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Remote Stereoinduction in the Organocuprate-Mediated Allylic Alkylation of Allylic *gem*-Dichlorides: Highly Diastereoselective Synthesis of (*Z*)-Chloroalkene Dipeptide Isosteres

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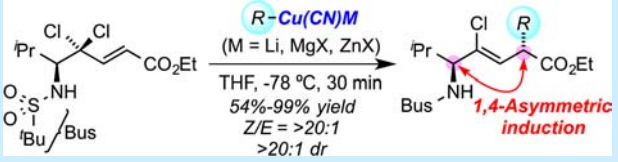
Supporting Information

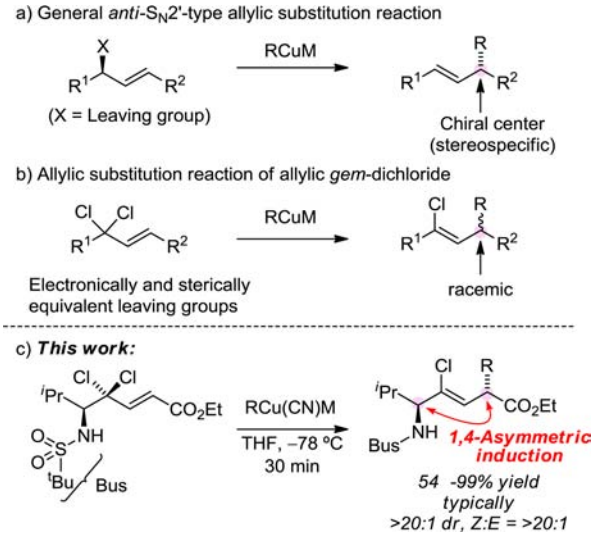
ABSTRACT: Highly diastereoselective synthesis of (*Z*)-chloroalkene dipeptide isosteres has been achieved by 1,4-asymmetric induction in the organocuprate-mediated allylic alkylation adjacent to the chiral center of allylic *gem*-dichlorides. The reaction proceeds with a variety of heterocuprates prepared from CuCN and various organometallic reagents. It allows rapid construction of valuable architectures of L,D-type and L,L-type (*Z*)-chloroalkene dipeptide isosteres from the corresponding (*E*)- and (*Z*)-allylic *gem*-dichlorides in high yields, with excellent (*Z*)-selectivity and diastereoselectivity.



The discovery of novel synthetic methods for stereoselective formation of structurally complex organic molecules with high levels of efficiency and selectivity remains a challenge in organic synthesis. Asymmetric inductions by preexisting stereogenic centers provide reliable methods for the facile construction of synthetically valuable building blocks bearing multiple chiral centers[1] and remote asymmetric inductions such as 1,4-,[2] 1,5-,[3] and 1,6-stereorelationships[4] are of particular interest because of the synthetic utility that can provide potentially intriguing synthetic strategies to complex molecules.[2c,3e,f,4a,b]

Our group has focused on the synthetic and application studies of chloroalkenes, which are synthetically versatile intermediates[5] and structural constituents of marine natural products.[6] Recently, we have identified 1,4-asymmetric induction in the allylic alkylation of allylic *gem*-dichlorides adjacent to the chiral center, which can provide facile access to trisubstituted (*Z*)-chloroalkenes flanking two stereogenic centers with moderate diastereoselectivity.[7] While the allylic substitution reaction with an organocopper reagent takes place stereospecifically on the *anti*-face to the leaving group of allylic electrophiles (*anti*-S_N2' manner, Scheme 1a),[8] the stereoselective reaction of allylic *gem*-dichlorides is particularly challenging since allylic *gem*-dichlorides have two electronically and sterically equivalent leaving groups that impose severe limitations on the *anti*-S_N2' strategy and depend on the stereochemistry of the leaving group (Scheme 1b). Our observed moderate diastereoselectivity in the allylic alkylation of allylic *gem*-dichlorides has been achieved by means of the induction exerted by the chiral center at C5 bearing noncoordinating phenyl and siloxy groups. These results suggest the possibility that the introduction of a coordinating group such as a sulfonamide[9] at C5 could control the facial attack of allylic electrophiles to provide the trisubstituted (*Z*)-chloroalkene flanking two stereogenic centers bearing the amino functionality.

Scheme 1. Allylic Substitution Reaction with Organocopper Reagents



These motifs are highly attractive for the peptidomimetics having a functionalized alkene as a peptide bond surrogate (alkene-type dipeptide isosteres: ADIs), which have been thought of as one of the most ideal dipeptide mimetics for the study of medicinal chemistry and chemical biology.[10] In this paper, we wish to report the first highly diastereoselective 1,4-asymmetric induction in the allylic alkylation of allylic *gem*-dichlorides utilizing various organocuprates to afford (*Z*)-chloroalkene

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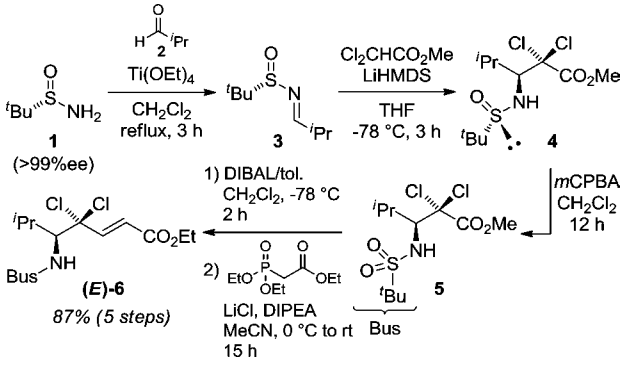
dipeptide isosteres (CADIs) in high yields and with excellent (*Z*)-selectivity and diastereoselectivity (Scheme 1c). Importantly, this method provides an efficient access to synthesis of both L,L-type and L,D-type (*Z*)-CADIs by simply switching the olefin geometry of the allylic *gem*-dichlorides.

Our study began with the preparation of the key intermediate, (2*E*)-γ,γ-dichloro-α,β-enoate (*E*)-**6**, with the chiral center at C5 bearing a sulfonamide group. In seeking to develop an effective approach, we employed for the protection of amine functionality an *N*-*tert*-butylsulfonyl (Bus) group[11] that would be tolerated in the multistep synthesis and that can be easily prepared by oxidation of an *N*-sulfinyl group[11] and removed by treatment with $AlCl_3$.[12] As shown in Scheme 2, nucleophilic addition of the

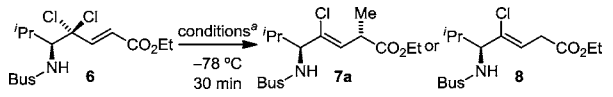
Scheme 2. Preparation of (*E*)-6



lithium enolate of methyl dichloroacetate to the chiral *N*-sulfinylaldimine **3**, prepared from (*S*)-*tert*-butylsulfinamide **1**[13] and isobutyl aldehyde **2**, provided the corresponding ester **4**[14] with high diastereoselectivity (>20:1) through the six-membered chairlike transition-state model.[15] Oxidation of the *N*-sulfinyl group with *m*-CPBA provided the *N*-Bus-protected α,α-dichloro-β-amino ester **5** as a single enantiomer. Reduction of **5** with DIBAL-H followed by Horner−Wadsworth−Emmons reaction afforded the desired (*E*)-enoate (*E*)-**6**. Since those five steps proceeded smoothly to provide the desired compounds, only one purification by flash chromatography was required in the last step to prepare (*E*)-**6** in 87% isolated yield (five steps).

With a suitable substrate in hand, we examined the allylic alkylation of (*E*)-**6** with various organocuprates (Table 1). All of the reactions tested provided (*Z*)-chloroalkene products **7a** and **8** with undetectable amounts of the (*E*)-chloroalkene isomers (*Z*/*E* = >20:1). It was found that the choice of organocuprates is critical. The use of Gilman cuprate ($Me_2CuLi{\cdot}LiI{\cdot}2LiBr$) afforded only the reductive dechlorinated compound **8** (Bus-L-Val-ψ[(*Z*)-CCl=CH]-Gly-OEt) in 97% yield via possibly a single-electron-transfer mechanism (entry 1).[16] On the other hand, cyanocuprates prepared from CuCN and organometallic reagents effectively provided the desired α-methylated compound **7a** (Bus-L-Val-ψ[(*Z*)-CCl=CH]-D-Ala-OEt) (entries 2−9). The reaction with MeCu(CN)Li·LiBr afforded **7a** in 90% yield, and remarkably, the reaction proceeded with an excellent degree of diastereoselectivity (entry 2). The absolute stereochemistry of **7a** was established by X-ray analysis and the single diastereomer obtained corresponded to an L,D-type isostere.[17] The addition of 1 equiv of LiCl against organocuprates resulted in a slightly improved yield and product selectivity (entry 3), whereas the reaction with additional LiCl or $BF_3{\cdot}OEt_2$ led to similar results (entries 4 and 5). We then turned our attention toward exploration of the use of other methylmetal species for

Table 1. Reactivity of (*E*)-6 with Organocuprates



entry	reagents	additive (equiv)	7a:8[b]	7a or 8 yield[c] (%)	dr[b], 7a
1	$Me_2CuLi{\cdot}LiI{\cdot}2LiBr$		1:>20	**8**, 97	
2	MeCu(CN)Li·LiBr		13:1	**7a**, 90	>20:1[d]
3	MeCu(CN)Li·LiBr	LiCl (4)	>20:1	**7a**, 99	>20:1[d]
4	MeCu(CN)Li·LiBr	LiCl (8)	16:1	**7a**, 91	>20:1[d]
5	MeCu(CN)Li·LiBr	LiCl (4), $BF_3{\cdot}OEt_2$ (4)	19:1	**7a**, 91	>20:1[d]
6	MeCu(CN)MgBr	LiCl (4)	7:1	**7a**, 84	>20:1[d]
7[e]	MeCu(CN)ZnCl	LiCl (8)	>20:1	**7a**, 86%	>20:1[d]
8[e]	MeCu(CN)ZnMe	LiCl (8)	>20:1	**7a**, 88%	>20:1[d]
9[f]	MeCu(CN)$AlMe_2$	LiCl (8)	>20:1	**7a**, 85%	>20:1[d]

[a]Unless otherwise noted, all reactions were carried out at −78 °C for 30 min on a 0.1 mmol scale with 4 equiv of organocuprates in the presence of metal salts. [b]Determined by ^{1}H NMR with an unpurified reaction mixture. [c]Yields are for the isolated products. [d]Only a single diastereomer was detected. [e]0 °C for 2 h. [f]0 °C for 4 h.

the preparation of methyl cyanocuprates (entries 6−9), since the acceptance of various organometallic reagents can give an advantage to the diversity of the α-substituent that corresponds to the side chain of amino acids. In all tested methylmetal species, full conversion was obtained and the type of organometallic reagents did not influence the stereochemical outcome of the reaction. The use of MeMgBr gave a slightly lower yield and product selectivity (entry 6). The use of MeZnCl obtained by transmetalation from MeMgBr with $ZnCl_2$ had a beneficial effect on the product selectivity and led to the exclusive formation of the desired α-methylated compound **7a** with excellent diastereoselectivity (entry 7). Further, Me_2Zn and Me_3Al can also be used without a decrease of diastereoselectivity, although with slightly lower yields (entries 8 and 9).

Having identified reliable conditions, the scope of this diastereoselective allylic alkylation was explored (Table 2). The reaction was found to tolerate various alkyl cyanocuprates, providing the regio- and diastereoselective 1,4-asymmetric induction products **7a−i** in moderate to excellent yields (54−99%) (entries 1−9). In all cases, α-alkylated products were obtained with excellent *Z*-selectivity and diastereoselectivity (>20:1). When the organocuprates, prepared from Et_2Zn, ^{n}BuLi, or ^{i}BuMgBr, were employed, the corresponding α-alkylated products **7b−d** could be isolated in excellent yield (entries 2−4). Similarly, the organocuprates, prepared from benzylMgCl or (2-naphthylmethyl)MgBr, effectively led to **7e** (Bus-L-Val-D-Phe-OEt) and **7f** (Bus-L-Val-D-Nal-OEt) in 99% and 94% yields, respectively (entries 5 and 6). The functionalized zinc−copper reagent, derived from zinc homoenolate which was generated *in situ* from $ZnCl_2$ and (1-ethoxycyclopropoxy)trimethylsilane),[18] also participated in diastereoselective alkylation to give the α-alkylated product **7g** (Bus-L-Val-D-Glu(OEt)-OEt) bearing an ester functionality (entry 7). Interestingly, this new strategy is also applicable to α-allylation (allyl−allyl cross-coupling), a challenging task in organocopper chemistry.[19−21] The allyl zinc−

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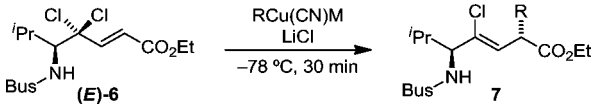
Table 2. Scope of Diastereoselective Allylic Alkylation of (*E*)-6



entry	RCu(CN)M[a]	*Z*/*E*[b]	7, yield[c] (%)	dr[b]
1	MeCu(CN)Li·LiBr[d]	>20:1	**7a**, 99	>20:1
2	EtCu(CN)ZnEt	>20:1	**7b**, 99	>20:1
3	^{n}BuCu(CN)Li	>20:1	**7c**, 94	>20:1
4	^{i}BuCu(CN)MgBr	>20:1	**7d**, 99	>20:1
5	benzylCu(CN)MgCl	>20:1	**7e**, 99	>20:1
6	(2-naphthyl)Cu(CN)MgBr	>20:1	**7f**, 94	>20:1
7	$EtO_2C(CH_2)_2Cu(CN)ZnCl$	>20:1	**7g**, 98	>20:1
8	allylCu(CN)ZnCl	>20:1	**7h**, 54	>20:1
9	2,6-diMe-C_6H_3Cu(CN)ZnCl	>20:1	**7i**, 96	>20:1

[a]Unless otherwise noted, all reactions were carried out at −78 °C for 30 min on a 0.1 or 0.3 mmol scale with 4 equiv of organocuprates in the presence of metal salts and an additional 8 equiv of LiCl. [b]The *Z*/*E* ratio and dr values were determined by ^{1}H NMR with an unpurified reaction mixture. [c]Yields are for the isolated product. [d]With an additional 4 equiv of LiCl.

copper reagent, obtained by transmetalation from allylmagnesium chloride with $ZnCl_2$, also reacts with excellent diastereoselectivity, furnishing the synthetically useful α-allylated product **7h** in moderate yield (entry 8). However, the allyl cyanocuprate, prepared directly from allylmagnesium bromide, gave only reduction product **8** and no alkylated product, clearly indicating the utility of transmetalation from Grignard reagents with Zn salts in this reaction system. A similar superiority was observed with a sterically hindered 2,6-dimethylphenyl cyanocuprate: the transmetalation from 2,6-dimethylphenylmagnesium bromide to 2,6-dimethylphenylzinc chloride produced **7i** with a significant increase in yield (from 65% to 96%) (entry 9).

This exclusive formation of L,D-type isosteres **7** with a (*Z*)-alkene structure suggests that allylic alkylation of (*E*)-**6** can occur only by the stereospecific facial attack of organocuprates to allylic electrophiles. The general *anti*-selectivity in organocuprate-mediated S_N2' reactions invoked two conformers **A** and **B**, either of them allowing the *anti*-parallel position of the organocuprate and the leaving chloride group (Scheme 3). Although the steric repulsion between the isopropyl group and an olefinic proton would partly destabilize the conformer **A**, the steric repulsions could be reduced between C4, bearing two chloride groups and C5, bearing bulky isopropyl and Bus-protected amino groups as shown in the staggered conformation **C**, in which the facial attack of organocuprates would be supported by the coordination effect of the sulfonamide group at C5, leading to the exclusive formation of **7a**. On the other hand, there is potential steric repulsion between the two chloride groups and the isopropyl group in the other staggered conformation **D**, resulting in the destabilization of the conformer **B** to prevent the formation of **9a**.[22]

To better rationalize the observed diastereoselectivity and stereochemical outcome, we have considered the geometry switching of the double bond from (*E*)-enoate to (*Z*)-enoate, which would lead to the stereoselective formation of L,L-type isosteres. Thus, (2*Z*)-γ,γ-dichloro-α,β-enoate (*Z*)-**6** was prepared and applied to the allylic alkylation (Table 3). It is noteworthy that (*Z*)-**6** also worked efficiently in the allylic alkylation to provide the corresponding α-alkylated products

Scheme 3. Possible Mechanism of Diastereoselectivity via 1,4-Asymmetric Induction

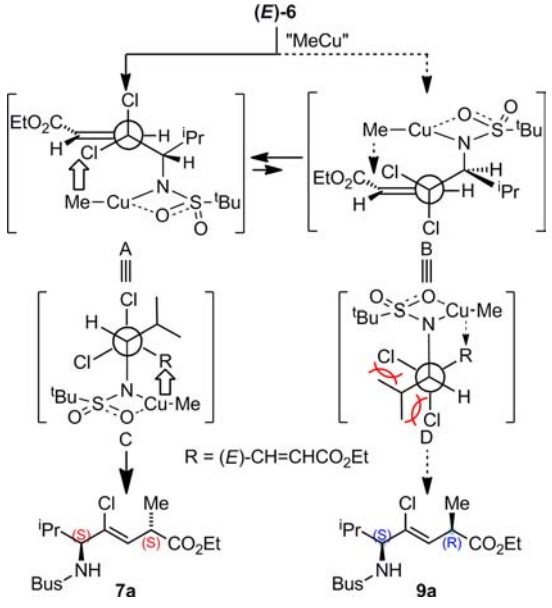
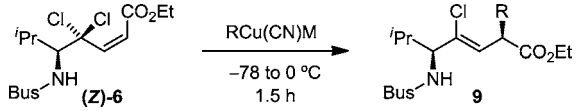


Table 3. Scope of Diastereoselective Allylic Alkylation of (*Z*)-6[a]



entry	RCu(CN)M	*Z*/*E*[b]	**9**, yield[c] (%)	dr[b]
1	MeCu(CN)ZnCl	>20:1	**9a**, 99	>20:1
2	EtCu(CN)ZnEt	>20:1	**9b**, 95	>20:1
3	^{n}BuCu(CN)ZnCl	>20:1	**9c**, 92	>20:1
4	^{i}BuCu(CN)ZnBr	>20:1	**9d**, 92	>20:1
5	benzylCu(CN)ZnBr	>20:1	**9e**, 99	>20:1
6	(2-naphthyl)Cu(CN)ZnCl	>20:1	**9f**, 99	>20:1
7	$EtO_2C(CH_2)_2Cu(CN)ZnCl$	>20:1	**9g**, 93	>20:1
8	allylCu(CN)ZnCl	>20:1	**9h**, 51	>20:1
9	2,6-diMe-C_6H_3Cu(CN)ZnCl	>20:1	**9i**, 94	>20:1

[a]All reactions were carried out at −78 °C for 1.5 h on a 0.3 mmol scale with 6 equiv of organocuprates in the presence of metal salts. [b]The *Z*/*E* ratio and dr values were determined by ^{1}H NMR with an unpurified reaction mixture. [c]Yields are for the isolated product.

9a−**i** without a significant decrease of reaction yields and diastereoselectivity (entry 1−9). As expected, the stereochemistry of **9a**−**i** corresponded to L,L-type isosteres, indicating that allylic alkylation of allylic *gem*-dichlorides proceeds through the stereospecific facial attacks of organocuprates, which is a key intermediate of the stereochemical outcome.

In conclusion, we have described a highly diastereoselective allylic alkylation of allylic *gem*-dichlorides with organocuprates via 1,4-asymmetric induction. The diastereoselective synthesis of both L,L-type and L,D-type (*Z*)-chloroalkene dipeptide isosteres can be achieved in high yields by this strategy with excellent (*Z*)-selectivity and diastereoselectivity. The use of zinc−copper reagents was found to increase the chemical yields and product selectivity of the reaction. Continuing investigations on the unique reactivity of allylic *gem*-dichlorides and studies on the applications of the obtained isosteres to the synthesis of biologically active peptides are proceeding.

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■ ASSOCIATED CONTENT

Supporting Information

Experimental detail, synthesis, characterization data, and X-ray data (CIF). The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b00611.

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Notes

The authors declare no competing financial interest.

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(22) An alternative explanation would involve the *syn*-S_N2' pathway from the conformer **B**. The leaving Cl group could potentially attract the organocuprate to afford **7a**. See the Supporting Information for details.

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