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**Copper Catalysis**

# Discrimination of Diazo Compounds Toward Carbenoids: Copper(I)-Catalyzed Synthesis of Substituted Cyclobutenes**

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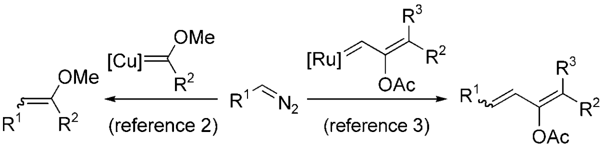
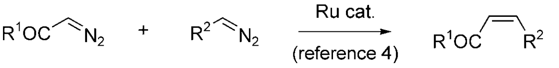
In the last few years the role of diazo compounds in organic synthesis, particularly in cyclization reactions via metal carbenoids (metal: ruthenium, copper, rhodium, etc.) has been prominent.[1] By taking advantage of the ease with which these metal carbenes collapse into the corresponding symmetrical alkenes (homocoupling), we and others have been able to access nonsymmetrical alkenes by the selective heterocoupling of diazoacetate esters with copper(I)[2] and ruthenium(II)[3] carbene complexes [Eq. (1)]. Interestingly, the metal-catalyzed selective cross-coupling reaction between two different diazo substrates has been reported recently [Eq. (2)].[4]

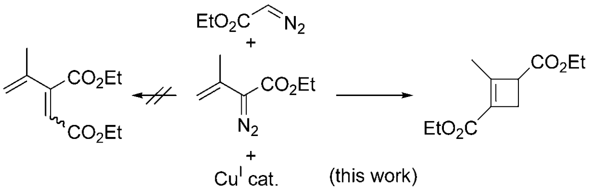


(1)



(2)

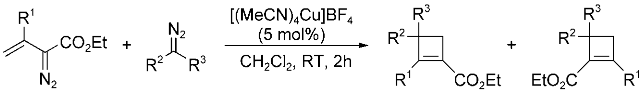
At this point, we became intrigued as to whether discrimination between appropriately selected diazo compounds, for instance simple diazo and vinyldiazo systems, could be attained. Firstly, we found that $[Cu(MeCN)_4]BF_4$ catalyzes the reaction between ethyl vinyldiazoacetate and ethyl diazoacetate at room temperature. Surprisingly, the expected cross-coupling conjugated diene was not formed, but diethyl 2-methylcyclobutene-1,3-dicarboxylate was obtained in moderate yield as the sole heterocoupling product [Eq. (3)].



(3)

This initial result seems to encompass, among others, two relevant features: 1) it represents a novel [3+1] coupling between diazo compounds, wherein two C–C bonds rather than one C=C bond are formed, and 2) it might provide direct access to a relevant, uncommon structure. Therefore, herein we report our preliminary studies on the synthesis of cyclobutene structures by copper(I)-catalyzed cyclization of vinyldiazoacetate esters and diazo compounds (Table 1).

***Table 1:*** Copper(I)-catalyzed synthesis of cyclobutene derivatives **3** and **4** from vinyldiazoacetates **1** and diazo compounds **2**.



**1** **2** **3** **4**

| Entry | $R^1$ | **1** | $R^2$ | $R^3$ | **2** | **3** (yield [%])/**4** (yield [%])[a] |
|---|---|---|---|---|---|---|
| 1 | Me | **1a** | $CO_2Et$ | H | **2a** | **3aa** (33) |
| 2 | Me | **1a** | $CO_2t$Bu | H | **2b** | **3ab** (45) |
| 3 | Me | **1a** | $CO_2Et$ | Ph | **2c** | **3ac** (56) |
| 4 | Me | **1a** | $CO_2t$Bu | Ph | **2d** | **3ad** (79) |
| 5 | Me | **1a** | COMe | Ph | **2e** | **3ae** (66) |
| 6 | H | **1b** | $CO_2Et$ | Ph | **2c** | **3bc** (44)/**4bc** (11) |
| 7 | H | **1b** | $CO_2t$Bu | Ph | **2d** | **3bd** (46)/**4bd** (15) |
| 8 | H | **1b** | COMe | Ph | **2e** | **3be** (51)/**4be** (13) |
| 9 | Me | **1a** | Ph | H | **2f** | **3af** + **4af** (52)[b] |
| 10 | Me | **1a** | $CO_2Et$ | PMP[c] | **2g** | **4ag** (63) |
| 11 | H | **1b** | $CO_2Et$ | PMP[c] | **2g** | **4bg** (66) |
| 12 | Me | **1a** | Ph | Ph | **2h** | **4ah** (57) |

[a] Yield of isolated products after column chromatography. [b] Isolated as a nonseparable 60:40 mixture of regioisomers. [c] PMP = 4-$MeOC_6H_4$.

First, $[Cu(MeCN)_4]BF_4$ (5 mol %) was added to a solution of ethyl 2-diazo-3-methylbut-3-enoate **1a** ($R^1$ = Me) and ethyl diazoacetate **2a** ($R^2 = CO_2Et$, $R^3$ = H) in $CH_2Cl_2$ at room temperature. After stirring the reaction mixture for two hours the solvent was removed and the resulting mixture was subjected to column chromatography, affording the cyclobutene **3aa** in 33 % yield along with ethyl maleate and ethyl fumarate (entry 1). The yield could be increased to 45 % using *tert*-butyl diazoacetate **2b** (entry 2). The cyclization of **1a** with

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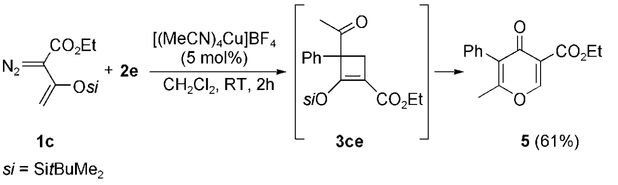
phenyl-substituted diazoacetates **2c,d** and diazoketone **2e** ($R^3$ = Ph) produced the expected cycloadducts **3ac–ae** in higher yields (56–79%) (entries 3–5). On the contrary, mixtures of regioisomers were in general obtained in the case of unsubstituted vinyldiazo substrate **1b** ($R^1$ = H) (entries 6–8). Therefore, the copper(I)-catalyzed reaction of **1b** and **2c–e** afforded a mixture of separable isomers **3bc–3be**/**4bc–be** (ratio **3**/**4** = 3.0–4.0) in moderate combined yields (55–64%). In the same way, phenyldiazomethane **2f** ($R^2$ = Ph; $R^3$ = H) and ethyl propenyldiazoacetate **1a** provided a nonseparable 3:2 mixture of **3af**/**4af** in 52% yield (entry 9).

Interestingly, complete reversal of the regioselectivity was encountered in the case of PMP-substituted diazo compounds **2** (PMP = 4-methoxyphenyl; entries 10 and 11). Thus, ethyl 2-diazo-2-(4-methoxyphenyl)acetate **2g** yielded exclusively the cycloadducts **4ag** and **4bg** (63–66% yield) upon reaction with both vinyldiazo esters **1a** and **1b**, respectively. Following the same regioselectivity pattern, diphenyldiazomethane **2h** reacted with vinyldiazo ester **1a** giving rise, selectively, to **4ah** (entry 12).

From Table 1 various points worth attention: 1) the yields are moderate to acceptable and can be notably increased in going from ethyl to *tert*-butyl diazoacetate esters; 2) the regioselectivity is dictated by the presence of either an electron-rich aryl group ($R^3$ = PMP) or two phenyl groups ($R^2 = R^3$ = Ph) in component **2** in favor of regioisomer **4** (entries 10–12); 3) the presence of a methyl group ($R^1$ = Me) in component **1** strongly favors regioisomer **3** (entries 1–5).

When the silyloxy-substituted vinyl diazoacetate **1c** ($R^1$ = $OSiMe_2t$Bu) was employed, the cyclobutene derivative **3ce** could not be isolated, but the 4*H*-pyran-4-one derivative **5** was obtained in 61% yield after chromatographic purification [Eq. (4)]. The formation of **5** from **3ce** would involve torquoselective 4π-electron ring-opening and subsequent 6π-electron ring-closing, chromatographic hydrolysis, and air-oxidation.[5]



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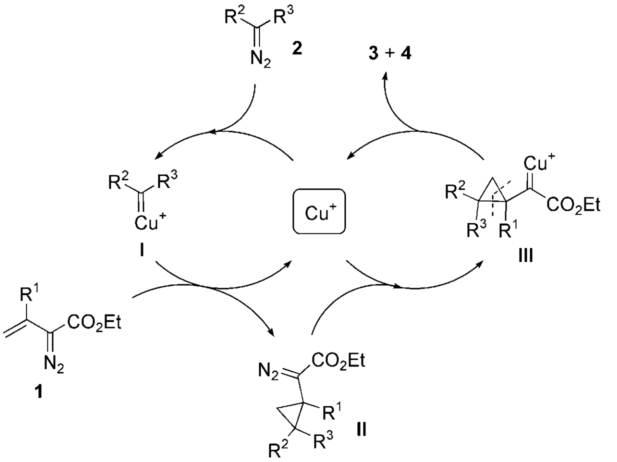


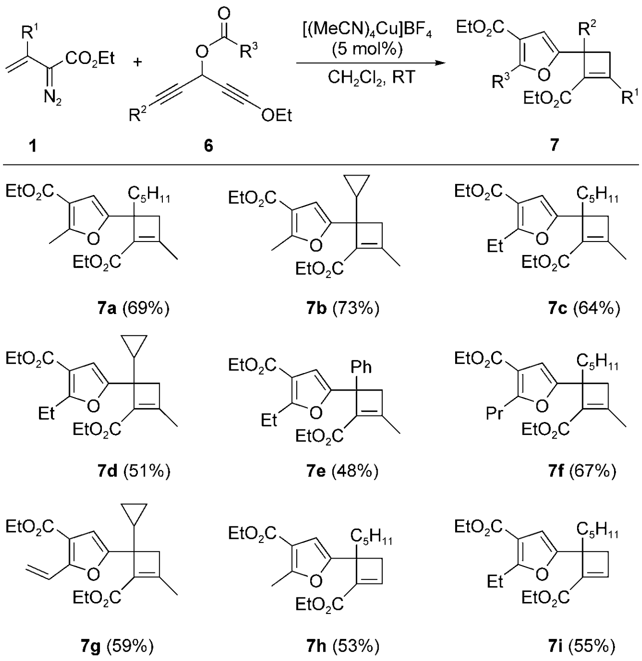
***Scheme 1.*** Proposed mechanism for the copper(I)-catalyzed synthesis of cyclobutene derivatives **3** and **4** from vinyldiazoacetates **1** and diazo compounds **2**.

A tentative reaction pathway based on the manifold participation of the copper catalyst is depicted in Scheme 1. The preferential formation of copper carbenoid **I** from diazo substrate **2**[6] would be then undergo cyclopropanation of the activated C=C functionality of **1**.[7] The newly formed cyclopropyldiazoacetate ester **II** would then lead to the cyclobutene structures **3**,**4** by copper-catalyzed decomposition to copper–cyclopropylcarbene **III** and rearrangement by cleavage of the bond between either C1–C2 ($CR^1$–$CR^2R^3$) or C1–C3 ($CR^1$–$CH_2$).[8] Apparently, both electronic and steric effects control the regiochemistry of the latter rearrangement. Thus, the formation of regioisomer **4** (C1–C2 cleavage) would be a consequence of the presence of group(s) capable of stabilizing the partial positive charge developed on C2 (PMP or two Ph groups). In the absence of such charge-stabilizing effect it seems that the less sterically hindered cyclobutene **3** (C1–C3 cleavage) is preferentially formed. This mechanistic proposal is in good agreement with a recent communication on the rearrangement of cyclopropyl metal carbenes to cyclobutenes reported by Tang and co-workers.[8a]

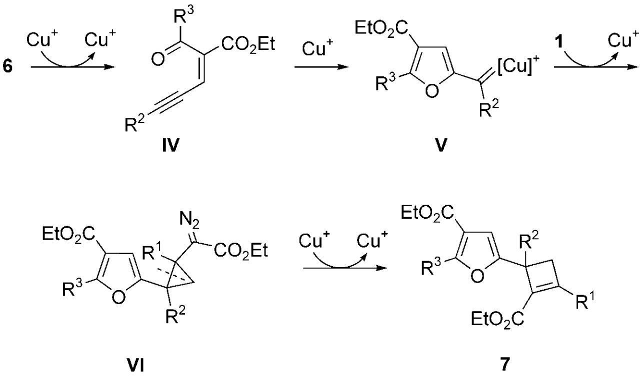
At this point we thought to additionally exploit the multifaceted nature of the copper catalyst by designing a longer cascade sequence. We recently reported the copper(I)-catalyzed cycloisomerization/furan formation sequence of bis(propargylic) esters **6**, which was assumed to involve a furyl carbene of copper(I).[9] Accordingly, we subjected an equimolecular mixture of vinyldiazoacetate esters **1a**,**b** and propargylic esters **6** in $CH_2Cl_2$ to the action of $[Cu(MeCN)_4]BF_4$ (5 mol%). After stirring the reaction mixture at room temperature for four hours, removal of the solvent, and chromatographic purification, the furyl-substituted cyclobutenes **7** were isolated as the sole isomer in 48–73% yield. With regard to the substrate **6**, different substitution patterns proved to work satisfactorily ($R^2$ = alkyl, cycloalkyl, phenyl; $R^3$ = alkyl, vinyl).

Compounds **7** (Scheme 2) are proposed to result from a cascade process wherein all steps involve a copper(I) species (Scheme 3). The initial isomerization of the propargylic substrate **6** to the (*E*)-Knoevenagel intermediate **IV** then undergoes a 5-*exo*-dig cyclization to generate the putative 2-furyl copper(I) carbene species **V**, as already reported.[9] Now, the carbenoid nature of **V** is strongly supported as it cyclopropanates substrate **1** leading to the cyclopropyldiazo intermediate **VI**, which in turn undergoes the metal-catalyzed ring expansion to the final cyclobutene **7**. As in the case of the PMP-substituted diazo substrates **2** (Table 1 and Scheme 1), the furyl substituent in **VI** perfectly controls the regioselectivity affording a single cyclobutene.

In conclusion, we have demonstrated that copper(I) is able to discriminate between simple and vinyldiazo systems towards carbenoid formation. The presumed C=C bond



*Scheme 2.* Copper(I)-catalyzed synthesis of furyl-substituted cyclobutenes **7** from vinyldiazoacetates **1** and propargylic esters **6**. The reported yields are those of the products isolated after column chromatography.



*Scheme 3.* Proposed intermediates in the copper(I)-catalyzed synthesis of furyl-substituted cyclobutene derivatives **7** from propargylic esters **6** and vinyldiazoacetates **1**.

coupling reaction does not occur, but both species nicely collapse through cyclopropanation and subsequent ring enlargement to produce cyclobutenes, a class of interesting compounds whose synthesis currently represents a challenging task.[10,11] The procedure depicted herein provides different substituted cyclobutenes yet in moderate yield in a straightforward, atom-economic, and simple manner. It is also proved that this concept can be integrated into more complex synthetic sequences that involve metal carbene species, a fact that demonstrates the great capability of copper(I) to sequentially catalyze various reactions of different nature.

## Experimental Section

Typical procedure for the copper(I)-catalyzed synthesis of cyclobutene derivatives **3** and **4**: $[Cu(MeCN)_4]BF_4$ (5 mol %) was added to a solution of vinyldiazoacetate esters **1** (0.5 mmol) and diazomethane derivatives **2** or bis(propargylic) esters **6** (0.5 mmol) in $CH_2Cl_2$ (5 mL). The reaction mixture was stirred at room temperature until disappearance of the starting diazo compounds (checked by TLC; 2–4 h). The solvent was removed under reduced pressure and the residue was purified by flash chromatography ($SiO_2$, 10:1 hexanes/ethyl acetate) to give the corresponding cyclobutene derivatives **3** or **4**.

Full experimental details and characterization data are given in the Supporting Information.

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