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STEREOCHEMISTRY OF THE S_N2' DISPLACEMENT OF CHIRAL 1,3-DISUBSTITUTED BROMOALLENES TO FORM CHIRAL ACETYLENES

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Summary: Optically active 1,3-disubstituted bromoallenes react with a variety of cuprate reagents preferentially in an S_N2' fashion with very high *anti* selectivity.

Cuprate reagents displace propargyl leaving groups in an S_N2' manner to produce alkylated allenes.[1] This reaction is especially interesting because it occurs with a decided *anti* bias,[1d-j] making possible the formation of optically active allenes. The stereochemistry of the converse reaction, S_N2' cuprate displacements of allenic leaving groups, has not been studied.

Reactions of 3-substituted- and 3,3-disubstituted-1-bromoallenes with lithium dialkylcuprates have been observed to give 1-alkylallenes via direct substitution.[1k,l] Previous work in these laboratories, however, has demonstrated that cuprates react with 3-substituted-3-haloallenes in an S_N2' manner to form alkynes.[3] We report herein on the stereochemistry of this type of S_N2' displacement using various cuprates and optically active 1,3-disubstituted bromoallenes of known configuration. The reactions proceed with high *anti* stereoselectivity, a finding which has both mechanistic and synthetic implications.

The starting materials for this investigation were the two bromoallenes *R*-**1a** and *R*-**1b**, prepared from the corresponding optically active 1,3-disubstituted propargyl alcohols by an S_Ni' rearrangement utilizing thionyl bromide.[4] The reaction of *R*-**1a** with a number of methyl cuprate reagents in tetrahydrofuran (THF) at 0° was examined. The homocuprate, $(CH_3)_2CuLi$, gave many undesired products, but a different cuprate, stoichiometry $(CH_3)_3Cu_2Li$,[5] gave mainly the S_N2' product **2** ($R' = CH_3$). A stabilized copper species, Bu_3PCuCH_3, gave better results, but the best yield of **2** was realized with the hetereocuprate $CH_3(CN)CuLi$.[6] The easy preparation, high stability, and efficient ligand transfer inherent in this reagent added to its attractiveness. Cyanocuprate reagents having R' other than methyl also gave good results with both **1a** and **1b**.

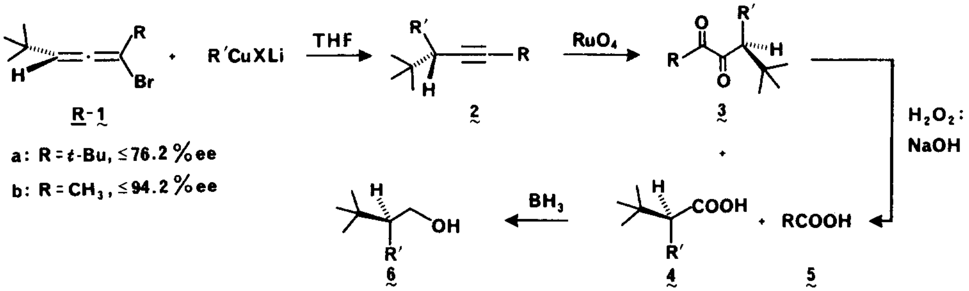
In order to determine the stereo- and enantio-specificity of the S_N2' displacement, degradation of the alkyne **2** to a compound of known absolute configuration was necessary (Scheme I). Oxidation of the triple bond (catalytic RuO_2, 2.5-3.5 equiv $NaIO_4$, 1:1:1.5 CCl_4:CH_3CN:H_2O)[7] led to a mixture of α-diketone **3** and acids **4** and **5**. In the cases where **3** was the predominant product (R = *tert*-butyl, all R' or R = CH_3, R' = *sec*-butyl) it was cleaved oxidatively to **4** and **5** (40 equiv 80:1 H_2O_2:NaOH, 4:1 $CH_3OH:H_2O$). The acid **4** was of known absolute configuration for both R' = CH_3[8] and R' = Ph,[9] with the *dextrorotatory* acid having the *S* configuration in each case. The absolute configurations thus determined for **2** along with that for the bromoallene (both as shown in Scheme I) revealed that the S_N2' displacements proceeded with an *anti* stereochemical preference.

The exact *anti* bias of the displacement was determined as follows. The crude acid mixture (**4** + **5**) was reduced to the corresponding alcohols (BH_3, THF, 0°), and the alcohol **6** was converted either to its *d*-10-camphorsulfonate ester (*d*-10-camphorsulfonyl chloride, triethylamine, benzene) (R' = CH_3) or its MTPA ester (MTPA-chloride, DMAP, CH_2Cl_2)[10] (R' ≠ CH_3). The diastereomeric purity was then determined by 270 MHz ^1H nmr analysis.[11] Correction for the maximum optical purity of *R*-**1** gave the *anti* : *syn* ratio for the cuprate displacement. These results, presented in Table I, show excellent *anti* selectivity for all of the displacements studied, approaching complete specificity in some cases.

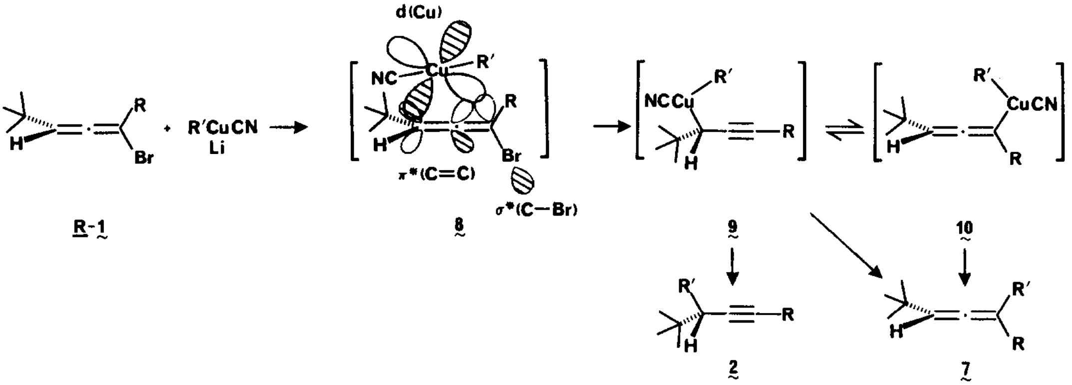
To provide mechanistic information, steric effects were examined by systematically increasing the bulk of R'. For *R*-**1b**, the proportion of allene **7** increased as the size of R' was increased (Table I). This allenic by-product **7** (R = CH_3, R' = ^{t}Bu) had a negative rotation ($[\alpha]_D^{18}$ -36.4° (*c* 0.89, pentane)), indicating an *S* configuration (from Lowe's extension[12] of Brewster's rules - polarizability order: CH_3 > *tert*-butyl > H) and overall inversion of configuration for the displacement.

Feasible mechanistic explanations for this reaction must account for both the *anti* selectivity and the acetylene : allene product ratios. The *anti* selectivity might be the result of an electrostatic effect which imposes maximum separation of the nucleophile ($RCuCN^-$) and the leaving group (Br^-) in the transition state. However, it is difficult to reconcile this with the high *anti* preference observed with the neutral reagent Bu_3PCuCH_3. It might also be argued that solvation or ion pairing effects impede the *syn* pathway. Although this possibility is difficult to dismiss, it is not at all obvious that it can account for the magnitude of the *anti* selectivity. We prefer the view that this *anti* preference originates from a stereoelectronic effect[13] associated with bidentate binding of nucleophilic copper (highest filled d orbital) with both the C-2/C-3 π^* orbital and the C-Br σ^* orbital (a weaker interaction) as in **8**. The stereoelectronic preferences arising from bidentate attack of organocopper reagents is discussed in more detail in the following note.[14]

A reaction trajectory such as this would lead to displacement of the bromine by nucleophilic copper in an *anti* sense, yielding Cu(III) intermediate **9**. This transient species can undergo either 1,2- or 1,4-reductive elimination (or, equivalently, a 1,3-π-slide to **10** and 1,2-reductive elimination) to give, respectively, alkyne **2** or allene **7**. Formation of **7** with inversion of configuration is favored only as R decreases and R' increases in bulk. This mechanistic proposal is similar to that previously outlined to account for S_N2' cuprate displacement of propargyl leaving groups.[1e, f, l, o, t, 16]



SCHEME I



SCHEME II[15]

TABLE I

Substrate	R'	Cuprate	Temp.	Relative Ratio 2 : 7[a]	Yield of 2	Anti : Syn Ratio[b]
R-1a	CH_3	$(CH_3)_3Cu_2Li$[c]	0°C	>98 : 2	82.1%	91 : 9
R-1a	CH_3	Bu_3PCuCH_3	0°C	>98 : 2	73.9%	96 : 4
R-1a	CH_3	$CH_3(CN)CuLi$	0°C	>98 : 2	91.7%	>99 : 1
R-1a	Ph	Ph(CN)CuLi	0°C	>98 : 2	≥95.7%[d]	>99 : 1
R-1a	^{n}Bu	^{n}Bu(CN)CuLi	0°C	>98 : 2	91.8%	97 : 3
R-1b	CH_3	$CH_3(CN)CuLi$	-78°C[e]	>98 : 2	97.9%	98 : 2
R-1b	Ph	Ph(CN)CuLi	-78°C	>98 : 2	90.1%	99 : 1
R-1b	^{n}Bu	^{n}Bu(CN)CuLi	-78°C	>98 : 2	88.1%	95 : 5
R-1b	^{s}Bu	^{s}Bu(CN)CuLi	-78°C	84 : 16	62.9%	97 : 3
R-1b	^{t}Bu	^{t}Bu(CN)CuLi	-78°C	<2 : 98	---[f]	---

a) By ^{1}H nmr investigation. Limit of detection at least 2%. b) By 270 MHz ^{1}H nmr investigation (accuracy ± 5%) of a diastereomeric derivative of 6.[11] c) 1.5 equiv cuprate used. All others used large excess (8 equiv). d) 2 Inseparable from biphenyl impurity. Yield based on overall yield from 1a to degradation products 4 + 5. e) Reaction at 0°C resulted in lower anti : syn ratio (73 : 27). f) Yield of purified 7 was 66.2%.

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15. For simplicity, the copper species is presented as a monomeric discrete complex - its actual structure is unknown.

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