

Alkane Carbon–Hydrogen Bond Functionalization with (NHC)MCl Precatalysts (M = Cu, Au; NHC = N-Heterocyclic Carbene)

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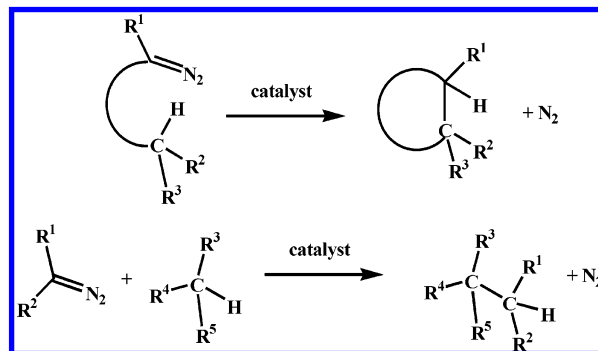
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Facile alkane functionalization by means of the insertion of :CHCO₂Et, from ethyl diazoacetate, into carbon–hydrogen bonds mediated by catalytic amounts of (NHC)MCl (NHC = N-heterocyclic ligand; M = Cu, Au) and a halide scavenger MX has been achieved. This chemistry includes the insertion of the carbene fragment into alkane primary positions with Cu- and Au-based catalysts. The nature of the counterion X and of the NHC ligand have a significant effect on the overall yields and regioselectivity of the reaction.

Introduction

The metal-catalyzed transfer of a carbene unit, :CR¹R², from diazo compounds N₂CR¹R² has been extensively studied during the last few decades.¹ The main transformations involving this fragment have centered on its addition to unsaturated bonds or, alternatively, its insertion into saturated X–H bonds. The most interesting example is when X is carbon, a case that results in the functionalization of carbon–hydrogen bonds by carbene insertion.² This procedure (Scheme 1) has been extensively employed in intramolecular reactions; however the intermolecular counterpart has been described only with a few metal-based catalysts. The first examples were performed with simple copper salts.³ The seminal work by Noels and co-workers⁴ with rhodium acetate was followed by work from several other groups⁵ that aimed at developing new catalysts based on rhodium. This methodology was quite limited in scope, and it was not until the end of the past decade when work by Davies and co-workers^{2,6} led to the renaissance of this method for the functionalization of carbon–hydrogen bonds. Interestingly, systems based on copper^{7a–d} and silver^{7d–f} have also been reported to insert a :CHCO₂Et unit from ethyl diazoacetate into the C–H bonds of several saturated substrates.

Scheme 1. Intra- and Intermolecular C–H Bond Functionalization by Carbene Insertion from Diazo Compounds



We have very recently reported on the catalytic properties of the complex (IPr)CuCl (**1**) [IPr: 1,3-bis(diisopropylphenyl)imidazol-2-ylidene] (Scheme 2) in the transfer of the :CHCO₂Et unit from ethyl diazoacetate to olefins, amines, and alcohols.⁸ We have also prepared and characterized the gold analogue (IPr)AuCl (**2**) and reported its catalytic competency for carbene transfer reactions, in what to the best of our knowledge represents the first example of this metal mediating

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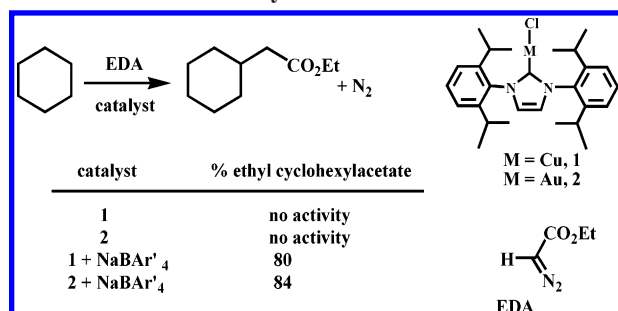
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Scheme 2. Cyclohexane Functionalization with Ethyl Diazoacetate (EDA) Using (IPr)MCl and NaBAR₄ as the Catalyst Precursors



such a transformation.⁹ With this recent finding, all metals in groups 8–11 have now been reported to decompose a diazo compound with the subsequent transfer of a carbene unit.¹⁰ Despite these interesting catalytic performances, the selective activation of primary C–H bonds by this method still remains a challenge, with the notable exceptions in reactions mediated by rhodium⁴ and silver.^{7e,f} With this specific selectivity in mind, we decided to investigate the potential of complexes **1** and **2** as precatalysts for the insertion of EDA into the carbon–hydrogen bonds of alkanes.

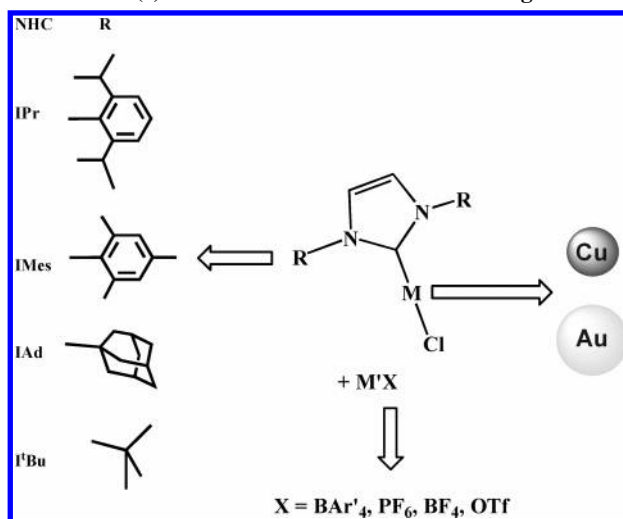
Results and Discussion

Initial catalytic tests were carried out using cyclohexane, as the model substrate, in the presence of **1** or **2**. Not surprisingly, no EDA was consumed under these conditions, even after a few hours. This is in agreement with the previously reported behavior of **1**. In the present (NHC)MCl precatalyst systems, we have proposed⁸ a cationic active species bearing a chloride counterion. The formation of an ionic, catalytically active species in situ proved feasible in the presence of donor substrates (olefins, amines, alcohols). However, the low donor ability of cyclohexane precluded, in the present case, the formation of the catalytic species. Therefore, the active catalytic species was generated by using an equimolar mixture of **1** or **2** and the sodium salt of the well-known noncoordinating anion tetrakis-(3,5-bis(trifluoromethyl)phenyl)borate, BAR₄ (Scheme 2).¹¹ The use of this additive rendered the transformation effective with high yields (based on EDA: 80% for **1** and 84% for **2**). NMR studies of the crude products carried out after reaction completion showed resonances identical to those observed when **1** or **2** was reacted with NaBAR₄ in the absence of EDA and/or alkane. This experiment suggests that catalyst death or deactivation does not occur readily in the present system.

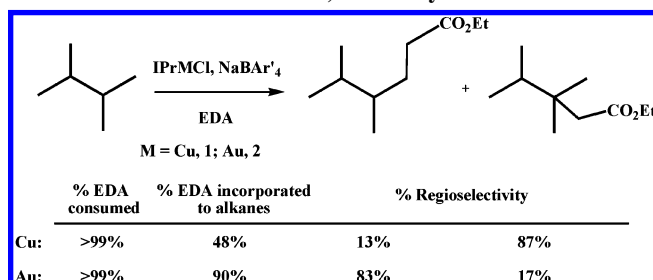
Having demonstrated the capabilities of this system to promote the insertion of the carbene :CHCO₂Et group into the C–H bond of cyclohexane, we then performed a study with a family of precatalyst formed varying the metal, the halide scavenger, and the NHC ligand (Scheme 3), to observe their independent effect on the catalytic reaction. To explore such effects, we chose 2,3-dimethylbutane as the substrate, where both tertiary and primary C–H bonds are available.

Effect of the Metal: Cu versus Au. In good accord with the previous observations with cyclohexane, no reaction of 2,3-

Scheme 3. Variables that Affect the Catalytic Process: (a) Nature of the Metal; (b) the R Group of the NHC Ligand; and (c) the Anion X of the Halide Scavenger



Scheme 4. Dependence of the Chemo- and Regioselectivity on the Metal (Cu, Au) in the Insertion of :CHCO₂Et into the C–H Bonds of 2,3-Dimethylbutane



dimethylbutane and EDA was observed in the presence of **1** and **2**. However, in the presence of equimolar amounts of NaBAR₄, the desired insertion into C–H bonds took place (Scheme 4). The use of copper- or gold-based catalysts induced different degrees of both chemo- and regioselectivities. Thus, only a 48% conversion (based on EDA) into the functionalized products was obtained with the Cu catalyst, whereas high (90%) conversions were observed in the Au case. The remaining EDA was converted into a mixture of diethyl fumarate and maleate. More interestingly, the regioselectivity of the reaction is completely reversed from copper to gold. The insertion into the tertiary C–H bond is clearly favored by **1** + NaBAR₄, while the gold catalyst led to a very high selectivity (83%) toward the derivative formed from the insertion into the primary sites. To our knowledge, this is the highest value for the regioselectivity toward the primary sites obtained through carbene insertion from diazo compounds. Previous work from this laboratory with a silver-based catalyst gave 59% of the primary activation product,^{7e} and very recently Dias, Lovely, et al observed an 80% regioselectivity for this substrate with a different silver catalyst.^{7f} In the present system, it is also worth mentioning that the observation of a modest 12% product resulting from insertion into the primary sites with the copper complex **1** + NaBAR₄ also constitutes the first example of the activation of such sites with copper. With the results presented herein, the three metals of group 11 have now been shown to induce such a transformation.

The relative regioselectivity obtained with Cu and Au illustrates a higher preference of the gold catalyst for primary over tertiary sites. The case of 2,3-dimethylbutane is very

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Scheme 5. Comparison of the Selectivities of the Styrene Cyclopropanation (top) and Pristane Functionalization (bottom) Using the IPrMCl + NaBAR'₄ Catalyst Precursors

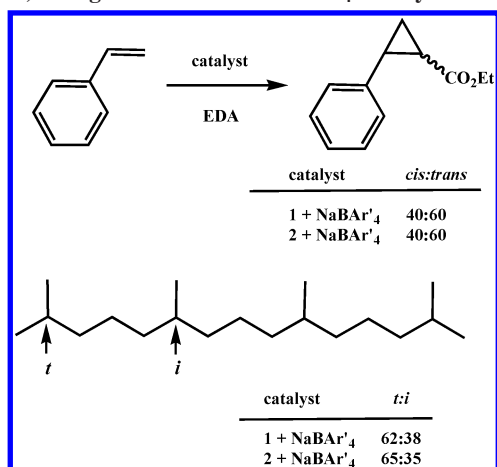


Table 1. Effect of the Counterion X in the Reaction of Ethyl Diazoacetate with 2,3-Dimethylbutane in the Presence of IPrCuCl + MX

MX	EDA consumed (%)	EDA incorp to alkane (%) ^a		
NaBAR' ₄	>99	48	10	90
NH ₄ PF ₆	>99	99	3	97
AgBF ₄	>99	74	nd	99
AgOTf	>99	55	nd	99

^a Diethyl maleate and fumarate accounted for 100% of initial EDA.

^b Percentage corresponds to the product distribution.

illustrative. Tertiary and primary sites were activated, but the regioselectivity was reversed on going from Cu (12:88, primary:tertiary) to Au (83:17, primary:tertiary). Since the unique variation in both experiments (Scheme 4) is the metal center, it seems obvious that the explanation for such a different behavior must be focused on this specific feature. Initially, one could argue that the main difference between the copper and gold catalysts could be the volume of the catalytic pocket. However, we have collected data that play down the role of this factor. As shown in Scheme 5, we employed catalytic amounts of **1** and **2** in two related experiments, corresponding to an addition (styrene cyclopropanation) and to an insertion (using 2,6,10,14-tetramethylpentadecane, pristane) of ethyl diazoacetate. In the case of styrene, the *cis:trans* ratio of cyclopropanes obtained was identical in both cases.¹² A similar result was found when pristane was employed as substrate. This result is obtained by examining the observed product ratio formed from the insertion of EDA into the tertiary sites (t, terminal; i, internal tertiary C–H bonds).^{7b} Since the selectivity in both reactions is supposed to be largely influenced by the size of the catalytic pocket, these data support the proposal that, despite the different atomic size of the metal center, the volume of the catalytic pocket is quite similar for both catalysts. Therefore, the observed differences in the regioselectivities shown in Table 1 must be attributed, mainly, to electronic effects.

Effect of the Counterion. The second variable that we studied is the effect of the anion in the halide scavenger employed. We have carried out a series of experiments in which the catalyst was generated by direct reaction of equimolar amounts of the complex IPrCuCl and one of the following

Table 2. Reaction of 2,3-Dimethylbutane and Ethyl Diazoacetate in the Presence of (NHC)AuCl and NaBAR'₄ as the Catalyst

NHC ligand	EDA consumed (%)	EDA incorp to alkane (%) ^a		
IPr	>99	85	83	17
IAd	>99	74	60	40
I ^t Bu	>99	61	53	47
IMes	>99	25	32	68

^a Diethyl fumarate and maleate accounted for total amount of initial EDA.

^b Regioselectivity as distribution of products.

salts: NaBAR'₄, AgBF₄, NH₄PF₆, and AgOTf, with the results shown in Table 1. It is clear that the use of different counterions has an effect on both the chemo- and regioselectivity. The PF₆[−]-containing precatalyst gave quantitative yields, whereas only 48% was obtained with the BAR'₄ counterion. However, the latter provided a 10% regioselectivity toward the primary insertion, whereas the triflate and tetrafluoroborate precatalysts were completely selective toward the tertiary sites. To ascertain the nature of the species formed from the reaction of IPrCuCl and the salts shown in Table 1, we have independently performed the reaction of IPrCuCl and the halide scavengers on a synthetic scale. The reaction of equimolar amounts of **1** and the salts, at room temperature, in acetonitrile, has allowed the isolation of a series of complexes of general formula [IPrCu(NCMe)]X, for X = BAR'₄, BF₄, or PF₆. In the case of the use of silver triflate, no coordinated acetonitrile has been detected, the spectroscopic data being consistent with the formulation IPrCuOTf. These four compounds have been characterized by NMR spectroscopy; their spectra are quite simple (see Experimental Section). Once characterized, these were tested as catalysts in the reaction of EDA and 2,3-dimethylbutane, in a series of experiments identical to those previously carried out with mixtures of IPrCuCl + MX. No significant differences between the two catalyst generation methods were observed, a fact that we interpret as evidence of the cationic moiety IPrCu⁺ as the active catalytic species. This is in good accord with previous work from this laboratory.⁸

Effect of the NHC Ligand. Once the influence of the metal and the anion of the halide scavenger in the catalytic reaction had been examined, we wondered whether the use of different NHC ligands, with a given metal–counterion pair, could affect the regioselectivity of this reaction. Studies of the electronic and steric effects of the NHC ligands have been recently performed.¹³ To gauge such effects in the present system, we conducted experiments with four complexes of general formula (NHC)AuCl¹⁴ (Scheme 3), again with 2,3-dimethylbutane as substrate. As shown in Table 2, there is a significant ligand effect both in the chemo- and in the regioselectivity of the reaction. In fact, there is a correlation between both selectivities: the higher the chemoselectivity, the higher the amount of products derived from the insertion into the primary sites. Since the electronic properties of these four NHC ligands have been proposed as very similar,¹³ it is reasonable to assume that the steric pressure around the catalytic pocket must be the main effect governing the regioselectivity.¹⁵ Such pressure should follow the order IPr > IAd > I^tBu > IMes. The unique reactivity

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(15) Steric pressure around the reactive center is different than overall steric parameter, as it involves substituents and their specific spatial orientation.

(12) Cyclopropanation of styrene using **2** as the catalyst provided not only the cyclopropane products but also the compounds formed by the formal insertion into the aromatic sp² C–H bonds. See ref 9.

Table 3. Catalytic Functionalization of Alkanes with Ethyl Diazoacetate in the Presence of $\text{IPrAuCl} + \text{NaBAR}'_4$

Substrate	% EDA incorp. to alkane ^a	Regioselectivity ^b		
		Primary C-H Products	Secondary C-H Products	Tertiary C-H Products
pentane	70	26%	55% 19%	---
hexane	78	24%	47% 29%	---
	91	83%	---	17%
	80	30% 18%	41% (both)	11%
	65	53% 5%	36%	6%
	65	83%	11%	6%

^a Diethyl maleate and fumarate accounted for 100% of initial EDA. ^bPercentage corresponds to the product distribution.

profile displayed by IPr in terms of yield and selectivity is evident, and we are presently evaluating the chemo-/regioselectivities of related ligands in this transformation.

Expansion to Other Alkanes. The results shown in the previous sections show that the highest conversions as well as the highest regioselectivities toward the primary sites have been achieved with a combination of the IPr ligand, the BAR'_4 sodium salt as the halide scavenger, and gold as the metal center. From these data, we employed this precatalyst (**2** + NaBAR'_4) with a series of alkanes, linear and branched, in their reaction with ethyl diazoacetate. Table 3 displays the results observed of this study. A consistent trend for the entire series is observed: this catalytic system *promoted the functionalization of primary C–H bonds in all substrates employed*. As mentioned above, the activation of alkane C–H bonds by the method of carbene insertion has been described with few metals as catalyst. This number is even smaller for systems capable of performing the insertion into the primary C–H bonds: only rhodium-based⁴ and very recently silver-based^{7e,f} catalysts are known to promote such functionalization. The direct comparison of the data shown in Table 3 with those reported with rhodium or silver indicates that the degree of primary site functionalization reached with this gold-based system is higher. Design of more selective catalysts can be envisaged on the basis of the availability of different NHC ligands, a task we are currently tackling in our laboratories.

In conclusion, we report on the catalytic behavior of (NHC)MCl complexes, in the presence of an halide scavenger, for the efficient insertion of the $:\text{CHCO}_2\text{Et}$ group (from ethyl diazoacetate) into C–H bonds of alkanes including primary C–H bonds. The regioselectivity is influenced by (i) the metal, (ii) the stereoelectronic properties of the ligand, and (iii) the counterion employed. The facile tunability of the present system is a key feature we are further exploring in this and related catalytic transformations.

Experimental Section.

General Procedures. NMR spectra were run in a Varian Mercury 400 MHz spectrometer, 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 hydrocarbons, the halide scavengers, and the EDA were purchased from Aldrich and employed without any further purification. The (NHC)MCl complexes were prepared according to literature methods.^{8,9}

Syntheses of the Complexes $[\text{IPrCu}(\text{NCMe})]\text{X}$ and $[\text{IPrCu}(\text{OTf})]$. Complex **1** was dissolved in acetonitrile, and 1 equiv of the salt (NaBAR'_4 , AgBF_4 , NH_4PF_6 , or AgOTf) was added to the solution. After stirring for 5 min, the mixture was filtered off, and the filtrate was concentrated under vacuum until a precipitate appeared. In the case of NH_4PF_6 the reaction mixture was stirred overnight. Cooling at -20°C overnight provided microcrystalline material of the complexes in 75–85% yields. NMR spectra were recorded in CDCl_3 , showing the formation of the desired compounds.

Selected NMR Data. $[\text{IPrCu}(\text{CH}_3\text{CN})]\text{BF}_4$. ^1H NMR (400 MHz, CDCl_3): δ 7.53 (t, $J = 7.8$ Hz, 2 H); 7.33 (d, $J = 7.8$ Hz, 4 H), 7.2 (s, 2 H), 2.49 (heptet, $J = 6.8$ Hz, 4 H), 2.1 (s, 3 H); 1.23 (m, 24 H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): 145.7, 134.2, 131.1, 124.5, 123.9, 29.0, 24.9, 24.2, 2.3. $[\text{IPrCu}(\text{CH}_3\text{CN})]\text{PF}_6$. ^1H NMR (400 MHz, CDCl_3): δ 7.54 (t, $J = 7.8$ Hz, 2 H); 7.36 (d, $J = 7.8$ Hz, 4 H), 7.22 (s, 2 H), 2.5 (heptet, $J = 6.8$ Hz, 4 H), 1.23 (m, 24 H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): 145.7, 134.2, 131.3, 124.6, 123.9, 28.9, 24.9, 24.1, 2.4. $^{31}\text{P}\{^1\text{H}\}$ NMR (CDCl_3): $-\text{143.4}$ (heptet, $J = 95$ Hz). $[\text{IPrCu}(\text{CH}_3\text{CN})]\text{BAR}'_4$. ^1H NMR (400 MHz, CDCl_3): δ 7.68 (s, 8 H), 7.54–7.46 (overlapping, 6 H); 7.3 (d, $J = 7.8$ Hz, 4 H), 7.21 (s, 2 H), 2.43 (heptet, $J = 6.8$ Hz, 4 H), 1.91 (s, 3 H); 1.2 (d, $J = 6.4$ Hz, 12 H); 1.2 (d, $J = 6.4$ Hz, 12 H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): 162 (q, $^1J_{\text{B-C}} = 25$ Hz), 145.7, 135.0, 131.3, 129.1 (q, $^2J_{\text{C-F}} = 34$ Hz), 124.9 (q, $^2J_{\text{C-F}} = 271$ Hz), 124.6, 124.3, 117.7, 28.9, 25.1, 23.8, 2.17. $[\text{IPrCu}(\text{OTf})]$. ^1H NMR (400 MHz, CDCl_3): δ 7.52 (t, $J = 7.8$ Hz, 2 H), 7.32 (d, $J = 7.8$ Hz, 4 H), 7.2 (s, 2 H), 2.5 (heptet, $J = 6.8$ Hz, 4 H), 1.2 (m, 24 H). $^{13}\text{C}\{^1\text{H}\}$ NMR (100 MHz, CDCl_3): 145.6, 134.2, 131.1, 124.6, 123.9, 28.9, 24.8, 24.2.

Catalytic Experiments. The catalysts were generated in situ (or in some cases previously isolated as in the previous paragraph) in the following manner: the complex **1** or **2** (0.025 mmol) was dissolved in a mixture of 5 mL of CH_2Cl_2 and 5 mL of the substrate, and 1 equiv of the halide scavenger was added to the solution. After 15 min of stirring, 0.5 mmol of EDA was added from a syringe pump (dissolved in CH_2Cl_2) for 12 h. After 1 h of additional stirring, the mixture was analyzed by GC and GC-MS. The volatiles were

removed and the residue analyzed by NMR and GC. The characterization of the products has previously been reported (refs 7a–c,e).

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