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Catalytic Copper-Mediated Ring Opening and Functionalization of Benzoxazoles

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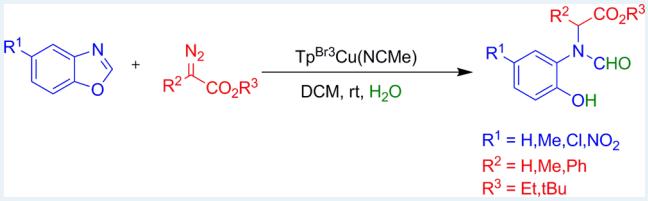
Supporting Information

ABSTRACT: A novel reaction involving benzoxazole, ethyl diazoacetate, and water has been discovered, with $Tp^{Br3}Cu$(NCMe) (Tp^{Br3} = hydrotris(3,4,5-tribromopyrazolyl)borate) as the catalyst. The fused azoles are converted into highly functionalized substituted benzenes bearing aldehyde, amine carboxylate and hydroxyl groups. The protocol has been applied for a series of benzoxazoles with several diazo compounds. Experimental data and theoretical calculations have led to a mechanistic proposal that includes carbene addition, ylide formation, and water addition to the latter, all those steps being catalyzed by the copper center.



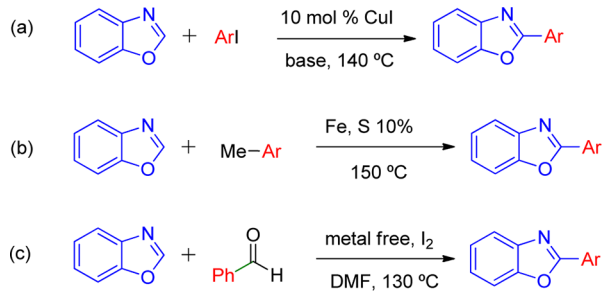
KEYWORDS: *benzoxazole functionalization, benzoxazole ring opening, copper catalysis, ethyl diazoacetate, carbene transfer*

INTRODUCTION

As a consequence of its appearance in the structure of natural products, benzoxazole derivatives have found applications in pharmaceuticals, agrochemicals, and photochromic compounds.[1] Conventional synthetic procedures usually employ condensation of anilines or 2-aminophenol with benzoic acids, aldehydes, dihaloalkanes, or more recently, with orthoesters.[2] As general features of those methodologies, harsh conditions are frequently used, and the reactions suffer from low atom economy. Therefore, the functionalization of these heterocyclic compounds yet constitutes an area of development that continues to receive considerable attention in recent years.[3]

Although rhodium- and palladium-based systems for the functionalization of such heterocycles are well established,[4] the use of the less expensive copper has grown in the past decade, mainly toward the functionalization of C−H bonds at C2 and carbon−carbon-bond-forming reactions.[5] Most of the reported methods consisted of the coupling reaction of aryl halides or aldehydes and the appropriate heterocyclic compound. The groups of both Daugulis and You independently reported the use of copper salts for the efficient coupled arylation of heterocyclic compounds (Scheme 1a).[6] Furthermore, Nguyen et al. demonstrated that under atom-economical conditions, 2-heteroaryl-benzoxazoles can be formed using cheap iron sulfide as a catalyst (Scheme 1b).[7] More rare is a recent alternative method based on the metal-free activation of benzoxazole with aryl halides mediated by oxidants (Scheme 1c).[8]

Scheme 1. Functionalization of C2 Position in Benzoxazoles



An alternative method to the above coupling reactions has been reported by the group of Wang employing *N*-tosylhydrazones from which a carbene moiety is formally added to the benzoxazole, in a process in which a copper−carbene intermediate has been proposed (Scheme 2).[9] Given our experience in the development of catalytic systems based on coinage metals for the catalytic transfer of carbene units

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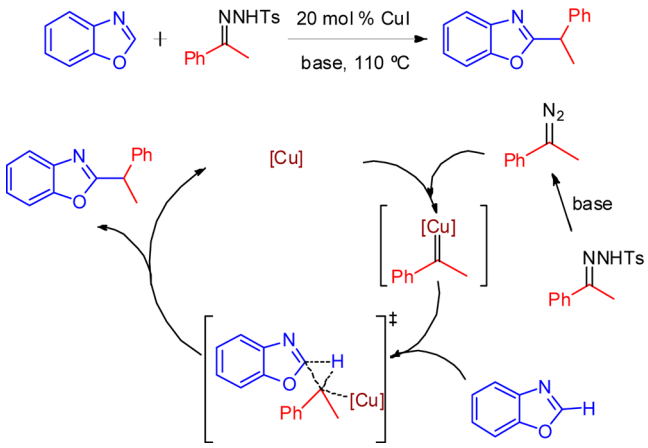
Scheme 2. Functionalization of Benzoxazole Described by Wang and Co-workers[9]



from diazo compounds to C−H bonds,[10] we decided to test the potential of a series of $Tp^{x}CuL$ complexes (Tp^{x} = hydrotris(pyrazolyl)borate ligand) for such purpose. However, during the course of these investigations, we have learned that instead of the targeted product (i.e., the C2 functionalized benzoxazole), a novel transformation took place in which the fused azole undergoes ring opening, water incorporation, and carbene addition to yield a family of compounds bearing aldehyde, ester, amine, and hydroxyl functionalities.

RESULTS AND DISCUSSION

Reaction of Benzoxazole with Ethyl Diazoacetate in the Presence of Copper Compounds as Catalysts. We first tested the catalytic capabilities of the complex $Tp^{*,Br}Cu(NCMe)$ ($Tp^{*,Br}$ = hydrotris(3,5-dimethyl-4-bromopyrazolyl)borate) toward the reaction of ethyl diazoacetate (EDA) and benzoxazole. After slow addition of the diazo reagent onto a solution containing the catalyst and the benzoxazole (1:40:50 ratio of catalyst/EDA/benzoxazole, 0.01 mmol of catalyst, 2.5 mol % catalyst loading referred to EDA) and workup, the reaction mixture was investigated by NMR, that showed the resonances of some diethyl fumarate and maleate (resulting from EDA dimerization) as well as those of a derivatized benzoxazole (**1**). Upon purification by column chromatography, we learned from the ^{1}H NMR spectrum (Figure 1) that the expected product (that from the formal insertion of the carbene moiety into the C−H bond at C2) had not been formed. In addition to aromatic resonances and those of the ethyl group of CO_2Et, three singlets located at 8.57, 8.21, and 4.33 with relative intensities of 1:1:2 were observed. The latter could correspond to a CH_2 group vicinal to carboxylate, that is, CH_2CO_2Et, in line with the targeted product. However, the singlets at 8.57 and 8.21 arose in a region in which no resonance should be observed for that compound. Heteronuclear $^{13}C-^{1}H$ NMR data provided complementary information: one of those resonances was associated with a singlet in the $^{13}C\{^{1}H\}$ NMR spectrum at 163.0 ppm, whereas no carbon nucleus was associated with the other resonance. In spite of this information, the exact structure of this compound could not be established on those bases because growing of single crystals resulting unsuccessful. Therefore, we changed the diazo reagent to $PhC(N_2)CO_2Et$, for which a similar reaction was observed. NMR spectral data also showed two singlets in the high-frequency region (9.23 and 8.24 ppm) in line with those observed with **1**. Fortunately, single crystals could be grown in this case, and an X-ray study was carried out (results shown in Scheme 3). The compound obtained from this reaction has been identified as ethyl 2-(*N*-(2-hydroxyphenyl)formamido)-2-phenylacetate (**2**) and formally contains a molecule of benzoxazole, a $C(Ph)CO_2Et$ unit from $PhC(N_2)CO_2Et$ and one molecule of water. This structure is in complete agreement with all the spectroscopic data collected for this compound as well as for those recorded for **1** (see Experimental section for full assignment).

After these results, we performed a screening of several copper salts and complexes as catalysts as well as of some conditions for the probe reaction of EDA and benzoxazole. To decrease the undesired carbene coupling side reaction, a 1:50:100 ratio of catalyst/EDA/benzoxazole was employed (0.01 mmol of catalyst, 2 mol % referred to EDA). Table 1 shows the results from this study, showing that simple copper(I) salts were not effective catalysts. The addition of EDA in one portion or by slow addition or the use of higher temperatures or bases also proved unsuccessful (entries 2−5).

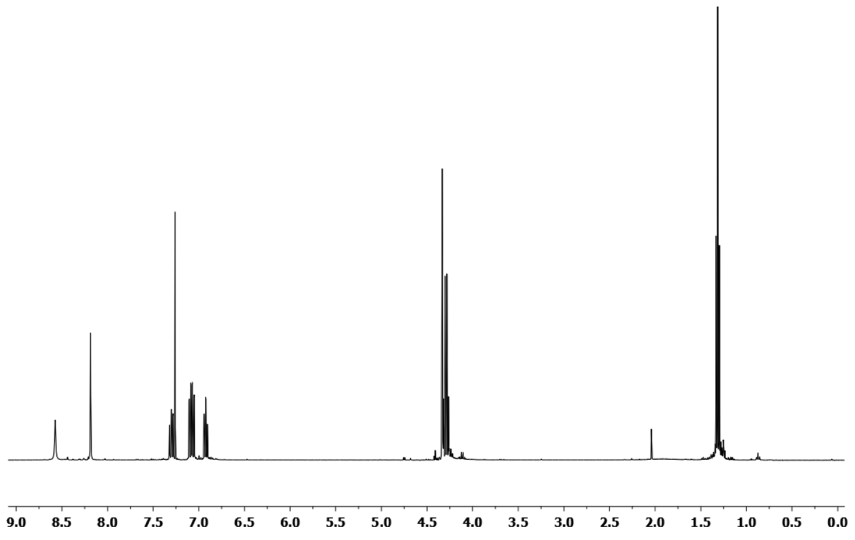


Figure 1. NMR spectrum of **1**, upon purification of the reaction mixture from benzoxazole, ethyl diazoacetate, and $Tp^{*,Br}Cu(NCMe)$ as catalyst.

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Scheme 3. Reaction between Benzoxazole and Diazocompounds with Tp*,BrCu(NCMe) as the Catalyst and the ORTEP View of One of the Molecules of 2

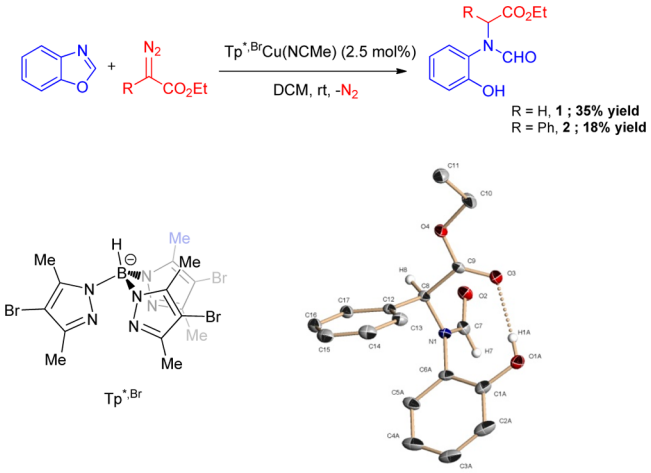
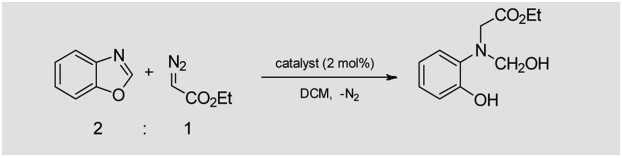


Table 1. Catalyst Screening and Optimization of Reaction Conditions for the Functionalization of Benzoxazole with EDA



entry	catalyst	temp (°C)	additive[c]	% yield of **1** (EDA conv. %)
1	-	r.t	-	-
2	CuI[a]	r.t	-	0(5)
3	CuI[a]	80	-	0(10)
4	CuI[a]	80	KO^{t}Bu	0(10)
5	CuI[b]	r.t	-	5(5)
6	IPrCuCl+NaBAr′$_4$[a]	r.t	-	0(100)
7	IPrCuCl+NaBAr′$_4$[a]	80	KO^{t}Bu	0(100)
8	IPrCuCl+NaBAr′$_4$[b]	r.t	-	10(40)
9	Tpm*,BrCu(NCMe)[b]	r.t	-	5(100)
10	Tpa*Cu(PF$_6$)[b]	r.t	-	50(100)
11	Tp^{Br3}Cu(NCMe)[a]	r.t	-	0(100)
12	Tp^{Br3}Cu(NCMe)[a]	80	KO^{t}Bu	0(100)
13	Tp^{Br3}Cu(NCMe)[b]	r.t	-	**92**(100)
14	Tp^{Ms}Cu(thf)[b]	r.t	-	24(100)
15	Tp*Cu(NCMe)[b]	r.t	-	62(100)
16	Tp^{Ph}Cu(NCMe)[b]	r.t	-	78(100)
17	Tp*,BrCu(NCMe)[b]	r.t	-	71(100)
18	Tp*,BrCu(NCMe)[c]	r.t	-	35(100)

[a]Reaction conditions: benzoxazole (1 mmol), EDA (0.5 mmol), catalyst (0.01 mmol). Addition of diazo compound in one portion (3 h of stirring). [b]Slow addition of EDA over 10 h. [c]Slow addition of EDA over 6 h.

Copper(I) complexes bearing neutral ligands such as NHC (N-heterocyclic carbene) or Tpm^x (trispyrazolylmethane) did not give significant yields into **1** (entries 6–9). In contrast, the Tpa^x (trispyrazolylmethylamine) derivative gave a moderate 50% yield (entry 10). However, it was the use of copper complexes containing anionic Tp^x ligands that led to the best results, the substituents in the ligand skeleton influencing the reaction outcome (entries 11–18). The best catalyst was Tp^{Br3}Cu-(NCMe) that gave 92% isolated yield of **1** upon slow addition of EDA for 10 h at room temperature. It is worth mentioning that in most cases shown in Table 1, conversion of initial EDA was complete, the difference between isolated yield of **1** and initial EDA being identified as diethyl fumarate and maleate (from carbene coupling from two molecules of EDA).[11]

To complete this section, the low activity observed for the Tp^{Ms}Cu-based catalyst deserves some explanation. We have isolated the Tp^{Ms}Cu(benzoxazole) adduct from this reaction, and we have characterized it by X-ray studies (see Supporting Information). It seems that in this case, the interaction of the aromatic ring of benzoxazole and the mesityl rings of the Tp^{Ms} ligand stabilizes the formation of such adduct, decreasing the catalytic activity.[12]

Reaction Scope. Once the optimal reaction conditions were established, we expanded this methodology to other substrates. Substituted benzoxazoles were prepared[13] and reacted under those conditions with three diazo compounds of general formula $R^2C(N_2)CO_2R^3$ (R^2 = H, Me, Ph; R^3 = Et, *t*-Bu, Scheme 4). With commercial ethyl diazoacetate (EDA), the best results were obtained with yields in the 70–95% interval. The influence of the R^2 group in the diazo reagent is illustrated by the comparison of the yields of compounds **1**, **2**, and **11** (Scheme 4). *t*-Butyldiazoacetate displayed by far the lowest reactivity, whereas ethyl diazopropionate was less reactive than that bearing the Ph substituent. This could be intended as a victory of the electronic effects over the steric hindrance in the step involving the carbene transfer from the metal center. Furthermore, we have not found a clear pattern of reactivity when electron-withdrawing or electron-donating substituents were located in the 1,3-azoles employed as reactants.

Other heterocycles such as benzothiazole or benzidimidazole were also tested, but no reaction took place; only diazo decomposition and carbene dimerization were observed. In the case of the former, a S-adduct of composition Tp^{Br3}Cu-(benzothiazole) was isolated and characterized by X-ray diffraction studies (see Supporting Information), the stability of that compound probably blocking further catalytic reactions.

Mechanistic Studies. The simplest retro synthetic analysis of **1** is shown in Scheme 5a: this product could be readily formed from the formal insertion of a carbene unit from the diazo compound. Since the complex Tp^{Br3}Cu(NCMe) has been previously described to catalyze such N–H functionalization reactions,[14] and it is also well-known that hydrolysis of 1,3-azoles is promoted by acidic conditions,[15] we investigated the direct reaction of commercial N-(2-hydroxyphenyl) formamide, and EDA (Scheme 5b) in the presence of the copper complex (that displays a Lewis acid behavior).[16] The inobservance of the formation of **1** led us to discard this reaction pathway.

To gain information about the mechanism, isotopic labeling studies were carried out (Scheme 6). We first synthesized the C2 deuterated benzoxazole and carried out the catalytic reaction. ^{2}H NMR studies showed that deuterium exclusively appeared in the aldehyde functionality (Scheme 6a). Because incorporation of adventitious water is required for the reaction to occur, a second experiment involved benzoxazole with deuterium oxide added to the reaction medium. In this case (Scheme 6b), the deuterium was observed in three positions: the hydroxyl, the aldehyde, and the methylene group bonded to nitrogen. This result could seem complex at first sight. Studying the interaction of a pure sample of **1** with D_2O, scrambling of deuterium with the OH and CHO groups was observed (Scheme 6c). Thus, there is incorporation of water in the

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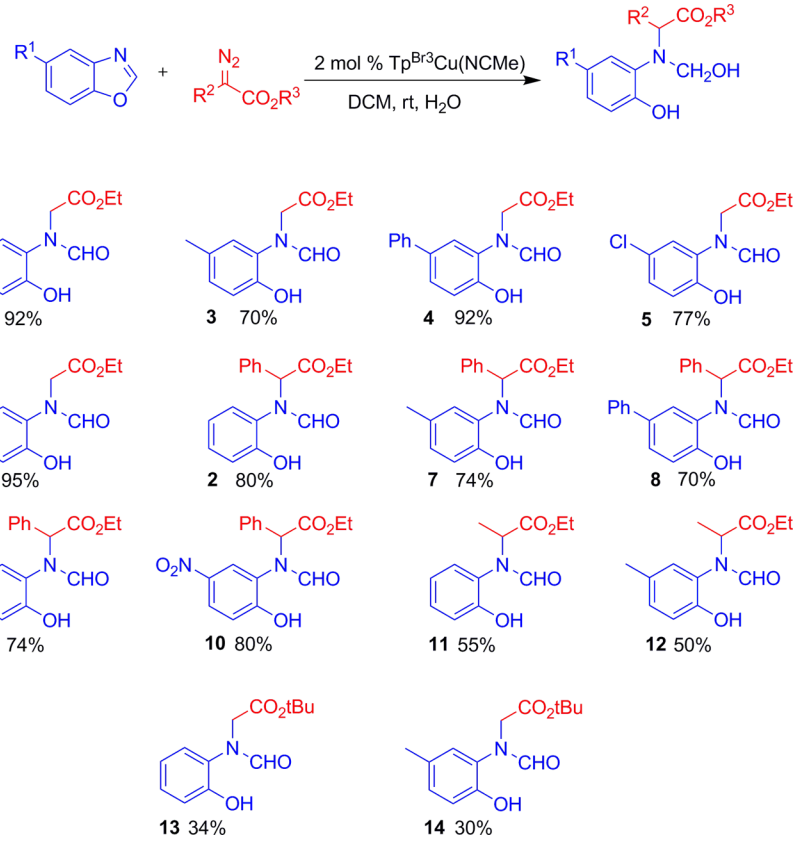
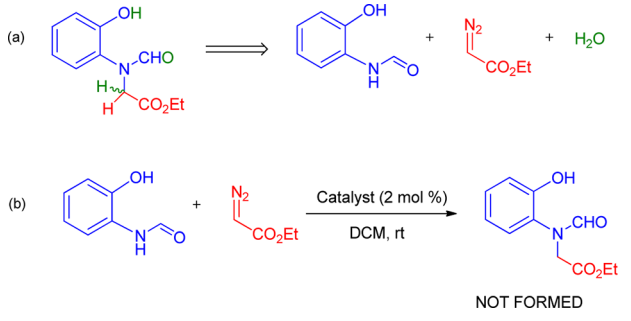
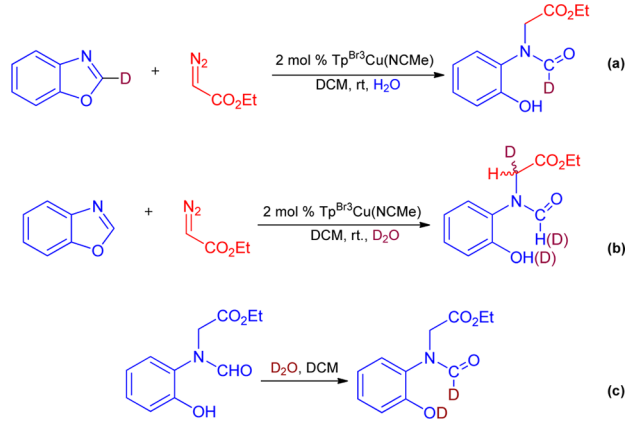
Scheme 4. Scope of the Ring Opening and Functionalization of Benzoxazoles with Diazo Compounds in the Presence of $Tp^{Br3}Cu(NCMe)$ as the Catalyst



Scheme 5. (a) Retro Synthetic Analysis of 1 and (b) Negative Test Reaction of the Retrosynthesis



Scheme 6. (a) Reaction of 2d-Benzoxazole and EDA; (b) Reaction of Benzoxazole and EDA in the presence of D_2O; (c) Treatment of Product 1 with D_2O



product. Water effectively adds a hydrogen atom at the methylene group, eliminating the scrambling effect.

On the basis of the available data, a tentative reaction mechanism could be proposed (Scheme 7). The reaction would start by formation of a copper–carbene intermediate[11a] from the Cu(I) complex and the diazo compound. Interaction of this species with benzoxazole could provide an ylidic-in-nature intermediate that could incorporate a molecule of water. However, we do not have experimental evidence on whether or not the copper center affects the ylide–water interaction. Therefore, we decided to find support for any reaction pathway by performing theoretical calculations, as discussed in the next section.

DFT Studies. The mechanism of the reaction catalyzed by $Tp^{Br3}Cu(NCMe)$ between benzoxazole (R^1 = H in Scheme 4) and the diazo compound (R^2 = H in Scheme 4) in the presence of water to achieve product **1** was computationally studied by DFT means (see Computational Details). We investigated different possible pathways for the different steps of the reaction, and our calculations lead us to postulate a detailed mechanism, which is compatible with the experimental data reported above. The reaction consists of four main processes, which are outlined in Schemes 8 and 9: (i) formation of the metallocarbene, (ii) electrophilic attack of the metallocarbene into benzoxazole, (iii) heterolytic cleavage of water, and (iv) water-assisted proton transfer and ring opening. The three first steps are copper-catalyzed, while the last one is metal-free. Scheme 8 shows a representation of the key minima (**M0**, **M1**,

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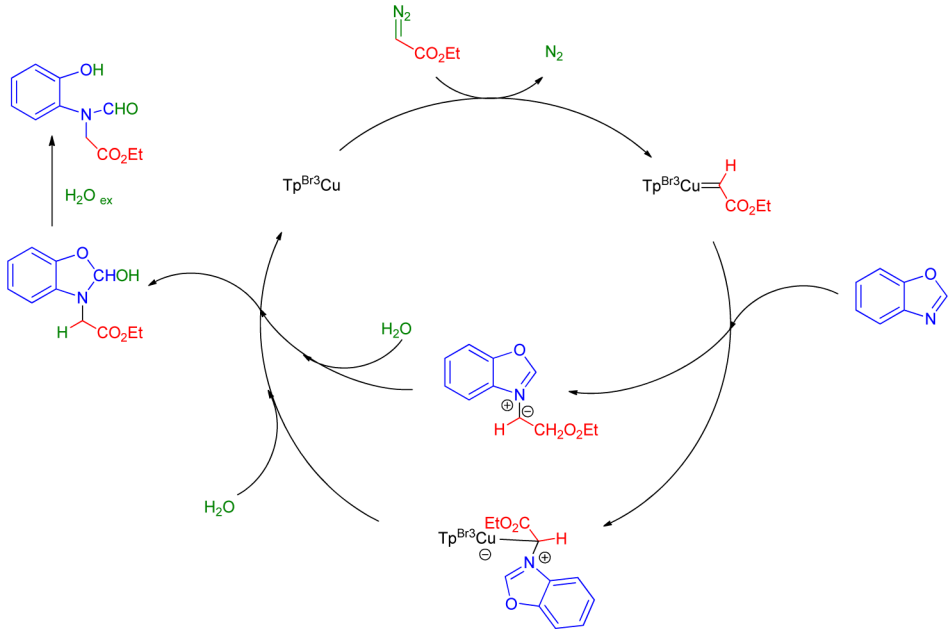
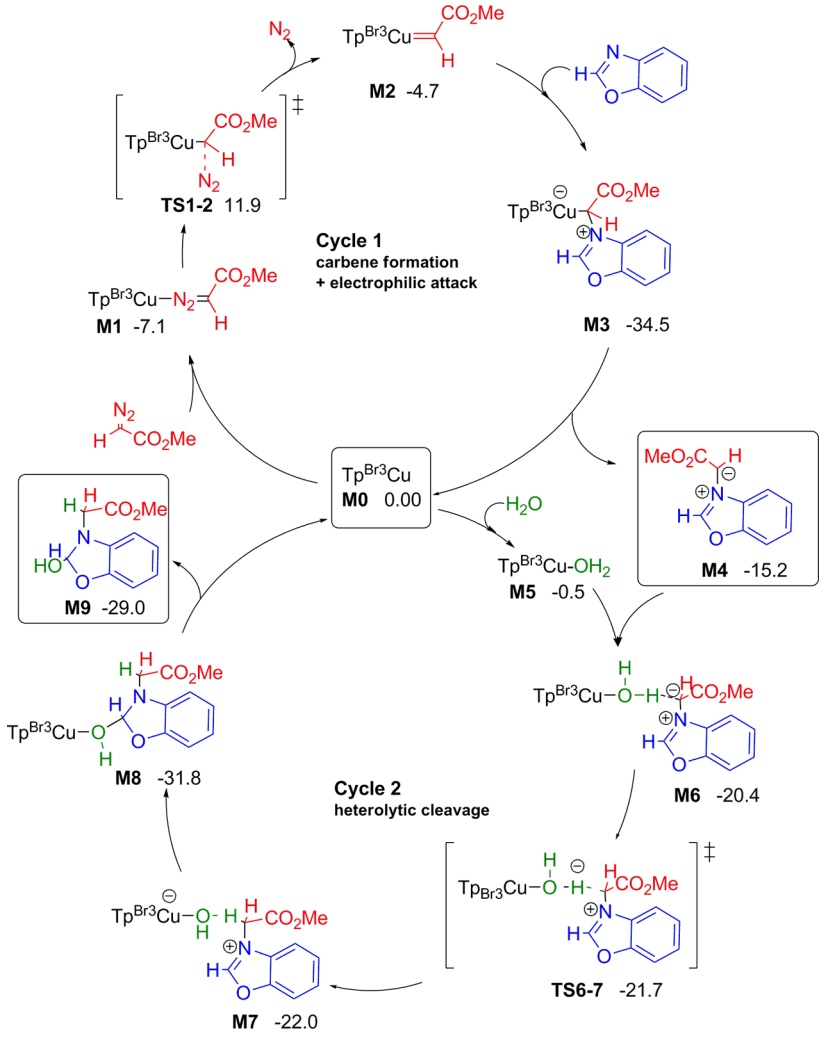
Scheme 7. Possible Reaction Pathways for the Benzoxazole Functionalization in Line with Experimental Data



Scheme 8. Postulated Computational Mechanism for the Formation of Intermediate M9 from Reactants[a]



[a]Catalytic cycle starts at center to the top. Free energies in kcal/mol.

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...) and transition states (**TS1−2**, **TS2−3**, ...) involved in steps (i) to (iii). Additional species connecting those reported in the schemes are included in the Supporting Information. Please note that processes (i) and (ii) take place in cycle 1 (top), and process (iii) takes place in cycle 2 (bottom). The same copper complex acts as catalyst in two separate cycles, in a mechanism similar to that of recently described for the functionalziation of esters with ethyl diazoacetate.[17]

The first part of cycle 1 (see Scheme 8) is the formation of the metallocarbene complex **M2** from the copper catalyst **M0** and the diazo compound. The reaction follows the steps that have been already outlined in other applications of this type of systems.[11a,12] An adduct **M1** where the diazo compound binds copper through the terminal nitrogen is first formed. **M1** then evolves toward **M2** through nitrogen extrusion in transition state **TS1−2**. **M1** is 7.1 kcal/mol below the separate reactants, while **TS1−2** is 11.9 kcal/mol above. The 19.0 kcal/mol separation betweenthese two species represents one of the higher free energy barriers that has to be overcome in the whole reaction. The **M2** copper−carbene complex generated in this transformation is located 4.7 kcal/mol below the separate reactants.

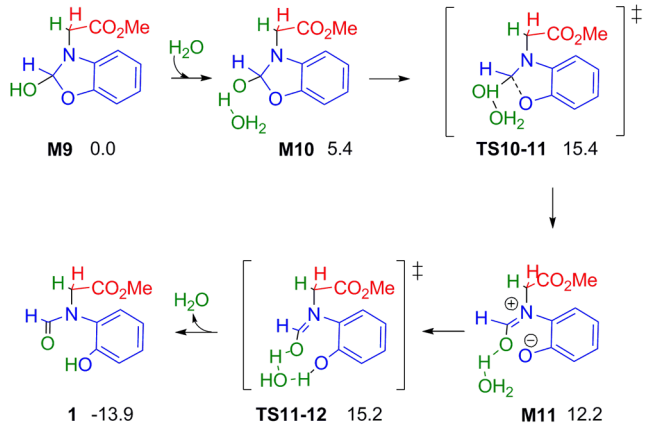
The metallo−carbene complex **M2** is highly electrophilic, as similar species have been shown to attack the electrons in a C−H bond. However, in this case, the attack takes place at the nitrogen lone pair, which is the most basic point in benzoxazole. The resulting species **M3** is a stable intermediate located 34.5 kcal/mol below reactants, and it can be viewed as a zwitterion bearing a positive charge on the benzoxazole nitrogen and a negative charge on Cu. Formation of **M3** is extremely favored, and no transition state between this species and the copper−carbene **M2** could be located. A scan on the C(carbene)-N(benzoxazole) coordinate was performed finding a monotonous decrease in the potential energy. The zwitterionic intermediate **M3** has no obvious path forward, and we postulate that at this point the organic fragment **M4** is separated from the copper center, the **M0** catalyst is recovered and cycle 1 is thus closed. **M4** can be viewed as an ylide and has a relative energy respect to reactants of −15.2 kcal/mol. Separation of **M4** from the complex has a free energy cost of 19.3 kcal/mol. This value is similar to the 19.0 kcal/mol reported above for the metallocarbene formation, and can be overcome in the experimental conditions. We would like, however, to mention that this is an upper limit for the cost of the process. We are assuming for simplicity that **M4** is fully separated from **M0**. There might be other possibilities in which **M4** remains loosely coordinated to start cycle 2 with a slightly lower free energy cost, but they have not been explored in detail, because they would not affect the overall mechanism.

The ylide intermediate **M4** already contains the N−C carbon that is key to product formation, but it still needs the formal addition of a water molecule. We could not find any low energy uncatalyzed pathway for the reaction between **M4** and water. Instead, we were able to find cycle 2 (bottom of Scheme 8), where the heterolytic cleavage of a water molecule is catalyzed by complex **M0**. Coordination of water to the $Tp^{Br3}Cu$ complex is favored by 0.5 kcal/mol and generates $Tp^{Br3}Cu{-}OH_2$ **M5**.

The approach of the organic ylide intermediate **M4** coming from cycle 1 results in the barrierless formation of intermediate **M6**. In intermediate **M6**, there is an O−H bond making a hydrogen bond to the formally anionic carbon center of the ylide. This is a strong hydrogen bond, and the transfer of a proton from the Cu−O(H)-H···C situation in **M6** to the Cu−O(H)...H−C situation in **M7** through **TS6−7** is practically isoergonic, with very small free energy changes in the range between −20.4 and −22.0 kcal/mol (the transition state is below **M6** in free energy, but it is slightly above it in potential energy). The resulting intermediate **M7** contains an anionic $Tp^{Br3}Cu{-}OH^-$ unit bound to a cationic organic fragment through a hydrogen bond. This species evolves to **M8**, as the binding situation is better when the anionic O emigrates to a cationic carbon center in order to make a O−C bond. **M8** is 31.7 kcal/mol below the reactants, and 9.8 kcal/mol below **M7**. The transition state between **M7** and **M8** could not be located, but it is likely to have a very low barrier, as a scan along the C−O reaction coordinate showed a monotonous decrease of potential energy. After **M8**, the organic intermediate **M9** is liberated, and the **M0** catalyst is regenerated. This last step, that closes cycle 2, has a free energy cost of only 2.8 kcal/mol.

M9 is not yet the experimentally observed final product **1**, as the five-membered ring must be opened. This is easily accomplished through the metal-free process outlined in Scheme 9. The organic reaction is assisted by a water molecule

Scheme 9. Water-Assisted Proton Transfer and Ring-Opening Mechanism for the Formation of 1 from M9



and takes place through two transition states, the first corresponds to the ring opening process and it is slightly higher in energy (15.4 kcal/mol above **M9**), and the second is the proton transfer. Formation of the final product **1** is exothermic by 13.9 kcal/mol from **M9**, and 43 kcal/mol from the reactants, benzoxazole, and diazo compound.

The computational results are clear in showing a mechanisms with low energy barriers. The copper catalyst has thus two roles: (i) catalyze nitrogen extrusion of the diazo compound and (ii) catalyze the heterolytic cleavage of water. Formation of the metallocarbene has a barrier of 19.0 kcal/mol; the barriers after the formation of the metallocarbene **M2** are a maximum of 19.3 kcal/mol to separate **M4** from the copper complex and 15.4 kcal/mol for the water assisted formation of the product. The other steps of the reaction have lower barriers.

We also computationally tested other mechanisms, but they were found to have a substantially higher barrier. An alternative path where benzoxazole is deprotonated and bound to the metal center had been proposed for related systems,[9] but the corresponding intermediate, containing a protonated Tp ligand, was found to have a free energy 22.4 kcal/mol above the separate reactants, which is 10.5 kcal/mol above the highest energy transition state reported above.

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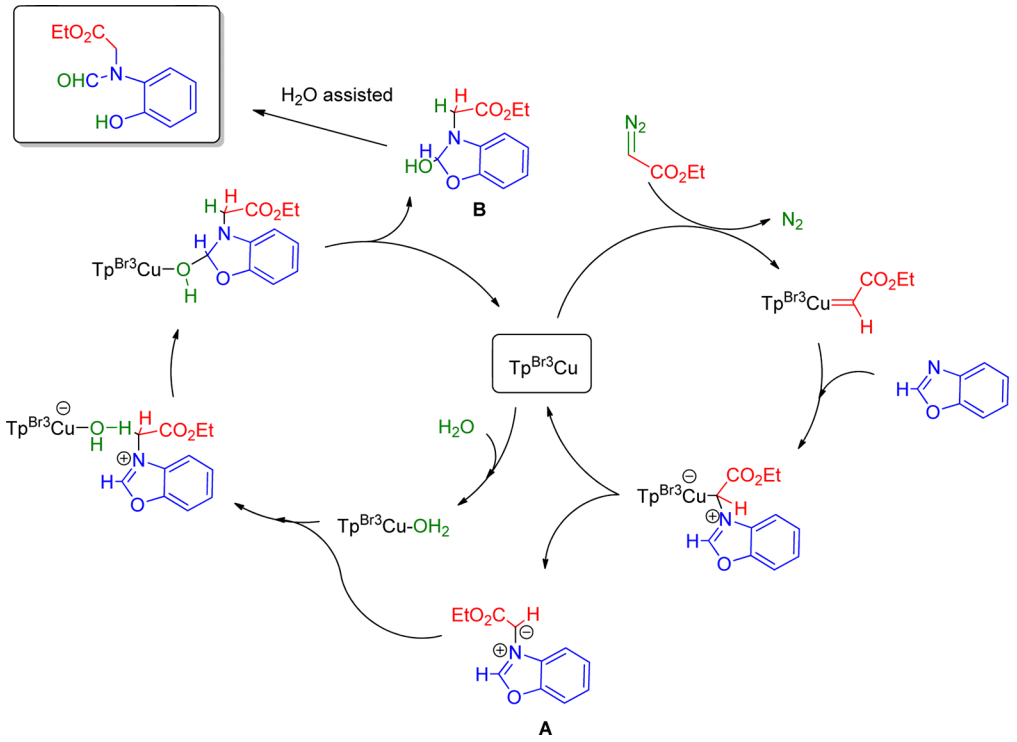
Scheme 10. Mechanistic Proposal for the Functionalization of Benzoxazol with Ethyl Diazoacetate in the Presence of $Tp^{Br3}Cu$ as Catalyst



Mechanistic Proposal. On the basis of available experimental and theoretical data, the mechanism for this novel transformation is shown in Scheme 10. The reaction is triggered by the formation of the copper−carbene intermediate from the ethyl diazoacetate and the Cu(I) source. Benzoxazole reacts with the metalocarbene rendering a ylide that decoordinates (**A**) from the copper center, which is released to coordinate a molecule of water. This aquo complex interacts with the above ylide **A** to promote the stepwise heterolytic cleavage and addition of water, producing the oxazole derivative **B** that undergoes ring opening by action of water yielding the final product **1**. This proposal is in full agreement with the deuteration experiments and the reactivity observed and already discussed in the previous paragraphs.

CONCLUSION

The complex $Tp^{Br3}Cu(NCMe)$ is an excellent catalyst precursor for a new transformation in which treatment of benzoxazole with ethyl diazoacetate and water generates a more complex molecule where the azole ring has opened, and amine, aldehyde, hydroxyl, and carboxylate functional groups are present. The reaction seems to be general for a series of benzoxazoles and diazo compounds. Mechanistic studies have shown the role of the copper center not only for the initial incorporation of a carbene group into the fused azole but also for the heterolytic cleavage of a molecule of water and subsequent addition to the organic substrate.

EXPERIMENTAL SECTION

General Methods. All reactions and manipulations were carried out under an oxygen-free nitrogen atmosphere with standard Schlenk techniques. Solvents were dried and degassed before use. Benzoxazoles were purchased from Aldrich and employed without any further purification, and the substituent benzoxazoles were prepared according to the literature procedures.[13] NMR solvents were stored over molecular sieves under nitrogen. NMR data were run in a Agilent 400 MR and 500 DD2 spectrometer using $CDCl_3$ as the solvent. GC analyses were recorded in a Varian CP-3800.

General Procedure for Ring-Opening Benzoxazole. A mixture of corresponding benzoxazole (1.0 mmol) and $Tp^xCu(NCMe)$ (0.01 mmol) was charged in a Schlenk tube equipped with a magnetic stirring bar under N_2 atmosphere, and 10 mL of CH_2Cl_2 was added. After stirring at room temperature for a few minutes, diazo compound (0.5 mmol) diluted with 10 mL of CH_2Cl_2 was added for 10 h with the aid of a syringe pump. The reaction mixture was stirred for an additional 2 h. After this time, the reaction mixture was studied by GC to check that all diazo compound was consumed, and the solvent was removed under vacuum. An internal standard (acetophenone, 0.5 mmol) was added and studied by NMR. To obtain the isolate purified product, the crude mixture was concentrated, and the residue was purified by column chromatography on silica gel (petroleum/EtOAc, 5:1) and methanol to afford the desire product. An alternative method to isolate the products was crystallization in a mixture petroleum/dichloromethane 4/1.

Computational Details. Calculations were performed with the Gaussian 09 package.[18] Grimme's DFT functional B97D,[19] which includes his correction of the dispersion effects (DFT-D2), was used together with the 6-31+g* basis set[20] for all atoms except for copper. For Cu, the SDD basis set with the associated ECP was used instead.[21]The solvent (dichloromethane) was modeled through the continuum solvent model SMD.[22] Geometry optimizations were carried out in solution. In our studies, we considered the real catalyst $Tp^{Br3}Cu$, the unsubstituted benzoxazole (R^1 = H) and EDA (R^2 = H), very similar to the simplest real species in solution for the formation

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of product **1**. The only simplification was that the ethyl group of the EDA was pruned to a methyl group for conformational simplicity. As a water molecule is one of the reactants, up to two explicit water molecules were included in our calculations. All energies presented correspond to free energies in solution and in kcal/mol. A temperature of 298 K and a pressure of 1 atm was assumed in the frequency calculations used to compute free energy corrections.

■ ASSOCIATED CONTENT

Supporting Information

Synthetic protocols, spectroscopic data, computational details and X-ray data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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