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

Bo Song,ab Chang-Bin Yu,a Yue Ji,a Mu-Wang Chena and Yong-Gui Zhou*a,c

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. 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 reactions and various enantioselective additions of cyclic N-sulfonyl imines 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. 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. 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). 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. 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.

Asymmetric reductive amination (ARA) represents a simple and elegant approach to construct optically active amine scaffolds. In the past decades, enormous attention has been focused on ARA via transition-metal-catalyzed hydrogenation, organocatalytic reduction, and biocatalytic reduction. Furthermore, the borrowing hydrogen activation of alcohols for C–N bond formation via ARA has also been documented. Generally, ammonia and simple alkyl- and arylamine are predominantly used as N-nucleophiles, and examples involving carbamates, hydrazides and Ellman’s sulfinamides 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. 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 Bronsted acid (Scheme 1), providing a wide range of valuable chiral γ- and δ-sultams with

† 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 benzyl functionalization of N-protected sulfonamides, 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; (2) the strong acid is also essential to promote the formation of N-sulfonylelimine 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, 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 advantageous as this reaction 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.6

The optimal conditions were established by further modifying the standard conditions for asymmetric hydrogenation of enesulfonamides. Using v-camphorsulfonic acid (v-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 ε-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. 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.6 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 2a

<table>
<thead>
<tr>
<th>Entry</th>
<th>R1</th>
<th>R2</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>Ph</td>
<td>96 (2a)</td>
<td>98 (%)</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>2-MeC6H4</td>
<td>98 (2b)</td>
<td>94 (%)</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>3-MeC6H4</td>
<td>90 (2c)</td>
<td>97 (%)</td>
</tr>
<tr>
<td>4</td>
<td>H</td>
<td>4-MeC6H4</td>
<td>92 (2d)</td>
<td>83 (%)</td>
</tr>
<tr>
<td>5</td>
<td>H</td>
<td>4-FC6H4</td>
<td>92 (2e)</td>
<td>96 (%)</td>
</tr>
<tr>
<td>6</td>
<td>H</td>
<td>Me</td>
<td>95 (2f)</td>
<td>95 (%)</td>
</tr>
<tr>
<td>7</td>
<td>H</td>
<td>n-Bu</td>
<td>96 (2g)</td>
<td>94 (%)</td>
</tr>
<tr>
<td>8</td>
<td>H</td>
<td>i-Bu</td>
<td>98 (2h)</td>
<td>95 (%)</td>
</tr>
<tr>
<td>9</td>
<td>H</td>
<td>Cy</td>
<td>96 (2i)</td>
<td>90 (%)</td>
</tr>
<tr>
<td>10</td>
<td>4-Me</td>
<td>Ph</td>
<td>94 (2j)</td>
<td>97 (+)</td>
</tr>
<tr>
<td>11</td>
<td>4-MeO</td>
<td>Ph</td>
<td>96 (2k)</td>
<td>97 (+)</td>
</tr>
<tr>
<td>12</td>
<td>4-Cl</td>
<td>Ph</td>
<td>95 (2l)</td>
<td>67 (+)</td>
</tr>
<tr>
<td>13</td>
<td>4-Me</td>
<td>n-Bu</td>
<td>96 (2m)</td>
<td>95 (-)</td>
</tr>
<tr>
<td>14</td>
<td>3-F, 6- Me</td>
<td>Ph</td>
<td>96 (2n)</td>
<td>89 (+)</td>
</tr>
</tbody>
</table>

* Reaction conditions: 1 (0.20 mmol), Pd(O(OOCF3)2)2 (3.0 mol%), (S,S)-tf-Binaph (L1, 3.3 mol%), d-CSA (100 mol%), H2 (600 psi), TFE (3.0 mL), 50 °C, 24 h. * Isolated yields. * Determined by chiral HPLC.

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

<table>
<thead>
<tr>
<th>Entry</th>
<th>R1</th>
<th>R2</th>
<th>Yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>Ph</td>
<td>96 (4a)</td>
<td>97 (%)</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>2-MeC6H4</td>
<td>89 (4b)</td>
<td>96 (%)</td>
</tr>
<tr>
<td>3</td>
<td>H</td>
<td>3-MeC6H4</td>
<td>96 (4c)</td>
<td>95 (R)</td>
</tr>
<tr>
<td>4</td>
<td>H</td>
<td>4-MeC6H4</td>
<td>95 (4d)</td>
<td>95 (R)</td>
</tr>
<tr>
<td>5</td>
<td>H</td>
<td>4-FC6H4</td>
<td>96 (4e)</td>
<td>98 (%)</td>
</tr>
<tr>
<td>6</td>
<td>H</td>
<td>Me</td>
<td>90 (4f)</td>
<td>97 (%)</td>
</tr>
<tr>
<td>7</td>
<td>H</td>
<td>n-C3H7</td>
<td>93 (4g)</td>
<td>95 (R)</td>
</tr>
<tr>
<td>8</td>
<td>H</td>
<td>Cy</td>
<td>92 (4h)</td>
<td>96 (%)</td>
</tr>
<tr>
<td>9</td>
<td>Me</td>
<td>Ph</td>
<td>94 (4i)</td>
<td>96 (+)</td>
</tr>
<tr>
<td>10</td>
<td>MeO</td>
<td>Ph</td>
<td>93 (4j)</td>
<td>96 (+)</td>
</tr>
<tr>
<td>11</td>
<td>F</td>
<td>Ph</td>
<td>96 (4k)</td>
<td>97 (+)</td>
</tr>
<tr>
<td>12</td>
<td>Me</td>
<td>n-Bu</td>
<td>96 (4l)</td>
<td>96 (+)</td>
</tr>
<tr>
<td>13</td>
<td>MeO</td>
<td>n-Bu</td>
<td>93 (4m)</td>
<td>96 (+)</td>
</tr>
</tbody>
</table>

* Reaction conditions: 3 (0.20 mmol), Pd(O(OOCF3)2)2 (3.0 mol%), (R,S) Cy-JosiPhos (L2, 3.3 mol%), d-CSA (100 mol%), H2 (200 psi), TFE (3.0 mL), 80 °C, 24 h. * Isolated yields. * Determined by chiral HPLC.
enantioselectivity was achieved by employing the electron-rich
and steric-demanding (R,S)-t-Bu-JosiPhos ligand L3 (see ESI†
Table S2). As illustrated in Table 3, this ARA protocol to
ketone sulfonamide was obtained with
95 (+) (entry 1, Table 1). The abovementioned experiments further
shows the high nucleophilic sulfonamides in the presence of 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 sulfamides
from simple starting materials. Further exploration of the
applications of sulfonamides in asymmetric amination is
currently underway.

**Notes and references**

1. a) S. Toyota, *Enantiomer*, 1999, 4, 25; (b) M. B. Tollefson, S. A. Kolodziej
and D. B. Reitz, W00047568 A2, 2000; (c) J. Vázquez, S. Fonquerna,
12, 1837; (d) P. Gillieron, N. Wlodarczyk, R. Houssin, M. Lacoade,
J.-F. Goossens, A. Lemoine, N. Pommery, J.-P. Henrichart and R. Milletta,
*Bioorg. Med. Chem. Lett.*, 2007, 17, 5465; (e) L. Kiefer, T. Gorjankina,
2010, 20, 7483; (f) A. K. Ganguly, S. S. Alluri, D. Caroccia, D. Biswas,
C.-H. Wang, E. Kang, Y. Zhang, A. T. McPhail, S. S. Carroll, C. Burleim,

Chem., Int. Ed.*, 2010, 49, 4955; (c) M. Ichinose, H. Suematsu,

Chem., Int. Ed.*, 2012, 51, 6762; (c) Y. Luo, H. B. Hepburn, N. Chotasaeng
and H. W. Lam, *Angew. Chem., Int. Ed.*, 2012, 51, 8309; (d) T. Nishimura,
(e) T. Nishimura, A. Y. Ebe and H. Fujimoto, *Chem. Commun.*, 2013,
135, 971; (g) H. Wang and M.-H. Xu, *Synthesis*, 2013, 2125; (h) G. Yang

4. For examples of Ru-, Rh- and Ni-catalyzed hydrogenation to synthe-
size sulfamates, see: (a) W. Oppolzer, M. Willis, C. Starkemann and
(c) J. M. Mao and D. C. Baker, *Org. Lett.*, 1999, 1, 841; (d) Y.-C. Chen,
E. A. M. Madison, J. P. Leocoudon and G. Thominot, *Tetrahedron:
Asymmetry*, 2003, 14, 3431; (f) P.-N. Liu, P.-M. Gu, J.-G. Deng,
J. Chem.*, 2010, 28, 1529; (i) H. Xu, P. Yang, P. Chauprasit, H. Hirao

5. For reviews of Pd-catalyzed asymmetric hydrogenation, see: (a) Q.-A.
42, 497; (b) J. Xie and Q. Zhou, *Acta Chim. Sin.*, 2012, 70, 1427; For
example of Pd-catalyzed hydrogenation to synthesize sulfamates, see:
(a) Q. Yang, G. Shang, W.-Z. Gao, J.-G. Deng and X. Zhang, *Angew.
Chem., Int. Ed.*, 2006, 45, 3832; (b) Y.-Q. Wang, S.-M. Lu and Y.-G.
Zhou, *J. Org. Chem.*, 2007, 72, 3729; (c) Y.-Q. Wang, C.-B. Yu, D.-W.
47, 5052; (f) H. Song, C.-B. Yu, W.-X. Huang, M.-W. Chen and

6. a) P. Gillieron, N. Wlodarczyk, R. Houssin, A. Farce, G. Lacoade,
J.-F. Goossens, A. Lemoine, N. Pommery, J.-P. Henrichart and R. Milletta,
*Bioorg. Med. Chem. Lett.*, 2007, 17, 5465; (b) L. Kiefer, T. Gorjankina,


