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Tandem Regio- and Stereoselective Organocuprate-Mediated Bis-Allylic Substitutions

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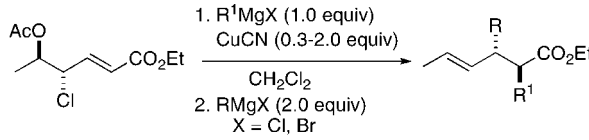
ABSTRACT



R^1 = ^{n}Bu, Et; R = Et, ^{n}Bu, ^{i}Pr 68-85% (92:8 to 98:2 dr)

***anti*-5-Acetoxy-4-halo-α,*β*-enoates undergo sequential or tandem reactions with two different magnesium cuprate reagents to afford *anti*-2,3-dialkyl-4,5-enoates in high chemical yield and with excellent diastereoselectivity. The one-pot tandem procedure can be achieved with 30 mol % of CuCN and affords a rapid stereoselective combinatorial approach to vicinal disubstituted *γ*,*δ*-enoates containing functionality at either end of the carbon chain for subsequent functional group elaboration. The methodology should provide a powerful practical strategy for acyclic stereoselection.**

Allylic substitution reactions mediated by organocopper,[1] palladium,[2] and less frequently nickel[1c] reagents constitute a powerful synthetic strategy for functional group transformations, substituent introduction, and chirality transfer. Although inherent problems of regio- (e.g., S_N2 vs S_N2') and stereocontrol (e.g., *anti* vs *syn*-S_N2') abound, regio- and stereoselectivity can be mediated by choice of metal reagent, leaving group, solvent, and other reaction conditions. While palladium-mediated tandem allylic substitutions have been described,[3] the reported reactions involve heteroatom (e.g., amines, alcohols) and/or malonate nucleophiles and generally encompass either two S_N2 reactions or one S_N2' reaction followed by an S_N2 reaction where the latter is not an allylic substitution. To our knowledge, there are no reports of two sequential or tandem S_N2'-allylic substitution reactions mediated by palladium or copper, although copper-mediated multipot sequential S_N2 reactions on vicinal epoxymesylates have been reported.[4] Although no precedent existed for these chemoselective bis-S_N2'-allylic substitutions, the synthetic utility of monoallylic substitutions[1,2] suggested that tandem or sequential copper mediated S_N2'-allylic substitution reactions on vinyl oxiranes or 3,4-diheteroatom-substituted alkenes could provide a powerful methodology for asymmetric acyclic stereoselection if solutions to the problems of chemo-, regio-, and stereocontrol could be found. We now

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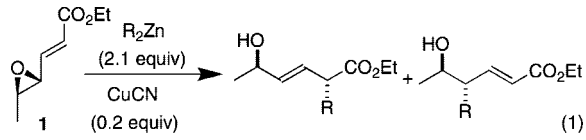
report solutions to these problems that afford a practical and versatile methodology for vicinal acyclic stereoselection.

Although enantioenriched vinyl oxiranes are readily available,[5] they undergo copper-mediated allylic substitution reactions with variable regioselectivity (i.e., S_N2' vs S_N2) depending upon the substitution pattern.[1e,f] The reactions of epoxide **1** (or the methyl ester)[6] and its aziridine[7] analogue with cuprate reagents have been studied by several groups, and similar transformations have been reported for nonepoxide γ,δ-dioxygenated α,β-enoates[8] and γ-bromo-α,β-enoates.[9] Although reaction of **1** with Me_2Zn/CuCN in DMF reportedly affords excellent S_N2'-regioselectivity (94:6), the reaction was only examined for the methylzinc cuprate reagent.[6a] We quickly ascertained that the reaction was not general, affording a comparable regioselectivity for Et_2Zn/CuCN, but lower regioselectivity (87:13) for the ^{n}Bu transferable ligand (eq 1) under comparable conditions. The major *anti*-diastereomer was formed in all three cases with excellent diastereoselectivity (dr = 97:3).

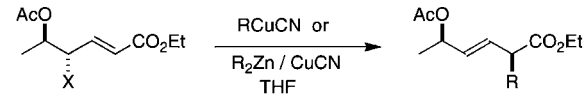


2a R = Et 84% (97:3 dr) **3a** 5%
2b R = ^{n}Bu 69% (97:3 dr) **3b** 11%

We turned our attention to δ-acetoxy-γ-halo-α,β-enoates **4a**,**b** (Table 1), which can be prepared from epoxide **1**.[10] Initially, treatment of **4a** with ^{n}Bu$_2$CuLi in THF gave low chemical yields of the S_N2' *syn*-diastereomer with modest diastereoselectivity (entry 1). Utilization of the less reactive alkylcyanocuprate reagent (i.e., RCuCNLi) gave good chemical yields with **4a**−**b** (entries 2 and 3), but with the same modest diastereoselectivity. Using exact and precise stoichiometries, the diastereoselectivity could be significantly improved (entries 4 and 5), suggesting stereochemical sensitivity to excess cuprate reagent. Utilization of the ^{n}Bu$_2$Zn/CuCN reagent afforded comparable yields of **5a** but diminished diastereoselectivities (entries 6 and 7). With stoichiometric quantities of CuCN, Et_2Zn gave good chemical yields and dr's of **5b** (entry 8), and the latter was significantly diminished when catalytic quantities of CuCN were employed (entries 9−11). Branched alkylcyanocuprates gave high to modest chemical yields and modest to high dr's (entries 12 and 13).

In several instances, formation of ethyl 2-alkyl-2,4-hexadienoates (entry 1: 60%) or ethyl sorbate (entry 13: 24%) point to the facility with which allylic acetates **5a**−**d** can undergo elimination and perhaps isomerization as the cause of low diastereoselectivity. Formation of ethyl 4-chloro-2,4-hexadienoate (20%) upon reaction of **4b** with ^{t}BuCuCNLi presumably arises via a reductive elimination pathway. Despite these sensitivities to side reactions, high chemical yields and diastereoselectivities could be achieved under the optimized reaction conditions.

Table 1. Reaction of Organometallic Reagents with δ-Acetoxy-γ-halo-α,β-enoates

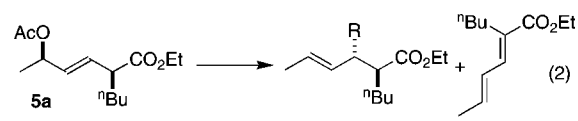


4a X = Br **5a** R = ^{n}Bu **c** R = ^{s}Bu
b X = Cl **b** R = Et **d** R = ^{t}Bu

entry	RX	R (RM)[a]	equiv[b]	product	% yield[c]	dr[d]
1	**4a**	^{n}Bu (A)	1.1	**5a**	25[e]	84:16
2	**4a**	^{n}Bu (B)	1.1	**5a**	85[e]	83.5:16.5
3	**4b**	^{n}Bu (B)	1.1	**5a**	89[e]	85:15
4	**4a**	^{n}Bu (B)	1.0	**5a**	86	93:7
5	**4b**	^{n}Bu (B)	1.0	**5a**	77	90:10
6	**4b**	^{n}Bu (C)	1.1	**5a**	83	88:12
7	**4a**	^{n}Bu (C)	1.1	**5a**	86[e]	87:13
8	**4b**	Et (C)	2.0	**5b**	90	92:8
9	**4a**	Et (C)[f]	2.0	**5b**	88	85:15
10	**4a**	Et (C)[h]	2.2	**5b**	89	89:11
11	**4b**	Et (C)[f]	2.0	**5b**	83	88:12
12	**4b**	^{s}Bu (B)	1.0	**5c**	87	85:15
13	**4b**	^{t}Bu (B)	1.0	**5d**	43[e,g]	>95:5

[a] A = R_2CuLi, −78 °C. B = RCuCNLi, −78 °C. C = R_2Zn/CuCN, −23 °C. [b] Equivalents of RCuCNLi and R_2Zn and CuCN unless otherwise noted. [c] Yields based upon isolated products purified by column chromatography. [d] Diastereomeric ratio determined from ^{1}H NMR integration values for the vinyl protons or alkene ^{13}C absorption peak heights. [e] Ethyl 2-*n*-butyl-2,4-hexadienoate (entry, % yield: 1, 60%; 2, 4%; 3, 2%; 7, 2%) or ethyl sorbate (entry 13, 24%) was formed. [f] Catalytic amounts of CuCN (0.1 equiv) were employed. [g] Ethyl 4-chloro-2,4-hexadienoate was also formed in 20% yield. [h] Catalytic amounts of CuCN (0.2 equiv) were employed. Reaction was run at −40 °C.

We next examined the possibility of effecting a stereospecific allylic substitution on allylic acetate **5a** formed from **4a** or **4b** via the first allylic substitution. Treatment of **5a** with the lithium alkyl(cyano)cuprate reagent afforded only diene via elimination of the acetate substituent (eq 2). A trialkylzincate reagent in the presence of CuCN gave clean S_N2'-substitution but with poor diastereoselectivity, while utilization of a magnesium dialkylcuprate reagent gave good chemical yield and modest diastereoselectivity (eq 2).



^{n}BuCuCNLi (1.1 equiv) - 90%
^{n}Bu$_3$ZnLi / CuCN (1.0 equiv) **8a** 79% (dr = 52:48) R = ^{n}Bu
$Et_2CuMgBr$ (1.0 equiv) **6a** 82% (dr = 84:16) R = Et

Having determined that magnesium dialkylcuprates were the reagents of choice, we examined a series of solvents in

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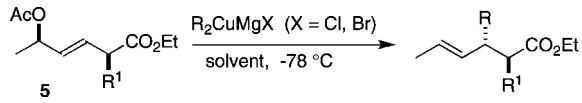
Table 2. Reaction of 5-Acetoxy-2-alkyl-3,4-enoates with Cuprate Reagents



a R^1 = ^{n}Bu **b** R^1 = Et **6** R = Et **7** R = ^{i}Pr **8** R = ^{n}Bu **9** R = Ph

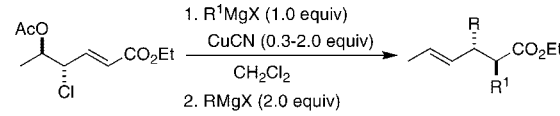
entry	ROAc	solvent[a]	product	% yield[b]	dr[c]
1	**5b**	Et_2O[d]	**6b**	89	90:10
2	**5b**	*t*-BuOMe	**6b**	84	92:8
3	**5a**	Et_2O[d]	**6b**	82	86:14
4	**5a**	CH_2Cl_2[d]	**6a**	85	93:7
5	**5a**	CH_2Cl_2[d]	**6a**	86	92:8
6	**5b**	Et_2O	**7b**	85	85:15
7	**5b**	Et_2O[e]	**7b**	92	85:15
8	**5b**	CH_2Cl_2[g]	**7b**	89	88:12
9	**5a**	Et_2O	**7a**	87	87:13
10	**5a**	$PhCH_3$	**7a**	83	85:15
11	**5a**	CH_2Cl_2	**7a**	90	93:7
12	**5b**	*t*-BuOMe[d,f]	**8b**	84	79:21
13	**5b**	CH_2Cl_2[g]	**8b**	77	94:6
14	**5a**	Et_2O	**8a**	81	83:17
15	**5a**	CH_2Cl_2[g]	**8a**	82	92:8
16	**5a**	*t*-BuOMe[g]	**8a**	90	91:9
17	**5a**	CH_2Cl_2[h]	**9a**	73	90:10
18	**5b**	CH_2Cl_2[h]	**9b**	71	86:14

[a] Reactions were run at −78 °C for approximately 8 h and then allowed to warm to room temperature before quenching, unless otherwise noted. [b] Yields are based upon isolated products purified by column chromatography. [c] Diastereomeric ratios were determined from integration of the ^{1}H NMR vinyl absorptions or via peak heights of ^{13}C NMR absorptions. [d] Consists of solvent/*t*-BuOMe (11−12:1) from the *t*-BuOMe solution of RMgBr. [e] Reaction was run at − 78 °C for 12 h, warmed to room temperature and quenched. [f] Quenched at −30 °C. [g] Consists of solvent:Et_2O (11−12:1) from the Et_2O solution of *n*-BuMgBr or *i*-PrMgCl. [h] Consists of solvent:THF (22:1) from the THF solution of PhMgCl.

an effort to optimize the diastereoselectivity (Table 2). While Et_2O uniformly gave modest to good dr's ranging between 83:17 to 90:10 (entries 1, 3, 6−7, 9, and 14), ^{t}BuOMe gave slightly better dr's (entry 2 vs 1, 16 vs 14). Toluene did not improve the stereoselectivity (entry 10 vs 9). Consistently better dr's were obtained when CH_2Cl_2 was used as solvent (entries 4−5, 11, 13, 15), except when a sterically bulky transferable ligand was employed (entries 8, 17−18). Utilization of ^{i}Pr or Ph transferable ligands generally resulted in a diminuation of the diastereoselectivity (entries 8, 17, and 18), although in one case good diastereoselectivity could be achieved in CH_2Cl_2 (entry 11). These results indicate that the stereochemical preference for *anti*-S_N2' substitution is the dominant control element and that steric factors in either the cuprate reagent or allylic substrate have minor effects on the stereoselectivity of the reaction.

With optimization of the magnesium dialkylcuprate reaction with allylic acetate **5** in hand (Table 2), we turned our attention to the development of a one-pot tandem bis S_N2'-allylic substitution protocol. Sequential treatment of **4b** with R^1CuCNMgX (X = Cl, Br) and then with R_2CuMgX (X = Cl, Br) under the reaction conditions developed for **5** afforded **6**−**8** in good chemical yields and with excellent diastereoselectivity (Table 3). The initial protocol utilized 2 equiv of

Table 3. Tandem Reactions of **4b** with Two Different Magnesium Cuprate Reagents



X = Cl, Br **a** R^1 = ^{n}Bu **b** R^1 = Et **6** R = Et **7** R = ^{i}Pr **8** R = ^{n}Bu

entry	CuCN quiv[a]	product	% yield[b]	dr[c]
1	2.0	**6a**	85	95:5
2	1.0	**6a**	70	92:8
3	2.0	**6b**	76	95:5
4	1.0	**6b**	74	95:5
5	2.0	**7a**	73	96:4
6	1.0	**7a**	70	94:6
7	1.0	**7b**	71	92:8
8	2.0	**8a**	71	97:3
9	1.0	**8a**	69	94:6
10	0.3	**8a**	68	93:7
11	2.0	**8b**	82	98:2

[a] Reactions conditions: (1) CuCN (2.0 equiv): (i) R^1CuCNMgX (1.0 equiv, X = Cl, Br), CH_2Cl_2, −78 °C, 4 h, warm to −40 °C, stir 2 h; (ii) CuCN (1.0 equiv), −78 °C, 10 min; (iii) RMgX (2.0 equiv, X = Cl, Br), −78 to 25 °C. (2) CuCN (0.3−1.0 equiv): (i) R^1MgX (1.0 equiv, X = Cl, Br), CuCN (0.3−1.0 equiv), CH_2Cl_2, −78 °C, 4 h, warm to −40 °C, stir 2 h; (ii) RMgX (2.0 equiv, X = Cl, Br), −78 to +25 °C. [b] Yields are based upon isolated products purified by column chromatography. [c] Diastereomeric ratios were determined from integration of the ^{1}H NMR vinyl absorptions or via peak heights of ^{13}C NMR absorptions.

CuCN (entries 1, 3, 5, 8, and 11) with the second equivalent of CuCN being added after completion of the first allylic substitution. Seeking to minimize the amount of CuCN employed, the tandem reaction was then carried out with one equivalent of CuCN and the chemical yields and diastereoselectivities were only slightly lower (entries 2 vs 1, 4 vs 3, 6 vs 5, and 9 vs 8). Utilization of 0.3 equiv of CuCN gave the same chemical yields and diastereoselectivity as 1.0 equiv of CuCN for **8a** (entry 10). When catalytic amounts of CuCN (5 mol %) were employed under otherwise identical reaction conditions for the reaction of **4b** with *n*-BuMgCl, **5a**, **8a**, and the elimination product ethyl 4-chloro-2,4-hexadienoate were formed in a 3:3:1 ratio. Thus, under these reaction conditions, 0.3 equiv of CuCN represents the minimum amount of Cu(I) salt that may be employed. This one-pot tandem protocol affords the *anti*-diastereomers[11] complementing formation of the *syn*-diastereomer obtained via epoxide **1**.

In summary, we have developed a versatile method for vicinal acyclic stereoselection that offers significant advantages over existing methods for the stereoselective preparation of *anti*-2,3-dialkyl-4-alkenoates. The existing procedures

(11) The stereochemistry of **7a** was confirmed by conversion of **7a** to the iodo lactone and X-ray analysis of the iodo lactone.

afford poor to good diastereoselectivity (e.g., Claisen rearrangements depending upon substitution patterns),[12] require the construction of unique substrate structures (e.g., Claisen rearrangements[12] or lithium amide alkylations[13] of 3-alkyl enoates) or are limited in choice of nucleophile (e.g., Pd-mediated allylic substitutions)[14] in contrast to the introduction of substituents via variation of the cuprate ligands. The utilization of lithium, zinc, and magnesium cuprate reagents offers the potential to introduce a variety of alkyl and aryl ligands onto an acyclic backbone in a highly stereoselective fashion. Extension of the methodology to enantioenriched epoxides and vicinal halo acetates will provide a versatile route to enantioenriched synthons containing functionality at both ends of the chain for further elaboration.

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Supporting Information Available: General experimental information, materials, data reduction, and ^{1}H and ^{13}C NMR spectra for **5a**−**d** and **6**(**a**−**b**)−**9**(**a**−**b**). This material is available free of charge via the Internet at http://pubs.acs.org.

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