Synthetic Methods

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Stereoretentive Halogenations and Azidations with Titanium(IV) Enabled by Chelating Leaving Groups**

Salvatore D. Lepore, Deboprosad Mondal, Song Ye Li, and Anjan K. Bhunia*

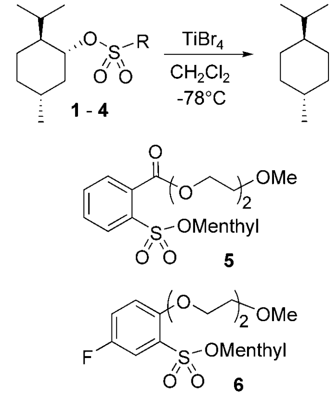
Dedicated to Professor Luigi Mandolini on the occasion of his 65th birthday

Stereospecific functional group conversions of nonracemic alcohols and diols and their derivatives are of increasing importance given the powerful catalytic asymmetric reactions available for their synthesis. If neighboring-group participation[1] and metal-catalyzed allylic substitution[2] are excluded, there are exceedingly few reports of nucleophilic displacement reactions on unactivated saturated carbon leading to products with a high degree of retention of configuration.[3]

We are interested in the development of new stereospecific reactions enabled by nucleophile-assisting leaving groups (NALGs) which contain chelating units.[4] One strategy to increase the likelihood of front-side attack (leading to stereoretentive products) is to minimize charge repulsion between nucleophile and leaving group.[5] We envisioned that this strategy could be achieved using Lewis acids containing nucleophilic ligands. In this conception, a Lewis acid could act to diminish partial negative charge in the leaving group through chelating interactions and, at the same time, deliver its nucleophilic ligand to the substrate from the front face (S_Ni mechanism). We have recently validated this strategy using $TiCl_4$ to bring about stereoretentive chlorination of secondary alkyl sulfonates.[6] Our continued study of this reaction with other titanium(IV) species reveals that this transformation is of significantly broader scope. Herein we describe several new titanium-mediated stereoretentive reactions including bromination,[7] iodination, and azidation that are enabled by new chelating leaving groups. We also demonstrate the unique selectivity of titanium(IV) reagents for secondary versus primary alkyl sulfonates.

As we previously disclosed, the tosylate of menthol (a challenging substrate for nucleophilic displacement[8]) was rapidly converted into the chloride with retention of configuration using $TiCl_4$.[6] However, the analogous reaction with $TiBr_4$ was far more sluggish (Table 1). Also, tosylates performed unacceptably with other titanium(IV) reagents, such as $Ti(N_3)_4$ and TiI_4, as discussed below. Thus, we examined a variety of both new and existing leaving groups in an attempt to recover the same level of reactivity as with the $TiCl_4$ reactions. Using our previously reported diethylene oxide-containing leaving group,[9] substrate **5** exhibited a slightly improved reaction rate and afforded menthyl bromide in 91% yield (Table 1, entry 5). A related leaving group also containing the diethylene oxide unit gave a similar result (Table 1, entry 6, 83% yield). We reasoned that a more Lewis basic chelator in the leaving group might be necessary to achieve further enhancement of the bromination reaction. Thus, we turned our attention to 8-quinoline sulfonate (quisylate) as the leaving group.[10] To our knowledge, the quisylate group has only been used twice as a leaving group, in E1-type pyrolysis reactions[11] and in nucleophilic bromination reactions leading to inversion of configuration.[12] Menthyl quisylate **4** reacted with $TiBr_4$ to give menthyl bromide product at over ten times the rate of naphthyl sulfonate **3** (Table 1, entries 3 and 4). The quisylate leaving group in substrate **4** also out-performed leaving groups in **5** and **6** each containing multiple ether oxygen atoms. This new stereoretentive bromination reaction appears to be fairly general for cyclic and acyclic systems with varying degrees of steric bulk near the carbinol center (Table 3).[13] The NALG and quisylate esters of 1-phenyl-2-butanol reacted with $TiBr_4$

Table 1: Leaving group effect on bromination reactions.



Entry	R	Substrate	t [min]	Yield[a] [%]
1	H_3C	**1**	360	42
2	toluyl	**2**	60	77
3	naphthyl	**3**	50	68
4	8-quinoyl	**4**	5	84
5	–	**5**	30	91
6	–	**6**	25	83

[a] Yields of isolated product.

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[*] S. D. Lepore, D. Mondal, S. Y. Li, A. K. Bhunia
Department of Chemistry and Biochemistry
Florida Atlantic University, Boca Raton, FL 33431 (USA)
Fax: (+1) 561-297-2759
E-mail: slepore@fau.edu
Homepage: http://wise.fau.edu/~slepore

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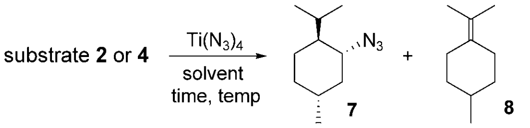
at −78 °C to afford bromide product with complete stereoretention (Table 3, entry 7). For $TiCl_4$, the same stereoretentive result is obtained with the quisylate of 1-phenyl-2-butanol (data not shown).[14]

Notably, the NALG and quisylate esters of α-hydroxypropionate were completely unreactive towards $TiBr_4$ at −78 °C (Table 3, entry 9). At room temperature, the titanium(IV) reactions required over 40 h, and led to inversion of configuration in the propionate product, suggesting a change in mechanism.[15]

In seeking to further extend the scope of this titanium(IV) reaction, we prepared $Ti(N_3)_4$, following a recently reported procedure,[16] and reacted it with tosylate **2** and quisylate **4** under a variety of conditions (Table 2).[17] Menthyl azide **7** was obtained with both substrates with complete retention of configuration. However, tosylate **2** gave a significant proportion of E1 product **8** under a variety of conditions (Table 2, entries 1–3), whereas quisylate **4** afforded high selectivity for the substitution product, especially when 1,2-dichloroethane was used as the reaction solvent (Table 2, entry 6). Using the quisylate leaving group, the azidation reaction works with a variety of secondary substrates, including acyclic systems (Table 3). To our knowledge, this reaction is the first reported stereoretentive azidation of alcohol derivatives not involving a double inversion technique.

Table 2: Role of leaving group, solvent, and reaction temperature in azidation reactions of substrates **2** and **4**.

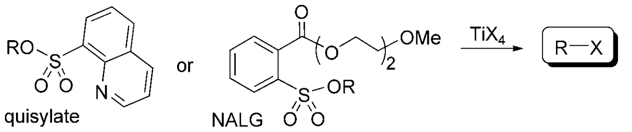


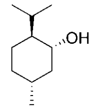
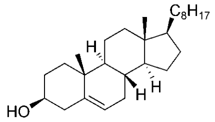
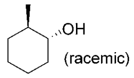
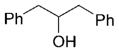
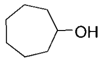
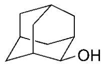
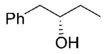
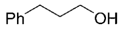
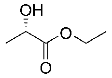
Entry	Substrate	*T* [°C]	Solvent	*t* [min]	**7**:**8**[a]	Yield **7**[b] [%]
1	**2**	RT	CH_2Cl_2	60	2.7:1	72
2	**2**	0	CH_2Cl_2	180	2.8:1	68
3	**2**	RT	$ClCH_2CH_2Cl$	60	2.7:1	48
4	**4**	0	CH_2Cl_2	540	19:1	80
5	**4**	RT	CH_2Cl_2	120	19:1	63
6	**4**	RT	$ClCH_2CH_2Cl$	60	**7** only	97

[a] Based on NMR spectroscopic analysis. [b] Yields of isolated product; complete retention of configuration.

Although our azidation reactions proceed in reasonable reaction times, we sought to increase the Lewis acidity and hence the reaction rate through the use of a mixed titanium(IV) reagent containing a non-transferable ligand with more electron-withdrawing capacity than azide. To achieve this result, trimethylsilyl triflate (TMSOTf, 1 equiv) was first added to TiF_4, most likely forming $TfOTiF_3$. Subsequent addition of $TMSN_3$ (3 equiv) led to a Lewis acid (presumably $TfOTi(N_3)_3$) which was significantly more reactive towards quisylate substrates. For example, the quisylate of menthol (Table 3, entry 1) was converted into the azide product in 6 h at −78 °C (compared to 8 h at 0 °C using $Ti(N_3)_4$). With the quisylate of 1-phenyl-2-butanol (Table 3, entry 7), the mixed Lewis acid gave azide products in less than 1 h at 0 °C with complete stereoretention. The use of triflate to activate our azidation reagent may prove a useful strategy in the development of future titanium(IV) reactions with NALGs involving reagents with diminished Lewis acidity.

Table 3: Substrate generality for stereoretentive halogenation and azidation.



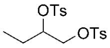
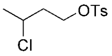
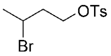
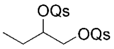
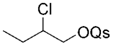
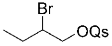
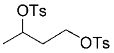
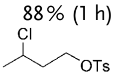
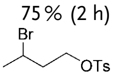
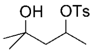
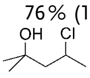
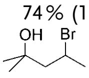
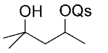
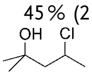
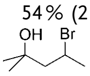
Entry	ROH	% Yield of RX (Reaction Time)[a] X = Br[b] NALG	 X = Br[b] Quisylate	 X = N_3[c] Quisylate
1		91 (30 min)	84 (5 min)	97[d] (8 h)
2		95 (15 min)	63 (10 min)	62 (3 h)
3		79 (15 min)	66 (10 min)	69 (5 h)
4		88 (2.5 h)	82 (10 min)	89 (7 h)
5		61 (15 min)	51 (10 min)	45 (6 h)
6		98 (15 min)	85 (10 min)	93 (5 h)
7		81 (30 min)	79 (30 min)	63[e] (4 h)
8		92[f] (14 h)	89[f] (5.5 h)	80[f] (72 h)
9		42[g] (20 h)	71[g] (40 h)	< 5 (24 h)

[a] Yields of isolated product. [b] Reaction conditions: −78 °C, CH_2Cl_2. [c] Reaction conditions: 0 °C, $ClCH_2CH_2Cl$. [d] Using $TfOTi(N_3)_3$ at −78 °C the reaction is complete in 6 h. [e] Normal conditions are room temperature, $ClCH_2CH_2Cl$. However, with $TfOTi(N_3)_3$ the reaction is completed in 1 h at 0 °C to give similar product yield and stereoretention. [f] Reaction conditions: Room temperature, CH_2Cl_2. [g] Reaction conditions: Room temperature, CH_2Cl_2. Substrates have undergone complete inversion of configuration suggesting a change of mechanism.

Preliminary data reveal that the titanium(IV) methodology can also be extended to iodination. Thus, menthol quisylate **4** was converted into the corresponding iodo product in 84 % yield with complete retention of configuration using TiI_4 at 0 °C in 1,2-dichloroethane. Under the same conditions, the quisylate of 1,3-diphenyl-2-propanol was converted into the corresponding iodide in 90 % yield in 5 h.

In addition to stereoretention, reactions using titanium(IV) reagents also afford chemoselectivity in favor of secondary sulfonate substrates (opposite of S_N2 reactivity). To compare the reactivity of primary versus secondary sulfonates, a series of racemic bistosylates and bisquisylates were reacted with $TiCl_4$ and $TiBr_4$ (Table 4). In general, the bisquisylates were better yielding and significantly more reactive, furnishing halogenated products in 1–2 h at −78 °C.

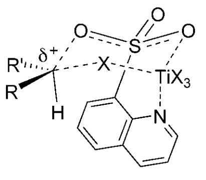
Table 4: Chemoselectivity of titanium(IV) reactions with substrates containing two sulfonate leaving groups.

Entry	Substrate	T [°C]	Product Yield (Reaction Time)[a]	
1		RT	 81 % (1.5 h)[b]	 20 % (15 h)[b]
2		−78	 88 % (1 h)	 75 % (2 h)
3		RT	 76 % (1 h)	 74 % (1 h)
4		RT	 45 % (2 h)	 54 % (2 h)
5		−78	 61 % (2 h)	 85 % (2.5 h)

[a] Yields of isolated product. All starting materials and products are racemic [b] Note that halogen position shifted relative to substrate.

Titanium(IV) reactions with 1,2-butanediol bistosylate gave the 3-halogenated products, presumably as a result of a hydride shift (Table 4, entry 1), whereas the 1,2-bisquisylate substrate led to 2-halogenated products in good yields (Table 4, entry 2). No rearrangement occurred in the reaction of the 1,3-bistosylate with titanium(IV) chloride and bromide, leading to the corresponding 3-halogenated products (Table 4, entry 3). Reasonable yields were also obtained with diol systems containing an unprotected tertiary alcohol with quisylates affording significantly better yields than tosylates (Table 4, entries 4 and 5).

In terms of formulating a mechanistic rationale for these titanium(IV)reactions, two reactivity trends described in this communication are revealing. Firstly, the poor reactivity of primary alcohol (Table 3, entry 8), α-hydroxy ester (Table 3, entry 9), and primary sulfonate moieties (Table 4) can be rationalized in terms of partial positive charge formation at the carbinol carbon in the transition state, the argument being that carbons of primary alcohols and α-hydroxy esters are less able to stabilize positive charge build-up, relative to secondary carbinol carbon centers. Secondly, we hypothesize that the aromatic nitrogen of the quisylate group stabilizes a concerted S_Ni-type (or non-solvent-separated S_N1) mechanism with titanium(IV) reagents. By comparison, tosylate substrate **2** (devoid of an aromatic nitrogen) underwent significant ionization, leading to elimination product **8** (Table 2, entries 1–3). The quisylate nitrogen also appears to increase the rate of substitution in most cases (for example, compare entries 3 and 4 of Table 1). A possible transition state, involving a quisylate nitrogen coordinated to titanium(IV), involves a stable six-membered-ring geometry (see Figure).



In conclusion, a series of titanium(IV) reagents have been shown to give alkyl bromides, iodides, and azides from sulfonates in reasonable yields and with complete retention of configuration. Critical to the design of these new titanium(IV) reactions has been the use of new chelating leaving groups (NALGs). The extension of this reagent class to new reactions including stereoretentive carbon-carbon bond formation is currently underway.

Experimental Section

General Procedure for bromination reactions: A cold (−78 °C) solution of quisylate ester (1.0 equiv) in dichloromethane (1.5 M) was added to a cold (−78 °C) solution of $TiBr_4$ (2.0 equiv) in dichloromethane (0.15 M). Following completion (usually within 15 min, monitored by thin-layer chromatography), the reaction mixture was quenched with water and extracted three times with dichloromethane. The collected organic extracts were concentrated and the resulting oil was purified by silica gel chromatography (usually using pure hexanes as eluent). For spectroscopic data, see Supporting Information.

General Procedure for azidation reactions: Azidotrimethylsilane (25 equiv) was added to a solution of TiF_4 (6.0 equiv) in 1,2-dichloroethane (0.2 M) at room temperature. After stirring for 30 min, the reaction slurry was cooled to 0 °C and quisylate ester (1.0 equiv) was added as a dichloroethane solution (1.5 M). The reaction was maintained at 0 °C until completion (< 8 h). Following completion, the reaction mixture was quenched with water and extracted three times with dichloromethane. The collected organic extracts were concentrated and the resulting residue was purified by silica gel chromatography (usually using pure hexanes as eluent). For spectroscopic data, see Supporting Information.

General Procedure for azidation reactions with mixed Lewis acid: Trimethylsilyl triflate (9.0 equiv) was added to a room temperature solution of TiF_4 (6.0 equiv) in dichloromethane (0.5 M). The resulting slurry was stirred for 15 min followed by the addition of azidotrimethylsilane (18.0 equiv) which was allowed to stir for an additional 15 min. The reaction slurry was then cooled (0 °C) and quisylate ester (1.0 equiv) was added as a dichloromethane solution (0.2 M). The reaction was maintained at 0 °C until completion (< 2 h). Following completion the reaction mixture was quenched with water and extracted three times with dichloromethane. The collected organic extracts were concentrated and the resulting oil was purified by silica gel chromatography (using pure hexane as eluent). For spectroscopic data, see Supporting Information.

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Keywords: azides · halogenation · leaving groups · nucleophilic substitution · titanium

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[1] Some recent examples include: a) L. X. Liu, P. Q. Huang, *Tetrahedron: Asymmetry* **2006**, *17*, 3265; b) J. M. Concellon, P. L. Bernad, J. R. Suarez, S. Garcia-Granda, M. R. Diaz, *J. Org. Chem.* **2005**, *70*, 9411; c) M. DePaolis, J. Blankenstein, M. Bois-Choussy, J. Zhu, *Org. Lett.* **2002**, *4*, 1235.
[2] Some recent examples include: a) G. C. Lloyd-Jones, S. W. Krska, D. L. Hughes, L. Gouriou, V. D. Bonnet, K. Jack, Y. Sun, R. A. Reamer, *J. Am. Chem. Soc.* **2004**, *126*, 702; b) Y. Sato, T. Yoshino, M. Mori, *Org. Lett.* **2003**, *5*, 31.
[3] Some examples include: a) I. Lee, H. Y. Kim, H. K. Kang, H. W. Lee, *J. Org. Chem.* **1988**, *53*, 2678; b) J. Gasteiger, K. Kaufmann, C. Herzig, T. W. Bentley, *Tetrahedron Lett.* **1985**, *26*, 4337; c) P. Cayzergues, C. Georgoulis, G. J. Ville, *J. Chem. Res. Synop.* **1978**, *9*, 325.
[4] S. D. Lepore, D. Mondal, *Tetrahedron* **2007**, *63*, 5103.
[5] N. T. Ahn, C. Minot, *J. Am. Chem. Soc.* **1980**, *102*, 103.

[6] S. D. Lepore, A. K. Bhunia, D. Mondal, P. C. Cohn, C. J. Lefkowitz, *J. Org. Chem.* **2006**, *71*, 3285.

[7] We briefly mentioned this stereoretentive bromination reaction based on preliminary data in our recent review article (see ref. [4]). This reaction has since been used in a total synthesis: J. Park, B. Kim, H. Kim, S. Kim, D. Kim, *Angew. Chem.* **2007**, *119*, 4810; *Angew. Chem. Int. Ed.* **2007**, *46*, 4726.

[8] M. Yamashita, Y. Soeda, N. Suzuki, M. Yamada, K. Tsenekawa, T. Oshikawa, S. Inokawa, *Bull. Chem. Soc. Jpn.* **1983**, *56*, 1871.

[9] S. D. Lepore, A. K. Bhunia, P. C. Cohn, *J. Org. Chem.* **2005**, *70*, 8117.

[10] Following the pattern of common names of other sulfonate-based leaving groups (mesyl, tosyl, etc.), we give the 8-quinoline sulfonyl and sulfonate systems the abbreviated names of quisyl and quisylate respectively.

[11] a) E. J. Corey, G. H. Posner, R. F. Atkinson, A. K. Wingard, D. J. Halloran, D. M. Radzik, J. J. Nash, *J. Org. Chem.* **1989**, *54*, 389; b) Corey has recently used 8-aminoquinolines as directing groups in C–H functionalization reactions B. V. Subba Reddy, L. R. Reddy, E. J. Corey, *Org. Lett.* **2006**, *8*, 3391.

[12] S. Hanessian, M. Kagotani, K. Komaglou, *Heterocycles* **1989**, *28*, 1115.

[13] All bromide and azide products in Table 3 with multiple stereocenters (entries 1–3) were produced as single diasteromers as characterized by NMR spectroscopy with no detectable inversion products. Based on NMR signal-to-noise ratios, the degree of stereoretention in each case is $>20{:}1$. The identity of each bromide and azide diastereomer was established by comparison with previously reported compounds. Products containing a single stereocenter (Table 3, entry 7) also showed complete retention of configuration by comparison of their specific rotation with the same materials produced using transformations based on an S_N2 mechanism. See Supporting Information for details.

[14] The reaction of the quisylate of 1-phenyl-2-butanol with $TiCl_4$ at $-78\,^{\circ}C$ in CH_2Cl_2 gave 87% yield of the chloride with $[\alpha]_D^{25} = +11.0\ \mathrm{deg\,cm^3\,g^{-1}\,dm^{-1}}$ ($c = 0.587\ \mathrm{g\,cm^{-3}}$, $CHCl_3$). To provide a sample for comparison, the tosylate of the alcohol was treated with LiCl giving the corresponding chloride substitution product with $[\alpha]_D^{25} = -11.2\ \mathrm{deg\,cm^3\,g^{-1}\,dm^{-1}}$ ($c = 1.1\ \mathrm{g\,cm^{-3}}$, $CHCl_3$) indicating nearly complete retention of configuration.

[15] The optical rotation of this product was $[\alpha]_D^{25} = +30.3\ \mathrm{deg\,cm^3\,g^{-1}\,dm^{-1}}$ ($c = 1.0\ \mathrm{g\,cm^{-3}}$, $CHCl_3$) and the value from the literature $+32.4\ \mathrm{deg\,cm^3\,g^{-1}\,dm^{-1}}$ ($c = 3.93\ \mathrm{g\,cm^{-3}}$, $CHCl_3$) for the (*R*)-2-bromo ester.

[16] R. Haiges, J. A. Boatz, S. Schneider, T. Schroer, M. Youosufuddin, K. O. Christe, *Angew. Chem.* **2004**, *116*, 3210; *Angew. Chem. Int. Ed.* **2004**, *43*, 3148.

[17] To our knowledge, this is the first application of titanium(IV) azide as a synthetic reagent.