ORGANIC LETTERS

2003
Vol. 5, No. 13
2367−2370

Diastereoselective Additions of Nucleophiles to α-Acetoxy Ethers Using the α-(Trimethylsilyl)benzyl Auxiliary

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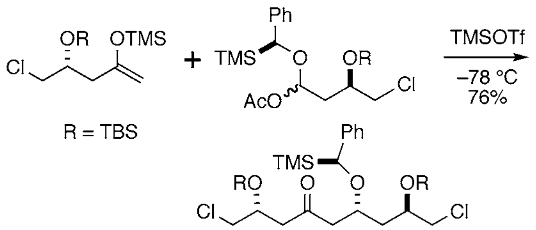
Received May 8, 2003

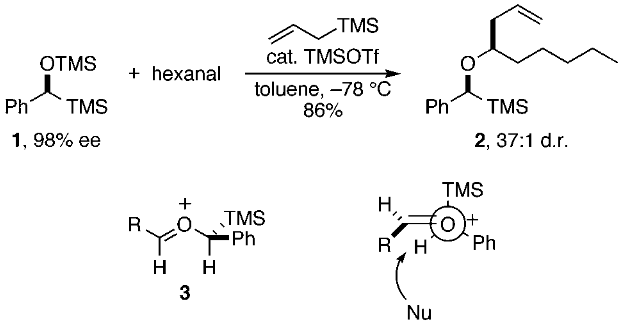
ABSTRACT



We report the diastereoselective addition of a variety of nucleophiles to α-(trimethylsilyl)benzyl-substituted oxocarbenium ions. The oxocarbenium ions are generated from α-acetoxy ethers, which are easily prepared via reductive acetylation of esters. The α-(trimethylsilyl)benzyl auxiliary produces good to excellent facial selectivity with a variety of nucleophiles, including silyl enol ethers, silyl ketene acetals, allylsilanes, and crotylsilanes. The utility of this auxiliary is further demonstrated in a complex ketone aldol coupling reaction.

Oxocarbenium ions are important intermediates in various reactions, including Prins cyclizations, cation−olefin cyclizations, and addition reactions. Efforts to impart high diastereofacial control in these reactions have led to the development of a number of chiral auxiliaries.[1] We recently reported the synthesis of a new oxocarbenium ion chiral auxiliary, α-(trimethylsilyl)benzyl alcohol (**4**).[2] This auxiliary offers several desirable features, including facile preparation of both enantiomers, high diastereofacial selectivity in addition reactions, and direct deprotection or conversion to a benzyl ether. In a preliminary demonstration of the auxiliary's utility, we found that allylations of auxiliary-based oxocarbenium ions, generated in situ according to Marko's protocol, proceeded with high diastereoselectivity (Scheme 1).[1h,2] The facial selectivity could be rationalized by Linderman's model, in which α-silyl oxocarbenium ions adopt a rigid conformation due to a stereoelectronic effect similar

Scheme 1. Diastereoselective Allylation of an in Situ-Generated Oxocarbenium Ion



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[1] (a) For a review of chiral acetals, see: Alexakis, A.; Mangeney, P. *Tetrahedron: Asymmetry* **1990**, *1*, 477−511. (b) Tietze, L. F.; Dolle, A.; Schiemann, K. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1372−1373. (c) Tietze, L. F.; Schiemann, K.; Wegner, C. *J. Am. Chem. Soc.* **1995**, *117*, 5851−5852. (d) Tietze, L. F.; Schiemann, K.; Wegner, C.; Wulff, C. *Chem. Eur. J.* **1996**, *2*, 1164−1172. (e) Tietze, L. F.; Volkel, L.; Wulff, C.; Weigand, B.; Bittner, C.; McGrath, P.; Johnson, K.; Schafer, M. *Chem. Eur. J.* **2001**, 7, 1304−1308. (f) Imwinkelried, R.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 765−766. (g) Mukaiyama, T.; Ohshima, M.; Miyoshi, N. *Chem. Lett.* **1987**, 1121−1124. (h) Mekhalfia, A.; Marko, I. E. *Tetrahedron Lett.* **1991**, *32*, 4779−4782. (i) Molander, G. A.; Haar, J. P. *J. Am. Chem. Soc.* **1993**, *115*, 40−49.

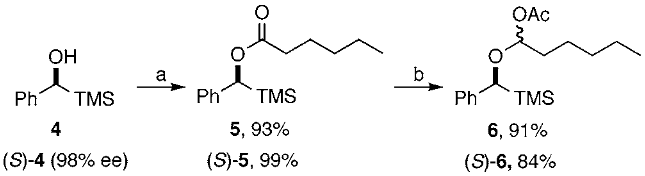
[2] Cossrow, J.; Rychnovsky, S. D. *Org. Lett.* **2002**, *4*, 147−150.

10.1021/ol0347904 CCC: $25.00 © 2003 American Chemical Society
Published on Web 06/05/2003

to the β-silyl effect.[3] While Marko's procedure is operationally convenient, it is limited to nucleophiles with reactivity sufficiently low to permit the formation of oxocarbenium ions in situ. We wished to expand the scope of the α-(trimethylsilyl)benzyl auxiliary by exploring the addition of a range of nucleophiles to oxocarbenium ion precursors. To this end, auxiliary-modified α-acetoxy ethers were prepared by reductive acetylation of esters.[4] These stable oxocarbenium ion precursors were then coupled with a variety of nucleophiles.

To investigate the efficacy of auxiliary **4** in directing various nucleophiles, α-acetoxy ether **6** was selected as the test substrate (Scheme 2). Both racemic and optically pure alcohols **4** were acylated using hexanoyl chloride. Reductive acetylation of ester **5** generated the α-acetoxy ether **6** in good yield as a mixture of diastereomers at the acetal center. Exploratory reactions were conducted with racemic **6**, and several couplings were performed with the optically pure substrate.

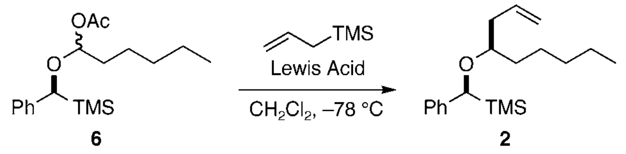
Scheme 2. Preparation of α-Acetoxy Ether **6**[a]



[a] Reaction conditions: (a) hexanoyl chloride, pyridine, CH_2Cl_2. (b) (i) DIBAL-H, CH_2Cl_2, −78 °C; (ii) pyridine, DMAP, Ac_2O.

The first nucleophile systematically investigated was allyltrimethylsilane. Use of this nucleophile in the in situ protocol with hexanal afforded adduct **2** in 86% yield with 37:1 diastereoselectivity (Scheme 1). The same product was accessed by Lewis acid-promoted allylation of α-acetoxy ether **6** (Table 1). Of the Lewis acids examined, TMSOTf was found to produce superior diastereoselectivity (entries 1−3). TMSOTf promotion in toluene provided the best combination of high yield and selectivity (entry 2). However, use of catalytic TMSOTf and excess 2,6-di-*tert*-butyl-4-methylpyridine (DBMP) resulted in the highest selectivity (65:1), suggesting that the selectivity may be lowered by adventitious triflic acid (entry 3). Triflic acid alone proved to be an effective catalyst, resulting in excellent yield and 28:1 selectivity (entry 4). Tin and titanium Lewis acids, as well as $BF_3{\cdot}OEt_2$, produced notably inferior selectivities (entries 5−7). Though allylation of α-acetoxy ether **6** was highly selective, Marko's one-pot procedure remains a comparably efficient and more convenient route to the desired homoallylic ether.

Table 1. Allylation of α-Acetoxy Ether **6**

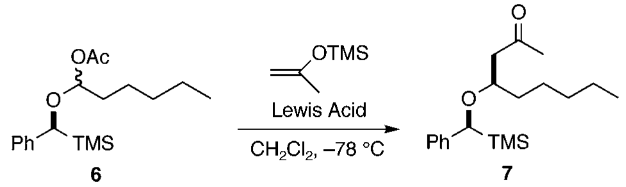


entry[a]	Lewis acid (equiv)	yield (%)[b]	dr[c]
1	TMSOTf (0.2)	87	47:1
2[d]	**TMSOTf (1.1)**	**93**	**44:1**
3[e]	TMSOTf (0.2)	83	65:1
4	TfOH (0.2)	97	28:1
5	$SnCl_4$ (1.1)	93	13:1
6	$BF_3{\cdot}OEt_2$ (1.3)	67	8:1
7	$TiCl_4$ (1.3)	76	5:1

[a] With 1.1 equiv of nucleophile used. [b] Yield of purified product. [c] Determined by GC analysis of unpurified product. [d] Result for (*S*)-**6** in toluene. [e] With 2 equiv of 2,6-di-*tert*-butyl-4-methylpyridine (DBMP) added.

To expand the scope of the auxiliary couplings, we turned to the investigation of other nucleophiles. The aldol-type reaction between a silyl enol ether and α-acetoxy ether **6** was explored (Table 2). A Lewis acid screen revealed that TMSOTf again yielded superior selectivities. TMSOTf promotion in dichloromethane produced the expected adduct **7** in excellent yield as a 30:1 mixture of diastereomers (entries 1, 2).[5] Replacing the solvent with toluene resulted in improved selectivity (67:1) but was accompanied by a reduction in yield (entry 3). Addition of the hindered base DBMP to the TMSOTf-catalyzed reaction in dichloro-

Table 2. Addition of 2-(Trimethylsilyloxy)propene to **6**



entry[a]	Lewis acid (equiv)	yield (%)[b]	dr[c]
1	TMSOTf (0.1)	98	30:1
2	TMSOTf (1.1)	93	28:1
3[d]	TMSOTf (1.1)	69	67:1
4[e]	**TMSOTf (0.2)**	**95**	40:1
5	TfOH (0.2)	61	23:1
6	$SnCl_4$ (1.1)	100	13:1
7	$BF_3{\cdot}OEt_2$ (1.1)	64	8:1
8	$TiCl_4$ (1.1)	90	4:1

[a] With 1.1 equiv of nucleophile used. [b] Yield of purified product. [c] Determined by GC analysis of unpurified product. [d] Result for (*S*)-**6** in toluene. [e] With 2 equiv of DBMP added.

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[3] (a) Linderman, R. J.; Anklekar, T. V. *J. Org. Chem.* **1992**, *57*, 5078−5080. (b) Linderman, R. J.; Chen, K. *J. Org. Chem.* **1996**, *61*, 2441−2453. (c) Linderman, R. J.; Chen, S. *Tetrahedron Lett.* **1995**, *43*, 7799−7802. (d) Linderman, R. J.; Chen, S. *Tetrahedron Lett.* **1996**, *37*, 3819−3822.

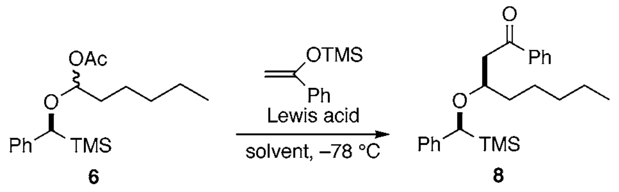
[4] (a) Dahanukar, V. H.; Rychnovsky, S. D. *J. Org. Chem.* **1996**, *61*, 8317−8320. (b) Kopecky, D. J.; Rychnovsky, S. D. *J. Org. Chem.* **2000**, *65*, 191−198.

[5] Configuration of adducts **7**−**9** were assigned by analogy to the allyltrimethylsilane addition and to the configuration of adduct **18**.

methane provided an optimal combination of high yield and diastereoselectivity (entry 4). Triflic acid catalysis led to slightly lower selectivity and significantly reduced yield (entry 5). Titanium tetrachloride, tin tetrachloride, and $BF_3{\cdot}OEt_2$ again gave modest selectivities (entries 6−8). Attempts to carry out this type of coupling by in situ formation of the oxocarbenium ion (by analogy to the Marko's protocol, Scheme 1) led instead to direct addition of the nucleophile to the aldehyde. The α-acetoxy ether-based aldol reaction represents a practical addition to existing asymmetric aldol methodology.

Another efficient coupling partner with the α-acetoxy ether **6** was α-(trimethylsilyloxy)styrene (Table 3). Catalysis of the reaction by TMSOTf in the presence of excess DBMP provided the desired adduct in excellent yield and high selectivity (entry 1).[5] TMSOTf promotion in toluene resulted in lower yield (entry 2), while use of tin tetrachloride gave excellent results comparable to the best case (entry 3). As previously observed, $TiCl_4$ promotion resulted in significant erosion of diastereoselectivity (entry 4).

Table 3. Addition of α-(Trimethylsilyloxy)styrene to **6**

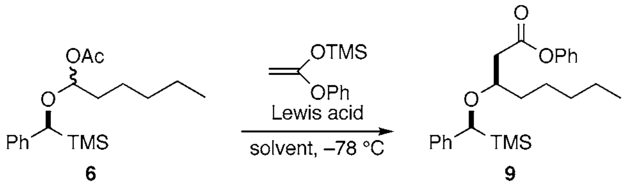


entry[a]	Lewis acid	solvent	yield (%)[b]	dr[c]
1[d]	**TMSOTf**	**CH_2Cl_2**	**98**	**>20:1**
2[e]	TMSOTf	$PhCH_3$	61	>20:1
3	$SnCl_4$	$PhCH_3$	97	>20:1
4	$TiCl_4$	CH_2Cl_2	71	2:1

[a] With 1.1 equiv of nucleophile used and 1.1 equiv of Lewis acid used. [b] Yield of purified product. [c] Determined by ^1H NMR analysis of unpurified product; diastereomers inseparable by GC. [d] With 0.2 equiv TMSOTf and 2 equiv of DBMP used. [e] Result for (*S*)-**6** in toluene.

In addition to silyl enol ethers, we found that a silyl ketene acetal couples to **6** with surprisingly high diastereoselectivity. Because silyl ketene acetals often give inferior selectivities compared with silyl enol ethers in diastereoselective additions to 2-acetoxy tetrahydropyrans,[6] we were concerned that the same might be true with our auxiliary. Gratifyingly, promotion of the coupling reaction with TMSOTf in toluene produced good yields and high selectivities (Table 4, entries 3−5).[5] Exceptional selectivity (80:1) was observed when excess TMSOTf and nucleophile were used (entry 5). Promotion by TMSOTf in dichloromethane gave markedly lower selectivity, while use of titanium tetrachloride afforded only a 2:1 mixture of diastereomers (entries 1, 2).

Table 4. Addition of a Silyl Ketene Acetal to **6**

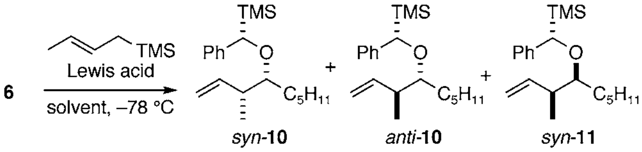


entry[a]	Lewis acid (equiv)	solvent	yield (%)[b]	dr[c]
1	$TiCl_4$ (1.1)	CH_2Cl_2	69	2:1
2	TMSOTf (1.1)	CH_2Cl_2	73	14:1
3	TMSOTf (0.2)	$PhCH_3$	74	44:1
4	TMSOTf (1.1)	$PhCH_3$	61	50:1
5[d]	**TMSOTf (2.5)**	**$PhCH_3$**	**87**	**80:1**

[a] With 1.1 equiv of nucleophile used. [b] Yield of purified product. [c] Deteremined by GC analysis of unpurified product. [d] With 1.5 equiv of nucleophile used. Subjecting (*S*)-**6** to these reaction conditions afforded 73% yield, 78:1 dr.

Extending this study to include crotylsilanes allowed for the generation of two adjacent stereocenters. Crotylsilanes add to oxocarbenium ions to produce two diastereomers with the syn product usually predominating.[7] Lewis acid-mediated solvolysis of α-acetoxy ether **6** in the presence of (*E*)-crotyltrimethylsilane afforded mixtures of four different diastereomers. The two major products, *syn*- and *anti*-**10,** result from Linderman-type facial selectivity in the addition to the oxocarbenium ion (Table 5). The minor isomers, *syn*-**11** and *anti*-**11** (not shown, undetected by GC), arise from addition to the opposite face of the oxocarbenium ion. Excellent Linderman-type facial selectivity was observed in toluene with TMSOTf, although the syn to anti ratio was only 3:1 in these cases (entries 2, 3). An optimal balance between the two modes of selectivity was found with

Table 5. Addition of (*E*)-Crotyltrimethylsilane to **6**



entry[a]	conditions	yield (%)[b]	diastereomer ratio[c] of *syn*-**10**:*anti*-**10**:*syn*-**11**
1	$SnCl_4$, $PhCH_3$	92	41:8:1
2[d]	TMSOTf, $PhCH_3$	68	128:38:1
3	TMSOTf, $PhCH_3$	72	109:32:1
4[e]	$SnCl_4$, CH_2Cl_2	92	7:1:1.1
5[f]	**TMSOTf, CH_2Cl_2**	**82**	**27:2.4:1**

[a] With 1.1 equiv of silane and 1.1 equiv of Lewis acid used. [b] Yield of purified product. [c] Determined by GC analysis of unpurified product; *anti*-**11** was not detected. [d] With 0.2 equiv TMSOTf used. [e] A minor impurity (potentially *anti*-**11**) was inseparable from *syn*-**10** by GC. [f] Subjecting (*S*)-**6** to these reaction conditions gave 78% yield, 22:2:1 *syn*-**10**:*anti*-**10**:*syn*-**11**.

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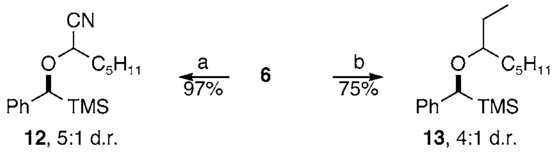
(6) For example, see: Paterson, I.; Smith, J. D.; Ward, R. A. *Tetrahedron* **1995**, *51*, 9413−9436.

(7) (a) Panek, J. S.; Yang, M.; Xu, F. *J. Org. Chem.* **1992**, *57*, 5790−5792. (b) Panek, J. S.; Cirillo, P. F. *J. Org. Chem.* **1993**, *58*, 999−1002.

TMSOTf promotion in dichloromethane (entry 5). Under these conditions, an 11:1 syn/anti ratio was found for the major products **10**, with a 29:1 selectivity for the Linderman/non-Linderman mode of addition (**10**:**11**). A similar trend was observed with catalysis by tin tetrachloride (entries 1, 4). Higher Linderman-type selectivity was observed in toluene, while slightly better syn/anti selectivity was achieved in dichloromethane.

All of the nucleophiles examined so far possess nucleophilic sp^2 carbon atoms. The final two nucleophiles in our survey have sp and sp^3 nucleophilic carbon atoms, respectively. Addition of TMSCN to α-acetoxy ether **6** afforded the expected adduct **12** in excellent yield but with a modest 5:1 diastereoselectivity (Scheme 3). Similarly, addition of diethylzinc to **6** produced the ether **13** in good yield with a 4:1 selectivity. These selectivities are significantly lower than those observed under similar reaction conditions with the sp^2 nucleophiles. These results may represent a limitation of the auxiliary, although the cause for the erosion in selectivity is unclear.

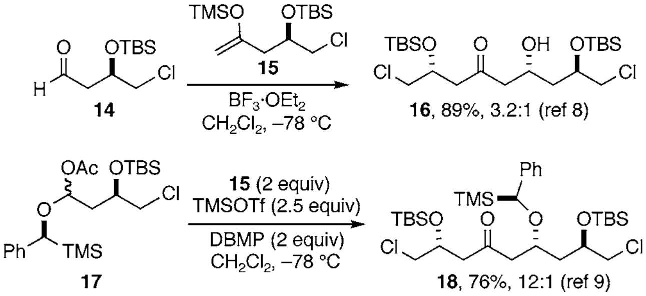
Scheme 3. Addition of TMSCN and Diethylzinc to **6**^{a}



^{a} Reaction conditions: (a) TMSCN (8 equiv), TMSOTf (2.5 equiv), $PhCH_3$, −78 °C; (b) Et_2Zn (2 equiv), TMSOTf (1.1 equiv), $PhCH_3$, −78 °C.

The final example, depicted in Scheme 4, shows the application of our auxiliary to a problematic coupling encountered in our recently reported synthesis of dermostatin A.[8] In the synthesis, Mukaiyama aldol coupling of aldehyde **14** and silyl enol ether **15** afforded adduct **16** in an optimized 3.2:1 anti/syn diastereomeric ratio. Several Lewis acids reported to promote the diastereoselective Mukaiyama reaction failed to improve the selectivity. The analogous auxiliary-controlled coupling between α-acetoxy ether **17** and silyl enol ether **15** gave the expected product **18** in good yield in a 12:1 ratio with a minor diastereomer.[9] In this case, our oxocarbenium ion auxiliary was more effective than any of the Mukaiyama aldol variants, including several chiral Lewis acids.

Scheme 4. Application to a Complex Aldol Coupling



The auxiliary-substituted oxocarbenium ion precursor **6** leads to high facial selectivity with a variety of carbon nucleophiles. Coupling complex nucleophiles to auxiliary-derived α-acetoxy ethers provides access to various optically active protected alcohols. We expect that this strategy for introducing new stereogenic centers will have many synthetic applications.

Acknowledgment. The donors of the Petroleum Research Fund, administered by the American Chemical Society (37325-AC), provided financial support.

Supporting Information Available: Representative coupling reactions and the preparation and characterization of aldol adduct **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(8) (a) Sinz, C. J.; Rychnovsky, S. D. *Angew. Chem., Int. Ed.* **2001**, *40*, 3224−3227. (b) Sinz, C. J.; Rychnovsky, S. D. *Tetrahedron* **2002**, *58*, 6561−6576. (c) Sinz, C. J., Ph.D. Thesis, University of California−Irvine, Irvine, 2001.

(9) Diastereomer ratio was estimated by ^{1}H NMR analysis of purified products. The minor diastereomer may be an artifact of the optical purity of α-acetoxy ether **17** (88% ee at TBS-protected alcohol, 98% ee at the α-TMS benzyloxy position) and silyl enol ether **15** (91% ee). These optical purities would lead to a diastereomeric mixture containing ca. 90% **18** with perfect selectivity in the coupling reaction. For proof of the stereochemistry, see Supporting Information.