ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue

Cite this: *Chem. Commun.*, 2017, 53, 1704

Received 29th November 2016,
Accepted 5th January 2017

DOI: 10.1039/c6cc09493g

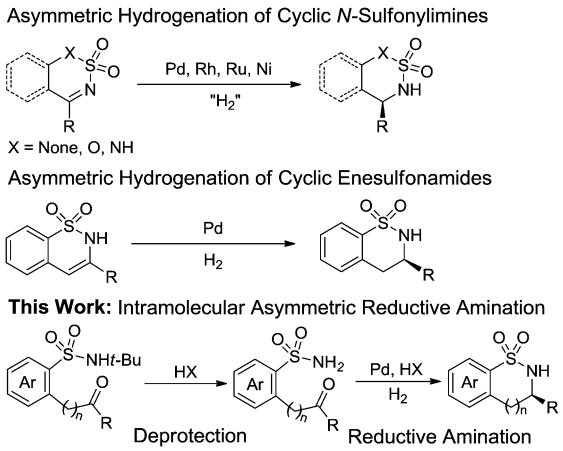
www.rsc.org/chemcomm

Synthesis of chiral sultams *via* palladium-catalyzed intramolecular asymmetric reductive amination†

Bo Song,[ab] Chang-Bin Yu,[a] Yue Ji,[a] Mu-Wang Chen[a] and Yong-Gui Zhou*[ac]

A novel palladium-catalyzed intramolecular reductive amination of ketones with weakly nucleophilic sulfonamides has been developed in the presence of a 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 to several related architectures.[1] In light of the growing demand for chiral sultam-based therapeutics, considerable interest has spurred for the development of efficient synthetic protocols. Consequently, several metal-catalyzed asymmetric cyclization[2] reactions and various enantioselective additions of cyclic *N*-sulfonyl imines[3] have been developed and are considered to be efficient and reliable methodologies. Furthermore, metal-catalyzed asymmetric hydrogenation is also a powerful method to construct chiral sultams, significantly enlarging their spectrum.[4,5] Since the pioneering study reported 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 for the facile construction of chiral sultams.[4,5] Moreover, the Zhou group recently described a new approach for the fabrication of chiral sultams based on palladium-catalyzed asymmetric hydrogenation of cyclic enesulfonamides (Scheme 1).[5g] Although some synthetic methods have been developed for 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, particularly chiral sultams in seven-member rings, is highly desirable.



Scheme 1 Synthesis of sultams via asymmetric hydrogenation.

Asymmetric reductive amination (ARA) represents a simple and elegant approach to construct optically active amine scaffolds.[7] In the past decades, enormous attention has been focused on ARA *via* 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 and simple alkyl- and arylamine are predominantly used as *N*-nucleophiles,[7,9] and examples involving carbamates,[10] hydrazides[11] and Ellman's sulfinamides[8f] as less electron-rich *N*-nucleophiles have also been described. However, the reductive amination of ketones using weakly nucleophilic sulfonamides is still a challenge. To the best of our knowledge, amination involving sulfonamide as *N*-nucleophile has been limited to amination of alcohols in the achiral form.[12] The ARA examples of ketones with sulfonamides are yet to be reported. Herein, we report a novel palladium-catalyzed intramolecular reductive amination of ketones with weak nucleophilic sulfonamides in the presence of a Brønsted acid (Scheme 1), providing a wide range of valuable chiral γ- and δ-sultams with

[a] *State Key Laboratory of Catalysis, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, P. R. China. E-mail: ygzhou@dicp.ac.cn*
[b] *University of Chinese Academy of Sciences, Beijing 100049, P. R. China*
[c] *Collaborative Innovation Centre of Chemical Science and Engineering, Tianjin 300071, P. R. China*

† Electronic supplementary information (ESI) available. CCDC 1507240 and 1414841. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c6cc09493g

up to 99% ee. The remarkably challenging framework of ε-sultams can also be implemented smoothly.

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 ESI†). Considering 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-catalyzed asymmetric hydrogenation is compatible with water and acidic conditions despite the side reaction of ketone reduction may pose an issue with chemoselectivity;[5a,15] we envisioned that a tandem sequence of deprotection and subsequent intramolecular ARA is feasible *via* a combination of a chiral palladium catalyst and a Brønsted acid. Such a process would be atom-economic by avoiding the removal of the protecting group and strenuous isolation of *N*-sulfonyl-imine intermediates.

Further optimization of the reaction conditions corroborated that the idea of a one-pot intramolecular asymmetric reductive amination of *N*-protected keto sulfonamides was feasible (see ESI,† 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 alkyl substituted keto sulfonamides to undergo direct reductive amination (entries 6–9). In addition, chiral substituted benzofused γ-sultams could also be obtained (entries 10–14).

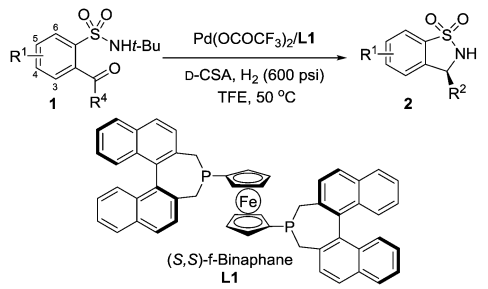
After successfully examining the reactions to synthesize γ-sultams, we next explored the possibility of asymmetric reductive amination of keto sulfonamides **3** to prepare chiral δ-sultams. Apparently different from the ARA to γ-sultams, the intramolecular reductive amination to δ-sultams proceeded *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 tautomerization.[5g]

The optimal conditions were established by further modifying the standard conditions for asymmetric hydrogen-nation of enesulfonamides.[5g] Using D-camphorsulfonic acid (D-CSA) as the additive, higher temperatures 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).

ε-Sultams are momentous building blocks of pharmaceutical agents.[1e,f] Compared to those of γ- and δ-sultams, general methods for the synthesis of chiral ε-sultams are still scarce despite a few examples of racemic versions.[6] The challenge of 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 in the formation of seven-membered rings, control of chemoselectivity will be more difficult.

To achieve a high level of chemoselectivity, an elevated temperature and a lower pressure of hydrogen gas were engaged. Further evaluation of reaction parameters indicated that high

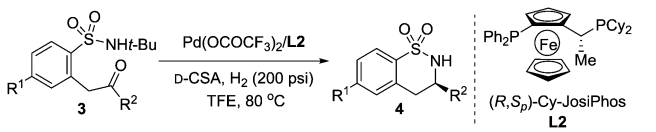
Table 1 Substrate scope for the synthesis of γ-sultams **2**[a]



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.

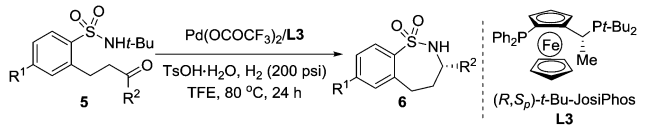
Table 2 Substrate scope for the synthesis of δ-sultams **4**[a]



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.

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



5 6

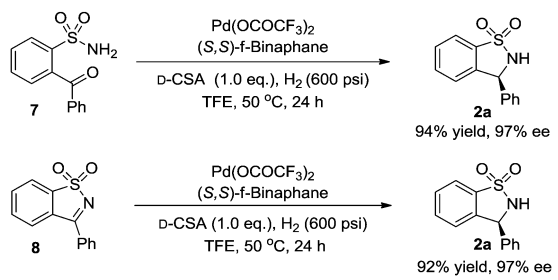
Entry	R^1	R^2	Yield[b] (%)	ee[c] (%)
1	H	Me	95 (**6a**)	98 (+)
2	H	*n*-Bu	98 (**6b**)	99 (+)
3	H	*n*-C_6H_{13}	96 (**6c**)	98 (+)
4[d]	Me	*n*-Bu	92 (**6d**)	98 (+)
5[d]	MeO	*n*-Bu	98 (**6e**)	99 (+)
6[d]	H	Ph	89 (**6f**)	94 (+)
7[d]	H	4-FC_6H_4	95 (**6g**)	93 (+)
8	H	4-ClC_6H_4	87 (**6h**)	97 (*S*)
9[d]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

enantioselectivity was achieved by employing the electron-rich and steric-demanding (R,S_p)-*t*-Bu-JosiPhos ligand **L3** (see ESI,† Table S2). As illustrated in Table 3, this ARA protocol to ε-sultams has a wide substrate scope. Both aliphatic and aromatic substituents were suitable. Substituents at the 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 the product was determined based on the single-crystal X-ray diffraction analysis (see ESI†).

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

In summary, we 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 for the fabrication of optically active sultam scaffolds from simple starting materials. Further exploration of the applications of sulfonamides in asymmetric amination is currently underway.



Scheme 2 Control experiment.

Financial support from the National Natural Science Foundation of China (21532006 and 21372220) and the Dalian Institute of Chemical Physics (DMTO 201501) is acknowledged.

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