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Organocopper-Triggered Cyclisation of Conjugated Diene-ynes: Diastereo- and Enantioselective Synthesis of Indenes

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Abstract: Organocopper reagents react with readily available chiral conjugated diene-ynes to give indene derivatives bearing two stereogenic centres. The investigation of this original reaction in optically pure series demonstrates that a double transfer of chirality is operating. A stereocontrolled cascade involving S_N2' followed by carbocupration and conjugate addition reactions accounts for the total recovery of the initial chirality. The scope and limitations of the reaction were investigated. The high diastereofacial discrimination in the cyclisation step allowed the construction of the quaternary stereocentre with excellent *dr* and *ee*, with the opposite configuration depending on the *E*- or *Z*-configuration of the alkene in the starting material. Post-functionalisation of indenes allowed the synthesis of indanyl derivatives containing four contiguous stereocentres.

Keywords: carbocycles; chirality; cuprates; cyclization; enynes

Introduction

Chirality transfer in the construction of carbocyclic and heterocyclic frameworks is still a challenge for synthetic chemists.[1] Allene chemistry, due to the unique electronic and chiroptical properties of the cumulated diene motif, finds its rightful place in the development of asymmetric synthesis.[2,3] An increasing number of enantioselective cyclisations based on chiral allenes has been reported over the last decade.[1,4,5]

Our interest in enantioselective cascade rearrangements of conjugated enediynes based on the memory of chirality phenomenon,[6] has recently led us to investigate whether the axial chirality of a transient allene could be transferred to the central chirality of the cyclic products in these reactions. This study resulted in the discovery of an original dialkyl cuprate-promoted bis-alkylating route to chiral benzofulvene derivatives.[7]

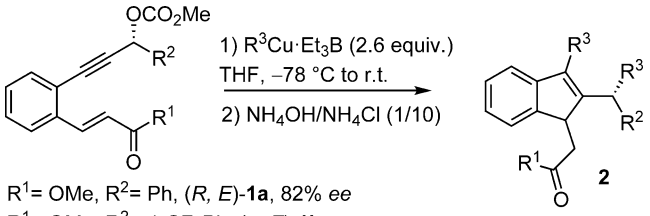
We report in this article an approach to the synthesis of chiral indenes based this time on the organocopper-promoted cyclisation of conjugated diene-ynes.[8] Indene scaffolds are present in natural products[9] and in bioactive compounds.[10] They are also used as precursors of cyclopentadienyl ligands for transition metal catalysts.[11] Egi and co-workers have very recently reported a two-step synthesis of chiral indenes bearing a quaternary stereocentre.[12] However, the enantioselective synthesis of this class of compounds is far from being widespread.[13]

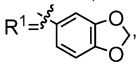
Results and Discussion

The presence of a Michael acceptor is the key structural feature to build the indenyl framework. It is worth noting that 1,4-conjugate additions of organocuprate reagents to enoates are very popular reactions and their mechanism has been widely studied.[14] Syntheses in which their intramolecular counterpart is incorporated in a tandem process are not so common,[15] and those occurring with transfer of chirality are even scarcer.[16]

The stereocontrolled S_N2' displacement of an enantiopure propargylic carbonate by an alkylcopper reagent was used to generate *in situ* a transient chiral allenic moiety from the diene-yne starting material **1** (Table 1).

Table 1. Reaction scope.[a]



R^1= OMe, R^2= Ph, (*R, E*)-**1a**, 82% *ee*
R^1= OMe, R^2= 4-CF_3Ph, (±, *E*)-**1b**
R^1=  , R^2= Ph, (*R, E*)-**1c**, 81% *ee*
R^1= OMe, R^2= Me, (±, *E*)-**1d**

Entry[a]	**1**	R^3	*dr*[b]	**2** [ee][c]	Yield [%]
1	**1a**	*n*-Bu	73:27	**2aa**(79/80)	65[d]
2	**1a**	Me[e]	76:24	**2ab**	47
3	**1a**	*i*-Bu	76:24	**2ac** (81/80)	68
4	**1a**	*t*-Bu	80:20	**2ad** (79/nd)	65
5	**1a**	CH_2TMS	90:10	**2ae** (nd)	63
6	(±)-**1b**	*n*-Bu[e]	70:30	**2ba**	43
7	**1c**	*n*-Bu	70:30	**2ca** (81/81)	67[f]
8	**1c**	*i*-Bu	65:35	**2cc** (78/82)	67[f]
9	**1c**	CH_2TMS	75:25	**2ce** (77.5/79)	61[f]
10	(±)-**1d**	*i*-Bu	84:16	**2dc**	55

[a] *Conditions:* a THF solution of diene-yne **1** was added dropwise to a solution of $R^3CuLi{\cdot}Et_3B$ in THF at −78 °C, then the reaction mixture was allowed to warm to room temperature for 1 h and the reaction was quenched with NH_4OH/NH_4Cl (1/10).
[b] Diastereomeric ratio measured by ^1H NMR analysis on the crude reaction mixture.
[c] Enantiomeric excess (of each diastereomer) measured by chiral HPLC; nd = not determined.
[d] The two diastereomers were separated by preparative HPLC.
[e] A THF solution of $Me_2CuLi{\cdot}LiI$ in THF was added dropwise to a solution of diene-yne **1** at 0 °C then the reaction mixture was allowed to warm to room temperature for 1 h and the reaction was quenched with NH_4OH/NH_4Cl (1/10).
[f] The two diastereomers were separated by preparative TLC.

Initially, carbonate **1a** was selected to test various experimental conditions and optimise the reaction. The most significant results are detailed in the Supporting Information.[17] The best yields were obtained by adding Et_3B (i.e., *n*-$BuCu{\cdot}Et_3B$, 2.6 equiv. instead of organocuprate reagent).

As selectivity is a continual challenge, it is important to highlight that this reaction is completely regio- and chemoselective. The S_N2' displacement of the carbonate is favoured over direct 1,4-addition of the organocopper and this avoids the formation of undesired by-products.

The formation of the enantio-enriched indene **2a** was envisaged from the enantio-enriched cinnamate **1a** [82% enantiomeric excess (*ee*)]. Interestingly, the enantiomeric excess of the starting material was almost entirely recovered in both the major and the minor diastereomers **2a** (79 and 80% *ee*, respectively) (Table 1, entry 1). The scope of the reaction is illustrated in Table 1. Whenever it was possible to measure the *ee* of each diastereomer, the same range of chirality transfer was observed from substrates **1a–c**.

Racemic **1b** was used as starting material to highlight the possible impact of the electronic effect of the substituent in the *para* position on the aryl group on the diastereoselectivity. No effect was noted since the same *dr* was observed from ^1H NMR analysis of the crude reaction mixture (Table 1, entry 6).

The introduction of chemical diversity by varying the nature of the organocopper reagent was then explored. Two methyl groups were successfully introduced according to a procedure involving a dialkylcuprate (procedure A) instead of $MeCu{\cdot}Et_3B$.[17] The addition of Et_3B resulted in a complex mixture. Unfortunately, the *ee* of the product could not be measured by chiral HPLC (entry 2). The product bearing two isobutyl groups was synthesized in 68% yield (entry 3) and the two diastereomers were enantioenriched (81% and 80% *ee*s, respectively).

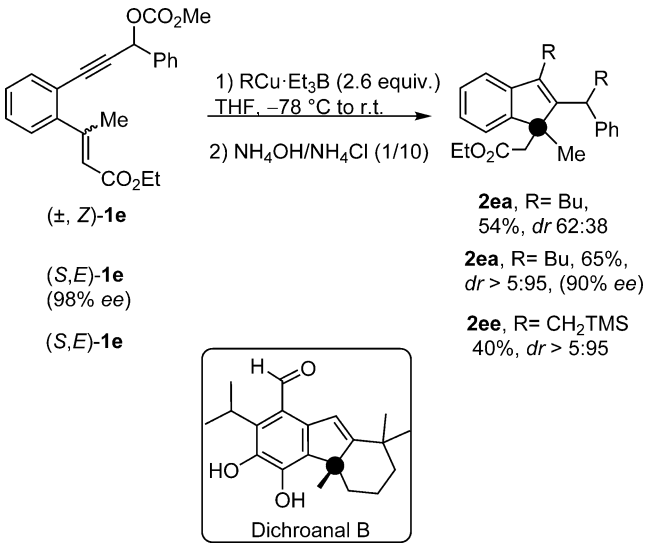
Remarkably, despite the bulkiness of *tert*-butyl groups, the product resulting from the reaction of **1a** with *t*-$BuCu{\cdot}BEt_3$ was isolated in 65% yield and the dr was 80:20 (entry 4). In this process, a nearly total chirality transfer was also registered (79% *ee* from 82% *ee*). It is important to recall that the reaction of enediyne analogues with the *tert*-butylcopper reagent stopped at the allene formation stage and thus, no benzofulvene was obtained.[7a]

The TMS-functionalized copper reagent was also successfully employed (entry 5). It afforded the highest diastereoselectivity in the series (90:10). The level of chirality transfer could not be determined because of the lack of polarity that renders the HPLC separation of enantiomers difficult. However, the reaction of substrate **1c** and $TMSCH_2Cu{\cdot}Et_3B$ afforded a high chirality transfer (entry 9), so we can reasonably assume a similar behaviour with **1a**.

The use of chalcone derived substrate **1c** led to the desired products in 61 to 67% yields with a *dr* ranging from 65:35 to 75:25. Again, a high level of chirality transfer was reached with all the organocopper reagents (entries 7–9).

The nature of the substituent at the stereogenic centre in the starting material also influences the diastereoselectivity of the cyclisation. Regarding the addition of *i*-$BuCu{\cdot}Et_3B$, the replacement of the phenyl group (substrate **1a**) by a methyl group (substrate **1d**) resulted in an increase of the *dr* from 76:24 to 84:16 (Table 1, entries 3 and 10).

The scope of the reaction was further expanded to the trisubstituted diene-yne **1e** with the aim to construct challenging targets bearing a quaternary stereo-

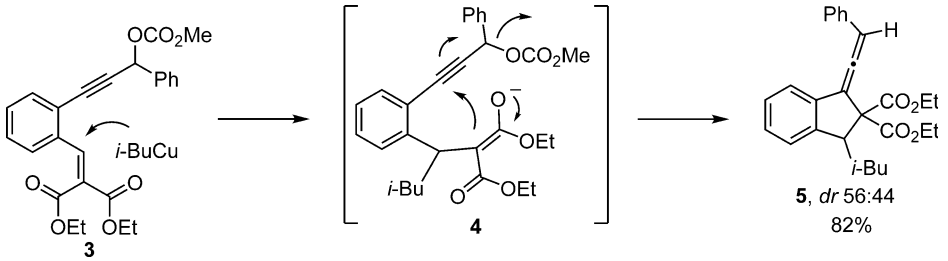


Scheme 1. Synthesis of an indene bearing an all-carbon quaternary stereocentre.

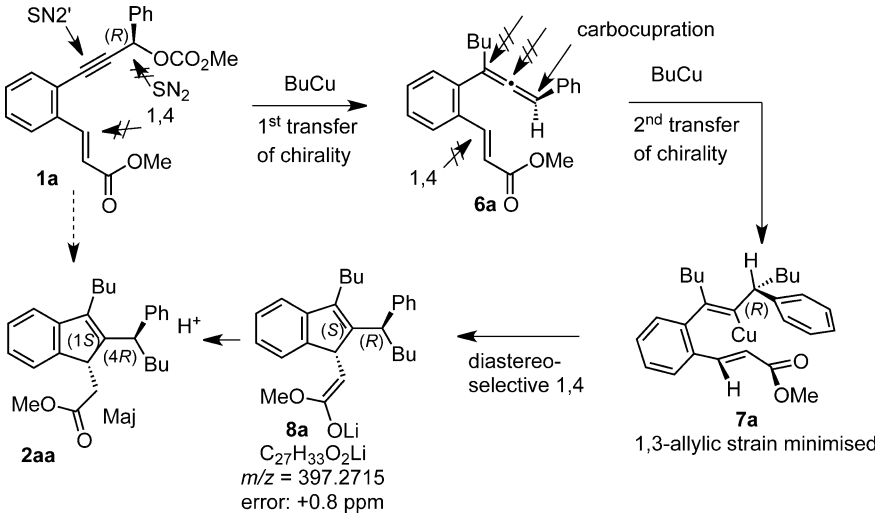
centre. The results are given in Scheme 1. Interestingly, when *Z*-**1e** was reacted with the *n*-butylcopper reagent, the indene **2ea** was isolated in 54% yield as a mixture of two diastereomers in 62:38 ratio. With *E*-**1e** the diastereoselectity was nearly total (>5:95) but with a reversal as regard to the preferred isomer.[18] The product **2ea** was isolated in 65% yield, and most importantly, a high level of chirality transfer (92%) was observed from the enantiopure starting material. Thus the reaction also enables the control of the quaternary indenyl stereocentre. Similarly, a totally diastereoselective bis-alkylating cyclisation of *(S,E)*-**1e** was achieved by reaction with $TMSCH_2Cu{\cdot}Et_3B$. It is interesting to highlight that the natural product dichroanal B bears an indenyl core with all-carbon quaternary stereocentre like in **2ea**.

To further explore the methodology limitations, substrate **3** was exposed to the optimised experimental conditions (Scheme 2). In this case, the chemoselectivity of the organocopper nucleophilic attack changes and the 1,4-addition leading to enolate **4** becomes faster than the S_N2' displacement of the propargyl carbonate. Intramolecular S_N2' substitution of the carbonate only occurs in the second elementary step to promote the formation of the allene **5** in 82% yield as a 56:44 mixture of two diastereomers.[19]

We propose the stepwise mechanism shown in Scheme 3 for the synthesis of **2aa**. Although two reactions can formally compete (1,4-addition and S_N2 reaction), it is the chemoselective S_N2' displacement of



Scheme 2. 1,4-Addition-triggered allenylindene synthesis.



Scheme 3. Mechanism proposed for the formation of indene **2aa**.

the carbonate that occurs first and allows the formation of a transient allene **6a** with a central-to-axial chirality transfer (Scheme 3).[20] The regio-, chemo- and stereoselective carbocupration of the allene moiety leads to **7a** as single enantiomer through a second chirality transfer (axial-to-central).[21] The intramolecular 1,4-addition leads to the lithium enolate **8a**. The presence of this enolate in the crude reaction mixture was confirmed by ESI-HR-MS.[17]

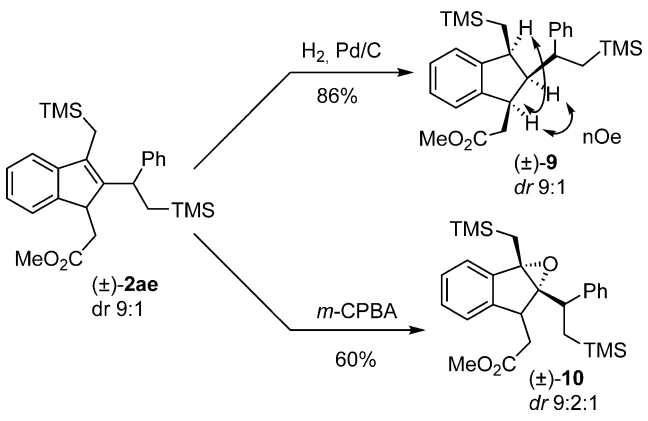
The coordination of copper to the conjugated C=C bond, should play a crucial role in the determination of the stereochemical outcome of the cyclisation step. The formation of the π-complex has been proposed and demonstrated by Krause for intermolecular 1,4-addition to acyclic α,β-unsaturated systems.[22]

The determination of absolute configurations (AC) was mandatory to propose a mechanism. Different techniques enable AC determination; we have been interested by ECD and VCD.[23]

On the basis of previous work,[7a] we could guess that the *R*-absolute configuration of the exocyclic stereogenic centre (bearing the *n*-Bu group) in **2** resulted from the *R*-starting material (*anti* S_N2' followed by *syn*-carbocupration). The absolute configurations of **2aa** diastereomers were assigned by ECD analyses and confirmed by VCD.[17] We were thus able to ascertain that the configuration of the stereocentre C-1 is *S* in the major diastereomer and *R* in the minor diastereomer resulting from *R*-**1a**. As expected, the configuration of the exocyclic stereogenic centre is *R* in both diastereomers. Accordingly, we assume that the stereochemical outcome is controlled by the allene axis. The 1,3-allylic strain should control the conformation around the C–C pivot bearing the stereogenic centre in the vinyl copper intermediate **7** (Scheme 3). The spatial orientation of the phenyl and butyl groups would explain the facial selectivity in the conjugate addition.

The diastereofacial discrimination in the cyclisation step should also depend on the *Z* or *E*-stereochemistry of the Michael acceptor.[18] The availability of both *E*-**1e** and *Z*-**1e** and the result discussed above allowed us to confirm this assumption.

Finally, post-functionalisation of racemic indene **2ae** was achieved (Scheme 4). The indanyl skeleton is known to exhibit interesting biological activities.[24] Indeed, hydrogenation of the double bond afforded the expected indane with a high diastereoselective control and a good yield (86%).[25] An nOe analysis allowed the *syn-syn* relative stereochemistry of the indane in **9** to be established. Furthermore, the double bond could be epoxidised to give **10**, which bears 4 stereocentres with a good diastereocontrol.



Scheme 4. Post-functionalisation of indene **2**.

Conclusions

In conclusion, we have devised a new method for the synthesis of chiral indenes bearing two stereogenic centres from readily available conjugated diene-ynes. This bis-alkylating cycloisomerisation, triggered by alkylcopper reagents, involves the cascade combination of S_N2' displacement of an enantiopure propargylic carbonate/carbocupration of the resulting allene/conjugate addition to the activated double bond. It allows the isolation of enantio-enriched indenes through a double transfer of chirality followed by a diastereoselective cyclisation. The substrate presenting an *E*-trisubstituted double bond afforded the expected target bearing a quaternary stereocentre with a high level of chirality transfer.

Experimental Section

Synthesis of Indenes 2aa–2ee

Procedure A: In a dried flask, carbonate **1a** (1 equiv.) was dissolved in freshly distilled THF (15 mL mmol^{-1}). The solution was cooled to 0 °C. In another dried Schlenk flask, distilled THF (15 mL mmol^{-1}) was added to CuBr·Me_2S (1.3 equiv.). To this stirred solution, cooled to −20 °C, MeLi (2.6 equiv., 1.6 M in ether) was added. The solution was stirred for 5 min. The solution of Me_2CuLi·LiBr was quickly added *via* syringe to the solution of carbonate **1a**. The resulting mixture was stirred for 5 min at 0 °C and then the reaction was allowed to warm to room temperature for 1 h. The reaction was quenched with a 10:1 solution of NH_4Cl/NH_4OH, and stirred for 30 min. After extraction with Et_2O, the organic layer was dried over $MgSO_4$, filtered, and the solvent was evaporated under reduced pressure and the crude product was purified by chromatography.

Procedure B: An oven-dried Schlenk tube was charged with CuBr·Me_2S (2.6 equiv.), evacuated and refilled with argon three times followed by addition of freshly distilled THF (15 mL mmol^{-1}). The resulting homogeneous solution was cooled to –40 °C and RLi (2.6 equiv.) was added drop-wise. The solution was stirred for 5 min at −40 °C and then cooled to −78 °C. Et_3B (2.6 equiv., 1 M in hexanes) was added drop-wise. After 5 min at −78 °C, a precooled solu-

tion (−78 °C) of carbonate **1a** in THF (15 mL mmol^{-1}) was quickly added *via* syringe to RCu·BEt_3, stirred for 5 min, then the cooling bath was removed and the reaction mixture was allowed to warm to room temperature over 15 min. After 1 h at room temperature, the reaction mixture was quenched with saturated aqueous NH_4Cl/NH_4OH (10:1) and further stirred for 30 min. The aqueous layer was extracted with Et_2O, dried ($MgSO_4$), filtered, evaporated under reduced pressure and the crude product was purified by chromatography.

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