CHEMCOMM
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A family of highly active copper(I)–homoscorpionate catalysts for the alkyne cyclopropenation reaction

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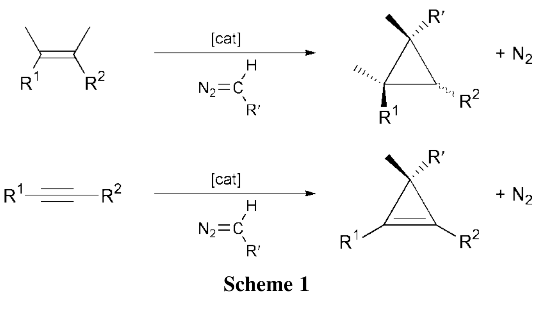
Received (in Cambridge, UK) 7th June 2001, Accepted 1st August 2001
First published as an Advance Article on the web 3rd September 2001

Equimolar mixtures of ethyl diazoacetate and alkynes can be converted into cyclopropenes in very high yields, at room temperature, through the intermediacy of readily available Cu(I) catalysts containing trispyrazolylborate ligands.

Carbon–carbon unsaturated bonds can be converted into three-membered rings by the intermediacy of metal-based catalysts and the appropriate carbene source.[1,2] Thus, a diazo compound and an olefin lead to cyclopropanes whereas the same carbene precursor and alkynes afford cyclopropenes (Scheme 1). Despite the obvious similarities between both reactions, most efforts have been devoted to the former transformation, the catalytic systems reported to date for the cyclopropenation reaction being reduced to a few, and mainly based on copper and rhodium. Copper bronze, Cu(I) and Cu(II) salts have been employed as catalysts for the cyclopropenation reaction, but high temperatures (90–140 °C) were required and yields were low.[3] At room temperature, $Rh_2(OAc)_4$ has been the catalyst of choice for this transformation, as reported by Hubert *et al.*[4] Related chiral derivatives of the type $Rh_2(L–L^*)_4$ have been developed by Doyle and co-workers,[5] inducing high enantiomeric excesses. However, there are two major drawbacks to address in this field. First, those rhodium catalysts do not operate with internal alkynes, or if so, yields are quite low. Secondly, and despite the use of high alkyne–EDA (ethyl diazoacetate) ratios, only moderate to high conversion yields have been achieved (40–85%), the quantitative conversion being still elusive.

The catalytic capabilities of the homoscorpionate complex $Tp^*Cu(C_2H_4)$ (**1**) (Tp* = hydrotris(3,5-dimethylpyrazol-1-yl)-borate (1), towards the alkyne cyclopropenation reaction were reported a few years ago.[6] Those preliminary results showed that both internal and alk-1-ynes could be converted into the corresponding cyclopropenes with moderate yields (40–65%). Complex Tp*Cu[7] (**2**) displays the same catalytic behaviour, with the advantage of its higher stability in comparison with **1**. Complexes **1** or **2** also catalyse the conversion of olefins into cyclopropanes[8] and epoxides,[9] both under homogeneous and heterogeneous conditions, as well as the aziridination of alkenes.[6,9] This remarkable behaviour has been now expanded to the achievement of higher degrees of alkyne cyclopropenation. It is worth mentioning that the main problem in these transformations is the formation of diazoacetate-coupling products: diethyl fumarate and maleate are also formed when EDA is employed as the carbene source. Usually, this is avoided by using a large excess of the alkyne with respect to EDA, and by adding the diazocompound by means of slow-addition devices onto the alkyne and catalyst-containing solution. As a consequence of our knowledge on the olefin cyclopropanation reaction, we have learnt that there is an enormous dependence of the three-membered ring yields on the reaction design, particularly the catalyst concentration and the carbene precursor addition rate. Fig. 1 shows the results of the hex-3-yne cyclopropenation reaction obtained from three experiments at three different concentrations of complex **2**. The initial hex-3-yne concentration was fixed at 0.45 M and EDA (0.15 M) was added with two different addition rates (0.15 and 1.5 mmol h^{-1}). The use of initial [**2**] of 0.0075 M (1:20:60 of [Cu]–[EDA]–[hex-3-yne]) induced the almost quantitative conversion into the corresponding cyclopropene, whereas a third of that value caused a 50% decrease of the product. As expected, an increase in the addition rate of EDA diminished the yields, but the same trend was observed upon varying [Cu]. These results are in accord with the reaction pathway proposed for the related cyclopropanation reaction with this type of catalyst.[10]



Scheme 1

With this knowledge, we have tested an array of trispyrazolylborate ligands[11] (Fig. 2) in which R^1–R^3 can be modified to tune the electronic and steric effects induced to the metal centre. The catalysts of general formula $Tp^XCu(I)$ were generated *in situ* by mixing equimolar amounts of CuI and the corresponding potassium or thalium salt of the homoscorpionate ligand. These preliminary experiments were run with a [Cu]–[EDA]–[hex-3-yne] ratio of 1:30:90, that corresponds to [Cu] 0.005 in Fig. 1. As inferred from data in Table 1, the 3-neopentyl and 3-cyclohexyl derivatives showed excellent, unprecedented degrees of conversion into ethyl 2,3-diethylcycloprop-1-enecarboxylate (95 and 97%, respectively) therefore

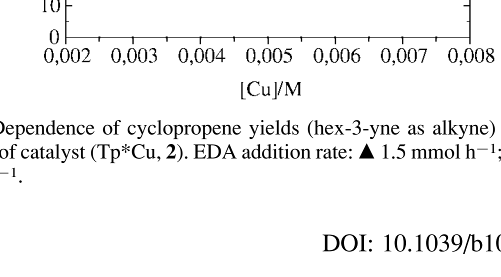


Fig. 1 Dependence of cyclopropene yields (hex-3-yne as alkyne) and the amount of catalyst (Tp*Cu, **2**). EDA addition rate: ▲ 1.5 mmol h^{-1}; ■ 0.15 mmol h^{-1}.

DOI: 10.1039/b105020f

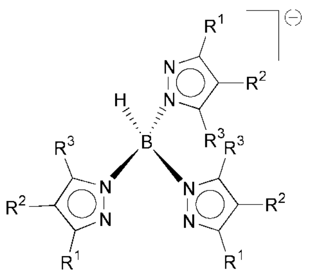


Fig. 2 Tp^X ligands.

Table 1 Cyclopropenation of hex-3-yne with Tp^X–Cu catalysts[a]

Entry	Tp^X	R^1	R^2	R^3	Yield[b]
1	Tp	H	H	H	32
2	Tp*	Me	H	Me	82
3	Tp$^{t\mathrm{Bu}}$	^{t}Bu	H	H	85
4	Tp$^{\mathrm{Np}}$	Np	H	H	95
5	Tp$^{\mathrm{Cy}}$	Cy	H	H	97
6	Tp$^{\mathrm{Ph}}$	Ph	H	H	21
7	Tp$^{\alpha\text{-Nt}}$	α-Nt	H	H	27
8	Tp$^{\mathrm{Ms}}$	Ms	H	H	31
9	Tp$^{\mathrm{ClPh}}$	*p*-C_6H_4Cl	H	H	52
10	Tp$^{\mathrm{An}}$	*p*-$C_6H_4OCH_3$	H	H	43
11	Tp$^{\mathrm{Tol}}$	*p*-$C_6H_4CH_3$	H	H	49

[a] See footnote† for experimental details. [b] Percentage of cyclopropene determined by GC after total EDA consumption. Diethyl fumarate and maleate accounted for the remaining diazoacetate employed.

minimising the formation of EDA-coupling products (ethyl fumarate and maleate). We have recently reported[12] an extraordinarily active and diastereoselective (towards the *cis* isomer) catalytic system for the olefin cyclopropanation reaction, in which aromatic substituents as R^1 provided the best results in comparison with the aliphatic groups in this position. But this situation reverses in the alkyne cyclopropenation reaction, since aliphatic groups as R^1 seem to be required for high conversions. This constitutes a significant difference between these two transformations that traditionally have been described to occur in a similar way.[1,2]

After this initial screening, optimisation of the reaction conditions and expansion to other alkynes afforded more interesting features. Table 2 displays the results of the cyclopropenation reaction of hex-1-yne, 1-phenylprop-1-yne and hex-3-yne with different [Cu]–[EDA]–[alkyne] ratios using the Tp$^{\mathrm{Cy}}$ derivative. The observed yields show dramatic improvement over any other reported catalytic system in terms of cyclopropene formation not only for alk-1-yne derivatives, but also for internal ones: the values for hex-3-yne are $>90\%$ in all cases and 1-phenylprop-1-yne also undergoes high conversions (73–94%). This remarkable activity is confirmed by data in Table 2, entry 5, in which an equimolar EDA–alkyne ratio was employed: yields of cyclopropene fall in the range 80–94%. The lack of alkyne excess in these high-yield transformations has no precedent in the literature: our system has obviated the need for an excess of alkyne to achieve noticeable yields, not only with the cyclohexyl derivative but also with other Tp^X ligands (X = alkyl). Thus, the cyclopropenation of hex-3-yne using an equimolar ratio of the alkyne and ethyl diazoacetate afforded the corresponding three-membered ring in 75–94% yield (Table 3).

Table 2 Cyclopropenation of alkynes with Tp$^{\mathrm{Cy}}$Cu[a]

Entry	Cu–EDA–alkyne[b]	Hex-1-yne[c]	Hex-3-yne[c]	1-Phenyl-prop-1-yne[c]
1	0.05:1.5:7.5	87	97	94
2	0.05:3:9	75	90	84
3	0.1:3:9	80	97	90
4	0.1:6:9	70	95	73
5	0.1:6:6	80	94	85

[a] See footnote† for experimental details. [b] In mmol. [c] Percentage of cyclopropene determined by GC after total EDA consumption. Diethyl fumarate and maleate accounted for the remaining diazoacetate employed.

Table 3 Equimolar EDA–hex-3-yne cyclopropenation experiments[a]

Entry	Tp^X	Yield[b]
1	Tp*	75
2	Tp$^{t\mathrm{Bu}}$	72
3	Tp$^{\mathrm{Np}}$	82
4	Tp$^{\mathrm{Cy}}$	94

[a] [Cu]–[EDA]–[hex-3-yne] ratio of 1:60:60, 0.1 mmol of Cu employed. [b] Percentage of cyclopropene determined by GC after total EDA consumption. Diethyl fumarate and maleate accounted for the remaining diazoacetate employed.

In conclusion, we have developed an extraordinarily efficient cyclopropenation system in which terminal and internal alkynes can be converted into the corresponding unsaturated rings in very high yields. In addition, no excess of the alkyne is required for those yields to be produced. Work aimed to extend these results to a number of other unsaturated substrates is currently underway in our laboratory.

Notes and references

† Experimental procedure: CuI and an equimolar amount of the MTp^X salt were dissolved in CH_2Cl_2 and the mixture was stirred for 2–3 h. After filtration volatiles were removed under reduced pressure. The residue was dissolved in 20 mL of 1,2-dichloroethane, and the resulting solution was charged with alkyne. A solution of EDA in 1,2-dichloroethane was slowly added with the aid of an automatic syringe pump. All reactions were performed at room temperature. After complete addition, the reaction mixture was analyzed by GC, only cyclopropenes and ethyl fumarate or maleate being detected. Yields are shown in Tables 1–3.

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