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Stereoselective Formation of Trisubstituted (*Z*)-Chloroalkenes Adjacent to a Tertiary Carbon Stereogenic Center by Organocuprate-Mediated Reduction/Alkylation

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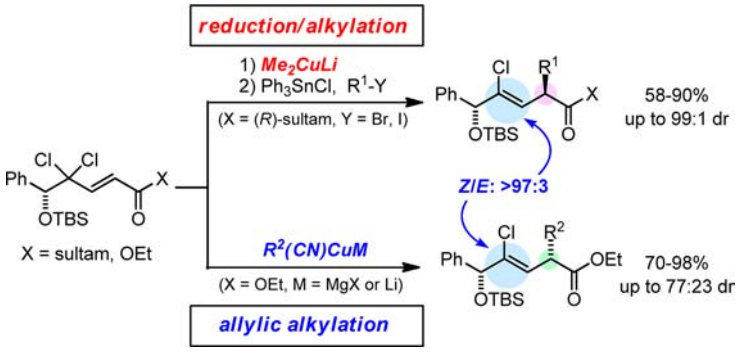
ABSTRACT



A robust and efficient method for the synthesis of trisubstituted (*Z*)-chloroalkenes is described. A one-pot reaction of γ,γ-dichloro-α,β-enoyl sultams involving organocuprate-mediated reduction/asymmetric alkylation affords α-chiral (*Z*)-chloroalkene derivatives in moderate to high yields with excellent diastereoselectivity, and allylic alkylation of internal allylic *gem*-dichlorides is also demonstrated. This study provides the first examples of the use of allylic *gem*-dichlorides adjacent to the chiral center for novel 1,4-asymmetric induction.

Stereoselective formation of functionalized alkenes is a challenging task in organic synthesis, and construction of halogenated alkenes while controlling the geometry of double bonds is of particular interest.[1] Among various halogenated alkenes, chloroalkenes have attracted considerable interest in recent years,[2−6] not only because of their potential as synthetically valuable intermediates[7] but also because of their importance as structural components of natural products.[8]

(1) (a) Guinchard, X.; Roulland, E. *Synlett* **2011**, *19*, 2779. (b) Shen, Y. *ACC. Chem. Res.* **1998**, *31*, 584.

(2) For selected reviews of chloroalkene syntheses, see: (a) *Comprehensive Organic Functional Group Transformations*; Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Eds.; Pergamon Press: Oxford, 1995; Vol. 2, pp 606−619. (b) *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Semmelheck, M. F., Eds.; Pergamon Press: Oxford, 1991; Vol. 4, pp 272−278. (c) *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Schreiber, S. L., Eds.; Pergamon Press: Oxford, 1991; Vol. 1, pp 807−809.

(3) For some examples of trisubstituted (*E*)-chloroalkene syntheses, see: (a) Kigoshi, H.; Kita, M.; Ogawa, S.; Itoh, M.; Uemura, D. *Org. Lett.* **2003**, *5*, 957. (b) Trost, B. M.; Pinkerton, A. B. *J. Am. Chem. Soc.* **1999**, *121*, 1988.

(4) For examples of terminal (*Z*)-chloroalkene syntheses, see: (a) Giannerini, M.; Fañanás-Mastral, M.; Feringa, B. L. *J. Am. Chem. Soc.* **2012**, *134*, 4108. (b) Sashuk, V.; Samojłowicz, C.; Szadkowska, A.; Grela, K. *Chem. Commun.* **2008**, 2468. (c) Barluenga, J.; Moriel, P.; Aznar, F.; Valdés, C. *Adv. Synth. Catal.* **2006**, *348*, 347. (d) Baati, R.; Barma, D. K.; Krishna, U. M.; Mioskowski, C.; Falck, J. R. *Tetrahedron Lett.* **2002**, *43*, 959 and references cited therein.

(5) (a) Baati, R.; Barma, D. K.; Falck, J. R.; Mioskowski, C. *J. Am. Chem. Soc.* **2001**, *123*, 9196. (b) Falck, J. R.; Bandyopadhyay, A.; Barma, D. K.; Shin, D.-S.; Kundu, A.; Kishore, R. V. K. *Tetrahedron Lett.* **2004**, *45*, 3039. (c) Baati, R.; Barma, D. K.; Falck, J. R.; Mioskowski, C. *Tetrahedron Lett.* **2002**, *43*, 2183. (d) Su, W.; Jin, C. *Org. Lett.* **2007**, *9*, 993.

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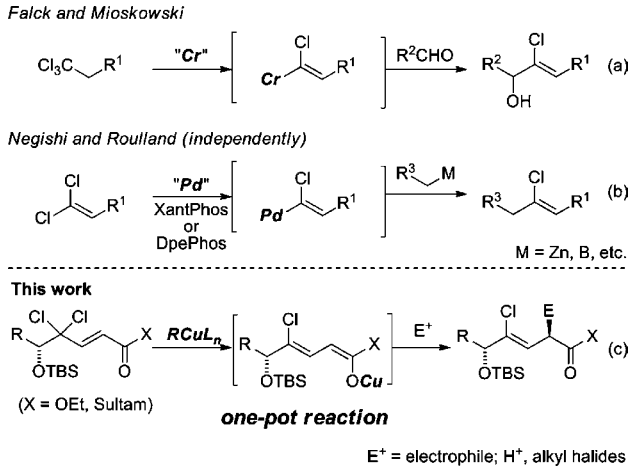
Despite the utility and importance of chloroalkenes, however, reactions leading to the stereoselective formation of trisubstituted (*Z*)-chloroalkenes are still limited.[5,6] Falck and Mioskowski reported that the reaction of $CrCl_2$ with 1,1,1-trichloroalkanes leads to the formation of (*E*)-chlorovinylidene chromium carbenoids, which can react with aldehydes to afford (*Z*)-chlorinated allylic alcohols (Scheme 1a).[5a] An alternative method is the Pd-catalyzed cross-coupling of 1,1-dichloro-1-alkenes with organometallic reagents.[6] In particular, Pd-catalyzed couplings with large bite angle bisphosphines such as Xantphos and DPEphos allow the selective formation of (*Z*)-chloroalkenes while avoiding the formation of bis-substituted products as has been described independently by Negishi[6a] and by Roulland[6b–d] (Scheme 1b). While these protocols have found widespread utility for the synthesis of these important structures, the development of efficient systems for stereoselective and divergent synthesis of trisubstituted (*Z*)-chloroalkenes bearing various functionalities remains challenging.

As part of a program aimed at development of novel approaches to chloroalkenes, we envisioned that the organocuprate-mediated reduction[9] of γ,γ-dichloro-α,β-unsaturated carbonyl compounds would permit an efficient access to (*Z*)-chlorinated dienolate intermediates, which can be trapped with an appropriate electrophile, providing trisubstituted (*Z*)-chloroalkenes (Scheme 1c).

Scheme 1. Synthesis of Trisubstituted (*Z*)-Chloroalkenes



In this paper, we describe the stereoselective formation of trisubstituted (*Z*)-chloroalkenes utilizing the organocuprate-mediated reduction/asymmetric alkylation of γ,γ-dichloro-α,β-enoyl sultam. This is a one-pot reaction which provides in high yield the synthetically valuable compounds containing a (*Z*)-chloroalkene flanking two stereogenic centers, the α-chiral-β,γ-unsaturated carbonyl motif, and a chiral allylic alcohol. In addition, we report the first allylic alkylation of *internal* allylic *gem*-dichlorides that provides an alternative method for the diastereoselective synthesis *via* 1,4-asymmetric induction of these important structural motifs.

We prepared sultam **1** and enoate **2** from chiral α,α-dichloro-β-hydroxyester,[10] reported by Imashiro and Kuroda, as suitable substrates for reaction development (Figure 1). At the onset of our studies, it was unclear if the reaction of those substrates with organocuprates would entail reduction, generating the dienolate intermediate. In order to estimate the electron-accepting ability, our investigation started with measurement of the reduction potentials (E_{Red}). The reduction potentials of sultam **1** and enoate **2** were -1.50 and -1.65 V, respectively. Based on these results and House's observation that α,β-unsaturated carbonyl compounds with reduction potentials between *ca.* -2.4 V and *ca.* -1.1 V can react with organocuprates such as Me_2CuLi to give the conjugate addition products,[11] these substrates were expected to promote both the single-electron transfer reduction and the allylic alkylation.

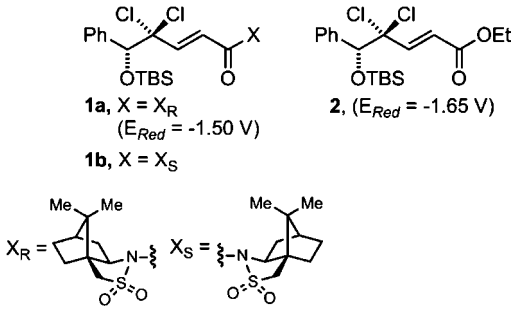


Figure 1. Substrates for organocuprate-mediated reduction and their reduction potentials (E_{Red}).

In order to control the reaction products, the reactivity of sultam **1a** with organocuprates was examined (Table 1),

(6) For selected examples of Pd-catalyzed cross-coupling, see: Cross-coupling with organozincs: (a) Tan, Z.; Negishi, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 762. Cross-coupling with organoborans: (b) Guinchard, X.; Bugaut, X.; Cook, C.; Roulland, E. *Chem.—Eur. J.* **2009**, *15*, 5793. (c) Roulland, E. *Angew Chem. Int. Ed.* **2008**, *47*, 3762. (d) Liron, F.; Fosse, C.; Pernolet, A.; Roulland, E. *J. Org. Chem.* **2007**, *72*, 2220. Cross-coupling with other organometallics, see ref 1a.

(7) (a) Geary, L. M.; Hultin, P. G. *J. Org. Chem.* **2010**, *75*, 6354. (b) Bell, M.; Poulsen, T. B.; Jørgensen, K. A. *J. Org. Chem.* **2007**, *72*, 3053. (c) Jones, G. B.; Wright, J. M.; Plourde, G. W., II; Hynd, G.; Huber, R. S.; Mathews, J. E. *J. Am. Chem. Soc.* **2000**, *122*, 1937. (d) Alami, M.; Gueugnot, S.; Domingues, E.; Linstrumelle, G. *Tetrahedron* **1995**, *51*, 1209.

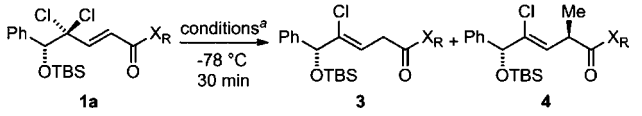
(8) For a recent example of the natural product bearing chloroalkene motif: Ando, H.; Ueoka, R.; Okada, S.; Fujita, T.; Iwashita, T.; Imai, T.; Yokoyama, T.; Matsumoto, Y.; van Soest, R. W. M.; Matsunaga, S. *J. Nat. Prod.* **2010**, *73*, 1947 and also ref 1a.

(9) For selected examples of organocuprate-mediated reduction, see: (a) Narumi, T.; Niida, A.; Tomita, K.; Oishi, S.; Otaka, A.; Ohno, H.; Fujii, N. *Chem. Commun.* **2006**, 4720. (b) Meyers, A. I.; Snyder, L. *J. Org. Chem.* **1992**, *57*, 3814. (c) Fujii, N.; Habashita, H.; Shigemori, N.; Otaka, A.; Ibuka, T.; Tanaka, M.; Yamamoto, Y. *Tetrahedron lett.* **1991**, *32*, 4969. (d) Takano, S.; Sekiguchi, Y.; Ogasawara, K. *J. Chem. Soc., Chem. Commun.* **1988**, 449 and references cited therein.

(10) Imashiro, R.; Kuroda, T. *J. Org. Chem.* **2003**, *68*, 974. For details of the preparation of sultam **1** and enoate **2**, see the Supporting Information.

(11) House, H. O.; Umen, M. J. *J. Org. Chem.* **1973**, *38*, 2417.

Table 1. Reactivity of Sultam **1a** with Organocuprates



entry	reagents	additives[b]	*Z*/*E* of **3**[c]	**3**+**4**, yield (%)[d]	**3**/**4**[c]
1	Me_2CuLi	–	>97:3	81	77:23
2	Me_2CuLi[e]	–	>97:3	93	>97:3
3	n-Bu_2CuLi[e]	–	>97:3	99	90:10
4	MeCu(CN)Li	–	>97:3	99	61:39[f]
5	Me_2CuLi[e]	TMSCl	>97:3	83	83:17
6	Me_2CuLi[e]	$BF_3\cdot OEt_2$	>97:3	91	31:69
7	Me_2CuLi[e]	HMPA	>97:3	76	>97:3
8	$Me_2Cu(CN)Li_2$	–	>97:3	99	>97:3

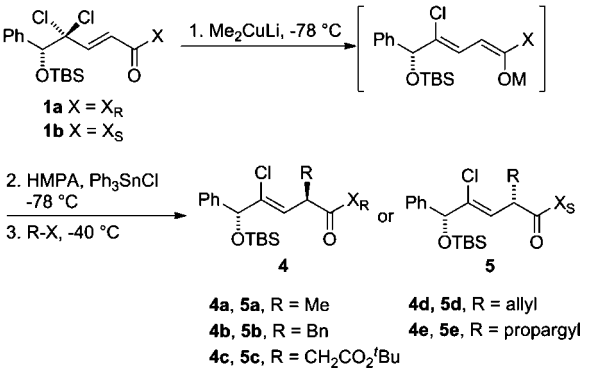
[a] All reactions were carried out on a 0.1 mmol scale with 4 equiv of organocuprates in the presence of Li salts. [b] 4 equiv. [c] Determined by ^{1}H NMR. [d] Yields of isolated products. [e] Higher order cuprates (*ca.* 0.4 equiv) were contained. [f] Diastereomeric ratio (dr) = 97:3.

and as expected, exposure of **1a** to Me_2CuLi followed by protic workup afforded a mixture of the reduced compound **3** and the α-alkylated product **4** in high yield (81%, entry 1). Significantly, excellent *Z*-selectivity was observed.[12] The use of a 2.4:1 MeLi·LiBr/CuI mixture enabled selective reduction, providing pure reduced compound **3** in excellent yield (93%, entry 2). Changing the methyl group of alkyl ligands to an *n*-butyl group resulted in decreased selectivity (entry 3). Although the reaction with lower order cyanocuprate or Me_2CuLi with TMSCl did not furnish better selectivity, addition of $BF_3\cdot OEt_2$ led to the preferable formation of α-alkylated product **4** (entries 4–6). In contrast, the reaction with HMPA provided excellent selectivity to the reduction but a decreased yield (76%, entry 7). The best result was obtained with higher order cyanocuprate, derived from CuCN·2LiCl and 2 equiv of MeLi·LiBr, which gave **3** in excellent yield and selectivity (entry 8). Having identified higher order cyanocuprate as the preferred reducing agent, we selected the Gilman reagent (Me_2CuLi) as an optimal reducing agent because of the sufficient reactivity and selectivity to reduction.

The optimized reduction condition in Table 1 (entry 2) was applied to the one-pot reduction/asymmetric alkylation (Table 2). Previous studies have revealed that the transmetalation from Cu and/or Li dienolate intermediates to the more reactive Sn dienolate intermediates is critical for smooth alkylation.[9a] A variety of alkyl halides were allowed to react with the (*Z*)-chlorinated dienolate intermediate to provide chloroalkenes **4a**–**4e** flanking two stereogenic centers in moderate to high yield with >97% *Z*-selectivity. HPLC analysis showed that all the reactions

(12) A NOESY cross-peak was observed between the olefinic proton and the allylic stereogenic center, suggesting that the geometry of the double bond was defined as shown; see the Supporting Information.

Table 2. One-Pot Reduction/Asymmetric Alkylation of (*R*)-Sultam **1a** and (*S*)-Sultam **1b**[a]



entry	substrate	R–X	**4** or **5**, yield (%)[b]	dr (%)[c]
1	**1a**	MeI	**4a**, 58	97:3
2[d]	**1a**	BnBr	**4b**, 83	99:1
3	**1a**	$BrCH_2CO_2{}^tBu$	**4c**, 90	97:3
4	**1a**	allylBr	**4d**, 81	97:3
5[d]	**1a**	propargylBr	**4e**, 82	>95:5[e]
6	**1b**	MeI	**5a**, 60	99:1
7	**1b**	BnBr	**5b**, 86	95:5
8	**1b**	$BrCH_2CO_2{}^tBu$	**5c**, 57	97:3
9	**1b**	allylBr	**5d**, 70	97:3
10[d]	**1b**	propargylBr	**5e**, 46	>95:5[e]

[a] All reactions were carried out with 4 equiv of organocuprates, 16 equiv of HMPA, 2 equiv of Ph_3SnCl, and 8 equiv of alkyl halide. [b] Yields of isolated products. [c] Determined by HPLC. [d] At −30 °C. [e] Determined by ^{1}H NMR.

proceeded with excellent diastereoselectivity. The reactions with methyl iodide and bezyl bromide provided the corresponding α-alkylated products **4a** and **4b** in 58% and 83% yields, respectively (entries 1 and 2), and the absolute configuration of **4a** was confirmed by single-crystal X-ray analysis (Figure 2). Importantly, this strategy is amenable to the introduction of functional groups such as ester, allyl, and propargyl groups suitable for further transformation. Treatment of dienolate with *tert*-butyl bromoacetate and allyl bromide afforded the desired (*Z*)-chloroalkenes **4c** and **4d** with ester and allyl functionality, in high yields (entries 3 and 4). Propargyl bromide also gave the corresponding (*Z*)-chloroalkene **4e** in moderate yield (entry 5). In addition, this one-pot strategy can be applied to (*S*)-sultam **1b**, providing the corresponding chloroalkenes **5a**–**5e** in moderate to high yields (entries 6–10).

Finally, allylic alkylation of allylic *gem*-dichlorides was examined. Recently, Feringa reported that terminal allylic *gem*-dichlorides undergo Cu-catalyzed asymmetric allylic alkylation with Grignard reagents affording (*Z*)-chloroalkenes bearing an allylic stereogenic center with excellent regio- and enantioselectivity.[4a] Guided by this work, we attempted Cu-catalyzed S_N2'-type alkylation with γ, γ-dichloro-α,β-enoate **2**, but these conditions did not work for enoate **2**, possibly due to the lower reactivity of the

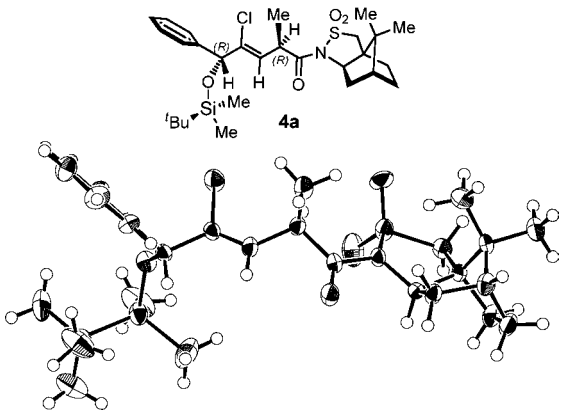
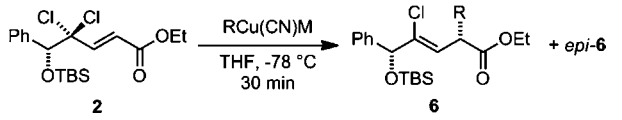


Figure 2. ORTEP representation of **4a**.

Table 3. Diastereoselective Allylic Alkylation of γ,γ-Dichloro-α,β-enoate **2** by 1,4-Asymmetric Induction[a]



entry	RCu(CN)M	Z/E[b]	**6**, yield (%)[c]	dr[d]
1	MeCu(CN)Li	>97:3	**6a**, 98	74:26
2	EtCu(CN)MgBr	>97:3	**6b**, 96	66:34
3	BnCu(CN)MgCl	>97:3	**6c**, 70	77:23
4	^{i}BuCu(CN)MgCl	>97:3	**6d**, 95	69:31

[a] All reactions were carried out on a 0.2 mmol scale with 4 equiv of organocuprates in the presence of Li salts. [b] Determined by ^{1}H NMR. [c] Yields of isolated products. [d] Determined by HPLC.

internal allylic system (see Supporting Information). Attention was therefore turned to the organocuprate-mediated allylic alkylation. As presented in Table 1 (entry 4), the lower order cyanocuprate (MeCu(CN)Li) promotes the allylic alkylation preferably to provide the α-methylated product **4a** with excellent diastereoselectivity (dr = 97:3). Extensive experimentation with MeCu(CN)Li revealed that the electron transfer from organocuprates competes significantly with allylic alkylation of the sultam **1a**, and the exclusive formation of **4a** was not realized. During the course of our studies on the allylic alkylation, we considered that the chiral center at C5 adjacent to the allylic *gem*-dichloride might induce the diastereoselectivity without chiral auxiliaries.

This hypothesis was tested with the enoate **2**. As shown in Table 3, treatment of **2** with MeCu(CN)Li afforded the α-methylated β,γ-enoate **6a** in 98% yield as a 74:26 mixture of diastereomers with excellent *Z*-selectivity. The major isomer was the (2*S*)-isomer, identified by the correlation with the same compound **6a**, prepared from the corresponding (*S*)-sultam-derived compound **5a**.[13] Similar results were obtained using EtCu(CN)MgBr, BnCu(CN)-MgCl, and *i*BuCu(CN)MgCl affording the corresponding α-alkylated chloroalkenes **6b**–**d** in high yields with similar selectivities (entries 2–4). Although the observed diastereoselectivity has not been rationalized,[14] these results suggest that stereochemistry at C2 can be controlled by the chiral center at C5 *via* 1,4-asymmetric induction.

In conclusion, we have described a one-pot organocuprate-mediated reduction/asymmetric alkylation of γ,γ-dichloro-α,β-unsaturated carbonyl compounds. This protocol allows not only the exclusive formation of trisubstituted (*Z*)-chloroalkenes in high yields but also the construction of an α-stereogenic center with excellent diastereoselectivity. The resulting products are notable for their high functionality and can perform as a potentially useful intermediate for this important class of molecules. In addition, we have identified a unique reactivity of substrates containing an allylic *gem*-dichloride system with organocuprates. These findings have proven to be useful for the development of novel reactions based on these classes of molecules. Efforts to elucidate the origin of novel 1,4-asymmetric induction and to extend this work to the diastereoselective synthesis of peptidomimetics with a chloroalkene moiety are currently in progress.

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Supporting Information Available. Representative procedures, characterization data, cif file of compound **4a**, and copies of NMR and HPLC spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

(13) See the Supporting Information for details.

(14) At the present stage of our understanding, the steric repulsions between the olefinic proton at C3 and the Ph group at C5 may destabilize the reactive conformer, which would lead to the (2*R*)-isomer. DFT calculations also suggest that the reactive conformer to the (2*S*)-isomer is favored by 4.42 kJ/mol over the conformer to the (2*R*)-isomer. See the Supporting Information.

The authors declare no competing financial interest.