ORGANIC LETTERS

2010
Vol. 12, No. 21
4908−4911

Trimethylsilyldiazomethane as a Versatile Stitching Agent for the Introduction of Aziridines into Functionalized Organic Molecules

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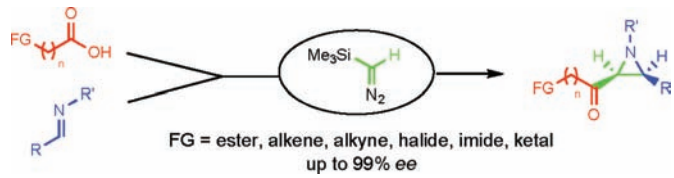
Received August 30, 2010

ABSTRACT



A highly enantioselective route for the introduction of aziridines into functionalized organic molecules was developed via a tandem acylation and aziridination of $TMSCHN_2$.

The formal addition of carbenes to Schiff bases to afford aziridines is well-known.[1] In particular, the formal transfer of carbenes in the guise of diazo compounds to imines is highly attractive and dates back to early observations involving boron trifluoride etherate and zinc iodide.[2] The generality of this process with simple nonchiral Lewis acids was not appreciated until the reports by Brookhart and Templeton in 1996 and Jorgensen in 1997.[3] In 1999 we reported a catalytic asymmetric aziridination of imines with diazo compounds catalyzed by a chiral spiro-boroxinate Brønsted acid derived from VANOL or VAPOL.[4−6] There have been additional methods reported for asymmetric catalytic synthesis of aziridines from imines and diazo compounds with chiral Brønsted acids[7,8] and chiral Lewis acids.[9] In addition, there have been a few reports of asymmetric synthesis of aziridines induced by chiral centers in the imine or the diazocompound.[10] With a single exception,[4e] these reactions involve the formation of aziridines from the reactions of imines with commercially

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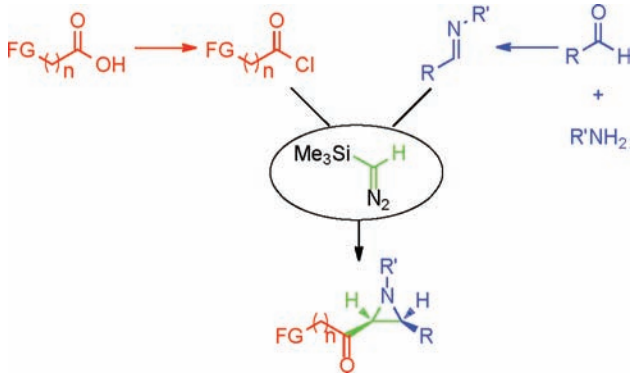
10.1021/ol102064b
Published on Web 10/05/2010

available ethyl diazoacetate (EDA) or *tert*-butyl diazoacetate or with corresponding amide derivatives.

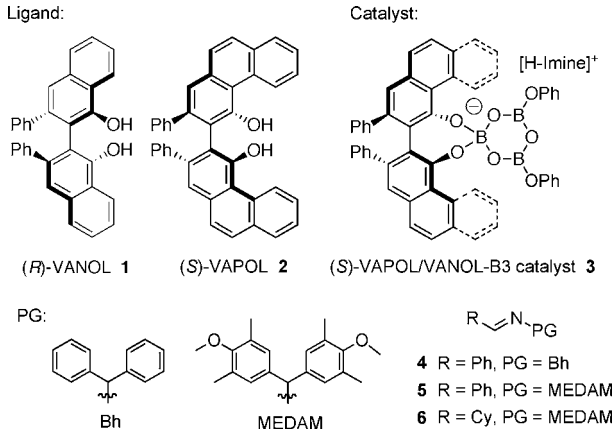
Our interests for the present study were directed toward the development of the catalytic asymmetric aziridinations with alternative diazo sources especially to those that would allow for the straightforward introduction of a variety of functional groups into the aziridine core (Scheme 1). The

Scheme 1. Tandem Acylation/Aziridination of $TMSCHN_2$



goals are 2-fold: define a facile catalytic asymmetric method for the introduction of aziridine units into functionalized organic molecules and determine the tolerance of the VAPOL/VANOL chiral polyborate catalyst (**3** in Scheme 2)

Scheme 2. Ligands, Catalyst, and N-Protecting Groups



to various common organic functional groups. We were attracted to the potential that trimethylsilyldiazomethane ($TMSCHN_2$) presents for realization of these goals in a synthetically convergent manner. Herein, we report a highly enantioselective route for the introduction of aziridines into functionalized organic molecules via a tandem acylation and aziridination with $TMSCHN_2$.

The acylation of $TMSCHN_2$ was first described by Shioiri and co-workers when they introduced this reagent as a stable and safe substitute for diazomethane in the Arndt−Eistert synthesis of esters.[11,12] In their protocol, an acid chloride was treated with $TMSCHN_2$ and the resulting diazomethyl ketone heated with an alcohol to give the corresponding homologated ester. They did demonstrate in one example (1-naphthoyl chloride) that the diazomethyl ketone could be isolated in good yield (74%). Shioiri's protocol for the Arndt−Eistert synthesis of esters with aliphatic acid chlorides requires 2.0 equiv of $TMSCHN_2$ to achieve optimal results.[13] While $TMSCHN_2$ is commercially available, for the sake of efficiency, it seemed highly desirable to determine if the need for excess $TMSCHN_2$ was evitable. Indeed it is.

The yield of the diazoketone **8a** is 62% with 2.0 equiv of $TMSCHN_2$ and 59% yield with 1.1 equiv (73% at 0 °C) (Table 1). This stoichiometry was found to be suitable for all of the functionalized diazoketones shown in Table 1.

We have reported evidence that suggests that the catalyst for the catalytic asymmetric aziridination reaction is a boroxinate-based chiral Brønsted acid of the type **3** (Scheme 2).[6] Initially, the precatalyst is prepared by heating the ligand with $B(OPh)_3$,[4g] and then upon the addition of the imine the assembly of the boroxinate catalyst is induced.[6] The boroxinate catalysts can be prepared from either VANOL[4j] or VAPOL,[6] and both catalysts were screened with the substrates in Table 1. It was deemed desirable to first determine the optimal nitrogen substituent on the imine, and thus the reaction of the first diazo compound **8a** was examined with the benzhydryl imine **4** and the dianisylmethyl (MEDAM) imine **5**. Not unexpected from our recent studies,[4h,k] the MEDAM imine **5** was found to be superior to the benzhydryl imine **4** giving 99% vs 92% ee for the VAPOL catalyst (Table 1, entries 3 and 1) and 94% vs 85% ee for the VANOL catalyst (Table 1, entries 4 and 2).

The scope of the tandem acylation/aziridination reactions was examined with seven different carboxylic acids **7** and with two different MEDAM imines **5** and **6** (Table 1). All reactions gave excellent asymmetric inductions for all aziridines with both VANOL and VAPOL catalysts and with both imines. The *cis*-aziridines were obtained with ≥50:1

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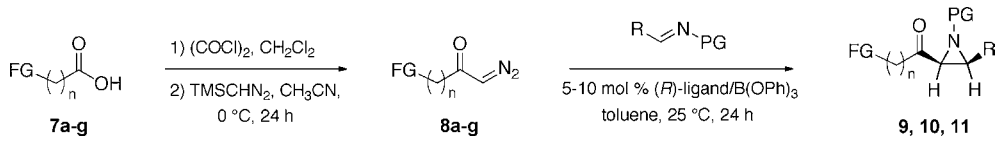
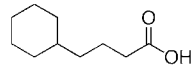
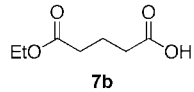
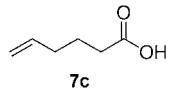
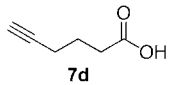
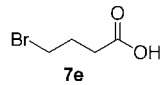
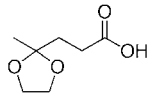
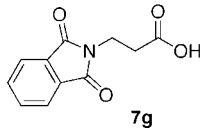
Table 1. Tandem Acylation/Aziridination of $TMSCHN_2$



entry [a]	carboxylic acid	% yield diazo ketone [b]	imine	R	ligand	aziridine	% yield aziridine [c]	% ee aziridine [d]
1	 **7a**	73 [e] (59)	**4**	Ph	(*S*)-VAPOL	**9a**	66	92
2			**4**	Ph	(*R*)-VANOL	**9a**	58	85
3			**5**	Ph	(*S*)-VAPOL	**10a**	72	99
4			**5**	Ph	(*R*)-VANOL	**10a**	85	94
5			**6**	Cy	(*S*)-VAPOL	**11a**	82	95
6			**6**	Cy	(*R*)-VANOL	**11a**	65	91
7	 **7b**	70 (91)	**5**	Ph	(*S*)-VAPOL	**10b**	76	99
8			**5**	Ph	(*R*)-VANOL	**10b**	78	96
9			**6**	Cy	(*S*)-VAPOL	**11b**	92	97
10			**6**	Cy	(*R*)-VANOL	**11b**	90	94
11	 **7c**	69 (65)	**5**	Ph	(*S*)-VAPOL	**10c**	77	99
12			**5**	Ph	(*R*)-VANOL	**10c**	82	96
13			**6**	Cy	(*S*)-VAPOL	**11c**	72	95
14			**6**	Cy	(*R*)-VANOL	**11c**	79	91
15	 **7d**	66 (60)	**5**	Ph	(*S*)-VAPOL	**10d**	89	99
16			**5**	Ph	(*R*)-VANOL	**10d**	95	99
17			**6**	Cy	(*S*)-VAPOL	**11d**	79	96
18			**6**	Cy	(*R*)-VANOL	**11d**	73	91
19	 **7e**	78	**5**	Ph	(*S*)-VAPOL	**10e**	85	95
20			**5**	Ph	(*R*)-VANOL	**10e**	78	98
21			**6**	Cy	(*S*)-VAPOL	**11e**	61	92
22			**6**	Cy	(*R*)-VANOL	**11e**	71	89
23	 **7f**	52	**5**	Ph	(*S*)-VAPOL	**10f**	88	97
24			**5**	Ph	(*R*)-VANOL	**10f**	85	93
25			**6**	Cy	(*S*)-VAPOL	**11f**	62	93
26			**6**	Cy	(*R*)-VANOL	**11f**	64	91
27	 **7g**	82	**5**	Ph	(*S*)-VAPOL	**10g**	80	98
28			**5**	Ph	(*R*)-VANOL	**10g**	85	93
29			**6**	Cy	(*S*)-VAPOL	**11g**	63	87
30			**6**	Cy	(*R*)-VANOL	**11g**	64	88

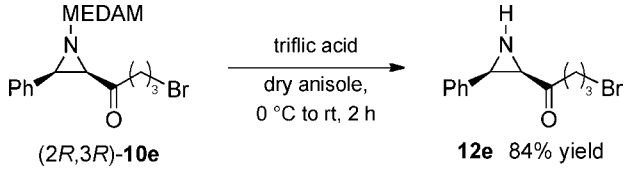
[a] Unless otherwise specified, the acylation of $TMSCHN_2$ was performed in MeCN at 0 °C for 24 h with 1.1 equiv of $TMSCHN_2$. A base workup was not used except in the preparation of **8a** and **8b**. All aziridinations were perfomred with 1.2 equiv of diazoketone at 0.5 M in imine in toluene at 25 °C for 24 h and went to 100% completion. The precatalyst was prepared by reaction of the ligand with 4 equiv of $B(OPh)_3$ and 1 equiv of H_2O in toluene at 80 °C for 1 h and then removal of volatiles at 80 °C (0.1 mmHg) for 0.5 h. Catalyst loading was 5 mol % for imines **4** and **5** and 10 mol % for imine **6**. The catalyst from (*S*)-ligands give *ent*-**9**, *ent*-**10**, and *ent*-**11**. The cis/trans selectivity is ≥50:1 for all reactions. [b] Yields in parentheses are at room temperature. [c] Isolated yield after silica gel chromatography. [d] Determined by HPLC on a Chiralcel OD-H column. [e] The yield of **8a** was 62% at 25 °C with 2.0 equiv of $TMSCHN_2$.

selectivity in all cases. Higher asymmetric inductions were observed with the VAPOL catalysts for both imines in all cases with the curious exception of 5-bromo-1-diazopentan-2-one **8e** (entries 19 and 20). With the diazoketone **8a** as the control, it can be seen that the boroxinate catalyst **3** is remarkably tolerant of the presence of a variety of functional groups with essentially no change in the asymmetric induction over the entire range of functional groups in the diazoketones.

The most efficient method for the deprotection of MEDAM-aziridines is treatment with triflic acid in anisole.[4f,k] However, this method was optimized for simple aziridines sans functionality. It was not clear if the functionalized aziridines generated in the present study would be tolerant of these

conditions. As a test, aziridine **10e** was subjected to 5 equiv of triflic acid in anisole for 2 h, and to our delight, cleavage of the MEDAM group could be achieved to give the N−H aziridine **12e** in excellent yield (Scheme 3). It was interesting

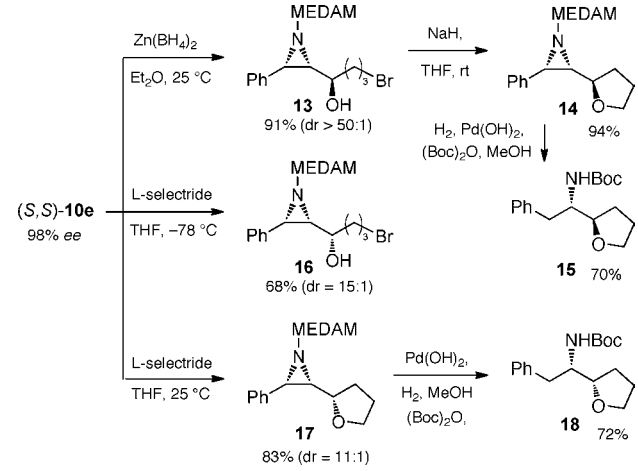
Scheme 3. Deprotection of the MEDAM Group from (2*R*,3*R*)-**10e**



to note that this molecule could be isolated and purified on silica gel with no evidence for intramolecular alkylation on nitrogen.

Tetrahydrofurylamines are widely used in the synthesis of various medical agents such as ion channel modulators,[14] enzyme inhibitors,[15] analgesics,[16] antibiotics[17] and neuotropics,[18] anticarcinogenic drugs,[19] and antifungal agents.[20] This type of compounds are also of particular interest with regard to ligands for asymmetric alkylation.[21] Despite the broad use and importance of tetrahydrofurylamines, a search of the literature produced few reports for the asymmetric preparation of tetrahydrofurylamines, especially those bearing two contiguous chiral centers. Key to the general access to all the stereoisomers of tetrahydrofurylamines from the aziridinyl ketone **10e** is the ability to control the stereochemistry in the reduction of the ketone function. The reduction was first examined with zinc borohydride, a well-known chelation-controlled reducing agent.[4e] Despite our concerns with the presence of the large MEDAM group on the nitrogen which might prevent the coordination of zinc, it proved possible to reduce the ketone moiety with >50:1 selectivity for diastereomer **13** (Scheme 4). Nonchelation-controlled reduction of the ketone functionality in **10e** could be effected with L-selectride at −78 °C in 68% yield and with a 15:1

Scheme 4. Diastereoselective Access to Enantiomeric Tetrahydrofurylamines



selectivity for diastereomer **16**. When the reduction with L-selectride was conducted at room temperature, the stereochemistry of the reduction only dropped to 11:1, and resulting lithium alkoxide cyclized to give the tetrahydrofurylaziridine **17**. Reductive opening of the aziridine and reductive cleavage of the MEDAM group in the presence of $(Boc)_2O$ afforded the tetrahydrofurylamine **18**. After cyclization of **13** with NaH, the diastereomeric tetrahydrofurylamine **15** could be obtained from **14** with the same protocol used in the conversion of **17** to **18**.

This work has demonstrated that the Shioiri acylation of trimethylsilyldiazomethane with aliphatic acid chlorides can be coupled to the catalytic asymmetric aziridination of aldimines with a chiral polyborate Brønsted acid catalyst derived from the vaulted biaryl ligands VANOL and VAPOL. The coupling of these methods led to a direct and highly enantioselective method for the rapid introduction of aziridine units into functionalized organic molecules. It is important to note that the very high asymmetric inductions of the boroxinate catalyst for the catalytic asymmetric aziridination were essentially unaffected by the nature of the functional group in the diazo component. The products of these tandem reactions are synthetically useful intermediates, and this was demonstrated in the stereocontrolled synthesis of tetrahydrofuryl amines.

Acknowledgment. This work was supported by NSF Grant CHE-0750319.

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

OL102064B

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