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Intramolecular Carbocupration Reaction of Unactivated Alkynes Bearing a Stabilized Nucleophile : Application to The Synthesis of Iridoid Monoterpenes.

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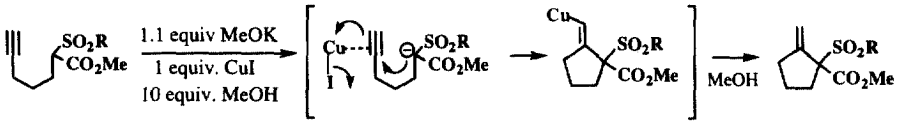
Abstract: The copper-promoted cycloisomerization of unsaturated alkynes bearing a stabilized nucleophile is described, providing a novel synthesis of various iridoid monoterpenes.

Keywords: alkynes, cyclization, vinyl copper, Iridoid monoterpenes.

Despite recent attention focusing on intramolecular carbometalation cyclizations onto unsaturated systems, only a few synthetic methods involving carbon nucleophiles such as stabilized carbanions have been reported.[1] Although several strategies have been successfully employed over the last decade for the cyclization of active methine compounds bearing a 4-alkynyl group to functionalized methylenecyclopentanes, these reactions generally suffer from a lack of generality : the Cobalt catalyzed ene reaction[2] and the basic sub-stoichiometric molybdenum-promoted carbocyclization[3] are restricted to ε-acetylenic β-ketoesters and the intramolecular carbolithiation reaction developed by Funk[4] is limited to activated alkynes (alkylthio- and alkoxyacetylenes).

A more general method allowing the cyclization of a variety of δ-acetylenic stabilized carbanions by using catalytic quantities of both a palladium complex and potassium *t*-butoxide has recently been developed in our laboratory.[5] However, this palladium-catalyzed carbocyclization could not be applied to α-sulfonyl ε-acetylenic esters.[6] It was found that copper iodide efficiently promotes the cyclization of these last compounds[7] but the reaction is limited by the need for stoichiometric quantities of base, metal and a protonating species (Scheme 1).



Scheme 1

A recent communication regarding the carbocyclization of various alkynylated active methine compounds in the presence of excess $TiCl_4$ and Et_3N[8] has prompted us to report our latest findings related to the use of catalytic amounts of base and copper salts for the cyclization of similar compounds of type **1**. On the basis of our earlier observation,[7] showing that in the stoichiometric copper-promoted cyclization of α-sulfonyl ε-acetylenic esters the vinylcopper intermediate could be protonated by an alcohol, a catalytic cycle for the intramolecular carbocupration reaction of active methine compounds can be envisioned as depicted in scheme 2. Indeed, it is well known that potassium *t*-butoxide reacts with cuprous halides to give copper *t*-butoxide.[9] Such a species should be able to promote the cyclization of the enolate as previously shown for copper iodide (scheme 1).Thus, the reaction mechanism would involve an attack of the enolate nucleophile onto the triple bond activated

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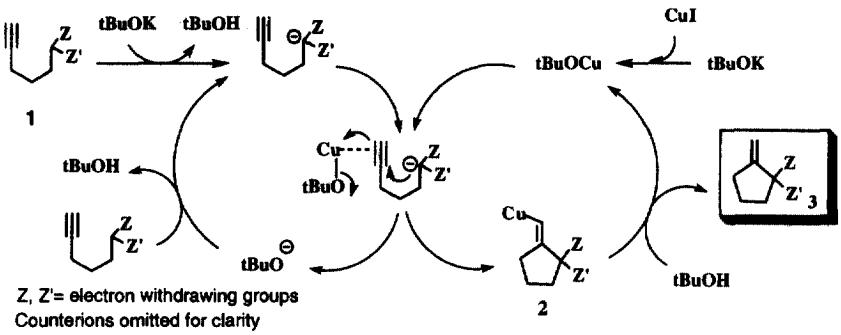
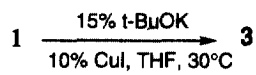
by the copper alkoxide. In order to initiate the process, the amount of base employed must be slightly greater than that of copper iodide. The *t* -butanol produced in the reaction may then protonate the resulting vinylcopper intermediate **2** leading to formation of the methylene derivative **3** and regeneration of the active copper catalyst.

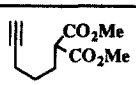
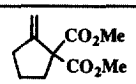
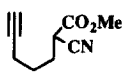
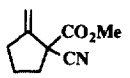
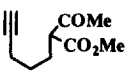
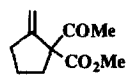
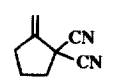


Scheme 2

Initially the copper-catalyzed cyclizations of terminal alkynes bearing different carbon nucleophiles were investigated. These compounds were simply stirred in THF, at 30°C, in the presence of 15% potassium *t*-butoxide and 10% copper iodide for the indicated time. The corresponding methylenecyclopentanes were isolated in excellent yields. Representative results are summarized in table 1.

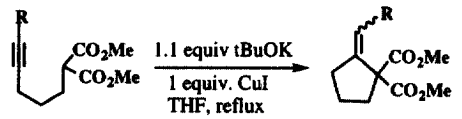
Table 1 Catalytic carbocupration reaction



Entry	Substrate	Time (h)	Product	Isolated Yields (%)
1	 **1a**	4.5	 **3a**	76
2	 **1b**	1	 **3b**	97
3	 **1c**	1	 **3c**	98
4	 **1d**	2.5	 **3d**	77

This copper-catalyzed reaction could not be applied to the disubstituted alkynes **1e** and **1f**, these substrates being recovered unchanged even when the reaction mixture was heated to reflux for 5h. However, when the reaction was carried out in the presence of stoichiometric amounts of both base and copper iodide

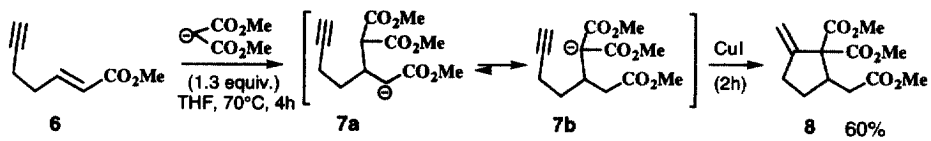
(68°C, 2h), **1e** was cleanly converted to Z-**4e** (88%) as the single product.[10] This result further supports a mechanism in which the malonate and the copper species add in a *trans* fashion across the unsaturated bond. It should be noted that the carbotitanation of the same substrate gave exclusively E-**4e** via the addition of the metal enolate across the triple bond.[8] When applied to the phenyl-substituted analogue **1f**, the reaction proved more difficult since it did not cyclize under identical reaction conditions. However, longer reaction times (68°C, 24h), gave rise to cyclization products isolated as a mixture of two diastereomers in a 70/30 ratio. The Z-isomer resulting from the *trans* addition process described above was found to be the major product. The minor E-isomer was identified by comparison of its spectral data (^{1}H and ^{13}C NMR), with an authentic sample prepared by means of a palladium-catalyzed carbocyclization of the unsaturated malonate **1a**.[11] This isomer is thought to result from isomerization of the Z-vinylcopper adduct to the thermodynamically more stable E-isomer during the course of the reaction, performed here at elevated temperature for a prolonged period of time (scheme 3).[12]



	Time	ratio (Z/E)	Yield (%)
1e R=Me	2h	100/0	88 (**4e**)
1f R=Ph	18h	70/30	65 (**4f**)

Scheme 3

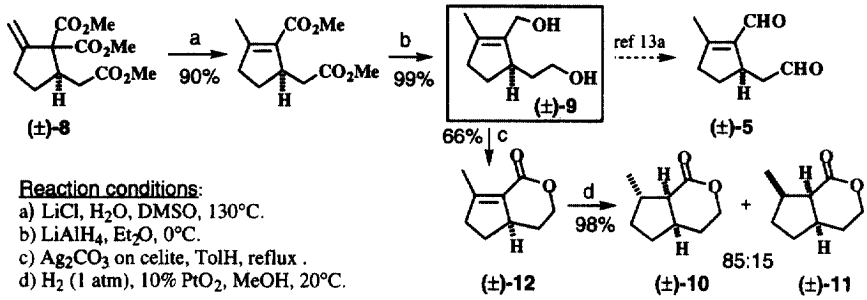
The utility of this methodology was demonstrated by the formal synthesis of [±]-rotundial (**5**)[13] a new natural mosquito repellent isolated from the leaves of *Vitex rotundiforia.* This synthesis was first accomplished by a sequential Michael addition-cyclization reaction (MIRC reaction [14]). This "one pot" two-step procedure consists of the conjugate addition of a malonic enolate (prepared from methylmalonate and *t*-BuOK) to the known unsaturated ester **6** forming the intermediate enolate **7a**. Proton-transfer leads to the enolate **7b** and addition of catalytic quantities of copper iodide (10%) to the reaction mixture allows the annulation process to take place. The resulting functionalized cyclopentane **8** was obtained in 60% yield (scheme 4).



6 **7a** **7b** **8** 60%

Scheme 4

Although numerous examples of cyclizations initiated by a Michael addition have been published, malonic esters are rarely employed as nucleophiles. In the method described herein, the malonate unit serves as the nucleophile in both processes, firstly as Michael addition initiator and secondly as the nucleophile involved in the ring closure.[15] Completion of our synthetic goal was achieved by demethoxycarbonylation of **8** using Krapcho's conditions[16] followed by a reduction with lithium aluminium hydride to give the known diol **9**[13a], the physical data obtained (^{1}H and ^{13}C NMR, IR, MS) were identical with those previously reported (scheme 5).



Scheme 5

Furthermore, the readily available diol **9** represents an attractive precursor to the simple iridoid monoterpene lactones such as mitsugashiwalactone (**10**) and onikulactone (**11**), which have attractive physiological action on the Felidae[17]. So treatment of **9** with silver carbonate on celite (Fetizon's reagent) afforded lactone **12** in 66% yield. Reaction of **12** with $[HCu(PPh_3)]_6$[18] failed to give the expected onikulactone selectively. However, hydrogenation of **12** over platinum oxide in methanol at ambient temperature and pressure afforded a 85:15 mixture of [±]-mitsugashiwalactone and [±]-onikulactone in 98 % combined yield (scheme 5). Spectral data for these two compounds were in agreement with that reported in the literature.[19]

Further evaluation of the synthetic potential of this reaction is in progress and will be reported in due course.

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