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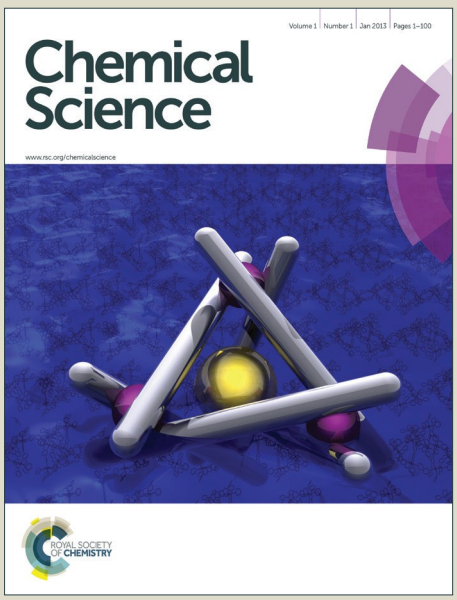

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ARTICLE

Diastereodivergent Combined Carbometalation – Zinc Homologation – C-C Fragmentation Reaction as an Efficient Tool to Prepare Acyclic Allylic Quaternary Carbon Stereocenters

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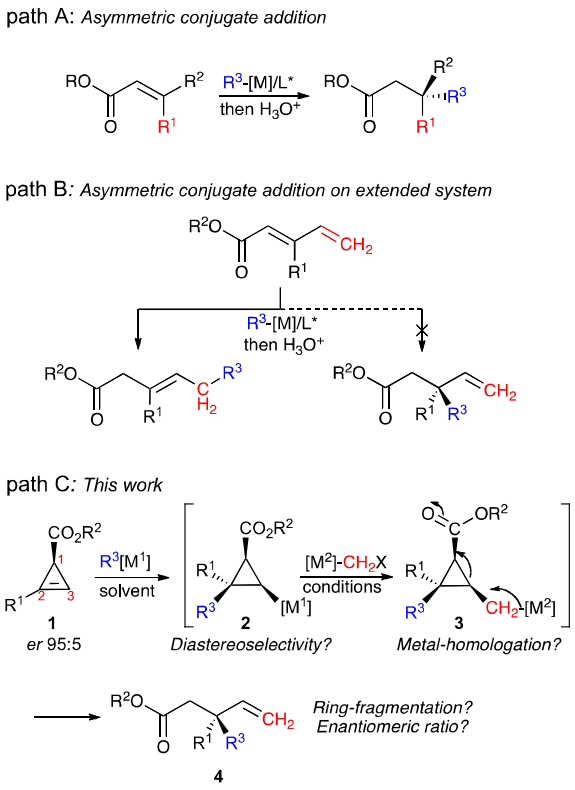
A new strategy has been developed to construct enantiomerically enriched acyclic allylic quaternary carbon stereocenters in a single-pot operation through a combined carbometalation - zinc homologation – fragmentation sequence. Proper tuning of the reaction condition enables the synthesis of the two enantiomers starting from a single enantiomer of the starting material.

Introduction

In the last few decades, numerous approaches to integrate multiple chemical steps in a single pot operation[1] have been described, offering reliable and powerful strategies for the synthesis of fine chemicals.[2] In this context, construction of several carbon-carbon (C-C) bonds with simultaneous control of newly formed asymmetric centers including the formation of challenging quaternary carbon stereocenters,[3] is of paramount importance for the development of complex molecular frameworks.[4] Particularly interesting would be the formation of such stereocenters adjacent to allylic motifs[4] as these sub-structures are abundant in biomolecules and natural products.[5] Although several excellent and highly selective approaches have been reported for the construction of these acyclic allylic carbon quaternary stereocenters,[6-10] it becomes eventually more intricate when the synthesis has to be performed in a single pot operation.[11] For instance and although the copper catalysed asymmetric conjugate addition is probably the most well established transformation (Figure 1, path A),[12] the asymmetric 1,4-addition to an extended conjugated system is more challenging as the 1,6-addition product is usually preferred over the 1,4-addition (Figure 1, path B).[13] A more successful alternative approach to reach the same products is the asymmetric 1,4-addition of vinyl metal species to Michael acceptors.[14] Despite that asymmetric catalysis coupled with fragmentation of strained building blocks have been recently reported, none could be used for the preparation of acyclic allylic carbon quaternary stereocenters.[15] Herein, we would like to report our efforts to address this issue by performing a new tandem approach leading to the formation of two new carbon-carbon bonds in a single-pot operation including the formation of the desired acyclic allylic quaternary carbon stereocenter (Figure 1, Path C) from easily accessible starting material.

Figure 1. Approaches to construct allylic quaternary stereocenter



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Electronic Supplementary Information (ESI) available: Experimental procedures, spectroscopic data and copies of ^{1}H and ^{13}C NMR spectra. See DOI: 10.1039/x0xx00000x

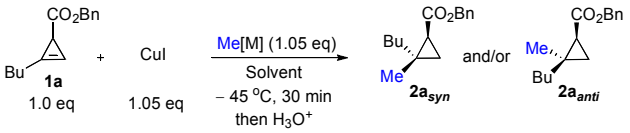
This combined reaction would consist in the diastereoselective carbometalation reaction[16] of enantiomerically enriched substituted cyclopropenyl esters **1**, followed by a homologation reaction[17] of the resulting cyclopropyl metal species **2** leading to a cyclopropylmethyl metal **3** that would subsequently undergo a carbon-carbon bond cleavage[18] to give the enantiomerically enriched acyclic allylic quaternary carbon stereocenter **4** as described in Figure 1, path C. Although this proposed sequence is very appealing, the unique formation of the linear product **4** directly from **1**, promoted by a combination of organometallic species in high chemical yield and with a high enantiomeric ratio, requires a cascade of high-yielding events with a perfect control of all the elementary steps. It should be noted that enantiomerically enriched starting cyclopropenyl esters **1** are readily accessible through the asymmetric metal-catalyzed decomposition of diazoester with alkynes,[19] the enantiomeric ratio of the acyclic allylic quaternary stereocenter in **4** results from the diastereoselectivity of the carbometalation reaction.

Results and discussion

We started our research by investigating first the diastereoselectivity of the carbometalation reaction of cyclopropenyl ester **1**. In our synthetic plans, the presence of the ester was not only needed to achieve good diastereoselectivity for the carbometalation reaction but was also a key-element for a successful ring-fragmentation of the newly formed donor-acceptor cyclopropylmethyl metal species **3**.[20]

Hence, to address the initial step of this sequence (transformation of **1** into **2**), our model substrate cyclopropenyl ester (racemic **1a**) was treated with various organocopper species in different solvents as described in Table 1. When **1a** was treated at -45 °C in THF with 1.05 equivalent of MeCu, easily prepared by mixing MeLi and CuI in a 1:1 ratio, the carbometalated product **2a**$_{anti}$ was rapidly obtained after hydrolysis (less than 30 minutes) with a very high *anti*-diastereoselectivity in good yield (Table 1, entry 1).[21] The configuration of **2a**$_{anti}$ has been established by NOE experiments (see Supplementary Information). The preferential formation of the diastereomer **2a**$_{anti}$ can only be possible when the carbometalation reaction is sterically driven. The coordinating solvent such as THF makes the organocopper species less prone to be chelated by the ester and therefore prefers to react on the *re*-face of the cyclopropene derivative **1a**. If the assumption that solvent plays a crucial role in the control of the diastereoselectivity of the carbometalation step, thus less Lewis basic solvent should favour the addition on the *si*-face through coordination of the organometallic species with the ester. Indeed, when slightly less coordinating solvent such as 2-methyl THF was used, the selectivity towards the formation of **2a**$_{anti}$ drops slightly (Table 1, entry 2). By further decreasing the Lewis basicity of the solvent, (Table 1, entries 3 to 5, Et_2O, hexane and toluene respectively), the aptitude of the organometallic species to be coordinated by the ester group increases and therefore the isomer **2a**$_{syn}$ can now be prepared as unique diastereoisomer (Table 1, entry 5). The relative configuration of **2a**$_{syn}$ has also been established by comparing the NOE and ^{13}C NMR experiments with **2a**$_{anti}$ (see Supplementary Information). The same trend was also found for the addition of organocopper species originating from Grignard reagent (prepared by mixing MeMgBr and CuI in a 1:1 ratio), although the formation of the *anti*-addition product **2a**$_{anti}$ in THF is less diastereoselective (Table 1, compare entries 1 and 6) but still excellent for the formation of the *syn*-diastereoisomer **2a**$_{syn}$ (Table 1, entry 8). It should be noted that such diastereoselective carbometalaton of cyclopropenyl ester such as **1a** have already been described but it was always achieved through variation of the organometallic species but never by simple variation of the solvent for a given organocopper entities.[16]

Table 1: Controlling the diastereoselectivity for the initial carbocupration step

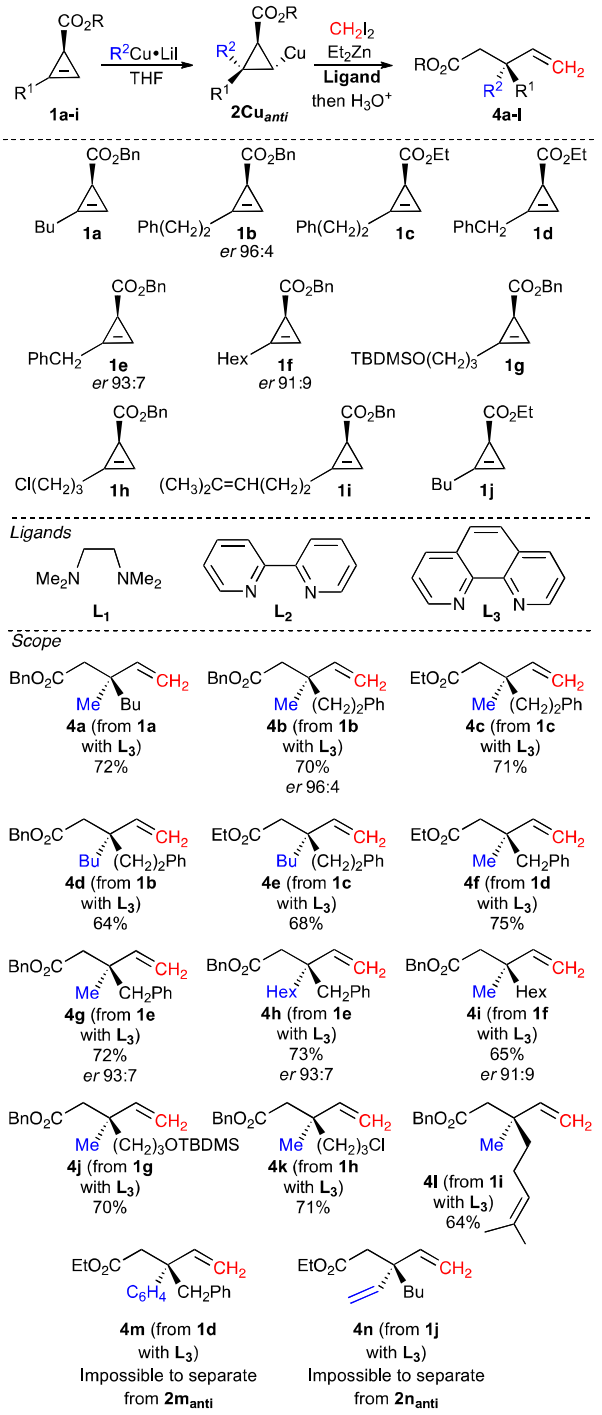


Entry	Me[M]	Solvent	2a$_{syn}$/2a$_{anti}$ [a]
1	MeLi	**THF**	**1:99** (75)
2	MeLi	2-MeTHF	6:94
3	MeLi	Et_2O	89:11
4	MeLi	Hexane	97:3
5	MeLi	**C_6H_4Me**	**99:1** (73)
6	MeMgBr	THF	28:72
7	MeMgBr	Et_2O	99:1
8	MeMgBr	**C_6H_4Me**	**99:1** (72)

[a] **1a** was consumed completely and the ratio between products **2a**$_{syn}$ and **2a**$_{anti}$ was determined by GC-MS of the crude reaction mixture. Numbers in parentheses represent the isolated yields after purification by column chromatography.

Having access to both *syn* and *anti* diastereoisomers of the carbometalated products at will according to the nature of the solvent, we then moved our attention to the zinc-homologation reaction of the racemic cyclopropyl copper species **2Cu**$_{anti}$, first, originating from the carbometalation reaction of MeCu in THF (from MeLi and CuI as described in Table 1, entry 1). For this purpose, CH_2I_2 and Et_2Zn, in a 1:1 ratio, were added at -45 °C to the reaction mixture and upon warming to -20 °C within 2 hours, the homologated cyclopropylmethyl zinc derivative[22] **3** gave **4a** as described in Figure 2. Indeed as cyclopropylcopper **2Cu**$_{anti}$ does not react with CH_2I_2, the reaction between Et_2Zn and CH_2I_2 occurred first to lead to the *in-situ* formation of the zinc carbenoid ICH_2ZnEt.[23] Then, **2Cu**$_{anti}$ is homologated by the zinc carbenoid to generate the *in-situ* reactive cyclopropylmethyl zinc (or copper) derivative **3** (see Figure 1) that instantaneously undergoes a C-C bond fragmentation[24]. Although the combined carbometalation – zinc homologation – fragmentation reactions proceeded smoothly according to our original plan to give **4a**, the conversion of **2Cu**$_{anti}$ into **4a** was only moderate (**2a**$_{anti}$/**4a** = 27/73 after hydrolysis).

Figure 2. Combined carbometalation – zinc homologation – fragmentation reactions on cyclopropenyl ester **1**.



To improve the conversion, it was then anticipated that increasing the nucleophilicity of the carbon atom bearing the organocopper species should increase its reactivity towards the ambiphilic zinc carbenoid species $EtZnCH_2I$.

To this end, various donor ligands were added to the reaction mixture to improve the reactivity of the cyclopropyl copper species (see ligands in Figure 2).[25] We were pleased to see that indeed the addition of TMEDA (**L$_1$**) or 2-2'-bipyridine (**L$_2$**) as ligand improved the conversion of the desired product **4a** (**2a$_{anti}$/4a** = 12/88 and 13/87 respectively after hydrolysis).

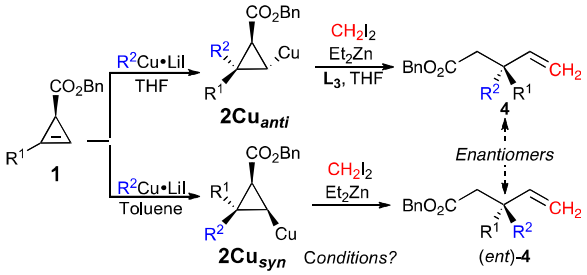
The best conversion could be reached when phenanthroline (**L$_3$**) was added to **2Cu$_{anti}$** as the ratio became excellent (**2a$_{anti}$/4a** = 6/94 after hydrolysis) and the final product **4a** could be isolated in 72% yield. This sequence of carbocupration – zinc homologation and C-C bond cleavage has been generalized to different functionalized substrates (see scope in Figure 2) and in all cases, the reactions proceed smoothly for the one-pot transformation of **1** into **4**.

First, both cyclopropenyl esters (–OEt and –OBn respectively) similarly undergo this combined transformation (compare **4b** to **4c**, **4d** to **4e** and **4f** to **4g** in Figure 2) but it should be noted that the products resulting from the reaction with the benzyl ester (**4b**, **4d**, **4g**) are easier to purify by column chromatography than the products possessing the ethyl ester (**4c**, **4e**, **4f**) from the remaining carbometalated products after hydrolysis **2$_{anti}$**. These combined reactions are not restricted to the introduction of a methyl group as various other alkyl groups could be added in good yields by simply changing the nature of the starting organocopper reagent (compare **4b** to **4d**, **4f** to **4h** and **4g** to **4h**, Figure 2). The reaction of cyclopropenyl ester **1d** with phenylcopper also proceeds but we were unable to separate the desired product **4m** from the carbometalated product **2m$_{anti}$** after hydrolysis. Similarly, when we treated vinylcopper derivative (prepared from ethenylmagnesium bromide and CuI in a 1:1 ratio) as a representative example of sp^2 organometallic species, with cyclopropenyl ester **1j**, the reaction proceeds smoothly but here again, we were unable to separate the desired product **4n** from the hydrolysed carbometalated product **2n$_{anti}$**. It is worthwhile mentioning that this sequence of vinyl cupration – zinc homologation – fragmentation opens new avenues to the preparation of skipped dienes possessing a quaternary carbon stereocenter. Notably, the presence of other functional groups in the starting alkyl chain of the cyclopropenyl esters is well tolerated (formation of **4j-l**, Figure 2). Having established an easy protocol for the preparation of racemic **4** from these very simple starting materials, the synthesis of enantiomerically enriched cyclopropenyl esters **1b** (R^1 = $Ph(CH_2)_2$), **1e** (R^1 = $PhCH_2$) and **1f** (R^1 = Hex) were easily achieved in good enantiomeric ratio (**1b** *er* 96:4, **1e** *er* 93:7 and **1f** *er* 91:9) through cyclopropenation of the terminal alkyne with benzyl diazoacetate and $Rh_2(OAc)(R,R\text{-DPTI})_3$ (DPTI = diphenyltriflylimidazolidinone) as catalyst.[26] Interestingly, the enantiomeric ratios of these cyclopropenyl benzyl esters are lower than the ones obtained for cyclopropenyl ethyl esters (ethyl diazoacetate generally leads to enantiomeric ratios in the range of 97:3) but for the sake of simplicity, we decided to illustrate our concept with a starting materials that would require a minimum numbers of chemical steps. When the sequence of carbocupration – zinc homologation and C-C bond fragmentation was performed on these enantiomerically enriched cyclopropenyl esters, enantioenriched acyclic allylic molecular architectures (**4b**,**g**,**h**,**i**) possessing the quaternary

carbon stereocenter were easily obtained through the creation of two C-C bonds in a single-pot operation. HPLC analyses (see Supplementary Information) show that the chiral information at the carbon atom holding the ester moiety in **1b**,**c**,**i** was quantitatively transferred to the final products **4b** (*er* 96:4), **4g** and **4h** (*er* 93:7) and **4i** (*er* 91:1), Figure 2. It was therefore clear that the quaternary stereocenter was at no risk of epimerization in the whole process and one could prepare the expected products with the same enantiomeric ratio as in the starting materials.

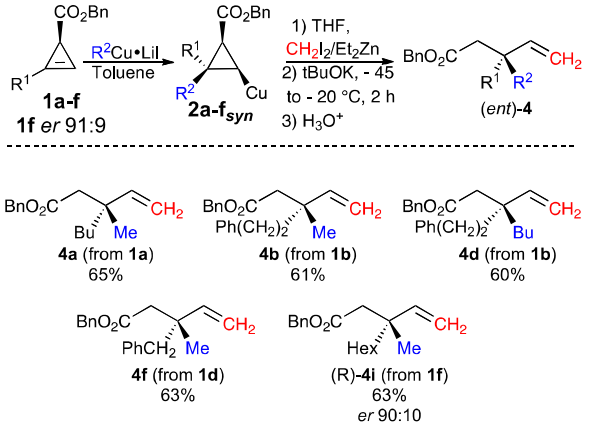
In contrast to any typical enantioselective synthesis where the independent formation of the two enantiomers of a product can only be achieved by changing the chirality of the ligand (or substrate) associated with the enantioselective transformation[27], the diastereodivergent carbometalation of **1**, controlled by the nature of the solvent as described in Table 1, should therefore lead to the enantiodivergent synthesis of **4** from the same enantiomerically enriched starting material **1** (as summarized in Figure 3).

Figure 3. Diastereodivergent combined carbometalation – zinc homologation – fragmentation *en route* to enantioenriched allylic quaternary carbon stereocenters.



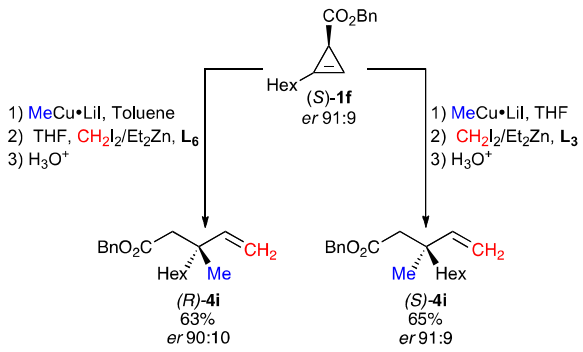
Although the best ligand to promote the zinc homologation of **2Cu$_{anti}$** was phenanthroline **L$_3$**, it was unclear that the same ligand would be optimal when the first step was performed in a non-polar solvent. To reach this new goal, one has to optimise again the reaction sequence for the formation of the desired products **4** from the *syn*-diastereomer **2Cu$_{syn}$** in the presence of non-polar solvent (such as toluene, see Table 1, entries 5 and 8). It was first rapidly found that the zinc homologation for the transformation of **2Cu$_{syn}$** into **4a** was more efficient when the initial organocopper species was prepared from an organolithium (R^2Cu•LiI, Table 1, entry 5) instead of an organomagnesium species (R^2Cu•MgX$_2$, Table 1, entry 7). After extensive experiments, we were pleased to see that the zinc homologation could now be best performed in the presence of the non-nucleophilic potassium *tert*-butoxide ligand (for all other ligands tested, see Supplementary Information) with addition of THF as co-solvent. It is important to note that the reaction performed under identical reaction condition but in the absence of the potassium *tert*-butoxide ligand results in very poor conversation, which underline the effect of this particular ligand on the nucleophilicity of the metalated carbon center stabilized by the chelating ester. Once the best experimental conditions were in hands, various allylic esters **4** possessing the quaternary carbon stereocenters were prepared in a single-pot operation from cyclopropenyl esters **1** as illustrated in Figure 4.

Figure 4: Combined carbometalation – zinc homologation – fragmentation reactions for the preparation of the opposite enantiomer



The scope of this new reaction sequence of *syn*-diastereoselective carbometalation – zinc homologation and selective C-C bond cleavage proceeds equally well albeit with slightly lower yields for the final products **4**. To illustrate the potential of this diastereodivergent approach, both enantiomers of **4i** were prepared from the same cyclopropenyl ester enantiomer **1f** (R^1 = Hex, *er* 91:9). When the carbocupration of (*S*)-**1f** was performed with MeCu•LiI in THF followed by the subsequent addition of CH_2I_2, Et_2Zn and phenanthroline (**L$_3$**) as ligand, the selective C-C bond cleavage leads to the corresponding allylic (*S*)-**4i** with an enantiomeric ratio of 91:9 in 65 % yield (Figure 5).

Figure 5: Diastereodivergent strategy for the preparation of enantioenriched **4**



On the other hand, if the same cyclopropenyl ester (*S*)-**1f** is added to the organocopper MeCu•LiI in toluene followed by the subsequent zinc-homologation in the presence of potassium *tert*-butoxide as ligand, the selective C-C bond cleavage provides the allylic (*R*)-**4i** in similar yield with almost the same enantiomeric ratio (*er* 90:10) in 63% yield (Figure 5).

Conclusions

A new sequence of diastereoselective carbometalation – zinc-homologation – C-C bond cleavage allows the easy transformation of enantiomerically enriched cyclopropenyl esters into acyclic allylic moiety bearing the challenging quaternary carbon stereocenters in a single-pot reaction through the formation of two new C-C bonds. As the carbometalation reaction may lead to two different diastereoisomers according to the nature of the solvent, this strategy paves the way to the diastereodivergent synthesis of both enantioenriched **4** at will.

Acknowledgements

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