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[3 + 2] Cycloaddition on Carbohydrate Templates: Stereoselective Synthesis of Pyrrolidines

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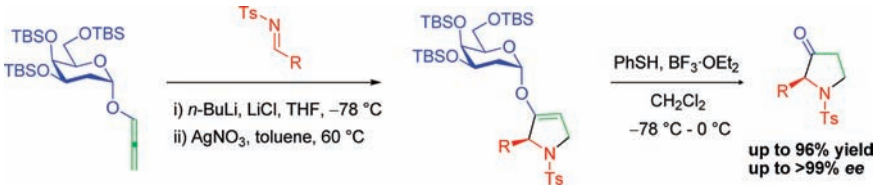
ABSTRACT



Pyrrolidine derivatives were prepared in high diastereoselectivities and good yields *via* a [3 + 2] cycloaddition of a *tert*-butyldimethylsilyl protected carbohydrate-based allene with a diverse range of imines. The subsequent removal of the carbohydrate auxiliary afforded a variety of pyrrolidines with excellent enantioselectivities (up to 99% ee). Selective reduction of the pyrrolidines further demonstrated the potential of this strategy.

A growing interest in the synthesis of optically pure pyrrolidine derivatives is principally attributed to the fact that they are components of many biologically active molecules (Figure 1)[1] that exhibit a wide variety of biological properties[2a] that include antibacterial, antifungal, and cytotoxic activities.[2b,c] They also serve as neuroexcitatory agents,[2d] antibiotics,[2e] and glycosidase inhibitors.[2f] Consequently, the therapeutic effects of pyrrolidines have led to substantial interest in their expedient synthesis.[3]

During the past few years, numerous synthetic strategies to synthesize stereoselective pyrrolidines and their derivatives have been demonstrated. Some of the existing protocols employ aza heterocycles,[4a] cyclizing bis-allylic amines,[4b] and utilize 1,3-dipolar cycloaddition of azomethine ylides in the presence of chiral auxiliaries.[4c] Among these strategies, cycloaddition-based reactions are attractive due to their inherent ability to induce exclusive stereoselectivity, engender remarkable efficiency, and improve atom economy, which can be achieved through constructing multiple bonds in a single step.[5] The initial deployment of chiral auxiliaries in such cycloaddition reactions predominantly utilized α-amino acids, terpenoids, and alkaloids.[6] The pioneering work of Vasella[7a] and Kunz[7b] exploited carbohydrates as chiral templates in a 1,3-dipolar cycloaddition reaction of chiral

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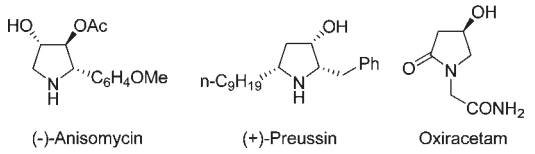


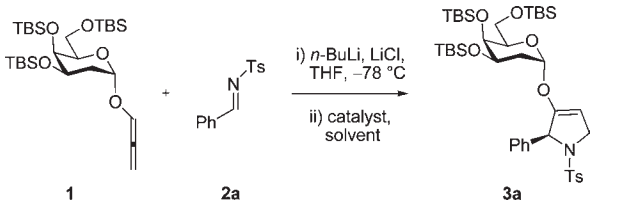
Figure 1. Biologically active natural products.

N-(alkoxyalkyl)nitrones and in a Diels−Alder reaction with acrylates respectively, which prompted a widespread exercise of carbohydrate matrices to construct diversified highly stereoselective molecular skeletons.[7c]

Indubitably, carbohydrates are enantiomerically pure candidates which exert their chirality on prochiral faces of the substrate to synthesize many chiral drugs as well as natural products.[8] In addition to their low cost,[9a] the most pre-eminent feature of carbohydrate auxiliaries lies in their differing configurations of the carbohydrate scaffold, which aid in installing diverse template geometries, thus enabling the introduction of a wide variety of coordinative sites.[9b] The efficient use of carbohydrate derivatives as stereodifferentiating auxiliaries in chiral synthesis, particularly in cycloaddition reactions, has been corroborated.[10] Notably, an allene ether version of the Nazarov cyclization was recently reported by Tius et al. which employed carbohydrate chiral auxiliaries appended to lithiated allenes.[11a] Over the past few decades, numerous examples of lithiated allenes as building blocks in the synthesis of pyrrolidines and pyrrole derivatives have been demonstrated.[11b] For example, Ressig reported a [3 + 2] cycloaddition, where a variety of pyrrolidines and pyrroles were synthesized from lithiated allenes.[12]

In line with our strong interests in carbohydrate synthesis and our efforts in developing new methodologies for the synthesis of biologically potent heterocycles,[13] herein we report a proficient synthesis of pyrrolidines *via* a [3 + 2] cycloaddition between a *tert*-butyldimethylsilyl (TBS) protected carbohydrate-based lithiated allene and a range of imines.

Table 1. Optimization Studies[a]



1 2a 3a

entry	catalyst	solvent	time (h)	yield[b] (%)	*de*[c] (%)
1	$AgBF_4$	acetone	3	20	79
2	$AgClO_4$	acetone	3	11	77
3	$AgNO_3$	acetone	1	71	86
4	AgOTf	acetone	2	54	81
5	AuCl	acetone	1	62	83
6	$AuCl_3$	acetone	1	64	84
7	$AgNO_3$	CH_2Cl_2	1	48	87
8	**$AgNO_3$**	**toluene**	**0.5**	**75**	**92**
9	$AgNO_3$	THF	0.5	71	90

[a] See ref 15. [b] Isolated yield of major diastereomer. [c] Determined by crude ^1H NMR spectroscopy.

As highlighted in the recent report by Tius, the TBS ether protected carbohydrate auxiliary not only produces good selectivity but also prevents aggregation during the addition of butyllithium, therefore bestowing a better nucleophile for the reaction with various imines.[14] This discovery underpinned our selection of a TBS ether protected carbohydrate as the auxiliary in this cycloaddition reaction. Therefore, the optimization studies were based on the cycloaddition reaction between a TBS ether protected carbohydrate allene **1** and an imine substrate with a simple phenyl substituent **2a** (Table 1).[15]

At the outset of the optimization studies, a variety of silver and gold catalysts were chosen for screening because of their high efficacy in many organic transformations;[16a,b] especially their role in many cycloaddition reactions is worthy of note.[16c,d] Intriguingly, our initial preliminary survey had shown that the choice of the catalyst is largely contingent on the yields of the products. The first set of experiments, utilizing $AgBF_4$ and $AgClO_4$ in acetone (Table 1, entries 1 and 2) did not provide satisfactory results, producing the pyrrolidine derivatives in low yields (20% and 11% respectively). However, in the above set of reactions, diastereoselectivities were found to be

(7) (a) Vasella, A. *Helv. Chim. Acta* **1977**, *60*, 1273. (b) Kunz, H.; Müller, B.; Schanzenbach, D. *Angew. Chem., Int. Ed.* **1987**, *26*, 267. (c) Boysen, M. *Chem.—Eur. J.* **2007**, *13*, 8648.

(8) Wang, Y.; Yu, J.; Miao, Z.; Chen, R. *Chem.—Eur. J.* **2009**, *15*, 9290.

(9) (a) King, S. B.; Ganem, B. *J. Am. Chem. Soc.* **1991**, *113*, 5089. (b) Howland, J. L. *Biochem. Educ.* **1996**, *24*, 69.

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(12) Kaden, S.; Brockmann, M.; Reissig, H. U. *Helv. Chim. Acta* **2005**, *88*, 1826.

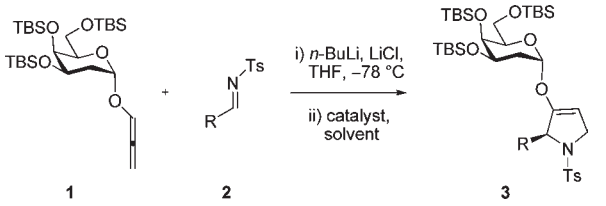
(13) (a) Lorpitthaya, R.; Xie, Z. Z.; Sophy, K. B.; Luo, J. L.; Liu, X.-W. *Chem.—Eur. J.* **2010**, *16*, 588. (b) Gorityala, B. K.; Cai, S.; Lorpitthaya, R.; Ma, J.; Pasunooti, K. K.; Liu, X.-W. *Tetrahedron Lett.* **2009**, *50*, 676. (c) Lorpitthaya, R.; Sophy, K. B.; Kuo, J. L.; Liu, X.-W. *Org. Biomol. Chem.* **2009**, *7*, 1284. (d) Vedachalam, S.; Zeng, J.; Gorityala, B. K.; Antonio, M.; Liu, X.-W. *Org. Lett.* **2009**, *12*, 352. (e) Liu, X.-W.; Le, T. N.; Lu, Y. P.; Xiao, Y. J.; Ma, J. M.; Li, X. *Org. Biomol. Chem.* **2008**, *6*, 3997. (f) Cheng, X.-M.; Liu, X.-W. *J. Comb. Chem.* **2007**, *9*, 906.

(14) Banaag, A. R.; Tius, M. A. *J. Am. Chem. Soc.* **2007**, *129*, 5328.

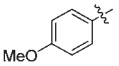
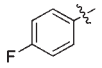
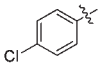
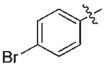
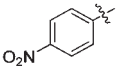
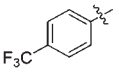
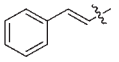
(15) To LiCl (3.0 equiv) was added a solution of **1** (1.0 equiv) in THF (5 mL) at −78 °C. The mixture was stirred for 5 min, and then *n*-BuLi (2.0 equiv) was added dropwise and stirred for 45 min. **2a** (2.0 equiv) in THF (10 mL) was then added over 15 min and stirred for 3 h at −78 °C. A brown oil was yielded after standard workup. To a solution of the brown oil in toluene (10 mL) was added $AgNO_3$ (0.2 equiv), and the mixture was stirred for 30 min at 60 °C. The mixture was filtered, evaporated, and purified by column chromatography to afford compound **3a** (see Supporting Information).

(16) (a) Naodovic, M.; Yamamoto, H. *Chem. Rev.* **2008**, *108*, 3132. (b) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. (c) Gung, B.; Craft, D.; Bailey, L.; Kirschbaum, K. *Chem.—Eur. J.* **2010**, *16*, 639. (d) Yamashita, Y.; Guo, X.-X.; Takashita, R.; Kobayashi, S. *J. Am. Chem. Soc.* **2010**, *132*, 3262.

Table 2. Exploration of the Substrate Scope of the Formation of Pyrrolidine Derivatives[a]



1 2 3

entry	3	R	yield[b] (%)	*de*[c] (%)
1	**a**		75	92
2	**b**		80	91
3	**c**		75	92
4	**d**		75	94
5	**e**		74	95
6	**f**		75	95
7	**g**		65	94
8	**h**		70	95
9	**i**		75	92
10	**j**		62	90
11	**k**		80	93
12	**l**		72	90
13	**m**		80	91

[a] See ref 15. [b] Isolated yield of the major diastereomer. [c] Determined by crude ^{1}H NMR spectroscopy.

promising. Among the silver catalysts tested, the reaction yield (71%) and diastereoselectivity (86% *de*) were significantly enhanced when $AgNO_3$ was employed. Subsequently, gold catalysts were examined as we envisioned that the usage of gold catalysts would produce good yields and diastereoselectivities. Gratifyingly, the results attained were in harmony with our predictions, as both AuCl and $AuCl_3$ (Table 1, entries 5 and 6) showed relatively good yields (62−64%) and diastereoselectivities (83−84%). However, in contrast to AuCl and $AuCl_3$, the choice of $AgNO_3$ allows the acquirement of good yields and diastereoselectivities at a much lower cost. The advantages displayed by $AgNO_3$ rendered its selection as the optimal catalyst for this cycloaddition reaction. With the influence

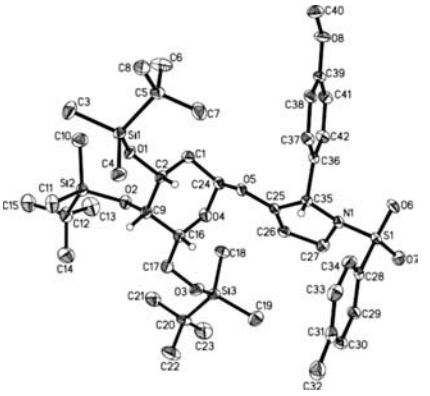
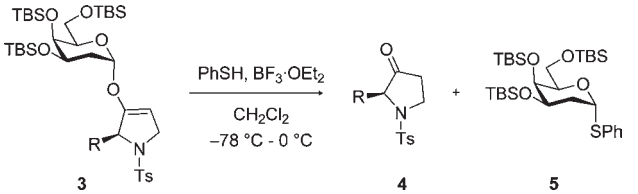


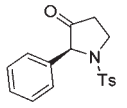
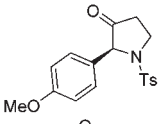
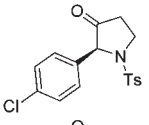
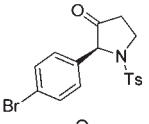
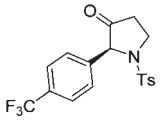
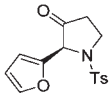
Figure 2. X-ray structure of pyrrolidine derivative **3c**.

of the catalyst established, we proceeded to examine solvent effects. Surprisingly, all of the screened solvents provided high diastereoselectivities, with minor variation in the reaction times (Table 1, entries 3, 7−9). Following a detailed analysis of the optimized results, toluene was identified as the most suitable solvent, furnishing **3a** in good yield (75%) and *de* (92%) within a short reaction time of 30 min (Table 1, entry 8). From the optimization results, we concluded that 0.2 equiv of $AgNO_3$ in toluene was the most suitable set of conditions for this cycloaddition reaction.

Finally, as this cycloaddition protocol was being delineated, we began to scrutinize the flexibility and scope of the reaction on a variety of imines. To our delight, this strategy was compatible with a wide array of aromatic as well as nonaromatic imines. Hence, diastereomers **3a**−**3m** were obtained in relatively good yields (62−80%) with high diastereoselectivities (90−95%) (Table 2). A careful examination of the results revealed several characteristics of this cycloaddition reaction that are noteworthy. The presence of electron-donating (**3b**−**3c**) (Figure 2) and electron-withdrawing substituents (**3d**−**3h**) on aromatic imines provided consistent yields, indicating that the choice of substituents on the aromatic imines have little or no effect on the yields of the reactions. However, it could be observed that imines bearing an electron-withdrawing NO_2 group (**3g**) and a furan moiety (**3j**) provided slightly lower yields of the cyclized product in contrast to the rest of the substituents. Interestingly, the substituents on the aromatic imines were relatively important determinants of the diastereoselectivities. As illustrated, most of the aromatic imines with electron-withdrawing substituents furnished the cyclized **3e**−**3h** with high *de* (~95%), while aromatic imines with electron-donating groups, aliphatic imines, and heterocyclic and naphthyl imines produced the desired product in slightly lower *de* (90−92%). Results pertaining to the aliphatic imines (**3k**−**3m**) also unveiled good yields (72−80%) and *de* (90−93%). This further supported and strengthened the foundation of our strategy by showcasing the good flexibility and tolerance of this cycloaddition reaction to a range of imine compounds.

Table 3. Evaluation of the Enantioselectivity of Pyrrolidine Derivatives



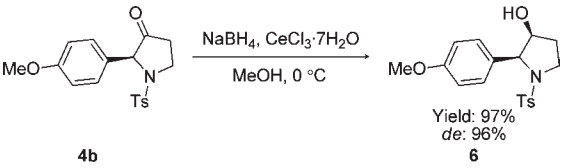
entry	4	product	yield[a] (%)	ee[b] (%)
1	**a**[c]		92	98
2	**b**		96	>99
3	**c**		94	97
4	**d**		94	99
5	**e**		94	99
6	**f**		92	89

[a] Isolated yield. [b] Determined by chiral HPLC. [c] Stereochemistry determined by optical rotation and X-ray crystallography (see Supporting Information).

The enantioselectivity was subsequently probed by removal of the carbohydrate auxiliary using Danishefsky's method.[17] In the presence of phenylthiol (5 equiv) and $BF_3 \cdot OEt_2$ (0.5 equiv), the major diastereomer was cleaved to recover the auxiliary (Table 3). This improves the atom economy, thus offering a unique advantage to the reaction. In addition, the resulting pyrrolidines were obtained in excellent yields (90−96%) with good to excellent enantiomeric selectivity (89−99%). Evaluation of the results showed that, for aromatic compounds substituted with bromine (**4d**) and trifluoromethyl (**4e**), an enantioselectivity of 99% was attained. This impressive selectivity was further substantiated for the methoxy (**4b**) substituted aromatic compound, in which a more than 99% enantiomeric ratio was obtained. Encouraged by these results, we further investigated the flexibility of the reaction by employing a heterocyclic substituted compound. Corresponding to the above results, a good enantioselectivity of 89% with 92% yield was achieved for a furan substituted compound (**4f**).

(17) Halcomb, R. L.; Boyer, S. H.; Wittman, M. D.; Olson, S. H.; Denhart, D. J.; Liu, K. K. C.; Danishefsky, S. J. *J. Am. Chem. Soc.* **1995**, *117*, 5720.

Scheme 1. Selective Reduction of Pyrrolidine **4b**



To exemplify the experimental success of this protocol and its potential utility in synthesis, we proceeded to reduce the pyrrolidine **4b** which is substituted with a methoxy group on the aromatic ring. The reduction of **4b** was performed by employing $NaBH_4$ in methanol with $CeCl_3 \cdot 7H_2O$ as the catalyst, providing **6** as the major isomer (Scheme 1). Subsequent evaluation of the crude ^1H NMR revealed a diastereomeric ratio of 96%. This strategy is useful in preserving the stereoselectivity of natural products such as (+)-preussin[18a] as these natural products are extremely important in peptidomimetics.[18b]

In conclusion, a [3 + 2] cycloaddition on a TBS ether protected carbohydrate template has been established. This methodology utilized lithiated allene and imines, in the presence of $AgNO_3$, to synthesize pyrrolidine derivatives in good yields and diastereoselectivities. In addition, excellent enantioselectivities were obtained for a range of pyrrolidines after removal of the carbohydrate auxiliary. Subsequently, selective reduction of the pyrrolidines reinforced the potential application of the strategy in organic synthesis, further justifying that our strategy is of importance to synthetic chemistry. This novel protocol constitutes one of the best examples in exploiting chiral carbohydrate auxiliaries in synthesizing optically pure bioactive pyrrolidines, thereby paving the way for further investigation in utilizing carbohydrate templates for enantioselective synthesis.

Acknowledgment. Financial support from Nanyang Technological University (RG50/08) and the Ministry of Health, Singapore (NMRC/H1N1R/001/2009) are gratefully acknowledged.

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

(18) (a) Huang, P.-Q.; Wu, T.-J.; Ruan, Y.-P. *Org. Lett.* **2003**, *5*, 4341. (b) Gante, J. *Angew. Chem., Int. Ed.* **1994**, *33*, 1699.