclic *N*-sulfonyl-imines have appeared as an ecological and atom-efficient method to the facile construction of chiral sultams.[4-5] Moreover, Zhou group recently described a new approach to chiral sultams based on palladium-catalyzed asymmetric hydrogenation of cyclic enesulfonamides (Scheme 1).[5g] Despite a handful of synthetic methods have been developed toward the enantioselective synthesis of *γ*- and *δ*-sultams, direct access to *ε*-sultams was sporadically addressed only in achiral transformations.[6] Importantly, drawbacks associated with pre-preparation of cyclic *N*-sulfonylimines or enesulfonamides and relatively limited substrate scope have also been witnessed. Therefore, developing a more practical and general route to these structural motifs, especially chiral sultams in seven-member ring, is highly desirable.



Scheme 1. Synthesis of Sultams *via* Asymmetric Hydrogenation

Asymmetric reductive amination (ARA) represents a simple and elegant approach to constructing optically active amine scaffolds.[7] In the past decades, enormous attention has been focused on ARA by transition-metal-catalyzed hydrogenation, organocatalytic reduction, and biocatalytic reduction.[7] Furthermore, the borrowing hydrogen activation of alcohols for C–N bond formation *via* ARA has also been documented.[8] Generally, ammonia, simple alkyl- and arylamine are predominant as *N*-nucleophiles,[7,9] and examples involving carbamates,[10] hydra-zides[11] and Ellman's sulfinamides[8f] as less electron-rich *N*-nucleophiles have also been described. However, the reductive amination of ketones using low nucleophilic sulfonamide is still a challenge. To the best of our knowledge, amination involving sulfonamide as *N*-nucleophile has been limited to amination of alcohols in achiral form.[12] The ARA examples of ketones with sulfonamides have yet to be reported. Herein, we reported a novel palladium-catalyzed intramolecular reductive amination of ketones with the low nucleophilic sulfonamides in the presence of Brønsted acid (Scheme 1), providing a wide range of valuable chiral *γ*- and *δ*-sultams with up to 99% ee. The remarkably challenging framework of *ε*-sultams can also be implemented smoothly.

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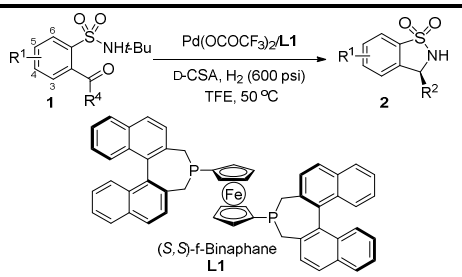
Due to the availability and highly selective *ortho*- or *benzylic* functionalization of *N*-protected sulfonamides,[13] various *N*-*t*-butyl protected keto sulfonamides can be conveniently synthesized (see Supporting Information). Considering of three key points: 1) the *t*-butyl protecting group of sulfonamides can be readily removed by Brønsted acid;[14] 2) the strong acid is also essential to promote the formation of *N*-sulfonylimine intermediates; 3) palladium-catalzyed asymmetric hydrogenation is well compatible with water and acidic condition despite the side reaction of ketone reduction may poses an issue of chemoselectivity;[5a,15] we envisioned that a tandem sequence of deprotection and subsequent intramolecular ARA is feasible by a combination of chiral palladium catalyst and Brønsted acid. Such a process would be advantageous, as this reaction would be step-economic by avoiding the removal of the protecting group and the strenuous isolation of *N*-sulfonylimine intermediates.

Table 1. Substrate scope for the synthesis of *γ*-sultams **2** [a]



Entry	R^1	R^2	Yield (%)[b]	Ee (%)[c]
1	H	Ph	96 (**2a**)	98 (*S*)
2	H	2-MeC_6H_4	98 (**2b**)	94 (*S*)
3	H	3-MeC_6H_4	90 (**2c**)	97 (*S*)
4	H	4-MeC_6H_4	92 (**2d**)	83 (*S*)
5	H	4-FC_6H_4	92 (**2e**)	96 (*S*)
6	H	Me	95 (**2f**)	95 (*S*)
7	H	*n*-Bu	96 (**2g**)	94 (*S*)
8	H	*i*-Bu	98 (**2h**)	96 (*S*)
9	H	Cy	96 (**2i**)	90 (*S*)
10	4-Me	Ph	94 (**2j**)	97 (+)
11	4-MeO	Ph	96 (**2k**)	97 (+)
12	4-Cl	Ph	95 (**2l**)	67 (+)
13	4-Me	*n*-Bu	96 (**2m**)	95 (-)
14	3-F, 6-Me	Ph	96 (**2n**)	89 (+)

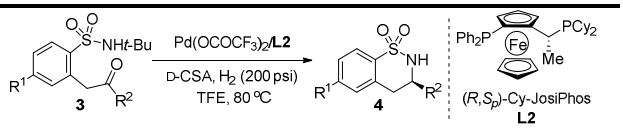
[a] Reaction conditions: **1** (0.20 mmol), $Pd(OCOCF_3)_2$ (3.0 mol %), (*S*,*S*)-f-Binaphane (**L1**, 3.3 mol %), D-CSA (100 mol %), H_2 (600 psi), TFE (3.0 mL), 50 °C, 24 h. [b] Isolated yields. [c] Determined by chiral HPLC.

Further optimization of the reaction conditions corroborated that the idea of one-pot intramolecular asymmetric reductive amination of *N*-protected keto sulfonamides turned out to be feasible (see Supporting Information, Table S1). Various keto sulfonamides **1** were converted to *γ*-sultams in excellent yields and high ee values under the optimal conditions (Table 1). Substituents at *ortho* and *meta* positions of the aryl ring had a negligible impact on the yield and enantioselectivity (entries 2 and 3). In contrast, the effect of *para* substituents differed depending on their electronic property (entries 4 and 5). Moreover, this protocol allowed for alkyl substituted keto sulfonamides to undergo the direct reductive amination (entries 6-9). Besides, chiral substituted benzofused *γ*-sultams could also be obtained (entries 10-14).

After successfully examining the reactions to synthesize *γ*-sultams, we next explored the possibility of asymmetric reductive amination of keto sulfonamides **3** to prepare chiral *δ*-sultams. Apparently different from the ARA to *γ*-sultams, the intramolecular reductive amination to *δ*-sultams proceeded *via* enamine intermediates and imine/enamine tautomerization. Brønsted acid not only promoted deprotection and cyclodehydration for the formation of enamine intermediate, but also served as a promoter for the tautomerization.[5g]

The optimal conditions were established by further modifying the standard conditions for asymmetric hydrogennation of enesulfonamides.[5g] Using D-camphorsulfonic acid (D-CSA) as the additive and higher temperature were required to promote the reductive amination of keto sulfonamides **3** (Table 2). In general, different aryl and alkyl groups were compatible, delivering the desired products in good yields and ee values. Similarly, it is worthwhile to note that the electronic properties for different substituents at the *para* position of the aryl ring have a dramatic influence on the enantioselectivities (entries 4 and 5). In addition, chiral 6-position substituted benzofused *δ*-sultams could also be obtained in high yields and enantioselectivities (entries 9-13).

Table 2. Substrate scope for the synthesis of *δ*-sultams **4** [a]



Entry	R^1	R^2	Yield (%)[b]	Ee (%)[c]
1	H	Ph	96 (**4a**)	97 (*R*)
2	H	2-MeC_6H_4	89 (**4b**)	96 (*R*)
3	H	3-MeC_6H_4	95 (**4c**)	95 (*R*)
4	H	4-MeC_6H_4	95 (**4d**)	79 (*R*)
5	H	4-FC_6H_4	98 (**4e**)	98 (*R*)
6	H	Me	90 (**4f**)	94 (*R*)
7	H	n-C_3H_7	93 (**4g**)	95 (*R*)
8	H	Cy	92 (**4h**)	96 (*R*)
9	Me	Ph	91 (**4i**)	88 (+)
10	MeO	Ph	93 (**4j**)	89 (+)
11	F	Ph	96 (**4k**)	96 (+)
12	Me	*n*-Bu	96 (**4l**)	96 (+)
13	MeO	*n*-Bu	93 (**4m**)	96 (+)

[a] Reaction conditions: **3** (0.20 mmol), $Pd(OCOCF_3)_2$ (3.0 mol %), (R,S_p)-Cy-JosiPhos (**L2**, 3.3 mol %), D-CSA (100 mol %), H_2 (200 psi), TFE (3.0 mL), 80 °C, 24 h. [b] Isolated yields. [c] Determined by chiral HPLC.

ε-Sultams are momentous building blocks of pharmaceutical agents.[1d-1f] As compared to *γ*-, and *δ*-sultams, general methods for the synthesis of chiral *ε*-sultams are still notoriously scarce despite a few examples of racemic versions.[6] The challenge of

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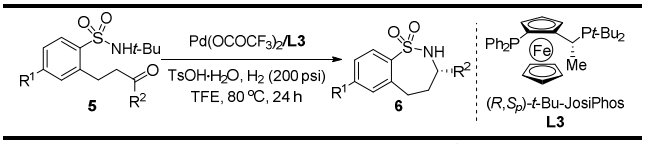
a strategy accessing ε-sultams is evident because of the general assumption that entropic factors do not favor cyclizations to form the seven-membered rings.[16] Due to the difficulty for formation of seven-membered ring, control of chemoselectivity will be more difficult.

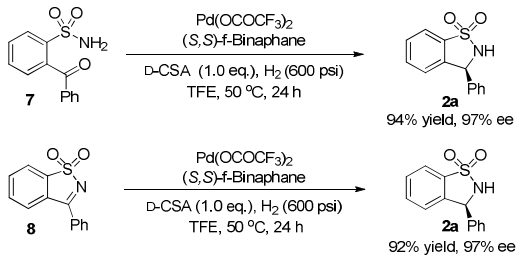
Table 3. Substrate scope for the synthesis of ε-sultams **6** [a]



Entry	R^1	R^2	Yield (%)[b]	Ee (%)[c]
1	H	Me	95 (**6a**)	98 (+)
2	H	*n*-Bu	98 (**6b**)	99 (+)
3	H	*n*-C_6H_{13}	96 (**6c**)	98 (+)
4[d]	Me	*n*-Bu	92 (**6d**)	98 (+)
5[d]	MeO	*n*-Bu	98 (**6e**)	99 (+)
6[d]	H	Ph	89 (**6f**)	94 (+)
7[d]	H	4-FC_6H_4	95 (**6g**)	93 (+)
8	H	4-ClC_6H_4	87 (**6h**)	97 (*S*)
9[d]	Me	Ph	88 (**6i**)	94 (+)
10[d]	MeO	Ph	93 (**6j**)	95 (+)

[a] Reaction conditions: **5** (0.20 mmol), $Pd(OCOCF_3)_2$ (3.0 mol %), (R,S_p)-*t*-Bu-JosiPhos (**L3**, 3.3 mol %), $TsOH·H_2O$ (100 mol %), H_2 (200 psi), TFE (3.0 mL), 80 °C, 24 h. [b] Isolated yields. [c] Determined by chiral HPLC. [d] 60 °C.

To achieve high level of chemoselectivity, elevated temperature and lower pressure of hydrogen gas were engaged. Further evaluation of reaction parameters indicated that high enantioselectivity was achieved by employing the electron-rich and steric-demanding (R,S_p)-*t*-Bu-JosiPhos ligand **L3** (see Supporting Information, Table S2). As illustrated in Table 3, this ARA protocol to ε-sultams indicated wide substrate scope. Both aliphatic and aromatic substituents were suitable. Substituents at 4-position on the phenyl ring of keto sulfonamides exerted no influence on the enantioselectivity (entries 4 vs 5, 9 vs 10). Moreover, halogen functional groups were also well tolerated, giving the desired products in remarkable yields and ee values (entries 7 and 8). The absolute configuration of product was determined based on the single-crystal X-ray diffraction analysis (see Supporting Information).



Scheme 2. Control Experiment

To understand the outcomes of the reaction, two control experiments were performed (Scheme 2). Keto sulfonamide **7** and cyclic sulfonylimine **8** were synthesized and submitted to the standard conditions, the desired product **2a** was obtained with the identical enantioselectivity and absolute configuration (entry 1, Table 1). The above experiments further confirmed the intramolecular reductive amination pathway.

Conclusions

In summary, we have successfully developed a novel and versatile palladium-catalyzed intramolecular reductive amination of ketones with the low nucleophilic sulfonamides in the presence of Brønsted acid, providing a wide range of valuable chiral γ-, δ-, and ε-sultams with high enantioselectivity from the readily available *N*-*tert*-butyl protected keto sulfonamides. This strategy would be beneficial for synthetic efficiency by precluding the removal of protecting groups and the isolation of the imine or enamine intermediates. The successful key issues for reductive amination include tolerable palladium catalysis system to water and Brønsted acid, easy removal of the protecting group, and easy formation of imine or enamine intermediates. This methodology provides a new and facile approach to optically active sultam scaffolds from the simple starting materials. Further exploring the applications of sulfonamides in asymmetric amination is currently underway.

Acknowledgements

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‡Footnotes relating to the main text should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

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