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Cu(I)-Catalyzed, α-Selective, Allylic Alkylation Reactions between Phosphorothioate Esters and Organomagnesium Reagents

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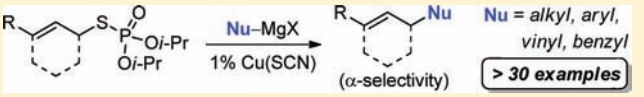
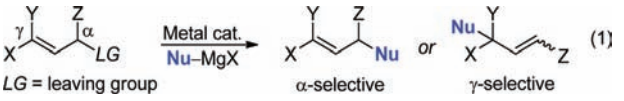
Supporting Information

ABSTRACT: Regiocontrol of allylic alkylation reactions involving hard nucleophiles remains a significant challenge and continues to be an active area of research. The lack of general methods in which α-alkylation is favored underscores the need for the development of new processes for achieving this type of selectivity. We report that Cu(I) catalyzes the allylic substitution of phosphorothioate esters with excellent α-regioselectivity, regardless of the nature of the Grignard reagent that is used. To the best of our knowledge, the Cu-catalyzed allylic alkylation of phosphorothioate esters has never been described. We have also developed a simple protocol for inducing high α selectivity starting from secondary allylic halides. This is accomplished by using sodium phosphorothioates as an additive.



INTRODUCTION

Transition metal-mediated alkylations of allylic electrophiles with hard nucleophiles such as Grignard reagents have received considerably less attention than reactions with stabilized nucleophiles. Regiocontrol of reactions involving hard nucleophiles remains a significant challenge since unsymmetrically substituted allylic substrates can furnish regioisomeric products which arise from either α- or γ-displacement of the leaving group (eq 1). Uncatalyzed reactions between Grignard reagents and allylic halides usually result in a mixture of both regioisomeric products.[1] Although the use of transition metals can promote cross-couplings with good regiocontrol, it overwhelmingly favors γ-alkylated products.[2]



In contrast, α-selective alkylations between Grignard reagents and allylic electrophiles are rarer and often limited in scope.[3] Most of these examples are interspersed among others in which the predominant mode of reactivity is at the γ-position. Substrates in which the leaving group is positioned on a secondary carbon center represent an especially difficult problem for two reasons. First, there is less of a steric difference between the α- and γ-positions, thereby making the two reactive ends more difficult to distinguish. Second, highly substituted secondary allylic halides and phosphates, especially those that are disubstituted in the γ-position, can be thermally unstable and are often incompatible with silica gel chromatography.[4] These compounds are usually prepared and used without purification. This practice is far from ideal since trace impurities can lead to catalyst deactivation and diminished selectivity. Because of these complicating issues, α selectivity in alkylation reactions between Grignard reagents and secondary allylic electrophiles is not common in the literature.[3f,g]

Primary allylic electrophiles are somewhat less problematic but also typically exhibit γ selectivity. While there are a few examples in which α-substituted products can be obtained using Cu(I) complexes, there remains no general method for achieving α regioselectivity. Bäckvall, Julia, and Calò have reported some α-selective, Cu(I)-promoted reactions with allylic acetates/chlorides, sulfones, benzothiazoles, respectively.[3a−d] As with secondary substrates, the primary focus of these studies was not the development of α-selective transformations.

With respect to other transition metals, Fürster and coworkers demonstrated that Fe complexes with formal −2 oxidation states are capable of catalyzing alkylation reactions between allylic chlorides and PhMgBr with good α selectivity.[5] However, vinyl chlorides also participate in the cross-coupling reaction, in principle, precluding their presence. Yamamoto has shown that Ni(II) and Fe(III) complexes furnish products with α selectivity.[6] Notably, the same reactions catalyzed by Cu(I) complexes completely reverse this selectivity to provide exclusively γ-substituted products.[7] Yamamoto and Butsugan both reported that, in the absence of transition metals, primary allylic phosphates undergo coupling reactions to give good α selectivities.[8] However, the former is limited to allylic Grignard reagents, while the latter is restricted to geranyl- and neryl-derived phosphates.

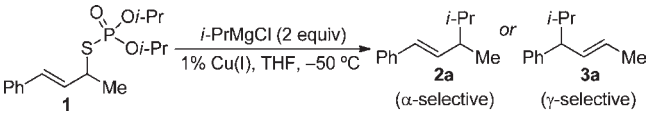
The lack of general methods in which α-alkylation is favored underscores the need for the development of new processes for achieving this type of selectivity. Our group previously demonstrated that phosphorothioate esters undergoes transition metal-free, allylic substitutions that exhibit α-selectivity when aromatic and vinyl Grignards are used while secondary aliphatic Grignards reacted at the γ position.[9] To the best of our knowledge, transition metal-catalyzed cross-coupling reactions utilizing allylic phosphorothioate esters have not been described before.

Received: March 31, 2011
Published: May 18, 2011

dx.doi.org/10.1021/ja202954b | J. Am. Chem. Soc. 2011, 133, 9119–9123

Herein, we report that Cu(I) catalyzes the allylic substitution of phosphorothioate esters[10] with excellent α-regioselectivity, regardless of the nature of the Grignard reagent. As we have previously disclosed, phosphorothioate esters can be conveniently prepared from electrophiles possessing oxygen-based leaving groups (i.e., alcohols, alkyl/benzyl/silyl ethers, benzoates) under photochemical or $Ga(OTf)_3$-catalyzed conditions.[9,11] In contrast to secondary allylic halides or phosphates, even highly substituted allylic phosphorothioate esters are air, moisture, and chromatographically stable.

Table 1. Reaction Optimization Studies



entry	catalyst	modifications	α:γ[a]	E/Z[a]	yield (%)[b]
1	none, rt	–	19:81	>95:5	–[d]
2	CuCl	–	87:13	>95:5	–[d]
3	CuBr	–	87:13	>95:5	–[d]
4	CuI	–	87:13	>95:5	–[d]
5	CuCN	–	<5:95	86:14	–[d]
6	CuTC[c]	–	87:13	>95:5	75
7	CuTC[c]	Et_2O solvent	87:13	>95:5	–[d]
9	CuSCN	–	87:13	>95:5	–[d]
10	CuSCN	*i*-PrMgCl·LiCl	**>95:5**	>95:5	91

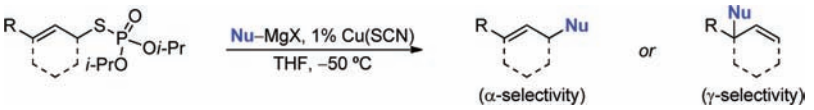
[a] As determined by ^1H NMR spectroscopy. [b] Isolated yields. [c] TC = thiophene-2-carboxylate. [d] Not determined.

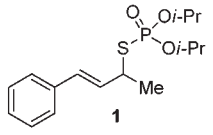
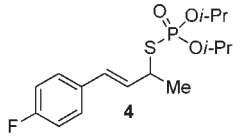
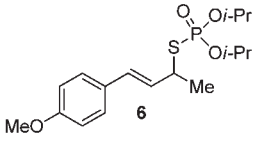
RESULTS AND DISCUSSION

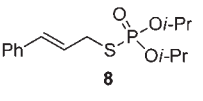
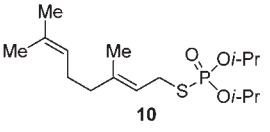
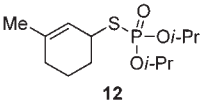
Table 1 summarizes some of the key experiments in our optimization study. A control reaction without the addition of Cu(I) proceeded with acceptable rates only at rt and favored formation of the γ-alkylated product with poor selectivity (entry 1). With the exception of CuCN, regioselectivity was generally insensitive to the copper source or solvent. When CuCN was employed, a complete reversal in selectivity was observed (entry 5). Others have also reported that CuCN appears to be unique in its ability to promote γ-selectivity in these types of alkylation reactions.[3h,i,12] The use of *i*-PrMgCl·LiCl complex provided only the α-alkylated product (entry 10). However, the addition of exogenous LiCl did not seem to affect the selectivities of reactions involving Grignard reagents other than in the case of *i*-PrMgCl. In all examples in which we observed α selectivity, *E* alkenes were formed exclusively.

Next, we conducted a survey of the reaction scope. As illustrated in Table 2, consistent excellent α-regioselectivities were observed in nearly every reaction. The electrophiles were selected on the bais of maximizing substrate diversity. The range of amenable nucleophiles includes primary and secondary aliphatic, benzylic, aromatic, and vinylic Grignards. Notably, the results for cyclohexenyl phosphorothioate ester **12** are complementary to those of our prior study in which transition metal-free alkylations with secondary aliphatic Grignard reagents proceeded with excellent γ-regioselectivities.[9] The products obtained when vinyl Grignard is employed are 1,4-dienes (i.e., "skipped dienes"). These are important structural motifs in numerous bioactive compounds.[13] Despite its large steric bulk, *t*-BuMgBr also participated, albeit with diminished regioselectivity (entry 7). Selectivity below 90:10 (α/γ) was observed in

Table 2. Scope of α-Selective Allylic Alkylation



entry	electrophile	Grignard	product	α : γ[a]	yield (%)[b]
1		*i*-PrMgCl·LiCl	**2a**	>95 : 5	91
2		MeMgBr	**2b**	>95 : 5	82
3		BnBr	**2c**	>95 : 5	67
4		PhMgBr	**2d**	>95 : 5	83
5		vinyl–MgBr	**2e**	>95 : 5	85
6		EtMgBr	**2f**	>95 : 5	75
7		*t*-BuMgBr	**2g**	70 : 30	–[c]
8		*i*-PrMgCl·LiCl	**5a**	92 : 8	85
9		MeMgBr	**5b**	>95 : 5	89
10		BnMgBr	**5c**	90 : 10	73
11		PhMgBr	**5d**	>95 : 5	81
12		vinyl–MgBr	**5e**	>95 : 5	81
13		*i*-PrMgCl·LiCl	**7a**	75 : 25	88
14		MeMgBr	**7b**	>95 : 5	92
15		BnMgBr	**7c**	70 : 30	68
16		PhMgBr	**7d**	>95 : 5	92
17		vinyl–MgBr	**7e**	>95 : 5	79

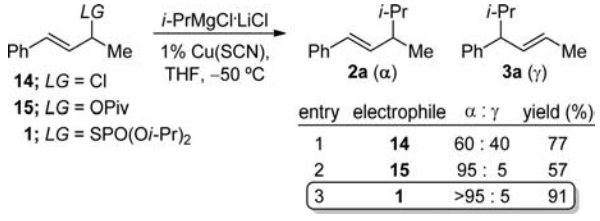
entry	electrophile	Grignard	product	α : γ[a]	yield (%)[b]
18		*i*-PrMgCl·LiCl	**9a**	>95 : 5[d]	84
19		MeMgBr	**9b**	>95 : 5	71
20		BnMgBr	**9c**	94 : 6	86
21		PhMgBr	**9d**	>95 : 5	90
22		vinyl–MgBr	**9e**	>95 : 5	74
23		*i*-PrMgCl·LiCl	**11a**	>95 : 5	89
24		MeMgBr	**11b**	>95 : 5	59
25		BnMgBr	**11c**	>95 : 5	67
26		PhMgBr	**11d**	>95 : 5	77
27		vinyl–MgBr	**11e**	>95 : 5	65
28		*i*-PrMgCl·LiCl	**13a**	>95 : 5	80
29		BnMgBr	**13b**	>95 : 5	89
30		PhMgBr	**13c**	>95 : 5	72

dx.doi.org/10.1021/ja202954b |*J. Am. Chem. Soc.* 2011, 133, 9119–9123

only two instances, each of which occurred with the electron-rich phosphorothioate ester **6** (entries 13, 15).

For purposes of comparison, we carried out an analogous cross-coupling with the corresponding secondary allylic chloride **14** (Table 3). Under the same conditions, this reaction resulted in very poor regioselectivity (entry 1). When the allylic pivaloate **15** was utilized, good α regioselectivity was observed; however, the product was isolated in low yield (57%, entry 2). Substantially superior results were achieved with the use of phosphorothioate **1** in which both excellent α regioselectivity and yields were obtained (entry 3).

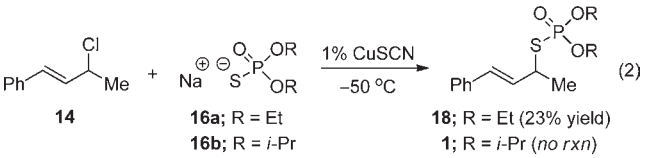
Table 3. Comparison with Other Electrophiles



entry	electrophile	α : γ	yield (%)
1	**14**	60 : 40	77
2	**15**	95 : 5	57
3	**1**	>95 : 5	91

We then developed a protocol to induce good α-selectivity starting with allylic chloride **14**. In principle, this could be accomplished by performing an in situ alkylation with sodium thioates **16a**–**b** to generate phosphorothioate ester **17** (Scheme 1). If the chloride displacement were carried out in the presence of CuSCN and a Grignard reagent, subsequent cross-coupling of the resultant phosphorothioate esters should proceed with high regioselectivity. This scenario is possible only if the rate of the Cu-catalyzed cross-coupling of allylic chloride **14** (which proceeds with poor regioselectivity, entry 1) is slower than the *overall* the rate of chloride displacement (**14** → **17**) followed by alkylation with the Grignard (**17** → **2a**). Indeed, when we performed the reaction between allylic chloride **14** and *i*-PrMgCl·LiCl in the presence of sodium thioate **16a** (1 equiv) and CuSCN (1 mol %), we isolated the desired product with high α-regioselectivity (94:6, entry 2). As expected, the addition of substoichiometric amounts of sodium thioate **16a** furnished substantially lower regioselectivity (entry 3). Curiously, the use of diisopropyl thioate **16b** (1 equiv) resulted in poor selectivity (entry 4).

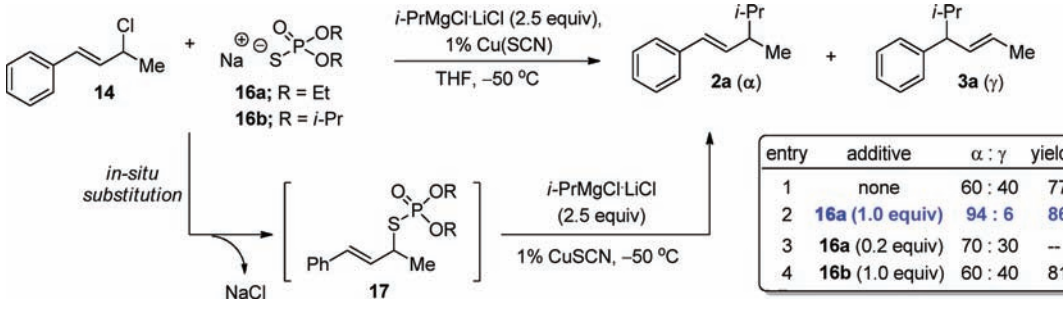
Equation 2 provides some insight regarding the disparate results obtained with **16a** and **16b**. Subjecting allylic chloride **14** and *diethyl* sodium thioate **16a** to typical cross-coupling reactions, without the addition of Grignard, yielded the expected phosphorothioate ester **18** (eq 2). This result supports the scenario outlined in Scheme 1 in which in situ alkylation precedes Cu-catalyzed allylic alkylation. Under these same conditions, we observed no reaction between *diisopropyl* thioate **16b** and allylic chloride **14**. It is likely that the greater van der Waals radius of isopropyl versus ethyl is responsible for retarding the rate of chloride displacement. Consequently, unselective cross-coupling between allylic chloride **14** and the Grignard occurs preferentially to formation of phosphorothioate ester **1**.



As proposed by several groups, we believe that initial formation of a π-Cu(I) complex is followed by oxidative addition to generate a transient σ-allyl Cu(III) intermediate **21** (Scheme 2).[2,14] This occurs with inversion of stereochemistry. Fast reductive elimination of **21** would lead to the kinetic product **22** (i.e., γ-selective).[15] This scenario is known to arise when strong-field ligands such as cyanide are present and/or with the use of monoalkyl copper reagents.[3a,12a,16] Indeed, during the course of our optimization studies, we observed that the use of CuCN yielded cross-coupling products which favored high γ selectivity (Table 1, entry 5). Alternatively, the presence of electron-rich ligands (i.e., $^{-}$SCN) and/or the use of dialkyl copper reagents, as in the present methodology, is thought to promote rapid equilibration between regioisomeric σ-allyl complexes **21** and **24**. Reductive elimination from **24** would lead to α selectivity.[3a,12a,16] Along this line of reasoning, it is possible that the displaced thioate leaving group **20** can act as an electron-rich ligand that facilitates σ-allyl equilibration, and therefore α selectivity. Formation of the regioisomer with the lower ground-state energy (i.e., conjugated) may also contribute to the observed selectivity.

We carried out several experiments to help support the proposed mechanism. First, we examined alkylations with sterically and electronically unbiased, deuterium-labeled phosphorothioate ester **26** (eq 3).[17] Although cross-couplings with this substrate resulted in the expected C–C bond formation, almost no regioselectivity was observed. When a 1:2 mixture of regioisomeric starting materials **31**/**1** was used, alkylation occurred to furnish only regioisomeric product **2a** (eq 4). This convergent regioselectivity stands in contrast to regiospecific transformations described by Yamamoto.[18] Few regioconvergent cross-coupling reactions of this sort are known, and they usually utilize stoichiometric amounts of dialkylcuprates.[3g,19] The results from eqs 3 and 4 support the scenario outlined in Scheme 2 in which reductive elimination from **21** (k_{RE1}) is slower than both

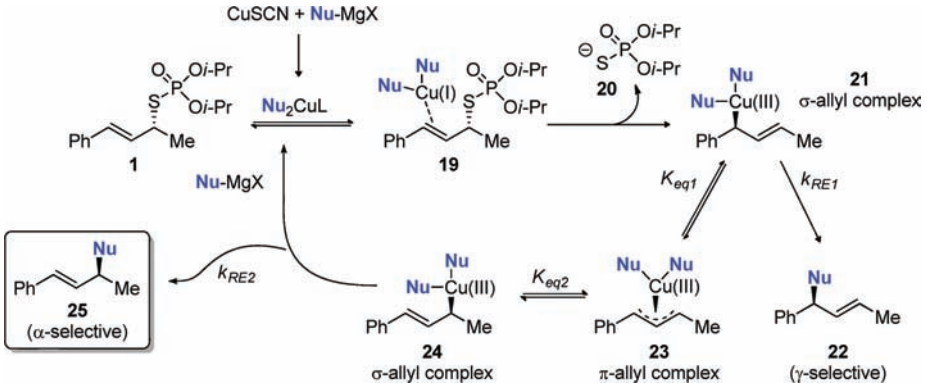
Scheme 1. α-Selective Alkylations of Allylic Chlorides



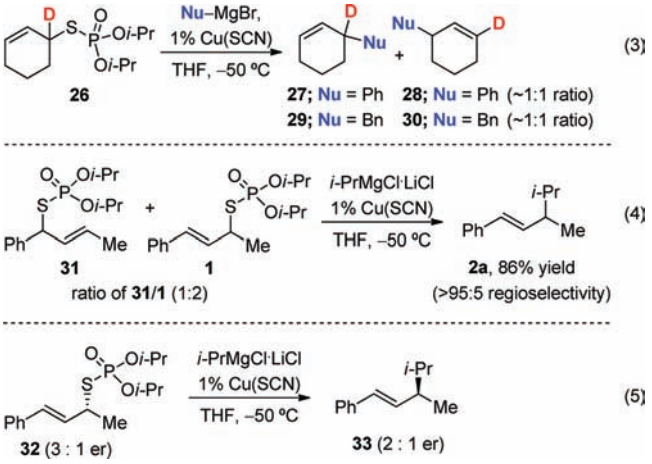
entry	additive	α : γ	yield%
1	none	60 : 40	77
2	**16a** (1.0 equiv)	94 : 6	86
3	**16a** (0.2 equiv)	70 : 30	--
4	**16b** (1.0 equiv)	60 : 40	81

dx.doi.org/10.1021/ja202954b | *J. Am. Chem. Soc.* 2011, 133, 9119–9123

Scheme 2. Proposed Mechanism



σ-complex equilibration and reductive elimination from **24** (k_{RE2}). We also examined the use of enantioenriched phosphorothioate **32**. As expected, cross-coupling of this substrate with *i*-PrMgCl·LiCl was stereospecific and yielded **33** with predominant inversion of stereochemistry (eq 5).[20]



In summary, we have described a highly α-regioselective, copper-catalyzed allylic alkylation of organomagnesium reagents utilizing phosphorothioate ester leaving groups. A wide range of Grignard reagents and electrophiles are amenable. We have also developed a method for achieving high α-regioselectivity starting with allylic chlorides by using sodium diethylphosphorothioate as a stoichiometric additive. Preliminary mechanistic probes indicate that, in contrast to regiospecific processes observed by others, the described methodology is regioconvergent when unsymmetrically substituted allylic phosphorothioate esters are utilized.

■ ASSOCIATED CONTENT

Supporting Information. Experimental details and characterization data for all new compounds. This information is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENT

Financial support for this research was provided by an NSF CAREER Award (CHE-1052824), Dartmouth College, and the Walter and Constance Burke Foundation.

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