Copper-Mediated Substitution Reactions of Alkylmagnesium Reagents with Allylic Carbamates: (*Z*)-Selective Alkene Synthesis

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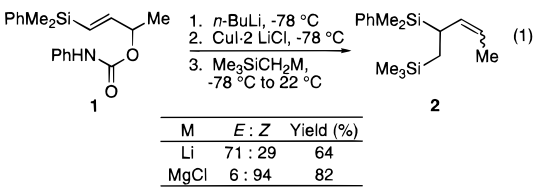
Copper-mediated allylic substitution reactions represent important methods for the construction of alkenes.[1,2] Both alkyllithium and alkylmagnesium reagents have been used since the initial report of these reactions with allylic acetates.[3] The regiochemistry of substitution with diorganocuprates is dependent upon the level of substitution of the allylic substrate, with substitution at the least hindered terminus predominating. Protocols have been developed, however, to effect clean γ-substitution (S_N2').[4−6] Among these modifications, Gallina and Ciattini reported a highly γ-selective substitution when allylic carbamates were treated with lithium dialkylcuprates.[7,8] As with other allylic substitutions, these reactions afforded (*E*)-alkenes, but with syn stereochemistry.[9,10] We have discovered that replacement of organolithium reagents in this transformation with organomagnesium reagents retained high γ-selectivity, but the reaction occurred with complete reversal of alkene stereoselectivity, providing (*Z*)-alkenes.[11] When a readily available, enantiomerically pure allylic carbamate was used, a (*Z*)-alkene of high optical purity was obtained. This methodology therefore provides access to chiral, non-racemic (*Z*)-allylsilanes, for which few alternative methods have been reported.[12,13]

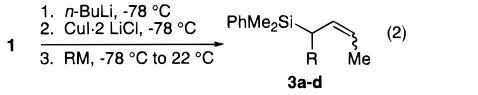
Upon examining synthetic routes to allylsilane **2**, we chose to use the copper-mediated alkylation of allylic carbamates[7,9] to favor γ-substitution at the more hindered allylic terminus. Deprotonation of carbamate **1**, followed by complexation with CuI·2LiCl, and addition of (trimethylsilyl)methyllithium[14] produced the (*E*)-allylsilane with low selectivity (*E*:*Z* = 71:29, eq 1).[15] In contrast, use of (trimethylsilyl)methylmagnesium chloride as the nucleophile surprisingly afforded **2** in good yield, with high γ-selectivity



M	*E* : *Z*	Yield (%)
Li	71 : 29	64
MgCl	6 : 94	82

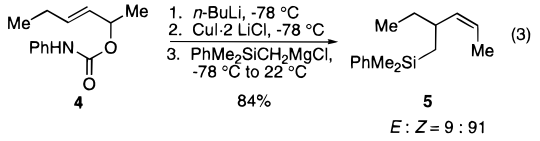
and *high (Z)-selectivity* (*E*:*Z* = 6:94).[16,17] This unexpected change in alkene stereoselectivity must be a function of the change in organometallic reagent, not an inherent selectivity of this substrate.

The reversal of selectivity observed with lithium versus magnesium reagents is a general phenomenon with allylic carbamate **1** as substrate. Upon changing only the metal in the nucleophile, in all cases alkyllithium reagents showed (*E*)-selectivity, whereas use of alkylmagnesium reagents resulted in high (*Z*)-selectivity (eq 2, Table 1).[17] Furthermore, γ:α-selectivity



(S_N2':S_N2) is consistently high for both lithium and magnesium. The drop in (*Z*)-selectivity with isopropylmagnesium chloride demonstrates that there may be a limit to the size of the group tolerated in the allylic position (entry 7). However, even with this secondary nucleophile, the (*Z*)-isomer is still favored (*E*:*Z* = 13:87).

The presence of the vinylsilane moiety on the allylic carbamate is not necessary for (*Z*)-selectivity, as demonstrated by the substitution reaction of carbamate **4**. Complexation of **4** with copper(I) iodide followed by treatment with (dimethylphenylsilyl)-methylmagnesium chloride afforded the (*Z*)-alkene **5** in high yield with high selectivity (*E*:*Z* = 9:91, eq 3).[17] This ratio is comparable



to that obtained with the corresponding vinylsilane **1** (*E*:*Z* = 4:96, entry 5, Table 1). Thus, the copper-mediated reactions of allylic carbamates with organomagnesium reagents represent a general synthesis of (*Z*)-olefins branched at the allylic position.

The stereochemistry at the newly formed allylic center was established by submission of optically active carbamate (*R*)-**1**[18]

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(15) Although the use of Goering's conditions (MeLi and CuI) gave comparable (*Z*)-selectivity, we found that using *n*-BuLi, lower temperatures, and CuI·2LiCl (a more soluble copper salt) resulted in more reproducible results and increased yields.

(16) Representative Experimental Procedure. To a cooled (−78 °C) solution of carbamate **1** (150 mg, 0.461 mmol) in 1.2 mL of THF was added dropwise by syringe *n*-BuLi (1.30 M solution in hexanes, 355 mL, 0.461 mmol). After 5 min, the clear yellow-orange reaction mixture was added dropwise by cannula to a cooled (−78 °C) solution of CuI·2LiCl [prepared by stirring CuI (90 mg, 0.47 mmol) and LiCl (39 mg, 0.92 mmol) in 2.3 mL of THF at 22 °C for 10 min]. After 30 min, Me_3SiCH_2MgCl (0.69 M solution in THF, 670 mL, 0.46 mmol) was added dropwise by syringe, and the reaction mixture was allowed to warm to 22 °C without removing the cold bath. After 16.5 h, 10 mL of 9:1 saturated aqueous NH_4Cl/NH_4OH and 20 mL of Et_2O were added, and the mixture was stirred for 30 min. The layers were separated, and the aqueous layer was extracted with 3 × 20 mL of Et_2O. The combined organic layers were washed with 25 mL of brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification by flash chromatography (pentane) afforded the product (*Z*)-**2** as a colorless oil (105 mg, 82%). The structure of the product was determined using IR, ^{1}H NMR, and ^{13}C NMR spectroscopies, HR-MS, and elemental analysis. The details are provided as Supporting Information.
(17) Alkene geometries were assigned by analysis of ^{1}H NMR coupling constants, by comparison of spectral data to reported data, or by comparison to reference materials. Details are provided as Supporting Information.
(18) (*R*)-**1** was prepared from the corresponding alcohol, obtained in ≥94% ee from Sharpless kinetic resolution (Kitano, Y.; Matsumoto, T.; Sato, F. *Tetrahedron* **1988**, *44*, 4073−4086). Details are provided as Supporting Information.

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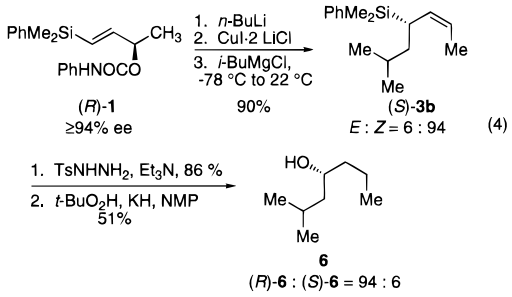
Table 1. Effect of Nucleophile on (*E*:*Z*)-Selectivity (eq 2)

entry	product	R	M	*E*:*Z*[a]	yield[b] (%)	γ:α[a]
1	**3a**	Me	MgCl	38:62	72	93:7
2			Li	92:8	72	94:6
3[c]	**3b**	*i*-Bu	MgCl	6:94	90	95:5
4			Li	91:9	69	99:1
5[d]	**3c**	$PhMe_2SiCH_2$	MgCl	4:96	68	99:1
6			Li	72:28	78	>99:1
7	**3d**	*i*-Pr	MgCl	13:87	71	>99:1

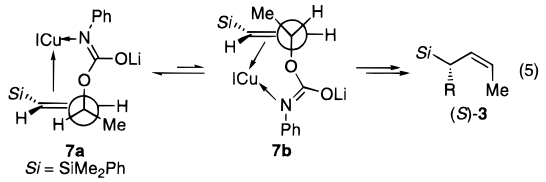
[a] Determined by GC analysis of the unpurified reaction mixture. [b] Yields reported for purified material. [c] Enantiomerically enriched **1** was employed (see eq 4). [d] CuI was used, and the reaction was performed at 0−22 °C.

to the copper-mediated reaction with isobutylmagnesium chloride (eq 4). The resultant allylsilane **3b** was reduced to the alkylsilane[19]



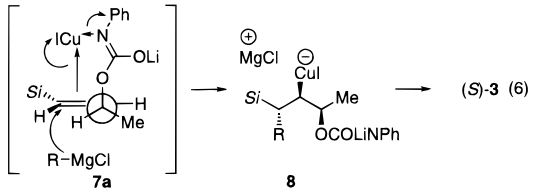
then oxidized[20] to afford the known, volatile alcohol **6** ($[\alpha]_D = -11.9°$, $[\alpha]_D$ lit. $= -11.9°$).[21] Analysis of the carbamate obtained from treatment of alcohol **6** with (*R*)-(α-methyl)benzylisocyanate by capillary GC indicated a 94:6 ratio of diastereomers. Comparison to a reference compound[22] indicated that the major diastereomer is the (*R*,*R*)-isomer. Since the oxidation of the C−Si bond occurs with retention of configuration,[20,23] this data indicates that the allylsilane **3b** has predominately the (*S*)-configuration. This experiment demonstrates that enantiomerically enriched (*Z*)-alkenes, including (*Z*)-allylsilanes, may be prepared using this methodology from readily available chiral, non-racemic allylic carbamates.

The formation of (*S*)-**3b** from (*R*)-**1** with high (*Z*)-selectivity and optical purity (eq 4) provides some insight into the mechanism of the copper-mediated substitution reactions with organomagnesium reagents. A pathway resembling the accepted mechanism for the copper-mediated syn-substitution of allylic carbamates with alkyllithium reagents[9] would be subject to serious constraints. Alkyllithium reagents are believed to provide (*E*)-alkenes by oxidative addition of the cuprate syn to the carbamate moiety in the lower energy conformation **7a** followed by reductive elimination (eq 5).[9] For the magnesium case, formation of the observed



(*Z*)-alkene by a similar syn oxidative addition[24] would require the higher energy conformer[25] **7b** to lead to the major product (eq 5). This analysis requires the reactivity of the reactant conformation to be a function of the organometallic reagent. Since the cause of this relationship between reactivity and nucleophile is not obvious, a fundamentally different mechanism may be operating.

An alternative model to explain the formation of (*Z*)-alkenes with alkylmagnesium reagents relies on an anti carbometalation followed by an anti elimination (eq 6). Since organomagnesium



reagents are less reactive than organolithium reagents,[26] formation of the alkyl cuprate of **7a** by transmetalation may be slow. Carbometalation by the Grignard reagent anti to the carbamate moiety of the copper complex, in its lower energy conformer **7a**, becomes an alternative pathway (eq 6).[27] Anti-elimination[28] from the acyclic[29] intermediate **8** would afford the observed (*Z*)-alkene.[30]

In conclusion, we have demonstrated that the use of organomagnesium reagents in copper-mediated reactions of allylic carbamates gives (*Z*)-alkenes, in a surprising reversal of stereoselectivity relative to their organolithium counterparts. This method permits the synthesis of (*Z*)-allylsilanes in high yield, with high selectivity, and with a high degree of enantiomeric purity. The change in selectivity exhibited by alkylmagnesium reagents is proposed to result from a change in the reaction pathway. Further studies to elucidate the reaction mechanism and efforts to extend the utility of this transformation are ongoing.

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Supporting Information Available: Full experimental and analytical details for all new compounds as well as detailed descriptions of the stereochemistry proofs (33 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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(24) Oxidative addition of copper anti to the carbamate moiety can be excluded. Anti oxidative addition of copper into lower energy rotamer **7a** would lead to the minor (*E*)-allylsilane. Anti oxidative addition into higher energy rotamer **7b** would have afforded the (*R*)-enantiomer of **3b**.

(25) To result in the observed (*E*:*Z*)-ratio of 4:96, the transition state resembling the disfavored methyl in-plane conformation would need to be favored by approximately 1.4 kcal/mol. For a discussion of allylic strain, see: Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841−1860.

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(30) The minor (*E*)-isomer of **3b** appears to possess the (*R*)-stereochemistry because of the relationship between (*E*:*Z*)-selectivity and optical purity (eq 4). This (*E*)-isomer of **3b** may be formed from the organomagnesium reagent by the mechanism accepted for alkyllithium reagents.