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Cycloaddition of Chiral *tert*-Butanesulfinimines with Trimethylenemethane

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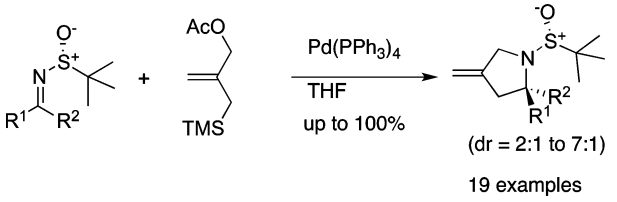
ABSTRACT



The cycloaddition of chiral *tert*-butanesulfinimines with trimethylenemethane is found to give facile access to methylene-pyrrolidines with good yields and diastereoselectivities. The full scope of the cycloaddition is explored, and a range of transformations of the formed methylenepyrrolidines to give a range of functionalized chiral pyrrolidines is presented.

Chiral amines are an important class of compounds for both the synthesis of complex natural products and drug discovery. In particular, the pyrrolidine substructure occurs in a wide range of biologically important natural products, such as preussin,[1] lactacystin,[2] and kainic acid.[3] One of the most common and practical methods for the synthesis of chiral amines is by reaction of a chiral sulfinimine with a nucleophile.[4] Over the past two decades, led by the seminal contributions of Davis[5] and Ellman,[6] hundreds of reports have been published on the transformations of chiral *p*-tolyl and *tert*-butane sulfinimines.[7] Despite this large body of work, reports on the cycloaddition chemistry of sulfinimines remain scarce, with just a few reports of the use of *p*-tolyl sulfinimines,[8] one report of polyfluorinated sulfinimines,[9] and a single example of the use of a *tert*-butane sulfinimine in a cycloaddition reaction.[10] Drawn by the highly useful trimethylenemethane cycloaddition methodology of Trost,[11] and encouraged by two reports of such a cycloaddition on aryl *N*-BOC imines[12] and on *N*-tosyl imines with a stabilized variant of the TMM reagent,[13] we decided to investigate the potential [3 + 2] cycloaddition of TMM with *tert*-butanesulfimines, which would yield chemically interesting methylenepyrrolidines as products.

Initially, we decided to optimize conditions using the benzaldehyde-derived *tert*-butanesulfinimine **1a**. As our

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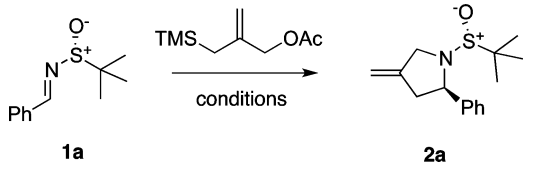
starting point, we decided to use conditions developed by Harrity for a TMM [3 + 3] cycloaddition to tosylaziridines,[14] which involved the use of palladium acetate, triisopropyl phosphite, and butyl lithium. We were encouraged by the successful outcome of this reaction, gaining the pyrrolidine product **2a** in 36% yield. With this initial successful cycloaddition in hand, we looked into optimizing the reaction conditions (Table 1). We found that tetrakis(triphenylphosphine) palladium was an excellent catalyst if freshly recrystallized prior to use. The reaction was found to work in acetonitrile, methanol, or dry THF as a solvent, with THF (freshly distilled from sodium benzophenone ketal) giving the best diastereoselectivities and good yields. The concentration of the reaction was found to be important, with 0.5 M being found to be best. Similarly, we found reactions at room temperature gave decent diastereoselectivities and much-increased yields compared to reactions at lower temperatures. It was found that the sulfinyl directing/protecting group could be removed in quantitative yield by treatment of **2** with 2 M HCl in ether.

Table 1. Screen of Reaction Conditions



1a **2a**

catalyst	solvent	temp	yield	dr
$Pd(OAc)_2$, $P(OiPr)_3$, BuLi	THF	65 °C	36%	2:1
$Pd_2(dba)_3$	THF	rt	0%	–
$Pd(PPh_3)_4$	THF	rt	95%	6:1
$Pd(PPh_3)_4$	THF	−78 °C	25%	8:1
$Pd(PPh_3)_4$	THF	65 °C	36%	2:1
$Pd(PPh_3)_4$	MeCN	rt	99%	4:1
$Pd(PPh_3)_4$	MeOH	rt	84%	4:1
$Pd(PPh_3)_4$	CH_2Cl_2	rt	0%	–
$Pd(PPh_3)_4$	toluene	rt	0%	–
$Pd(PPh_3)_4$	EtOAc	rt	0%	–

Having found a reliable set of conditions for the cycloaddition, we set about determining the scope and limitations. A wide range of sulfinimines were synthesized using Ellman's standard procedures. The result of the reactions of a range of aldimines is shown in Table 2.

We decided initially to test the directing group ability of both *N*-*tert*-butane and *N*-mesityl sulfinimines.[15] Thus both types of sulfinimine were made using benzaldehyde as a precursor and subjected to the optimized conditions.

(14) Harrity, J. P. A; Provoost, O. Y.; Hazelwood, A. J. *Beilstein J. Org. Chem.* **2007**, *3*, 8.

(15) Davis, F. A.; Ramachandar, T.; Wu, Y. *J. Org. Chem.* **2003**, *68*, 6894. Roe, C.; Moragas Solá, T.; Sasraku-Neequaye, L.; Hobbs, H.; Churcher, I.; MacPherson, D.; Stockman, R. A. *Chem. Commun.* **2011**, *47*, 7491.

The *tert*-butyl sulfinimine **2a** gave far superior yields and diastereoselectivities compared to the mesityl sulfinimine **2b**, and thus we decided to investigate solely *tert*-butyl sulfinimines for the rest of the study. It was found that, once purified, the major diastereomer of **2a** could be crystallized, and we were able to gain an X-ray crystal structure (Figure 1). From this, it can be seen that the overall stereoinduction is derived from the dipole−dipole repulsion of the sulfinimine, which places the *tert*-butyl group on the Re face, and thus the cycloaddition occurs from the Si face as this is less sterically encumbered.

In general, yields were found to be decent to excellent for a wide range of aryl, heteroaryl, and alkyl sulfinimines, with aryl chlorides and bromides tolerated under the reaction conditions, which will prove useful for leaving functional groups suitable for further elaboration. The free phenolic OH was found to hinder the yield and stereoselectivity in the formation of **2e**. A similar erosion of yield and dr was found in the formation of naphthalene-derived **2n**, as this reaction required heating to reflux in order for the reaction to take place.

With these successful results in hand, we decided to test the tolerance and scope of the cycloaddition reaction, by investigating the reaction of TMM with sulfinyl ketimines. The results of these investigations are summarized in Table 3.

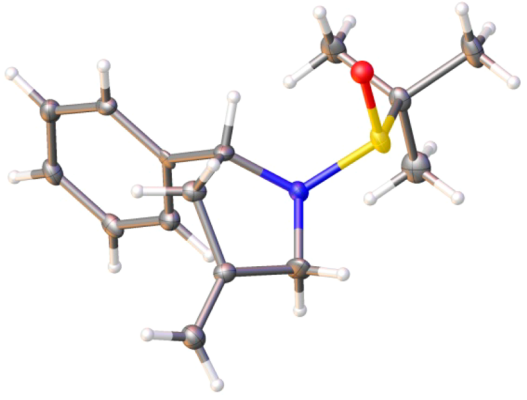
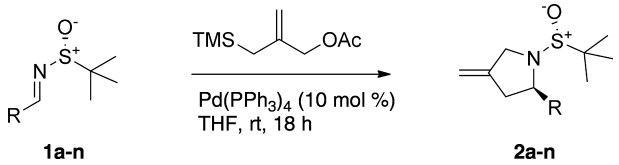


Figure 1. X-ray structure of major diastereomer of **2a**.

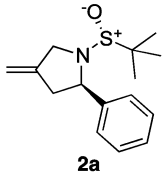
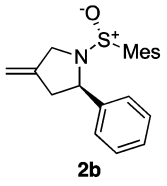
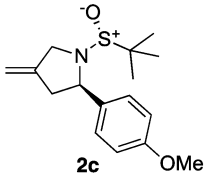
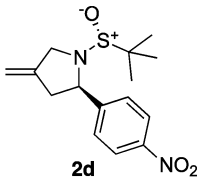
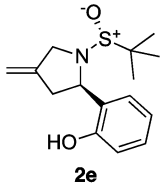
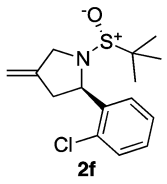
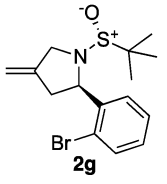
Ketimines are much more sterically hindered, and thus we found the yields of cycloaddition were lower than in the case of aldimine substrates. Similarly, diastereoselectivities were found to be poorer for these substrates, although the indanone-based spiro compound, **3e**, was formed in a respectable yield and diastereoselectivity for such a short synthetic sequence to access this type of complex building block.

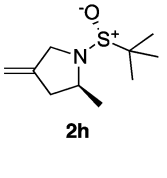
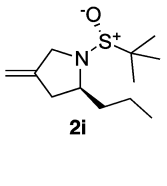
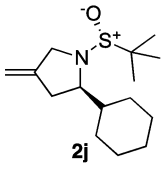
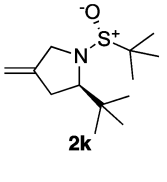
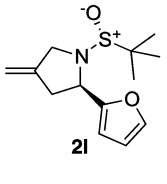
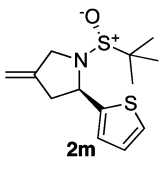
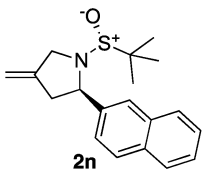
Next, we decided to investigate the exploitation of the methylene pyrrolidines for the formation of further functionalized building blocks for synthesis, and in particular as scaffolds for early stage drug discovery. To this end, we investigated a number of transformations of the pure diastereomer **2a**, as shown in Scheme 1.

Table 2. Reaction of *tert*-Butanesulfinyl Aldimines with TMM



1a-n **2a-n**

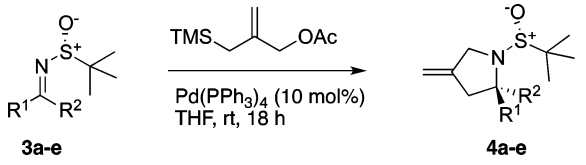
entry	2	yield	dr[b]
1	 **2a**	95%	6:1
2	 **2b**	53%	2:1
3	 **2c**	95%	4:1
4	 **2d**	100%	7:1
5	 **2e**	34%	2:1
6	 **2f**	89%	6:1
7	 **2g**	71%	6:1

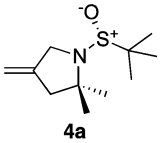
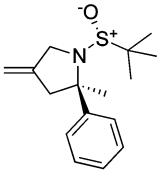
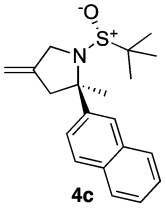
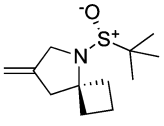
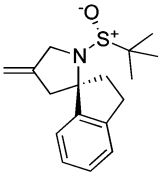
entry	2	yield	dr[c]
8	 **2h**	91%	6:1
9	 **2i**	57%	6:1
10	 **2j**	98%	3:1
11	 **2k**	81%	4:1
12	 **2l**	48%[a]	4:1
13	 **2m**	86%	4:1
14	 **2n**	42%[a]	3:1

[a] Reaction carried out at reflux. [b] Dr determined from comparison of *tert*-butyl peaks in ^{1}H NMR of crude reaction mixture after workup. [c] Diastereomers were separable by column chromatography.

Initially we looked into the removal of the sulfinyl group, which was found to be easily achieved by the use of 2 M HCl in diethyl ether, to give N−H pyrrolidine **5** after basic workup. Hydrogenation of the alkene of **2a** was possible, and the use of platinum oxide was found to give excellent yields of **6**, and also to leave the sulfinyl

Table 3. Reaction of Sulfinyl Ketimines with TMM

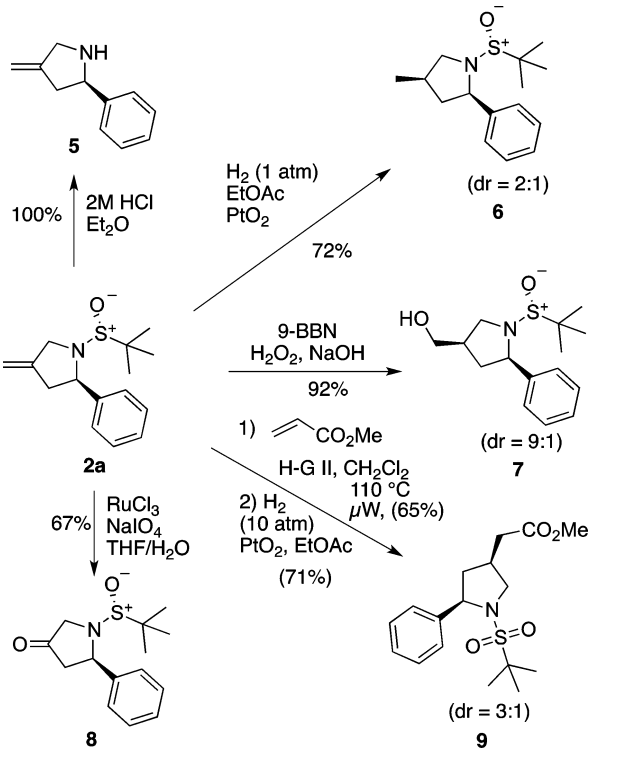


entry	4	temp	yield	dr
1	 **4a**	rt	54%	-
2	 **4b**	reflux	38%	2:1
3	 **4c**	reflux	67%	2:1
4	 **4d**	rt	29%	-
5	 **4e**	reflux	50%	4:1

group intact. Hydroboration of **2a** with 9-BBN, followed by *in situ* oxidation, gave the hydroxymethyl compound **6** with a good degree of diastereoselectivity. Oxidative cleavage of the exoalkene of **2a** to give ketone **8** also oxidized the silfinyl group to a BUS[16] group. Alkene **2a** could be converted into γ-amino acid derivative **9** by cross-metathesis using the Hoveyda–Grubbs second generation catalyst[17] in dichloromethane in a microwave at 110 °C, followed by hydrogenation.

In conclusion, we have demonstrated the first general cycloadditions of chiral *tert*-butane sulfinimines. The pyrrolidine products are of great potential use as building blocks for screening collections[18] or for potential use in the synthesis of natural products. Studies toward these ends are ongoing in our laboratories and will be reported in due course.

Scheme 1. Exploratory Reactions Using **2a** as a Building Block



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Supporting Information Available. Experimental procedures, NMR, IR, ms data and NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

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(18) Nadin, A.; Hattotuwagama, C.; Churcher, I. *Angew. Chem. Int Ed.* **2012**, *51*, 1114.