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Regio- and Enantioselective Control in the Reactions of α-(*N*-Carbamoyl)alkylcuprates with Allylic Phosphates

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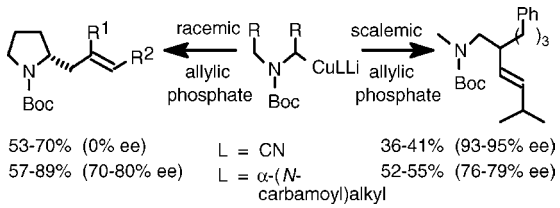
ABSTRACT



α-(*N*-Carbamoyl)alkylcuprates (RCuCNLi or R_2CuLi) react with allylic phosphates to afford homoallylic amines in good chemical yields. Regioselectivity is governed by steric factors in both the cuprate reagent and phosphate substrate and systems can be designed to give either the S_N2' or S_N2 substitution product cleanly. Excellent enantioselectivities can be achieved with either a scalemic α-di[(*N*-carbamoyl)-alkyl]cuprate and an achiral phosphate or with a scalemic allylic phosphate and an achiral cuprate reagent.

Although α-(*N*-carbamoyl)alkylcuprate chemistry[1] is a potentially powerful synthetic methodology for the synthesis of nitrogen heterocycles,[2] the utilization of allylic substrates remains undeveloped.[3] Allylation of organometallic reagents offers rich opportunities for C−C bond construction,[4] enantiocontrol using either scalemic substrates[4b,c,5] or organometallic reagents,[4c,6] and subsequent functional group interconversions. Efforts to exercise regiocontrol in allylic substitution have focused on the organometallic reagent, the leaving group in the allylic substrate, and solvent influences.[4−5,7−12] Generally, reaction conditions

(1) For a review see: Dieter, R. K. Heteroatomcuprates and α-Heteroatomalkylcuprates in Organic Synthesis. In *Modern Organocopper Chemistry*; Krause, N., Ed.; John Wiley & Sons: New York, 2002; Chapter 3, p 79.

(2) (a) Li, S.-L.; Dieter, R. K. *J. Org. Chem.* **2003**, *68*, 969. (b) Dieter, R. K.; Watson, R. *Tetrahedron Lett.* **2002**, *43*, 7725. (c) Dieter, R. K.; Lu, K. *J. Org. Chem.* **2002**, *67*, 847. (d) Dieter, R. K.; Yu, H. *Org. Lett.* **2000**, *2*, 2283.

(3) Dieter, R. K.; Velu, S. E.; Nice, L. E. *Synlett* **1997**, 1114.

(4) For reviews of organocopper-mediated allylic substitution, see: (a) Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135. (b) Breit, B.; Demel, P. Copper-Mediated Diastereoselective Conjugate Addition and Allylic Substitution Reactions. In *Modern Organocopper Chemistry*; Krause, N., Ed.; John Wiley & Sons: New York, 2002; Chapter 6, p 188. (c) Sofia, A.; Karlström, E.; Bäckvall, J.-E. Copper-Mediated Enantioselective Substitution Reactions. In *Modern Organocopper Chemistry*; Krause, N., Ed.; John Wiley & Sons: New York, 2002; Chapter 8, p 259.

(5) (a) Chong, J. M.; Belelie, J. L. *J. Org. Chem.* **2001**, *66*, 5552. (b) Belelie, J. L.; Chong, J. M. *J. Org. Chem.* **2002**, *67*, 3000. (c) Calaza, M. I.; Hupe, E.; Knochel, P. *Org. Lett.* **2003**, *5*, 1059. (d) Harrington-Frost, N.; Leuser, H.; Calaza, M. I.; Kneisel, F. F.; Knochel, P. *Org. Lett.* **2003**, *5*, 2111.

(6) Dieter, R. K.; Topping, C. M.; Chandupatla, K. R.; Lu, K. *J. Am. Chem. Soc.* **2001**, *123*, 5132.

(7) For a review see: (a) Nakamura, E.; Mori, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 3750.

(8) (a) Tseng, C. C.; Yen, S.-J.; Goering, H. L. *J. Org. Chem.* **1986**, *51*, 2892. (b) Tseng, C. C.; Paisley, S. D.; Goering, H. L. *J. Org. Chem.* **1986**, *51*, 2884. (c) Bäckvall, J.-E.; Sellén, M.; Grant, B. *J. Am. Chem. Soc.* **1990**, *112*, 6615. (d) Persson, E. S. M.; Bäckvall, J.-E. *Acta Chim. Scand.* **1995**, *49*, 899.

(9) Bäckvall, J.-E.; Persson, E. S. M.; Bombrun, A. *J. Org. Chem.* **1994**, *59*, 4126.

(10) (a) Valverde, S.; Bernabé, M.; Gómez, A. M.; Puebla, P. *J. Org. Chem.* **1992**, *57*, 4546. (b) Caló, V.; Lopez, L.; Carlucci, W. F. *J. Chem. Soc., Perkin Trans. 1* **1983**, 2953.

(11) (a) Goering, H. L.; Kantner, S. S.; Seitz, E. P., Jr. *J. Org. Chem.* **1985**, *50*, 5495. (b) Goering, H. L.; Kantner, S. S. *J. Org. Chem.* **1983**, *48*, 721. (c) Goering, H. L.; Seitz, E. P., Jr.; Tseng, C. C. *J. Org. Chem.* **1981**, *46*, 5304.

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favoring formation of R_2CuM (M = Li, MgX) reagents facilitate formal S_N2 substitution, while conditions favoring formation of RCuXM (X = Cl, CN; M = Li, MgX) promote S_N2' substitution involving allylic rearrangement. Use of Lewis acid additives enhances S_N2' selectivity.[7,8] This general pattern holds for reactions involving copper(I)-catalyzed Grignard reagents with allylic esters,[8] halides,[8c,9] and sulfides of benzothiozole-2-thiol.[10] Reactions of organocopper(I) or lithium cuprate reagents with allylic halides display the same general patterns.[11] Et_2O as a solvent generally favors S_N2' substitution, while THF favors S_N2 substitution, although in Et_2O the choice of Cu(X) (X = Cl, Br, I, CN)[8c−d] can determine selectivity. Allylic phosphates[12] strongly favor *anti* S_N2' substitution with cuprates prepared from CuCN, while CuOTf and CuSCN favor S_N2 substitution. These results illustrate the sensitivity of organocopper-mediated reactions to solvent effects,[8c−d,13a−c] Cu(I) salt,[8b,12,13d] and the nature of the reagent.[4b,c,5,8b−d]

Recent studies suggest that *anti* S_N2' regioselectivity may be enhanced by use of allylic phosphates,[5a−c,12] allylic perfluorobenzoates,[5d] CuCN-derived cuprates[5,8c−d,12] or zinc cuprate[5c−d] reagents alone or in combination. With these caveats in mind, the development of regio- and stereoselective reactions between allylic phosphates and α-(*N*-carbamoyl)alkylcuprates was undertaken. We now report that α-(*N*-carbamoyl)alkylcuprates undergo allylic substitution reactions in high yield and that excellent S_N2 or S_N2' regioselectivity can be obtained by judicious choice of cuprate reagent, α-(*N*-carbamoyl)alkyl ligand, and reaction conditions. Utilization of scalemic α-(*N*-carbamoyl)alkylcuprates or scalemic allylic phosphates affords good to excellent enantiocontrol.

Allylic phosphates **1a**−**e** (Figure 1) were prepared by reaction of the allylic alcohol [THF, Et_3N, 25 °C][5a] with

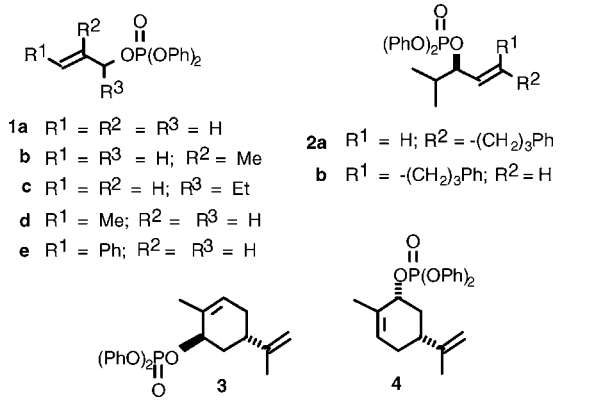
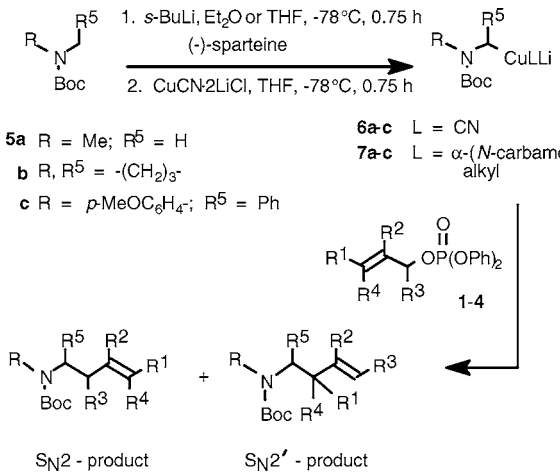


Figure 1. Allylic phosphates.

$(PhO)_2P(O)Cl$ in 65−90% yields after purification. Allylic phosphates **2a**,**b**, **3**, and **4** were prepared by reaction of the corresponding alkoxides [LDA, −50 °C, THF] with $(PhO)_2P(O)Cl$. These allylic phosphates, along with **1e**, were unstable to chromatographic purification (e.g., silica gel, alumina, or florisil), and the crude preparations were used. The requisite scalemic allylic alcohols needed for phosphates **2a**,**b** were obtained by asymmetric addition of 1-(5-phenyl)pentynylzinc to isobutrylaldehyde (82%, 92% ee)[14] followed by reduction to either the *trans*[15] or *cis*[16] allylic alcohols. *trans*-Carveol[17] was converted to phosphate **3**, while *cis*-carveol[18] was converted to phosphate **4**.

Deprotonation of carbamates **5a**−**c** (Scheme 1) according to Beak's procedure[19] followed by treatment with THF-

Scheme 1



soluble CuCN·2LiCl afforded either the lithium alkylcyanocuprates **6a**−**c** (i.e., RCuCNLi) or the lithium dialkylcuprates **7a**−**c** (i.e., R_2CuLi). Formation of scalemic cuprates from **5b** required asymmetric deprotonation in Et_2O followed by addition of THF soluble CuCN·2LiCl to afford a 1:1 Et_2O/THF solvent mixture of the stereogenic cuprate reagent.[6] The reaction of cuprate reagents **6a**−**c** or **7a**−**c** with allylic phosphates gave homoallylic amines (Scheme 1, Table 1) in modest to excellent yields.

Reaction of cuprate reagents with allylic phosphates **1a**,**b** affords the same substitution product via either reaction pathway. The alkylcyanocuprates **6a**,**b** gave higher yields of carbamoyl alkenes **8a**,**b** than the corresponding lithium dialkylcuprates **7a**,**b** upon reaction with **1a** (Table 1, entries 1−4). In the reactions of lithium dialkylcuprates **7a**,**b** with **1a**, homocoupling dimers [i.e., $Me(Boc)NCH_2CH_2N(Boc)Me$ (37%) and bis-*N*-Boc-pyrrolidine (22%), respectively] were

(12) (a) Yanagisawa, A.; Nomura, N.; Yamamoto, H. *Tetrahedron* **1994**, *50*, 6017 and references therein. (b) Yanagisawa, A.; Nomura, N.; Noritake, Y.; Yamamoto, H. *Synthesis* **1991**, 1130.

(13) (a) House, H. O.; Lee, T. V. *J. Org. Chem.* **1978**, *43*, 4369. (b) Bertz, S. H.; Dabbagh, G. *Tetrahedron* **1989**, *45*, 425. (c) Christenson, B.; Hallnemo, G.; Ullenius, C. *Tetrahedron* **1991**, *47*, 4739. (d) Bertz, S. H.; Gibson, C. P.; Dabbagh, G. *Tetrahedron Lett.* **1987**, *28*, 4251.

(14) Jiang, B.; Chen, Z.; Tang, X. *Org. Lett.* **2002**, *4*, 3451.

(15) Andre's, J. M.; Pedrosa, R. *Tetrahedron: Asymmetry* **1998**, *9*, 2493.

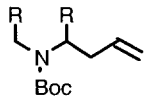
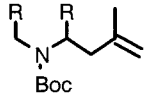
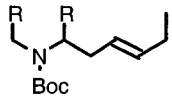
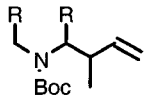
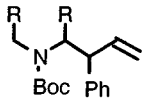
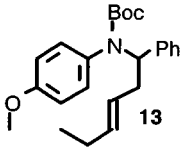
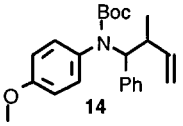
(16) Burgstahler, A. W.; Widiger, G. *J. Org. Chem.* **1973**, *38*, 3652.

(17) Dupuy, C.; Luche, J. L. *Tetrahedron* **1989**, *45*, 3437.

(18) Ireland, R. E.; Maienfisch, P. *J. Org. Chem.* **1988**, *53*, 640.

(19) Beak, P.; Basu, A.; Gallaghar, D. J.; Park, Y. S.; Thayumanavan, S. *Acc. Chem. Res.* **1996**, *29*, 552 and references therein.

Table 1. Reaction of α-(*N*-Carbamoyl)alkylcuprates with Acyclic Allylic Phosphates

entry	cuprate[a]	E^+	S_N2'-product	S_N2'/S_N2[b]	% yield[c]	% ee[d]
1	**6a**	**1a**		-	81	-
2	**7a**	**1a**		-	43	-
3	**6b**	**1a**		-	83	0
4	**7b**	**1a**	**8a** R = H **b** R = -$(CH_2)_2$-	-	57	80
5	**6a**	**1b**		-	57	-
6	**7a**	**1b**		-	92	-
7	**6b**	**1b**		-	58	0
8	**7b**	**1b**	**9a** R = H **b** R = -$(CH_2)_2$-	-	89	70
9	**6a**	**1c**		88:12	78	-
10	**7a**	**1c**		94:6	86	-
11	**6b**	**1c**		93:7	70	0
12	**7b**	**1c**	**10a** R = H **b** R = -$(CH_2)_2$-	94:6	86	75
13	**6a**	**1d**		95:5	76	-
14	**7a**	**1d**		89:11	93	-
15	**6b**	**1d**		77:23	68[e]	-[f]
16	**7b**	**1d**	**11a** R = H **b** R = -$(CH_2)_2$-	58:42	93[g]	-[f]
17	**6a**	**1e**		94:6	40	-
18	**7a**	**1e**		57:43	55	-
19	**6b**	**1e**		60:40	41[h]	0[i]
20	**7b**	**1e**	**12a** R = H **b** R = -$(CH_2)_2$-	28:72	87[j]	70[i]
21	**6c**	**1c**		100:0	42	0
22	**7c**	**1c**	**13**	100:0	100	0
23	**6c**	**1d**		16:84	55	0
24	**7c**	**1d**	**14**	0:100	87	0

[a] *N*-Boc deprotonation [*s*-BuLi, THF, or Et_2O, (−)-sparteine, −78 °C, 45 min], cuprate formation [−78 °C, 45 min] followed by reaction with the allyl phosphate [−78 to 25 °C, 12 h]. [b] Determined by NMR and GC-MS measurements. [c] Based upon isolated material purified by colunm chromatography. [d] Enantiomeric ratios determined by chiral stationary phase HPLC on a CHIRALCEL OD column [cellulose tris-(3,5-dimethylphenyl-carbamate) on silica gel]. [e] Diastereomeric ratio (dr) = 61.5:38.5. [f] No separation on HPLC. [g] Dr = 57:43. [h] Dr = 60:40. [i] For S_N2 product. [j] Dr = 56:44.

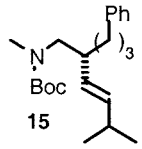
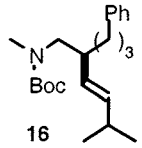
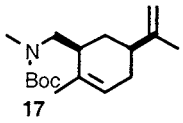
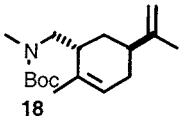
also isolated. In contrast, the dialkylcuprates **7a**,**b** gave higher yields than the alkylcyanocuprates **6a**,**b** upon reaction with **1b**−**e** (entries 5−20). The same pattern was observed for the combination of allylic phosphates **1c**,**d** and benzylic α-(*N*-carbamoyl)alkylcuprates **6c** and **7c** (entries 21−24), with the latter reagent affording significantly higher chemical yields. Chemical yields thus appear to reflect matching reactivities between the allylic phosphate and the cuprate reagents. The combination of the less reactive cuprate reagent with the more reactive phosphate, as well as that of the more reactive cuprate reagent with the less reactive phosphate, gives higher chemical yields. When the R_2CuLi reagents **7a**−**c** give higher chemical yields than the RCuCNLi reagents, it may also reflect formation of RCuCNLi upon reaction of R_2CuLi with allylic phosphates.

The S_N2'/S_N2 product distributions reflect substitution patterns in both the cuprate transferable ligand and in the allylic phosphates, as well as the actual cuprate reagent employed. With allylic phosphate **1c**, there is little difference in regioselectivity between cuprates **6a**,**b** (RCuCNLi) and **7a**,**b** (R_2CuLi), although the difference is larger for the less sterically hindered cuprates **6a** and **7a** (entries 9−12). The primary allylic phosphate with a methyl substituent on the olefin (i.e., **1d**) regioselectively affords the S_N2' substitution product but with reduced selectivity, and now cuprates **6a**,**b** give a higher S_N2'/S_N2 ratio than cuprates **7a**,**b** (13−16). Almost no regioselectivity is observed with the lithium dipyrrolidinylcuprate **7b** and **1d** (entry16), reflecting steric congestion at both reacting centers. Similarly, *trans*-cinnamyl phosphate **1e** containing a primary alkyl phosphate and a phenyl substitutent affords higher S_N2'/S_N2 ratios with **6a**,**b** than with **7a**,**b**, and with pyrrolidinylcuprate **7b** the S_N2 pathway predominates with modest selectivity (entries 17−20). The benzylic α-(*N*-carbamoyl)alkylcuprates adhere to the same pattern but with generally excellent regioselectivity. Reaction of **6c** or **7c** with phosphate **1c** gives exclusively the S_N2' substitution product (entries 21−22), while reaction with **1d** gives the S_N2 substitution product predominately with **6c** and exclusively with **7c** (entries 23−24). Reaction of the pyrrolidinylcuprates **6b** and **7b** with allylic phosphates **1d**−**e** generate two new stereogenic centers, yielding mixtures of diastereomers ranging between 56:44 and 62:38 (entries 15−16 and 19−20).

Asymmetric deprotonation of *N*-Boc pyrrolidine generates a scalemic organolithium reagent that can be converted into a scalemic organocopper reagent if the transmetalation is performed at −78 °C in a mixed solvent system employing THF-soluble CuCN·2LiCl. Utilizing this protocol, lithium dipyrrolidinylcuprate **7b** reacted with allylic phosphates **1a**−**c** and **1e** to give the *R*-enantiomers[6] with good enantioselectivities (entries 4, 8, 12, 20; er = 90:10 to 85:15), while no enantioselectivity was observed with the alkylcyanocuprate reagent **6b** (entries 3, 7, 11, and 19). A complex mixture of diastereomers and regioisomers precluded enantiomer analysis for the reaction of **7b** with **1d** (entry 16). No effort was made to optimize these preliminary results, which suggest that high enantioselectivities can be achieved with scalemic α-(*N*-carbamoyl)alkylcuprates and allylic phosphates.

Chirality may be introduced into the allylic phosphate and potentially exploited for enantiocontrol given the generally *anti* S_N2' preference[4c] for cuprate-mediated allylic substitutions. Reaction of **6a** with acyclic allylic phosphates **2a**,**b** containing either a *trans*- or *cis*-substituted olefin gave modest chemical yields of the substitution product (Table 2, entries 1−4). Higher chemical yields were achieved with the cyclic allylic phosphates **3**−**4**. *Trans*-disubstituted cyclohexenyl allylic phosphate **3** gave good enantioselectivity with **6a** and poor ees with **6b**, while both reagents gave excellent

Table 2. Reaction of α-(*N*-Carbamoyl)alkylcuprates Derived from *N*-Boc-*N*,*N*-Dimethylamine with Scalemic Allylic Phosphates

entry	cuprate[a]	E^+	S_N2'-product	S_N2'/S_N2[b]	% yield[c]	% ee[d]
1	**6a**	**2a**	 **15**	100:0	41	93
2	**7a**	**2a**		100:0	55	79
3	**6a**	**2b**	 **16**	100:0	36	95
4	**7a**	**2b**		100:0	52	76
5	**6a**	**3**	 **17**	-[e]	68	76
6	**7a**	**3**		-[e,f]	63	31
7	**6a**	**4**	 **18**	-[e]	65	99
8	**7a**	**4**		-[e,g]	57	80

[a] *N*-Boc deprotonation [*s*-BuLi, THF, or Et_2O, (−)-sparteine, −78 °C, 45 min], cuprate formation [−78 °C, 45 min] followed by reaction with the allyl phosphate [−78 to 25 °C, 12 h]. [b] Determined by NMR and GC-MS measurements. [c] Based upon isolated material purified by colunm chromatography. [d] Enantiomeric ratios determined by chiral stationary phase HPLC on a CHIRALCEL OD column [cellulose tris-(3,5-dimethylphenyl-carbamate) on silica gel]. [e] S_N2':S_N2 ratios are the same as the ees determined for the *anti* S_N2' products. *Anti* S_N2':*Syn* S_N2' = 92:8[f] to 86:14[g].

ees with the *cis*-disubstituted cyclohexenyl allylic phosphate **4** (entries 5−8). The *trans* diastereomer **3** has one axial and one equatorial substituent, while the *cis* diastereomer **4** has two axial substituents in the putative conformation required for *anti* S_N2' substitution and minor amounts of *syn* S_N2' products are observed from both **3** and **4**. The role of cuprate−substrate interactions in the disparity of ees between **3** and **4** is unclear.[12b] Cuprate **6a** uniformly gives higher ees than **7a** (Table 2) consistent with a more rapid reductive elimination when the Cu(III) intermediate contains an electron-withdrawing group (i.e., CN vs α-(*N*-carbamoyl)). This parallels the effect of cuprate reagent on regiocontrol observed for primary allylic phosphates **1d**,**e** (Table 1, entries 13−20, 23−24) where steric effects do not dominate at the allylic phosphate center.

In summary, we have shown that excellent regioselectivity can be achieved in the reactions of α-(*N*-carbamoyl)-alkylcuprates with allylic phosphates and that the selectivity is largely governed by steric factors in both the cuprate reagent and phosphate substrate. Excellent enantioselectivities can be achieved by either the combination of scalemic stereogenic α-(*N*-carbamoyl)alkylcuprate reagents and achiral allylic phosphates or with achiral carbamoylalkylcuprates and scalemic allylic phosphates. Reaction of allylic phosphates with stereogenic R_2CuLi α-pyrrolidinylcuprates gives good ees, while use of the RCuCNLi reagent gives excellent ees with scalemic allylic phosphates. Thus, good to excellent regiocontrol and good to excellent enantiocontrol at 2-pyrrolidinyl stereocenters and at the allylic stereogenic centers can be achieved in the reactions of α-(*N*-carbamoyl)-alkylcuprates with allylic phophates by judicious choice of reagent and substrate combinations. Generation of adjacent chiral centers affords poor diastereomeric ratios, and efforts are underway to control the diastereoselectivity of the reaction. These preliminary studies suggest that modification of cuprate reagents, cuprate compositions, and allylic phosphates will provide ample opportunities for synthetic applications yielding high regio- and enantioselectivities.

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Supporting Information Available: General experimental procedures for preparation and reactions of α-(*N*-carbamoyl)alkylcuprates with allylic phosphates and data reduction for compounds **8a**, **9a**,**b**, **10a**,**b**, **11a**,**b**, **13**−**18**; ^{13}C NMR for **11b**, **13**, **14**, **16**−**18**; and HPLC traces for **15**−**18**. This material is available free of charge via the Internet at http://pubs.acs.org.

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