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Catalytic Functionalization of Indoles by Copper-Mediated Carbene Transfer

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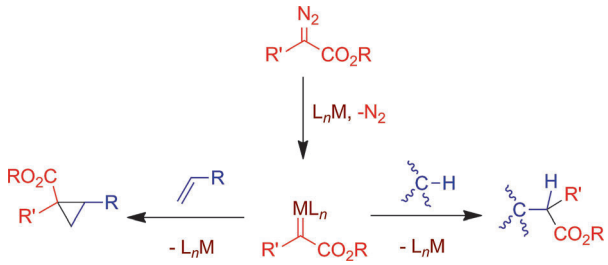
The complex [Tp^{Br3}Cu(NCMe)] (Tp^{Br3} = hydrotris(3,4,5-tribromo)-pyrazolylborate) efficiently catalyzes the C–H functionalization of indole derivatives at C3 by carbene transfer from different diazoesters in a high-yield transformation involving low catalyst loadings and short reaction times. This system has shown that the previously proposed dichotomy of carbene addition (to the double bond) vs carbene insertion (to the C–H bond) corresponds to two consecutive reaction steps: the cyclopropane intermediates, observed in the reaction mixtures, are the precursors of the final C–H functionalization derivatives in a ring-opening process involving acid catalysis. Those in situ generated cyclopropanes undergo nucleophilic ring opening with Me_2CuLi to afford both C2 and C3 functionalized indoles.

Introduction

The metal-mediated transfer of carbene groups from diazo compounds to organic substrates is nowadays considered a common tool in synthesis.[1] Among the plethora of reactions reported with this strategy, the olefin cyclopropanation and the carbon–hydrogen bond functionalization are of great interest (Scheme 1). Indoles are found within the many substrates that have been considered to be functionalized with that methodology. Because the indole structure appears in a large number of pharmaceuticals and agrochemicals,[2] the development of mild and efficient protocols for the synthesis of indoles derivatives remains a field of intensive research.[3] The metal-catalyzed functionalization of indoles with diazo compounds has been described mainly with use of copper-based[4] and rhodium-based[5] catalysts and rarely with use of several other compounds of iron, ruthenium, or indium.[6] The reported reaction outcome of indoles reacting with diazo compounds is shown in Scheme 2. For nitrogen-protected indoles, most of the known catalytic systems have provided the products derived from the formal insertion of such a unit into the C–H bonds of C3 (route A).[4d–f,5a,c–g,6b,c] Derivatization at C2 has been achieved if there was a substituent at C3 (route B),[4f,h,5a] except in a case with ruthenium-based catalysts.[6a] If the protecting group at nitrogen has been Boc (Boc = *tert*-butyloxycarbonyl) or acetyl, the carbene moiety instead adds to the unsaturated C–C bond, which yields a cyclopropane derivative (route C).[4a–d,g] For nonprotected indoles, the above pattern of functionalization at C2 or C3 has been described, which can also be accompanied by the insertion of the carbene group in the N–H bond.[4c,f,5a] Finally, the addition to the aromatic six-member ring has also been reported.[5b]



Scheme 1. The strategy for functionalization of olefins or C–H bonds on the basis of metal-mediated carbene transfer from diazo compounds.

A previous work from our laboratory has shown that [Tp^xCu(NCMe)] (Tp^x = hydrotrispyrazolylborate ligand) and IPrCuCl [IPr = 1,3-bis(diisopropylphenyl)imidazol-2-ylidene] complexes promote the transfer of carbene groups from diazo compounds to saturated and unsaturated fragments.[7] On the basis of this experience and the aforementioned interest in the functionalization of indoles, we decided to test the catalytic capabilities of these complexes for indole derivatization. We found that the complex [Tp^{Br3}Cu(NCMe)] (Tp^{Br3} = hydrotris(3,4,5-tribromo)pyrazolylborate) efficiently catalyzes the reaction of ethyl diazoacetate (EDA) and several indoles. In all

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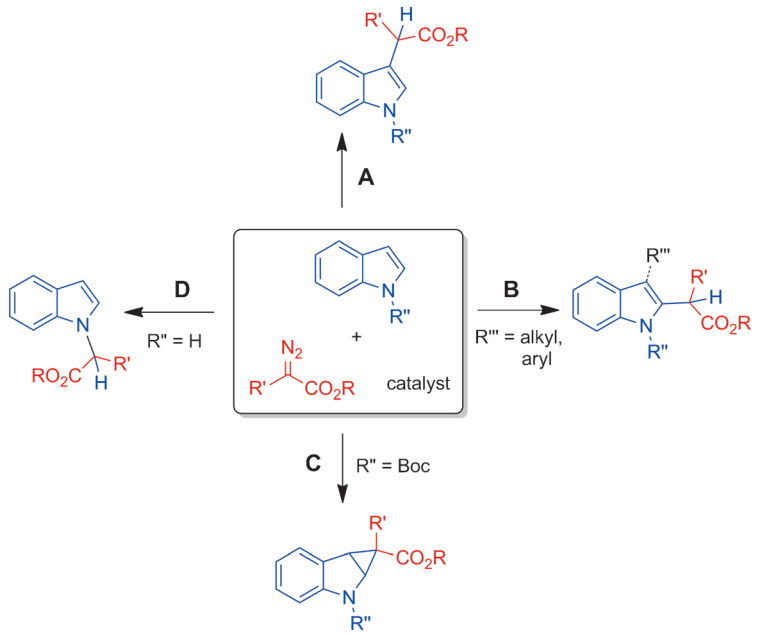


Scheme 2. Functionalization of indoles by transition metal-catalyzed carbene transfer from diazo compounds.

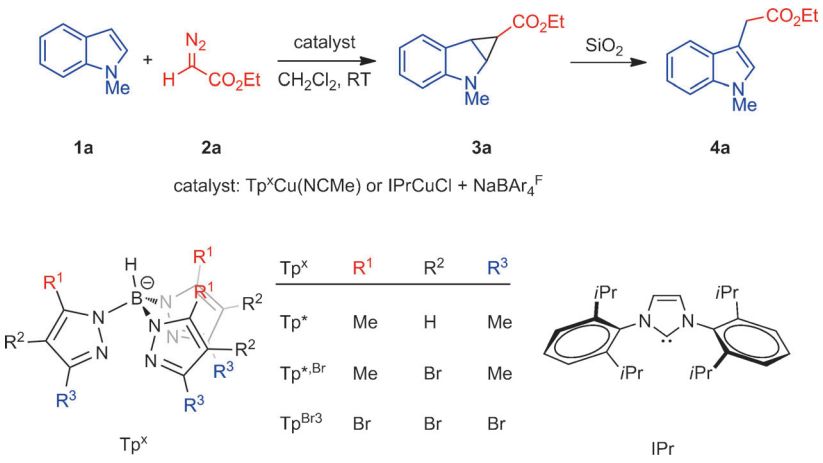
cases, the cyclopropane derivative was obtained with simple methyl-protected indoles. Furthermore, treatment of such cyclopropanes with silica gel induces the quantitative conversion into the corresponding C3 insertion products, which demonstrates that the cyclopropanes are intermediates in the formation of insertion products.[8] This method also functionalizes the cyclopropane intermediates upon reaction with Me_2CuLi, which provides C2 and C3-difunctionalized indoles.

Results and Discussion

We first investigated the catalytic potential of a series of [Tp^{x}Cu(NCMe)] complexes as well as that of IPrCuCl complexes in the reaction of 1-methylindole (**1a**) with EDA (**2a**). A 5 mol% of the catalyst was used in an experiment performed in CH_2Cl_2 at room temperature (Scheme 3 and Table 1). The four complexes led to the formation of the cyclopropanation product **3a**, as inferred from the ^{1}H NMR spectra of the reaction crude. This finding is at variance with the aforementioned previous work by others who used copper-based catalysts in which, to that purpose, the indole should be nitrogen-protected with groups such as Boc or acetyl.[4a–d,g] In our case, the methyl-protected indole gave the corresponding cyclopropane along with minor amounts of the C3-functionalized product **4a**. Diethyl fumarate and diethyl maleate completed the mass balance for the initial EDA. The [Tp^{Br3}Cu(NCMe)] complex demonstrated the best catalytic behavior, with complete EDA consumption within just 1 min, which afforded **3a** in 68% yield. Further optimization experiments indicated that it was possible to reduce the catalyst amount to 1 mol% but maintaining the product yield (Table 1, entry 5). To minimize the formation of by-products, the diazo compound was added over 1 h by using a syringe pump, which afforded **3a** in 83% yield (Table 1, entry 6).

We found a second interesting feature of this system after purifying compound **3a** by using silica gel column chromatography: a complete and clean conversion into **4a**, which was obtained as a pure yellowish oil in variable yield that depends on the reaction conditions. In those experiments involving 1 mol% of the catalyst and 1 h of slow addition of EDA, **4a** was obtained in 98% yield relative to the initial indole (Table 1, entry 6).

The reaction of EDA was examined with various 1-methylindole substrates under the optimal conditions. Cyclopropane derivatives were obtained either with indoles bearing electron-withdrawing groups or those bearing electron-donating groups in the benzenoid ring. All those compounds were straightforward and quantitatively converted into the corresponding C3-substituted derivatives (Table 2, **4b–d**) upon treatment with silica gel. In the reactions with C2 and C3-substituted indoles,



Tp^x	R^1	R^2	R^3
Tp*	Me	H	Me
Tp^{*,Br}	Me	Br	Me
Tp^{Br3}	Br	Br	Br

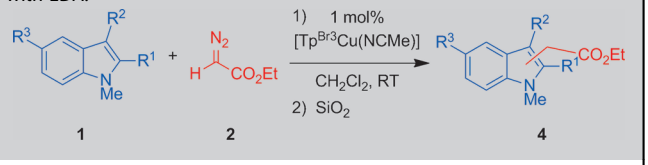
Scheme 3. Catalytic functionalization of 1-methylindole with EDA.

Table 1. Screening of the catalytic potential of some copper complexes.[a]

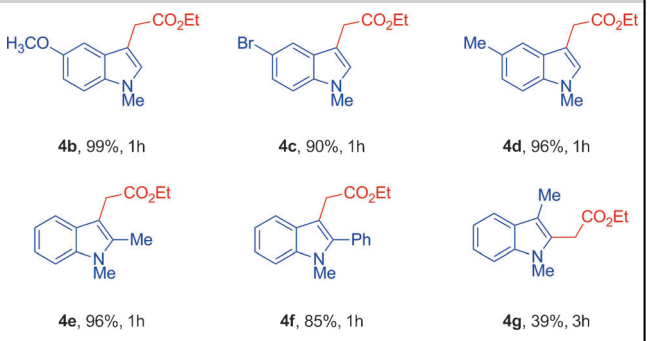
Entry	Catalyst	t	Yield [%][b]	
			3a/**4a**	**4a** (treated with SiO_2)
1[c]	IPrCuCl + $NaBAr^F_4$	12 h	36/10	46
2[c]	[Tp*Cu(NCMe)]	12 h	42/6	48
3[c]	[Tp^{*,Br}Cu(NCMe)]	25 min	59/9	68
4[c]	[Tp^{Br3}Cu(NCMe)]	1 min	68/15	79
5[c]	[Tp^{Br3}Cu(NCMe)]	15 min	63/16	79
6[d]	[Tp^{Br3}Cu(NCMe)]	1 h	83/15	98

[a] Reaction conditions: 1 mmol of indole, 0.5 mmol of EDA, 5 mol% catalyst (entries 1–4) or 1 mol% catalyst (entries 5–6), 4 mL of CH_2Cl_2 at RT. [b] Isolated yield after silica gel chromatography. [c] EDA was added in one portion. [d] EDA was added slowly for 1 h by using a syringe pump.

Table 2. Copper-mediated functionalization of 1-methylindole substrates with EDA.[a–c]



1 2 4

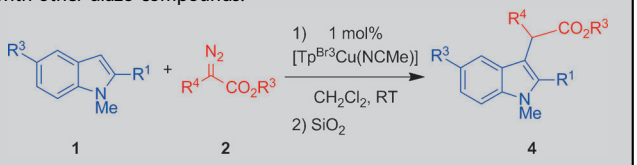


4b, 99%, 1h **4c**, 90%, 1h **4d**, 96%, 1h

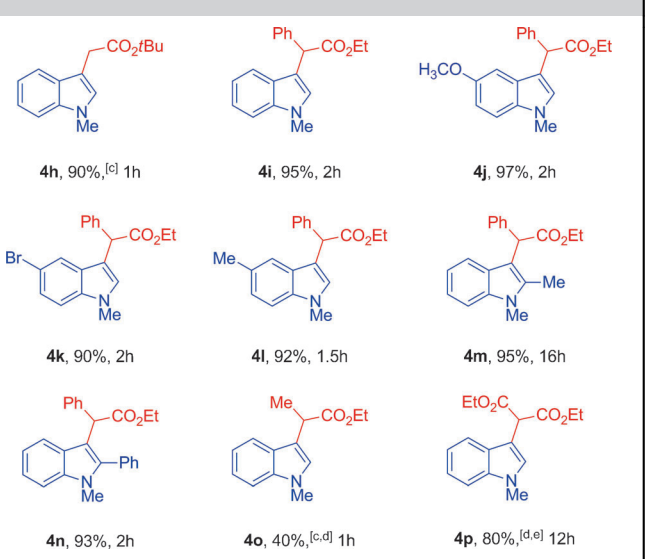
4e, 96%, 1h **4f**, 85%, 1h **4g**, 39%, 3h

[a] Reaction conditions: 1 mmol of indole, 0.5 mmol of EDA, 1 mol% of [Tp^{Br3}Cu(NCMe)], 4 mL of CH_2Cl_2 at RT. R^1 = H, Me, Ph; R^2 = Me; R^3 = OCH_3, Br, Me. [b] Isolated yield obtained by using silica gel chromatography. [c] EDA was added over 1 h by using a syringe pump.

Table 3. Copper-mediated functionalization of 1-methylindole substrates with other diazo compounds.[a,b]



1 2 4



4h, 90%,[c] 1h **4i**, 95%, 2h **4j**, 97%, 2h

4k, 90%, 2h **4l**, 92%, 1.5h **4m**, 95%, 16h

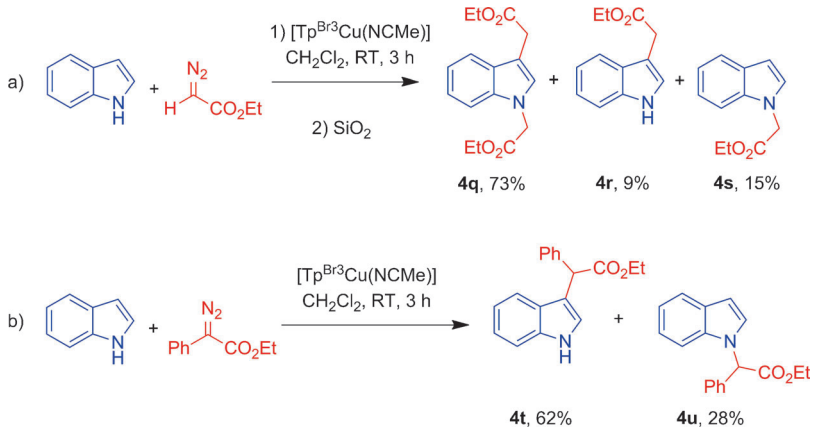
4n, 93%, 2h **4o**, 40%,[c,d] 1h **4p**, 80%,[d,e] 12h

[a] Reaction conditions: 1 mmol of indole, 0.5 mmol of the diazo compound, 1 mol% of [Tp^{Br3}Cu(NCMe)], 4 mL of CH_2Cl_2 at RT. R^1 = H, Me, Ph; R^3 = OCH_3, Br, Me; R^4 = H, Ph, Me, CO_2Et. [b] Isolated yield obtained by using silica gel chromatography. [c] The diazo compound was added over 1 h by using a syringe pump. [d] Reaction at 40 °C. [e] 2 mol% of [Tp^{Br3}Cu(NCMe)].

cyclopropylindole intermediates were not observed. Thus, substitution at the C2 position of the indole with a methyl or even with a phenyl group was well tolerated, which afforded the corresponding products in 96 and 85% yields, respectively (**4e** and **f**). In contrast, substitution at the C3 position of the indole gave the C2 insertion product in moderate yield after 3 h (**4g**).

We have also investigated the use of other diazo compounds. More sterically hindered *tert*-butyl diazoacetate also demonstrated good reactivity, and the reaction reached completion in 1 h with 90% yield (**4h**). In contrast, ethyl α-diazophenylacetate demonstrated high reactivity with different substituted indoles, which afforded the corresponding C3 insertion products in excellent yields and short reactions times (**4i–n**). In this case, NMR studies performed at the end of the reaction (1 h) showed these products as the unique component of the reaction crude and no cyclopropanation product was observed. However, if the [Tp*Cu(NCMe)] complex (Tp* = tris(3,5-dimethyl-pyrazolyl)borate) was employed as a catalyst, NMR analysis revealed the presence of cyclopropylindole in the reaction mixture in small amounts during the transformation, evidencing the intermediacy of such species in the formation of compounds **4i–n**. In contrast, the reaction of the less reactive ethyl α-diazomethylacetate afforded a highly stable cyclopropanation product, which remained unchanged after purification by using silica gel column chromatography. It was necessary to stir the reaction crude for 30 min and to add silica gel to induce the formation of the C3 insertion product (**4o**). Finally, the less reactive ethyl diazomalonate required 2 mol% of the catalyst and longer reaction times to give the C3 insertion product in 80% yield (**4p**; Table 3).

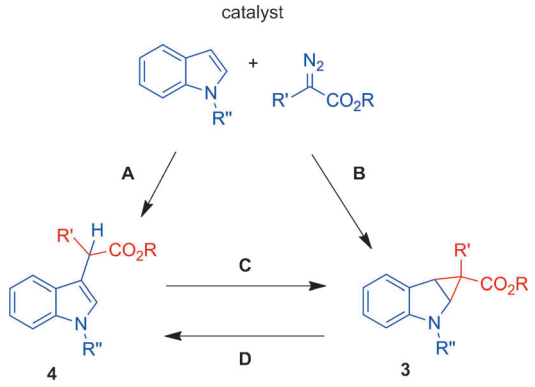
Furthermore, we studied the functionalization of a nonprotected indole with EDA and ethyl α-diazophenylacetate (Scheme 4). The reaction with EDA was performed under the same reaction conditions used for *N*-alkyl indoles (1 mmol of indole, 0.5 mmol of EDA, and 1 mol% of the catalyst). The ^{1}H NMR spectrum of the reaction mixture indicated a mixture of three compounds. Although some resonances attributable to cyclopropane rings could be observed, the complexity of the mixture prevented us from performing a complete spectroscopic characterization. However, after treatment with silica gel and column separation, compounds **4q–s** were obtained in 73, 9, and 15% yields, respectively (Scheme 4a). The reaction outcome did not change with the use of equimolar amounts of indole and EDA. We then studied the reaction with ethyl α-diazophenylacetate. In this case, the one-pot addition of ethyl α-diazophenylacetate afforded a mixture of C3 and N–H insertion products in 50 and 40% isolated yields, respectively (Scheme 4b). Fortunately, the slow addition of the diazo compound over 2 h with a syringe pump improved the selectivity, and compounds **4t** and **u** were isolated in 62 and 28% yields, respectively. Notably, the catalytic carbene insertion into N–H bonds was observed with amines in a previous work from our laboratory.[9] The interaction of the metallocarbene intermediate with the N–H bond probably occurs through the N-lone pair. Therefore, we do not consider this byproduct in the mechanistic studies.



Scheme 4. Reaction of nonprotected indole with EDA and ethyl α-diazophenylacetate.

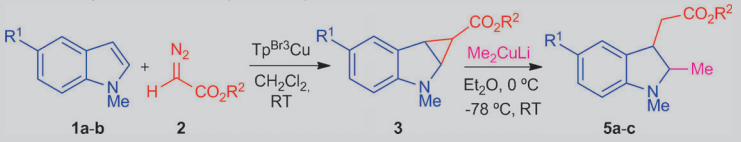
Cyclopropane ring-opening reactions

The indoline subunit functionalized at C2 and C3 positions is found in a range of natural products.[10] Bearing in mind that the indole functionalization occurs via a cyclopropyl intermediate, we developed a selective ring-opening reaction to obtain those compounds. After testing different nucleophilic reagents, we observed that Me_2CuLi could open the cyclopropyl ring under mild reaction conditions and afforded products in excellent yields (Table 4). The ring-opening reaction was performed by adding the reaction crude of the diazo compound and indole dissolved in diethyl ether to a solution of Me_2CuLi, which was prepared in situ in the same solvent, and this reaction led to the formation of compounds **5a–c** in excellent yields (Table 4, entries 1–3).



Scheme 5. Reaction pathways proposed for the formation of compounds **3** and **4**.

Table 4. Cyclopropane ring opening with Me_2CuLi.[a]



Entry	R^1	R^2	Product	Yield[b] [%]	*dr*[c]
1	H	Et	**5a**	89	52:48
2	H	*t*Bu	**5b**	81	70:30
3	OMe	Et	**5c**	92	57:43

[a] Reaction conditions: Indole (1 mmol), diazo compound (0.5 mmol), [Tp^{Br3}Cu(NCMe)] (1 mol%), CH_2Cl_2 (4 mL), RT. Then, CuI (0.54 mmol), Et_2O (3 mL), MeLi (1.078 mmol, 1.6 M in ether), $T = 0\,^{\circ}C$. [b] Isolated yield. [c] *dr* = Diastereomeric ratio.

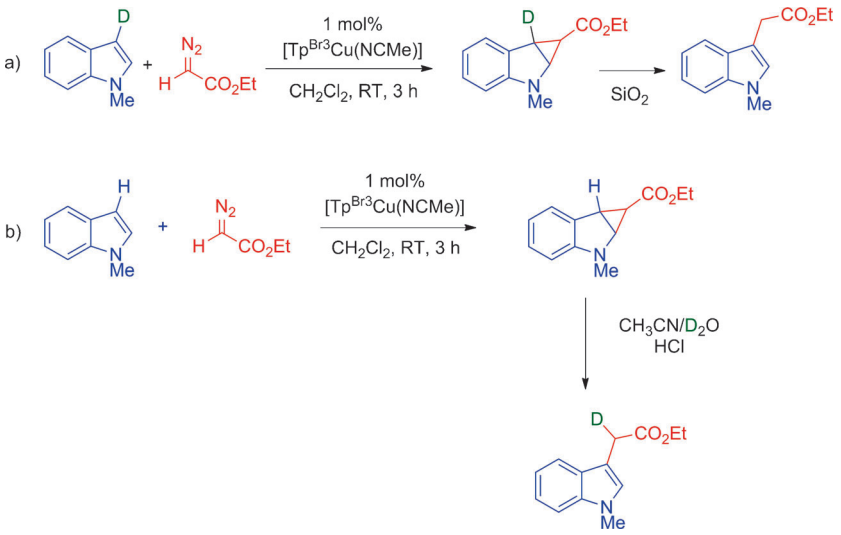
Mechanistic considerations

In spite of the number of catalytic systems described for this transformation to date, mechanistic proposals supported with experimental evidences are scarce. Some authors have proposed independent pathways for the formation of the carbene insertion products (Scheme 5, route A) or the addition products (Scheme 5, route B) on the basis of the attack of the metallocarbene moiety on the substrate. Others have proposed that insertion occurs before the formation of the cyclopropane ring (Scheme 5, route C). And the last proposal is based on the formation of the cyclopropane ring that later converts into the insertion products (Scheme 5, route D). The results discussed in the previous sections indicate that route D in Scheme 5, which contains the sequential cyclopropanation and ring-opening steps in the reaction of indole and the diazo compound, governs this transformation with [Tp^{Br3}Cu(NCMe)] as the catalyst precursor. Notably, this finding could be applied to other systems, particularly to those in which no NMR studies of the reaction crude were performed, and the reaction outcome was evaluated after column purification. Moreover, in those systems in which the *N*-Boc indole was used, no ring opening was observed because electron-withdrawing groups would not stabilize the zwitterionic intermediate (see below).

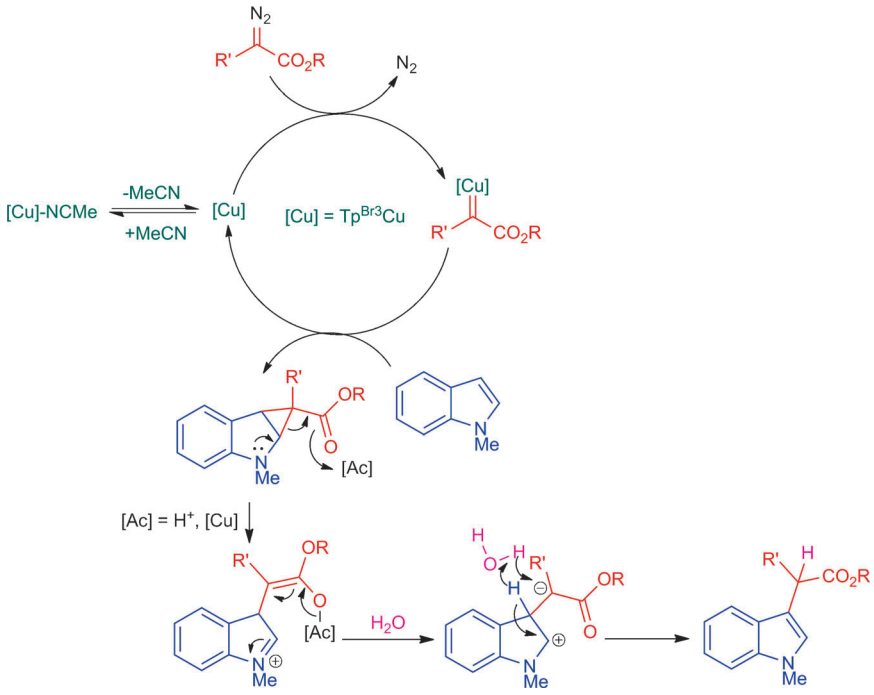
An explanation is required for the ring-opening reaction that follows cyclopropane formation. To elucidate whether a proton migration from the C3 position of the indole to the α position of the ester occurs, 3-deutero-1-methylindole was synthesized by using a slightly modified method described in the literature.[11] Upon reaction with EDA (Scheme 6a), no deuterium was observed in the final product, which indicated that elimination could occur from cyclopropane. To confirm this hypothesis, in which the proton in the α position of the final product should come from the reaction medium, the ring opening of cyclopropylindole was performed in a 1:1 mixture of acetonitrile and deuterium oxide in the presence of catalytic amounts of hydrochloric acid (Scheme 6b). After stirring the mixture for 30 min, the deuterated product in the α position was obtained selectively (see the Supporting Infor-

mation for details). Moreover, a competition experiment with the deutero and protio derivatives was performed and the ratio of cyclopropanes was 42:58, which slightly favored (kinetic isotope effect = 1.38) the protio-containing cyclopropane. Unfortunately, it is not possible to obtain data on the final products because elimination from C3 occurs and either deuterium or hydrogen resulted in elimination.

On the basis of all data collected, an overall catalytic cycle is proposed in Scheme 7. The first step is the copper-mediated cyclopropyl ring formation. In the presence of an acid catalyst (silica gel), the cyclopropane ring undergoes opening through the acid-catalyzed hydrogen elimination followed by proton transfer from the medium to the α position of the ester, which leads to the final product **4**. This mechanism also explains the poor stability of the cyclopropanation product if ethyl α-diazophenylacetate or ethyl diazomalonate is used. In these cases, the zwitterionic intermediate is stabilized by the electron-withdrawing groups, phenyl or CO_2Et, which provides a rapid ring-opening reaction. Such stabilization is not possible with EDA or ethyl α-diazomethylacetate. Notably, important differences exist between our observations and those reported with rhodium-based catalysts. It is quite likely that both metals operate in a distinct manner regarding this transformation.



Scheme 6. Selective deuteration experiments.



Scheme 7. Mechanistic proposal for the indole functionalization by copper-catalyzed carbene addition and subsequent ring opening.

Conclusions

The [Tp^{Br3}Cu(NCMe)] complex has demonstrated high catalytic activity for the functionalization of nitrogen-protected indoles through the formal carbene insertion (from diazo compounds) into the C–H bond located at C3. The activity compares well with that of the most active rhodium-based catalysts known to date, and it can be considered superior to that of other copper(II)-, indium- or iron-based catalysts reported earlier. The desired products are obtained in excellent yields with only 1 mol% of the catalyst and in a short reaction time. In addition, experimental data collected indicate that the reaction proceeds via a cyclopropanation–ring-opening sequence. The intermediacy of the cyclopropyl species has been used to achieve the C2 and C3 functionalization through consecutive cyclopropanation and cyclopropane nucleophilic ring-opening reactions using Me_2CuLi and affording excellent yields.

Experimental Section

Insertion reactions

General procedure: [Tp^{Br3}Cu(NCMe)] (1–2 mol%) and the corresponding indole (1 mmol) were dissolved in CH_2Cl_2 (4 mL) in a Schlenk tube equipped with a magnetic stir bar under an N_2 atmosphere. Then, the diazo compound (0.5 mmol) was added in one portion or dissolved in CH_2Cl_2 (1 mL) and added over 1 h by using a syringe pump. The reaction mixture was stirred at RT for a given time (15 min to 16 h), and the volatiles were removed under vacuum. The residue was purified by using silica gel column chromatography (diethyl ether/petroleum ether = 1:7 with 1% of Et_3N) to afford the desired product.

Consecutive cyclopropanation–cyclopropane ring-opening reactions

General procedure: [Tp^{Br3}Cu(NCMe)] (1 mol%) and the corresponding indole (1 mmol) were dissolved in CH_2Cl_2 (4 mL) in a Schlenk tube equipped with a magnetic stir bar. Then, the diazo compound (0.5 mmol) was added slowly for 1 h at RT under an N_2 atmosphere. The reaction mixture was stirred for 5 min; the volatiles were removed under vacuum; and the residue was redissolved in diethyl ether. In contrast, in another Schlenk tube equipped with a magnetic stir bar, CuI (0.539 mmol) was dissolved in diethyl ether (3 mL), methyllithium (1.078 mmol, 1.6 M in diethyl ether) was added, and the reaction mixture was stirred for 5 min at 0 °C. Then, the reaction crude of indole and the diazo compound was redissolved in diethyl ether and added to the above mixture, which was stirred for another 5 min at 0 °C before cooling to −78 °C. Temperature was maintained that low for 4 h, and then volatiles were removed under vacuum at RT. The residue was dissolved in water and extracted with CH_2Cl_2 (3×5 mL). The combined organic layers were washed with brine and dried over Na_2SO_4, and volatiles were evaporated in vacuo. The product was purified by using silica gel column chromatography (petroleum ether/diethyl ether = 20:1 with 1% Et_3N).

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Keywords: carbenes · diazo compounds · indole · ligand effects · reaction mechanisms

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