Notes

Reaction of Ethyl Diazoacetate with Alkyl-Aromatic Substrates: Influence of the Tp^xCu Catalyst in the Addition versus Insertion Chemoselectivity (Tp^x = Homoscorpionate)

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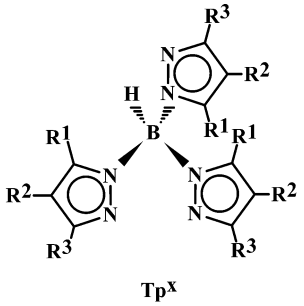
*Summary: The complexes $Tp^{Br3}Cu(NCMe)$ (**1**) and $Tp^{Ms}Cu$ (**2**) catalyze the addition of the :$CHCO_2Et$ unit (generated from N_2CHCO_2Et, EDA) to benzene to give a cycloheptatriene ring, in analogy with the Büchner reaction. When alkyl groups are attached to the aromatic rings, the selectivity of the reaction can be oriented toward addition or, alternatively, to the insertion into an alkyl C−H bond by using **1** or **2**, respectively.*

Introduction

The reaction of benzene and ethyl diazoacetate under thermal or photochemical conditions was reported by Büchner almost a century ago.[1] The mixture of cycloheptatrienes obtained in that way was formed upon the formal addition of a carbene group to a double bond of benzene, followed by the ring expansion of the cyclopropane intermediate. In 1981, Noels and co-workers[2] reported the use of $Rh_2(OOCCF_3)_4$ to efficiently catalyze this reaction, affording one major isomer in very high yield. Later, Callot et al.[3] showed using porphyrin-containing rhodium catalysts that several methyl-aromatic substrates could undergo a competition between the addition to the double bond (leading to cycloheptatrienes) and the insertion into an sp^3 C−H bond of the methyl group. In recent years, Davies and co-workers have demonstrated[4] with chiral rhodium catalysts that when methylene groups are attached to the benzene rings, these benzylic sites are preferred for the insertion reaction, using phenyl- or vinyl-diazocetates as the carbene source. Although copper-based catalysts have been reported to induce this transformation for intramolecular processes,[1] to our knowledge there are no reports of the use of this metal for the intermolecular version of such transformation, at least with noticeable degrees of conversion. We have recently described[5,6] the use of the complexes $Tp^{Br3}Cu(NCMe)$ (**1**) and $Tp^{Ms}Cu$ (**2**) as catalysts for the insertion of ethyl diazoacetate (EDA) into the C−H bonds of hydrocarbons and ethers. In this contribution we present the results obtained with those complexes as the catalysts for the reaction of EDA with aromatic substrates.



Tp^x

Tp^{Br3}: $R^1 = R^2 = R^3 = Br$
Tp^{Ms}: $R^1 = R^2 = H$; R^3 = mesityl

Results and Discussion

As a first test, we have studied the reaction of EDA and benzene in the presence of **1**, an experiment that led to a 60% conversion (based in EDA) of the cycloheptatriene product (eq 1). This result has supposed the first example of a copper-induced transformation of this

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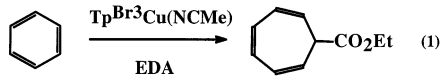
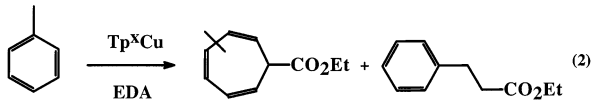
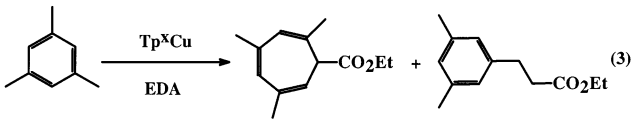
type, with a reasonable yield. Interestingly, the use of **2** as the catalyst gave no reaction at all, only diethyl fumarate and maleate being observed by GC and NMR, despite the well-known capabilities of this complex to catalyze the olefin cyclopropanation reaction.[7]





$Tp^x = Tp^{Ms}, Tp^{Br3}$

Having established the potential of the Tp^xCu system for this reaction, we have studied toluene as the substrate (eq 2). Under the same conditions as those employed with benzene, we have used **1** or **2** as the catalyst, with very different results being observed in each case. The $Tp^{Br3}Cu(NCMe)$ complex favored the addition pathway, leading to a 62% conversion into the cycloheptatriene ring. All three possible isomers were detected,[2,3,8] with the regioselectivity ratio 2-methyl, 3-methyl, 4-methyl 13:29:58. The insertion product, which entails a two-carbon methyl group homologation of toluene,[3] was detected in only 8% yield (the remaining 30% corresponded to diethyl fumarate and maleate). The use of **2** as the catalyst, under the same conditions, reversed the chemoselectivity: only the insertion product (ethyl 3-phenylpropionate) was obtained with no cycloheptatriene derivatives being observed (in the NMR detection limit). The overall yield was 20% (80% of diethyl fumarate and maleate), again **1** displaying a higher catalytic activity than **2**. However, these results are quite interesting when compared with those known for rhodium. The seminal work by Noels et al.[2] showed that the rhodium(II) trifluoroacetate provided only the cycloheptatriene compounds, with no insertion products being observed. The already mentioned rhodium-porphyrin catalysts also gave mixtures of the insertion and the addition products, always favoring the latter. In no case has a catalyst been reported to give the former, i.e., the dihydrocinnamate derivative, as the sole product of the reaction, as it is the case of the $Tp^{Ms}Cu$ catalyst. To ascertain if the activation of the primary C−H bond of toluene could be extended to other substrates, we have carried out a similar experiment with mesitylene (eq 3). As shown in Table 1, the results obtained were



$Tp^x = Tp^{Ms}, Tp^{Br3}$

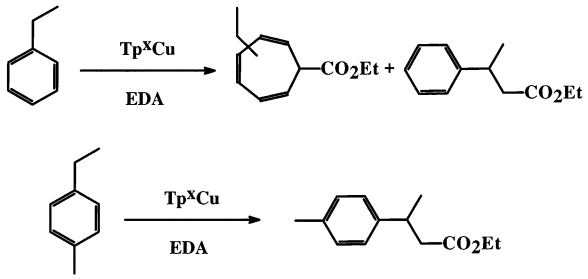
quite similar in both cases. Complex **1** induced the addition (and subsequent ring expansion) of EDA to the double bond, whereas **2** favored insertion into the methyl C−H bonds, as the preferred, respective transformations. It is also worth mentioning that the yields obtained with these substrates were comparable to those already reported with rhodium catalysts and EDA as the carbene source. Thus, **1** promoted overall yields of 70% and 87% for toluene and mesitylene, which are higher than the 58% and 73%, respectively, reported with rhodium.[3] As far as selectivity, the control toward the insertion reaction induced by **2** has no precedent, although yield optimization is still to be achieved.

Table 1. Reactions of Ethyl Diazoacetate with Alkylaromatic Substrates with 1 or 2 as the Catalyst

	$Tp^{Br3}Cu(NCMe)$ (**1**)		$Tp^{Ms}Cu$ (**2**)	
substrate	% insertion[a]	% addition[a]	% insertion[a]	% addition[a]
toluene	8	62	20	nd
mesitylene	12	75	30	<5
ethylbenzene	30	18	56	nd
ethyltoluene	45[b]	nd	58[b]	nd

[a] Determined by GC, diethyl fumarate and maleate accounted for 100%. [b] An unknown compound appeared in 10−15% yield.

Scheme 1. Reactions of EDA with Ethylbenzene and Ethyltoluene



$Tp^x = Tp^{Ms}, Tp^{Br3}$

The above results demonstrate that a certain control of the selectivity in the addition versus insertion system can be achieved by appropriate election of the Tp^xCu catalyst, but only when dealing with the double bond−methyl group couple. Since the benzylic position has been shown to be preferred[4] for the rhodium-based catalysts, we have also studied two substrates with such methylene groups: ethylbenzene and ethyltoluene. As shown in Scheme 1, insertion into benzylic bonds took place in both cases, as expected from the well-known lower energy of such bonds compared with the primary ones.[9] In fact, with these substrates the addition reaction, and subsequent ring expansion, was minimized, in the case of ethylbenzene, or completely suppressed, in the case of ethyltoluene. This behavior could be explained in terms of the presence of several factors, such as the already mentioned bond energy of the methylene C−H bonds, the steric effect of the *para*-substituted toluene, and even the electronic effect of those groups in the *para* position, already demonstrated by Davies.[4b] To compare the reactivity of those methylenic C−H bonds with other secondary sites, we have performed intermolecular competition experiments with ethylbenzene and cyclohexane, in the presence of **1** or **2** as the catalyst (eq 4). In both cases, we have obtained the ethylbenzene derivative as the major product, the selectivity depending on the catalyst employed. It is worth mentioning that both **1** and **2** have been reported

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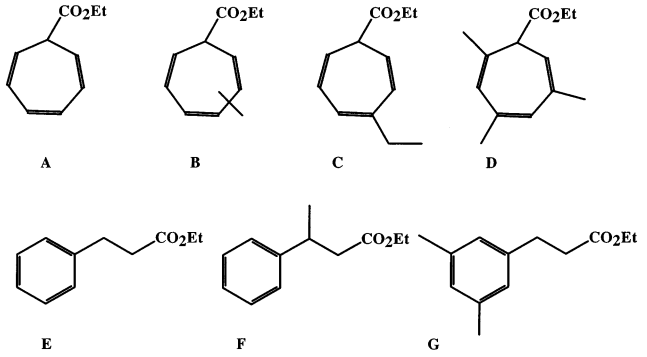
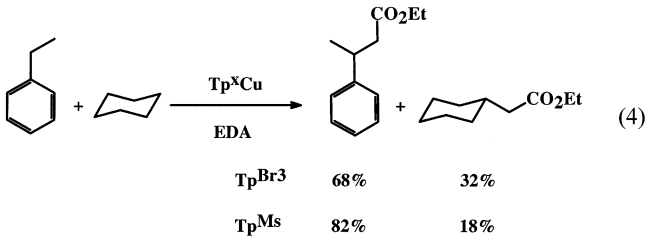
Scheme 2. Esters Synthesized in This Work



to induce the functionalization of cyclohexane in moderate (54%, **2**)[6] to high (90%, **1**)[5] yield.



(4)

Since all the results shown in Table 1 have been obtained from catalytic experiments under the same conditions, the following trends should be commented on. For each catalyst, **1** or **2**, the insertion into the secondary C−H bond seems to be favored over that into a primary C−H bond, the benzylic bonds being more reactive than those of cyclohexane. The addition reaction competes only with the insertion into primary C−H bonds, in the absence of secondary ones. In that case, **1** was the catalyst of choice to obtain cycloheptatrienes, whereas **2** should be employed if the insertion products were to be preferred.

Conclusion

The use of the Tp^xCu catalysts for the intermolecular transformation of aromatic substrates highlights the rediscovery of this metal for this chemistry, with activities and selectivities that compete with those already known for rhodium. The study of related catalysts to achieve higher activity and selectivity is currently underway in our laboratory.

Experimental Section

General Methods. ^{1}H NMR spectra were run in a Varian Mercury 400 MHz using $CDCl_3$ as the solvent. Mass spectra were carried out in a Varian Saturn 2100T. GC analyses were recorded in a Varian CP-3800. Solvents were dried and degassed before use. All the hydrocarbons were purchased and employed without any further purification. Syntheses of the copper catalysts were carried out as reported previously.[5,6]

General Catalytic Experiment. A solution of the Tp^xCu complex (0.05 mmol) in neat substrate (20 mL) was prepared under nitrogen. The diazo compound (1 mmol of EDA) was added with the aid of a syringe pump for 20 h. After removal of volatiles under vacuum, the crude residue was investigated by NMR. The spectra were compared with the data already reported for cycloheptatrienes[2,3] and the insertion products.[2−4]

Compound Characterization. Although most of the organic esters obtained by the above methodology have been previously prepared, we report herein their relevant NMR data.

Ester A. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.64 (2H), 6.25 (2H), 5.43 (2H), 4.24 (2H, $CO_2CH_2CH_3$), 2.54 (1H, CH-$CO_2CH_2CH_3$), 1.29 (3H, $CO_2CH_2CH_3$). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 133.8 (2C), 125.7 (2C), 117.4 (2C), 61.6 ($CO_2CH_2CH_3$), 44.6 ($CH-CO_2CH_2CH_3$), 14.5 ($CO_2CH_2CH_3$). GC/MS: 164 (M^+), 136 ($M^+ - 28$), 118 ($M^+ - 46$).

Ester B. Three isomers, with NMR data similar to that reported for the methyl esters,[2b] were obtained. Major isomer: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.10 (2H), 6.07 (1H), 5.34 (2 H), 4.20 (2H, $CO_2CH_2CH_3$), 2.55 (1H, CH-$CO_2CH_2CH_3$), 2.07 (3H, *Me*) 1.30 (3H, $CO_2CH_2CH_3$). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 128.5, 126.0, 125.0, 115.1, 114.3 (5C), 61.4 (CO_2CH_2-CH_3), 43.9 ($CH-CO_2CH_2CH_3$), 14.6 ($CO_2CH_2CH_3$). GC/MS: 178 (M^+), 150 ($M^+ - 28$), 132 ($M^+ - 46$), 121 ($M^+ - 57$). Minor isomers, selected data: (i) ^{1}H NMR ($CDCl_3$, 400 MHz): 2.36 (3H, CH_3), 2.24 (1H, $CH-CO_2CH_2CH_3$). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): 39.8 ($CH-CO_2CH_2CH_3$), 22.1 (CH_3). (ii) ^{1}H NMR ($CDCl_3$, 400 MHz): 2.83 (1H, $CH-CO_2CH_2CH_3$), 1.95 (3H, Me). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): 47.5 ($CH-CO_2CH_2CH_3$), 21.8 (CH_3).

Ester C. Only one major isomer was detected by NMR, very similar to one of the above toluene derivatives. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.40 (1H), 6.20 (1H), 6.11 (1H), 5.40 (1H), 5.32 (1H), 4.20 (2H, $CO_2CH_2CH_3$), 2.55 (1H, $CH-CO_2CH_2CH_3$), 1.30 (3H, $CO_2CH_2CH_3$)

Ester D. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.22 (1H), 5.82 (1H), 5.36 (1H), 4.20 (2H, $CO_2CH_2CH_3$), 2.83 (1H, $CH-CO_2CH_2CH_3$), 1.97, 1.99, 1.95 (3H each, 3 *Me*), 1.30 (3H, $CO_2CH_2CH_3$). ^{13}C-{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 129.7 (1C), 125.5 (1C), 114.5 (1C), 62.1 ($CO_2CH_2CH_3$), 48.5 ($CH-CO_2CH_2CH_3$), 20.5, 210.1, 18.4 (3C, 3 *Me*) 15.2 ($CO_2CH_2CH_3$).

Ester E. The spectroscopic data were identical to those of a commercial sample from Aldrich.

Ester F. Selected NMR data: ^{1}H NMR ($CDCl_3$, 400 MHz): δ 4.21 (2H, $CO_2CH_2CH_3$), 3.28 (1H, $CH(CH_3)-CO_2CH_2CH_3$), 2.60 (2H, $CH_2-CO_2CH_2CH_3$), 1.53 (3H, CH_3), 1.30 (3H, CO_2-CH_2CH_3).

Ester G. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.81 (1H), 6.58 (2H), 4.20 (2H, $CO_2CH_2CH_3$), 2.87 (2H, $CH_2CH_2-CO_2CH_2CH_3$), 2.61 (2H, $CH_2CH_2-CO_2CH_2CH_3$), 2.28 (6H, 2 Me), 1.30 (3H, CO_2-CH_2CH_3). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): δ 127.4 (2C), 127.1 (1C), 62.2 ($CO_2CH_2CH_3$), 36.5 ($CH_2CH_2-CO_2CH_2CH_3$), 31.2 ($CH_2CH_2-CO_2CH_2CH_3$), 21.1 (2 CH_3), 14.9 ($CO_2CH_2CH_3$).

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