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# Copper-Catalyzed Regio- and Enantioselective Synthesis of Chiral Enol Acetates and β-Substituted Aldehydes

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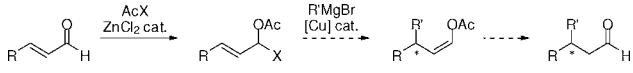
***Abstract:*** The in situ transformation of α,β-unsaturated aldehydes into α-chloroallylic acetates and subsequent copper-catalyzed regio- and enantioselective (up to 94% ee) allylic alkylation with Grignard reagents provides chiral enol acetates and chiral β-substituted aldehydes in a one-pot protocol.

In recent years, major breakthroughs in enantioselective copper-catalyzed conjugate addition and allylic substitution with Grignard reagents, two of the most powerful C−C bond-forming reactions, have been achieved.[1] However, these strategies have not been applied to the synthesis of chiral enol acetates, which are versatile intermediates in organic synthesis.[2]

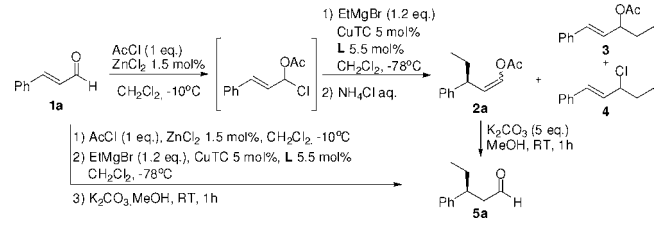
It has long been known that aldehydes can be transformed into α-haloacetates by reacting them with an acid halide in the presence of a catalytic amount of zinc chloride.[3] In contrast to allylic geminal diacetates, which have been applied in asymmetric Pd-catalyzed allylic alkylation,[4] to our knowledge allylic α-haloacetates have not been used in any enantioselective transformation. We envisioned the possibility of converting in situ an α,β-unsaturated aldehyde into the corresponding allylic α-haloacetate and then carrying out a copper-catalyzed enantioselective allylic alkylation.[1] This reaction would lead to a chiral enol acetate, which additionally could be easily converted in a one-pot operation into the corresponding chiral β-substituted aldehyde. This overall transformation can be considered as a catalytic asymmetric formal conjugate addition of a Grignard reagent to an α,β-unsaturated aldehyde (Scheme 1). This strategy would result in a synthetically useful alternative to the direct catalytic enantioselective conjugate addition to enals, which is particularly difficult to achieve because of their high reactivity toward 1,2-addition and double-addition products.[5,6]

***Scheme 1.*** Approach to Chiral Enol Acetates and β-Substituted Aldehydes




We started our investigation with the reaction between cinnamaldehyde (**1a**) and ethylmagnesium bromide (Table 1). After some preliminary experiments using different chiral ligands and copper sources,[7] we found that the use of a 1:1.1 ratio of copper(I) thiophenecarboxylate (CuTC) to phosphoramidite **L1** was an optimal catalyst for this process.[8] Thus, when ethylmagnesium bromide was added to a solution of the in situ-formed chloroacetate and a 5 mol % loading of this chiral Cu-catalyst, enol acetate **2a** was obtained as the major product as a mixture of *Z* and *E* isomers in 80% yield. Subsequently, hydrolysis afforded aldehyde **5a**, which was obtained in quantitative yield and 74% ee (Table 1, entry 1). It is important to note that enol acetate **2a** can either be isolated and then hydrolyzed or transformed in situ to aldehyde **5a** by quenching the reaction with methanol, adding potassium carbonate, and stirring the mixture for 1 h. Although different phosphoramidites (Figure 1) were tested using these conditions, **L1** was found to be the most effective. The use of **L2** led to a mismatch effect affording, after hydrolysis, the same enantiomer of aldehyde **5a** with 27% ee (Table 1, entry 2). The 3,3′-disubstituted ligand **L3** enhanced the *Z*/*E* ratio of enol acetate **2a** (14:1), but aldehyde **5a** was obtained with a moderate 40% ee (entry 3). The change of the amine group for a pyrrolidine ring or the replacement of the binaphthol ring for a biphenol or a Taddol group led to similar regioselectivities, but lower enantioselectivities were obtained.[7]

***Table 1.*** Screening of Phosphoramidite Ligands and Conditions[a]




| | | yield (%)[b] | | | | ee (%) | |
|---|---|---|---|---|---|---|---|
| entry | L | 2a | 3 | 4 | *Z*/*E*[c] | 2a[d] | 5a[e] |
| 1 | **L1**[f] | 80 | 6 | 2 | 4:1 | *Z*: 72<br>*E*: 91 | 74 |
| 2 | **L2**[f] | 76 | 9 | 6 | 3:1 | *Z*: 27<br>*E*: 25 | 27 |
| 3 | **L3**[f] | 68 | 4 | 2 | 14:1 | *Z*: −43<br>*E*: n.d.[j] | −40[i] |
| 4 | **L1**[g] | 82 | 2 | 1 | 5:1 | *Z*: 78<br>*E*: 95 | 82 |
| 5 | **L1**[h] | 89 | − | − | 13:1 | *Z*: 91<br>*E*: 92 | 92 |
| 6 | **L4**[h] | 90 | 1 | − | 4:1 | *Z*: 39<br>*E*: 55 | 42 |
| 7 | **L5**[h] | 88 | − | − | 3:1 | *Z*: 65<br>*E*: 96 | 84 |
| 8 | **L6**[h] | 80 | 8 | − | 17:1 | *Z*: 90<br>*E*: n.d.[j] | 90 |

[a] Reactions were run on a 0.5 mmol scale by adding 1.2 equiv of EtMgBr diluted with $CH_2Cl_2$ (0.7 mL). [b] Isolated yield. [c] Determined by $^1$H NMR spectroscopy. [d] Determined by chiral HPLC. [e] Determined by chiral GC. [f] EtMgBr was added over 1 h. [g] EtMgBr was added over 4 h. [h] EtMgBr was added over 6 h. [i] The negative ee value indicates that the opposite enantiomer was formed. [j] Not determined.

As the addition rate is often crucial in C−C bond-forming reactions with highly reactive Grignard reagents, we examined different addition times while keeping **L1** as the ligand. Slow addition of the Grignard reagent over 4 h increased the regio- and enantioselectivity (82% ee, entry 4). An addition time of 6 h allowed us to obtain exclusively enol acetate **2a**, almost exclusively as the *Z* isomer (13:1 *Z*/*E*). The subsequent hydrolysis afforded aldehyde



**10.1021/ja105585y** 

**5a** with a high enantiomeric excess (92% ee; entry 5).[9] Using the optimal addition time of 6 h, we also checked ligands **L4** and **L5** (entries 6 and 7), which have been shown to work well in the copper-catalyzed allylic alkylation of simple cinnamyl-type allylic chlorides.[1,10] In these cases, we observed a mismatch effect opposite to the one observed for ligands **L1** and **L2**, with (*S*,*S*,*S*)-**L5** as the most effective of the two ortho-substituted ligands. However, the enantioselectivity was not higher than the one obtained for **L1**. It is also important to note that in these cases, the *Z*/*E* ratio of enol acetate **2a** was significantly lower than the ratio observed for ligand **L1**. Finally, we checked the very bulky ligand **L6** (entry 8), which led to 90% ee but lower regioselectivity.

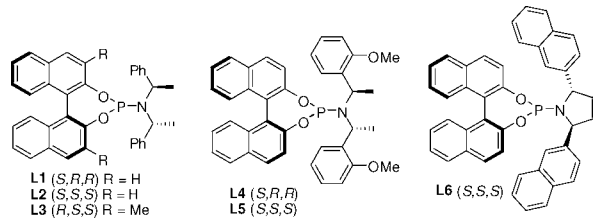
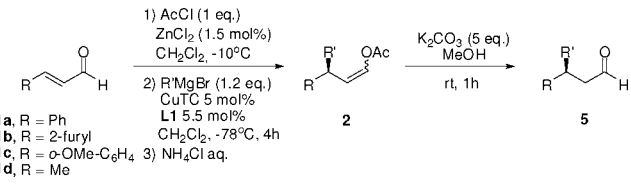



***Figure 1.*** Chiral phosphoramidites used in the optimization experiments.

Having established the optimized conditions (Table 1, entry 5), we examined the scope of this new method (Table 2). This new

***Table 2.*** Scope of Substrates and Grignard Reagents[a]



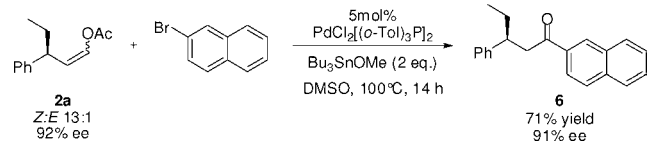

| entry | 1 | R′ | yield of **2** (%)[b] | **2**/**3**[c] | *Z*/*E*[d] | yield of **5** (%)[e] | ee of **5** (%)[f] |
|---|---|---|---|---|---|---|---|
| 1 | **1a** | Et | **2a**, 89 | 99:1 | 13:1 | **5a**, 89 | 92 |
| 2 | **1a** | *n*-Hex | **2b**, 88 | 99:1 | 10:1 | **5b**, 88 | 94 |
| 3 | **1a** | Me | **2c**, 66 | 74:26 | 7:1 | **5c**, 66 | 72 |
| 4 | **1a** | *i*-Bu | **2d**, 85 | 97:3 | 12:1 | **5d**, 80 | 48 |
| 5[g] | **1b** | Et | **2e**, 75 | 99:1 | 18:1 | **5e**, 68 | 90 |
| 6[g] | **1b** | *n*-Hex | **2f**, 69 | 99:1 | 17:1 | **5f**, 63 | 90 |
| 7[g] | **1c** | Et | **2g**, 77 | 98:2 | 16:1 | **5g**, 77 | 91 |
| 8[g] | **1c** | *n*-Hex | **2h**, 81 | 99:1 | 20:1 | **5h**, 79 | 93 |
| 9 | **1d** | *n*-Hex | **2i**, 86 | 98:2 | 2:1 | **5i**, 81 | 92 |

[a] Reactions were run on a 0.5 mmol scale using 1.2 equiv of R′MgBr diluted with $CH_2Cl_2$ (0.7 mL) and added over 6 h. [b] Isolated yield. [c] Based on GC. [d] Determined by $^1$H NMR spectroscopy. [e] Isolated yield for the one-pot process. [f] Determined by chiral HPLC or GC. [g] The chloroacetate was formed at −78 °C.

one-pot procedure was found to be very efficient with primary alkyl Grignard reagents, which gave excellent regioselectivity and very high enantioselectivities ranging from 90 to 94% (entries 1, 2, and 5−9). Although the reaction still showed excellent regioselectivity, a lower enantiomeric excess was observed when isobutylmagnesium bromide was used (entry 4). A decrease in the regioselectivity was observed when MeMgBr was used (entry 3).[11] However, it is important to note that the reaction can be successfully carried out using crotonaldehyde as the starting material. With this reverse approach, the corresponding $\beta$-methyl-substituted aldehyde was obtained with excellent regio- and enantioselectivity (98:2, 92% ee; entry 9). Excellent results were also obtained when heteroaromatic or substituted aryl aldehydes were used (entries 5−8).

An attractive feature of this new transformation is the fact that chiral enol acetates are versatile intermediates for cross-coupling reactions. Thus, the Pd-catalyzed coupling of enol acetate **2a** with 2-bromonaphthalene in the presence of tributyltin methoxide[12] led to aryl ketone **6** in 71% yield with retention of the stereochemistry (91% ee) (Scheme 2).

***Scheme 2.*** Formation of Chiral $\beta$-Substituted Aryl Ketone **6**




It should be pointed out that the enantioselective Cu-catalyzed conjugate addition of Grignard reagents to aliphatic $\alpha,\beta$-unsaturated enones provides optically active $\beta$-substituted ketones with high yields and enantioselectivities.[13] However, carrying out this transformation with aromatic enones has to date provided only modest ee's. Thus, the above-described enantioselective formation of enol acetates combined with the coupling reaction shown in Scheme 2 provides an alternative to the conjugate addition of Grignard reagents to aromatic $\alpha,\beta$-unsaturated enones.

In summary, we have developed a catalytic asymmetric synthesis of chiral enol acetates based on in situ conversion of an $\alpha,\beta$-unsaturated aldehyde into an $\alpha$-chloroallylic acetate and subsequent regio- and enantioselective allylic alkylation. This new methodology can also be used to access highly desirable $\beta$-substituted aldehydes or, alternatively, $\beta$-substituted ketones.

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**Supporting Information Available:** 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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(7) See the Supporting Information.
(8) For a recent review of phosphoramidites, see: Teichert, J. F.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2010**, *49*, 2486.
(9) As the substrate is a racemic chloroacetate, it is probable that in situ racemization of the starting material or isomerization of the copper intermediate occurs during slow addition of the Grignard reagent. Because of the high sensitivity of the in situ-formed chloroacetate, to date it has not been possible to monitor the ee of the substrate during the reaction (kinetic resolution).
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