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Z-Selective Copper-Catalyzed Asymmetric Allylic Alkylation with Grignard Reagents

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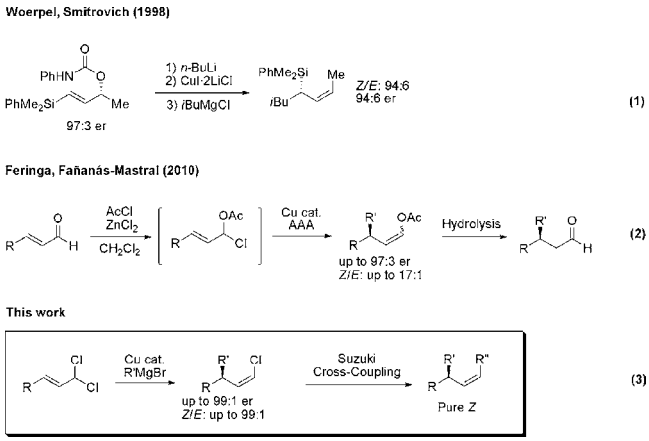
Supporting Information

ABSTRACT: Allylic *gem*-dichlorides undergo regio- and enanantioselective (er up to 99:1) copper-catalyzed allylic alkylation with Grignard reagents affording chiral *Z*-vinyl chlorides. This highly versatile class of synthons can be subjected to Suzuki cross coupling affording optically active *Z*-alkenes and 1,3-*cis,trans* dienes.

The alkene moiety is one of the most widespread functional groups in chemistry and the chemo- and the stereoselective formation and conversion of a carbon−carbon double bond is key to numerous synthetic transformations.[1,2] So far catalytic methodologies for the exclusive preparation of the higher-energy *Z*-stereoisomer are scarce.[3,4] Despite significant recent progress[3,4] new procedures capable to ensure the formation of a *Z*-olefin, in particular bearing functionality enabling stereoselective cross-coupling reactions, will provide precious tools for synthetic chemistry. As the presence of multiple stereochemical elements is a recurrent feature in biological active molecules, it is worthwhile to note that frequently a *Z*-olefin (or diene) is accompanied by a stereocenter in the allylic position.[5] Therefore, a highly desirable and attractive approach toward these structures is an enantioselective catalytic process capable of both generating the α-stereocenter and the *Z*-olefin in a single step; methodology we present here.

Allylic substitution[6] represents a powerful method for C−C bond formation, in particular when simultaneously a stereocenter is introduced in the allylic position of the resulting alkene product. However, the control of the geometry of the double bond still remains a major issue. Goering et al. showed that the S_N2' substitution of 1,1-disubstituted allylic substrates with alkyl cuprates leads predominantly to the formation of the *E*-isomer.[7] Few nonenantioselective examples have been reported in which the allylic substitution promoted the formation of the *Z*-isomer. The Cu-catalyzed addition of Grignard reagents to 1-alkynyl-2-propenyl acetates results in the formation of *Z*-enynes as described by Piccardi and co-workers.[8] Hoveyda et al. showed that, by placing a directing phosphine group in the substrate, a nickel-catalyzed γ-allylic alkylation gives rise to a predominance in the formation of the *Z*-isomer, depending on the nature of the substrate and the position of the phosphine group.[9] Trost and co-workers reported how the use of a chiral racemic ligand in a Pd-catalyzed α-allylic substitution with substrates with a pre-existing *E* double bond could lead to a *Z*-olefin in the product.[10] A chiral substrate-based stoichiometric protocol for

Scheme 1. State of the Art on Asymmetric *Z*-Selective γ-Allylic Alkylation



the *Z*-selective γ-allylic alkylation of optically active allylcarbamates with Grignard reagents in the presence of copper (Scheme 1, eq 1) was introduced by Woerpel and co-workers.[11]

Cu-catalyzed asymmetric allylic alkylation (AAA)[12] has been extensively applied to the synthesis of chiral nonracemic terminal olefins. However, the possibility of obtaining enantioenriched internal olefins with the *Z-geometry* via this procedure has been scarcely explored. Recently our group reported how in situ generated α-chloroacetates undergo AAA to afford enol acetates with *Z*-selectivity (Scheme 1, eq 2).[13] These products can be subsequently hydrolyzed to α,β-unsaturated aldehydes. In contrast, a Cu-catalyzed AAA protocol applied to racemic 1-methyl-substituted allylchlorides showed good enantioselectivity but gave rise to the corresponding alkenes as 1:1 *E*/*Z* mixtures.[14]

Inspired by our results achieved with α-chloroacetates[13] and realizing that the presence of two chlorides in a substrate might allow a dual role as leaving group and stereocontrol element, we envisioned that a new AAA method based on *gem*-dichlorides[15] might result in high stereoselectivity giving access, in a single step, to chiral *Z*-vinyl chorides[16] (Scheme 1, eq 3). Furthermore these products are highly valuable building blocks for cross-coupling[17] reactions giving access to, e.g., 1,3-*cis,trans*-diene moieties bearing a stereocenter in the α position (vide infra).[5]

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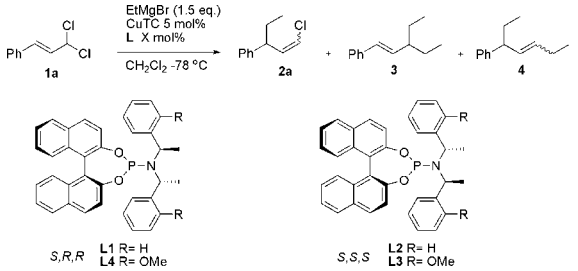
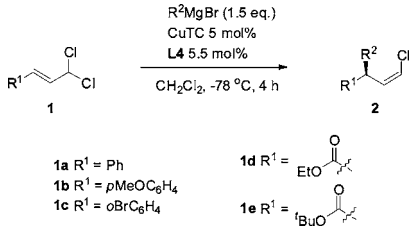
Table 1. Screening of Ligands and Conditions



entry[a]	L	X	add. time (h)	conv. (%)	**2a**/(**3** + **4**)[b]	*Z*/*E*[b,c]	er (%)[d]
1	**L1**	5.5	1	100	91:9	73:27	*Z*:81:19
							E:91:9
2	**L1**	5.5	6	100	96:4	75:25	*Z*:95:5
							E:99:1
3	**L1**	10	6	100	>98:2	75:25	*Z*:97:3
							E:99:1
4	**L2**	5.5	6	50	>98:2	95:5	*Z*:93:7
							E: n.a.[e]
5	**L3**	5.5	6	68	>98:2	93:7	*Z*:80:20
							E: n.a.[e]
6	**L4**	**5.5**	**6**	**100**	**>98:2**	**99:1**	**Z:99:1**
							***E*: n.a.**[e]

[a]Reactions were run on a 0.3 mmol scale using 1.5 equiv of EtMgBr (3.0 M in Et_2O) diluted with CH_2Cl_2 (final conc. 0.5 M) and added via syringe pump. Reaction mixture stirred for 16 h at −78 °C. [b]Determined by ^1H NMR. [c]Determined by GC. [d]Determined by chiral HPLC. [e]n.a. = not applicable.

Table 2. Scope of the Reaction



entry[a]	**1**	R^2	*Z*/*E*[b]	**2**, yield (%)	er (%)[c]
1	**1a**	Et	99:1	**2a**, 74	99:1
2	**1a**	*n*-hex	96:4	**2b**, 77	97:3
3	**1a**	Me	96:4	**2c**, 56[d]	95:5
4	**1a**	6-heptenyl	96:4	**2d**, 72	98:2
5	**1a**	*i*Bu	95:5	**2e**, 74	90:10
6	**1b**	Et	95:5	**2f**, 75	95:5
7	**1c**	Et	91:9	**2g**, 78	98:2
8	**1d**	Et	95:5	**2h**, 71	97:3
9	**1d**	*n*-hex	93:7	**2i**, 76	97:3
10	**1e**	Et	99:1	**2j**, 67	98:2

[a]Reactions were run on a 0.3 mmol scale using 1.5 equiv of R^2MgBr (sol. in Et_2O) diluted with CH_2Cl_2 and added over 6 h using a syringe pump. No S_N2 products were observed by ^1H NMR analysis of the crude mixture unless otherwise indicated. [b]Determined by GC. [c]Determined by chiral HPLC or GC. [d]S_N2'/S_N2 88:12, 90% conv.

We started our studies with the reaction between cinnamyl-derivate **1a** (see Supporting Information for details on the synthesis of dichlorides **1**) and ethylmagnesium bromide (addition time 1 h) using copper(I)-thiophene-2-carboxylate (CuTC)[18] in combination with phosphoramidite **L1**[19] (Table 1, entry 1). In this initial experiment the chemo-, regio-, and enantioselectivity of the reaction was already very high, but the most important observation was the formation of the *Z*-isomer of **2a** as the predominant product. The addition rate is often a crucial parameter in this C−C bond-forming reaction involving Grignard reagents.[13] Although a slow addition over 6 h of the organometallic reagent enhanced both the regio- and the enantioselectivity, the *Z*:*E* ratio was not affected (entry 2). The use of a 2:1 ligand/Cu ratio (entry 3) gave rise to similar results; for this reason a 1:1 ratio was employed throughout.

The most effective approach to increase selectivity was found to be through ligand screening. The use of ligand **L2** gave excellent regio- and *Z*-selectivity, but full conversion could not be achieved (entry 4). Poor conversion and lower er were also observed using ligand **L3** (entry 5). *O*-Methoxy-substituted

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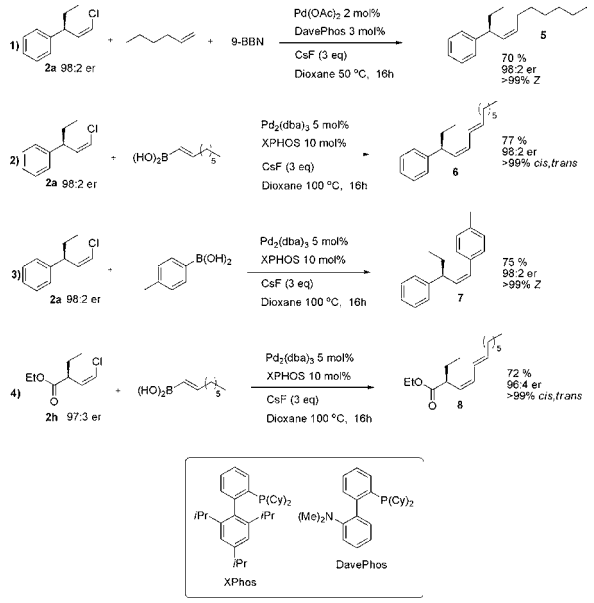
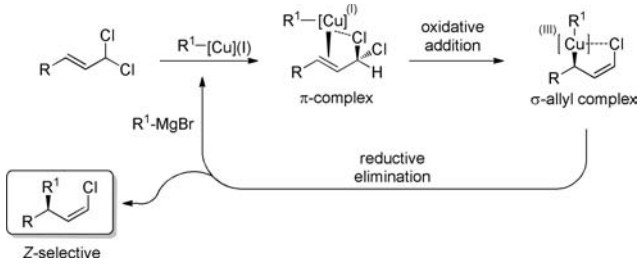
Scheme 2. Synthetic Application of *Z*-Vinyl Chlorides



phosphoramidite **L4** instead turned out to be the ligand of choice capable of imparting excellent selectivity not only for the formation of the desired branched product **2a** but also providing near perfect asymmetric induction (99:1 er). Moreover full control of the olefin geometry was obtained with exclusive formation of the *Z*-isomer (99:1 *Z*:*E* ratio, entry 6).

Once the optimized conditions were established, we studied the scope of the reaction using different dichlorides **1** and Grignard reagents. The high selectivity toward the *Z*-olefin and excellent enantioselectivity are a characteristic feature of this reaction irrespective of the nature of the substrate or the organometallic reagent (see Table 2). This includes Grignard reagents bearing a longer alkyl chain (entry 2) and MeMgBr[20] both showing high *Z*-selectivity. In the latter case the lower reactivity of MeMgBr and higher volatility of the product resulted in a decreased yield (56%) (entry 3). Also a sterically hindered Grignard such as *i*BuMgBr could be used without alteration of the selectivity of the reaction and with satisfactory enantioselectivity (entry 5). To our delight a functionalized Grignard reagent, which provides important opportunities for subsequent elaboration of the product,[21] participated in the reaction with high selectivity (entry 4). Both electron-withdrawing and donating groups are tolerated in the cinnamyl-derived substrates like **1b** and **1c** (Table 2, entries 6 and 7). An important result was obtained using ester-substituted dichlorides **1d** and **1e**. Albeit at least two competitive reactions are possible[22] (1,2- or 1,4-addition to the carbonyl moiety) the catalytic transformation still proceeds without formation of any traces of the 1,2- or 1,4-adduct nor of the α-alkylation product. The selectivity toward the *Z* double bond geometry as well as the enantioselectivity in the formation of chiral ester-functionalized vinylchlorides **2h**−**2j** remained excellent (Table 2, entries 8−10). This is a particular valuable transformation not only facing the complexity of discerning between four possible reaction pathways but also for providing easy access to optically active multifunctional optically active synthons in view of the presence of both the vinylchloride and ester moieties.

Scheme 3. Proposed Rationale for the *Z*-Selectivity Observed



Major efforts dedicated in recent years to expand the scope of the Suzuki cross-coupling[17] resulted in the development of efficient protocols involving vinyl chlorides.[23,24] We chose the Suzuki cross-coupling to illustrate the versatility of the optically active *Z*-vinyl chlorides **2** in the transformation into more elaborate olefinic compounds preserving the geometry of the double bond and without any deterioration of the chiral information (Scheme 2). For instance, by using **2a** and in situ prepared alkylborane, with $Pd(OAc)_2$/DavePhos as catalyst in the presence of CsF/dioxane as the base/solvent system, the chiral *Z*-dialkyl-substituted olefin **5** was formed exclusively (>99% *Z*, er 98:2). Employing $Pd_2(dba)3$/XPhos and the appropriate alkenyl- or aryl-boronic acid, the 1,3-*cis*,*trans*-diene **6** and aryl-substituted *Z*-olefin **7** were obtained again with excellent selectivities. Applying this catalytic procedure starting with alkenylchloride **2h** afforded the synthetically versatile ester-substituted 1,3-*cis*,*trans*-diene **8** without any racemization.

It is worthy to comment on the robust *Z*-selectivity observed during this study. In analogy with the proposed mechanism by Goering and co-workers[7e] a catalytic cycle[25] depicted in Scheme 3 can be proposed in order to rationalize the results. Coordination between the copper complex[26] and a chloride in the π-Cu(I) intermediate would impose a conformation favoring the *Z*-geometry after oxidative addition to form a Cu(III) σ-allyl complex. Reductive elimination would than preserve this configuration, leading exclusively to the *Z*-vinyl chloride product.

In conclusion we have developed a new copper-catalyzed AAA methodology using Grignard reagents capable of generating in a single step *Z*-alkenyl chlorides with an allylic stereogenic center showing excellent regio- and enantioselectivity. The use of a new class of substrates for the enantioselective allylic alkylation, i.e. *gem*-dichlorides, provides chiral building blocks that turn out to be highly versatile substrates for subsequent Suzuki cross-coupling reactions. This two-stage catalytic process, comprising the formation of both the α-stereocenter and the *Z*-olefin followed by a selective cross-coupling, allows a rapid entry into optically active *Z*-alkyl- and aryl-substituted alkenes and *Z*−*E* dienes. Studies toward the elucidation of the mechanism of this copper-catalyzed AAA and in particular the origin of the high *Z*-selectivity will be reported in due course.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and spectroscopic data for the reaction products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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