

Copper-Catalyzed Enantioselective Synthesis of *trans*-1-Alkyl-2-substituted Cyclopropanes via Tandem Conjugate Addition–Intramolecular Enolate Trapping

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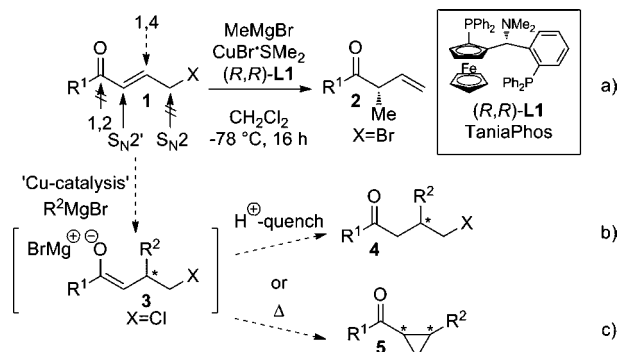
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Abstract: Cu-TolBINAP-catalyzed conjugate addition of Grignard reagents to 4-chloro- α,β -unsaturated esters, thioesters, and ketones leads to 4-chloro-3-alkyl-substituted thioesters and ketones in up to 84% yield and up to 96% ee upon protonation of the corresponding enolates at low temperature. Tandem conjugate addition–enolate trapping, however, yields *trans*-1-alkyl-2-substituted cyclopropanes in up to 92% yield and up to 98% ee. The versatility of this reaction is illustrated by the formation of key intermediates for the formal syntheses of cascarillic acid and grenadamide.

The enantioselective Simmons–Smith cyclopropanation with a stoichiometric amount of a chiral dioxaborolane, introduced by Charette and co-workers,¹ is currently the benchmark reaction for the synthesis of *trans*-1-alkyl-2-substituted cyclopropanes. Only a few catalytic² asymmetric methods^{3,4} can compete with this method¹ in terms of efficiency and yield. This is in sharp contrast to the well-known catalytic asymmetric synthesis of *trans*-1-aryl-2-substituted cyclopropanes.^{5,6} Although Michael addition-initiated ring-closure reactions (MIRCs) are well-known for the diastereo- and enantioselective preparation of substituted cyclopropanes,⁵ to the best of our knowledge the use of organometallic reagents for the catalytic asymmetric^{6,7} preparation of *trans*-1,2-disubstituted cyclopropanes^{6a,b,e,1} via MIRC is unprecedented in the literature.⁸

Recently, we explored the asymmetric allylic alkylation⁹ of 4-halocrotonates using Grignard reagents for the preparation of α -Me-substituted ester **2** in high yield and high regio- and enantioselectivity (Scheme 1a, R¹ = OBn).¹⁰ Here we report the Cu-catalyzed asymmetric 1,4-addition (ACA) of Grignard reagents^{9b,c,11} to 4-chlorocrotonates using the readily available TolBINAP as ligand. This transformation provides a route to 4-chloro-3-alkyl-substituted thioesters and ketones (Scheme 1b, **4**, X = Cl) and a general method to form *trans*-1,2-disubstituted cyclopropanes (Scheme 1c, **5**, X = Cl) with excellent enantioselectivities.

Scheme 1. Switch in Regioselectivity for the Reactions of 4-Halocrotonates with Grignard Reagents



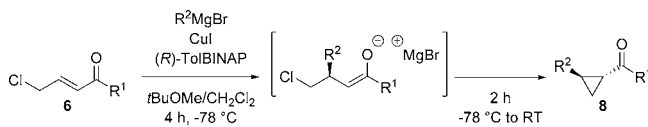
To synthesize *trans*-cyclopropanes via tandem ACA–enolate trapping, initially the ACA of Grignard reagents to 4-halocrotonates was studied while varying the ligand (Table 1). The low yield observed¹² for the ACA to bromo-substituted thioester **6a** (entry 1) prompted us to investigate the chloro-substituted analogue **6b** for this reaction (entry 2). Addition of hexylmagnesium bromide to **6b** using Cu-TolBINAP at -78 °C gave, after quenching at this temperature, 4-chloro-3-hexyl thioester **7b** in good yield (83%) and excellent ee (94%). For 4-halo- α,β -unsaturated aliphatic ketones and esters, similar results were obtained. For instance, reactions of the bromo-substituted substrates **6c** and **6d** with Grignard reagents gave low yields of, respectively, cyclopropanes **8c** and **8d** (entries 3 and 4). In contrast, the reaction of the 4-chloro-substituted α,β -unsaturated ketone **6e** gave **7e** in good yield (entry 5, 84%) and excellent ee (96%). The Cu-catalyzed reaction of ester **6f** with phenethylmagnesium bromide at -40 °C gave cyclopropane **8f** as the main product, along with traces of **7f**, in a reasonable yield (65%, entry 6) and excellent ee (>95%). Already at -40 °C, the enolate formed from **6f** undergoes slow ring-closure to yield the corresponding cyclopropane, **8f**.

Table 1. Substrate Screening for ACA to 4-Halocrotonates^a

| entry | LG | R ¹ | R ² | product | yield (%) | ee ^b (%) | |
|----------------|----|----------------|---------------------------------|-------------------|-----------|---------------------|------|
| 1 | Br | 6a | SEt | hexyl | 8a | <20 ^c | – |
| 2 | Cl | 6b | SEt | hexyl | 7b | 83 | 94 |
| 3 | Br | 6c | C ₁₁ H ₂₃ | hexyl | 8c | 32 ^d | n.d. |
| 4 ^e | Br | 6d | OMe | BnCH ₂ | 8d | <20 ^c | – |
| 5 | Cl | 6e | C ₁₁ H ₂₃ | BnCH ₂ | 7e | 84 | 96 |
| 6 ^e | Cl | 6f | OMe | BnCH ₂ | 8f | 65 ^g | >95 |

^a Conditions: **6** (0.5 mmol) in CH₂Cl₂ added over 2 h to a solution of CuI (1 mol %), TolBINAP (1.5 mol %), and Grignard reagent (1.2 equiv) in *t*BuOMe. ^b Determined by chiral GC or HPLC. ^c Based on GC–MS. ^d 20% of **6c** and 18% of (*E*)-pentadec-2-en-4-one obtained. ^e Reaction performed at -40 °C, 4 h reaction time. ^f In addition, traces (<10%) of **7f** were obtained; in all other entries, exclusively **7** or **8** was obtained. ^g Combined yield of **7f** and **8f**.

The formation of cyclopropanes via tandem ACA–enolate trapping was subsequently investigated. The reaction of hexylmagnesium bromide and **6b**, after completion of the ACA and warming to room temperature, afforded the diastereomerically pure *trans*-cyclopropane **8b** in high yield (Table 2, entry 1). Both **7b** and **8b** were obtained with 94% ee. However, precise control of the amount of Grignard reagent is essential to obtain good yields of the cyclopropanes. When less than 1.2 equiv of hexylmagnesium bromide was used, a small but significant

Table 2. Scope of Alkyl Grignard Reagents and Electron-Withdrawing Groups for Tandem ACA–Enolate Trapping toward *trans*-Cyclopropanes^a

| entry | R ¹ | | R ² | product | yield (%) | ee ^b (%) |
|----------------|---------------------------------|-----------|--------------------------------------|-----------|------------------|---------------------|
| 1 | SEt | 6b | hexyl | 8b | 87 | 94 |
| 2 | SEt | 6b | Me | 8g | 56 | 87 |
| 3 | SEt | 6b | Et | 8h | 67 | 95 |
| 4 | SEt | 6b | <i>i</i> Pr | 8i | 89 | 70 |
| 5 | SEt | 6b | <i>i</i> Bu | 8j | 91 | 84 |
| 6 ^c | SEt | 6b | but-3-enyl | 8k | 88 | 94 |
| 7 ^d | SEt | 6b | (CH ₂) ₃ OrBu | 8l | >95 ^d | 96 |
| 8 | SEt | 6b | BnCH ₂ | 8m | 92 | 84 |
| 9 ^d | SEt | 6b | Ph | 8n | 50 | 26 |
| 10 | C ₁₁ H ₂₃ | 6e | BnCH ₂ | 8e | 75 | 96 |
| 11 | C ₁₁ H ₂₃ | 6e | Me | 8o | 87 | 98 |
| 12 | OMe | 6f | BnCH ₂ | 8f | 68 | >95 |

^a For conditions see Table 1, 1.0 mmol scale. ^b Determined by chiral GC or HPLC. ^c 3.0 mmol scale. ^d Conversion; the cyclopropane proved inseparable by column chromatography from the dimer of the Grignard reagent. ^e 0.5 mmol scale.

amount of acyclic product **7b** was obtained. When more than 1.2 equiv of the Grignard reagent was used, the corresponding cyclopropane bearing a tertiary alcohol was formed, as a result of a subsequent two-fold addition of the Grignard reagent to the thioester moiety.

With the procedure for the synthesis of *trans*-cyclopropanes developed, the scope of the alkyl Grignard reagents for this transformation was explored. The use of both MeMgBr and EtMgBr gave the corresponding volatile *trans*-cyclopropanes **8g** and **8h** with good to excellent ee (entries 2 and 3). The Cu-catalyzed transformation of **6b** with the sterically encumbered Grignard reagents *i*PrMgBr and *i*BuMgBr gave the corresponding cyclopropanes **8i** and **8j** in slightly lower ee but high yield (entries 4 and 5). The catalytic asymmetric synthesis of cyclopropanes using functionalized Grignard reagents includes those substituted with olefin, ether, and aryl groups. These functionalized Grignard reagents gave cyclopropanes **8k**, **8l**, and **8m** with ee's ranging from 84 to 96% (entries 6–8). Finally, when PhMgBr was used the product **8n** was obtained in both low yield and ee (entry 9).

Ketone substrate **6e** gave, upon allowing the reaction mixture to reach room temperature, the corresponding cyclopropane with 96% ee (Table 2, entry 10). The reaction of **6e** with MeMgBr gave cyclopropane **8o** in excellent yield and 98% ee (entry 11). When the reaction mixture of **6f** and phenethylmagnesium bromide was allowed to warm to room temperature, exclusively cyclopropane **8f** was obtained, virtually enantiomerically pure (entry 12).

To illustrate the versatility of the developed method, cyclopropane **8b** was selectively reduced to the aldehyde (see Supporting Information, SI Scheme 1), which is a key intermediate in a reported synthesis¹³ of cascarillic acid.^{14,15} Furthermore, the reaction of **6b** with heptylmagnesium bromide gave cyclopropane **8p** in 84% yield and 95% ee. Reduction of **8p** to the corresponding aldehyde then gave an intermediate for the synthesis¹⁶ of grenadamide.^{17,18}

In summary, a new and versatile enantioselective synthesis of 4-chloro-3-alkyl-substituted thioesters and ketones and *trans*-1-alkyl-2-substituted cyclopropane esters, thioesters, and ketones has been developed using an extremely simple catalytic system,

based on a commercial chiral ligand, CuI, and Grignard reagents. Application of this methodology in natural product synthesis and other ring structures will be reported in due course.

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Supporting Information Available: Experimental details, data, and spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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