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Pd-catalyzed [3 + 2] cycloaddition of cyclic ketimines and trimethylenemethanes toward *N*-fused pyrrolidines bearing a quaternary carbon†

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A Pd-catalyzed [3 + 2] cycloaddition of *N*-sulfonyl cyclic ketimines and trimethylenemethanes (TMM) was developed that afforded *N*-fused pyrrolidines bearing a quaternary carbon. Under mild reaction conditions, structurally diverse *N*-sulfonyl cyclic imines, including sulfamate-fused aldimines, aryl- or styryl-substituted sulfamate-derived ketimines, and *N*-sulfonyl cyclic ketimines, were tolerated as reactants, affording *N*-fused pyrrolidines with high efficiency.

Introduction

Heterocycles bearing quaternary carbon stereocenters are found in a wide range of biologically active natural compounds and pharmaceuticals.[1] In particular, alkaloids containing *N*-fused pyrrolidines with quaternary carbons have been observed to exhibit a wide range of biological properties (Fig. 1), such as anti-tumoral and anti-inflammatory activities, as well as the ability to potently reverse the multidrug resistance of cancers.[2] Given the pronounced bioactivities of marketed drugs comprising the pyrrolidine scaffold,[3] over the past three decades or so, many synthetic methods have been developed to access pyrrolidines.[4] However, few reports have been published on the synthesis of *N*-fused pyrrolidine bearing quaternary carbons.[5] One of the reasons that renders the construction of quaternary carbons a challenging task in organic synthesis is their congested nature.[6] Considering the specific bioactivities of quaternary carbon centers in heterocycles, there is clearly an unmet need for convenient and efficient methods for the synthesis of quaternary carbon-containing pyrrolidines.

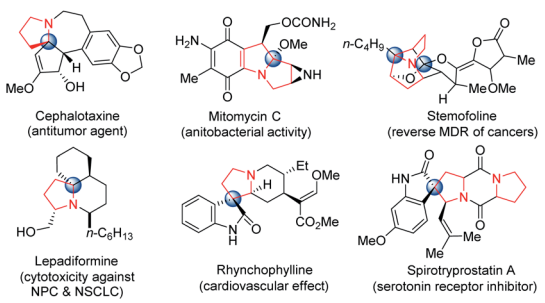

Fig. 1 Representative alkaloids containing *N*-fused pyrrolidines bearing quaternary carbons.

Transition metal-catalyzed dipolar cycloadditions have proven to be efficient and practical approaches to the synthesis of valuable cyclic compounds.[7] In particular, the recently developed approach whereby sulfamate-fused imines are used in cycloaddition reactions appears to be an extremely promising strategy for the synthesis of *N*-fused heterocycles. The sulfamate moiety is an important structural motif in pharmacology due to its potent bioactivities, such as anticancer, antibiotic, and antiviral properties; moreover, this moiety serves as a reactive intermediate that can be readily converted to other useful heterocycles.[8] Accordingly, significant efforts have been devoted to developing cycloadditions of sulfamate-derived aldimines coupled with various types of dipoles, affording sulfamate-functionalized heterocycles characterized by diverse ring sizes.[9] For the preparation of sulfamate-fused pyrrolidines, the Pd-catalyzed [3 + 2] cycloaddition between vinylcyclopropanes and sulfamate-derived aldimines has been developed, which demonstrated high efficiency under mild reaction conditions (Scheme 1a).[10] An asymmetric strategy based on the organocatalytic Mannich/Aza-Michael cascade reaction using *cis* δ-formyl α,β-unsaturated ketones with sulfamate-derived aldimines has also been reported (Scheme 1b).[11] In stark contrast to the cycloadditions of sulfamate-derived aldimines, only recently have a few examples of catalytic cycloadditions of sulfamate-derived ketimines generating quaternary carbons in nitrogen-containing heterocycles been reported, and they involved a limited number of ketimines, such as cyclic *N*-sulfonyl trifluoromethylated ketimines[12] and styryl-substituted ketimines.[13] The variety of examples of such reactions possibly

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† Electronic supplementary information (ESI) available: Experimental details, reaction optimization, characterization data, crystallographic data of **5i** (CCDC 2114538), and ^{1}H and ^{13}C NMR spectra of all products. CCDC 2114538. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/d1ra08579d

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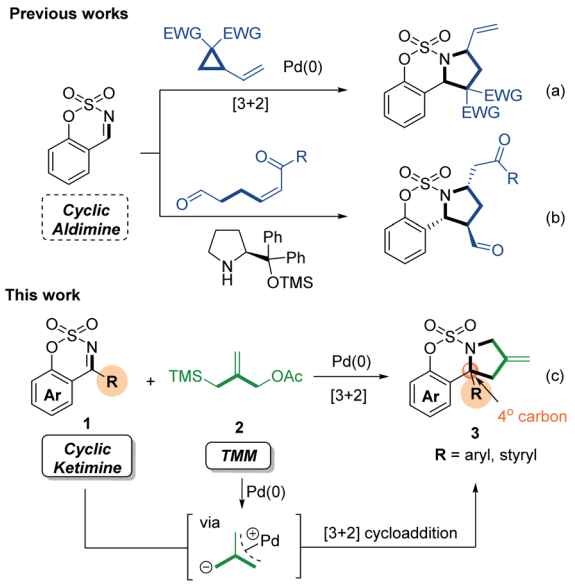


Scheme 1 Synthetic approaches implemented to access sulfamate-fused pyrrolidines.

descends from the inherent lability and inactivity of ketimine derivatives.[14] In the present study, we established a Pd-catalyzed [3 + 2] cycloaddition affording sulfamate-fused pyrrolidines bearing a quaternary carbon, starting from commercially available trimethylenemethane (TMM) and sulfamate-derived ketimines serving as prochiral sp^2-carbons (Scheme 1c).

Since Trost first reported the use of TMMs in Pd-catalyzed cycloadditions, a variety of [3 + *n*] cycloadditions reacting with dipolarophiles, such as activated alkenes, aldehydes, ketones, and acyclic imines, have been developed.[15] In the presence of Pd(0) species, a TMM can form a zwitterionic Pd complex, which can be considered a C-nucleophilic/C-electrophilic 1,3-dipole intermediate. Accordingly, the utilization of TMMs in Pd catalysis has emerged as a reliable synthetic strategy for providing three-carbon synthons for the preparation of various carbocycles and heterocycles. Surprisingly, despite the great importance of the sulfamate moiety and recent advances in the catalytic cycloadditions of sulfamate-derived imines,[8,9] the Pd-catalyzed cycloaddition of sulfamate-derived cyclic imines achieved employing TMMs as reactive 1,3-dipoles has never been reported. Herein, we describe an efficient Pd-catalyzed [3 + 2] cycloaddition of a TMM with both sulfamate-derived cyclic aldimines and ketimines conducted under mild reaction conditions.

Results and discussion

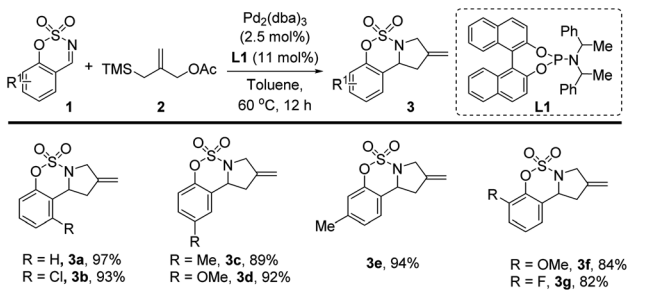
Initially, to test the feasibility of the [3 + 2] cycloaddition of sulfamate-derived cyclic imines and a TMM, the reaction of the cyclic aldimine **1a** with 1.5 equiv. of TMM **2** was attempted in the presence of a Pd catalyst. On the basis of previously published studies,[15,16] we chose tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$) as the palladium source, and we screened the effects of various ligands on the catalytic reaction conducted in toluene at 60 °C (see the ESI for details†). We observed that the reaction efficiency was largely dependent on the identity of the ligand. Among the screened phosphine and phosphoramidite ligands, phosphoramidite **L1** was found to be the most effective for this Pd-catalyzed [3 + 2] cycloaddition reaction; by employing it, the desired product **3a** was afforded in 97% isolated yield. The use of other Pd(II) catalysts, such as $Pd(OAc)_2$ and $PdCp(\eta^3\text{-allyl})$, and solvents was also investigated in the presence of **L1** at 60 °C, but none of these catalysts and solvents afforded yields higher than that obtained using $Pd_2(dba)_3$ in toluene. Moreover, reducing the equiv. of **2** or decreasing the reaction temperature were observed to be associated with decreases in the yield of **3a** (see the ESI for details†).

With the optimized reaction conditions in hand, we first examined the Pd-catalyzed [3 + 2] cycloaddition reactions of various cyclic aldimines **1** and **2** to investigate the scope of the reaction (Table 1). Sulfamate-derived cyclic aldimines **1a–g** bearing electron-donating (–Me, –OMe) and electron-withdrawing (–Cl, –F) groups in different positions of the arene were well tolerated in this catalytic system, producing sulfamate-fused pyrrolidines **3a–g** in 82–97% yields.

Encouraged by these results, we focused on the cycloadditions between cyclic ketimines **4** and TMMs to afford *N*-fused pyrrolidine derivatives bearing a quaternary carbon. We applied the reaction conditions optimized using aldimines **1** to the reaction of ketimine **4a** with **2**, and we observed the production of cyclic adduct **5a** in excellent yield. Notably, the reaction could be conducted in milder catalytic conditions than those implemented in the reaction between **1** and **2**, even though ketimines **4** are considered less reactive substrates than aldimines **1**.[14] After further optimization, the desired product **5a** was obtained in 95% yield by using 1.2 equiv. of **2** at 30 °C.

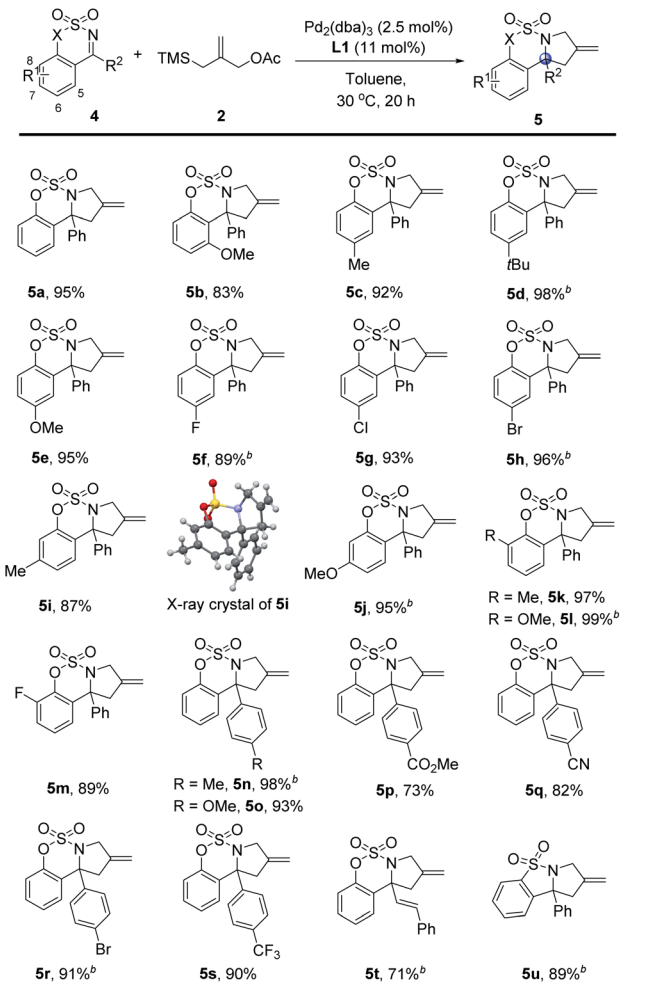
Subsequently, a wide range of cyclic ketimines **4** were tested as substrates using **2** under mild reaction conditions (Table 2). The reactions of the sterically demanding ketimine **4b** and ketimines **4c–g**, which bear electron-donating (–Me, –^{t}Bu, –OMe) or halogen (–F, –Cl) substituents at the 6-position on the phenyl ring, proceeded efficiently to afford sulfamate-fused pyrrolidines **5b–g** comprising a quaternary carbon in 83–98% yields, although in the cases of substrates **4d** and **4f** the amount

Table 1 Scope of the cycloaddition reaction involving sulfamate-derived cyclic aldimine[a]



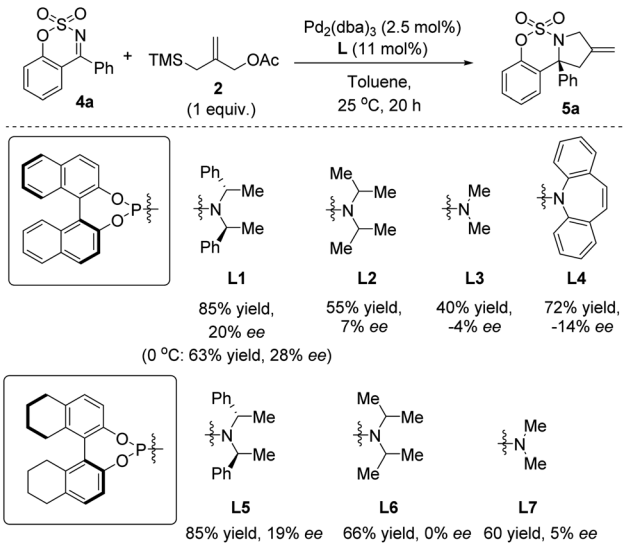
[a] Reaction conditions: **1** (0.1 mmol), **2** (0.15 mmol), $Pd_2(dba)_3$ (2.5 mol%), and **L1** (11 mol%) in toluene (1.0 mL) at 60 °C for 12 h under argon, isolated yields after column chromatography.

Table 2 Scope of the cycloaddition reaction involving sulfamate-derived cyclic ketimines[a]



[a] Reaction conditions: **4** (0.1 mmol), **2** (0.12 mmol), $Pd_2(dba)_3$ (2.5 mol%), and **L1** (11 mol%) in toluene (1.0 mL) at 30 °C under argon, 20 h, isolated yields after column chromatography. [b] **2** (0.15 mmol) was added.

of TMM had to be increased. The presence of a bromide substituent on the aryl ketimine was tolerated in this Pd-catalysis; in the relevant case, the corresponding product **5h** was obtained in 96% yield. The ketimines containing different substituents at the 6- and 7-positions of the aryl moiety of **4** smoothly underwent the [3 + 2] cycloaddition to afford *N*-fused pyrrolidines **5i–m** in excellent yields, up to 99%; moreover, the structure of **5i** was determined by X-ray diffraction analysis of a single crystal. A range of different R^2 substituents on ketimines **4** were also tested; evidence indicated that use of various para-substituted phenyls with different electronic properties afforded the corresponding products **5n–s** in good-to-excellent yields. In particular, ketimines **4p** and **4q**, comprising the ester and cyanide groups, respectively, proved compatible with the present Pd-catalyzed [3 + 2] cycloaddition. To our delight, the described cycloaddition reaction also tolerated the α,β-unsaturated ketimine **4t**, in which an electron-deficient alkene

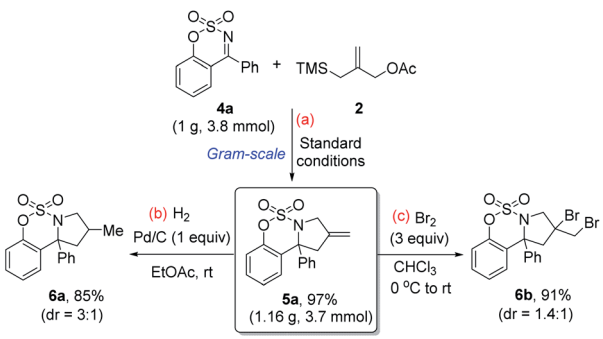


Scheme 2 Results of the investigation on the feasibility of the asymmetric [3 + 2] cycloaddition.

can participate in the cycloaddition to provide a cyclopentane derivative.[17] Indeed, the desired product **5t** was selectively obtained in good yield. The reagents compatible with this catalytic reaction were not limited to sulfamate-derived ketimines, and use of the *N*-sulfonyl cyclic ketimine **4u** provided *N*-sulfonyl pyrrolidine **5u** in 89% yield.

We then investigated the Pd-catalyzed asymmetric [3 + 2] cycloaddition of cyclic ketimine **4a** and TMM **2**, and the preliminary results of a ligand screening effort are reported in Scheme 2. The different phosphoramidite ligands bearing the 1,1′-bi-2-naphthol (BINOL) backbone (**L1–4**) and the octahydro-1,1′-2-naphthol backbone (**L5–7**) were employed in the reaction between **4a** and **2** affording the sulfamate-fused pyrrolidine **5a** comprising a stereogenic center. Unfortunately, only a 20% *ee* value for compound **5a** was obtained when the chiral phosphoramidite **L1** was employed, and only a slight increase in enantioselectivity (28% *ee*) was achieved conducting the cycloaddition reaction at 0 °C.

Next, to demonstrate that the reaction is a practical protocol for the synthesis of pyrrolidine derivatives, a gram-scale reaction between ketimine **4a** and **2** was performed. To our delight,



Scheme 3 Gram-scale synthesis of compound **5a** and its transformation.

the reaction proceeded smoothly, delivering the corresponding pyrrolidine **5a** in 97% yield without the loss of reactivity (Scheme 3a). To probe the utility of the synthesized pyrrolidine **5a**, which contains the versatile exocyclic double bond, organic transformations aimed at producing pyrrolidines bearing two stereogenic centers were attempted. The exocyclic double bond in **5a** could be readily converted to the methyl substituted pyrrolidine **6a** in 85% yield with 3 : 1 diastereomeric ratio by hydrogenation (Scheme 3b). Bromination of **5a** with Br_2 (3 equiv.) in $CHCl_3$ afforded the vicinal dibromides product **6b**[18] containing two quaternary carbons in 91% yield (Scheme 3c).

Conclusions

In summary, we have developed a facile method for the synthesis of *N*-fused pyrrolidines *via* Pd-catalyzed [3 + 2] cycloaddition of *N*-sulfonyl imines and a commercially available TMM. The reaction proceeded efficiently under mild conditions, and afforded *N*-fused pyrrolidines, which are important skeletons of biologically active compounds. Notably, a wide range of ketimines (*e.g.*, sulfamate-derived ketimines bearing aryl and styryl substituents and *N*-sulfonyl cyclic ketimine) were tolerated as substrates, providing *N*-sulfonyl pyrrolidines comprising quaternary carbon centers in good-to-excellent yields. To demonstrate the scalability and the utility of the synthesized product, sulfamated-fused pyrrolidine with exocyclic double bond derived from TMM, a gram-scale reaction and synthetic transformations were performed.

Experimental

General procedure for the synthesis of compound 3

To a flame-dried Schlenk tube, $Pd_2(dba)_3$ (2.3 mg, 2.5 mol%) and **L1** (6.0 mg, 11 mol%) were added in a glove box; subsequently, aldimine **1** (0.1 mmol), 2-((trimethylsilyl)methyl)allyl acetate **2** (0.15 mmol), and toluene (1.0 mL) were added under argon atmosphere. The reaction mixture was stirred at 60 °C for 12 h. After completion of the reaction, the solvent was removed by evaporation, and the product was isolated by silica gel column chromatography using an appropriate eluent. The product yields were determined by ^{1}H NMR analysis.

General procedure for the synthesis of compound 5

To a flame-dried Schlenk tube, $Pd_2(dba)_3$ (2.3 mg, 2.5 mol%) and **L1** (6.0 mg, 11 mol%) were added in a glove box; subsequently, ketimine **4** (0.1 mmol), 2-((trimethylsilyl)methyl)allyl acetate **2** (0.12 mmol), and toluene (1.0 mL) were added under argon atmosphere. The reaction mixture was stirred at 30 °C for 20 h. After completion of the reaction, the solvent was removed by evaporation, and the product was isolated by silica gel column chromatography using an appropriate eluent. The product yields were determined by ^{1}H NMR analysis.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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