Synthetic Methods

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# Enantiomerically Pure Cyclopropenylcarbinols as a Source of Chiral Alkylidenecyclopropane Derivatives**

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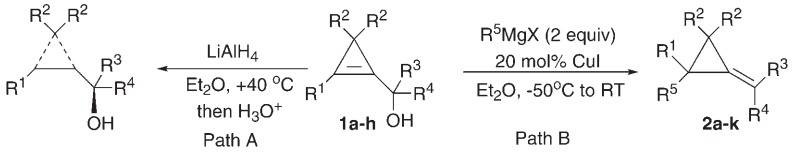
Over the past few decades, racemic cyclopropene and alkylidenecyclopropane (ACP) derivatives have been established as powerful tools in synthetic chemistry. Indeed, on one hand, cyclopropene derivatives can be readily transformed into more complex molecules by hydro- or carbometalation reactions[1] on the strained internal double bond,[2] whereas ACP derivatives have proven their usefulness by their unique reactivity with transition-metal catalysts.[3] These catalyzed transformations, also based on the release of the high level of strain, can be performed either on the distal or proximal bonds of the three-membered ring and the *exo*-alkylidene moiety.[4] Despite this mounting interest, the synthesis of enantiomerically pure cyclopropenes, particularly 1,2-disubstituted (internal) cyclopropenes and chiral ACPs are still in their infancy.[5] In the course of our study on the functionalization of cyclopropenyl derivatives, we have recently shown that cyclopropenylcarbinols (readily prepared in a one-pot operation from 1,1,2-trihalogenocyclopropane[6]) are regio- and diastereoselectively reduced with $LiAlH_4$ in $Et_2O$ into cyclopropylcarbinols as single *trans* isomers (Scheme 1, path A).[1a] Herein, we document the first preparation of racemic and then enantiomerically pure ACPs **2** from cyclopropenylcarbinol derivatives **1** (Scheme 1, path B) through a copper-catalyzed addition of various Grignard reagents. In our initial investigations, the regio- and stereochemistry of the reaction was first checked on racemic cyclopropenylcarbinol derivatives **1a–h**, and the results reported in Table 1 fulfilled our expectations.




***Scheme 1.*** General preparation of ACPs.

***Table 1:*** Synthesis of ACP derivatives.

| Entry | Substrate | $R^1$ | $R^2$ | $R^3$ | $R^4$ | $R^5$ | ACP | $E/Z$[a] | Yield [%][b] |
|---|---|---|---|---|---|---|---|---|---|
| 1 | **1a** | $CH_3$ | H | $C_2H_5$ | $C_2H_5$ | $C_4H_9$ | **2a** | – | 76 |
| 2 | **1a** | $CH_3$ | H | $C_2H_5$ | $C_2H_5$ | $C_6H_5$ | **2b** | – | 81 |
| 3 | **1b** | $CH_3$ | H | $C_6H_5$ | $C_6H_5$ | $C_6H_5$ | **2c** | - | 61 |
| 4 | **1c** | $C_4H_9$ | H | $C_6H_5$ | $C_6H_5$ | $C_6H_5$ | **2d** | – | 62 |
| 5 | **1d** | $C_4H_9$ | H | *i*Pr | H | $CH_3$ | **2e** | 100:0 | 82 |
| 6 | **1e** | $CH_3$ | H | *i*Pr | H | $C_4H_9$ | **2e** | 100:0 | 91 |
| 7 | **1f** | $CH_3$ | H | $C_6H_5$ | H | $C_4H_9$ | **2f** | 97:3 | 70 |
| 8 | **1f** | $CH_3$ | H | $C_6H_5$ | H | $C_6H_5$ | **2g** | 87:13 | 66 |
| 9 | **1f** | $CH_3$ | H | $C_6H_5$ | H | $CH_3$ | **2h** | 92:8 | 81 |
| 10 | **1f** | $CH_3$ | H | $C_6H_5$ | H | $C_2H_5$ | **2i** | 96:4 | 72 |
| 11 | **1g** | $CH_3$ | H | Ar[c] | H | $C_2H_5$ | **2j** | 95:5 | 88 |
| 12 | **1h** | H | $CH_3$ | *p*-tol | H | $CH_3$ | **2k** | 12:88 | 91 |

[a] Determined on crude NMR spectroscopic and gas-chromatographic analysis. [b] Yield of isolated product after purification by column chromatography. [c] Ar = *p*-$BrC_6H_4$.

In all experiments, ACPs were obtained in good-to-excellent yields which resulted from a formal copper-catalyzed $S_N2'$ reaction of alkyl and aryl magnesium halides $R^5MgX$ (X = Br, I) with the free allylic alcohol **1a–h**. Tertiary and secondary alcohol derivatives (Table 1, entries 1–4 and 5–12, respectively) led similarly to ACP derivatives. Substituents on the double bond of the cyclopropenyl ring ($R^1$) can be either alkyl groups (entries 1–11) or a hydrogen atom (entry 12). The same is true for substituent $R^2$. Substituents $R^3$ and $R^4$ can be either alkyl, aryl, or hydrogen groups. When secondary alcohols were used ($R^3$ = alkyl or aryl, $R^4$ = H; entries 5–12), the fate of the stereochemistry of the double bond was raised. In all these experiments, we always found that the unique or major isomer was *E* configured (in entry 12, the configuration of the double bond was identical but the configuration of the product became *Z* because of the interconversion of substituents $R^1$ and $R^2$).[7] Without a copper salt, the reaction did not proceed.

With a straightforward method for the preparation of ACPs from cyclopropenylcarbinol derivatives in hand, we then turned our attention to their asymmetric synthesis. Considering that cyclopropenylcarbinols are strained allylic alcohols, we envisaged the enantiomerically enriched preparation of the ACPs to be through the Sharpless kinetic resolution (Scheme 2).[8] When the racemic allylic alcohol **1f** (Table 2, entry 1) was subjected to the epoxidation reaction conditions using (*R*,*R*)-(+)-diethyl tartrate as the chiral ligand, we were pleased to observe, despite the highly reactive nature of the strained double bond, a very efficient kinetic resolution at −20 °C. Only one enantiomer is epoxi-

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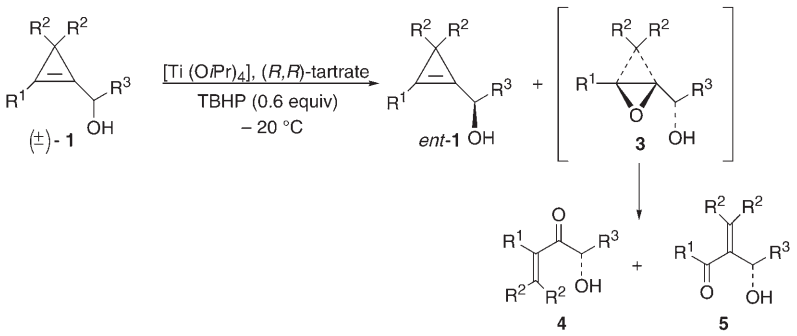



***Scheme 2.*** Kinetic resolution of cyclopropenylcarbinol derivatives. TBHP = *tert*-butyl hydroperoxide.

***Table 2:*** Kinetic resolution of cyclopropenylcarbinol derivatives.

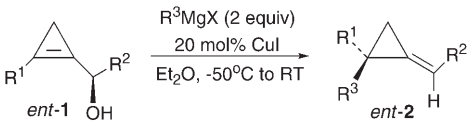
| Entry | $R^1$ | $R^2$ | $R^3$ | Products | Yield [%][b] | *ee* [%][a] |
|---|---|---|---|---|---|---|
| 1 | $CH_3$ | H | $C_6H_5$ | **1f** | 46 | 99 |
| 2 | $CH_3$ | H | *p*-$BrC_6H_4$ | **1g** | 44 | 99 |
| 3 | $C_4H_9$ | H | $C_6H_5$ | **1i** | 44 | 99 |
| 4 | $CH_3$ | H | $CH_2CH_2C_6H_5$ | **1j** | 42 | 96 |
| 5 | $CH_3$ | $CH_3$ | $C_6H_5$ | **1k** | 47 | 99 |
| 6 | $CH_3$ | $CH_3$ | $CH_2CH_2C_6H_5$ | **1l** | 40 | 95 |

[a] Yield of the isolated product after kinetic resolution and purification by column chromatography. [b] Enantiomeric excess was determined by gas-chromatographic analysis on chiral column (cyclodextrin B; see the Supporting Information).

dized to lead to the putative unstable chiral 2-oxabicyclo-[1.1.0]butane **3**.

Two enantiomerically pure α,β-unsaturated ketols **4** and **5**, formed in equal amounts (each in 22–25% yield of isolated product) as a result of the isomerization of the oxabicyclobutane by cleavage of the two pheripheral σ bonds.[9] Oxabicyclobutanes have been postulated several times to be intermediates in various thermal[10a] and photochemical reactions.[10b] In none of these cases, however, were oxabicyclobutanes detected. Although we were also not able to isolate this intermediate, the Sharpless kinetic resolution implies that the corresponding oxabicyclobutane was formed as a reactive intermediate. The remaining non-oxidized products, namely, the cyclopropenylcarbinols **1** were obtained with very high enantiomeric excess and yields (95–99% *ee* and 40–47% yield of isolated product). The scope of the kinetic resolution is broad, as several different alkyl groups can be present either on the double bond of the cyclopropenyl unit ($R^1 = CH_3$ and $C_4H_9$) or on the cyclopropene ring itself ($R^2 = H$ or $CH_3$; Table 2, entries 1–4 and 5 and 6, respectively).

Aryl and alkyl groups can be interchangeably used as secondary substituents at the allylic position, although the enantiomeric excess is slightly higher when $R^3$ is an aryl group (99% *ee*; entries 1–3 and 5) relative to an alkyl group (≈95% *ee*; entries 4 and 6). Following the strategy we described in Scheme 1, path B for the preparation of ACPs from cyclopropenylcarbinols, alcohols **1f**,**g** were treated with various Grignard reagents in the presence of 20 mol% of CuI (Scheme 3 and Table 3). The reaction proceeds with an




***Scheme 3.*** Preparation of enantiomerically pure ACPs.

excellent transfer of chirality from chiral cyclopropenylcarbinol to ACP regardless of the nature of the alkyl magnesium halides ($R^3$ = aryl or alkyl; Table 3, entries 1–4).

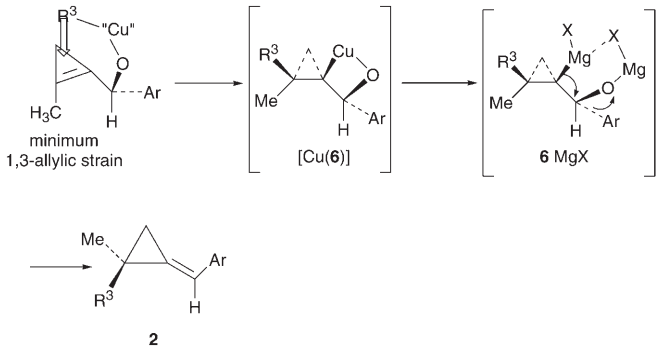
The absolute configuration of **2j** was determined as *S* by using both computational methods[11] and X-ray analysis of functionalized **2j** (see the Supporting Information).

***Table 3:*** Enantioselective preparation of ACPs.

| Entry | Substrate | $R^1$ | $R^2$ | $R^3$ | Product | *E*/*Z* | Yield [%][a] | *ee* [%][b] |
|---|---|---|---|---|---|---|---|---|
| 1 | **1f** | $CH_3$ | $C_6H_5$ | $C_6H_5$ | **2g** | 87:13 | 66 | 97 |
| 2 | **1f** | $CH_3$ | $C_6H_5$ | $C_4H_9$ | **2f** | 97:3 | 70 | 97 |
| 3 | **1f** | $CH_3$ | $C_6H_5$ | $C_2H_5$ | **2i** | 96:4 | 72 | 95 |
| 4 | **1g** | $CH_3$ | *p*-$BrC_6H_4$ | $C_2H_5$ | **2j** | 97:3 | 88 | 99 |

[a] Yield of isolated product after purification by column chromatography. [b] Enantiomeric excess of the *E* isomer was determined by gas-chromatographic analysis on chiral column (cyclodextrin B; see the Supporting Information).

The absolute configurations of the starting cyclopropenylcarbinol **1g** and the final ACP **2j** imply an overall *syn* $S_N2'$ displacement of the alcohol moiety. Starting at −50 °C, the stirred mixture was slowly warmed to room temperature and carefully followed by analysis of hydrolyzed aliquots. Under these conditions, we were able to isolate the addition products (after hydrolysis of aliquots of [Cu(**6**)]). These cyclopropyl–metal complexes ([Cu(**6**)] or **6**MgX) disappear in favor of the ACP **2**, which is obtained in good yield. As the deprotonation of the alcohol precedes the addition, the most stable conformer of the cyclopropenylcarbinolate is given in Scheme 4, with the smallest substituent (hydrogen) at the pre-existing orientation "inside" and the aryl group "outside", away from the allylic methyl substituent (minimum 1,3-strain). Thus, this catalytic reaction proceeds through a *syn* addition/*syn* elimination mechanism (Scheme 4).




***Scheme 4.*** Mechanistic hypothesis for the overall *syn* $S_N2$ process.

In conclusion, the copper-catalyzed carbomagnesiation reaction of chiral cyclopropenylcarbinol derivatives, obtained through the kinetic resolution of secondary allylic alcohols, leads to a straightforward, new preparation of enantiomerically pure alkylidenecyclopropane derivatives.

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