Carbocations

DOI: 10.1002/anie.200804025

$Bi(OTf)_3$-Catalyzed Diastereoselective S_N1-Type Reactions of Chiral Propargylic Acetates**

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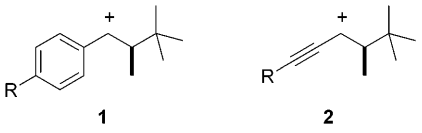
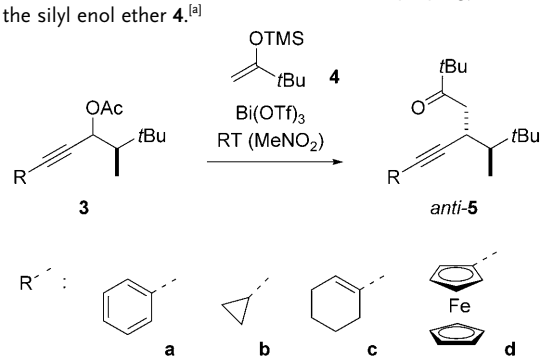
The facial diastereoselectivity of intermolecular S_N1 reactions in which chiral carbocations are putative intermediates has not been studied extensively.[1] Recently, we started to investigate more closely the reactions of benzylic carbocations,[2] which often exhibit a very high degree of facial diastereoselectivity. We prepared the chiral cation **1** (R = H) and established its preferred conformation spectroscopically.[2a,b] The results led us to address the question, whether propargylic carbocations with the general structure **2** react in a similar fashion, and to investigate which parameters control their selectivity. We now report a highly diastereoselective, $Bi(OTf)_3$-catalyzed[3,4] reaction of chiral propargylic acetates with various weak carbon nucleophiles,[5,6] in which chiral carbocations are very likely to be involved as intermediates. The diastereoselectivity of the reaction cannot be immediately accounted for by the preferred conformation of the cation **2**.



We optimized the reaction conditions for propargylic S_N1 substrates by studying the reaction of the propargylic acetate **3a**[5j] and the silyl enol ether **4**[7] (Table 1). Among a wide array of potential catalysts (including $FeCl_3$, $InCl_3$, $AuCl_3$, $Cu(OTf)_2$, $[Au(PPh_3)]SbF_6$, and BF_3), $Bi(OTf)_3$ proved to be the most effective for the transformation of **3a** into **5a** (Table 1, entry 1). TMSOTf was nearly as effective (79% yield), whereas lower yields were observed with HOTf (54%). The diastereoselectivity of these reactions was very good (d.r. 92:8) in all cases in which product formation was observed. In the formation of **5a**, the acetate leaving group in combination with $Bi(OTf)_3$ as the catalyst proved to be superior to an α-chloroacetate (54% yield) or diethylphosphate (40% yield) group. No conversion was observed with the corresponding alcohol. We were particularly interested in the product configuration, which could be proven for the major diastereoisomer *anti*-**5a** by single-crystal X-ray analysis of a hydrazone derivative (see the Supporting Information). The propargylic acetates **3b–d**[5j] were converted with high diastereoselectivity into the corresponding products **5b–d** in an analogous fashion (Table 1, entries 2–4).

Table 1: Diastereoselective substitution of chiral propargylic acetates **3** with the silyl enol ether **4**.[a]



Entry	Substrate	t [h][b]	d.r.[c]	Product	Yield [%][d]
1	**3a**	2	92:8	**5a**	89
2	**3b**	0.5	97:3	**5b**	88
3	**3c**	1	97:3	**5c**	74
4	**3d**	0.5	99:1	**5d**	84

[a] The propargylic acetate **3** (0.25 mmol) and the silyl enol ether **4** (1.0 mmol) were dissolved in nitromethane (2 mL). $Bi(OTf)_3$ (10 mol%, 16 mg) was then added at ambient temperature, and the reaction mixture was stirred for the indicated period of time. [b] Reaction time for full conversion. [c] The diastereomeric ratio (*anti*-**5**/*syn*-**5**) was determined by ^1H NMR spectroscopy. [d] Yield of the isolated product.

In general, the reactions were conducted with 10 mol% of the catalyst. However, the turnover number (TON) is higher than 10, as full conversion was observed with 5, 2.5, and even 1 mol% of the catalyst. Substrate **3b** (Table 1, entry 2) was converted into **5b** in 91% yield (d.r. 97:3) with 5 mol% $Bi(OTf)_3$ ($t = 0.75$ h) under otherwise identical reaction conditions; with 2.5 mol% $Bi(OTf)_3$ ($t = 1$ h), **5b** was formed in 86% yield (d.r. 97:3), and with 1 mol% $Bi(OTf)_3$ ($t = 1$ h), **5b** was formed in 92% yield (d.r. 97:3). The reaction with 1 mol% $Bi(OTf)_3$ was performed with 1 mmol of **3b** and 2.0 mmol of **4** in 2 mL of nitromethane. Substrate **3b** was also selected to prove the stereoconvergency of the reaction: an important indication that the reaction proceeds via a free carbenium ion. Both diastereoisomers, *anti*-**3b** and *syn*-**3b**

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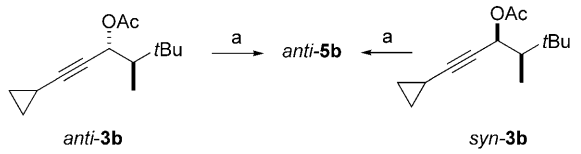
[**] This project was supported by the Deutsche Forschungsgemeinschaft (Ba 1372-12) and by the graduate program "NanoCat" (scholarship to P.R.). Tf = trifluoromethanesulfonyl.

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.200804025.

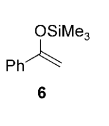
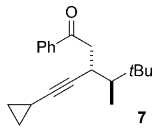
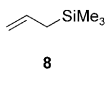
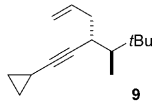
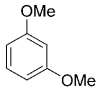
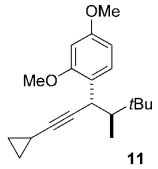
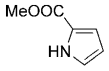
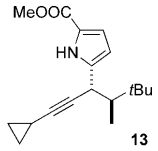
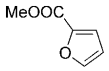
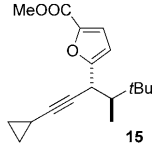
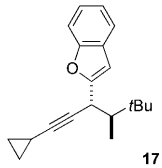
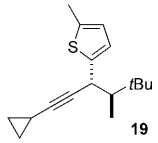
(see the Supporting Information), were treated separately with the silyl enol ether **4**. In both cases, *anti*-**5b** was formed preferentially (d.r. 97:3; Scheme 1).

Further nucleophiles that react with propargylic acetates are shown in Table 2. The reaction was successful with other



Scheme 1. Stereoconvergent reaction of the diastereomeric propargylic acetates *anti*-**3b** and *syn*-**3b**: a) **4** (4 equiv), $Bi(OTf)_3$ (10 mol%), $MeNO_2$, room temperature, 1 h, 86% from *anti*-**3b**, 88% from *syn*-**3b**.

Table 2: Diastereoselective substitution of the propargylic acetate **3b** with different nucleophiles.[a]

NuH/NuSiMe$_3$	Product	*t* [h][b]	d.r.[c]	Yield [%][d]
 **6**	 **7**	1	96:4	80
 **8**	 **9**	0.5	94:6	97
 **10**	 **11**	0.25	95:5	80
 **12**	 **13**	0.5	94:6	82
 **14**	 **15**	0.5	99:1	80
 **16**	 **17**	1	99:1	83
 **18**	 **19**	2	96:4	68

[a] Compound **3b** (125 μmol) and the corresponding nucleophile (0.5 mmol) were dissolved in nitromethane (1 mL). $Bi(OTf)_3$ (10 mol%, 8 mg) was then added at ambient temperature, and the reaction mixture was stirred for the indicated period of time. [b] Reaction time for full conversion. [c] The diastereomeric ratio (*anti*/*syn*) was determined by ^{1}H NMR spectroscopy. [d] Yield of the isolated product.

silyl nucleophiles, such as the silyl enol ether **6**[7] and the allyl silane **8**, as well as with arenes in a Friedel–Crafts alkylation. Examples of aromatic nucleophiles include resorcin dimethyl ether (**10**), methyl pyrrole-2-carboxylate (**12**), methyl furan-2-carboxylate (**14**), benzofuran (**16**), and 2-methylthiophene (**18**). The *anti* configuration of product **7** was proven by single-crystal X-ray analysis of a hydrazone derivative (see the Supporting Information).

To gain a better understanding of the facial diastereoselectivity of the reaction, we considered, as previously for cations **1**, all conceivable conformations of a propargylic cation. By means of DFT calculations,[8] we undertook a conformational analysis of cations **2**, as depicted representatively for cation **2a** (R = Ph) in Figure 1. Cations **2b** and **2c**

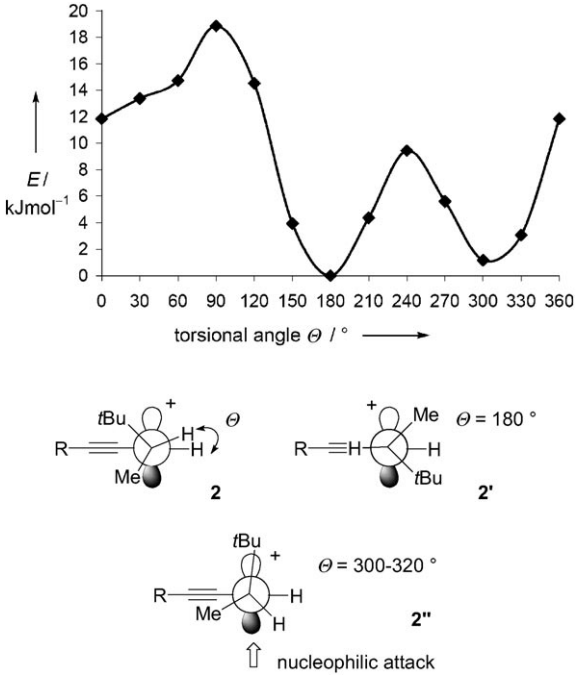


Figure 1. Conformational analysis of cations **2** on the basis of DFT calculations, depicted representatively for cation **2a**.

showed similar behavior (see the Supporting Information). Rotation about the depicted C–C bond was studied more closely, and the energy was calculated with respect to the dihedral angle Θ.[12] The observed minima were additionally subjected to a full optimization. As expected, the dihedral angle of the global minimum **2′** is very close to 180°. This conformation, as observed for the benzylic cations **1**, would favor attack from the top side to give the *syn* product. However, a second minimum **2″**, which is only 0.7–2.0 kJ mol^{-1} higher in energy than the global minimum and which is characterized by a dihedral angle of 300–320° (depending on the cation and basis set), was also found. In this conformation, the *tert*-butyl group adopts an almost antiperiplanar orientation to a nucleophile approaching from the bottom side (see Figure 1), the attack of which leads to the *anti* product. We consequently favor a transition state in which this conformation dominates the reaction event to

explain the observed selectivity. As a relatively good σ acceptor, the *tert*-butyl group would stabilize the incipient antiperiplanar bond in a similar manner to that postulated in the Felkin–Anh model.[13]

In conclusion, propargylic acetates **3** react with high diastereoselectivity under S_N1 conditions to give the corresponding substitution products. With regard to the diastereoselectivity, evidence has been collected for a stereoelectronically controlled reaction of chiral carbocations, as the configuration of the products cannot be explained on the basis of the preferred ground-state conformation of the cations. Further studies will be directed towards the extension of the reaction to other substrates, the investigation of suitable applications in total synthesis, and the improvement of our understanding of the parameters that determine the selectivity of the reaction.

Experimental Section

Representative procedure: Compounds **3b** (56 mg, 0.25 mmol) and **4** (172 mg, 1.0 mmol) were dissolved in nitromethane (2 mL). $Bi(OTf)_3$ (16 mg, 10 mol%) was then added at room temperature, and the reaction mixture was stirred for 0.5 h. The reaction was quenched by the addition of a saturated solution of $NaHCO_3$, and the mixture was diluted with CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 (2×20 mL) and ethyl acetate (20 mL). The combined organic layers were washed with brine and dried with Na_2SO_4. The crude product was purified by flash column chromatography on silica gel (ethyl acetate/pentane 1:40). Compound **5b** (58 mg, 88%, d.r. 97:3) was isolated as a colorless oil. ^{1}H NMR (360 MHz, $CDCl_3$): $\delta = 0.51$–0.55 (m, 2H), 0.61–0.68 (m, 2H), 0.90 (d, $^3J = 6.9$ Hz, 3H), 0.93 (s, 9H), 1.05 (qd, $^3J = 6.9$ Hz, $^3J = 1.8$ Hz, 1H), 1.10–1.16 (m, 1H), 1.12 (s, 9H), 2.51 (dd, $^2J = 17.2$ Hz, $^3J = 7.4$ Hz), 2.70 (dd, $^2J = 17.2$ Hz, $^3J = 6.4$ Hz), 3.25–3.30 ppm (m, 1H); ^{13}C NMR (90.6 MHz, $CDCl_3$): $\delta = -0.2$ (d), 7.9 (t), 7.9 (t), 10.6 (q), 26.3 (q), 27.9 (d), 28.1 (q), 34.0 (s), 42.9 (t), 44.2 (s), 45.2 (d), 77.1 (s), 85.8 (s), 213.6 ppm (s); HRMS: *m/z* calcd for $C_{17}H_{27}O$: 247.2062; found: 247.2061.

Received: August 14, 2008
Published online: November 17, 2008

Keywords: alkynes · bismuth · carbocations · Lewis acids · nucleophilic substitution

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[8] All calculations were performed with Gaussian03.[9] The density-functional hybrid Becke3LYP[10] was used together with basis sets 6-31G(d) and 6-311++G(d,p). To calculate the rotational barriers, only one dihedral angle was constrained on the 6-31G(d) level of theory. To investigate the two minima, we fully optimized the structures at both levels of theory. All reported intermediates were verified as true minima by vibrational frequency analysis through the absence of negative eigenvalues. We observed only small differences in the results for the different levels of theory. All energies reported herein are electronic energies. Details are given in the Supporting information. For visualization, we used the program MOLDEN.[11]

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