Auxiliary-Based, Asymmetric S_N2' Reactions: A Case of 1,7-Relative Stereogenesis

Scott E. Denmark* and Lyndon K. Marble

Roger Adams Laboratory, Department of Chemistry, University of Illinois, Urbana, Illinois 61801

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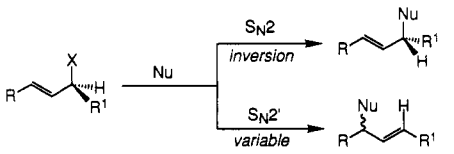
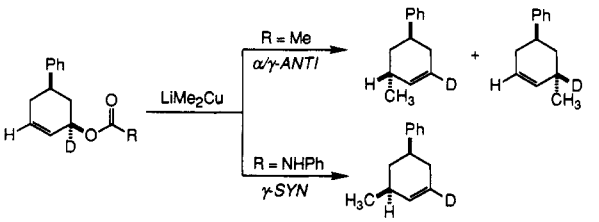
Summary: The asymmetric S_N2' substitution of chiral carbamates derived from an achiral allylic alcohol has been developed. Using optically active amines as auxiliaries, the reaction has been optimized to give up to 92% ee with an S_N2'/S_N2 ratio of >100:1 with various copper reagents.

The inversion of configuration that accompanies bimolecular nucleophilic aliphatic substitution (S_N2 reaction) is one of the most documented facts of organic chemistry.[1] By contrast, the stereochemical course of *vinylogous* bimolecular nucleophilic aliphatic substitution (S_N2' reaction) is characterized by much greater variability (Scheme I).[2] A strong, intrinsic preference for the stereochemistry of S_N2' reactions has not been established as both syn- and anti-selective reactions have been reported.[3] Although mechanistically not well understood, the S_N2' reactions of organocuprates[4] show an overwhelming preference for anti substitution with allylic carboxylates,[5] sulfonates,[6] alcohols,[7] and oxiranes[8] as well as with propargylic[9] and allenic[10] substrates. A notable exception to this rule was reported by Gallina[11] who demonstrated a remarkable γ-syn-substitution preference for organocuprates with allylic carbamates (Scheme II). Further studies by Goering[12] suggested that intramolecular delivery of the nucleophile was responsible for the marked change in regio- and stereochemistry.

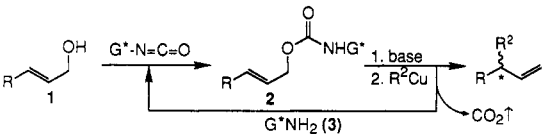
Scheme I



Scheme II



Scheme III



Scheme IV

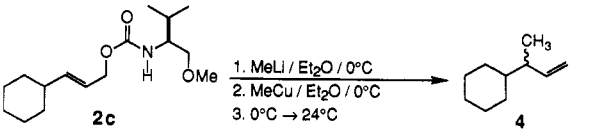
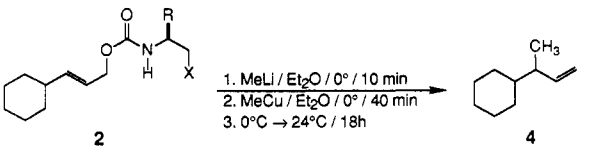


Table I. Survey of Chiral Auxiliaries[a]



substrate	R	X	configuration[b]	yield,[c] %	ee, %[d] (configuration)
2a	Ph	H	*R*	49 (64)	13 (*S*)
2b	1-naphthyl	H	*R*	50 (71)	38 (*S*)
2c	*i*-Pr	OMe	*S*	75 (100)	31 (*R*)
2d	*t*-Bu	OMe	*S*	52 (65)	32 (*R*)
2e	$PhCH_2$	OMe	*S*	64 (82)	63 (*R*)
2f	Ph	OMe	*S*	62 (86)	82 (*R*)
2g	4-anisyl	OMe	*S*	57 (67)	82 (*R*)
2h	1-naphthyl	OMe	*S*[e]	49 (63)	92 (*R*)
2i	1-naphthyl	OMEM	*S*[f]	35 (64)	92 (*R*)

[a] All reactions using 1 equiv of MeCu in Et_2O, by inverse addition (see text). [b] Enantiomeric purities are all >99% except as noted. [c] Yield based on recovered **2** in parentheses. [d] Corrected for ee of **2**. [e] 97.1% ee. [f] 94.3% ee.

In all of these substitutions, the creation of a new stereogenic center is intimately coupled with the destruction of the original center in the substrate (self-immolative reaction).[13] While the net result is generally

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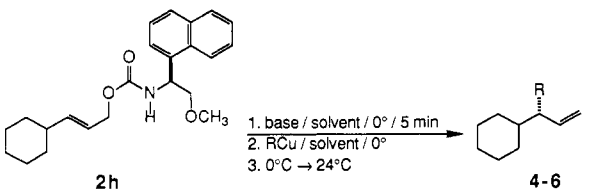
0022-3263/90/1955-1984$02.50/0

Table II. Optimization of Reactions with 2h



2h 4-6

entry	base	solvent	RCu (equiv)	method	time,[a] h	conc, M	product	yield,[b] %	ee, %
1	MeLi	Et_2O	MeCu (1)	inverse	23	0.088	**4**	42 (60)	93
2	MeLi	Et_2O	MeCu (1)	inverse	23	0.273	**4**	66 (74)	91
3	MeLi	Et_2O	MeCu (1.5)	inverse	4	0.195	**4**	56 (66)	95
4	*n*-BuLi	Et_2O	MeCu (2)	normal	23	0.164	**4**	50 (52)	91
5	MeLi	THF	MeCu (1)	inverse	4	0.330	**4**	62 (70)	82
6	*n*-BuLi	Et_2O	*n*-BuCu (1)	normal	22[c]	0.174	**5**	49 (100)	*d*
7	*n*-BuLi	Et_2O	*n*-BuCu (2)	normal	22[c]	0.183	**5**	64 (80)	88
8	*n*-BuLi	Et_2O	PhCu (2)	normal	18	0.150	**6**	70 (70)	91[e]

[a] Total reaction time after addition of Li^+ **2**$^-$. [b] Yield based on recovered **2** in parentheses. [c] Reaction run at −30 °C → 0 °C. [d] Racemic **2h** was used. [e] Determined by Pirkle analysis of the alcohol from ozonolysis–reduction ($NaBH_4$).

useful, we were intrigued by the possibility of stereoselectively installing a new carbon–carbon bond in an *achiral allylic alcohol*, **1**, by moving the stereodirecting group (G*) to the nucleofuge (Scheme III).[14] We report herein the successful realization of this concept with a remarkable level of stereocontrol.

The substrate chosen for study is an aliphatic allylic alcohol **1** (R = cyclohexyl, E/Z = 97/3). The carbamates **2** derived from **1** were prepared either by reaction with the appropriate isocyanate[15] or by prior activation of **1** as a 4-nitrophenyl carbonate[16] followed by reaction with the amine G*NH_2 (**3**). Orienting experiments were conducted with carbamate **2c** derived from (*S*)-valinol methyl ether.[17] Initial studies were aimed at optimizing the S_N2' to S_N2 ratio and maximizing the conversion of substrate (Scheme IV). After surveying the four reaction protocols reported by Goering,[12] we found that a modified procedure[18] involving combination of the lithiocarbamate (Li^+**2c**$^-$) with a suspension of MeCu (Et_2O, 0 °C) followed by warming to room temperature gave up to 75% yield of isolated alkene (**4**) with a >100:1 S_N2':S_N2 ratio.[19,20] Both normal (Li^+**2**$^-$ added to RCu) and inverse (RCu added to Li^+**2**$^-$) addition sequences could be used.

Using the optimized protocol, we surveyed a variety of optically active amines for their potential as auxiliaries in asymmetric induction (Table I). In all of the reactions, 1 equiv of MeCu was used. The yields corrected for unreacted carbamate (generally 60–80% conversion) are given in parentheses. The enantioselectivity of the reactions (corrected for enantiomeric excess of the carbamates) was established by HPLC analysis of the carboxylic acid derived from **4**[21] as its 3,5-dinitroanilide.[22] All of the auxiliaries examined in which X = OMe gave (*R*)-**4** as the major product.[23]

The poor selectivities observed with **2a** and **2b** are not surprising though the effect of the naphthyl group is noteworthy. The incorporation of a coordinating appendage (X = OR) was readily achieved by use of auxiliaries derived from α-amino acids.[24] The striking difference between auxiliaries with aliphatic (**2c**, **2d**) versus aromatic residues (**2e**, **2f**) suggested that more than simple steric effects were involved. A significant change in the π-basicity of the residue (**2g**) had no effect on selectivity. Recalling the improvement from phenyl to naphthyl in the X = H series, we next examined carbamate **2h** derived from (*S*)-α-naphthylglycine.[25] We were delighted to find the highest enantioselectivity (92%) with this substrate. Further modifications of this auxiliary, exemplified by **2i**, did not improve the enantioselectivity.

Optimization of this substitution using **2h** involved fine tuning of various parameters. As shown in Table II, concentration has a significant effect on conversion (entries 1 and 2). Although reactions were much faster in THF, the enantioselectivity dropped unacceptably (entry 5). We have briefly examined the use of other organolithium derived nucleophiles in this substitution (Table II). For both *n*-BuCu and PhCu, 2 equiv of the nucleophile were necessary for high conversions in contrast to MeCu (entries 6–8). The major isomers of **5** and **6** had the same absolute configuration[26] as **4**, and the enantioselectivites were comparable.

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In recent years, extensive studies on the structure of cuprates[27] and mechanism[28] of their reactions have been reported. Any reasonable explanation for the selectivity observed in this substitution requires a clearer picture of the specific carbamate–cuprate complex. Nevertheless, the level of asymmetric induction in this transformation is remarkable considering the six intervening bonds between the original and created stereogenic centers. Further studies on nucleophile and substrate variability as well as reagent structure are ongoing.

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Supplementary Material Available: A general procedure for reactions of **2h** (3 pages). Ordering information is given on any current masthead page.

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Articles

2,2′:4,4″:4′,4‴-Quaterpyridyl: A Building Block for the Preparation of Novel Redox Reagents. 1. Preparation and Quaternization

Robert J. Morgan and A. David Baker*

Department of Chemistry, City University of New York, Queens College, Flushing, New York 11367

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An efficient preparation of 2,2′:4,4″:4′,4‴-quaterpyridyl (qpy) from 4,4′-bipyridine is described, using palladium on charcoal. Conditions are described for the selective methylation of the nitrogen atoms present. This has allowed the preparation of mono- and dimethylquaternary salts that retain an α-diimine site for complexation to a metal. These quaternary salts can be used to prepare complexes in which metal ions are coordinated to viologen-type ligands. Electrochemical and spectroscopic measurements of the diquaternary salt derived from qpy suggest that it behaves as two separate or weakly interacting monoquat moieties.

Introduction

Bipyridines and polypyridines have attracted attention in recent years as synthetic components of useful redox reagents such as the viologens[1] and polypyridyl complexes of Ru(II) and other metal ions.[2] These reagents have played a central role in the study of photoactivated electron-transfer reactions and in applications to energy conversion,[2,3] synthetic methodology,[4] electrochromic devices,[5] and related areas.[6]

As knowledge in these areas has accumulated, a need has arisen for structurally more complex bipyridines, polypyridines, and analogues so that more specialized systems can be developed and explored. Of particular interest has been the incorporation of two or more distinct molecular entities into a single "supermolecule" and the design of modified reagents that can participate in transient supramolecular interactions. Examples of systems that have been studied include the bis- and polyviologens that function as multielectron acceptors,[7] metal complexes of 2,2′-bipyrazine, used in the photoreduction of carbon dioxide to methane,[8] and molecules containing a light-activated electron-donor site covalently linked to an electron-aceptor site to explore the role of structure on the electron-transfer process.[9] Also of interest are systems in which the conformational relationship among neighboring pyridyl units is either rigidly defined,[10] and/or is controllable by molecular modification,[11] and systems

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