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Catalytic insertion of diazo compounds into N–H bonds: the copper alternative

M. Esther Morilla,[a] M. Mar Díaz-Requejo,[a] Tomás R. Belderrain,[a] M. Carmen Nicasio,[a] Swiatoslaw Trofimenko[b] and Pedro J. Pérez*[a]

[a] *Departamento de Química y Ciencia de los Materiales, Universidad de Huelva, Carretera de Palos de la Ffrontera s/n, E-21819 Huelva, Spain. E-mail: perez@dqcm.uhu.es; Fax: +34 959 017414; Tel: +34 959 0174112*

[b] *Department of Chemistry and Biochemistry, University of Delaware, Newark, DE 19716, USA*

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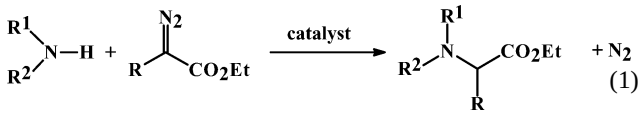
The complexes Tp^XCu (Tp^X = homoscorpionate) catalyse the insertion of diazo compounds into nitrogen–hydrogen bonds of amines and amides, under very mild conditions, with quantitative yields being obtained with equimolar ratios of reactants.

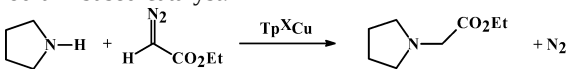
The use of *in situ* generated metallacarbenoid species as the catalytic active species for the transfer of a carbene moiety from a diazo source to several organic substrates has received much attention in the last few decades.[1] Most of the work reported to date in this area originates from a common starting point: the discovery by the Belgian group in the 1970s of the excellent catalytic activity of $Rh_2(OAc)_4$ in these transformations.[2] From the olefin cyclopropanation[2a] to the alkyne cyclopropenation,[2b] from the insertion of the carbene group into aliphatic C–H bonds[2c] to the conversion of aromatic rings into cycloheptatriene derivatives,[2d] this simple catalyst has been extensively employed. High degrees of enantioselectivity have been achieved for this type of transformations employing analogous Rh-based chiral catalysts.[1] The metal-mediated, insertion reaction into X–H bonds (X = N, O, S, P) has also been studied using rhodium catalysts, with moderate to high degrees of conversions being obtained.[1]



(1)

It is interesting that in the case of the insertion of a diazoacetate derivative into the N–H bond, an aminoacid precursor is obtained [eqn. (1)]. In spite of the interest in such a synthetic route, very few reports have appeared in the literature. Previously to the appearance of $Rh_2(OAc)_4$, Yates[3] reported the use of copper bronze for the low yield reaction of aniline and α-diazoacetophenone. Later, Saegusa *et al.*[4] described the use of CuCN for the reaction of ethyl diazoacetate (EDA) and piperidine (10 °C, 72% yield, 25% catalyst referred to EDA). Nicoud and Kagan[5] applied this catalyst for the conversion of amines into alanine derivatives (50 °C, 50% yield). However, copper was discarded as the catalyst for this transformation upon the emergence of $Rh_2(OAc)_4$, that provided higher yields for the insertion reaction of the diazo compound into the aniline NH bond (80 °C, 70% yield).[6] Since then, this complex has been employed to induce this insertion, both in the inter- and intramolecular versions, and particularly in the syntheses of pharmaceuticals.[7] Recently, very interesting applications of rhodium acetate have been described by Moody and co-workers that involve the formation of α-aminoacids and α-aminophosphonic acids[8] as well as in an unprecedented preparation of peptides.[9]

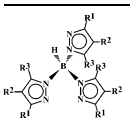
In recent years, we have studied the use of copper(I) complexes with homoscorpionate ligands[10] (Tp^X) as catalysts for several reactions such olefin cyclopropanation,[11] aziridination[11a,b] and epoxidation,[12a] alkyne cyclopropenation[12b] and carbon–hydrogen bond functionalisation.[13] We wish to report herein the results we have obtained with this type of catalysts toward the insertion of diazo compounds into N–H bonds, that have provided degrees of conversions comparable or even superior to those already known with the aforementioned rhodium-based catalyst.



(2)

We first performed a test reaction with pyrrolidine as the amine and ethyl diazoacetate, EDA, as the carbene source with four different catalysts [eqn. (2)]. The molar ratio employed was 1:50:50 for [cat]:[EDA]:[amine]. The results are shown in Table 1.† Quantitative conversions of equimolar mixtures of EDA and the amine were observed in all cases, the difference being established in the time required for the completion of the transformation. The experiments were carried out at room temperature, in a one-pot fashion (without the use of any slow-addition device). It is of note that when employing Cu(OTf) or $[Cu(MeCN)_4]PF_6$ as the catalysts, under the same conditions, yields ranged between 70–80%, and the time required for the complete EDA consumption were longer than those observed with the Tp^XCu catalysts (180 min for Cu(OTf) and 1 day for $[Cu(MeCN)_4]PF_6$). The presence of the homoscorpionate ligands is therefore crucial for the achievement of the quantitative yields.

Table 1 Tp^XCu-catalysed insertion of EDA into pyrrolidine N–H bond.

	Tp^X	R^1	R^2	R^3	Time[a]/min	Yield[b] (%)
	Tp^*	Me	H	Me	20	> 95
	Tp^{Cy}	Cy	H	H	20	> 95
	Tp^{Ph}	Ph	H	H	120	> 95
	Tp^{Ms}	Ms	H	H	240	> 95

[a] Required for complete consumption of EDA by GC. [b] Determined by GC, diethyl fumarate and maleate accounted for 100%.

In order to extend these results to other amines, we have studied the catalytic properties of Tp*Cu toward a series of primary and secondary amines, with the results described in Table 2. The insertion of one equiv. of EDA into the N–H bond of secondary amines was achieved quantitatively. In addition, in the case of primary amines such as aniline or *tert*-butylamine, both the mono- or disubstituted products could be cleanly

Table 2 Amine conversion into glycinate derivatives catalyzed by Tp*Cu.[a]

Amine	Product	Yield[a] (%)
Morpholine	$O(CH_2CH_2)_2NCH_2CO_2Et$	> 95
Diphenylamine	$(C_6H_5)_2NCH_2CO_2Et$	90
Diethylamine	$(C_2H_5)_2NCH_2CO_2Et$	> 95
Aniline	$(C_6H_5)N(H)CH_2CO_2Et$	> 95
tert-Butylamine	$^tBuN(H)CH_2CO_2Et$	> 95
Aniline[b]	$(C_6H_5)N(CH_2CO_2Et)_2$	> 95
tert-Butylamine[b]	$^tBuN(CH_2CO_2Et)_2$	> 95

[a] Determined by GC, diethyl fumarate and maleate accounted for 100%. [b] EDA:amine ratio 2:1.

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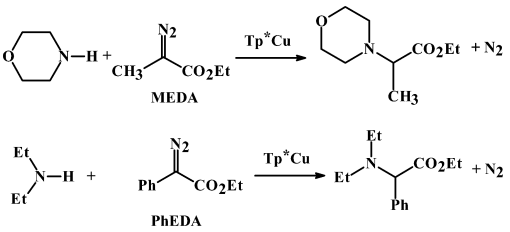
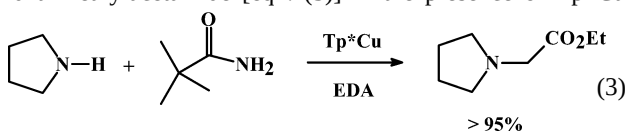
obtained by simply adding one or two equiv. of the carbene precursor. To our knowledge, all these results improve any other value reported in the literature for this transformation, due to the following reasons: (i) the reactions were carried out at room temperature whereas other copper catalysts[4,5,14] as well as $Rh_2(OAc)_4$[6,7] usually required heating of the reaction mixture; (ii) an equimolar mixture of the amine and EDA has been employed, therefore avoiding the excess of amine commonly needed by other catalysts and (iii) the general quantitative yields observed for primary and secondary, aliphatic or aromatic amines finds no precedent either with copper- or rhodium-based catalysts.

This exceptional catalytic activity has also been extended to other diazo reagents. Thus, the use of ethyl diazopropionate (MEDA) or ethyl 2-phenyldiazoacetate (PhEDA) has allowed the formation, with the intermediacy of Tp*Cu as the catalyst, of alanine and phenylglycine derivatives (Scheme 1). The reaction of equimolar amounts of morpholine and $CH_3C(N_2)CO_2Et$ in the presence of Tp*Cu (5% molar ratio) produced the corresponding insertion product in quantitative yield. Similar results have been obtained with $PhC(N_2)CO_2Et$ (80% yield), thus affording the phenylglycine derivative. This procedure provides a route for the synthesis of amino acid derivatives under very mild conditions and with no need for excess of amine.



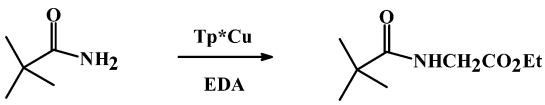
Scheme 1 Syntheses of Ala and Phg derivatives.

As mentioned above, Moody *et al.* have recently applied the insertion of diazocompounds into amide N–H bonds to generate dipeptides, leading to an unprecedented route to this type of compounds.[9] In order to check the potential of our copper system towards amide functionalisation, we have carried out a competition experiment with equimolar amounts of pyrrolidine and trimethylacetamide [eqn. (3)] in the presence of Tp*Cu



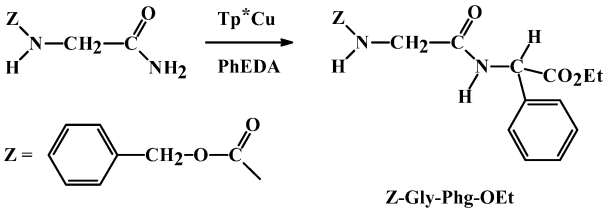
(3)

(1 : 20 : 50 ratio for [Cu] : [EDA] : [amine + amide], 0.05 mmol of Tp*Cu, 1 : 1 amine : amide). After completion, NMR studies revealed the existence of more than 95% (EDA-based) of the amine-derivative, with only traces of the amide derivative being detected. Since these transformations seem to occur through the intermediacy of electrophilic metallocarbene species, this result is in good agreement with the order of acidity of these N–H bonds (amidic N–H > aminic N–H), therefore favoring the more basic substrate. In the absence of amine, it was possible to activate the N–H bonds of the trimethylacetamide. When reacting this substrate with EDA under equimolar conditions,† the insertion product was observed in 85% yield (diethyl maleate and fumarate accounted for 100% of EDA) (eqn. (4)].



(4)

In addition to plain amides, amino amides have also been tested. Following Moody's work, we have carried out the reaction of an equimolar mixture of Z-gly-NH_2 (Z = benzoyloxocarboxy protecting group) with the bulkier ethyl 2-phenyldiazoacetate [eqn. (5)]. in the presence of catalytic amounts of Tp*Cu. The Z-gly-Phg-OEt dipeptide derivative has been



(5)

Z-Gly-Phg-OEt

obtained in high yield (80%) as the result of the selective insertion of the diazo group in one of the terminal amidic nitrogen–hydrogen bonds.

In conclusion, the Tp^XCu complexes promote the insertion of diazo compounds into amine or amide N–H bonds in very high yield and under very mild conditions. This heralds the rediscovery of copper as a real alternative to rhodium-based catalysts for this transformation.

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Notes and references

† *General experimental procedure*: the catalysts were prepared as in refs. 11*c* and 12*b*. A solution of the Tp^XCu complex (0.05 mmol) in 1,2-dichloroethane and pyrrolidine (2.5 mmol) was prepared under nitrogen. The diazo compound (2.5 mmol of EDA) was added in one portion and the mixture stirred until no diazo was detected by GC. Only in the case of the primary amines, diphenylamine and amides a syringe pump was employed to add the EDA for 1 h. Yields were determined after EDA consumption by GC and also by ^{1}H NMR.

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