Synthetic Methods

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Diastereodivergent Carbometalation/Oxidation/Selective Ring Opening: Formation of All-Carbon Quaternary Stereogenic Centers in Acyclic Systems**

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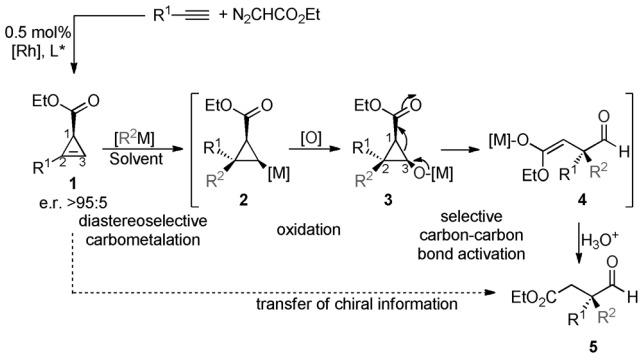
The development of new methods for the activation of single carbon–carbon bonds is nowadays a field of great interest as it may lead to functionalized adducts from simple precursors.[1] These fundamental reactions are based either on oxidative addition or β-carbon and radical cleavage. The oxidative addition of unstrained molecules usually requires some chelation assisted processes, and the introduction of pincer-type ligands for such C–C bond activation allowed new perspectives[1,2] by bringing a metal center close to the "hidden" C–C bonds. In contrast, strained substrates do not require such precoordination but the selectivity of the carbon–carbon bond cleavage may be difficult to control.[3] Controlling such selectivity would be crucial for further synthetic applications,[4] particularly if the selectivity leads to the formation of enantiomerically enriched products such as ones possessing challenging all-carbon quaternary stereocenters in acyclic systems.[5] In this context, we have developed in the past few years various approaches to selectively cleave the primary carbon–carbon bond of enantiomerically enriched alkylidenecyclopropanes.[6] Although these transformations lead to the formation of the expected all-carbon quaternary stereocenters in acyclic systems in excellent chemical yields,[6] enantiomerically enriched alkylidenecyclopropane derivatives have to be independently prepared.[7] Ideally, if one could prepare these quaternary stereocenters in a single-pot operation from simple starting materials through a selective carbon–carbon bond activation, it would not only answer this challenging synthetic problem but also pave the way for the efficient formation of new functionalized adducts.

Our plan was to initially perform a diastereoselective carbometalation reaction of the cyclopropenyl ester **1** to give the diastereomerically enriched functionalized cyclopropylmetal species **2** (Scheme 1).[8] Then, in a subsequent step, **2** would be oxidized into the corresponding metal cyclopropanolate **3** which would undergo a regioselective ring-opening reaction to provide the versatile metal homoenolate **4**.[9]



Scheme 1. Proposed diastereoselective carbometalation/oxidation/selective ring-opening reactions.

Aldehydes **5**, bearing the expected all-carbon quaternary stereocenters in acyclic system, would then be obtained after acid hydrolysis, The entire sequence would proceed in a single pot from the starting alkene. Although there are a variety of catalytic asymmetric reactions to construct α-quaternary stereogenic centers,[5a] methods allowing the preparation of aldehydes possessing these α stereocenters are much less abundant and are based on the creation of a single new bond between two prochiral substrates.[10] In this particular case, the reaction leads to the rather uncommon metal homoenolate **4** and little is known about its stability despite the fact that these synthons are of a great interest for further manipulations.[11] Importantly, the metal-catalyzed enantioselective cyclopropenation of terminal alkynes with diazoacetate and Rh^{II}, Co^{II}, or Ir^{II} catalysts are well established methods and as a result, 2-substituted 2-cyclopropenecarboxylic acid esters (**1**) are easily obtained with excellent enantiomeric ratios and yields.[8,12] So, from the enantiomerically enriched **1**, easily prepared from simple terminal alkynes, the formation of these challenging aldehydes (**5**) could be carried out in a single-pot operation through a sequence of diastereoselective carbometalation/oxidation/selective ring-opening reactions (Scheme 1).

The diastereoselectivity of the carbometalation should be controlled by the stereogenicity of the carbon atom holding the ester moiety (C1; Scheme 1). In the subsequent reactions, this point of chirality is transferred upon selective C3–C1 bond activation to give the enolate **4** with an all-carbon stereogenic center. Thus, the diastereomeric ratio of **2** will consequently be transferred as an enantiomeric ratio for **5**. To reach such functionalized molecular architectures (e.g., **5**) with high enantiomeric ratios, highly diastereoselective carbometalation of cyclopropenes is therefore required.[8,13]

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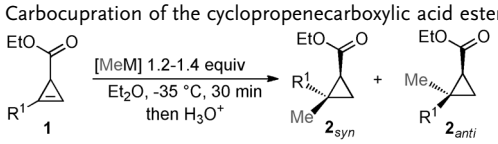
After the pioneering work from the groups of Gevorgyan, Rubin, Orchin, and Nakamura,[14] who used directing groups for various metal-catalyzed additions to cyclopropenes, Fox and co-workers reported the directed copper-catalyzed carbozincation of cyclopropenyl esters in good yields and selectivities.[15] However, in some cases, a large amount of diorganozinc is required for optimal reactivity (i.e., Me_2Zn 4 equiv), that is not compatible with our oxidation step.

As organocopper species are known for their high stereo- and chemoselectivity,[16] the carbocupration reaction[17] of **1** was investigated in detail for the introduction of the most challenging group (Me) as described in Table 1. When the

Table 1: Carbocupration of the cyclopropenecarboxylic acid esters **1**.



Entry	R^1	[MeM]	$\mathbf{2}_{syn}/\mathbf{2}_{anti}$[a]	Yield [%][b]
1	Bu (**1a**)	$MeCu{\cdot}MgX_2$	$\mathbf{2a}_{syn}/\mathbf{2a}_{anti}$ >95:5	72
2	Bu (**1a**)	MeMgBr, CuI (10 mol%)	$\mathbf{2a}_{syn}/\mathbf{2a}_{anti}$ >99:1	73
3	Bu (**1a**)	MeCuLi	$\mathbf{2a}_{syn}/\mathbf{2a}_{anti}$ 87:13	71
4	Bu (**1a**)	MeCuCNLi	$\mathbf{2a}_{syn}/\mathbf{2a}_{anti}$ 8:92	72
5	Hex (**1b**)	MeMgBr, CuI (10 mol%)	$\mathbf{2b}_{syn}/\mathbf{2b}_{anti}$ 99:1	86
6	Hex (**1b**)	MeCuCNLi	$\mathbf{2b}_{syn}/\mathbf{2b}_{anti}$ 4:96	66
7	Bn (**1c**)	MeMgBr, CuI (10 mol%)	$\mathbf{2c}_{syn}/\mathbf{2c}_{anti}$ >99:1	81
8	Bn (**1c**)	MeCuCNLi	$\mathbf{2c}_{syn}/\mathbf{2c}_{anti}$ 8:92	68
9	Pr (**1d**)	MeMgBr, CuI (10 mol%)	$\mathbf{2d}_{syn}/\mathbf{2d}_{anti}$ >97:3	71
10	$BuCO(CH_2)_3$ (**1e**)	MeCuCNLi	$\mathbf{2e}_{syn}/\mathbf{2e}_{anti}$ 3:97	76

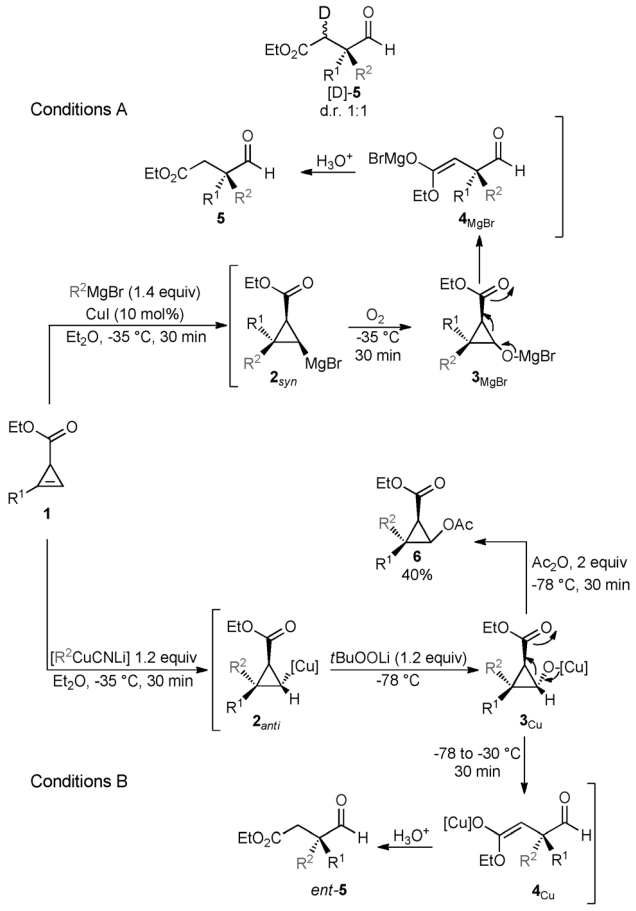
[a] Determined by ^1H NMR and ^{13}C NMR spectroscopy, or gas chromatography. [b] Yield of isolated product after purification by column chromatography.

cyclopropene **1a** (R^1 = Bu) was added at −35 °C to 1.2 equivalents of an organocopper reagent, which is easily obtained by mixing MeMgBr and CuI in a 1:1 ratio, the carbometalated adduct **2a** was obtained with a very high *syn* diastereoselectivity and good yield after only 30 minutes (Table 1, entry 1). The configuration has been established by comparison with an authentic sample.[15] The formation of the *syn*-adduct **2a** can be rationalized by the existence of a chelated transition state between the carbonyl group of the ester and the Lewis-acidic organometallic species (or with its associated salts).[18] As organomagnesium species can tolerate a broad range of functional groups and in particular esters,[19] we thought that the copper-catalyzed carbomagnesiation could also undergo a carbometalation reaction on the activated double bond without reacting with the functional group at low temperature. We were pleased to see that, indeed, the copper-catalyzed methylmagnesiation could lead to the *syn*-adduct in excellent yield and diastereomeric ratio (Table 1, entry 2). By decreasing the Lewis-acid character of the copper center, the reaction was expected to proceed with a lower selectivity. Indeed, when two equivalents of MeLi were added to the same copper salt, the resulting organocuprate added to **1a** in similar yield but with a lower $\mathbf{2a}_{syn}/\mathbf{2a}_{anti}$ ratio of 87:13 (Table 1, entry 3).

By further decreasing the electrophilicity of the copper center,[20] a complete reversal of the diastereoselectivity was observed. Indeed, when CuCN was used, the lower-order cyanocuprate RCuCNLi is formed and exhibits a different reactivity, thus leading to the formation of the opposite diastereomer, $\mathbf{2a}_{anti}$, with a $\mathbf{2a}_{syn}/\mathbf{2a}_{anti}$ ratio of 8:92 (Table 1, entry 4).[21] The diastereodivergent behavior of these organometallic species are of synthetic interest since both the diastereomers $\mathbf{2}_{syn}$ and $\mathbf{2}_{anti}$ can be obtained, at will, from the same precursor (**1**). This diastereodivergent carbometalation was extended to various starting cyclopropenyl derivatives (**1b–d**) with equal efficiency both for the *syn* and *anti* isomers depending on the organometallic species used (Table 1, entries 5–9). Notably, the addition of MeCuCNLi to the functionalized cyclopropenyl ester **1e** (Table 1, entry 10) proceeds nicely despite the presence of a ketone in the aliphatic chain. These carbometalation reactions are not restricted to the introduction of a methyl group as the addition of BuCuCNLi as well as BuMgBr and CuI (10 mol%) to **1c** led to the *anti*- and *syn*-carbometalated products, respectively, in good yields and diastereomeric ratio (64%, d.r. 8:92 and 65%, d.r. 93:7, respectively; not described in Table 1). Similarly, the copper-catalyzed carbomagnesiation of **1b** with BuMgBr and PhMgBr led to the corresponding cyclopropanes in 70 and 64% yield, with a diastereomeric ratio higher than 97:3 in both cases.

Having mastered the diastereodivergent carbometalation reaction of **1**, we moved on to the oxidation reaction of the cyclopropyl magnesium species **2**, obtained by the copper-catalyzed carbomagnesiation reaction (Table 1, entries 2, 3, 5, 7, and 9). Although the simplest oxidant that one could use is molecular oxygen, it is known that the oxidation of organomagnesium species is initiated by an electron transfer to the oxidizing agent, and a partial epimerization of the organometallic stereocenter is usually observed.[22] Nevertheless, as long as no dimers are formed in the oxidation reaction (resulting from a recombination of cyclopropyl radical entities) the stereochemistry of the oxidation is not a critical issue as the next step, namely the C–C bond cleavage, converts an sp^3-carbon atom into an sp^2-carbon atom. By adding dry molecular oxygen to the cyclopropylmagnesium bromide $\mathbf{2}_{syn}$ at −35 °C, we were pleased to observed a fast and clean oxidation reaction leading to the formation of the

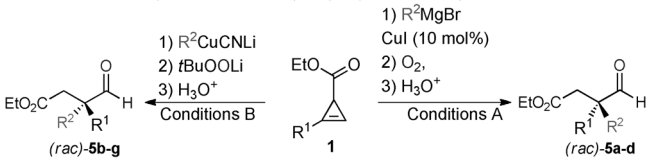
magnesium cyclopropanolate intermediate $\mathbf{3}_{MgBr}$ which undergoes the C–C bond activation leading to the acyclic magnesium homoenolate $\mathbf{4}_{MgBr}$, and ultimately to the formation of **5** after hydrolysis (Scheme 2, Conditions A). To trap $\mathbf{3}_{MgBr}$



Scheme 2. Carbometalation/oxidation/C–C bond activation sequence.

before the ring-opening reaction, we performed the oxidation at lower temperature (i.e., −70 °C) but in this case, the reaction becomes sluggish and the yield drops considerably (25–30 % conversion), and is therefore neither representative nor synthetically useful. In contrast, when the reaction was performed under our standard reaction conditions, and a large excess of D_3O^+ was added at the end of the reaction sequence, the adduct [D]-**5** was isolated with a complete incorporation of deuterium in an expected 1:1 diastereomeric ratio. This result shows that $\mathbf{4}_{MgBr}$ indeed exists in the reaction mixture. This sequence of copper-catalyzed carbomagnesiation/oxidation with O_2 and C–C bond activation has been generalized to different substrates (Table 2, entries 1–4). In all cases, the one-pot transformation of **1** into **5**, possessing the desired all-carbon quaternary stereogenic center, proceed nicely although it was found that these aldehydes are rather sensitive to purification by column chromatography (the yields of the isolated aldehydes **5** are generally 20 % lower than those determined by ^{1}H NMR spectroscopy using an internal standard; yields are nevertheless based on **1** after two consecutive chemical steps).

Table 2: Carbocupration of the cyclopropenecarboxylic acid esters **1**.

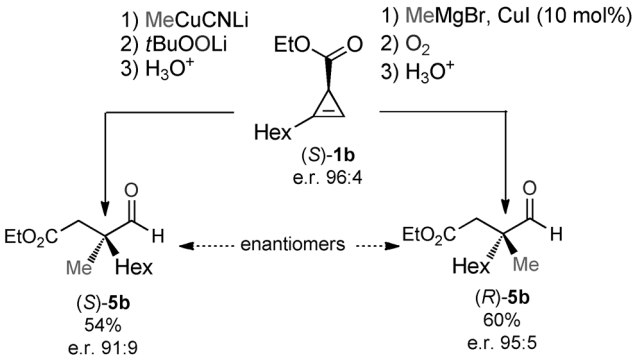


Entry	R^1	R^2	Conditions[a]	5	Yield [%][b]
1	Bu (**1a**)	Me	A	**5a**	75 (55)
2	Hex (**1b**)	Me	A	**5b**	88 (61)
3	Bn (**1c**)	Me	A	**5c**	73 (64)
4	Pr (**1d**)	Me	A	**5d**	74 (51)
5	Bu (**1a**)	Me	B	**5a**	– (56)
6	Hex (**1b**)	Me	B	**5b**	– (53)
7	Bn (**1c**)	Me	B	**5c**	– (51)
8	Bn (**1c**)	Bu	B	**5e**	– (52)
9	Bn (**1c**)	Hex	B	**5f**	– (52)
10	Bu (**1a**)	Hex	B	**5g**	– (52)

[a] Conditions A: 1) R^2MgBr (1.4 equiv), CuI (10 mol %), Et_2O, −35 °C, 30 min; 2) O_2, −35 °C, 30 min; 3) H_3O^+. Conditions B: 1) R^2CuCNLi (1.2 equiv), Et_2O, −35 °C, 30 min; 2) *t*BuOOLi (1.2 equiv), −78 °C then −78 to −30 °C, 30 min; 3) H_3O^+. [b] Yield determined by NMR spectroscopy using 1,4-dinitrobenzene as an internal standard. Yield within parentheses is that of the product isolated after purification by column chromatography.

When the carbometalation reaction is performed with R^2CuCNLi, the diastereomers $\mathbf{2}_{anti}$ are obtained in excellent yields. However, organocuprates are not easily oxidized by addition of O_2 as it leads to a dimer (R–R) through electron-transfer processes ($Cu^I \rightarrow Cu^{III}$).[23] In contrast, when oxenoid *t*BuOOLi is added to organocuprate species, the corresponding alcohol ROH is usually obtained through a nucleophilic mechanism.[23] Oxenoid has been recently used for the stereoselective oxidation of vinylcopper as a new source of trisubstituted enolate species en route to aldol adducts possessing all-carbon quaternary stereocenters.[24] Therefore, an equimolar amount of *t*BuOOLi, which is easily obtained by addition of *n*BuLi to *t*BuOOH at low temperature, was added $\mathbf{2}_{anti}$, generated by carbocupration reaction of **1** with R^2CuCNLi. The oxidation reaction proceeded rapidly at low temperature and gave the corresponding copper cyclopropanolate[25] $\mathbf{3}_{Cu}$ as evidenced by the formation of **6** after addition of acetic anhydride at low temperature.[26] If $\mathbf{3}_{Cu}$ was warmed to −30 °C and then subjected to acidic hydrolysis, the selective C–C bond activation leads directly to the formation of **5** (Table 2, entries 5–10).

This sequence is quite general and various aldehydes (**5**) have been easily prepared in a single-pot operation from **1**. Moreover, the diastereodivergent carbometalation reaction should lead, from the same enantiomer of **1**, to the formation of the two enantiomers of **5** through the subsequent oxidation, C–C ring cleavage. Therefore, the Rh^{II}-catalyzed enantioselective addition of ethyl diazoacetate to 1-octyne was performed and gave **1b** in 90 % yield with an excellent 96:4 enantiomeric ratio.[27] When (*S*)-**1b** was first engaged in the copper-catalyzed carbomagnesiation reaction, subsequent treatment with dioxygen, and selective C–C bond activation, the corresponding aldehyde (*R*)-**5b** was obtained with an enantiomeric ratio of 95:5 in 60 % yield (Scheme 3). The ratio



Scheme 3. Preparation of enantiomeric enriched aldehydes **5**.

is almost identical of that of the optical purity of **1**.[28] In contrast, the addition of $Me_2CuCNLi$ to (*S*)-**1b** leads to the diastereomer $\mathbf{2b}_{anti}$ which undergoes an oxidation reaction with the oxenoid *t*BuOOLi and subsequent selective C–C bond activation to give (*S*)-**5b** in similar yield with an enantiomeric ratio of 91:9.[28]

In conclusion, a new carbometalation/oxidation/carbon–carbon bond cleavage sequence for cyclopropenes has been developed, thus allowing the preparation of aldehydes bearing α-quaternary stereocenters in a one-pot reaction from readily available starting materials. By a diastereodivergent carbometalation reaction, both enantiomers of the final aldehyde were obtained from the same initial cyclopropene derivative.

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