Silver-Catalyzed Functionalization of Esters by Carbene Transfer: The Role of Ylide Zwitterionic Intermediates

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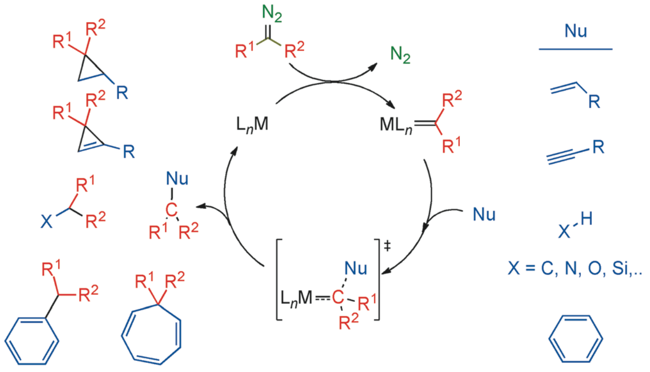
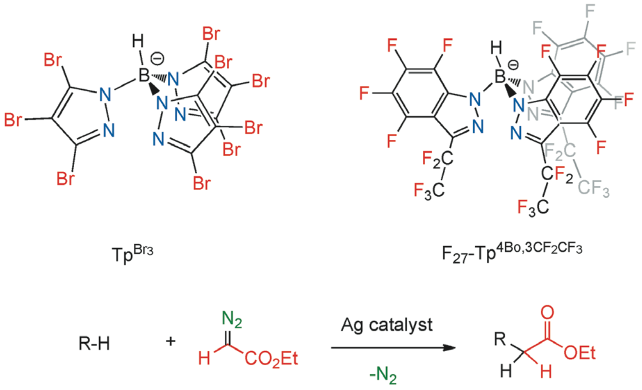
The reaction of esters with ethyl diazoacetate catalyzed by the complex [F_{27}–$Tp^{4Bo,3CF_2CF_3}$Ag(acetone)] generates α-(acyloxy)acetates in moderate to high yields. This is a novel transformation in the context of carbene-transfer reactions from diazo compounds that, according to experimental and theoretical data, is suggested to occur through zwitterionic intermediates.

Catalytic carbene-transfer reactions from diazo compounds constitute a significant transformation[1] in organic synthesis. Unsaturated or saturated substrates (Scheme 1) are effectively transformed, usually under mild conditions, into value-added products. This process is based on the formation of a strongly electrophilic metallocarbene intermediate that reacts with nucleophiles to give the desired products. One of the most significant examples is the functionalization of C–H bonds of nonactivated alkanes.[2,3] Our group has been involved in this area for the last decade and has developed a family of copper and silver complexes supported by tris(pyrazolyl)borate or tris(indazolyl)borate ligands with various substituents, Tp^x, that have been employed as catalysts in such reactions.[4,5] The most efficient catalysts are those based on silver associated with ligands bearing electron-withdrawing groups, which thus lead to complexes in which the metal has strong electrophilic character. This is the case of [Tp^{Br_3}Ag(acetone)][5a] and [F_N–$Tp^{4Bo,3C_nF_{2n+1}}$Ag(L)] ($N=6n+15$; $n=1, 2, 3, 4, 6$; L = acetone or THF).[5b,c] The diazo compound used as the carbene source is ethyl diazoacetate (EDA). Thereby, nonactivated alkanes R–H, including methane, despite their large C–H bond dissociation energies,[6] have been converted into esters R–CH_2CO_2Et (Scheme 2).[7]



Scheme 1. General transition-metal-catalyzed carbene transfer to saturated and unsaturated substrates. Nu = Nucleophile.

Given that this strategy employs the substrate as the solvent in most cases, a consecutive double insertion of the carbene group into the same molecule of the alkane has never been observed. Therefore, we decided to study the influence of Tp^xAgL complexes on the reaction of esters R–CH_2CO_2Et with EDA with the aim of observing such unprecedented double insertion. Instead, to our surprise, a novel transformation was found: the formation of α-(acyloxy)acetates by using [F_N–$Tp^{4Bo,3C_nF_{2n+1}}$Ag(L)] complexes as catalysts. This reaction has been reported with amides, esters, and aldehydes,[1] but to the



Scheme 2. The catalytic functionalization of an alkane by silver-catalyzed carbene transfer from ethyl diazoacetate.

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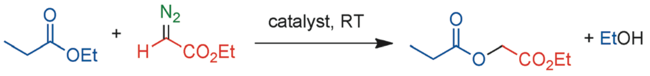
best of our knowledge, the use of esters for such a purpose is unknown.

Results and Discussion

In a first set of experiments, we treated ethyl propionate (4 mL), as the model substrate and the reaction solvent, with EDA (0.25 mmol) in the presence of either [Tp^{Br_3}Ag(acetone)] or [F$_{27}$–Tp^{4Bo,3CF_2CF_3}Ag(acetone)] (0.01 mmol) as the catalyst (Scheme 3). After 2 h, the diazo compound was completely consumed, as inferred by analysis of the reaction mixture by GC and ^{1}H NMR spectroscopy. NMR spectroscopy studies showed that 2-ethoxy-2-oxoethyl propionate was the product formed from the carbene-transfer reaction with both [Tp^{Br_3}Ag(acetone)] and [F$_{27}$–Tp^{4Bo,3CF_2CF_3}Ag(acetone)]. This product was formed in 17 and 66% yield (determined by ^{1}H NMR spectroscopy), respectively, and all of the EDA was consumed. Some insertion of the carbene group was observed into the alkyl chain of the ester to account for the entire initial amount of the diazo compound. GC and NMR spectroscopy studies also confirmed the presence of ethanol as a stoichiometric byproduct relative to the amount of the (acyloxy)acetate derivative formed.



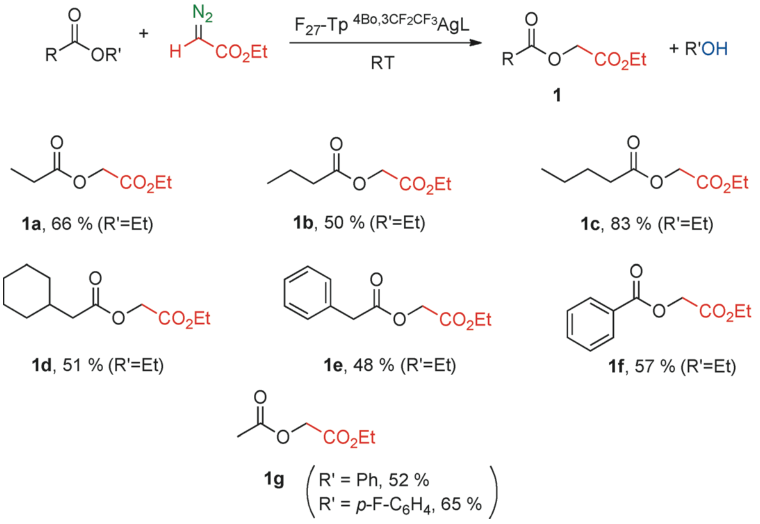
Catalyst	Yield [%]
Tp^{Br_3}Ag(acetone)	17
F$_{27}$-Tp^{4Bo,3CF_2CF_3}Ag(acetone)	66

Scheme 3. Reaction of ethyl propionate with EDA catalyzed by several Tp^{x}Ag complexes.

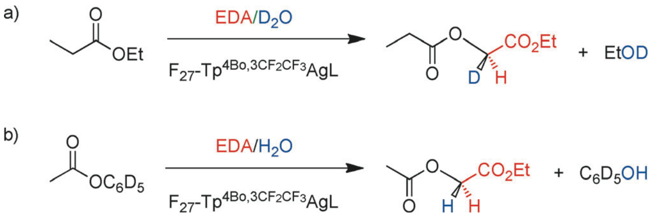
To examine the scope of this transformation, a series of aliphatic and aromatic esters were treated with EDA in the presence of [F$_{27}$–Tp^{4Bo,3CF_2CF_3}Ag(acetone)] as the catalyst. After 2 h, analysis of the crude reaction mixture by GC and ^{1}H NMR spectroscopy showed the formation of the corresponding α-(acyloxy)acetate (RCO$_2$CH$_2$CO$_2$Et) in moderate to high yields (Scheme 4). The remaining amount of the initial EDA led to products resulting from carbene insertion into the alkyl C–H bonds of the esters. In the case of aromatic esters, the Buchner reaction (addition to the aromatic double bond followed by ring expansion to cycloheptatriene)[1] was also observed to a minor extent. α-(Acyloxy)acetates were the major products in all cases. Notably, EtOH was detected during the synthesis of **1 a**–**1 f**, whereas for **1 g**, phenol and *p*-fluorophenol were observed in the crude reaction mixture.

α-(Acyloxy)acetates are normally employed as intermediates in the synthesis of α-hydroxy β-keto esters (Chan rearrangement),[8] a significant transformation in the context of the preparation of several antibiotics and natural products.[9,10] These compounds are commonly prepared by condensation of a halo ester with a carboxylic acid in anhydrous potassium carbonate. To our knowledge, their formation upon direct reaction of a diazo compound and an ester is unknown, despite the fact that other related substrates such as aldehydes, ketones, and amides have been employed as reactants with several diazo reagents.[1]

The formation of alcohols and phenols during the course of the reaction could be related to the presence of water in the reaction medium. To obtain information on the mechanism that controls this transformation, two experiments were performed. First, the reaction of ethyl propionate with EDA by using [F$_{27}$–Tp^{4Bo,3CF_2CF_3}Ag(acetone)] as the catalyst was performed in the presence of added D$_2$O (Scheme 5 a). The ^{2}H NMR spectrum of this reaction showed a doublet ($^2J_{H,D}$ = 2.5 Hz) centered at 4.6 ppm, which was assigned to the –OC(H)*D*COO– group. A singlet located at 5.4 ppm corresponding to EtOD was also observed. In line with these results, the ^{1}H NMR spectrum showed a 1:1:1 triplet ($^2J_{H,D}$ = 2.5 Hz) at 4.56 ppm corresponding to the –OC(*H*)DCOO– group (see the Supporting Information). In the second experiment, we employed the deuterated ester CH$_3$COOC$_6$D$_5$ as the substrate (Scheme 5 b); C$_6$D$_5$OH was the only deuterated compound observed in the ^{2}H NMR spectrum at the end of the reaction, in agreement with the role of water in this reaction.

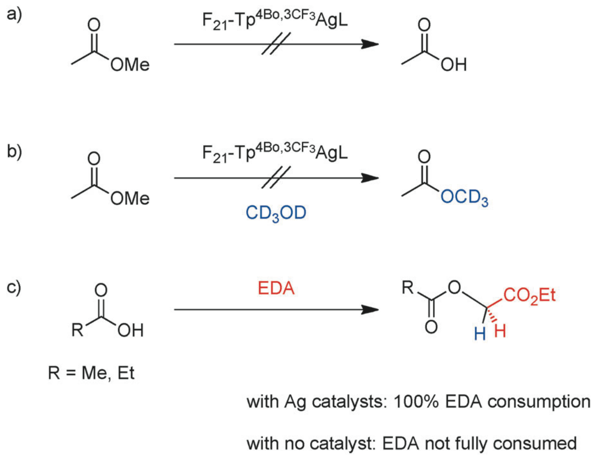


Scheme 4. Carbene-transfer reaction to esters catalyzed by F$_{27}$–Tp^{4Bo,3CF_2CF_3}Ag(acetone). General conditions: [Tp^{x}AgL] (0.01 mmol), EDA (0.25 mmol), ester (4 mL), 2 h, RT. Reactions were quantified by GC by using calibration curves.



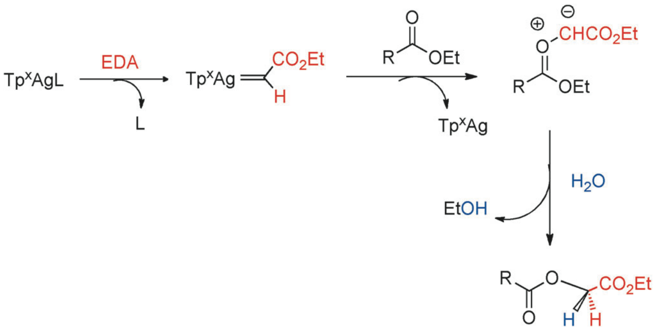
Scheme 5. Proposed mechanism for the formation of α-(acyloxy)acetates from esters and EDA.

The products formed in this reaction are identical to those that would be formed from the direct reaction of the parent organic acids of the esters and ethyl diazoacetate by direct, metal-catalyzed carbene transfer to the OH bond. Given the high electrophilic character of those silver complexes,[5c] we wondered if the metal center would induce ester hydrolysis and subsequent functionalization of the acid. To test our hypothesis, methyl acetate was stirred with catalytic amounts of $[F_{21}\text{–}Tp^{4Bo,3CF_3}Ag(acetone)]$ for 24 h. NMR spectroscopy studies (^1H and ^{13}C) showed no evidence of hydrolysis after that time, and the ester remained unchanged in solution and no acetic acid was detected (Scheme 6a). Alternatively such hydrolysis could be involved in an equilibrium lying to the left, and consequently, small, undetectable amounts of the acid would be available. To evaluate this possibility, a second experiment was performed in which methyl acetate, $[F_{21}\text{–}Tp^{4Bo,3CF_3}Ag(acetone)]$, and $[D_4]$MeOH were stirred at room temperature for 72 h. Monitoring of the reaction by ^2H NMR spectroscopy showed no incorporation of any OCD_3 into methyl acetate (Scheme 6c); this confirmed the stability of the ester in the presence of the silver complex. Therefore, we can exclude the participation of the free acid in this transformation. However, for the sake of completeness, we performed the reaction of acetic and propionic acids with EDA in the presence and absence of silver complexes. We found that with the added catalyst, ethyl diazoacetate was completely consumed and the corresponding products were obtained (Scheme 6c), whereas the direct reaction without the catalyst provided the products in lower yields and without complete consumption of the diazo reagent.[11] In any case, this transformation has no impact on the transformation of the esters on the basis of the above experiments.



Scheme 6. Mechanistic experiments.

As mentioned above, intermolecular reactions of esters and diazo compounds such as these are unprecedented, in contrast to the known reactions of aldehydes, amides, and ketones with diazo reagents.[1,12] In the latter examples, the formation of carbonyl ylide intermediates from a metal–carbene species has been invoked to explain the catalytic transformation. On that basis and that of the experiments shown in Schemes 5 and 6, a plausible reaction pathway would involve the formation of a silver metallocarbene that reacts with the ester to give a carbonyl ylide (Scheme 7). Attack of H_2O would deliver one H to the ylide moiety, whereas the elimination of the R group of the ester with the O–H group would afford the observed alcohols. However, some questions arise from this proposal:



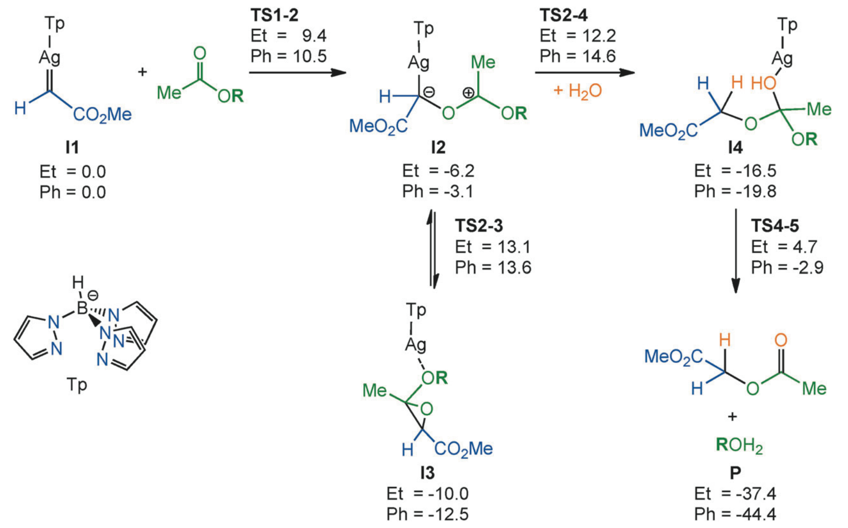
Scheme 7. Proposed mechanism for the formation of α-(acyloxy)acetates from esters and EDA.

1) Is the ylide a true intermediate?
2) What is the fate of the electrophilic silver moiety Tp^xAg after carbene transfer?
3) Does it influence hydrolysis of the ylide and ethanol formation?

To address the intimate nature of this reaction and to provide answers to the above questions, a DFT study was performed. We computationally studied a model system consisting of AcOR (R = ethyl, phenyl) plus methyl diazoacetate plus TpAg plus water. With respect to the experimental system, Tp [Tp = hydrotris(pyrazolyl)borate] replaces $F_{27}\text{–}Tp^{4Bo,3CF_2CF_3}$ and methyl diazoacetate replaces ethyl diazoacetate. Scheme 8 summarizes the computational results. Only the most representative intermediates and transition states (TS) are mentioned. Detailed energy profiles are given in the Supporting Information.

Reaction from metallocarbene **I1** to product **P** takes place through two key intermediates, **I2** and **I4**. Intermediate **I2** is a zwitterionic complex that can be viewed formally as the coordination of the hypothetical ylide molecule to the silver complex. Intermediate **I4** appears after incorporation and cleavage of the water molecule and contains the OH^- and H^+ fragments bound to the zwitterion mentioned above. The mechanism is further complicated by the presence of intermediate **I3**, an epoxide that can be reached from **I2**, but which seems to be a dead end.

The relative energies of intermediates and transition states, also reported in Scheme 8, are compatible with a reaction occurring at room temperature. The case of ethyl acetate (R = Et) is detailed here. Intermediate **I2** should convert mostly into **I4** rather than into **I3** (**TS2–4**, 12.2 kcal mol^{-1}; **TS2–3**, 13.1 kcal mol^{-1}). With such close barriers (separated by 0.9 kcal mol^{-1}), part of the molecules would convert into epoxide **I3**, but they



Scheme 8. Computationally postulated mechanism for the formation of α-(acyloxy)acetates from esters and EDA. Energies given in [kcal mol^{-1}].

would evolve also into the main product by overcoming a barrier of 23.1 kcal mol^{-1} (from **I3** to **TS2–3**). For phenyl acetate, a slightly higher barrier of 27.1 kcal mol^{-1} should be overcome from **I3**. Although this value could be lowered by method or model improvement, we consider the overall mechanism to be correct.

The most complex part of Scheme 8 is the transformation of **I2** into **I4**. The highest energy point for this step is **TS2–4**; this does not correspond to water splitting but to the dissociation of the zwitterion, which is then replaced by water as a ligand on silver. Remarkably, the whole process takes place in the coordination sphere of silver. There is no free ylide in solution, and water splitting is assisted by the silver complex. Uncatalyzed water cleavage would cost over 40 kcal mol^{-1}. More details on this alternative mechanism are provided in the Supporting Information. Thus, the silver catalyst plays a double role: it is required for the generation of carbene **I1** and for the water-splitting process.

An alternative pathway could involve the coordination of the diazo reagent to the silver center by the N donor, which would therefore activate the methine carbon atom on the ester for electrophilic attack. In this case, no metallocarbene intermediate would be formed, and the catalysis would be triggered by the Lewis acid nature of Ag^{I}. We are not confident in this route because a well-known Lewis acid such as scandium(III) trifluoromethanesulfonate [Sc(OTf)$_3$] does not catalyze the reaction of EDA with ethyl acetate and because the reactions described in this contribution are not catalyzed to the same extent with copper analogues, despite the higher acidity of Cu^{I} relative to that of Ag^{I}. For the sake of completeness, we also examined this possibility computationally. We computed the three transition states shown in Figure 1. The first of them corresponds to the reaction of the diazoacetate with the TpAg catalyst to lead to metallocarbene **I1**, and its free energy is 18.4 kcal mol^{-1} above the separate reactants. The other two transition states correspond to possible pathways not involving this metallocarbene. One of them is a cycloaddition that forms C–N and C–O bonds at the same time to result in a five-membered ring. The other one is an S$_N$2-like transition state in which the nitrogen atom of EDA is substituted by the oxygen atom of the ester. Both of these two alternative processes are unfavorable with very high energies, 45.7 and 52.8 kcal mol^{-1}, respectively, above the separate reactants. So, the formation of metallocarbene **I1** is expected, and the reaction should proceed afterwards through the path outlined in Scheme 8.

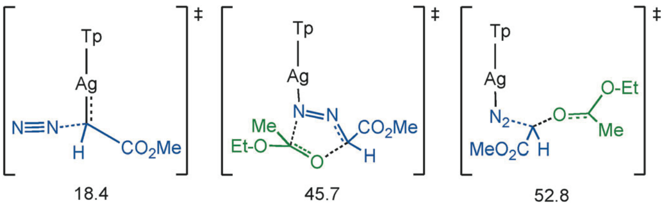


Figure 1. Computed transition states for the direct reaction between TpAg and other species in the medium. Energies given in [kcal mol^{-1}].

Conclusions

We found that the silver complex [F$_{27}$–Tp$^{4\mathrm{Bo},3\mathrm{CF_2CF_3}}$Ag(acetone)] catalyzes the reaction of alkyl and aryl esters with ethyl diazoacetate to give α-(acyloxy)acetates, and this constitutes a novel reaction based on the strategy of metal-catalyzed decomposition of diazo compounds and subsequent carbene transfer. Mechanistic studies showed the involvement of carbonyl ylide intermediates as well as the metal center for the incorporation of a water molecule to afford the final products.

Experimental Section

General methods

All preparations and manipulations were performed either under an oxygen-free nitrogen atmosphere by using conventional Schlenk techniques or inside a dry box. All the esters and ethyl diazoacetate (EDA) were purchased from Aldrich or Alfa Aesar and were employed without further purification. The complexes [Tp$^{\mathrm{Br_3}}$]Ag(thf)[5a] and [F$_{27}$–Tp$^{4\mathrm{Bo},3\mathrm{CF_2CF_3}}$]Ag(COMe$_2$)[5b,c] were prepared according to literature procedures. NMR spectroscopy experiments were run with Agilent Technologies 400 and 500 MHz spectrometers. Chemical shift values for ^{1}H and ^{13}C are reported as δ values (ppm) relative to internal SiMe$_4$. GC studies were performed by using Varian 3900 and Varian Saturn 2100T instruments.

Catalytic reactions with esters

General procedure: $[F_{27}\text{–}Tp^{4Bo,3CF_2CF_3}]Ag(COMe_2)$ (10.4 mg, 0.01 mmol) was dissolved in the corresponding ester (4 mL) and EDA (27 µL, 0.25 mmol) was added in one portion. The solution was stirred for 2 h at RT until complete consumption of EDA, as verified by GC. Reaction yields were determined by GC by using calibration curves performed with synthesized samples; these data were corroborated by NMR spectroscopy by using 1,4-dimethoxybenzene as an internal standard.

Reaction of ethyl propionate and EDA in D_2O

$[F_{27}\text{–}Tp^{4Bo,3CF_2CF_3}]Ag(COMe_2)$ (10.4 mg, 0.01 mmol) was dissolved in the desired ester (4 mL) and then D_2O (10 µL, 0.55 mmol) and EDA (27 µL, 0.25 mmol) were added at once. The solution was stirred for 2 h at RT until complete consumption of EDA, as detected by GC. The product was characterized by NMR spectroscopy.

Synthesis of $[D_5]$phenyl acetate

A flask was charged with $[D_6]$phenol (1 g, 0.01 mol) and dry dichloromethane (5 mL) as the solvent. Acetyl chloride (0.78 mL, 0.011 mol) was added over 0.5 h at 0°C, and then triethylamine (2.5 mL, 0.018 mol) was incorporated into the mixture, which was stirred overnight. The mixture was then transferred to a separatory funnel and extracted with a saturated solution of sodium bicarbonate. The combined organic layer was washed with a saturated sodium chloride solution and then dried with magnesium sulfate. After filtration, the volatiles were removed under vacuum. The product was characterized by NMR spectroscopy.

Computational details

The reaction was modeled by considering the reactants methyl diazoacetate (model of ethyl diazoacetate) and the real substrates ethyl acetate and phenyl acetate. The catalyst $Tp^{F21}Ag$ was simplified to Tp by removing the second rings and the CF_2CF_3 groups. Calculations were performed by using the Gaussian 09 package.[13] The B97D method[14] was used together with the standard 6-31+G(d,p) basis sets[15] to describe all atoms, except for Ag for which the large core scalar relativistic pseudopotentials by Dolg et al. were used coupled to a double-ζ quality basis set.[16] Full geometry optimizations were performed in methyl acetate, which was used as the model solvent under the SMD approach ($\varepsilon = 6.9$).[17] The nature of the stationary points was characterized by a vibrational analysis performed within the harmonic approximation at 298 K and 101.3 kPa. Transition states were identified by the presence of one imaginary frequency and minima by a full set of real frequencies. Isomers of the organic fragments were searched by using Macromodel[18] and reoptimized with Gaussian 09 at the level described above; the geometries of the lower organic energy isomers were used to search manually the isomers for the metal complexes. All energies presented correspond to free energies [kcal mol^{-1}] in solution.

Acknowledgements

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