

Silver-Catalyzed C-C Bond Formation between Methane and Ethyl Diazoacetate in Supercritical CO₂

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Even in the context of hydrocarbon's general resistance to selective functionalization, methane's volatility and strong bonds pose a particular challenge. We report here that silver complexes bearing perfluorinated indazolylborate ligands catalyze the reaction of methane (CH₄) with ethyl diazoacetate (N₂CHCO₂Et) to yield ethyl propionate (CH₃CH₂CO₂Et). Key to the reaction's success is the use of supercritical carbon dioxide (scCO₂) as the solvent. Although the catalyst is only sparingly soluble in CH₄/CO₂ mixtures, presently optimized conditions result in a 19 % of ethyl propionate (based on starting quantity of the diazoester) at 40 °C over 14 h.

The use of methane, the lightest hydrocarbon and primary component of natural gas, as a source for fine chemicals production remains an appealing goal on scientific, economic and environmental grounds (1-4). Transition metal catalyzed C-H bond activation is a promising approach to achieve functionalization of the strong and relatively inert C-H bonds of alkanes more generally. In one possible scenario, these reactions proceed by metal-promoted C-H bond oxidative cleavage followed by insertion of a suitable X group into the M-C bond and release of the functionalized product by means of reductive elimination of the C-X-H unit (5). Individual reaction steps for this and related catalytic cycles have been widely reported (6), but a major challenge has been that removal of the functionalized fragments from the metal coordination sphere is often unfavorable, due to the robustness of the M-C bonds. Only

a few examples of catalytic C-H bond functionalizations of alkanes with transition metal complexes have been described (4, 6), including C-H/C-D exchange (7), dehydrogenation (8), tandem dehydrogenation-metathesis (9) dehydrogenative silylation (10) and borylation (11) processes.

None of the scarce examples mentioned above have led to the catalytic functionalization of methane. On the other hand, an early example of the distinct, electrophilic activation was Shilov's landmark discovery of the conversion of alkanes, including methane, into alcohols under acidic conditions (12). Using Shilov-type chemistry (Figure 2), Periana and co-workers have developed catalytic systems based on mercury (13), platinum (14) or gold (15) that convert methane into methyl bisulfate, usually in sulphuric acid media and at high temperature. Subsequently, Periana (16) and Pombeiro (17) independently reported conversion of methane into acetic acid, respectively using palladium- and vanadium-based catalysts.

A different approach to the catalytic functionalization of alkanes involves electrophilic X-atom insertion into C-H bonds, described for the heteroatom insertion into methane C-H bonds catalyzed by superacids, with hydrogen peroxide, ozone or chlorine as X sources (18, 19). In transition metal catalyzed versions of this approach a polarized M-X bond is formed prior to the X-atom insertion into the C-H bond. This process implies no direct metal-alkane interaction and, consequently, release of the reaction products does not require cleavage of strong M-C or M-X bonds. An example is the metal catalyzed carbene insertion into a hydrocarbon C-H bond by reaction with a diazocompound (20, 21) which has been successfully applied to simple alkanes using rhodium (22, 23) and group 11 (copper, silver, gold) metal-based catalysts (24). However, it is yet unknown for methane.

We have previously designed highly electrophilic silver catalysts based on perbrominated tris(pyrazolyl)- or perfluorinated tris(indazolyl)borate ligands. We first reported the functionalization of alkanes (25) using ethyl diazoacetate as the carbene source, catalyzed by $[\text{Tp}^{\text{Br}_3}\text{Ag}]_2$ (**1**); $[\text{F}_{21}\text{-Tp}^{4\text{Bo},3\text{CF}_3}\text{Ag}(\text{OCMe}_2)]$ (**2**) was found later (26) to be more active and selective toward primary sites (Figure 1). With pentane as a representative example, both catalysts, as well as the new complex $[\text{F}_{27}\text{-Tp}^{4\text{Bo},3\text{CF}_2\text{CF}_3}\text{Ag}(\text{thf})]$ (**3**) (thf = tetrahydrofuran), that we report herein, led to mixtures of the three products resulting from the insertion of the carbene $:\text{CHCO}_2\text{Et}$ into the primary and the secondary C-H bonds.

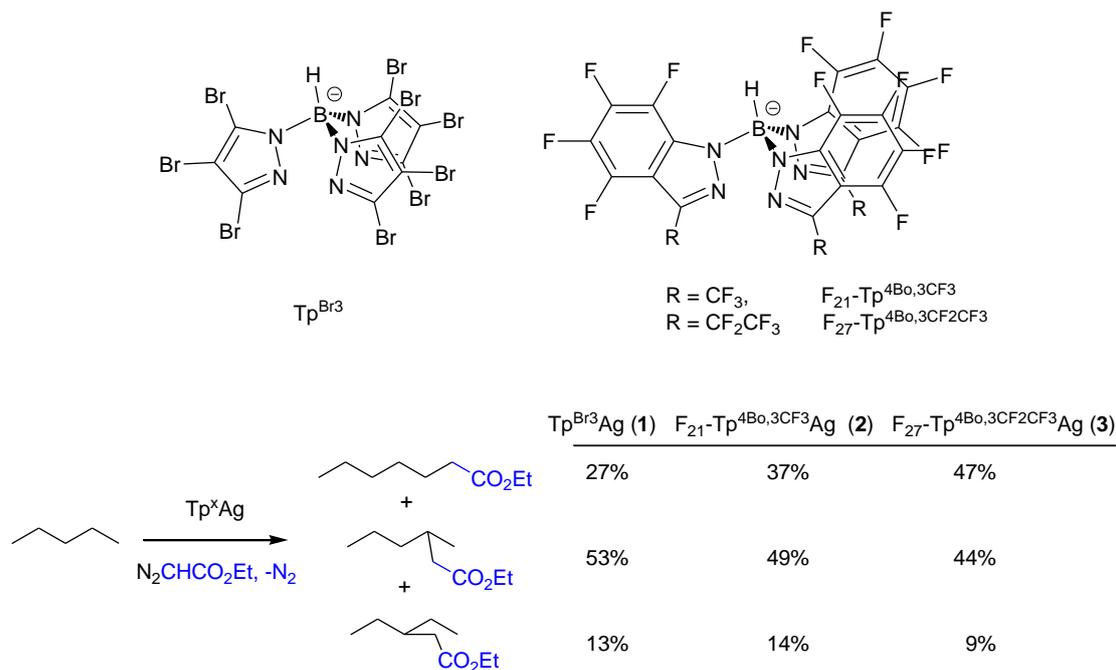


Fig. 1. Functionalization of C-H bonds by carbene insertion from ethyl diazoacetate using Tp^xAg complexes as catalysts. Percentage corresponds to yields after complete consumption of the initial EDA (the remaining up to 100 % of initial EDA correspond to diethyl fumarate and maleate, formed by catalytic dimerization of EDA). Bo = benzo.

Challenges arose in applying this methodology to methane, due to its gaseous nature ($p_C = 45.96$ atm, $T_C = -82.7$ °C), its low solubility in organic solvents and its poor solvating ability. Moreover carbene insertion into any C-H bond present in the reaction medium would be faster than reaction of the stronger bonds in methane, and chlorinated solvents do not represent a viable alternative, as these silver catalysts preferentially induce the insertion of $:CHCO_2Et$ units into C-X (X = halogen) bonds (28).

In the present contribution, these difficulties have been circumvented by the use of supercritical carbon dioxide (scCO₂) as the reaction solvent, given its inertness toward reactive intermediates, its complete miscibility with methane, its strong solvating ability towards ethyl diazoacetate (EDA) and its excellent transport properties (29). We performed an initial set of experiments by placing ethyl diazoacetate and one of the silver complexes **1-3** (0.03 mmol of silver, initial molar ratio Tp^xAg:EDA 1:100) into separate polypropylene containers fitted into a high pressure reactor thermostated at 40 °C (30). The system was charged with 160 atm of methane and then pressurized up to 250 atm with carbon dioxide. A 0.96 n_{CH₄}:n_{CO₂} ratio of gases was determined by weighing the reactor immediately after charging with each of them. Observation through the reactor sapphire windows revealed that the solid catalyst did not dissolve

catalyst was employed), but pleasingly complexes **2** and **3** as catalyst precursors gave 0.198 and 0.204 mmol of EP, respectively. These results demonstrate the ability of complexes **2** and **3** to catalyze the formal insertion of the carbene :CHCO₂Et into a C-H bond of methane, with the formation of a new C-C bond.

As indicated above, the catalyst seems to remain undissolved in the reaction vessel. In fact, the weight of the catalyst-containing vessel appeared unchanged before and after the experiment. However, a homogeneous process catalyzed by small amounts ($<10^{-3}$ mmol) of the silver complex cannot be ruled out. To gain further insight a catalytic experiment was run in which the volatile products of the reaction were collected in a cold trap. The catalyst vessel was then removed and the reactor washed with CH₂Cl₂. No measurable variation in the initial catalyst weight could be recorded, and Inductively Coupled Plasma Mass Spectroscopy (ICP-MS) analysis of the combined extracts from the cold trap and the reactor revealed the presence of *ca.* 4.2×10^{-4} mmol of silver (corresponding to dissolution of less than 0.1 mg of the starting complex). We then performed a series of experiments identical to that above but with varied relative pressures of methane and carbon dioxide, with the amount of dissolved silver complex **3** again determined by ICP-MS (Table 1). The exact ratio of methane and carbon dioxide was determined by weight.

These studies revealed that the solubility of the silver catalyst is enhanced by increasing the proportion of carbon dioxide in the fluid, in good agreement with the well-known capacity of scCO₂ to dissolve fluorinated compounds (29). Specifically, a linear correlation pertained between the catalyst concentration in the fluid and the

Table 1. Methane functionalization with ethyl diazoacetate using complex **3** as catalyst. Reactions conditions described in Figure 2.

Entry	P _{CH₄} :P _{CO₂}	n _{CH₄} /n _{CO₂} *	mmol EP	mmol Ag dissolved	TON**
1	160:90	0.96	0.204	0.00042	478
2	125:125	0.88	0.130	0.0043	30
3	80:170	0.34	0.140	0.023	6
4	0:250	0	0	0.031	0

*Determined by weight (see Supporting Online Material). ** Defined as mmol EP / mmol Ag dissolved.

relative $n_{\text{CH}_4}:n_{\text{CO}_2}$ ratio (Figure 3). Unfortunately, the corresponding conversion to the desired product (EP) decreased with rising CO_2 :methane ratios. We attribute this result to higher catalyst concentrations promoting not only the formation of ethyl propionate but also the competing formation of undesired diethyl fumarate and maleate products via carbene dimerization. The latter transformation is enhanced at lower hydrocarbon concentration and at high catalyst loadings (32).

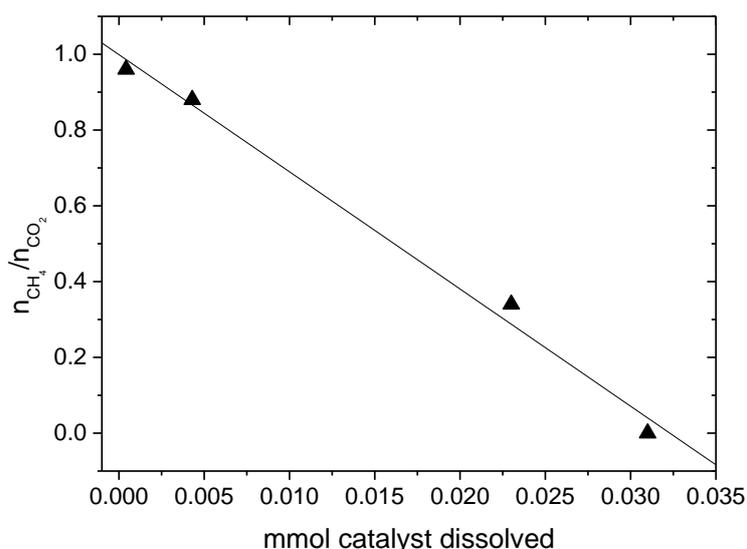


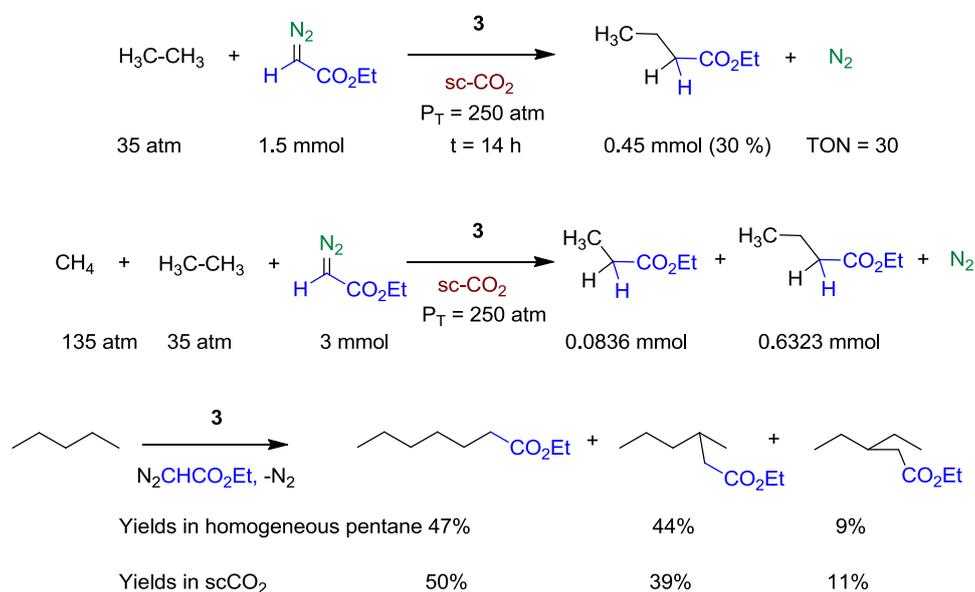
Fig. 3. Dependence of the solubility of $\text{F}_{27}\text{-Tp}^{4\text{Bo.3CF}_2\text{CF}_3}\text{Ag}$ (**3**) on the fluid composition.

An initial catalyst loading of only 0.007 mmol (instead of 0.03 mmol) was employed in additional experiments while keeping a 1:100 ratio of [**3**]: [EDA] under 160 atm of methane and CO_2 up to a total pressure of 250 atm. After 14h, 0.134 mmol of EP were detected by GC, along with some unreacted EDA. In a second run, with a longer reaction time of 70 h, 0.162 mmol of EP were obtained. It is worth pointing out that those values represent 19% and 23% yields into EP based in the initial amount of EDA, the remaining initial diazocompound being converted into diethyl fumarate and maleate.

We found that complex **3** also catalyzed reaction of EDA with ethane (Scheme 1) affording ethyl butyrate over 14 h with a TON value of 30, under a total pressure of 250 atm (35 atm of ethane; $n_{\text{CO}_2}:n_{\text{C}_2\text{H}_6} = 7.35$). The lower hydrocarbon pressure needed in this case is in agreement with the lower BDE of the ethane C-H bond (*ca* 101

kcal/mol vs. 104.5 kcal/mol in methane) (27). Complex **3** completely dissolved under these reaction conditions. The low TON value results from the low ethane concentration in the mixture. In order to establish the relative reactivities of methane and ethane, a competition experiment was performed at 40 °C using 0.03 mmol of **3** in a mixture of 135 atm of CH₄, 35 atm of C₂H₆ and a balance of CO₂ to reach a total pressure of 250 atm (Scheme 1). The distribution of products favored the ethane derivative by a factor of ca 7.5. Taking into account the experimentally determined mass ratio of the gases, and the statistical correction for the number of C-H bonds, the selectivity C-H_{methane}:C-H_{ethane} was estimated to be ca 1:14 (see Supporting Material for details).

Scheme 1. Methane, ethane and pentane functionalization.



Pentane C-H functionalization was also investigated in scCO₂. In 2 mL of pentane under 200 atm of CO₂ at 40 °C, catalyst **3** (0.03 mmol) partially dissolved (ca. 60% according to ICP-MS studies) to yield a mixture of insertion products (Scheme 1), with a regioselectivity virtually identical to that obtained under homogeneous conditions using pentane as both solvent and reactant (Fig. 1). These results suggest that the insertion mechanism operative in homogeneous solution is conserved in the supercritical medium.

A plausible mechanism for C-H functionalization of methane (and other hydrocarbons) involves metal-catalyzed N₂ elimination from the diazo substrate

followed by carbene transfer (33, 34) mediated by a highly electrophilic metal carbene intermediate (**A** in Figure 4) (35). The reactivity of **A** toward C-H bonds gives a product distribution that is governed, at least in part, by the bond dissociation energy of the C-H bonds, justifying the observation that ethane functionalization is favored over methane by a factor of about 14.

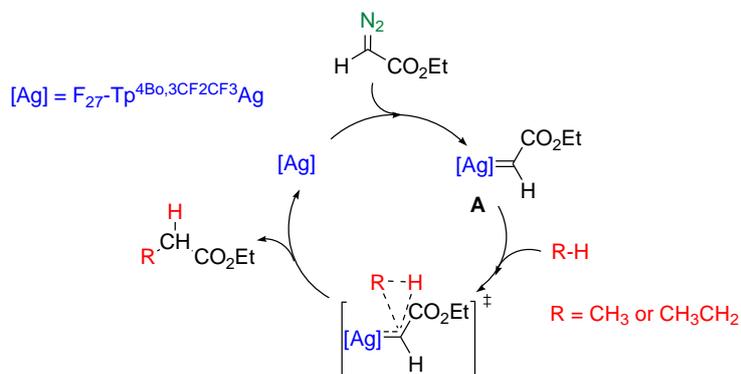


Fig. 4. Mechanistic hypothesis for silver-catalyzed alkane functionalization by ethyl diazoacetate.

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