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Development of a Stepwise [3 + 3] Annelation to Functionalized Piperidines

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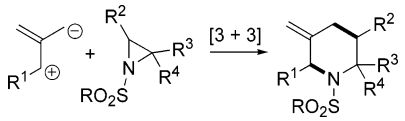
ABSTRACT

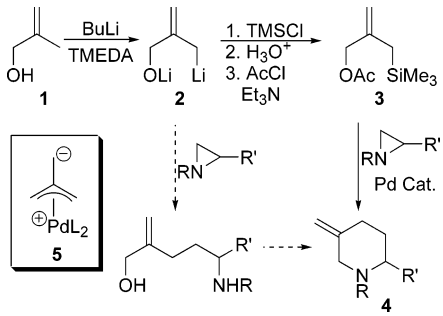


A stepwise formal [3 + 3] cycloaddition sequence via a Grignard addition–cyclization reaction leads to a much improved piperidine synthesis. This methodology provides improved flexibility in both the aziridine substrate and TMM equivalent.

We have recently been investigating a new approach to enantiopure piperidines via a formal [3 + 3] cycloaddition reaction of aziridines with Pd−TMM species.[1,2] This technique provides an expedient route to enantiopure 2-piperidines because the precursor aziridines are readily made in enantiomerically pure form from the corresponding amino acids.[3] During the course of our studies on the reaction scope and the employment of this methodology in target synthesis, we have uncovered several instances where the Pd−TMM reagent fails to add to the aziridine or does so with low levels of conversion. Accordingly, we have attempted to uncover a more nucleophilic alternative to the Pd−TMM for use with less reactive aziridines and report herein our preliminary findings.

Our piperidine forming strategy comprises the formal addition of trimethylenemethane[4] to an aziridine (Figure 1). In practice, we have employed Trost's conjunctive reagent (2-[(trimethylsilyl)methyl]-2-propen-1-yl acetate) **3**, which is in turn prepared from methallyl alcohol **1** (Scheme 1).[5]

Scheme 1



While the conversion of **3** to piperidines **4** takes place in one pot, the low conversions observed in some of our [3 +

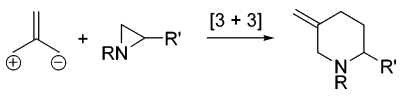


Figure 1. [3 + 3] Cycloaddition to piperidines.

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[‡] Merck, Sharp and Dohme.

(1) (a) Hedley, S. J.; Moran, W. J.; Prenzel, A. H. G. P.; Price, D. A.; Harrity, J. P. A. *Synlett* **2001**, 1596. (b) Hedley, S. J.; Moran, W. J.; Price, D. A.; Harrity, J. P. A. *J. Org. Chem.* **2003**, *68*, 4286.

(2) For reviews of alternative [3 + 3] approaches to piperidine systems, see: (a) Harrity, J. P. A.; Provoost, O. *Org. Bio. Chem.* **2005**, 1349. (b) Hsung, R. P.; Kurdyumov, A. V.; Sydorenko, N. *Eur. J. Org. Chem.* **2005**, 23.

(3) Craig, D.; Berry, M. B. *Synlett* **1992**, 41.

(4) For a review of Pd-TMM cycloadditions see: (a) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1.

(5) Trost, B. M.; Chan, D. M. T.; Nanninga, T. M. *Org. Synth.* **1984**, *62*, 58.

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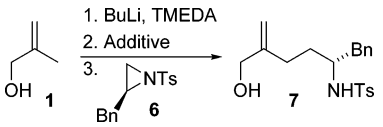
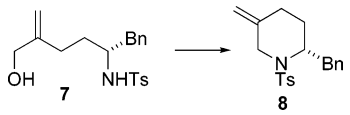
Table 1. Optimization of Aziridine Ring Opening[a]



entry	equiv of **1**	additive	conditions	yield (%)
1	10		25 °C, 2 h	19
2	3	$MgBr_2$	25 °C, 18 h	53
3	4	$MgBr_2$	25 °C, 2 h	65
4	5	$MgBr_2$	25 °C, 2 h	87
5	5	$MgBr_2$	25 °C, 18 h	88
6	5	$MgCl_2$	25 °C, 2 h	75

[a] Organomagnesium reagent prepared by addition of TMEDA (2.6 equiv) and *n*-BuLi (3.0 equiv) to **1** followed by MgX_2 (2.6 equiv).

Table 2. Ring Closure to Piperidine **8**[a]



entry	conditions[a]	yield (%)
1	5 mol % of $PdCl_2$, THF	0
2	5 mol % of $Pd(OAc)_2$, 20 mol % of PBu_3 60 mol % of Et_3B, THF	75[b]
3	10 mol % of $Pd(OAc)_2$, 40 mol % of PPh_3 25 mol % of Ti(OPr-*i*)$_4$, 4 Å MS, benzene	72
4	10 mol % of $Pd(OAc)_2$, 40 mol % of PPh_3 25 mol % of Ti(OPr-*i*)$_4$, 4 Å MS, toluene	100

[a] All reactions run at reflux over 18 h. [b] Reaction run for 48 h and product contaminated by endocyclic isomer.

3] cycloadditions suggested that the in situ generated Pd−TMM reagent **5** was only moderately reactive toward aziridines. In an effort to address this limitation, we contemplated the use of more nucleophilic TMM equivalents. As depicted in Scheme 1, reagent **3** ultimately emanates from the allylmetal reagent **2**. This raised an intriguing question as to the feasibility of using **2** in a stepwise addition−cyclization process that we envisaged could provide an alternative method of piperidine synthesis with hitherto unreactive aziridines.[6]

To test this hypothesis, we set out to investigate the addition of **1** to aziridine **6**; our results are shown in Table 1. Double deprotonation of methallyl alcohol and addition of the organolithium reagent to **6** only succeeded in furnishing **7** after a large excess of reagent was employed (entry 1). We therefore opted to perform a transmetalation to the organomagnesium reagent by addition of $MgBr_2$. Pleasingly, addition of the Grignard reagent to **6** provided **7** in moderate yield over an extended reaction time (entry 2). Further optimization showed that excellent yields of product could be obtained when aziridine **6** was added to 5 equiv of Grignard reagent and that the reaction was effectively complete within 2 h (entries 4 and 5). Unsurprisingly, the use of $MgCl_2$ also delivered an efficient addition reaction, although **7** was generated in slightly lower overall yield in this case (entry 6).

Our next task was to develop an efficient method for the cyclization process. Early studies toward the synthesis of *Nuphar* alkaloids showed that this ring closure could be carried out in a single step using Mitsunobu conditions.[7] This method provided the piperidine product in a single step when tributylphosphine and ADDP were used; however, this stoichiometric route was rather expensive and resulted in purification problems. In an attempt to find a more efficient cyclization process, we were attracted by the prospect of employing Pd catalysis. Specifically, Hirai and Makabe have reported that Pd(II) catalysts mediate the closure of carbamates onto allylic alcohols without need for preactivation of the hydroxyl group.[8] Additionally, Ti-[9] and B-mediated[10] amination of allylic alcohols have been reported that are proposed to proceed via the intermediacy of a Pd π-allyl intermediate. We decided to employ these procedures in our cyclization reaction, and the results are shown in Table 2.

Attempts to promote the cyclization using $PdCl_2$ were unsuccessful, and starting material was recovered from the reaction mixture (entry 1). In contrast, the B-promoted amination proceeded with good conversion although **8** was contaminated with alkene isomerization product (entry 2). Pleasingly, the Ti-promoted reaction proceeded smoothly to give the desired piperidine **8** in high yield with the optimal conditions resulting from overnight reflux in toluene (entries 3 and 4).

We were now in a position to investigate the scope of the stepwise piperidine forming reaction and, in particular, to compare the efficiency of this process with the Pd−TMM cycloaddition methodology. We began by investigating the scope of 2-alkyl-substituted aziridine substrates, our results are outlined in entries 1−5 of Table 3. We first investigated the effect of N-protecting group as the Pd−TMM technique was restricted to arylsulfonamide containing aziridines. Indeed, the stepwise annelation of SES-protected aziridine **12** generated piperidine **14** albeit in modest overall yield (entry 3). Phenyl-substituted aziridine **15** had performed efficiently in the Pd−TMM [3 + 3] cycloaddition but provided an almost equal mixture of regioisomeric products. Interestingly, the use of the organomagnesium reagent resulted in much more useful levels of regiocontrol in favor of the 3,5-disubstituted piperidine, allowing **17** to be isolated

(6) Addition of a related Grignard reagent to epoxides has been shown to produce pyrans: van der Louw, J.; van der Baan, J. L.; Out, G. J. J.; de Kanter, F. J. J.; Bickelhaupt, F.; Klumpp, G. W. *Tetrahedron* **1992**, *48*, 9901.

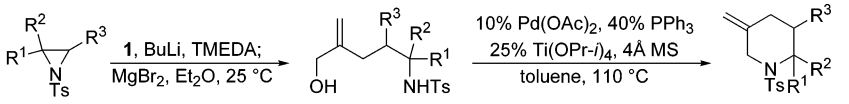
(7) (a) Moran, W. J.; Goodenough, K. M.; Raubo, P.; Harrity, J. P. A. *Org. Lett.* **2003**, *5*, 3427. (b) Goodenough, K. M.; Moran, W. J.; Raubo, P.; Harrity, J. P. A. *J. Org. Chem.* **2005**, *70*, 207.

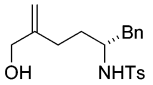
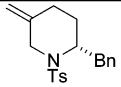
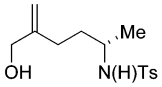
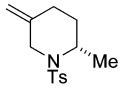
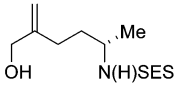
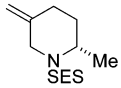
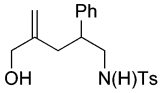
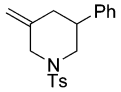
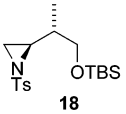
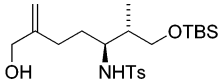
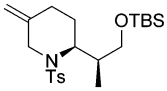
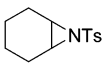
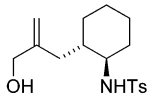
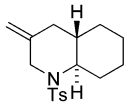
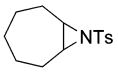
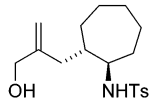
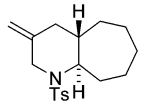
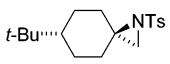
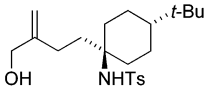
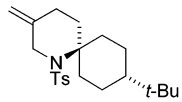
(8) (a) Yokoyama, H.; Otaya, K.; Kobayashi, H.; Miyazawa, M.; Yamaguchi, S.; Hirai, Y. *Org. Lett.* **2000**, *2*, 2427. (b) Makabe, H.; Kong, L. K.; Hirota, M. *Org. Lett.* **2003**, *5*, 27.

(9) Yang, S.-C.; Hung, C.-W. *J. Org. Chem.* **1999**, *64*, 5000.

(10) Kimura, M.; Futamata, M.; Shibata, K.; Tamaru, Y. *Chem. Commun.* **2003**, 234.

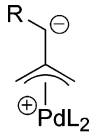
Table 3. Stepwise Annelation of Aziridines



entry	aziridine	adduct	piperidine	overall yield	Pd-TMM yield
1	 **6**	 **7;** 87%	 **8;**100%	87%	79%
2	 **9**	 **10;** 93%	 **11;**67%	62%	82%
3	 **12**	 **13;** 63%	 **14;**62%	38%	0%
4	 **15**	 **16;** 81%	 **17;**76%	62% (8:1)	68% 1.6:1
5	 **18**	 **19;** 92%	 **20;** 81%	74%	15%
6	 **21**	 **22;** 79%	 **23;** 87%	69%	31%
7	 **24**	 **25;** 76%	 **26;** 77%	58%	0%
8	 **27**	 **28;** 75%	 **29;** 63%	47%	0%

in high yield. Finally, aziridine **18** had been found to be surprisingly sluggish in the [3 + 3] cycloaddition chemistry but was converted to **20** in excellent overall yield using this modified procedure (entry 5). Moreover, we were pleased to find that this technique could also be extended to provide bicyclic piperidines (entries 6 and 7) and spirocyclic products (entry 8) in high overall yield.

One final limitation of the Pd−TMM methodology that we hoped to overcome was in the addition of substituted conjunctive reagents to aziridines. While Trost and co-workers have shown that substituted Pd−TMM reagents **30** can add to Michael acceptor systems,[11] we found that these reagents would not participate in [3 + 3] cycloadditions. We therefore set out to investigate if the stepwise addition process would allow us to successfully prepare more heavily substituted piperidines by this route.

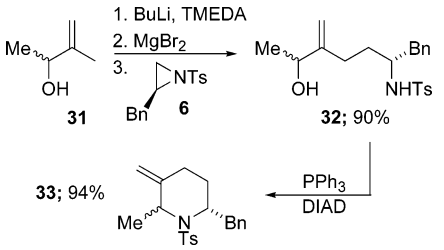


30

As outlined in Scheme 2, double deprotonation of methallyl alcohol **31**, transmetalation with $MgBr_2$, and addition to aziridine **6** gave the corresponding adduct **32** in excellent yield. Initial attempts to convert **32** into the desired piperidine **33** using the Pd-catalyzed cyclization furnished a mixture of products that resulted from addition of the sulfonamide unit at either end of the putative[8] Pd π-allyl intermediate.

(11) Trost, B. M.; King, S. A. *J. Am. Chem. Soc.* **1990**, *112*, 408.

Scheme 2



Accordingly, we returned to use of the Mitsunobu reaction to complete the cyclization and were pleased to find that this took place efficiently to provide the trisubstituted piperidine **33** as an equal mixture of diastereomers at C-6.

In conclusion, we report a complementary and stepwise annelation procedure that rivals our previously developed Pd−TMM-mediated cycloaddition reaction toward piperidines. This technique expands the scope of the [3 + 3] strategy both in terms of participating aziridines and conjunctive reagents and promises to allow a broader range of heterocycle targets to be made available.

Acknowledgment. We thank the EPSRC and MSD for financial support.

Supporting Information Available: Full experimental details for the syntheses reported are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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