CHEMISTRY
A EUROPEAN JOURNAL

FULL PAPER

DOI: 10.1002/chem.201203566

Functionalization of Non-activated C−H Bonds of Alkanes: An Effective and Recyclable Catalytic System Based on Fluorinated Silver Catalysts and Solvents

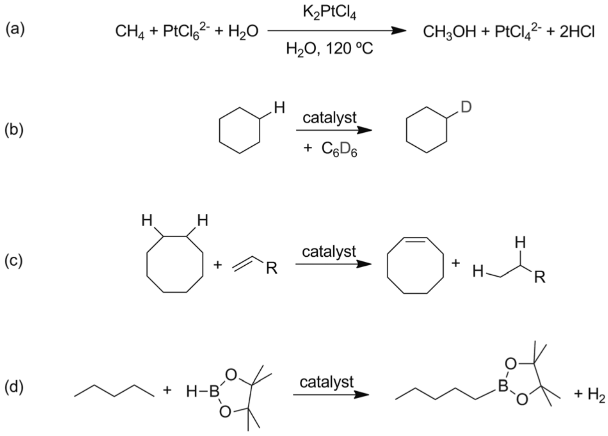
M. Ángeles Fuentes,[a] Bianca K. Muñoz,[b, c] Kane Jacob,[b, c] Laure Vendier,[b, c]
Ana Caballero,*[a] Michel Etienne,*[b, c] and Pedro J. Pérez*[a]

Abstract: The complexes F_n-$Tp^{4Bo,3R_f}Ag(L)$ (F_n-$Tp^{4Bo,3R_f}$ = a perfluorinated hydrotris(indazolyl) borate ligand; L = acetone or tetrahydrofuran) efficiently catalyze the functionalization of non-activated alkanes such as hexane, 2,3-dimethylbutane, or 2-methylpentane by insertion of $CHCO_2Et$ units (from N_2CHCO_2Et, ethyl diazoacetate, EDA) into their C−H bonds. The reactions are quantitative (EDA-based), with no byproducts derived from diazo coupling being formed. In the case of hexane, the functionalization of the methyl C−H bonds has been achieved with the highest regioselectivity known to date with this diazo compound. This catalytic system also operates under biphasic conditions by using fluorous solvents such as Fomblin or perfluorophenanthrene. Several cycles of catalyst recovery and reuse have been performed, with identical chemo- and regioselectivities.

Keywords: alkanes · biphasic catalysis · carbenes · fluorous catalysis · silver

Introduction

The functionalization of non-activated alkanes remains one of the most challenging goals of modern catalysis,[1] because their high inertness usually preclude their conversion into value-added products by simple reactions and under mild conditions. Yet, their availability as raw materials make them attractive starting materials in reactions in which new C−C or C−X bonds are formed.[2] Despite considerable efforts in the last few decades, only a few catalytic systems based on organometallic activations that operate with simple, non-activated C−H bonds have been described; among them, the electrophilic activation (Scheme 1 a),[3] the C−H/C−D exchange (Scheme 1 b),[4] the alkane dehydrogenation (Scheme 1, c),[5] and the alkane borylation (Scheme 1 d).[6] These transformations occur through the interaction of the carbon–hydrogen bonds with the metal center, and the subsequent formation of M−C and/or M−H bonds.[7]



Scheme 1. Alkane C−H bond catalytic-functionalization processes involving the formation of M−C and/or M−H bonds.

Precisely, the formation of these linkages has been invoked as the explanation for the lack of a larger number of catalytic systems based on this strategy: their high stability and inertness usually precludes the formation of catalytic cycles beyond their formation.[1,2] The alkane oxygenation reaction has also provided neat alkane functionalization although through different pathways.[1]

---

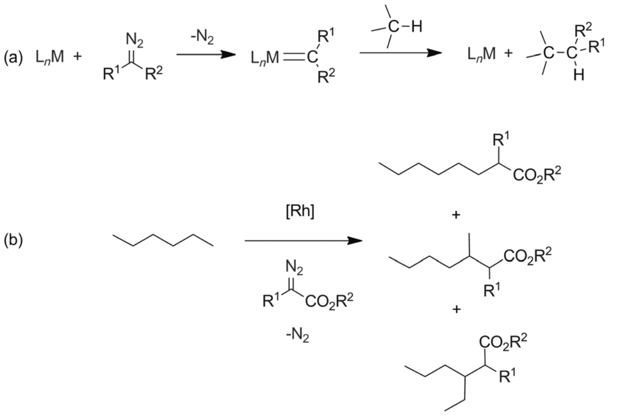
[a] M. Á. Fuentes, Dr. A. Caballero, Prof. P. J. Pérez
Laboratorio de Catálisis Homogénea
Departamento de Química y Ciencia de los Materiales
Unidad Asociada al CSIC, Centro de Investigación
en Química Sostenible (CIQSO)
Campus de El Carmen s/n
Universidad de Huelva, 21007-Huelva (Spain)
Fax: (+34) 959219942
E-mail: ana.caballero@dqcm.uhu.es
perez@dqcm.uhu.es

[b] Dr. B. K. Muñoz, K. Jacob, Dr. L. Vendier, Prof. M. Etienne
CNRS; LCC (Laboratoire de Chimie de Coordination)
205, route de Narbonne, BP44099
F-31077 Toulouse Cedex 4 (France)

[c] Dr. B. K. Muñoz, K. Jacob, Dr. L. Vendier, Prof. M. Etienne
Université de Toulouse
UPS, INPT; LCC
F-31077 Toulouse Cedex 4 (France)
E-mail: michel.etienne@lcc-toulouse.fr

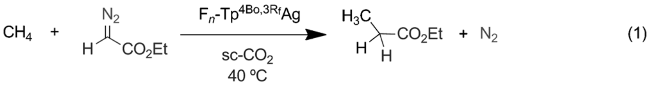
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201203566.

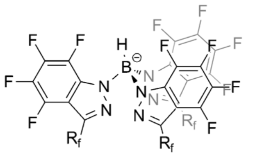
An alternative approach consists of avoiding the direct interaction of the C–H bonds with the metal center, the functionalization of the alkane being achieved through the interaction of an electrophilic ligand with that bond. Thus, the well-known capabilities of a number of transition-metal complexes to form metallocarbene species upon reaction with diazocompounds has been employed in that sense,[8] the carbene unit being transferred and inserted into the C–H bond (Scheme 2a). This methodology was first reported by Scott and DeCicco[9] nearly 40 years ago, and was later expanded, but yet not exhaustively exploited.[10] Subsequent work by the groups of Noels,[11] Callot,[12] Davies[13] and Che[14] demonstrated the potential of dirhodium tetraacetate and related Rh_2L_4 complexes to catalyze the functionalization of plain, non-activated alkanes such as *n*-hexane into carboxylate derivatives (Scheme 2b).



Scheme 2. Carbon–hydrogen bond functionalization by carbene insertion following the diazo-compound strategy.

Our group has developed catalytic systems for the alkane functionalization by the carbene insertion methodology based on Group 11 metal complexes,[10c,d] bearing either tris(pyrazolyl)borate or *N*-heterocyclic carbene ligands. Along the years we have improved the catalytic activity of our catalysts, by 1) increasing the electrophilic nature of the metal center by employing anchoring ligands with low donor capabilities and 2) providing steric protection of the metal center. As a result of such progress, we have recently described the catalytic functionalization of methane,[15] the most inert alkane, by using silver complexes containing perfluorinated tris(indazolyl)borate ligands as catalysts [Eq. (1)], ethyl diazoacetate as the carbene source and supercritical carbon dioxide as the reaction medium.


$$\mathrm{CH_4} + \mathrm{N_2{=}CH{-}CO_2Et} \xrightarrow[\text{sc-CO}_2,\ 40\,^{\circ}\text{C}]{F_n\text{-Tp}^{4Bo,3R_f}\text{Ag}} \mathrm{H_3C{-}CH_2{-}CO_2Et} + \mathrm{N_2} \qquad (1)$$

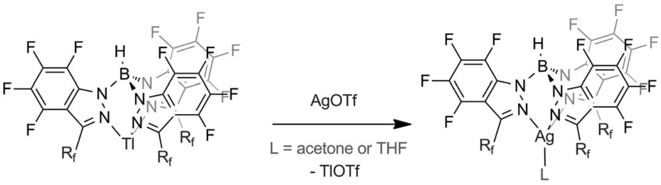


$R_f = CF_3$, F_{21}-$Tp^{4Bo,3CF_3}$
$R_f = CF_2CF_3$ F_{27}-$Tp^{4Bo,3CF_2CF_3}$

The results described to date by the different groups[10–14,16] involved in this area demonstrate that this methodology constitutes an efficient tool for the effective carbon–hydrogen bond functionalization of plain, non-activated alkanes. However, to facilitate the use of these catalysts for such a purpose, an effective catalyst separation methodology should be developed. Very few reports based on biphasic catalysis with ionic liquids[17] or fluorinated solvents,[18] met with limited success, since the catalytic activity dropped significantly from the first cycle to the next. Based on the latter report by Endres and Maas[18] with fluorinated Rh_2L_4 complexes, and the interest of fluorous biphasic catalysis (FBC)[19] in terms of green chemistry, we decided to study the potential of a series of perfluorinated tris(indazolyl)borate complexes of silver in the alkane functionalization reaction with ethyl diazoacetate under FBC conditions. We have found that with the appropriate election of the catalysts and of the fluorous phase, quantitative (diazo-based) conversions of alkanes into the corresponding carboxylate derivatives can be achieved for several cycles of catalyst separation and reuse, yet an unprecedented feature in the area of alkane functionalization by carbene insertion.

Results and Discussion

Synthesis and characterization of the silver complexes F_n-$Tp^{4Bo,3R_f}AgL$: Previous work from our laboratories led to the synthesis of the complexes F_{21}-$Tp^{4Bo,3CF_3}$Ag(acetone) (**1**)[20,21] and F_{27}-$Tp^{4Bo,3CF_2CF_3}$Ag(THF) (**2**).[15] Given the well-known solubility of complexes containing fluorinated ponytails in fluorinated solvents, we decided to synthesize three more complexes with ligands similar to those above, bearing longer fluorinated alkyl chains with three, four, and six carbon atoms. As a general protocol, complexes **3**–**5** were synthesized under inert atmosphere by the reaction of the corresponding thallium salts TlF_n-$Tp^{4Bo,3R_f}$ with silver triflate in acetone or tetrahydrofuran as solvent (Scheme 3), in the same manner as that previously reported for compounds **1**



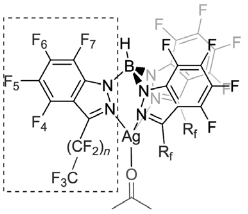
$R_f = CF_3$ (F_{21}-$Tp^{4Bo,3CF_3}$)$Ag(CH_3COCH_3)$ **1**
$R_f = CF_2CF_3$ (F_{27}-$Tp^{4Bo,3CF_2CF_3}$)Ag(THF) **2**
$R_f = (CF_2)_2CF_3$ (F_{33}-$Tp^{4Bo,3(CF_2)_2CF_3}$)Ag(L) **3**
$R_f = (CF_2)_3CF_3$ (F_{39}-$Tp^{4Bo,3(CF_2)_3CF_3}$)$Ag(CH_3COCH_3)$ **4**
$R_f = (CF_2)_5CF_3$ (F_{51}-$Tp^{4Bo,3(CF_2)_5CF_3}$)$Ag(CH_3COCH_3)$ **5**

Scheme 3. Synthesis of the tris(indazolyl)borate silver complexes employed in this work.

and **2**. Yields of the isolated product ranged within 72–91 %; the complexes being obtained as white solids of composition F_n-$Tp^{4Bo,3R_f}$Ag(solvent).

Table 1 contains selected ^{19}F NMR data for compounds **3**–**5**. At room temperature, most resonances appear as broad signals, a feature that is enhanced when the fluorinated ponytail is enlarged. This effect is similar to that reported for perfluorobutyric and perfluorooctanoic acids.[22] The spectra are quite simple since they contain, in all cases, a unique set of resonances for the three indazolyl rings, as a consequence of the C_{3v} symmetry in solution. The four different aromatic C–F nuclei give rise to four resonances within the range $\delta = -166$ to -145 ppm, whereas the fluorinated ponytails exhibit two distinct sets of resonances for the CF_3 (at ca. $\delta = -82$ ppm) and the CF_2 groups. For the latter, the fluorine nuclei resonate around $\delta = -120$ ppm, and each added CF_2 group shifts to higher field. Thus, for the longer chain in F_{51}-$Tp^{4Bo,3(CF_2)_5CF_3}$Ag(CH_3COCH_3) (**5**), the four CF_2 resonances appear at $\delta = -107.8$, -122.1, -122.1 -123.5 and -126.9 ppm, for $C_\alpha F_2$, C_β, C_γ, C_δ, and C_ε, respectively, with C_α directly bonded to the indazolyl skeleton.

Table 1. ^{19}F NMR chemical shifts (δ) and J_{FF} (Hz) of silver complexes **3**–**5** in [D$_6$]acetone.



	3a	**4**	**5**
F_4	-145.47 (m)	-145.32 (m)	-145.14 (m)
F_5	-166.68 (br s)	-166.29 (dd) $^3J_{F5-F6} = {}^3J_{F5-F4} = 17$	-165.58 (dd) $^3J_{F5\text{-}F6} = {}^3J_{F5-F4} = 15$
F_6	-155.12 (br s)	-154.78 (br s)	-154.13 (br s)
F_7	-161.31 (br s)	-160.67 (br s)	-158.2 (br s)
CF_2	C_α -108.17 (br s) C_β -127.17 (d) $^4J = 9.8$	C_α -107.58 (m) C_β -123.32 (br s) C_γ -126.34 (br s)	C_α -107.79 (m) $C_{\beta,\gamma}$ -122.13 (m) C_δ -123.55 (m) C_ε -126.96 (m)
CF_3	-81.13 (m) $^4J = 9.8$	-82.17 (t) $^4J = 10$	-81.86 (t) $^4J = 10.5$

Crystallization of complex F_{33}-$Tp^{4Bo,3(CF_2)_2CF_3}$Ag(THF) (**3b**) gave single crystals suitable for X-ray diffraction studies. As shown in Figure 1, the silver center is coordinated to the three nitrogen donors of the tris(indazolyl)borate ligand in a κ^3-N,N',N'' fashion, as well as to the O atom of tetrahydrofuran. The angles around the metal center indicate a distorted tetrahedral geometry. The distances and angles observed are very similar to those already reported for other silver complexes containing perfluorinated indazolylborate ligands. The average Ag–N distance of 2.387 Å compares well with that of $Tp^{(CF_3)_2}$Ag(THF)[23] (2.364 Å) and it is slightly longer than the same distance in F_{21}-Tp^{4Bo,CF_3}Ag(CO)[20] (2.310 Å). The Ag–O bond length of 2.228(5) Å is also very close to that of $Tp^{(CF_3)_2}$Ag(THF) (2.234(4) Å). A C_2F_5 end (C21–C22) in the C_3F_7 chain of the N3–N4 indazolyl group was highly disordered and was only isotropically refined.

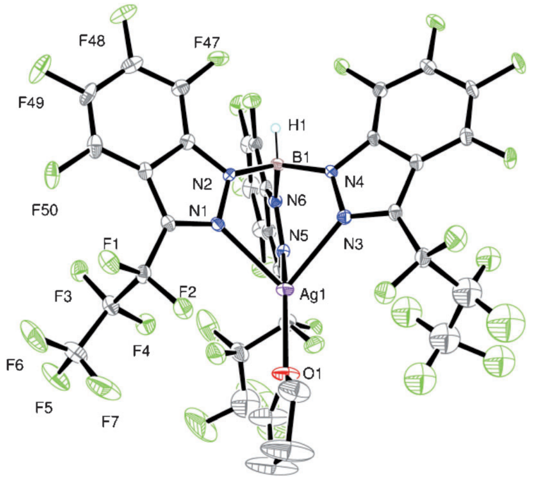


Figure 1. ORTEP diagram of F_{33}-$Tp^{4Bo,3(CF_2)_2CF_3}$Ag(THF) (**3b**). Hydrogen atoms have been omitted for clarity. Thermal ellipsoids are drawn at the 30 % probability level. Selected bond lengths [Å] and angles [°] Ag1–O1 2.228(5), Ag1–N1 2.378(5), Ag1–N3 2.377(5), Ag1–N5 2.406(5); O1-Ag1-N3 131.10(19), O1-Ag1-N1 126.3(2), N3-Ag1-N1 83.47(17), O1-Ag1-N5 134.90(19), N3-Ag1-N5 80.69(17), N1-Ag1-N5 81.67(17).

We have already reported that the reaction of complex **1** with carbon monoxide in dichloromethane formed the corresponding silver-carbonyl adduct F_{21}-Tp^{4Bo,CF_3}Ag(CO),[20] a non-classical carbonyl complex[24] that was spectroscopically and structurally characterized. The IR spectrum (dichloromethane) showed a strong absorption centered at 2167 cm^{-1} assigned to ν(CO), slightly higher than that reported for $Tp^{(CF_3)_2}$Ag(CO) in the same solvent ($\nu(CO) = 2164$ cm^{-1}).[23b] Similar treatment of complexes **2**–**5** with CO led to the in situ observation of the corresponding series of carbonyl adducts F_n-$Tp^{4Bo,3R_f}$Ag(CO), for which we focused on their ν(CO) values. As shown in Scheme 4, there is no change in the ν(CO) value with the number of CF_2 groups sequentially added to the ligand. Therefore, this group of ligands provides similar electron density at the metal center, whereas somewhat different steric requirements could be expected.

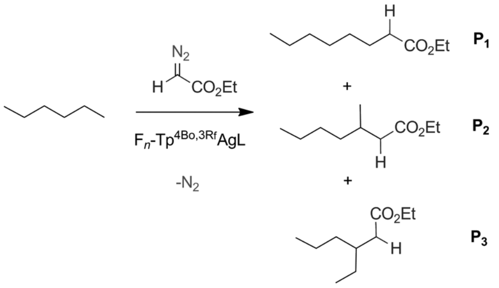
Catalytic functionalization of carbon–hydrogen bonds of alkanes under homogeneous conditions: The tris(indazolyl)borate silver complexes **1**–**5** have been employed as catalysts

$$F_n\text{-}Tp^{4Bo,3R_f}Ag(L) \xrightarrow[CO]{CH_2Cl_2} F_n\text{-}Tp^{4Bo,3R_f}Ag(CO)$$

F_n-$Tp^{4Bo,3R_f}$	ν(CO) (cm^{-1})
F_{21}-$Tp^{4Bo,3CF_3}$	2167
F_{27}-$Tp^{4Bo,3CF_2CF_3}$	2166
F_{33}-$Tp^{4Bo,3(CF_2)_2CF_3}$	2166
F_{39}-$Tp^{4Bo,3(CF_2)_3CF_3}$	2166
F_{51}-$Tp^{4Bo,3(CF_2)_5CF_3}$	2166

Scheme 4. The IR data (dichloromethane solution) for the series of carbonyl adducts showing similar electron density at silver.

in the reaction of *n*-hexane with ethyl diazoacetate (N_2CHCO_2Et, EDA), by using the alkane as the reaction solvent. Complex **1** had already been tested in this transformation, leading to the formation of a mixture of three products derived from the insertion of the $CHCO_2Et$ group into the three different types of hexane C–H bonds (Scheme 5 and Table 2). This is now being observed with the other four compounds **2**–**5**, that induced the complete chemoselectivity toward the alkane functionalization products; no diethyl fumarate or maleate (derived from the catalytic coupling of two carbene moieties) were detected by GC at the end of the reaction even if the EDA was added in one portion, in contrast with most of the other reported catalytic systems.[8,10] Even more interestingly, the progressive increase of the fluorinated chain-length of the ligand caused an increase of the amount of the product derived from the functionalization of the methyl group, reaching up to 47 % in the case of **5.** This translates to a normalized (per C–H bond) primary/secondary regioselectivity of 1:0.84. Dias and co-workers[16] reported a 1:1.43 ratio for pentane with $Tp^{(CF_3)_2}Ag(THF)$ as the catalyst, a value close to that of complex **1** (1:1.33), also bearing a CF_3 substituent.



Scheme 5. The functionalization of hexane with ethyl diazoacetate by using complexes **1**–**5** as catalysts.

Table 2. Catalytic functionalization of hexane with EDA and complexes **1**–**5** as catalysts.[a]

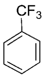
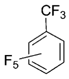
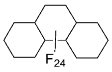
Catalyst	% $\mathbf{P_1}$	% $\mathbf{P_2}$	% $\mathbf{P_3}$	Yield [%]
F_{21}-$Tp^{4Bo,3CF_3}Ag$ (**1**)	36	49	15	> 99
F_{27}-$Tp^{4Bo,3CF_2CF_3}Ag$ (**2**)	44	45	10	> 99
F_{33}-$Tp^{4Bo,3(CF_2)_2CF_3}Ag$ (**3**)	45	43	12	> 99
F_{39}-$Tp^{4Bo,3(CF_2)_3CF_3}Ag$ (**4**)	45	45	10	> 99
F_{51}-$Tp^{4Bo,3(CF_2)_5CF_3}Ag$ (**5**)	47	42	11	> 99

[a] [Ag]/[EDA] = 1:100. Reaction time: 12 h. See the Experimental Section for details. Yields and regioselectivities were determined by GC.

Thus the difference in regioselectivity is a double consequence of electronic and steric effects, an indication for future catalyst design toward enhanced primary functionalization: the more electrophilic and the more sterically crowded the catalyst, the more selective it is for primary C–H bonds. To the best of our knowledge, this is the highest regioselectivity toward the functionalization of primary sites in linear alkanes with this methodology using ethyl diazoacetate as the carbene source. Only Che and co-workers[14] have provided higher regioselectivities by using the much bulkier diazocompound $PhC(N_2)CO_2Et$.

Catalytic functionalization of carbon–hydrogen bonds of alkanes. Screening of the fluorous phase: Having demonstrated the catalytic ability of complexes **1**–**5** for the functionalization of non-activated C–H bonds of alkanes by carbene insertion, we focused on the use of fluorous biphasic conditions. We chose complex **4** as a representative sample of our catalysts and hexane as a probe, with several fluorinated substrates as the fluorous phase: 1,1,1-trifluorotoluene, perfluorotoluene, Fomblin, and perfluorophenanthrene. A series of two cycles (in which the fluorous phase was separated and reused) were then performed, with the results shown in Table 3.

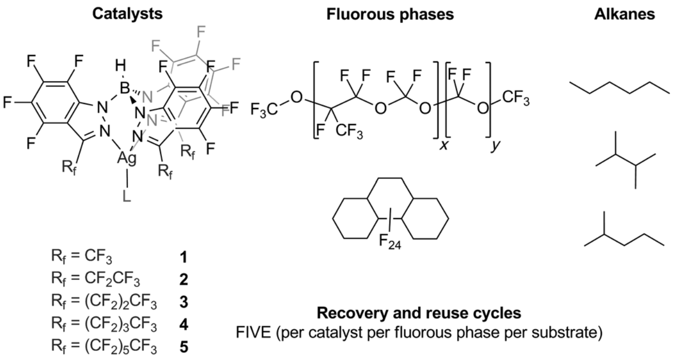
Table 3. Screening of the fluorous phase in the functionalization of hexane with EDA and complex **4** as the catalyst.

Entry	Fluorous phase	Run	% $\mathbf{P_1}$	% $\mathbf{P_2}$	% $\mathbf{P_3}$	Yield [%][a]
1	none	–	45	45	10	> 99
2		1	44	41	15	> 30[b]
		2	44	41	15	> 30[b]
3		1	43	41	16	> 99
		2	43	41	16	> 99
4	Fomblin	1	46	41	13	> 99
		2	44	42	14	> 99
5		1	46	40	14	> 99
		2	49	38	13	> 99

[a] [Ag]/[EDA] = 1:20. Reaction time: 12 h. See the Experimental Section for details. Yields and regioselectivities were determined by GC. [b] Other products from arene ring activation were observed.

With trifluorotoluene (Table 3, entry 2) the functionalization of the arene ring as well as the targeted hexane functionalization was observed. To avoid this undesired reaction, perfluorinated toluene was considered (Table 3, entry 3). Yields and regioselectivity were similar to those in the homogeneous system (Table 3, entry 1). However, the relatively low boiling point of this solvent originated problems during the workup. The next fluorous phases were therefore chosen with high boiling points: Fomblin (Table 3, entry 4), a fluorinated polyester, and perfluorophenanthrene (Table 3, entry 5). In both cases, the reactions with hexane were quantitative into the functionalization products and the regioselectivity almost identical to that of the homogeneous system. On the basis of this screening, the latter two fluorous solvents were chosen for a in depth study of the catalytic activity of complexes **1**–**5** under biphasic conditions with a series of linear and branched alkanes and ethyl diazoacetate as the carbene source.

General catalytic functionalization of alkanes under fluorous conditions: This study has been performed (Scheme 6) with



Scheme 6. Catalysts, fluorous solvents, substrates, and number of cycles used in this study.

three alkanes (hexane, 2,3-dimethylbutane and 2-methylpentane), two fluorous phases (Fomblin and perfluorophenanthrene), and five catalysts (complexes **1**–**5**).

In each case, four to five cycles of catalyst separation and reuse have been carried out to ascertain the degree of recyclability of this catalytic system (Figure 2). Overall, 135 different experiments have been performed, from which the following trends have been extracted. First, the high catalytic activity of complexes **1**–**5** have led to the functionalization of nearly all available different sites in the alkanes investigated. In addition to the already commented three products derived from hexane ($\mathbf{P_1}$–$\mathbf{P_3}$, Scheme 5), two products from 2,3-dimethylbutane ($\mathbf{P_4}$ and $\mathbf{P_5}$, Scheme 7) and four products from 2-methylpentane ($\mathbf{P_6}$–$\mathbf{P_9}$, Scheme 7) have been obtained. As observed previously, only one type of secondary site of 2-methylpentane (that which is remote from the tertiary carbon), could be derivatized.[20]

The general procedure consisted of the dissolution of the catalyst **1**–**5** (0.005 mmol) in the fluorous phase (4 mL) followed by the addition of the alkane (1 mL) and ethyl diazoacetate (0.1 mmol, 20 equiv with respect to the catalyst).

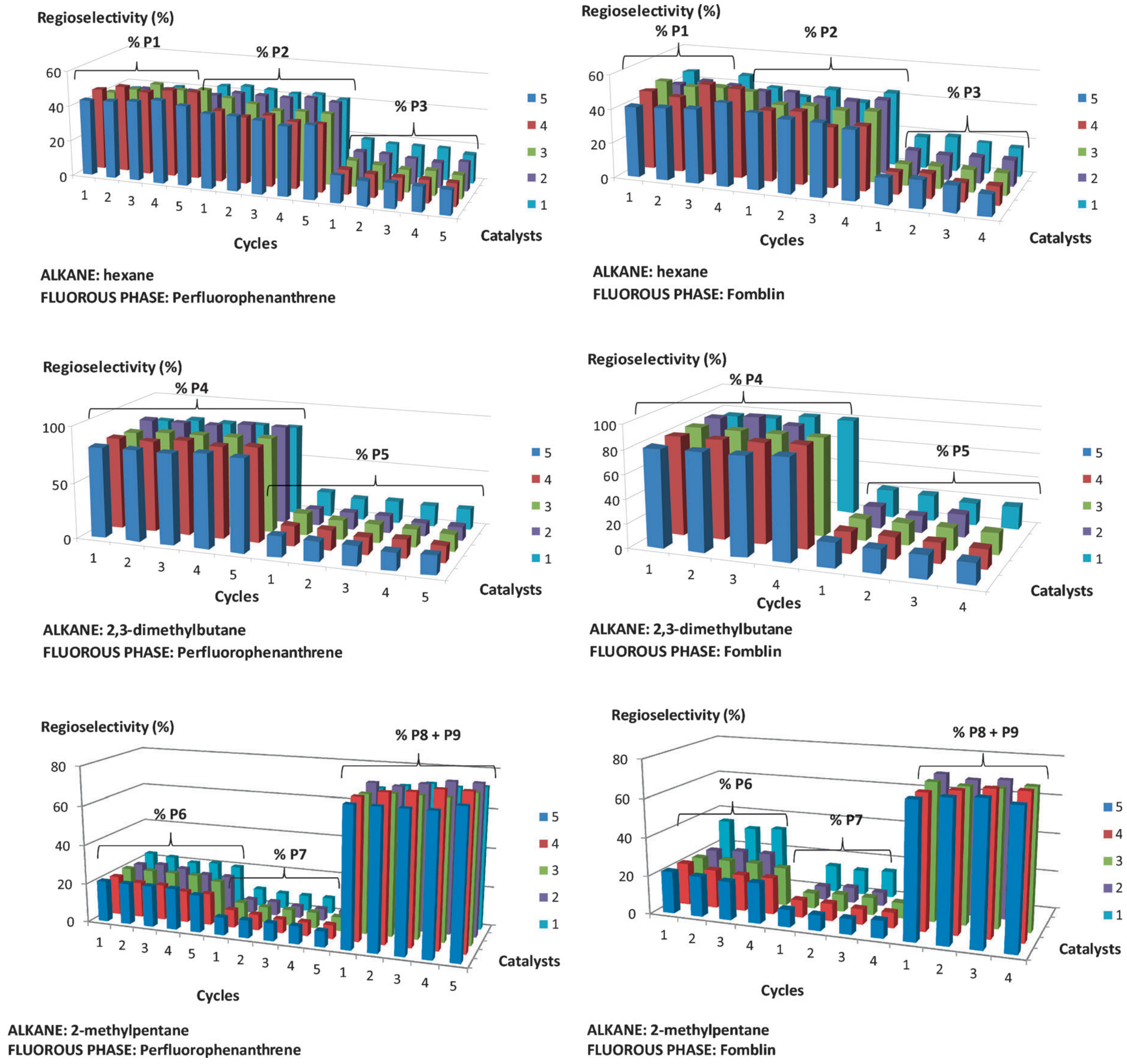
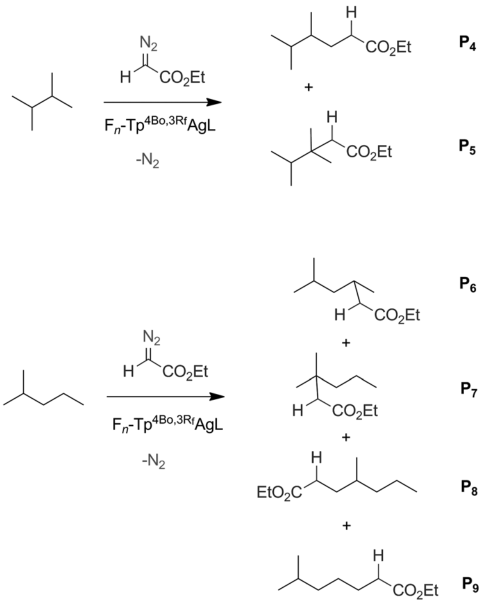


Figure 2. The catalytic functionalization of hexane, 2,3-dimetylbutane and 2-methylpentane in Fomblin or perfluorophenanthrene: regioselectivity as a function of catalyst type and catalyst recycling.



Scheme 7. The catalytic functionalization of 2,3-dimethylbutane (top) and 2-methylpentane (bottom).

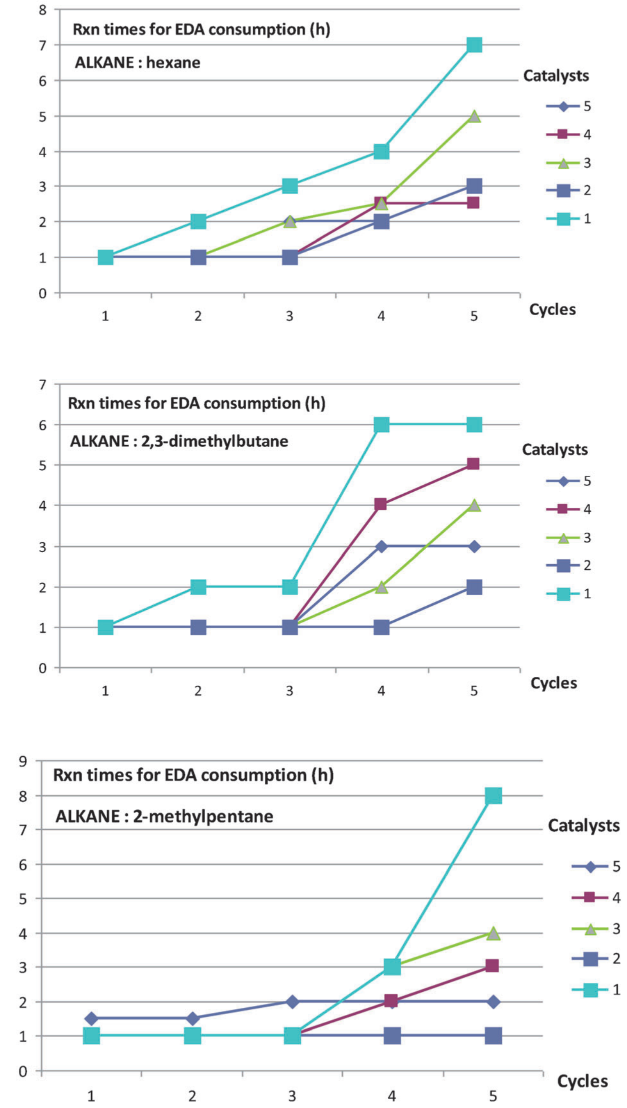


Figure 3. Variation of the reaction time required for complete EDA consumption along the number of cycles of catalyst recovery, with perfluorophenanthrene as the fluorous phase

This mixture was homogeneous at room temperature, at variance with other biphasic fluorous systems that need heating to be homogeneous, and was vigorously stirred until no EDA was detected by GC. In all cases, no products derived from carbene coupling, that is, diethyl fumarate or maleate, were detected; thus the alkane functionalization is completely chemoselective. Recent theoretical studies with the related Tp^{Br_3}M (M = Cu, Ag) complexes have explained such selectivity and the lack of carbene coupling.[25] To achieve catalyst recycling and reuse we have performed two different strategies. The first one required cooling down the mixture to −20 °C, inducing the formation of two phases, and the subsequent separation (through a cannula) of the organic phase containing the products as well as the excess of the alkane. However, this procedure revealed that some catalyst leached out of the fluorous phase. Because of this, a second, more effective procedure was applied, based on a trap-to-trap distillation under vacuum of the final reaction mixture: the excess of the alkane as well as the functionalized products were separated from the fluorous phase in this manner, the latter completely retaining the soluble catalyst. Figure 2 depicts the composition of the final mixtures upon EDA consumption for the three alkanes, the five catalysts and the different cycles. A simple look at the data nicely demonstrates that regioselectivity is maintained all along the cycles; four in the case of Fomblin and five in the case of the perfluorophenanthrene. More interestingly, these values are identical to those obtained under homogenous conditions, and did not significantly vary from one fluorous phase to another (see the Supporting Information for the complete set of values for each experiment).

The variation of the reaction times along the cycles of catalyst recovery deserves some comment (Figure 3). In all cases, the first cycle was completed in less than 1 h for most catalysts. Beyond that point, the stability of the catalysts slightly varied for the second and third cycles, most of them completing the reaction in less than 2 h. The fourth and fifth cycles showed differences between complexes **1**–**5** in terms of stability: complex **1** required the longest reaction times for the three alkanes, whereas complex **2** provided very good yields in relatively short reaction times upon five cycles (1 h for 2-methylpentane, 2 h for 2,3-dimethylbutane or 3 h for hexane, after 5 cycles each). Complexes **3**–**5** showed reaction times within the range described by **1** and **2**. Therefore, there is not a simple correlation between the lengths of the fluorinated R_f chain with catalyst stability under the reaction conditions.

Since the above study was carried out with 0.1 mmol of EDA as the limiting reagent, we have scaled-up this transformation by a tenfold, employing 1 mmol of EDA. As representative examples we have chosen hexane and 2,3-dimethylbutane as the reactants, and perfluorophenanthrene as the fluorous phase. The catalyst activity and the regioselectivities are again maintained for several cycles (see the Supporting Information), showing the validity of this system at a higher scale. This set of experiments was carried out by using a 1:40 catalyst/EDA ratio in contrast to the previous experiments that were performed with a 1:20 ratio. Therefore, these scale-up experiments are even more efficient (a turnover number (TON) per cycle of 40) than the former (20 TON per cycle) and confirm the absence of byproducts.

Conclusion

We have found that the fluorinated tris(indazolyl)borate silver complexes F_n-$Tp^{4Bo,3R_f}AgL$ (**1**–**5**) efficiently catalyze the transfer of the $CHCO_2Et$ group from ethyl diazoacetate into the C–H bonds of hexane, 2,3-dimethylbutane or 2-methylpentane. The transformation is completely chemoselective, with no observation of any product derived from the homocoupling of the carbene groups. In the case of hexane, the catalyst bearing the longest n-C_6F_{13} ponytail has yielded the highest regioselectivity toward the primary sites reported with ethyl diazoacetate.

The use of a fluorous phase (Fomblin or perfluorophenanthrene) has provided a recyclable system that maintains both the chemo- and regioselectivity observed in the homogeneous phase. In addition, the catalysts can be separated and reused four or five times without loss of both selectivities, and in a number of cases, with a relatively small increase of the reaction times.

Experimental Section

General procedures: All syntheses requiring inert atmosphere (Ar or N_2) were carried out by using Schlenk tube or glovebox techniques. The solvents were dried and distilled using a SBS-Mbraun system or by conventional methods: diethyl ether and tetrahydrofuran (Na/benzophenone), dichloromethane and pentane (calcium hydride). Acetone was degassed and stored on molecular sieves under argon. TlF_n-$Tp^{4Bo,3R_f}$ complexes were prepared according to the method previously reported.[15] A full account of their syntheses and properties will be reported in due course. The complexes F_{21}-$Tp^{4Bo,3CF_3}Ag(OCMe_2)$ and F_{27}-$Tp^{4Bo,3CF_2CF_3}Ag(THF)$ were prepared according to the literature.[15,20] The silver triflate, alkanes, fluorous phases, and ethyl diazoacetate were purchased from Aldrich and employed without further purification. GC data were collected with a Varian 3900 instrument. NMR experiments were acquired at 298 K using ARX250, DPX300, AV300, AV400 Bruker spectrometers and a Varian Mercury 400 MHz. Elemental analyses were performed in the Analytic Services of our laboratory. Mass spectrometry measurements were recorded on a QTRAP Applied Biosystems Mass Spectrometer.

Synthesis of silver complexes

Synthesis of F_{33}-$Tp^{4Bo,3(CF_2)_2CF_3}Ag(L)$: L = acetone (**3a**) or THF (**3b**): In a glove-box, F_{33}-$Tp^{4Bo,3(CF_2)_2CF_3}Tl$ (50 mg, 0.039 mmol) and silver triflate (10 mg, 0.039 mmol) were mixed in a Schlenk tube covered with aluminum foil and acetone (5 mL) was added. The solution was stirred at room temperature for 2 h, then the solvent was removed under reduced pressure and the residue was extracted into dichloromethane (10 mL). After filtration through celite the solvent was evaporated and the solid was washed several times with pentane to afford **3a** as a white powder (36 mg, 72 %). ^{19}F NMR (282.4 MHz, $[D_6]$acetone): $\delta = -166.68$ (br s, 1F, F5), -161.31 (br s, 1F, F7), -155.12 (br s, 1F, F6), -145.47 (m, 1F, F4), -127.17 (d, $J = 10$ Hz, 2F, CF_2), -108.17 (m, 2F, CF_2), -81.14 ppm (pseudo-t, $J = 9$ Hz, 3F, CF_3). DCI-MS: m/z: calculated for $C_{30}H_2AgBF_{33}N_6$: 1190.90; found: 1191.00 [$M-$acetone]; elemental analysis calcd (%) for $C_{33}H_7AgBF_{33}N_6O$: C 31.73, H 0.56, N 6.73; found: C 31.95, H 1.0, N 6.62. Complex **3b** was prepared following the same procedure but using tetrahydrofuran instead of acetone as the reaction solvent.

Synthesis of F_{39}-$Tp^{4Bo,3(CF_2)_3CF_3}Ag(acetone)$ (4): Following the same procedure as for **3a**, F_{39}-$Tp^{4Bo,3(CF_2)_3CF_3}Tl$ (50 mg, 0.035 mmol) and silver triflate (8.5 mg, 0.033 mmol) yielded complex **4** as a white powder (45 mg, 91 %). ^1H NMR (300.13 MHz, $[D_6]$acetone): $\delta = 2.84$ ppm (m, 6H, $CH_3C(O)CH_3$); ^{19}F NMR (282.4 MHz, $[D_6]$acetone): $\delta = -166.29$ (pseudo-t, $J = 17$ Hz, 1F, F5), -160.66 (br s, 1F, F7), -154.8 (br s, 1F, F6), -145.32 (m, 1F, F4), -126.31 (m, 2F, CF_2), -123.32 (m, 2F, CF_2), -107.58 (m, 2F, CF_2), -82.17 ppm (pseudo-t, $J = 10$ Hz, 3F, CF_3); ^{11}B NMR (75.47 MHz, $[D_6]$acetone): $\delta = 0.3$ ppm (br, BH); elemental analysis calcd (%) for $C_{36}H_7AgBF_{39}N_6O$: C 30.90, H 0.50, N 6.01; found: C 30.87, H 0.38, N 6.34.

Synthesis of F_{51}-$Tp^{4Bo,3(CF_2)_5CF_3}Ag(acetone)$ (5): Following the same procedure as for **3a**, F_{51}-$Tp^{4Bo,3(CF_2)_5CF_3}Tl$ (110 mg; 0.063 mmol) and silver triflate (14.8 mg; 0.057 mmol) yielded complex **4** as a white powder (79 mg, 82 %). ^1H NMR (300.13 MHz, $[D_6]$acetone): $\delta = 2.85$ ppm (m, 6H, $CH_3C(O)CH_3$). ^{19}F NMR (282.4 MHz, $[D_6]$acetone): $\delta = -165.58$ (pseudo-t, $J = 15$ Hz, 1F, F5), -159.48 (br s, 1F, F7), -154.13 (br s, 1F, F6), -145.14 (m, 1F, F4), -126.96 (br s, 2F, CF_2), -123.55 (br s, 2F, CF_2), -122.13 (br s, 4F, CF_2CF_2), -107.80 (br s, 2F, CF_2), -81.86 ppm (pseudo-t, $J = 10.5$ Hz, 3F, CF_3); ^{11}B NMR (75.47 MHz, $[D_6]$acetone): $\delta = -0.7$ ppm (br, BH); elemental analysis calcd. (%) for $C_{42}H_7AgBF_{51}N_6O$: C 29.69, H 0.42, N 4.95; found: C 29.53, H 0.30, N 4.71.

X-ray analysis of 3b: Data for **3b** was collected at 180 K on an Xcalibur Oxford Diffraction diffractometer equipped with an Oxford Instrument Cooler Device using a graphite-monochromated $Mo_{K\alpha}$ radiation ($\lambda = 0.71073$ Å). The structure has been solved by direct methods using SIR92,[26] and refined by means of least-squares procedures on F^2 with the aid of the program SHELXL97[27] included in the software package WinGX version 1.63.[28] Hydrogen atoms were geometrically placed and refined by using a riding model. All but a few non-hydrogens atoms were anisotropically refined, and in the last cycles of refinement a weighting Scheme was used, in which weights are calculated from the following formula: $w = 1/[\sigma^2(F_o^2) + (aP)^2 + bP]$ where $P = (F_o^2 + 2F_c^2)/3$. One of the peripheral CF_2CF_3 was too highly disordered to be refined in anisotropic mode. The disorder was treated by using the "part" option of SHELXL97 and the atoms C(21), C(22), F(10), F(11), F(12 A), F(12B), F(13 A) and F(13B) were refined isotropically. This disorder is responsible for the generation of alerts in the chekcif. Crystal data and refinement: crystal size $0.2 \times 0.12 \times 0.03$ mm, monoclinic, $P2/n$, $a = 18.3960(11)$, $b = 13.0560(5)$, $c = 19.0630(11)$ Å, $\beta = 117.290(7)°$, $V = 4068.9(4)$ Å^3, $Z = 4$, $\rho_{calcd} = 2.062$ Mg m^{-3}, θ range = 2.94 to 25.68°, $F(000) = 2448$, reflections collected/unique 28767/7725 [$R(int) = 0.0523$], completeness to $\theta = 25.68° = 99.8$ %, semiempirical absorption correction from equivalents ($\mu = 0.689$ mm^{-1}, max./min. transmission = 0.978/0.932), data/restraints/parameters = 7725/9/650, gof on $F^2 = 1.064$, final R indices [$I > 2\sigma(I)$] $R1 = 0.0637$, $wR2 = 0.180$, R indices (all data) $R1 = 0.098$, $wR2 = 0.1956$, largest diff. peak/hole = 2.328/−1.895 e Å^{-3}. The drawing of Figure 1 was performed with the program ORTEP32[29] with 30 % probability displacement ellipsoids for non-hydrogen atoms.

CCDC-891320 (**3b**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

General catalytic experiment under homogeneous conditions: F_n-$Tp^{4Bo,3R_f}Ag(CH_3COCH_3)$ (0.005 mmol) was dissolved in the corresponding alkane (10 mL). Ethyl diazoacetate (52 μL, 0.5 mmol) was added in one portion. The reaction was followed by GC. After stirring overnight, no ethyl diazoacetate was detected. The products were identified by

NMR spectroscopy and GC studies. Quantification was carried out by GC using calibration curves previously registered with pure products. The Supporting Information contains GC traces, as well as NMR data of reaction mixtures showing the lack of diethyl fumarate and maleate.

The yields of isolated products from experiments carried out at a higher scale[20] were obtained within the range 88–93 % upon column chromatography using petroleum ether/ethyl acetate as eluent (5:1).

General catalytic experiment in a biphasic system: *Fomblin HVAC 140/13 as a fluorous medium*: F_n-$Tp^{4Bo,3R_f}Ag(CH_3COCH_3)$ (0.005 mmol) was dissolved in Fomblin HVAC (4 mL, 1.2 mmol) and the corresponding alkane (1 mL, 7.6 mmol) and ethyl diazoacetate (10.5 μL, 0.1 mmol) were added at room temperature, leading to a homogeneous mixture. After a first catalytic run, the products and starting material were collected by trap-to-trap vacuum distillation at room temperature. The soluble catalyst and the fluorous phase remained and fresh alkane (1 mL, 7.6 mmol) and ethyl diazoacetate (10.5 μL, 0.1 mmol) were added for the second run, this procedure being repeated along the cycles. Yields were determined as described above.

Perfluorophenanthrene as a fluorous medium: F_n-$Tp^{4Bo,3R_f}Ag(CH_3COCH_3)$ (0.005 mmol) was dissolved in perfluorophenanthrene (4 mL, 3.2 mmol) and the corresponding alkane (1 mL, 7.6 mmol) and ethyl diazoacetate (10.5 μL, 0.1 mmol) were added at room temperature. Again, the mixture was homogeneous at room temperature. The procedure from this step was identical to that detailed above with Fomblin.

Scale-up experiments were carried out with EDA (1 mmol) and the silver catalyst (0.025 mmol) following the above procedure but adding the ethyl diazoacetate with the aid of a syringe pump at a low rate for 2 h.

Acknowledgements

We thank the MEC (Proyecto CTQ2011-28942-CO2-01), the ERA-Chemistry Programme (2nd call "Chemical activation of carbon dioxide and methane", contract number 1736154) and the Institut de Chimie of the CNRS for financial support. M.A.F. also thanks MEC for a research fellowship. We thank Dr Emmanuelle Despagnet-Ayoub for helpful discussions.

---

[1] a) *Alkane C–H Activation by Single-Site Metal Catalysis* (Ed.: P. J. Pérez), Springer, Dordrecht, **2012**; b) *Activation and functionalization of C–H bonds* (Eds.: K. I. Goldberg, A. S. Goldman), ACS Symp. Ser. 885, Am. Chem. Soc., Washington DC, **2004**; c) *Handbook of C–H transformations, Vol. 1* (Ed.: G. Dyker), Wiley-VCH, Weinheim, **2005**; d) A. E. Shilov, G. B. Shul'pin, *Activation and Catalytic Reactions of saturated hydrocarbons in the presence of metal complexes.* Kluwer, Dordrecht, **2000**; e) see also special issues of the following: *Chem. Rev.* **2010**, *110*, issue 2 and *Acc. Chem. Res.* **2012**, *45*, issue 6.

[2] a) R. G. Bergman, *Nature* **2007**, *446*, 391–393; b) J. A. Labinger, J. E. Bercaw, *Nature* **2002**, *417*, 507–513; c) B. A. Arndtsen, R. G. Bergman, T. A. Mobley, T. H. Peterson, *Acc. Chem. Res.* **1995**, *28*, 154–162.

[3] A. E. Shilov, G. B. Shul'pin, *Chem. Rev.* **1997**, *97*, 2879–2932.

[4] J. T. Golden, R. A. Andersen, R. G. Bergman, *J. Am. Chem. Soc.* **2001**, *123*, 5837–5838.

[5] a) C. M. Jensen, *Chem. Commun.* **1999**, 2443–2449; b) A. S. Goldman, A. H. Roy, Z. Huang, R. Ahuja, W. Schinski, M. Brookhart, *Science* **2006**, *312*, 257–261.

[6] I. A. I. Mkhalid, J. H. Barnard, T. B. Marder, J. M. Murphy, J. F. Hartwig, *Chem. Rev.* **2010**, *110*, 890–931.

[7] J. F. Hartwig, *Organotransition Metal Chemistry: From Bonding to Catalysis*, University Science books, **2009**.

[8] a) M. P. Doyle, M. A. McKervey, T. Ye, *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*, Wiley, New York, **1998**; b) M. P. Doyle, R. Duffy, M. Ratnikov, L. Zhou, *Chem. Rev.* **2010**, *110*, 704–724.

[9] L. T. Scott, G. J. DeCicco, *J. Am. Chem. Soc.* **1974**, *96*, 322–323.

[10] a) H. M. L. Davies, A. R. Dick, *Top. Curr. Chem.* **2010**, *292*, 303–345; b) M. M. Díaz-Requejo, P. J. Pérez, *Chem. Rev.* **2008**, *108*, 3379–3394; c) M. M. Díaz-Requejo, T. R. Belderraín, M. C. Nicasio, P. J. Pérez, *Dalton Trans.* **2006**, 5559–5566; d) H. M. L. Davies, R. E. J. Beckwith, *Chem. Rev.* **2003**, *103*, 2861–2903.

[11] a) A. Demonceau, A. F. Noels, A. Hubert, P. Teyssié, *J. Chem. Soc. Chem. Commun.* **1981**, 688–689; b) A. Demonceau, A. F. Noels, A. Hubert, P. Teyssié, *Bull. Soc. Chim. Belg.* **1984**, *93*, 945–948; c) A. Demonceau, A. F. Noels, P. Teyssié, A. Hubert, *J. Mol. Catal.* **1988**, *49*, L13–L17; d) A. Demonceau, A. F. Noels, A. Hubert, *J. Mol. Catal.* **1989**, *57*, 149–152.

[12] H. J. Callot, F. Metz, *Tetrahedron Lett.* **1982**, *23*, 4321–4324.

[13] a) H. M. L. Davies, T. Hansen, M. R. J. Churchill, *J. Am. Chem. Soc.* **2000**, *122*, 3063–3070; b) H. M. L. Davies, T. Hansen, *J. Am. Chem. Soc.* **1997**, *119*, 9075–9076; c) H. M. L. Davies, E. G. Antoulinakis, *J. Organomet. Chem.* **2001**, *617–618*, 47–55.

[14] H.-Y. Thu, G. S.-M. Tong, J.-S. Huang, S. L.-F. Chan, Q.-H. Deng, C.-M. Che, *Angew. Chem.* **2008**, *120*, 9893–9897; *Angew. Chem. Int. Ed.* **2008**, *47*, 9747–9751.

[15] A. Caballero, E. Despagnet-Ayoub, M. M. Díaz-Requejo, A. Díaz-Rodríguez, M. E. González-Núñez, R. Mello, B. K. Muñoz, W.-S. Ojo, G. Asensio, M. Etienne, P. J. Pérez, *Science* **2011**, *332*, 835–838.

[16] a) H. V. R. Dias, R. G. Browning, S. A. Richey, C. J. Lovely, *Organometallics* **2004**, *23*, 1200–1202; b) H. V. R. Dias, R. G. Browning, S. A. Richey, C. J. Lovely, *Organometallics* **2005**, *24*, 5784–5784.

[17] P. Rodríguez, E. Álvarez, M. C. Nicasio, P. J. Pérez, *Organometallics* **2007**, *26*, 6661–6668.

[18] A. Endres, G. Maas, *J. Organomet. Chem.* **2002**, *643*, 174–180.

[19] a) I. T. Horváth, J. Rábai, *Science* **1994**, *266*, 72–75; b) J. A. Gladysz, D. P. Curran, I. T. Horváth, *Handbook of Fluorous Chemistry*, Wiley-VCH, Weinheim, **2004**; c) I. T. Horvath, *Acc. Chem. Res.* **1998**, *31*, 641–650; d) A. P. Dobbs, M. R. Kimberley, *J. Fluorine Chem.* **2002**, *118*, 3–17.

[20] E. Despagnet-Ayoub, K. Jacob, L. Vendier, M. Etienne, E. Álvarez, A. Caballero, M. M. Díaz-Requejo, P. J. Pérez, *Organometallics* **2008**, *27*, 4779–4787.

[21] The formulation of F_n-$Tp^{4Bo,3R_f}$, in which F_n is the total number of F atoms and R_f the nature of the fluorinated alkyl chain at position 3, is adopted to keep the merit and spirit of the nomenclature proposed by Trofimenko for the parent, fully hydrogenated tris(indazolyl)borate ligand Tp^{4Bo} and the corresponding $Tp^{4Bo,3R}$ derivatives. See a) S. Trofimenko, *Scorpionates, The coordination Chemistry of Polypyrazolylborate Ligands*; Imperial College Press, London, **1999**; b) C. Pettinari, *Scorpionates II. Chelating Borate Ligands*, Imperial College Press, London, **2008**.

[22] D. A. Ellis, K. A. Denkenberger, T. E. Burrow, S. A. Mabury, *J. Phys. Chem. A* **2004**, *108*, 10099–10106.

[23] a) H. V. R. Dias, Z. Wang, W. Jin, *Inorg. Chem.* **1997**, *36*, 6205–6215; b) H. V. R. Dias, W. Jin, *J. Am. Chem. Soc.* **1995**, *117*, 11381–11382.

[24] P. K. Hurlburt, J. J. Rack, J. S. Luck, S. F. Dec, J. D. Webb, O. P. Anderson, S. H. Strauss, *J. Am. Chem. Soc.* **1994**, *116*, 10003–10014.

[25] A. A. C. Braga, A. Caballero, J. Urbano, M. M. Díaz-Requejo, P. J. Pérez, F. Maseras, *ChemCatChem* **2011**, *3*, 1646–1652.

[26] A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, *J. Appl. Crystallogr.* **1993**, *26*, 343–350.

[27] SHELX97 [Includes SHELXS97, SHELXL97, CIFTAB]—*Programs for Crystal Structure Analysis (Release 97–2).* G. M. Sheldrick, Institüt für Anorganische Chemie der Universität, Tammanstrasse 4, 3400 Göttingen, Germany, **1998**.

[28] L. J. Farrugia, *J. Appl. Crystallogr.* **1999**, *32*, 837–838.

[29] L. J. Farrugia, *J. Appl. Crystallogr.* **1997**, *30*, 565–565.

Received: October 6, 2012
Revised: November 6, 2012