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Regio- and Stereocontrol in the Reactions of α-Halo-β,γ-enoates and α-O-Phosphono-β,γ-enenitriles with Organocuprates

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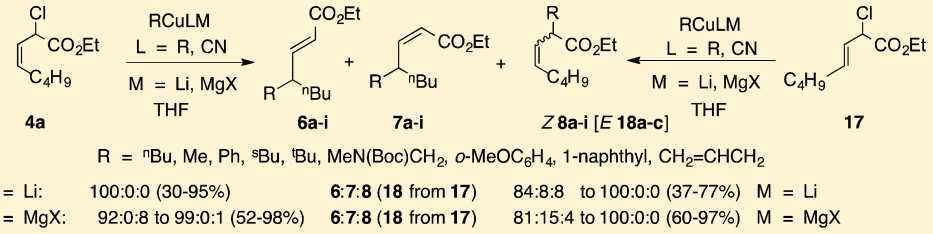
Supporting Information



ABSTRACT: The reactions of (*Z*)- and (*E*)-ethyl 2-chloro-3-octenoate (**4a** and **17**) and (*E*)- and (*Z*)-diethyl (1-cyano-2-heptenyl)phosphate (**21a** and **21b**) with organocuprates were investigated as potential substrates for preparing γ-substituted α,β-enoates and enenitriles. In these copper-mediated allylic substitution reactions, the *Z*-isomer **4a** displayed complete regio- and stereoselectivity (i.e., *E*:*Z*), while the regio- and stereoselectivity for *E*-isomer **17** varied as a function of solvent, cuprate reagent, transferable ligand, and cuprate counterion (e.g., Li^+ vs MgX^+). Excellent selectivities could be achieved with **17** and ^{n}BuCuCNLi in Et_2O. Conditions for improved selectivities in the reactions of allylic cyanophosphates over those previously reported were found. A series of relative rate and competition experiments was performed, and the degree of regio- and stereoselectivity for each system was rationalized in the light of the current mechanistic understanding of cuprate-mediated allylic substitution reactions.

INTRODUCTION

Small, highly functionalized synthons provide opportunities for divergent synthesis via chemo-, regio-, and stereocontrolled reaction pathways and through tandem or sequential reactions.[1,2] The presence of multiple functional groups along a connected sequence of carbon atoms also provides opportunities for remote functionalization. Allylic systems with additional functionality on the allylic position containing the leaving group are attractive candidates for employing this strategy. Although copper-mediated allylic substitution reactions have been extensively studied and developed, control of regio- and stereoselectivity is too often substrate- and reagent-dependent and difficult to control.[3] Much progress has been made in the development of asymmetric allylic substitution (AAS) reactions involving chiral substrates or chiral reagents.[3,4] Enantioenriched α-alkylations have been achieved with α,β-enoates with a leaving group in the γ-position,[4e−h] while racemic vinyloxiranes[2d] and δ-acetoxy-γ-halo-α,β-enoates[2f] afford excellent diastereoselectivity in a one-pot bis-allylic substitution methodology. Mixtures of products with (S_N2') and without (S_N2) rearrangement of the double bond, present as *E*:*Z* double bond isomers or as diastereomeric mixtures when additional stereogenic centers are present, are often obtained, and these mixtures are normally difficult to separate.[2d,5−7] These difficulties have been recently reported in copper-mediated alkylation of α-chloro-β,γ-unsaturated esters[5,6] and allylic cyanohydrin phosphates[7] with organocopper reagents.

Organocuprate-mediated allylic substitution on dialkyl α-cyano-β-alkenylphosphate derivatives was first performed on enantioenriched (*E*)-allylic cyanohydrin *O*-phosphates to afford α,β-conjugated nitriles,[7] which were then hydrolyzed with strong acids to yield the unsaturated esters after esterification. The protocol always afforded alkene *E*:*Z* mixtures with poor stereoselectivity. Subsequently, Posner and co-workers prepared enantioenriched (*E*)-α-chloro-β,γ-enoates from (*E*)-γ-seleno-α,β-enoates by modification of the protocol of Paulmier and co-workers[8] and explored organocopper-mediated allylic substitution reactions on these substrates. Although the method was used for the preparation of γ-methyl-α,β-enoates,[5] γ-amino-α,β-enoates,[5] and rhodanines,[9] the method was largely limited to methylation using $Me_2CuMgBr$. Cuprates with Ph, allyl, and vinyl ligands gave no reaction, while Et-, ^{i}Pr-, and ^{t}Bu-derived cuprates gave nonseparable mixtures of S_N2 and S_N2' products.[6] We now report our efforts to control the regio- and stereoselectivity in the reactions of organocuprates with α-nucleofuge-substituted-β,γ-enoates and nitriles through examination of solvent, temperature, leaving group, cuprate composition, and alkene configuration (i.e., *E* vs *Z*) of the substrate.

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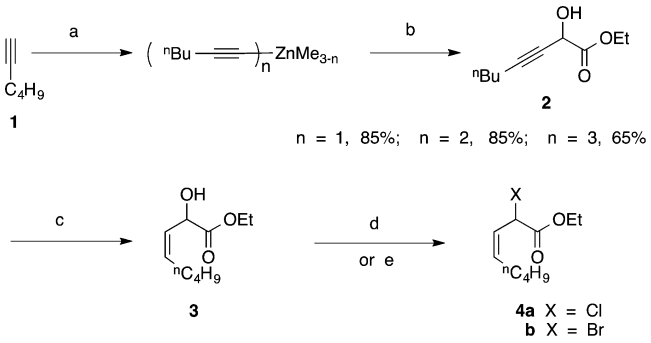
RESULTS

Although α-chloro-β,γ-unsaturated esters have been employed[10] for the allylation of aldehydes and imines via bis-allylpalladium intermediates and photochemical studies have been reported for α-fluoro derivatives,[11] there are few methods available for their preparation. They can be prepared from trimethylsiloxy-α-diazocarbonyl esters but this method gives mixtures of α- and γ-halo unsaturated esters.[12] The *trans*-α-chloro and -α-bromo-β,γ-unsaturated esters used in this study were most easily prepared from γ-phenylseleno-α,β-unsaturated esters,[8] while the *Z*-isomers were prepared in two steps from terminal alkynes (Scheme 1). Although alkynyl alcohol **2** has been prepared in low yields by addition of alkynyl Grignard reagents to esters of oxalic acid (28%),[13] we developed a more effective procedure using organozincate reagents. The dialkynyl(methyl)zincate reagent proved to be most effective, as it transferred both alkynyl ligands. Lindlar reduction[14] of alkyne **2** followed by conversion of alcohol **3** into chloride[15] **4a** completed the synthesis without double bond migration or *E*/*Z*-isomerization of the *Z*-alkene. Allylic alcohol **3** has also been prepared enantioselectively from ethyl glyoxylate and (*Z*)-1-trimethylsilyl-1-hexene.[16] Preparation of compound **4b** from **3** with PBr_3 afforded the *E*-isomer as a minor impurity.

Scheme 1. Synthesis of (*Z*)-Ethyl 2-Chloro-3-octenoate[a]



[a]Reagents and conditions: (a) (i) **1** (*n* equiv), ^{n}BuLi (*n* equiv), THF, −78 °C, 1 h; (ii) $ZnBr_2$ (*n* = 1, 2, 3:1.0, 0.5, 0.33 equiv, respectively); (iii) MeLi (3 − *n* equiv), −60 to 25 °C, 1.5 h. (b) Freshly distilled $HOCCO_2Et$, PhMe, −60 to −20 °C (85%). (c) Lindlar catalyst, quinoline (1.1 equiv), MeOH, H_2, 25 °C, 4 h (88%). (d) PPh_3 (1.3 equiv), CCl_4, 75 °C, 1.5 h (85%). (e) PBr_3 (2.0 equiv), DMF, −15 °C, 1 h (75%).

In pursuit of a synthetic objective, we attempted to couple the *N*-Boc-2-pyrrolidinyl ligand with various (*Z*)-α-nucleofuge-substituted-β,γ-enoates without success. Examination of these substrates (i.e., **5a−d** and **4a,b**) was then undertaken in order to understand their reactivity profile with lithium alkyl(cyano)- (i.e., RCuCNLi) and dialkylcuprates (i.e., R_2CuLi). The allylic phosphates **5a,b**,[17] mesylate **5c**,[18] pentafluorobenzoate[17b,19] **5d**, and halides **4a,b** all gave a single product in modest to good yields with methyl and *n*-butylcuprates (Table 1). Higher yields were obtained with the *n*-butylcuprates, and surprisingly, similar yields were obtained with both RCuCNLi and R_2CuLi reagents (entries 1 vs 2, 3 vs 4, 5 vs 6, 7 vs 8) with phosphates **5a,b**. In situ generation of the phosphate ester gave slightly higher yields than utilization of the preformed substrate (entries 10 vs 5, 11 vs 7). Yields were generally comparable along the series $-OPO(OR)_2 \approx -OMs \approx -CO_2C_6F_5$ and slightly higher for the halides with the ^{n}Bu- and methylcuprates (entries 1, 5, 10, 15, 18, 23, and 27 and 3, 7, 11, 16, 19, 24). Phenyl(cyano)-cuprates gave low yields with the phosphates (entries 9 and 12), mesylate (entry 17), and pentafluorobenzoate (entry 20) due to biphenyl formation[2b,20,21] and modest yields with the chloride **4a** (entry 25), suggesting a higher reactivity for the latter substrate. In most cases, low yields were obtained with the α-(*N*-carbamoyl)alkyl(cyano)cuprates (entries 13, 21, and 28), with chloride **4a** giving the highest yield (entry 26) and the

Table 1. Reaction of Allylic Substrates 5a−d and 4a,b Containing Different Nucleofuges with Lithium Alkyl- and Phenylcuprate Reagents

6a-d

5a X = $OP(O)(OPh)_2$
b X = $OP(O)(OEt)_2$
c X = $OS(O)_2Me$
d X = $OCOC_6F_5$
4a X = Cl
b X = Br

a R = ^{n}Bu **c** R = Ph
b R = Me **d** R = MeN(Boc)CH_2

entry[a]	substrate	reagent (equiv)[b]	product	yield (%)[c]
1	**5a**	^{n}BuCuCNLi (1.2)	**6a**	76
2	**5a**	$^n Bu_2CuLi$ (1.0)	**6a**	73
3	**5a**	MeCuCNLi (1.2)	**6b**	55
4	**5a**	Me_2CuLi (1.0)	**6b**	53
5	**5b**	^{n}BuCuCNLi (1.2)	**6a**	75
6	**5b**	$^n Bu_2CuLi$ (1.0)	**6a**	71
7	**5b**	MeCuCNLi (1.2)	**6b**	56
8	**5b**	Me_2CuLi (1.0)	**6b**	55
9[d]	**5b**	PhCuCNLi (1.2)	**6c**	18
10[e]	**5b**	^{n}BuCuCNLi (1.2)	**6a**	88
11[e]	**5b**	MeCuCNLi (1.2)	**6b**	63
12[d,e]	**5b**	PhCuCNLi (1.2)	**6c**	20
13[e−g]	**5b**	$CH_3N(Boc)CH_2CuCNLi$ (1.2)	**6d**	22
14[e,g,h]	**5b**	$(CH_3N(Boc)CH_2)_2CuLi$ (1.0)	**6d**	11
15	**5c**	^{n}BuCuCNLi (1.2)	**6a**	78
16	**5c**	MeCuCNLi (1.2)	**6b**	68
17[d]	**5c**	PhCuCNLi (1.2)	**6c**	33
18	**5d**	^{n}BuCuCNLi (1.2)	**6a**	82
19	**5d**	MeCuCNLi (1.2)	**6b**	65
20[d]	**5d**	PhCuCNLi (1.2)	**6c**	38
21[f,g,i]	**5d**	$CH_3N(Boc)CH_2CuCNLi$(1.2)	**6d**	58
22[g,h]	**5d**	$(CH_3N(Boc)CH_2)_2CuLi$ (1.0)	**6d**	26
23	**4a**	^{n}BuCuCNLi (1.2)	**6a**	95
24	**4a**	MeCuCNLi (1.2)	**6b**	88
25	**4a**	PhCuCNLi (0.9)	**6c**	63
26[h,i]	**4a**	$CH_3N(Boc)CH_2CuCNLi$ (1.2)	**6d**	75
27	**4b**	^{n}BuCuCNLi (1.2)	**6a**	98
28[f,g]	**4b**	$CH_3N(Boc)CH_2CuCNLi$ (1.2)	**6d**	53
29[g,h]	**4b**	$(CH_3N(Boc)CH_2)_2CuLi$ (1.0)	**6d**	40

[a]THF as solvent with a composition for the reaction of 10/1 solvent/organometallic solvent unless otherwise noted. Cuprates were prepared from THF-soluble CuCN·2LiCl. [b]Reactions were performed at −78 °C for 2 h and then warmed up to room temperature (rt) with overall stirring of 8−12 h. [c]Upon the basis of isolated material purified by column chromatography. [d]Biphenyl was the major product of this reaction. [e]Phosphate prepared in situ. [f]Solvent THF:Et_2O (1:2). [g]Starting material was recovered. [h]Solvent THF:Et_2O (1:1). [i]Reaction conditions: −40 °C for 1 h and then slowly warmed to rt (−40 to 25 °C, 2 h, then 12 h at 25 °C).

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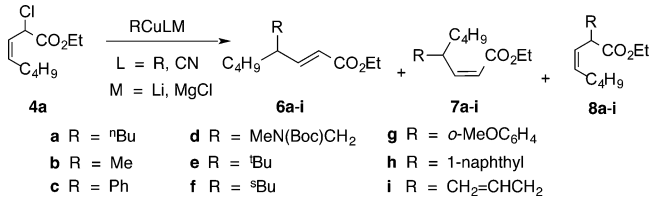
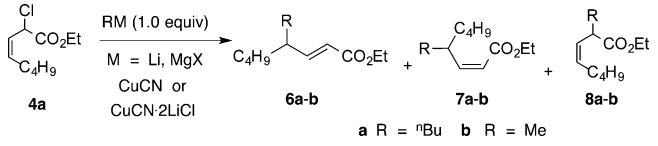
Table 2. Reaction of (*Z*)-Ethyl 2-Chloro-3-octenoate with Organocuprate Reagents



entry[a]	reagent (equiv)[b]	yield (%)[c]	product	6:7:8[d]
1	$^{n}Bu_2CuLi$ (1.0)	75	**6a**	100:0:0
2	^{n}BuCuCNLi (1.0−1.2)	85−95	**6a**	100:0:0
3[e]	^{n}BuCuCNLi (1.2)	76	**6a**	100:0:0
4[f]	^{n}BuCuCNLi (1.2)	31	**6a**	100:0:0[g]
5[h]	^{n}BuCuCNLi (1.2)	17	**8a**	**8a** major[i]
6[j]	^{n}BuCuCNLi (1.2)	23	**7a**	**7a** major[i]
7	^{n}BuCuCNMgCl (1.2)	77	**6a**	94:0:6
8	$^{n}Bu_2CuMgCl$ (1.0)	78	**6a**	92:0:8
9	MeCuCNLi (1.2)	88	**6b**	100:0:0
10	Me_2CuLi (1.0)	59	**6b**	100:0:0
11	^{s}BuCuCNLi (1.2)	57	**6f**	100:0:0
12	^{t}BuCuCNLi (1.2)	81	**6e**	100:0:0
13	$^{t}Bu_2CuLi$ (1.0)	50	**6e**	100:0:0
14[k,l]	$CH_3N(Boc)CH_2CuCNLi$ (1.0−1.2)	70−75	**6d**	100:0:0
15[m]	Ph_2CuLi (1.0)	30	**6c**	100:0:0
16	PhCuCNLi (0.9−1.2)	60−63	**6c**	100:0:0
17	$CH_3OC_6H_4CuCNLi$ (1.2)	73	**6g**	100:0:0
18	$C_{10}H_8CuCNLi$ (1.2)	75	**6h**	100:0:0
19	CH_2=CH−$CH_2CuCNMgCl$ (1.2)	66	**6i**	99:0:1
20	$(CH_2$=CH−$CH_2)_2CuMgCl$ (1.2)	52	**6i**	100:0:0

[a]THF as solvent with a composition for the reaction of 10/1 solvent/organometallic solvent unless otherwise noted. Cuprates were prepared from THF-soluble CuCN·2LiCl. [b]Reactions were performed at −78 °C for 2 h and then warmed up to rt with overall stirring of 8−12 h. [c]Upon the basis of isolated material purified by column chromatography. [d]Determined by ^{1}H NMR integration of absorption peaks for the vinyl protons. [e]Solvent Et_2O. [f]Solvent CH_2Cl_2. [g]Starting material recovered. [h]Solvent DMF. [i]Unidentified byproducts found. [j]Solvent CH_3CN. [k]Solvent THF:Et_2O (1:2). [l]Reaction was run at −78 (26%), −40 (75%), and 0 °C (58%) for 1 h and then slowly warmed to rt. [m]Biphenyl was the major product of this reaction.

Table 3. Catalytic Procedure for γ-Alkylation of (*Z*)-Ethyl 2-Chloro-3-octenoate



entry	reagent (equiv)[a]	solvent[b]	yield (%)[c]	product	6:7:8[d]
1[e]	^{n}BuMgCl, CuCN (0.15)	THF	70	**6a**	94:0:6[f]
2[e]	^{n}BuLi, CuCN·2LiCl (0.33)	THF	72	**6a**	100:0:0[f]
3[e]	^{n}BuMgCl, CuCN (0.33)	THF	88	**6a**	91:0:9[f]
4[e]	^{n}BuLi, CuCN (0.33)	Et_2O	67	**6a**	100:0:0[f]
5[e]	^{n}BuMgCl, CuCN (0.33)	Et_2O	81	**6a**	98:0:2[f]
6[g]	^{n}BuLi, CuCN (0.33)	Et_2O	81	**6a**	100:0:0[h]
7[g]	^{n}BuMgCl, CuCN (0.33)	Et_2O	97	**6a**	98:0:2
8[g]	^{n}BuLi, CuCN (0.33)	THF	56	**6a**	100:0:0[h]
9[g]	^{n}BuMgCl, CuCN (0.33)	THF	76	**6a**	74:0:16
10[g]	MeMgBr, CuCN (0.33)	Et_2O	44	**6b**	88:0:12

[a]Cuprate reagent was prepared over 30 min from −60 to −30 °C from solid CuCN unless otherwise noted. [b]Solvent with a composition for the reaction of solvent/organometallic solvent of 10/1. [c]Upon the basis of isolated material purified by column chromatography. [d]Isomer ratios were determined from integration of the ^{1}H NMR absorption peaks for the vinyl protons. [e]Reaction quenched after 4 h at −78 °C. [f]Starting material recovered. [g]Reaction done for 1 h at −78 °C and then slowly warmed up to room temperature for an overall reaction time of 4 h. [h]Unidentified byproducts found.

bis α-(*N*-carbamoyl)alkylcuprates (entries 14, 22, and 29) giving significantly lower yields. The coupling of *N*-Boc-2-pyrrolidinylcuprates with substrates **5a−d** and **4a,b** could not be accomplished. Formation of homocoupling products

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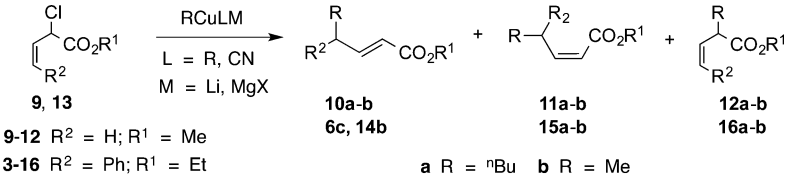
Table 4. Cuprate Allylic Alkylation of Methyl 2-Chloro-3-butenoate (9) and (*Z*)-Ethyl 2-Chloro-4-phenyl-3-butenoate (13)



entry[a]	halide	reagent (equiv)[b]	major isomer	yield (%)[c]	**10**:**11**:**12**[d] or **14**:**15**:**16**
1	**9**	^{n}BuCuCNLi (1.2)	**10a**	35	89:11:0[e]
2	**9**	^{n}BuCuCNLi (0.75)	**10a**	38	91:9:0[e]
3	**9**	^{n}BuCuCNMgCl (0.75)	**10a**	31	88:12:0[e]
4	**13**	^{n}BuCuCNLi (1.2)	**6c**	93	55:0:45
5[f]	**13**	^{n}BuCuCNLi (1.2)	**6c**	76	75:0:25
6[f]	**13**	^{n}BuLi (1.2)/CuCN (0.33)	**6c**	62	85:0:15[e]
7	**13**	^{n}BuCuCNMgCl (1.2)	**16a**	80	30:0:70
8[f]	**13**	^{n}BuCuCNMgCl (1.2)	**6c**	67	51:0:49[g]
9	**13**	MeCuCNLi (1.2)	**14b**	88	84:0:16
10[f]	**13**	MeLi (1.2)/CuCN (0.33)	**14b**	53	78:0:22[e]
11	**13**	MeCuCNMgBr (1.35)	**16b**	91	28:0:72

[a]THF as solvent, unless otherwise noted, with a composition for the reaction of 10/1 solvent/organometallic solvent unless otherwise noted. Cuprates were prepared from THF-soluble CuCN·2LiCl. [b]Reactions were performed at −78 °C for 2 h and then warmed up to room temperature with overall stirring of 8−12 h. [c]Yields are based upon isolated products purified by column chromatography. [d]Isomer ratios were determined from integration of the ^{1}H NMR absorption peaks of the vinyl protons. [e]Unidentified byproducts found. [f]Solvent Et_2O. Cuprates were prepared from solid, insoluble CuCN [from −70 °C (or −60 °C, substoichiometric CuCN) to −40 °C (or −30 °C, substoichiometric CuCN)], by stirring for 30 min before cooling to −78 °C. [g]Starting material was recovered.

suggests that a single electron transfer (SET) reaction takes place over the intended allylic substitution.[20]

Upon completion of the leaving group and cuprate composition studies, we turned our attention to exploring the scope of ligand efficacy in these allylic substitution reactions. Although the phosphate, mesylate, and pentafluorobenzoate leaving groups[2,19] all gave comparable yields, ethyl (*Z*)-2-chloro-3-octenoate (**4a**) was chosen for further study because it afforded higher product yields upon reaction with PhCuCNLi and $CH_3N(Boc)CH_2CuCNLi$ (entries 25 and 26). Additionally, **4a** was easier to prepare and was stable to *Z* to *E* isomerization in the refrigerator for 6 months.[22]

Although lithium di-*n*-butylcuprate and lithium *n*-butyl(cyano)cuprate reagents gave comparable yields of **6a** in THF and Et_2O (Table 2, entries 1−3), low yields were obtained in CH_2Cl_2 (entry 4), DMF (entry 5), or CH_3CN (entry 6). For the solvents CH_2Cl_2, DMF, and CH_3CN, the cuprate reagent was prepared by mixing RLi and CuCN·2LiCl in THF and then adding the desired solvent. Utilization of magnesium *n*-butylcuprate reagents afforded similar yields of **6a** but slightly reduced S_N2':S_N2 regioselectivity (entries 7 and 8). It is interesting to note that the S_N2-regioisomer (i.e., **8a**) retained the alkene *Z*-configuration. Similar results were obtained for the Me, ^{s}Bu, and ^{t}Bu transferable ligands, giving modest to good yields of **6b**, **6f**, and **6e**, respectively, and excellent regioselectivity (entries 9−13). Again, the alkyl(cyano)cuprates gave higher yields than the dialkylcuprate reagents (entries 9 vs 10, and 12 vs 13). Good results were obtained for the *N*-(*tert*-butoxycarbonyl)-*N*-methylaminomethylcuprate reagent to give **6d** (entry 14) but the procedure could not be extended to the 2-pyrrolidinylcuprate analogue. The arylcuprates generally gave good chemical yields of **6c**, **6g**, and **6h** and excellent S_N2':S_N2-regioselectivity (entries 16−18) with the exception of Ph_2CuLi (entry 15), which gave low yields of **6c** due to homocoupling and biaryl formation.[20,21] The magnesium allylcuprate reagents displayed the same pattern (entries 19 and 20), giving lower yields of **6i** for the diallylcuprate reagent.

In pursuit of a catalytic procedure, several reactions were run using 0.15−0.33 equiv of solid CuCN with either alkyl lithium or magnesium reagents. Initially the reaction mixtures were quenched at −74 °C, giving good yields of products **6a,b** (Table 3, entries 1−5) but accompanied by recovery of 10−20% of starting material. The reactions could be brought to completion by slowly allowing the reaction mixture to warm to room temperature (entries 6−10), and with the magnesium cuprate a yield of 97% could be achieved (entry 7) with the *n*-butyl Grignard reagent. Utilization of Grignard reagents generally gave lower S_N2':S_N2-regioselectivity (entries 1, 3, 5, 7, 9, and 10), while regiospecificity was obtained with the lithium reagents (entries 2, 4, 6, and 8). In accord with prior studies,[2e] use of lithium reagents required a minimum of 0.33 equiv of a Cu(I) salts, while lower amounts of Cu(I) salts could be employed with the Grignard reagents (entry 1). The stability of these substrates to the presence of organolithium reagents is noteworthy.

Two additional substrates were examined to explore the scope of the reaction. These included the γ-unsubstituted analogue **9**[23] and the phenyl-substituted derivative **13**[15,24] (Table 4). Allylic chloride **9** gave low yields of alkylation products accompanied by an orange brown precipitate in the reaction mixture, indicative of polymer formation,[25] and significant amounts of the *Z*-alkene stereoisomer **11a** when reacted with ^{n}BuCuCNM (M = Li, MgCl, entries 1−3). The phenyl-substituted derivative **13** gave the S_N2-substitution products **16a,b** either in significant amounts (entries 4−6 and 8−10) or as the major stereoisomer (e.g., entries 7 and 11). For the lithium cuprates, higher S_N2'-regioselectivity was achieved in Et_2O than in THF (entries 5 and 6 vs 4) and with substoichiometric amounts of CuCN (entry 6), where R_2CuLi is presumed to be the active agent. The magnesium *n*-butyl(cyano)cuprate gave the S_N2-product **16a** as the major

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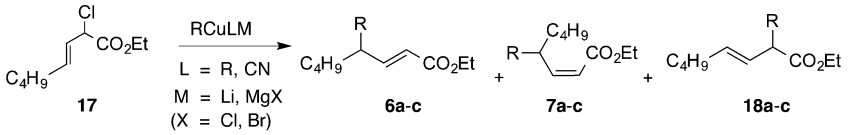
Table 5. Reaction of (*E*)-Ethyl 2-Chloro-3-octenoate with Organocuprate Reagents



a R = ^{n}Bu **b** R = Me **c** R = Ph

entry[a]	reagent (equiv)[b]	yield (%)[c]	product	6:7:18[d]
1	^{n}BuCuCNLi (1.2)	70	**6a**	89:6:5
2[e]	^{n}BuCuCNLi (1.2)	83	**6a**	98:0:2
3[f]	^{n}BuCuCNLi (1.2)	9	**6a**	100:0:0[g]
4	^{n}Bu$_2$CuLi (1.0)	56	**6a**	84:8:8[h]
5	^{n}BuCuCNMgCl (1.2)	97	**6a**	82:14:4
6[e]	^{n}BuCuCNMgCl (1.2)	71	**6a**	86:10:4
7[f]	^{n}BuCuCNMgCl (1.2)	49	**6a**	32:23:45
8	^{n}Bu$_2$CuMgCl (1.0)	71	**6a**	79:17:4
9[i]	^{n}BuCuCNMgCl (1.2)	96	**6a**	83:12:5
10	^{n}BuMgCl (1.2), CuCN (0.15)	95	**6a**	81:15:4
11[j]	^{n}BuMgCl (2.10), CuCN (1.05)	95	**6a**	76:24:0
12[k]	^{n}BuMgCl (1.2), CuCN (0.15)	60	**6a**	86:14:0
13[e,k]	^{n}BuLi (1.2), CuCN (0.33)	77	**6a**	97:1:2
14[e,k]	^{n}BuMgCl (1.2), CuCN (0.33)	88	**6a**	91:7:2
15	MeCuCNLi (1.2)	55	**6b**	97:1:2
16	Me$_2$CuLi (1.0)	37	**6b**	100:0:0[h]
17	MeCuCNMgBr (1.2)	89	**6b**	84:3:13
18	Me$_2$CuMgBr (1.0)	67	**6b**	94:2:4
19[f]	MeCuCNMgBr (1.2)	85	**6b**	88:3:9
20	MeMgBr (1.2), CuCN (0.15)	95	**6b**	98:1:1
21[j]	MeMgBr (2.10), CuCN (1.05)	87	**6b**	100:0:0
22	PhCuCNLi (1.1)	43	**6c**	100:0:0[h]

[a]THF as solvent with a composition for the reaction of 10/1 solvent/organometallic solvent unless otherwise noted. Cuprates were prepared from THF soluble CuCN·2LiCl. [b]Reactions were performed at −78 °C for 2 h and then warmed up to room temperature with overall stirring for 8−12 h. [c]Yields are based upon isolated products purified by column chromatography. [d]Ratios were determined by ^{13}C NMR peak heights. [e]Solvent Et$_2$O. Cuprates were prepared from solid insoluble CuCN [from −70 °C (or −60 °C, substoichiometric CuCN) to −40 °C (or −30 °C, substoichiometric CuCN), stir for 30 min before cooling to −78 °C]. [f]Solvent CH$_2$Cl$_2$. Cuprates prepared from CuCN·2LiCl in THF and then diluted 10 times with CH$_2$Cl$_2$. [g]Starting material recovered. [h]Unidentified byproducts found. [i]Reaction conditions: −40 °C for 1 h and then slowly warm to 25 °C. [j]Posner's procedure: LiCl was not used. Cuprate formation and reaction conditions: 30 min at −78 °C, reaction mixture quenched at −78 °C 30 min after the addition of the electrophile. [k]Reaction quenched after 4 h at −78 °C.

regioisomer in THF (entry 7) and a nearly 1:1 mixture of stereoisomers in Et$_2$O (entry 8). The putative reagent Me$_2$CuLi gave a slightly lower S_N2'-regioselectivity (entry 10) than MeCuCNLi (entry 9), although different solvents were employed. A less reactive magnesium methyl(cyano)cuprate reagent gave the S_N2-substitution product **16b** as the major isomer in THF (entry 11).

Posner and co-workers had reported the clean S_N2'-methylation of (*E*)-*α*-chloro-*β*,*γ*-unsaturated esters but noted complex product mixtures for other alkylcuprate reagents.[5] We decided to reinvestigate this reaction in order to explore the role of substrate *E*:*Z* geometry (Table 5). As observed by Posner and co-workers, *E*-stereoisomer **17** afforded more complex reaction mixtures upon reaction, with cuprate reagents generally yielding mixtures of S_N2'-derived *E*:*Z* stereoisomers (i.e., **6** and **7**) and the S_N2-regioisomer **18**. The highest regio- and stereoselectivity for **6a** was achieved with lithium *n*-butyl(cyano)cuprate (entries 1−3). Although the greatest selectivity was achieved in CH$_2$Cl$_2$ (entry 3), this solvent afforded very low product yields. The magnesium *n*-butylcuprates gave poor stereo- and regioselectivity (entries 5, 6, and 8−12) with the lowest yields and selectivities observed in CH$_2$Cl$_2$ (entry 7). For both the lithium and magnesium cuprates, utilization of substoichiometric amounts of CuCN afforded excellent regio- and stereoselectivities (entries 13 and 14). Consistent with Posner and co-worker's report,[5] the magnesium methylcuprates gave high chemical yields and selectivities for **6b** under both stoichiometric (entries 17−19, 21) and catalytic conditions (entry 20). The lithium cuprates gave excellent selectivities but lower chemical yields (entries 15 and 16). The phenyl(cyano)cuprate gave modest chemical yields of **6c** but excellent regio- and *E*:*Z*-stereoselectivity (entry 22).

In an effort to gain some mechanistic insight into the regio- and stereoselectivity of these reactions, several relative rate and competition experiments were performed (eqs 1−4 in Chart 1). Relative rate experiments on **4a** (eq 1, Chart 1) revealed that the lithium cuprate was only slightly faster than the magnesium cuprate (i.e., 1% vs 12% recovered **4a** after 30 min at −78 °C) and that the ^{n}BuCuCNLi reagent reacted with **4a** faster than the MeCuCNLi reagent. The former reagent, prepared from CuCN, was only slightly faster in THF than in Et$_2$O. These experiments show that the relative rate of reaction of **4a** with these cuprates is comparable, regardless of the metal cation (i.e., Li$^+$ or MgCl$^+$) or ethereal solvent (i.e., THF or Et$_2$O). The rate of allylic substitution is not sensitive to the electronic

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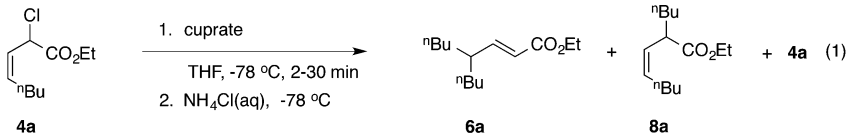
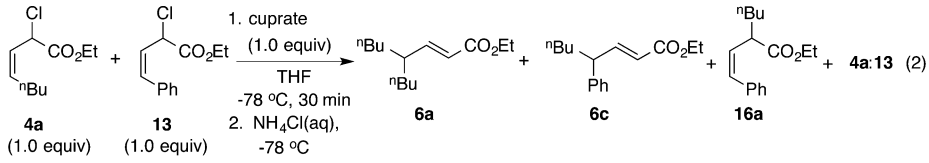
Chart 1



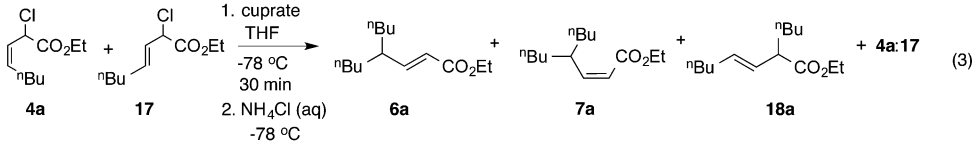
Cu(I) salt	reagent			
CuCN·2LiCl	^{n}BuCuCNLi (1.1 equiv)	99	-	1[a]
CuCN	^{n}BuCuCNLi (1.0 equiv)	86	-	14
CuCN	^{n}BuCuCNLi (1.0 equiv), Et_2O	80	-	20
CuCN·2LiCl	^{n}BuCuCNMgCl (1.1 equiv)	84	4	12[b]
CuCN·2LiCl	MeCuCNLi (1.1 equiv)	76	-	24

[a] The same ratio was observed after quenching at 15 min. and at 2 min. [b] The ratios of 84:5:11 and 87:5:8 were observed upon quenching at 15 and 2 min respectively.

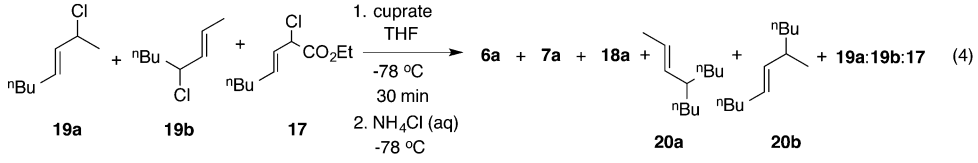


^{n}BuCuCNLi	59 (55)	21 (23)	20 (22)	46:54
^{n}BuCuCNMgCl	57 (55)	15 (18)	28 (27)	46:54

( ) ratios determined from ^{13}C-peak heights



^{n}BuCuCNLi (1.0 equiv)	95	2	3	61:39
^{n}BuCuCNMgCl (1.0 equiv)	92	5	3	62:38



^{n}BuCuCNLi (1.0 equiv)	80	5	5	2	8	30:58:12
^{n}BuCuCNMgCl (1.0 equiv)	78	10	3	1	3	34:49:16

properties of the substituent at the 4-position of **4a** or **13**, since both give comparable product yields and recovered starting material in a competition experiment (eq 2, Chart 1). Surprisingly, the trans isomer **17** reacted nearly twice as fast as the cis isomer **4a**, as evidenced by a competition experiment (eq 3, Chart 1). Finally, **17** is roughly 5−7 times more reactive than a mixture of allylic chlorides **19a,b** (eq 4, Chart 1) revealing the accelerating effect of the ester functionality.

In the light of these results, we decided to briefly re-examine the α-cyano allylic phosphates originally studied by Najera and co-workers.[7] The cyanophosphates **21a** and **21b**,[26] prepared by an established procedure,[27] exhibited S_N2'-regiospecificity and modest *E*:*Z* stereospecific alkylation (Table 6), with the *E*-isomer **21a** giving the *Z*-alkenylnitrile **23** preferentially (entries 1−5) and the *Z*-isomer **21b** affording predominantly the *E*-alkenylnitrile **22** (entries 6−10). For **21a**, the highest *E*:*Z*-stereoselectivity was achieved with the magnesium cuprate prepared from CuBr·SMe_2. The *Z*-isomer **21b** gave *E*:*Z* selectivity for both the lithium and magnesium cuprates (entries 6−10) and the lowest selectivity for the lithium cuprate prepared from CuBr·SMe_2 (entry 9).

DISCUSSION

The primary control element in cuprate -mediated allylic substitution reactions is the preference for anti-S_N2'-substitution pathways,[28] which are enhanced by use of alkyl- or aryl(cyano)cuprate reagents,[2d,29] magnesium cuprates,[2d,29] and phosphate leaving groups.[2d] The greater S_N2'-regioselectivity observed for RCuCNLi reagents has been attributed to a trans effect with the more electron rich R-group on the cuprate reagent preferring (i.e., lower transition state energy) to be trans to the substrate leaving group (cf. Scheme 4).[29] Predominant formation of the *E*-diastereomer reflects the influence of $A^{1,3}$-strain[30] in the transition state of the substrate−cuprate interaction (Scheme 2).[2d,3a] For *Z*-substrate **4a**, the ^{n}Bu/CO_2Et $A^{1,3}$-strain in the transition state arising from

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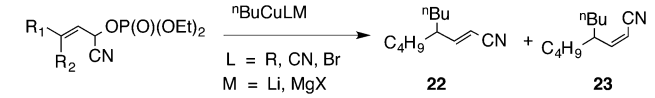
Table 6. γ-Alkylation of Allylic Cyanohydrin Phosphates

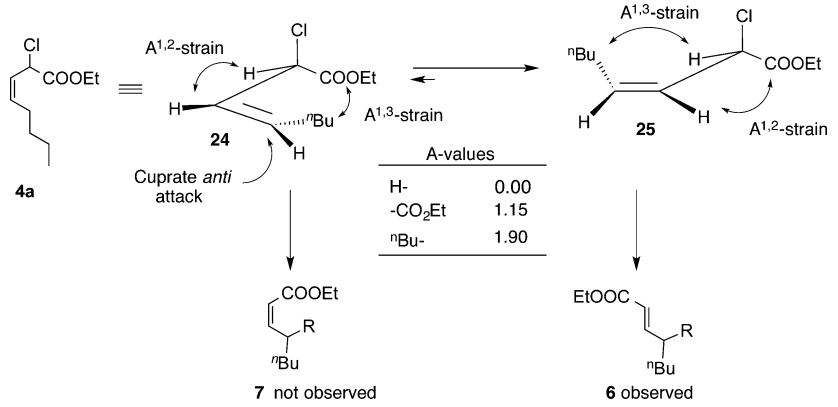


21a R^1 = $^nC_4H_9$, R^2 = H
b R^1 = H; R^2 = $^nC_4H_9$

entry[a]	substrate	reagent (equiv)[b]	yield (%)[c]	major isomer	22:23[d]
1[e]	**21a**	^{n}BuCuCNLi (1.2)	60	**23**	20:80
2	**21a**	^{n}BuCuCNLi (1.2)	66	**23**	32:68
3	**21a**	^{n}BuLi (1.2)/CuCN (0.33)	63	**23**	40:60
4	**21a**	^{n}BuLi (1.2)/CuBr·Me_2S (1.2)	68	**23**	20:80
5	**21a**	^{n}BuMgCl (1.2)/CuBr·Me_2S (1.2)	62	**23**	8:92[f]
6[e]	**21b**	^{n}BuCuCNLi (1.2)	69	**22**	70:30[g]
7	**21b**	^{n}BuLi (1.2)/CuCN (1.2)	70	**22**	85:15[f]
8	**21b**	^{n}BuCuCNLi (1.2)	75	**22**	88:12
9	**21b**	^{n}BuLi (1.2)/CuBr.Me_2S (1.2)	72	**22**	67:33[g]
10	**21b**	^{n}BuCuCNMgCl (1.2)	68	**22**	82:18

[a]THF as solvent with a composition for the reaction of 10/1 solvent/organometallic solvent unless otherwise noted. Cuprates were prepared from THF-soluble CuCN·2LiCl unless otherwise noted. Cuprates (entries 1−2, 6−7) were prepared from solid, insoluble CuCN (from −70 to −40 °C, stir for 30 min before cooling to −78 °C). [b]Reactions done at −78 °C for 2 h then warmed up to rt with overall stirring of 8−12 h. [c]Isolated yield. [d]*E*:*Z* isomer ratios were determined by integration of the ^{1}H NMR absorption peaks for the vinyl protons. [e]Solvent Et_2O. [f]Starting material recovered. [g]Unidentified byproducts found.

Scheme 2. Model for S_N2'-Regioselectivity in the Reactions of (*Z*)-α-Chloro-β,γ-unsaturated Esters with Organocuprates



conformer **24** and leading to **7** is sufficiently greater[31] than the ^{n}Bu/H $A^{1,3}$-strain in the transition state arising from **25** and leading to **6** such that only the *E*-diastereomer **6** is observed in these reactions (Tables 1−3). Although no S_N2-substitution product is observed for the lithium cuprate reagents (Tables 1−3) except in DMF (Table 2, entry 5), small amounts are observed for magnesium cuprates (Tables 2 and 3), where utilization of magnesium cuprates gives greater amounts of S_N2-product in THF than in Et_2O (Table 2, entries 7 and 8; Table 3, entries 3 vs 5, and 9 vs 7 for THF vs Et_2O). These results suggest that complexation phenomena[2d] (cf., $\mathbf{TS}_{Z\text{-enoate}}$ in Scheme 3) are not playing a role here, since the experimental results are inconsistent with solvent, cation (i.e., Li vs Mg), and trans effects.[2d] A slower reductive elimination step for the magnesium cuprates would allow sufficient time for equilibration between two σ-allyl copper(III) complexes[32] via a π-allyl copper(III) complex (cf. Scheme 4)[4d,32a,33,34] that is facilitated by THF.[34a] The propensity of magnesium cuprates to favor S_N2'-selectivity generally occurs under conditions that favor formation of RCuXMgX (X = heteroatom)[33a,34a] and the influence of the trans-effect (i.e, oxidative addition step) and does not mitigate against the additional influence of rates of reductive elimination upon S_N2':S_N2 selectivity ratios. Fast reductive elimination from the π-allyl copper(III) or enyl[σ + π] complex should favor greater S_N2'-regioselectivity.[29,33a,34] The single-point rate experiments (eq 1, Chart 1) are inconclusive, revealing that these reactions are very fast and the failure of the magnesium cuprates to go to completion may reflect the difficulty of accurate titration of Grignard reagent concentration. If the rate-determining step is oxidative addition, the influence of the rate of reductive elimination cannot be probed by kinetic studies. The increased formation of S_N2 byproducts with methyl magnesium cuprate even in Et_2O (Table 3, entry 10) is consistent with the speculative influence of reductive elimination rates.

Similar consideration of allylic strain can account for the lower *E*:*Z*-diastereoselectivity observed in the allylic substitution reactions of the *E*-substrate **17**. Here the combination of $A^{1,3}$- and $A^{1,2}$-strain[30] in the transition state is such that a mixture of *E* (i.e., **6**) and *Z*-diastereomers (i.e., **7**) are formed (Scheme 3). As expected, $A^{1,3}$-strain predominates[30b] as a controlling factor and the *E*-enoate **6** is formed as the major isomer. In the reactions of the *E*-diasteromer **17**, magnesium cuprates give larger amounts of the *Z*-diastereomeric product **7**

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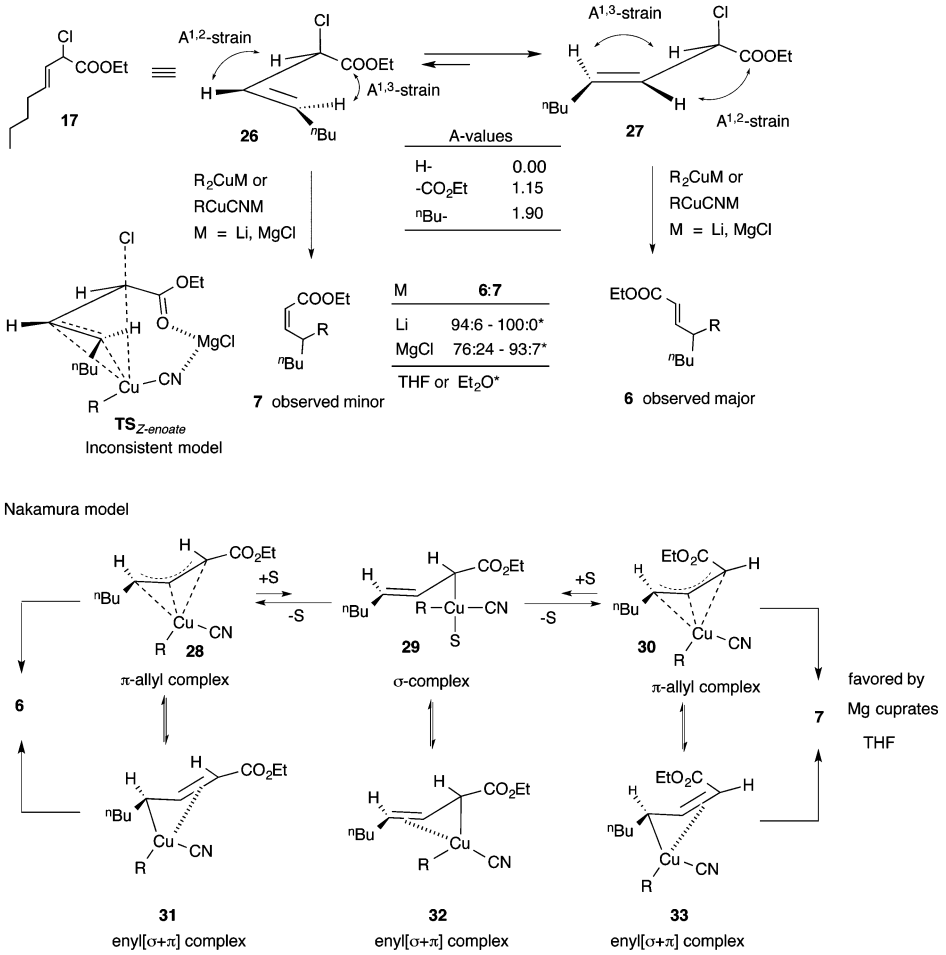
Scheme 3. Model for S_N2'-Regioselectivity in Reactions of (*E*)-α-Chloro-β,γ-unsaturated Esters with Organocuprates



than the lithium cuprates. Although it is tempting to invoke a complexation model (e.g., $TS_{Z\text{-enoate}}$, Scheme 3) given the ubiquity of coordination effects invoked in computational models[29,34,35] of cuprate reactions, solution NMR studies,[36] and cuprate X-ray structure determinations,[37] this model is inconsistent with the greater *E*-selectivity observed in Et_2O than in THF. The solvent and counterion (i.e., Li^+ vs $MgCl^+$) effects are more consistent with a solvent-induced isomerization[34a] of the C2-stereogenic center attached to the Cu-atom in an intermediate σ-copper(III) complex (e.g., **29** of Scheme 3, Nakamura model). Isomerization (i.e., **29** to **30**) will be enhanced in THF, where cuprate reagents can form solvent-separated ion pairs (SSIP), in contrast to Et_2O, where they tend to exist as contact ion pairs (CIP).[36a,b] Although it is tempting to attribute the greater amounts of isomerization observed for the magnesium cuprates to slower reductive elimination rates, attempts to gauge the relative rates of lithium vs magnesium cuprates were inconclusive (eq 1, Chart 1).[38]

The fact that trans isomer **17** reacts nearly twice as fast as the cis isomer **4a** and 5−7 times faster than **19a**/**19b** with both the magnesium and lithium *n*-butyl(cyano)cuprate reagents (eq 3, Chart 1) indicates that steric factors (i.e., $A^{1,3}$- and $A^{1,2}$-strain) are not insignificant. Significantly, although enantioenriched chiral α-(*N*-carbamoyl)alkylcuprate reagents show good configurational stability, isomerization is observed in slow reactions and is faster in THF than in Et_2O.[39] RCuCNM reagents undergo faster reductive elimination[29] than R_2CuM reagents and would be expected to display higher *E*-selectivity. This is in fact observed for the ^{n}Bu cuprates (Table 5, entries 1 vs 4, and 5 vs 8) but not for the less reactive methylcuprates (entries 15 vs 16, and 17 vs 18), although the differences are very small and within experimental error.

The excellent regioselectivity observed for **17** is consistent with computational studies that show that the activation energy for reductive elimination increases for electron-withdrawing groups alpha to the Cu center[34a] and should be greater for **32** than for either **31** or **33**, consistent with the observed product ratios in THF and Et_2O (Table 5). Dichloromethane provides an exception where the S_N2-product is the major isomer (Table 5, entry 7). It is interesting to note that the faster reaction rate of **17** relative to those of **19a**/**19b** in competition experiments (eq 4, Chart 1) must be manifest in the oxidative addition step.

Allylic chloride **9** gave no S_N2-substitution products and mixtures of *E*:*Z* geometrical isomers (Table 4) arising from S_N2'-allylic substitution, consistent with the trans effect (i.e., R group on copper trans to the Cl leaving group in $TS_{R,Cl(trans)}$) and lack of substituents on C4. For C1-monosubstituted π-allylcopper complexes, the transition state energy for reductive elimination is always greater for C1 than for C3, and both energies are raised by electron-withdrawing groups (EWG).[34a] The lower *E*:*Z*-stereoselectivity for **9** vs **4a** reflects the relative *A*-value of the H and ^{n}Bu substituents in **9** and **4a**, respectively.

For allylic chloride **13** containing a 4-phenyl substituent, the trans effect should render $TS_{R,Cl(trans)}$ more stable than $TS_{CN,Cl(trans)}$ and this should normally lead to significantly enhanced S_N2'-regioselectivity for RCuCNM (M = Li, MgX)

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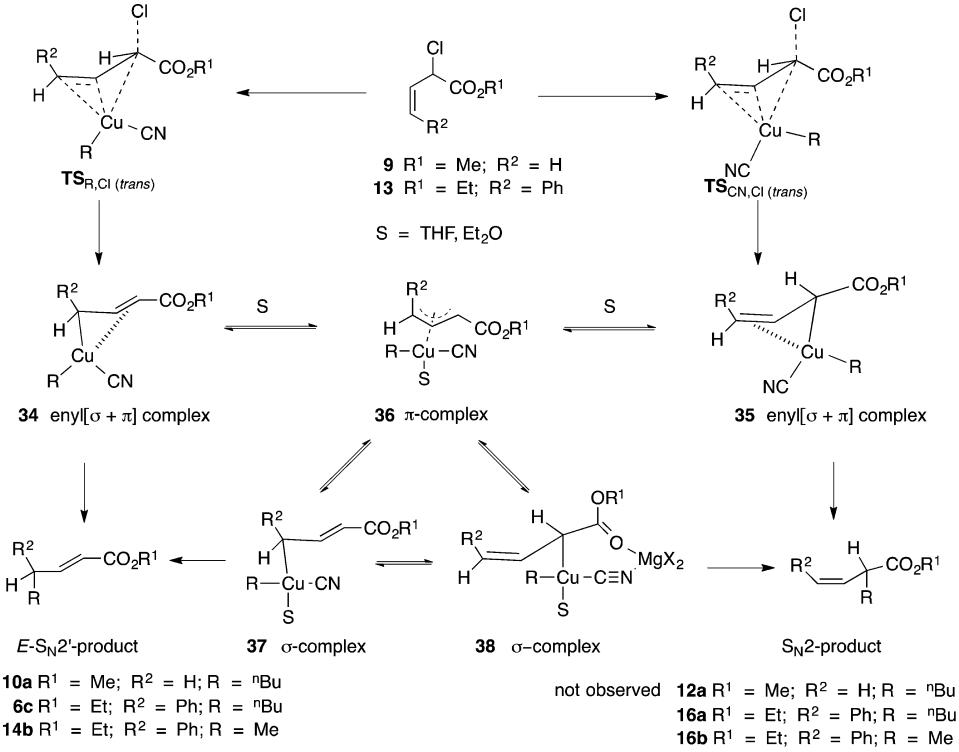
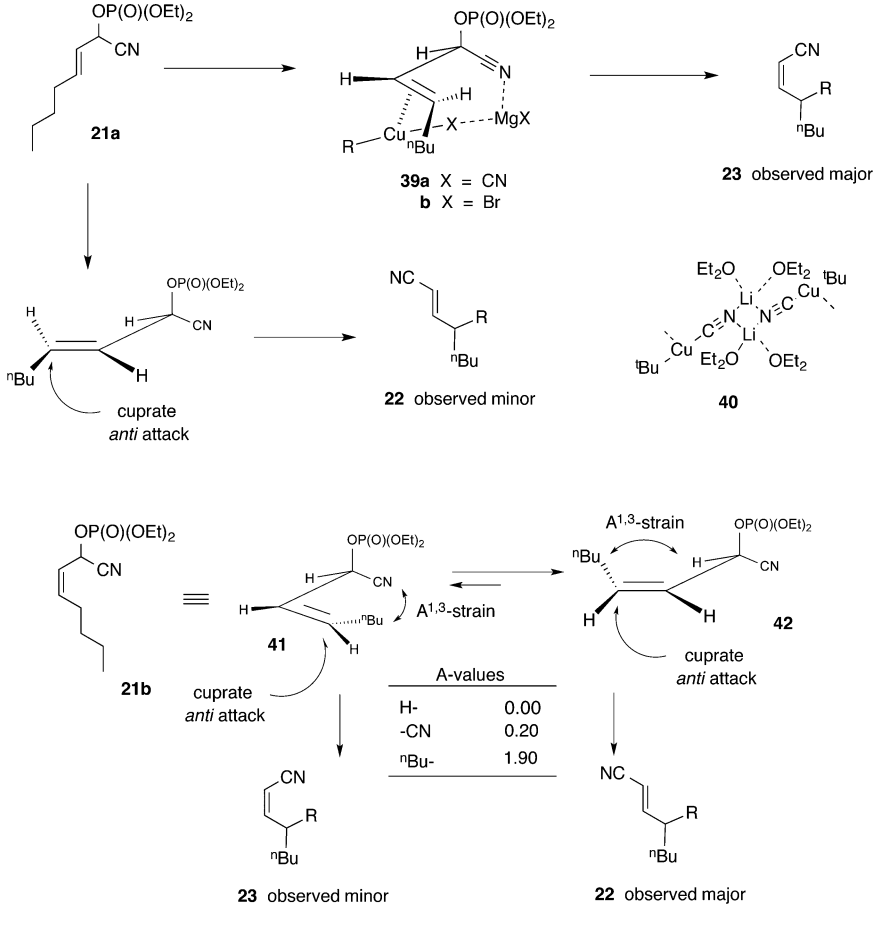
Scheme 4. Model for S_N2' and S_N2 Regioselectivity in the Reactions of Lithium and Magnesium Cuprates with (*Z*)-α-Chloro-β,γ-enoates 9 and 13



Scheme 5. Models for *E*:*Z* Diastereoselectivity in the Reactions of Magnesium Cuprates with *E*-Cyanohydrin Phosphate 21a and *Z*-Cyanohydrin Phosphate 21b



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reagents,[29] contrary to our observations (Table 4). For the ^{n}Bu cuprates, reaction of the Li-cuprate in THF gives large amounts of the S_N2-product (45%), while the Mg-cuprate is S_N2-selective (70%) in THF (S_N2'-selective in Et_2O, 51%), consistent with conversion of a σ-enyl complex **34** to a π-allyl complex **36** via solvent participation.[34a] π-Allyl complex **36** provides a mechanistic pathway for equilibration of σ-complexes **37** and **38**. The magnesium counterion increases the amount of S_N2-product observed, perhaps by decreasing the rate of product formation (cf. competition experiment, eq 1, Chart 1), thereby allowing equilibration of the two σ-complexes (i.e., **37** and **38**) by a coordination effect with the ester functionality in **38** or by subtle changes in the cuprate structure. A similar S_N2-regioselectivity for ^{n}BuCuCNMgCl (30:70, THF) and MeCuCNMgCl (28:72, THF) points to a chelation effect (e.g., Mg^+ coordination of the CN and ester groups) favoring σ-complex **38**, since the two cuprates are expected to have different steric and reactivity profiles (cf. eq 1, Chart 1). Although chelation effects are generally more manifest in Et_2O than in THF,[2d] THF is expected to facilitate the equilibration between σ-complexes[34a] **37** and **38**, and **38** may either be stabilized[34a,40] relative to **37** by electronic effects (i.e., the ester EWG raises the energy of activation for reductive eliminatio-n[34a]) or by chelation. Computational studies[34a] indicate that the transition state leading from enyl[$\sigma + \pi$] complex **34** should be lower in energy, affording S_N2'-product **6c**, which is formed in modest but diminished selectivity compared to **4a** in ether and for lithium cuprates. Increased amounts of S_N2-products are observed in THF and for magnesium cuprates, suggesting that these conditions favor reaction through σ-complex **38** or enyl[$\sigma + \pi$] complex **35**. In this regard, an α-EWG reduces the rate of reductive elimination (i.e., **35** should be slower than **34**), but alkene π-donation to the cuprate p-orbital should favor **35** over **34**.[34a] The increased formation of S_N2-products from **13** is inconsistent with the computational prediction[34a,40] of substituent electronic effects (e.g., Ph vs CO_2Et), suggesting that steric factors (i.e., alkene substituents and cuprate structure) are playing a role in the transition state for reductive elimination. Allylic chlorides **4a** (S_N2'-regioselective) and **13** (nonregioselective) display comparable rates in competition experiments for both the lithium and magnesium cuprates (cf. eq 2, Chart 1), and the S_N2-regioselectivity for the magnesium cuprate with **13** nearly doubles compared to that of the lithium cuprate. The importance of the trans effect in the reactions of **13** can be seen in the slightly greater S_N2'-selectivity of MeCuCNLi in THF (i.e., 84:16), vs the combination of MeLi (1.2 equiv)/CuCN (0.33 equiv) presumably forming Me_2CuLi ($S_N2':S_N2$, 78:22, Table 4, entries 9 vs 10), even though the latter reaction was conducted in Et_2O. The greater $S_N2':S_N2$-regioselectivity for reaction of **13** with MeCuCNLi (84:16) vs ^{n}BuCuCNLi (55:45) in THF again suggests that steric interactions between the phenyl substituent and cuprate ligand (e.g., Me vs ^{n}Bu) are also playing a role.

The cyanohydrin phosphates **21a,b** displayed modest regiospecificity with *E*-**21a** affording *Z*-enenitrile **23** and *Z*-**21b** affording *E*-enenitrile **22** predominantly. The *E*-isomer **21a** has accessible a gauche conformer (with respect to the vinyl and CN substituents) with low $A^{1,3}$-strain (i.e., vinyl H, CN) that allows for magnesium complexation to the nitrile N-atom[41] and copper complexation to the alkene (i.e., complex **39**, Scheme 5). In the solid state, alkyl(cyano)cuprates exist as oligomers where the monomeric units reveal the propensity of metal cation coordination through the cyano ligands (e.g., **40**).[37a,b] The high Z-selectivity achieved with $CuBr{\cdot}SMe_2$ on *E*-**21a** suggests that the Br-ligand on copper can play the same role as the cyanide ligand in bridging the magnesium cation between the allylic substrate and the cuprate reagent (i.e., **39a,b**). Previous studies [RMgX (3.0 equiv), CuX (1.5 equiv)] only examined the *E*-isomer (i.e., an analogue of **21a**) and concluded that steric factors involving the transferable ligand were unimportant in determining the Z-selectivity.[7] Slightly higher Z-stereoselectivity is achieved in Et_2O than in THF for **21a** (Table 6, entries 1 vs 2), with use of $CuBr{\cdot}SMe_2$ for preparation of the lithium cuprates (entries 4 vs 2) and with magnesium rather than lithium cuprates (entries 5 vs 4), consistent with complexation phenomena.[2d] $A^{1,3}$-strain generally leads to formation of the *E*-diasteromeric alkene product, and formation of the *Z*-isomer is often accounted for on the basis of intramolecular cuprate complexation to a heteroatom moiety within the substrate.

Coherently, the preference of *Z*-isomer **21b** for formation of *E*-enenitrile **22** is controlled by $A^{1,3}$-strain (i.e., ^{n}Bu, CN) in the transition state, and the stereoselectivity is relatively consistent across cuprate reagents. The use of Et_2O, ^{n}BuLi/$CuBr{\cdot}SMe_2$, and magnesium cuprates gave lower *E*:*Z*-selectivity for **21b** than ^{n}BuCuCNLi (Table 6, entries 6, 9, and 10, respectively, vs 7 and 8) as expected for conditions that should favor cuprate nitrile (i.e., substrate) complexation and reaction from conformer **41**. Again, the examination of both *E*-**21a** and *Z*-**21b** revealed the varied importance of $A^{1,3}$-strain in the transition state of the oxidative addition step.

■ CONCLUSIONS

In summary, cuprate alkylation of β,γ-unsaturated esters and nitriles containing an α-nucleofuge substituent provides opportunities for remote C−C bond formation in the product enoates and enenitriles with control of regio- and stereochemistry dependent upon the alkene geometry in the substrate. The *Z*-alkenyl esters display complete regio- and stereoselectivity, while the *E*-alkenyl esters display diminished selectivities that can be enhanced by use of lithium instead of magnesium cuprates and in some cases by use of substoichiometric amounts of Cu(I) salts. In an asymmetric protocol, the *E*- and *Z*-alkenyl esters will afford enantiomeric products, allowing enantiodifferentiation to be achieved by either altering the configuration at the stereogenic center containing the leaving group or by changing the alkene configuration. The 100% regioselectivity in the S_N2' vs S_N2 pathway can be achieved with the combination of alkyl or aryl lithium cuprates and α-nucleofuge-substituted-*Z*-β,γ-unsaturated esters. The *E*- and *Z*-allylic cyanohydrin phosphates display modest regiospecificity arising from the ability of the nitrile functionality to effectively complex with the cuprate reagent in the *E*-isomer **21a**. The present work significantly extends the range of cuprate reagents and opportunities for regio- and stereocontrol in cuprate-mediated allylic substitutions in this class of substrates. Enantioenriched α-hydroxy-*Z*-β,γ-unsaturated esters can be prepared by the reduction of acetylenic α,β-ketoesters with alpine borane, providing access to an enantioselective protocol.[14]

■ EXPERIMENTAL SECTION

General. NMR spectra were recorded as $CDCl_3$ solutions on a 500 MHz instrument. The ^1H NMR chemical shits are reported as δ values in parts per million (ppm) relative to tetramethylsilane (TMS, δ = 0.00). The residual chloroform signal ($CHCl_3$ δ = 7.28) was used as

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reference. ^{13}C NMR chemical shifts are reported as δ values in parts per million (ppm) relative to TMS and the $CDCl_3$ signal (triplet, centerline δ = 77.0) as reference. Infrared (IR) spectra were recorded as neat samples (liquid films on NaCl plates). Gas chromatography mass spectrometry (GC–MS) measurements were performed on equipment coupled to a mass spectrometer with a quadrupole detector at 70 eV. Analytical thin layer chromatography (TLC) was performed on silica gel plates (200 μm with F254 indicator). Flash column chromatography was performed with 200–400 μm silica or with silica–$AgNO_3$ (10% by weight). Yields are reported as pure material after isolation by column chromatography. Compounds for high-resolution mass spectrometry (HRMS) were analyzed by positive mode electron ionization (EI) using a Q-TOF detector.

Materials. Tetrahydrofuran (THF) and diethyl ether (Et_2O) were distilled from sodium/benzophenone. All other solvents were dried over 4 Å molecular sieves. Commercially available alkyllithium solutions were titrated with *sec*-butyl alcohol and 1,10-phenanthroline.[42] Commercially available Grignard solutions were titrated with menthol and 1,10-phenanthroline.[43] Cuprates were made from CuCN dried under vacuum over P_2O_5 into an Abderhalden's drying tube and flame-dried LiCl. Cuprates in Table 2 (entries 4–6) were prepared first in THF and then diluted 10 times with the corresponding solvent (CH_2Cl_2, DMF, or CH_3CN). The glassware was flame-dried and cooled under nitrogen. Low-temperature baths (−78 °C) were made from dry ice and 2-propanol. All the reactions were carried out under positive pressure of nitrogen passed over a trap of desiccant agent (Drierite). Silica–$AgNO_3$ (10% by weight) was prepared with 30 g of 200–400 μm silica and 3.3 g of $AgNO_3$ dissolved in 8 mL of H_2O. The silver nitrate solution was added to the silica, and the mixture was ground with a mortar and pestle, dried for 2–3 h in an oven at 170 °C, and then stored and protected from light.

For compounds **2**, **3**, **6b**, and **14b**, ^{13}C NMR, ^1H NMR, GC–MS, and IR data reductions are included. These compounds have been fully characterized and reported.[13,16,44,45] For new compounds **4a**, **6a**, **6c**, **6d**, **6e**, **6g**, **6h**, **6i**, **13**, **16a**, **22**, and **23**, ^{13}C NMR, ^1H NMR, GC–MS, IR, and HRMS data reductions are provided.

General Procedure A. Synthesis of γ-Substituted-α,β-unsaturated Esters Using Alkyl(cyano)- or Dialkylcuprates (Tables 1 and 2). A round-bottom flask with a magnetic stir bar and with LiCl (2.0 mmol, 85 mg) was flame-dried and cooled under vacuum, CuCN (1.0 equiv, 1.0 mmol, 90 mg) was added inside of an AtmosBag (trade mark of Sigma-Aldrich) filled with N_2, and the flask was sealed with a rubber septum. The flask was connected to a N_2 line and then loaded with THF (6.0 mL), and the mixture stirred at room temperature for 20–30 min. This solution of CuCN·2LiCl was cooled at −78 °C and the alkyllithium or Grignard solution was added dropwise (for the preparation of cyanocuprates, RCuCNM, 1.0 equiv of alkyllithium or Grignard was added, and for the dialkylcuprates, R_2CuM, 2.0 equiv of alkyllithium or Grignard was used; M = Li, MgX). This mixture was allowed to stir for 30–45 min at −78 °C. For the formation of ArCuCNLi or Ar_2CuLi, the cuprate was stirred only for 15 min at −78 °C to avoid the formation of the byproduct, Ar–Ar. After this period, the *Z*-α-substituted-β,γ-unsaturated ester, **4a,b** or **5a–d** (0.85 mmol), was added quickly dropwise to the reaction mixture at −78 °C, the temperature was kept for 2 h at −78 °C, and then the reaction was allowed to warm to room temperature slowly for a total stirring time of 8–12 h. The mixture was quenched with a saturated aqueous solution of NH_4Cl, extracted with Et_2O three times, concentrated in vacuo, and purified (silica gel, 5% Et_2O/95% hexanes for products **6a–c,e–i** and 10% EtOAc/90% hexanes for product **6d**).

General Procedure B. Catalytic Procedure. Synthesis of γ-Substituted-α,β-unsaturated Esters from α-Chloro-β,γ-unsaturated Esters (Table 3). A round-bottom flask equipped with a magnetic stir bar and septum was flame-dried under N_2. CuCN (0.15–0.33 mmol) was added inside an AtmosBag, and the flask was sealed with a rubber septum; the flask was then connected to a N_2 line and the solvent (6.0 mL) was added. This mixture was cooled down to −60 °C and the alkyllithium (1.0 equiv, 1.0 mmol) or alkylmagnesium (1.0 equiv, 1.0 mmol) was added dropwise. The mixture was allowed to warm to −30 °C (30 min), and after this period, all the solid was dissolved and there was no indication of decomposition. The reaction mixture was cooled down to −78 °C, and the *Z*-α-chloro-β,γ-unsaturated ester **4a** (0.85 mmol, 173 mg) was added quickly dropwise. The mixture was kept at −78 °C over 4 h and quenched at this temperature for entries 1–5 (Table 3), and for entries 6–10 (Table 3), it was kept 1 h at −78 °C and then warmed up slowly to room temperature for a total stirring time of 4 h. It was quenched with a saturated aqueous solution of NH_4Cl, extracted with Et_2O three times, concentrated in vacuo, and purified (silica gel, 5% Et_2O/95% hexanes).

General Procedure C. S_N2' γ-Alkylation of Cyanohydrin Phosphates (Table 6) 21a and 21b. These compounds were synthesized by adapting procedures from Hoover and Stahl[26] and Najera and co-workers.[27] Alkylcyanocuprates were prepared as described in general procedure A. Cyanohydrin phosphate **21a** or **21b** (0.50 mmol) was quickly added dropwise to a −78 °C solution of ^{n}BuCuLM (0.60 mmol, L = CN, Br; M = Li, MgCl) in the corresponding solvent (5.0 mL). The reaction mixture was stirred for 2 h at −78 °C and then allowed to warm slowly to room temperature overnight. It was quenched with brine, extracted with Et_2O three times, concentrated in vacuo, and purified (silica gel with silver nitrate, 5% Et_2O/95% hexanes).

Ethyl 2-Hydroxy-3-octynoate (2). A round-bottom flask equipped with septum and a magnetic stir bar was flame-dried under N_2. THF (20 mL) and 1-hexyne (**1**) (2.3 mL, 20 mmol) were added, the mixture was cooled down to −78 °C, ^{n}BuLi (2.5 M in hexanes, 8.0 mL, 20 mmol) was slowly added, and the mixture was kept at this temperature over 1 h to complete the deprotonation of the alkyne. After this period, the solution was brought to −60 °C. In another flask, flame-dried $ZnBr_2$ (2.3 g, 10 mmol) was dissolved in THF (10 mL) and slowly added by cannula to the previous solution at −60 °C; once added, this new reaction mixture was allowed to warm from −60 to 0 °C over 45 min and was then kept at 0 °C over another 15 min. MeLi (1.5 M in Et_2O, 6.7 mL, 10 mmol) was then slowly added to the dialkylzinc solution. At this point the reaction mixture was stirred at 0 °C over 30 and 15 min at room temperature and then it was cooled down to −60 °C. Fleshly distilled ethyl glyoxylate (45 mmol) in toluene was added to the just prepared triorganoalkyl zincate solution. The mixture was allowed to stir over 2 h from −60 to −20 °C (it is important not to go over −20 °C to avoid the formation of byproducts), quenched at this temperature with a saturated aqueous solution of NH_4Cl, extracted with Et_2O three times, concentrated in vacuo, and purified (silica gel, eluding first with 50–75 mL of hexanes to remove the remaining toluene and then with 15% EtOAc/85% hexanes). After purification, a pale yellow oil was obtained (3.1 g, 85%): IR (neat) 3474 (br, s), 2960 (s), 2936 (s), 2874 (m), 2293 (w), 2237 (m), 1745 (s), 1633 (w), 1467 (m), 1369 (m), 1263 (m), 1205 (m), 1144 (m), 1073 (m), 731 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.91 (t, J = 7.3 Hz, 3H), 1.33 (t, J = 7.3 Hz, 3H), 1.37–1.44 (m, 2H), 1.46–1.54 (m, 2H), 2.22 (dt, J = 1.8, 7.3 Hz, 2H), 3.07 (d, J = 7.3 Hz, 1H), 4.31 (q, J = 7.3 Hz, 2H), 4.81 (dt, J = 1.8, 7.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.5, 14.0, 18.3, 21.8, 30.2, 61.6, 62.5, 75.5, 86.6, 170.8; mass spectrum m/z (relative intensity) EI 184 (0.10, M^+), 142 (5), 111 (100), 96 (12), 77 (12), 67 (11), 55 (39), 41 (25).

(*Z*)-Ethyl 2-Hydroxy-3-octenoate (3). A round-bottom flask provided with a magnetic stir bar and septum was loaded with the α-hydroxy-β,γ-acetylenic ester **2** (3.7 g, 20 mmol), Lindlar catalyst (Pd/$BaSO_4$/Pb, 200 mg), quinoline (2.6 mL, 22 mmol), and methanol (30 mL). A needle attached to a continuous source of H_2 was inserted deep inside the reaction mixture to allow positive flow of H_2; another needle was set in the septum to allow evacuation of the excess gas. This mixture was vigorously stirred and kept under slow but continuous flow of H_2 for 4–5 h. After this period, all the material was reduced to allylic alcohol **3**, and no evidence of over-reduced product was found. The reaction crude material was filtrated over a small layer of silica gel to remove the palladium catalyst and then eluted with 50% Et_2O/50% hexanes. Concentration in vacuo and purification (silica gel, 15% EtOAc/85% hexanes) gave a pale yellow oil (3.3 g, 88%): IR (neat) 3473 (br, s), 3011 (m), 2959 (s), 2931 (s), 2873 (m), 1736 (s), 1655 (w), 1466 (m), 1369 (m), 1201 (s), 1085

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(s), 1040 (m), 925 (w), 810 (w), 743 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.92 (t, J = 7.3 Hz, 3H), 1.27−1.45 (m, 7H), 2.17−2.25 (m, 2H), 3.00 (d, J = 6.0 Hz, 1H), 4.20−4.29 (m, 2H), 4.92 (dd, J = 0.9, 6.0 Hz, 1H), 5.31−5.38 (m, 1H), 5.70 (dt, J = 0.9, 7.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 14.0, 22.3, 27.6, 31.4, 61.9, 67.6, 126.1, 136.0, 147.2; mass spectrum m/z (relative intensity) EI 186 (0.20, M^+), 168 (4.5), 157 (1), 140 (1), 113 (45), 95 (66), 83 (6), 57 (100), 55 (11).

(*Z*)-Ethyl 2-Chloro-3-octenoate (4a). The *Z*-allylic alcohol **3** was chlorinated by adapting the procedure from Calzada and Hooz:[15] To a round-bottom flask equipped with a magnetic stir bar and septum was added the *Z*-α-hydroxy-β,γ-unsaturated ester **3** (4.0 g, 21.5 mmol) and CCl_4 (18 mL), and this mixture was stirred for 15−20 min at room temperature. Then PPh_3 (7.3 g, 28 mmol) was added in two portions and the mixture stirred for 15 min to ensure a complete dissolution of all the solid. A condenser was attached and the reaction mixture was heated in an oil bath up to 75 °C (external temperature). Higher temperatures should be avoided to prevent mixtures of cis and trans products. The reaction was followed by TLC and normally after 1.5 h it is complete; a bulky precipitated was present at this point. Once cooled down to room temperature, the reaction crude was filtered over a small layer of SiO_2, eluted with 20% Et_2O/80% hexanes, concentrated in vacuo, and purified (silica gel 3% Et_2O/97% hexanes). After purification, a pale yellow oil was obtained (3.7 g, 85%): IR (neat) 3032 (w), 2961 (m), 2933 (m), 2874 (m), 1747 (s), 1651 (w), 1466 (m), 1312 (m), 1262 (m), 1162 (s), 1027 (m), 819 (s) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.93 (t, J = 6.9 Hz, 3H), 1.29−1.45 (m, 7H), 2.12−2.22 (m, 2H), 4.25 (q, J = 6.9 Hz, 2H), 5.09 (d, J = 9.6 Hz, 1H), 5.66−5.79 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.8, 13.9, 22.2, 27.3, 31.2, 52.4, 62.2, 124.1, 163.9, 168.6; mass spectrum m/z (relative intensity) EI 204 (0.10, M^+), 169 (55), 141 (17), 125 (22), 95 (100), 81 (26), 67 (28), 55 (36), 41 (26); HRMS (EI) calcd for $[C_{10}H_{17}ClO_2]^+$ 204.0917, found 204.0915.

(*E*)-Ethyl 4-Butyl-2-octenoate (6a). Compound **6a** was prepared using general procedure A. After purification (silica gel, 5% Et_2O/95% hexanes), a colorless oil was obtained (182 mg, 95%): IR (neat) 2959 (s), 2930 (s), 2860 (s), 1722 (s), 1652 (m), 1466 (m), 1369 (m), 1307 (m), 1266 (m), 1216 (m), 1176 (m), 1144 (m), 1043 (m), 988 (m), 864 (w), 730 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, J = 7.3 Hz, 3H), 1.16−1.48 (m, 15H), 2.08−2.18 (m, 1H), 4.20 (q, J = 7.3 Hz, 2H), 5.77 (d, J = 15.6 Hz, 1H), 6.75 (dd, J = 9.2, 15.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 14.3, 22.7, 29.4, 34.2, 42.7, 60.1, 120.8, 154.0, 166.8; mass spectrum m/z (relative intensity) EI 226 (3.5, M^+), 197 (2), 184 (25), 181 (39), 155 (18), 138 (67), 123 (28), 110 (37), 96 (200), 81 (56), 47 (69), 55 (85), 41 (10); HRMS (EI) calcd for $[C_{14}H_{26}O_2]^+$ 226.1933, found 226.1932.

(*E*)-Ethyl 4-Methyl-2-octenoate (6b). Compound **6b** was prepared using general procedure A. After purification (silica gel, 5% Et_2O/95% hexanes), a colorless oil was obtained (137 mg, 88%): IR (neat) 2961 (m), 2931 (m), 2874 (m), 1722 (s), 1652 (m), 1461 (m), 1266 (m), 1181 (m), 1040 (m), 985 (w), 864 (w), 725 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, J = 7.3 Hz, 3H), 1.04 (d, J = 6.9 Hz, 3H), 1.21−1.41 (m, 9H), 2.24−2.34 (m, 1H), 4.19 (q, J = 7.3 Hz, 2H), 5.77 (d, J = 15.6 Hz, 1H), 6.86 (dd, J = 7.8, 15.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 14.2, 19.4, 22.7, 29.3, 35.7, 36.5, 60.1, 119.5, 154.7, 166.9; mass spectrum m/z (relative intensity) EI 184 (4.5, M^+), 169 (1.5), 155 (7), 142 (80), 139 (60), 113 (45), 96 (98), 81 (43), 69 (93), 55 (100), 41 (53).

(*E*)-Ethyl 4-Phenyl-2-octenoate (6c). Compound **6c** was prepared using general procedure A. After purification (silica gel, 5% Et_2O/95% hexanes), a clear oil was obtained (132 mg, 63%): IR (neat) 3063 (w), 3029 (w), 2959 (m), 2932 (s), 2860 (m), 1720 (s), 1650 (m), 1602 (w), 1494 (w), 1454 (m), 1368 (m), 1309 (m), 1267 (m), 1171 (m), 1043 (m), 985 (m), 867 (w), 761 (w), 700 (m), 560 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, J = 7.3 Hz, 3H), 1.20−1.37 (m, 7H), 1.73−1.86 (m, 2H), 3.36−3.43 (m, 1H), 4.19 (q, J = 7.3 Hz, 2H), 5.80 (dd, J = 0.9, 15.6 Hz, 1H), 7.08 (dd, J = 7.8, 15.6 Hz, 1H), 7.17−7.36 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 14.2, 22.5, 29.6, 34.6, 48.5, 60.2, 120.6, 126.7, 127.7, 128.6, 142.4, 152.0, 166.7; mass spectrum m/z (relative intensity) EI 246 (14, M^+), 217 (2), 204 (18), 189 (8), 172 (9), 158 (40), 143 (41), 133 (38), 115 (100), 91 (36), 77 (8), 55 (10), 41 (11). HRMS (EI) calcd for $[C_{16}H_{22}O_2]^+$ 246.1620, found 246.1622.

(*E*)-Ethyl 4-(*N*-*tert*-Butoxycarbamoyl-*N*-methylamino)-2-octenoate (6d). Compound **6d** was prepared using general procedure A. After purification (silica gel, 10% EtOAc/90% hexanes), a clear oil was obtained (200 mg, 75%): IR (neat) 2961 (m), 2932 (m), 2974 (w), 2966 (w) 1721 (s), 1698 (s), 1654 (w), 1463 (m), 1394 (m), 1367 (m), 1268 (m), 1152 (m), 1043 (m), 983 (w), 879 (w), 771 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) (minor rotamer) δ 0.82−0.90 (br, s, 3H), 1.14−1.34 (m, 9H), 1.36−1.46 (br, s, 9H), 2.42−2.57 (br, m, 1H), (2.73) 2.81 (s, 3H), (3.07−3.17) 3.19−3.31 (m, 2H), 4.16 (q, J = 7.3 Hz, 2H), 5.77 (d, J = 15.6 Hz, 1H), 6.68−6.78 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) (minor rotamer) δ 13.8, 14.2, 22.6, 28.3, 29.2, 31.4, 34.7 (35.2), (42.0) 42.2, (52.6) 53.1, 60.2, (79.3) 79.5, 122.4, 150.5 (150.7), 155.4 (155.8), 166.2; mass spectrum m/z (relative intensity) EI 313 (0.03, M^+), 240 (5), 194 (4), 170 (28), 144 (44), 127 (21), 99 (13), 88 (14), 57 (78), 44 (100), 41 (23); HRMS (EI) calcd for $[C_{17}H_{31}NO_4]^+$ 313.2253, found 313.2258.

(*E*)-Ethyl 4-(1,1-Dimethyl ethyl)-2-octenoate (6e). Compound **6e** was prepared using general procedure A. After purification (silica gel, 5% Et_2O/95% hexanes), a clear oil was obtained (156 mg, 81%): IR (neat) 2961 (s), 2871 (m), 1722 (s), 1651 (m), 1468 (m), 1368 (m), 1344 (m), 1266 (m), 1212 (m), 1162 (m), 1137 (m), 1040 (m), 992 (m), 864 (w), 730 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.82−0.92 (m, 12H), 0.98−1.08 (m, 1H), 1.16−1.36 (m, 7H), 1.51−1.60 (m, 1H), 1.81 (dt, J = 2.3, 10.5 Hz, 1H), 4.20 (q, J = 7.3 Hz, 2H), 5.75 (d, J = 15.6 Hz, 1H), 6.78 (dd, J = 10.5, 15.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.0, 14.2, 22.7, 27.7, 28.2, 30.4, 33.1, 53.7, 60.1, 122.4, 151.6, 166.5; mass spectrum m/z (relative intensity) EI 170 (100, $M^+ - {}^t$Bu), 127 (79), 99 (57), 81 (18), 57 (40), 41 (24); HRMS (EI) calcd for $[C_{14}H_{26}O_2 + H]^+$ 227.2011, found 227.2014.

(*E*)-Ethyl 4-(2-Methoxyphenyl)-2-octenoate (6g). Compound **6g** was prepared using general procedure A. After purification (silica gel, 5% Et_2O/95% hexanes), a clear oil was obtained (171 mg, 73%): IR (neat) 3032 (w), 2958 (s), 2933 (s), 2861 (m), 2839 (m), 1717 (s), 1650 (m), 1599 (m), 1493 (m), 1464 (m), 1440 (m), 1368 (m), 1244 (s), 1176 (s), 1032 (s), 867 (w), 754 (s), 574 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.88 (t, J = 7.3 Hz, 3H), 1.19−1.37 (m, 7H), 1.73−1.84 (m, 2H), 3.83 (s, 3H), 3.88−3.93 (m, 1H), 4.18 (q, J = 7.3 Hz, 2H), 5.79 (dd, J = 1.4, 15.6 Hz, 1H), 6.88 (d, J = 8.3 Hz, 1H), 6.95 (t, J = 6.9 Hz, 1H), 7.10 (dd, J = 7.8, 15.6 Hz, 1H), 7.15 (dd, J = 1.4, 7.3 Hz, 1H), 7.22 (dt, J = 1.4, 7.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 14.2, 22.6, 29.7, 33.4, 40.8, 55.4, 60.1, 110.7, 120.3, 120.7, 127.5, 127.9, 130.6, 152.0, 157.0, 167.0; mass spectrum m/z (relative intensity) EI 276 (46, M^+), 231 (25), 219 (44), 188 (22), 175 (52), 145 (100), 115 (35), 91 (29), 77 (14), 55 (9), 41 (9); HRMS (EI) calcd for $[C_{17}H_{24}O_3]^+$ 276.1725, found 276.1725.

(*E*)-Ethyl 4-(1-Naphthyl)-2-octenoate (6h). Compound **6h** was prepared using general procedure A. After purification (silica gel, 5% Et_2O/95% hexanes), a clear oil was obtained (189 mg, 75%): IR (neat) 3049 (m), 2958 (s), 2932 (s), 2861 (m), 1936 (w), 1716 (s), 1650 (m), 1598 (w), 1510 (w), 1465 (m), 1368 (m), 1309 (m), 1269 (s), 1177 (s), 1072 (m), 986 (m), 860 (w), 798 (m), 779 (s), 733 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.78 (t, J = 6.9 Hz, 3H), 1.14−1.32 (m, 7H), 1.83−1.93 (m, 1H), 4.06 (q, J = 6.9 Hz, 2H), 4.14−4.20 (m, 1H), 5.74 (dd, J = 0.9, 15.6 Hz, 1H), 7.10−7.18 (m, 1H), 7.29−7.46 (m, 4H), 7.67 (d, J = 7.8 Hz, 1H), 7.78 (d, J = 7.3 Hz, 1H), 7.97 (d, J = 8.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 14.2, 22.7, 29.9, 34.4, 42.8, 60.3, 121.0, 123.0, 124.4, 125.4, 125.5, 126.0, 127.2, 129.0, 131.6, 134.0, 138.4, 151.7, 166.7; mass spectrum m/z (relative intensity) EI 296 (25, M^+), 251 (7), 239 (13), 223 (6), 208 (5), 179 (6), 165 (100), 153 (10), 128 (4), 115 (4), 55 (3), 41 (4) ; HRMS (EI) calcd for $[C_{20}H_{24}O_2]^+$ 296.1776, found 296.1776.

(*E*)-Ethyl 4-[1-(2-Propenyl)]-2-octenoate (6i). Compound **6i** was prepared using general procedure A. After purification (silica gel, 5% Et_2O/95% hexanes), a colorless oil was obtained (118 mg, 66%): IR (neat) 3079 (w), 2960 (m), 2930 (m), 2860 (w), 1722 (s), 1654 (m), 1466 (w), 1369 (m), 1308 (m), 1267 (m), 1221 (m), 1176 (m), 1142 (m), 1043 (m), 987 (m), 914 (m), 862 (w), 726 (w) cm^{-1}; ^1H

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NMR (500 MHz, $CDCl_3$) δ 0.81 (t, J = 7.3 Hz, 3H), 1.08−1.44 (m, 9H), 2.02−2.20 (m, 3H), 4.12 (q, J = 7.3 Hz, 2H), 4.90−4.99 (m, 2H), 5.59−5.68 (m, 1H), 5.70 (d, J = 15.6 Hz, 1H), 6.70 (dd, J = 8.7, 15.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 14.2, 22.6, 29.2, 33.4, 38.7, 42.3, 60.1, 116.5, 121.1, 135.9, 152.8, 166.7; mass spectrum m/z (relative intensity) EI 210 (0.70, M^+), 169 (50), 165 (15), 136 (22), 123 (23), 95 (100), 81 (65), 67 (35), 55 (50), 41 (29); HRMS (EI) calcd for $[C_{13}H_{22}O_2]^+$ 210.1620, found 210.1619.

(*Z*)-Ethyl 2-Chloro-4-phenyl-3-butenoate (13). Compound **13** was prepared by adapting the procedure from Calzada and Hooz[15] for ethyl (3*Z*)-2-hydroxy-4-phenylbut-3-enoate using *Z*-PhCH=CHCH(OH)COOEt as starting material. After purification (silica gel, 3% Et_2O/97% hexanes), a pale yellow oil was obtained (3.8 g, 80%): IR (neat) 3060 (w), 3029 (w), 2984 (m), 2939 (w), 2907 (w), 1961 (w), 1887 (w), 1746 (s), 1641 (w), 1494 (m), 1447 (m), 1369 (m), 1317 (s), 1262 (s), 1177 (s), 1026 (m), 818 (m), 770 (m), 700 (s), 526 (w), 486 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.33 (t, J = 7.3 Hz, 3H), 4.29 (q, J = 7.3 Hz, 2H), 5.22 (t, J = 10.5 Hz, 1H), 6.00 (t, J = 11.0 Hz, 1H), 6.81 (d, J = 11.5 Hz, 1H), 7.33−7.46 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 53.1, 62.4, 125.2, 128.1, 128.6, 128.7, 134.7, 135.1, 168.3; mass spectrum m/z (relative intensity) EI 224 (0.60, M^+), 189 (90), 151 (45), 115 (100), 105 (5), 89 (16), 63 (10), 51 (7); HRMS (EI) calcd for $[C_{12}H_{13}ClO_2]^+$ 224.0604, found 224.0604.

(*E*)-Ethyl 4-Phenyl-2-pentenoate (14b). Compound **14b** was prepared using general procedure A, with *Z*-α-chloro-β,γ-unsaturated ester **13** (0.75 mmol) as starting material. Initial purification over silica gel (5% Et_2O/95% hexanes) yielded a mixture of *E* and *Z* isomers (128 mg, 84%). A second purification done with SiO_2−$AgNO_3$ (3% Et_2O/97% hexanes) to isolate the *E*-isomer **14b** gave a clear oil: IR (neat) 3065 (w), 3029 (m), 2960 (m), 2931 (s), 1721 (s), 1650 (m), 1460 (m), 1170 (s), 1040 (m), 700 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.29 (t, J = 6.9 Hz, 3H), 1.45 (d, J = 6.9 Hz, 3H), 3.61−3.67 (m, 1H), 4.20 (q, J = 6.9 Hz, 2H), 5.82 (dd, J = 1.4, 15.6 Hz, 1H), 7.13 (dd, J = 6.9, 15.6 Hz, 1H), 7.21−7.39 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 20.0, 41.9, 60.3, 120.1, 126.7, 127.3, 128.7, 143.0, 152.6, 166.5; mass spectrum m/z (relative intensity) EI 204 (21, M^+), 158 (5), 131 (100), 115 (10), 91 (27), 77 (5), 65 (4), 53 (3).

(*Z*)-Ethyl 2-Butyl-4-phenyl-3-butenoate (16a). Compound **16a** was prepared using general procedure A, with *Z*-α-chloro-β,γ-unsaturated ester **13** (0.35 mmol) as starting material. Initial purification over silica gel (5% Et_2O/95% hexanes) yielded a mixture of *E* and *Z* isomers (69 mg, 80%). A second purification done with SiO_2−$AgNO_3$ (3% Et_2O/97% hexanes) to isolate the *Z*-isomer **16a** gave a clear oil: IR (neat) 3060 (w), 3025 (m), 2959 (s), 2933 (s), 2862 (m), 1733 (s), 1494 (w), 1448 (m), 1255 (m), 1224 (m), 1172 (s), 1031 (m), 768 (m), 701 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.80 (t, J = 7.3 Hz, 3H), 1.09−1.29 (m, 7H), 1.69−1.79 (m, 1H), 3.47−3.55 (m, 1H), 4.14 (q, J = 7.3 Hz, 2H), 5.61 (dd, J = 11.0, 11.5 Hz, 1H), 6.55 (d, J = 11.5 Hz, 1H), 7.18−7.33 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 14.2, 22.4, 29.1, 33.0, 44.7, 60.5, 127.0, 128.3, 128.7, 130.0, 131.1, 136.8, 174.3; mass spectrum m/z (relative intensity) EI 246 (27, M^+), 203 (4), 190 (6), 173 (52), 157 (4), 131 (18), 117 (100), 91 (54), 69 (6), 41 (8); HRMS (EI) calcd for $[C_{16}H_{22}O_2]^+$ 246.1620, found 246.1622.

(*E*)-4-Butyl-2-octenenitrile (22). Compound **22** was prepared using general procedure C. Initial purification over silica gel (5% Et_2O/95% hexanes) yielded a mixture of *E* and *Z* isomers (67 mg, 75%). A second purification done with SiO_2−$AgNO_3$ (5% Et_2O/95% hexanes) to isolate the *E*-isomer **22** gave a colorless oil: IR (neat) 3052 (w), 2959 (s), 2931 (s), 2860 (m), 2224 (m), 1632 (m), 1466 (m), 1380 (w), 973 (m), 731 (w) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89 (t, J = 7.3 Hz, 6H), 1.14−1.36 (m, 10H), 1.39−1.50 (m, 2H), 2.08−2.18 (m, 1H), 5.28 (d, J = 16.5 Hz, 1H), 6.50 (dd, J = 9.2, 16.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 22.6, 29.2, 33.7, 44.0, 99.1, 117.6, 160.7; mass spectrum m/z (relative intensity) EI 179 (0.25, M^+), 178 (1.25), 164 (6), 150 (11), 124 (23), 110 (61), 94 (37), 80 (97), 56 (60), 55 (95), 41 (100); HRMS (EI) calcd for $[C_{12}H_{21}N]^+$ 179.1674, found 179.1692.

(*Z*)-4-Butyl-2-octenenitrile (23). Compound **23** was prepared using general procedure C. Initial purification over silica gel (5% Et_2O/95% hexanes) yielded a mixture of *E* and *Z* isomers (55 mg, 62%). A second purification done with SiO_2−$AgNO_3$ (5% Et_2O/95% hexanes) to isolate the *Z*-isomer **23** gave a colorless oil: IR (neat) 3068 (w), 2959 (s), 2930 (s), 2860 (m), 2220 (m), 1621 (m), 1466 (m), 1380 (w), 755 (m) cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.90 (t, J = 7.3 Hz, 6H), 1.22−1.38 (m, 10H), 1.45−1.55 (m, 2H), 2.59−2.69 (m, 1H), 5.33 (d, J = 11.0 Hz, 1H), 6.21 (dd, J = 10.5, 11.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.9, 22.6, 29.3, 34.4, 42.6, 99.0, 116.4, 159.9; mass spectrum m/z (relative intensity) EI 179 (0.25, M^+), 178 (1.5), 164 (5), 150 (10), 136 (11), 124 (20), 110 (57), 94 (32), 80 (100), 69 (38), 55 (54), 41 (67); HRMS (EI) calcd for $[C_{12}H_{21}N]^+$ 179.1674, found 179.1674.

■ ASSOCIATED CONTENT

Supporting Information

^{1}H and ^{13}C NMR spectra for **2**, **3**, **4a**, **6a**−**e**, **6g**−**i**, **13**, **14b**, **16a**, **22**, and **23** are provided. This material is available free of charge via the Internet at http://pubs.acs.org

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Notes

The authors declare no competing financial interest.

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