

Complete Control of the Chemoselectivity in Catalytic Carbene Transfer Reactions from Ethyl Diazoacetate: An *N*-Heterocyclic Carbene–Cu System That Suppresses Diazo Coupling

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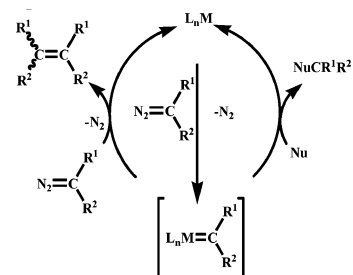
Diazocompounds have been extensively employed as a carbene source in organic synthesis.¹ In the past decade, the incorporation of such fragments to a variety of substrates has been accomplished in many cases with the aid of an appropriate transition-metal complex acting as catalyst.² It is well-established that this transformation occurs via an electrophilic metalcarbene intermediate,^{2,3} although this species has only been detected once.⁴ As shown in Scheme 1, the transfer of the carbene unit to a nucleophile affords the desired product and releases the metal center to reinitiate the catalytic cycle. The main drawback of this methodology is the existence of an undesirable side reaction, the homocoupling of the diazocompound (Scheme 1, left). This problem has been usually overcome by using slow addition devices and/or using excess of the nucleophilic substrate. The vast majority of systems capable of mediating this reaction bear nitrogen-donor ligands,¹ and they all display a similar behavior: ethyl diazoacetate is readily converted into diethyl fumarate and maleate because of this unwanted side reaction. On the other hand, phosphorus-containing ligands are not useful for this chemistry because of the facile carbene transfer to phosphorus to produce ylide derivatives.

During the course of our investigations aimed at developing new catalysts that could avoid the aforementioned diazo coupling reaction, we examined the potential of complexes containing the emerging *N*-heterocyclic carbene (NHC) ligands⁵ toward the diazocompound decomposition reaction in the presence of several substrates. NHC-based catalytic systems have been reported for several processes such as hydrogenation,⁶ hydrosilylation,⁷ C–C⁸ and C–N⁹ bonds formation, olefin metathesis,¹⁰ and ATRP.¹¹ However, very few examples (Ru- and Rh-based) of application to diazo decomposition and carbene transfer have been reported using such systems.¹²

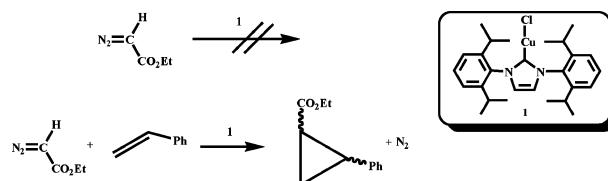
We prepared complex IPrCuCl¹³ (**1**) [IPr: 1,3-bis(diisopropylphenyl)imidazole-2-ylidene] and employed it as catalyst in two test experiments (Scheme 2): the cyclopropanation of styrene with ethyl diazoacetate (EDA) and the decomposition of EDA to give fumarate and maleate. In both cases, a solution of 0.025 mmol of **1** in dichloromethane was mixed with 0.625 mmol of EDA, for a 1:25 EDA/catalyst ratio (4% of catalyst). In the cyclopropanation test, 3.25 mmol of styrene was also added (1:25:125 molar ratio for [1]/[EDA]/[styrene]).

After stirring the solution for 6 h, we monitored the reaction mixtures by GC. The styrene-containing solution showed a greater than 90% conversion to cyclopropanes (referenced to EDA), with no remaining diazoester being detected. Surprisingly, the experiment carried out with EDA alone showed *no consumption* of the diazo reagent, the catalyst remaining unaffected for prolonged time periods. These experiments were repeated four times, using different

Scheme 1. Transition-Metal-Catalyzed Carbene Transfer from Diazocompounds



Scheme 2. Reactions of EDA in the Presence of **1**



batches of catalyst and EDA, leading to identical results: in the absence of styrene, EDA did not decompose to any extent in the presence of **1**.

Two kinetic experiments were conducted to monitor the lifetime of EDA in the presence of **1**. Solutions of **1** and EDA were prepared, stirred at room temperature, and periodically monitored by GC to quantify the amount of EDA present in the reaction mixture. No decomposition of EDA was observed after 3 h. After this time, styrene (4 equiv with respect to EDA) was added to one of the solutions, inducing the immediate consumption of EDA, as inferred from the observed decay and the subsequent formation of cyclopropane products in very high yield (Figure 1). The non-styrene-containing solution did not undergo any noticeable change along the time interval studied (13 h), in what can be considered a rare example in the field of metal-catalyzed diazocompound decomposition.^{2,14} Styrene and cyclooctene could be readily converted into the corresponding cyclopropanes in nearly quantitative yields in the presence of **1** (Table 1), affording the diastereoselectivities *cis/trans* 32:68 and *exo/endo* 73:27, respectively. We have also studied the related insertion of the :CHCO₂Et unit into the X–H bonds of amines and alcohols. The N–H bonds of aniline or pyrrolidine, as well as the O–H bonds of ethanol or *sec*-butanol, were functionalized, following a similar procedure to that used with styrene. Very high product yields (Table 1, entries 3–6) have been obtained, the amounts being comparable to those of very active copper-based catalysts already known.¹⁵ Previously reported copper(I) complexes displayed an extremely high activity² toward EDA decomposition, in contrast with the observed behavior of IPrCuCl, which does not react with EDA. Substrate (olefin, amine, and alcohol) addition

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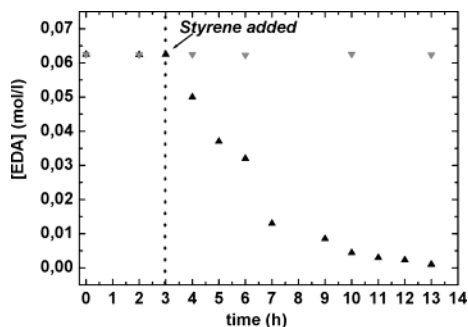


Figure 1. EDA decomposition in the presence of **1**. (▼) EDA as the sole reagent. (▲) Styrene added at 3 h. Dibromomethane used as internal standard.

Table 1. Carbene Transfer from Ethyl Diazoacetate (EDA) Using **1** as the Catalyst^a

Entry	Substrate	Product	Yields ^b	
			EDA:substrate 1:1	1:X
1			72(63) ^c	99(93) ^f
2			71(64) ^c	99(91) ^f
3			99(91) ^d	99(89) ^e
4			99(92) ^e	99(92) ^e
5			85(78) ^e	95(85) ^e
6			79(70) ^e	95(90) ^e

^a Reactions performed at room temperature with 0.025 mmol of **1**, 4% with respect to EDA. ^b Percentage of the product, based in EDA, determined by GC after total consumption of EDA with dibromomethane as internal standard. Diethyl fumarate and maleate accounted for the remaining EDA. Isolated yields are given in brackets. Average of two runs. ^c EDA added in 3 portions. ^d Addition of EDA in 1 portion gave a 10% of the disubstituted PhN(CH₂CO₂Et)₂. Addition in 2 portions avoided the double activation. ^e 1 portion addition. ^f X = 10. ^g X = 6.

leads to initiation of the catalytic cycle and to a species that has preferred interaction with the diazo reagent yet in the absence of substrate is inactive toward diazo activation (and degradation). Therefore, the chemoselectivity in this system appears to be self-controlled and requires the presence of a substrate in the reaction mixture, a result that, to our knowledge, finds no precedent in the metal-mediated catalytic carbene transfer from ethyl diazoacetate. It is also worth mentioning that reactions were performed with simultaneous addition of EDA and substrate, without the need for slow addition techniques, at room temperature, with excess of the substrate. We have also performed the equimolar EDA/substrate experiments, with the results shown in Table 1. The olefins were converted into cyclopropanes with a ca. 70% yield, whereas higher conversions were observed for amines and alcohols.¹⁶ The preference for interaction with X–H bonds was further confirmed by a competition experiment carried out with styrene and aniline yielding the aniline derivative as the major product (<95%).

Although mechanistic studies are currently underway, we believe that the absence of the reactivity of **1** toward EDA suggests that **1** is not the active catalytic species and that the substrate helps generate the active species responsible for diazo decomposition. In fact, the addition of a small amount (nearly stoichiometric referred to catalyst) of diethyl fumarate or maleate to a solution

containing **1** and EDA initiated consumption of the diazoester. Similar behavior was observed with all substrates shown in Table 1, as well as with other weak donors such as benzene. A possible explanation might involve the formation of an active species being a substrate-containing complex, probably cationic in nature, with chloride as a counterion.

In conclusion, we have shown that complex IPrCuCl catalyzes the transfer of the :CHCO₂Et group (from ethyl diazoacetate) to unsaturated and saturated substrates (olefins, amine, alcohols) with very high yields. The unique behavior of this system constitutes, in our opinion, the starting point for the development of new catalysts that avoid the already mentioned main drawback of this methodology, the diazo compound dimerization reaction.

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Supporting Information Available: General experimental procedures and NMR spectra of the products in Table 1 (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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