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S_N1 Reactions with Planar Chiral (Arene)$Cr(CO)_3$-Substituted α-Propargyl Cations – Regio- and Diastereoselective Additions to Novel Ambident Electrophiles

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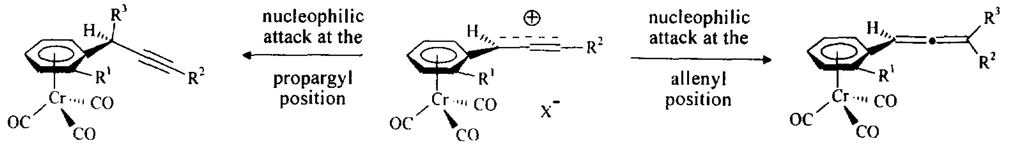
Summary: Planar chiral *ortho* substituted (arene)$Cr(CO)_3$-stabilized α-propargylic cations **4** react in a S_N1 fashion with sulfur, nitrogen and π-nucleophiles to give regioselectively the corresponding propargyl derivatives **5** in good yields and excellent diastereoselectivities (d.r. > 9:1).

Nucleophilic substitutions classically proceeding through the trigonal planar carbenium ion inherently loose the stereochemical integrity at that center and only a few cases of neighbor group assistance led to stereocontrolled substitution products.[1] However, the advent of transition metal stabilization of α-carbenium ions[2] by the through space interaction of the filled d (transition metal fragment) with the vacant p_z orbital enables nucleophilic substitution with carbenium ions with retention of configuration as a result of a double inversion mechanism.[2f] Therefore, chromiumcarbonyl complexed benzylic cations have found applications in organic syntheses.[3] As a part of our program initiated to investigate the reactivity and the electronical properties of $Cr(CO)_3$-complexed arenes with conjugated substituents[4] we are particularly interested in the reactivity of ambident cationic sidechains.[4e] Thus, the addition of nucleophiles to propargyl-allenyl cations discloses intriguing pathways to sidechain functionalizations *via* propargyl and/or allenyl derivatives[5] (Scheme 1).



Scheme 1

Recently, we have studied the electronic structure of a (phenyl)$Cr(CO)_3$-substituted α-propargyl cation and found an interesting nucleophile dependence on the regioselectivity of the nucleophilic attack.[4e] This prompted us to screen the synthetic potential of this novel organometallic class of ambident electrophiles. Here, we communicate our first findings on diastereoselective S_N1 reactions with planar chiral (arene)$Cr(CO)_3$-stabilized α-propargyl cations.

Our strategy to *ortho* substituted (arene)$Cr(CO)_3$-stabilized α-propargylic cations commences with the nucleophilic addition of lithium acetylides **2** to racemic *ortho* substituted η^6-(benzaldehyde)$Cr(CO)_3$ complexes **1** at -78 °C in THF[6] followed by the addition of acetic anhydride to give rise to the formation of planar chiral (arene)$Cr(CO)_3$-substituted propargyl acetates **3** in good yields and with excellent diastereoselectivity (Scheme 2).

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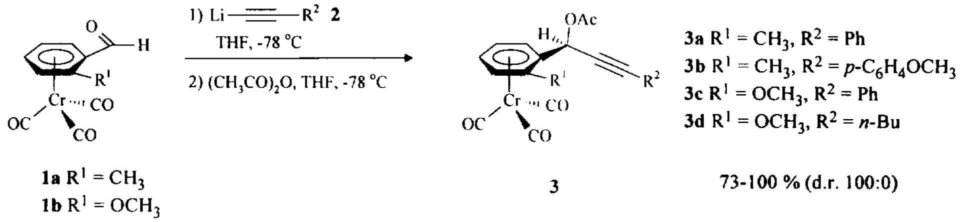
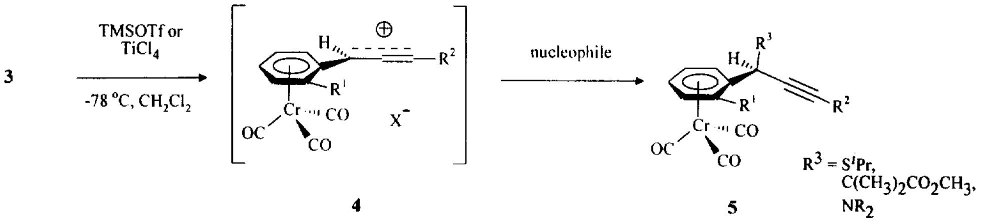


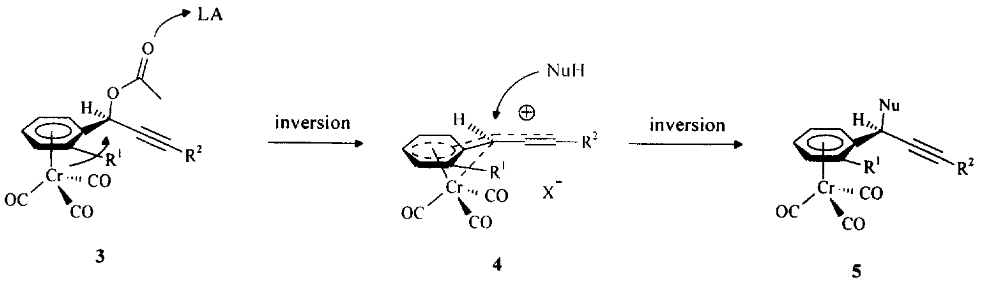
Scheme 2

The ionization of the propargyl acetates **3** with trimethylsilyl triflate (TMSOTf) or titanium tetrachloride is accompanied by a color change from light yellow to deep purple (**4a**, **4c**, **4d**) or deep blue (**4b**) indicating the formation of the (arene)$Cr(CO)_3$-substituted α-propargyl cations **4** (Scheme 3). At low temperatures (< -40 °C) the deep colored specimens are stable for several hours and can be subjected to trapping reactions with π-, S- and N-nucleophiles (Table 1).



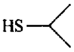
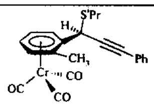
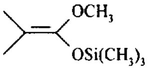
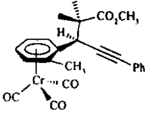
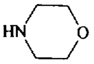
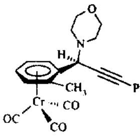
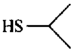
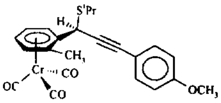
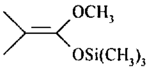
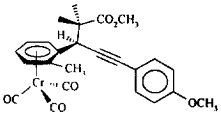
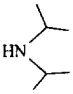
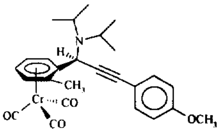
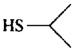
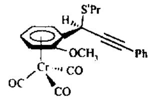
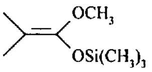
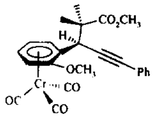
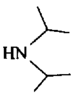
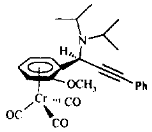
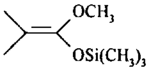
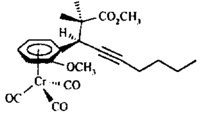
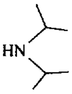
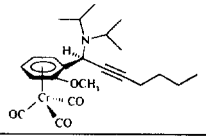
Scheme 3

Remarkably and in contrast to the system without *ortho* substituents[4e] the nucleophilic additions occur exclusively at the α-position to give the propargylic derivatives **5** in good yields and with excellent diastereoselectivities.[7a] The relative stereochemistry[7b] of the products **5** can be rationalized on the basis of a double inversion mechanism[2f] that results in a retention of the configuration at the epimeric center. Assuming a complete and irreversible *anti*-periplanar Lewis acid mediated extrusion of the acetate leaving group a diastereotopic propargyl cation intermediate **4** is formed (Scheme 4). Thus, the nucleophile attacks in an *exo*-fashion with respect to the ambident electrophile **4**.



Scheme 4

Table 1. (Arene)Cr(CO)$_3$-substituted propargyl derivatives **5**[a] by nucleophilic additions to the cations **4**.

entry	propargyl cation **4**	nucleophile	propargylated product **5**	isolated yield (d.r.[b])
1	**3a** + TMSOTf			79 % (93:7)
2	**3a** + TMSOTf			67 % (93:7)
3	**3a** + TMSOTf			71 % (100:0)
4	**3b** + TMSOTf			78 % (91:9)
5	**3b** + TMSOTf			68 % (87:13)
6	**3b** + TMSOTf			53 % (94:6)
7	**3c** + TMSOTf			82 % (100:0)
8	**3c** + TMSOTf			83 % (>95:5)
9	**3c** + TMSOTf			89 % (>95:5)
10	**3d** + TiCl$_4$			49 % (89:11)
11	**3d** + TiCl$_4$			81 % (95:5)

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[a] All complexes **5** are spectroscopically characterized and give satisfactory elemental analyses. [b] The diastereoselectivities were determined by ^{1}H NMR spectroscopy of the crude product after chromatography.

Since the epimerization at the propargylic center can only occur through a rotation around the C_{ipso}-C_{alpha} bond, obviously, the configurational stability of the cationic propargyl sidechain (*syn vs anti*) is preserved by the chromiumcarbonyl neighbor group participation and the substituent effect (+M/+I) at the *ortho* position. Although, the differences in the diastereomeric ratio are relatively small (d.r. from 9:1 to 10:0) the dependence on the configurational stability of the cation can be easily recognized. The most stable propargyl cation (**3c** + TMSOTf) (entries 7-9) gives rise to the highest diastereoselectivities regardless of the attacking nucleophile. An aryl substituent at the γ-position definitely enhances the stability of the cationic intermediate **4** but even γ-alkyl substituents (entry 10 and 11) can be successfully applied in diastereoselective S_N1 reactions. Furthermore, the incoming nucleophile also exerts an influence on the diastereoselectivity of these kinetically controlled additions. Secondary amines react faster than silyl ketene acetals (entries 5, 6, 8, 9, 10 and 11).

In conclusion the diastereoselective nucleophilic addition to stable (arene)$Cr(CO)_3$-substituted α-propargyl cations **4** is a valuable stereoselective propargylation complementary to that of Nicholas' cations.[1e,8] Further studies are directed to the closer inspection of the intermediates **4**, their electrophilicity and their application to more sophisticated sidechain functionalizations.

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7. a) Typical experimental procedure. A dichloromethane solution (5 ml) of **3c** (0.49 mmol) was ionized with TMSOTf (0.53 mmol) under argon at –78 °C to form a deep red solution. After stirring for 1 h at –78 °C the silyl ketene acetal (1 mmol) was added dropwise and the reaction mixture was stirred for 1 h. Aqueous workup, extraction and chromatography on silica gel (diethyl ether/pentane 1:1) gave rise to 83 % of pure **5** (entry 8) as yellow crystals. Analytical data of **5** (entry 8): mp = 138-139 °C, ^1H NMR ([D_6]DMSO, 400 MHz): δ = 1.26 (s, 3 H), 1,27 (s, 3 H), 3.62 (s, 3 H), 3.88 (s, 1 H), 5.14 (dd, J = 6.3 Hz, 1 H), 5.64 (d, J = 7.1 Hz, 1 H), 5.96 (dd, J = 6.5 Hz, 1 H), 6.04 (d, J = 6.4 Hz, 1 H), 7.32-7.39 (m, 5 H), anal. calcd. for $C_{24}H_{22}CrO_6$: C 62.88, H 4.84, found: C 63.24, H 4.99; b) The relative stereochemistry of this product (entry 8) has been elaborated by an X-ray crystal structure that will be published elsewhere.
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