# Easy Alkane Catalytic Functionalization

B. Pilar Gómez-Emeterio, Juan Urbano, M. Mar Díaz-Requejo,* and Pedro J. Pérez*

*Laboratorio de Catálisis Homogénea, Departamento de Química y Ciencia de los Materiales, Unidad Asociada al CSIC, Campus de El Carmen s/n, Universidad de Huelva, 21007-Huelva, Spain*

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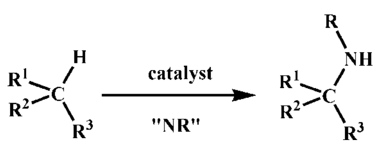
The carbon−hydrogen bonds of alkanes, R−H, can be converted in high yields into amino functionalities (R−NHTs; Ts = *p*-toluensulfonyl), with the aid of silver-based catalysts in a reaction implying the thermal (80 °C) insertion of a nitrene NTs unit into the C−H bond of the hydrocarbon. Complexes $Tp^xAg$ ($Tp^x$ = hydrotris(pyrazolyl)borate ligand) serve as catalysts and PhI=NTs serves as the nitrene source.

## 1. Introduction

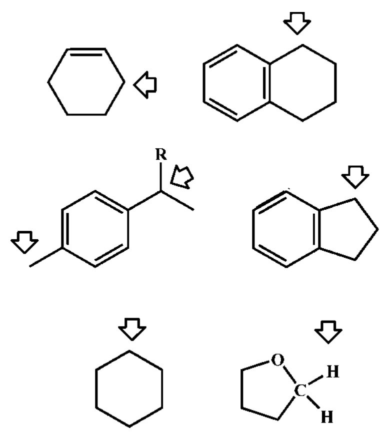
The development of efficient processes to convert readily available alkanes into value-added products remains a challenge in spite of the efforts of the organometallic community in the past decades, from which few different examples of neat alkane functionalization have been reported to date.[1] First studies with platinum-based catalysts led to the oxidation of the alkane in the so-called electrophilic activation.[2] More recently, the rhodium-catalyzed borylation of alkanes[3] constituted a breakthrough in this area, leading to the formation of alkylboranes that could be further converted into other functionalities. The iridium-catalyzed alkane dehydrogenation has also constituted an important advantage to this field,[4a] particularly when combined with olefin metathesis catalysts, in a tandem reaction that has allowed the activation of the alkane and its functionalization by chain enlargement.[4b] In those transformations, new C−O, C−B, or C−C bonds are formed upon C−H bond functionalization processes. In contrast, the formation of carbon−nitrogen bonds with plain alkanes as the starting material has only been scarcely reported to date: most of the methods described for the generation of C−N bonds are based on the use of already functionalized molecules.[5,6]




(1)

With the goal of achieving the conversion of an alkane C−H bond into a C−N bond in a catalytic manner, we have focused on the intermolecular nitrene insertion methodology,[7] a strategy in which this group would formally insert into the C−H bond of the alkane, leading to the formation of an amino functionality (eq 1). After the seminal work by Breslow and co-workers,[8] this methodology has been reported[9] for the functionalization of several $sp^3$ C−H bonds (Scheme 1) usually occupying benzylic positions in aromatic substrates, or other activated bonds (allylic, α-C−H bonds of cyclic ethers or amines), mainly with rhodium or copper-based catalysts. Not surprisingly, the C−H bonds of such substrates display bond dissociation energies (BDE) substantially lower than those of plain, linear, branched, or cyclic alkanes.[10]

**Scheme 1. Commonly Employed Substrates in the Functionalization of C−H bonds by Intermolecular Metal-Catalyzed Nitrene Insertion, with the Preferred Reaction Sites (⇒)**



He and co-workers have reported the first catalytic system based on silver for this transformation.[11] Although most of the

* Corresponding author. E-mail: perez@dqcm.uhu.es mmdiaz@dqcm.uhu.es.

(1) (a) Bergman, R. G. *Nature* **2007**, *446*, 391. (b) Labinger, J. A.; Bercaw, J. E. *Nature* **2002**, *417*, 507.
(2) (a) Goldshleger, N. F.; Eskova, V. V.; Shilov, A. E.; Shteinman, A. A. *Zh. Fiz. Khim. (Engl. Transl.)* **1972**, *46*, 785. (b) Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.* **1997**, *97*, 2879.
(3) (a) Chen, H.; Schlecht, S.; Semple, T. C.; Hartwig, J. F. *Science* **2000**, *287*, 1995. (b) Waltz, K. M.; Hartwig, J. F. *J. Am. Chem. Soc.* **2000**, *122*, 11358.
(4) (a) Gupta, M.; Hagen, C.; Kaska, W. C.; Cramer, R. E.; Jensen, C. M. *J. Am. Chem. Soc.* **1997**, *119*, 840. (b) Goldman, A. S.; Roy, A. H.; Huang, Z.; Ahuja, R.; Schinski, W.; Brookhart, M. *Science* **2006**, *312*, 257.
(5) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400.
(6) Buchwald, S. L.; Mauger, C.; Mignani, G.; Scholz, U. *Adv. Synth. Catal.* **2006**, *348*, 23.
(7) (a) Müller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905. (b) Halfen, J. A. *Curr. Org. Chem* **2005**, *9*, 657. (c) Davies, H. M. L.; Manning, J. R. *Nature* **2008**, *451*, 417.
(8) (a) Breslow, R.; Gellman, S. H. *J. Chem. Soc., Chem. Commun.* **1982**, 1400. (b) Svastist, E. W.; Dawson, J. H.; Breslow, R.; Gellman, S. H. *J. Am. Chem. Soc.* **1985**, *107*, 6427.
(9) Representative examples of the catalytic amination of these bonds: (a) Fiori, K. W.; Du Bois, J. *J. Am. Chem. Soc.* **2007**, *129*, 562. (b) Liang, C.; Robert-Peillard, F.; Fruit, C.; Müller, P.; Dodd, R. H.; Dauban, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 4641. (c) Liang, J.-L.; Yuan, S.-X.; Chan, P. W. H.; Che, C.-M. *Org. Lett.* **2002**, *4*, 4507. (d) Yang, J.; Weinberg, R.; Breslow, R. *Chem. Commun.* **2000**, 531. (e) Yamawaki, M.; Tsutsui, H.; Kitagaki, S.; Anada, M.; Hashimoto, S. *Tetrahedron Lett.* **2002**, *43*, 9561. (f) Kohmura, Y.; Katsuki, T. *Tetrahedron Lett.* **2001**, *42*, 3339. (g) Lebel, H.; Huard, K. *Org. Lett.* **2007**, *9*, 639.
(10) (a) Blanksby, S. J.; Ellison, G. B. *Acc. Chem. Res.* **2003**, *36*, 255. (b) Tian, Z.; Fattahi, A.; Lis, L.; Kass, S. R. *J. Am. Chem. Soc.* **2006**, *128*, 17087. (c) Burkey, T. J.; Castelhano, A. L.; Griller, D.; Lossing, F. P. *J. Am. Chem. Soc.* **1983**, *105*, 4701. (d) Cruickshank, F. R.; Benson, S. W. *J. Am. Chem. Soc.* **1969**, *91*, 1289.

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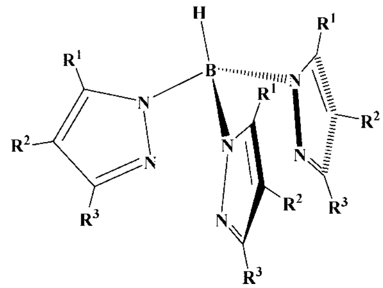
substrates studied were of the type shown in Scheme 1, i.e., with activated C−H bonds, one example of the activation of a noncyclic alkane (2-methylbutane), albeit in low yield (22%), was included.[11b] More recent is a work by Müller and co-workers with a chiral rhodium-based system in which, again, only 2-methylbutane was also amidated in 36% yield.[12] These contributions and an early work by Mansuy and co-workers[13] with iron- and manganese-containing porphyrin ligands as catalysts that converted alkanes such as heptane or cyclohexane into amides in low yields (5−10%) are the only examples, to the best of our knowledge, that have been reported for the direct amidation of an alkane by this methodology. In this contribution we report a catalytic system based on silver capable of inducing the conversion of plain, linear, or branched alkanes into amides in high yields using the nitrene transfer methodology and PhI═NTs as the nitrene source.

## 2. Results and Discussion

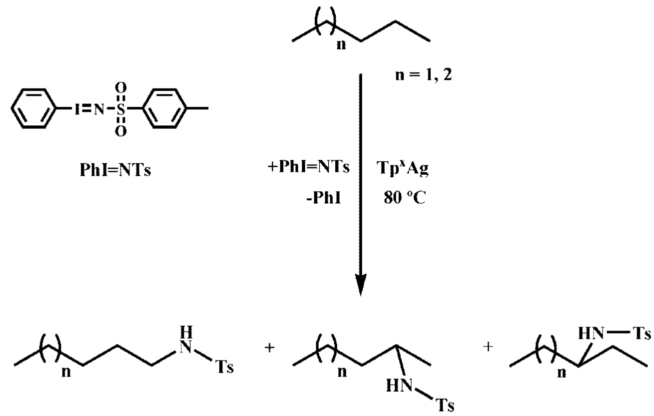
We have previously reported[14] that the complex $Tp^{Br3}$-Cu(NCMe) ($Tp^{Br3}$ = hydrotris(3,4,5-tribromo)pyrazolyl borate) catalyzes the transfer of the NTs group (Ts = *p*-toluenesulfonyl) from PhI═NTs to several hydrocarbons, inducing the insertion of such a unit into the C−H bonds of benzene, cyclohexane, and the alkyl C−H groups of a series of alkyl aromatics. In all cases, the benzylic C−H was the preferred site for the insertion to occur; however, the unprecedented functionalization of the *β*-methyl group was also observed to a certain extent in ethyl and isopropyl derivatives. Since this position is substantially less activated than the benzylic one, we envisaged the possibility that unreactive $sp^3$ C−H bonds could be functionalized by this methodology with the appropriate catalyst. Previous work from this laboratory toward alkane functionalization by carbene insertion showed an increase of the catalytic activity when replacing copper by silver in $Tp^{Br3}$M catalysts,[15] in good accord with Dias, Lovely, and co-workers when moving from $Tp^{(CF3)2}$Cu to $Tp^{(CF3)2}$Ag.[16] On the basis of this background, we chose four silver complexes of composition $Tp^xAg$ ($Tp^x$ = hydrotrispyrazolylborate ligand; Scheme 2) as potential candidates for catalysts for the nitrene insertion reaction. Indeed, $Tp^xAg$ catalysts have been found to react with pentane and hexane (see Scheme 3 and Table 1 for conditions and catalytic data) to give the corresponding amines derived from nitrene insertion into the primary (C1) and secondary (C2 and C3) C−H bonds of the hydrocarbons. The achieved conversions and regioselectivities depended on the $Tp^xAg$ catalyst employed, the maximum conversion (65% and 70% for pentane and hexane, respectively) having been found for $Tp^{*,Br}Ag$. Blank experiments showed that no alkane amination took place in the absence of the silver complexes, whereas partial hydrolysis of PhI═NTs to $TsNH_2$ was observed (ca. 20%) by action of adventitious water.

**Scheme 2. Scorpionate Ligands Used in This Work**




| $Tp^x$ | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| $Tp^{Br3}$ | Br | Br | Br |
| $Tp^{Ms}$ | H | H | mesytil |
| $Tp^{*,Br}$ | Me | Br | Me |
| $Tp^*$ | Me | H | Me |

**Scheme 3. Catalytic Functionalization of *n*-Pentane and *n*-Hexane**




The above results have been extended to several branched and cyclic hydrocarbons (Table 1). For all substrates investigated conversion follows the order $Tp^{*,Br}Ag > Tp^*Ag \geq Tp^{Ms}Ag > Tp^{Br3}Ag$. The efficiency of these silver catalysts for *alkane* functionalization largely surpasses the already mentioned previous reports[11−13] to make it unique. With regard to regioselectivity, tertiary sites are clearly preferred. Thus, use of 2,3-dimethylbutane gave, exclusively, the product of insertion into the tertiary C−H bond, independently of the catalyst employed. For 2-methylbutane, insertion of NTs into the tertiary site was again preferred. However, as already indicated, for the linear pentane and hexane, amination of the C−H bonds of C2 and C3 occurred with comparable selectivities, although minor, albeit detectable amounts of the products generated by functionalization of primary C−H bonds were also formed (5−15%). The observation of different regioselectivities depending upon the catalyst employed supports the implication of the metal center in the nitrene transfer step, as well as some control over this step. Thus the $Tp^{Ms}Ag$ catalyst provided the highest values of the primary site activation products, and this may be interpreted as a consequence of the steric pressure of the mesityl substituents, which reduces the size of the catalytic pocket, disfavoring activation of the more sterically demanding sites. Finally, cycloalkanes such as cyclopentane or cyclohexane were converted into the corresponding amines with moderate to high yield by these silver catalysts. These substrates had been reported to undergo this reaction but to a lower extent.[9,11−14] It is worth mentioning that NMR studies carried out at the end of the reaction showed the resonances of the initial $Tp^xAg$ catalyst; therefore no decomposition takes place during the catalytic transformation.

Although the metal-catalyzed nitrene transfer from PhI═NTs has been widely explored for the olefin aziridination reaction,

(11) (a) Li, Z.; Capretto, D. A.; Rahaman, R. O.; He, C. *Angew. Chem., Int. Ed.* **2007**, *46*, 5184. (b) Although the previous reference does not include in the text any linear or branched alkanes, the Supporting Information contains the results of 2-methylpentane. This substrate was converted into the amine derived from the insertion of the nitrene moiety into the tertiary C−H bond in 22% yield.

(12) Liang, C.; Collet, F.; Robert-Peillard, F.; Müller, P.; Dodd, R. H.; Dauban, P. *J. Am. Chem. Soc.* **2008**, *130*, 343.

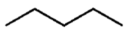
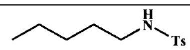
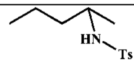
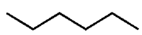
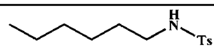
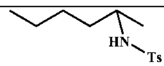
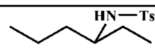
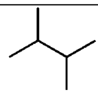
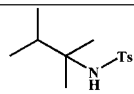
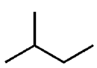
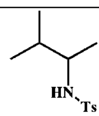
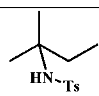
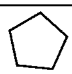
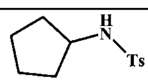
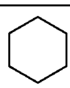
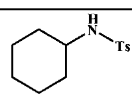
(13) Mahy, J.-P.; Bedy, G.; Battioni, P.; Mansuy, D. *New J. Chem.* **1989**, *13*, 651.

(14) (a) Fructos, M. R.; Trofimenko, S.; Díaz-Requejo, M. M.; Pérez, P. J. *J. Am. Chem. Soc.* **2006**, *128*, 11784. (b) Díaz-Requejo, M. M.; Belderrain, T. R.; Nicasio, M. C.; Trofimenko, S.; Pérez, P. J. *J. Am. Chem. Soc.* **2003**, *125*, 12078.

(15) Urbano, J.; Belderrain, T. R.; Nicasio, M. C.; Trofimenko, S.; Díaz-Requejo, M. M.; Pérez, P. J. *Organometallics* **2005**, *24*, 1528.

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

**Table 1. Functionalization of Alkanes by Nitrene Insertion from PhI═NTs Using Silver Catalysts**[a]

| | | % Yield/ % Distribution of products (D.P.)[b] | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Tp*Ag | | Tp$^{*,Br}$Ag | | Tp$^{Ms}$Ag | | Tp$^{Br3}$Ag | |
| Substrate | Products | Yield | D.P. | Yield | D.P. | Yield | D.P. | Yield | D.P. |
|  |  | 40 | 7 | 65 | 10 | 40 | 15 | 15 | n.d. |
| |  | | 58 | | 59 | | 53 | | 70 |
| |  | | 35 | | 31 | | 32 | | 30 |
|  |  | 40 | 5 | 70 | 5 | 35 | 15 | 10 | n.d. |
| |  | | 58 | | 60 | | 53 | | 72 |
| |  | | 37 | | 35 | | 32 | | 28 |
|  |  | 65 | >99 | 75 | >99 | 25 | >99 | 10 | >99 |
|  |  | 40 | 9 | 80 | 10 | 15 | 24 | 8 | 22 |
| |  | | 91 | | 90 | | 76 | | 78 |
|  |  | 70 | 100 | 80 | 100 | 65 | 100 | 55 | 100 |
|  |  | 65 | 100 | 90 | 100 | 60 | 100 | 50 | 100 |

[a] Reactions carried out in neat alkane (5 mL) at 80 °C for 4 h, with a 1:20 ratio of [Ag]:[PhI═NTs], and $1.75 \times 10^{-2}$ mmol of catalyst. [b] Average of two runs. Determined by $^1$H NMR with an internal standard at the end of the reaction and referred to initial PhI═NTs.

it is substantially less developed for C−H activation reactions. It is well established that this reaction occurs with formation of a metallonitrene species,[7] similarly to the related metallocarbene intermediates commonly proposed for the metal-catalyzed carbene transfer from diazo compounds.[17] However, the latter transformation usually takes place through a concerted pathway, whereas for the former there is evidence for both concerted and radical processes.[7,9a,13,18,19] To test for radical participation in this reaction, experiments with 2,3-dimethylbutane as the substrate and the four silver complexes as the catalyst have been carried out in the presence of 2 equiv (with respect to the catalyst) of the radical inhibitor 2,6-di-*tert*-butylhydroxytoluene (BHT). The conversions into the functionalized product were reduced to ca. half of the values shown in Table 1. A second series of experiments was run with 2,3-dimetylbutane and variable amounts of the inhibitor. Figure 1 shows the variation in yields depending of the ratio [BHT]:[PhI═NTs].

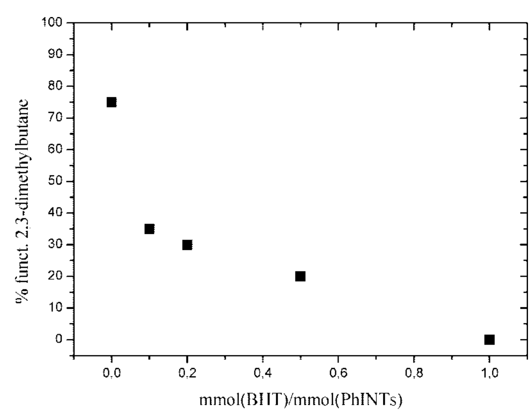
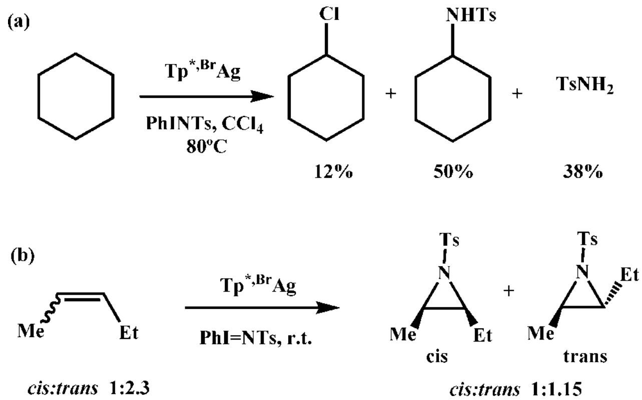



**Figure 1.** Inhibition of the functionalization reaction of 2,3-dimethylbutane in the presence of BHT.

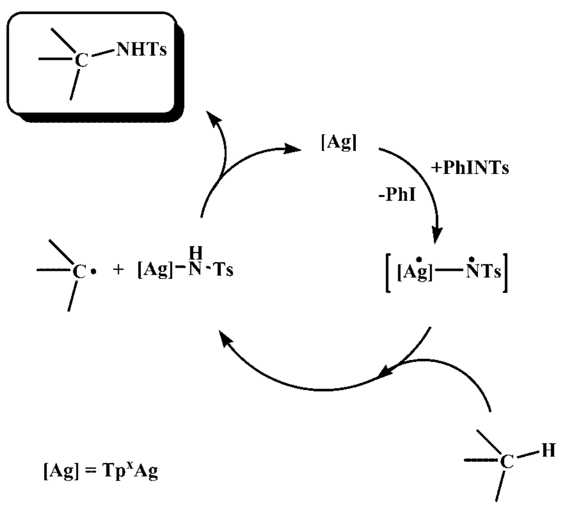
Although we believe that these results are in agreement with the existence of a radical-based pathway to account for this transformation, we have collected more data to support such a proposal. A radical trapping experiment with $CCl_4$ was carried out using cyclohexane as the substrate (Scheme 4a). In addition to the expected *N*-cyclohexyltosylamine (50%), chlorocyclohexane was also formed in 12% yield, in good accord with a

(17) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; John Wiley & Sons: New York, 1998.
(18) Brandt, P.; Södergren, M. J.; Andersson, P. G.; Norrby, P.-O. *J. Am. Chem. Soc.* **2000**, *122*, 8013.
(19) Díaz-Requejo, M. M.; Pérez, P. J.; Brookhart, M.; Templeton, J. L. *Organometallics* **1997**, *16*, 4399.

**Scheme 4. Evidences for the Involvement of Radical Intermediates**




**Scheme 5. Mechanistic Proposal for the Formal Nitrene Insertion into Alkane C−H Bonds**




related experiment described in the aforementioned Fe- and Mn-based catalytic system.[13] Additional evidence for radical involvement was obtained from the aziridination of a 1:2.3 mixture of *cis*- and *trans*-2 pentene with PhINTs, using Tp$^{*,Br}$Ag as the catalyst (Scheme 4b). A mixture of the corresponding *cis* and *trans* aziridines in a 1:1.15 ratio was obtained. The change in the initial configuration must be taken as an indication of the existence of a radical, stepwise pathway.[18] Finally, when *n*-hexane was employed as substrate in two identical experiments carried out in the presence and absence of BHT, the relative ratio of products did not vary (see Supporting Information).

A possible mechanistic pathway is shown in Scheme 5. The initial Tp$^x$Ag(I) complex would react with PhINTs to generate a silver−nitrene intermediate. Such species could display both singlet and triplet configurations. A theoretical study based on copper showed that these two structures are similar in energy.[18] Triplet reactivity could be responsible for a hydrogen abstraction process from the alkane (Scheme 5) and the subsequent formation of an alkyl radical, in a similar manner to that previously proposed for manganese.[13] This mechanism is in good agreement with the experimental data, since it explains (i) the inhibition of the process in the presence of BHT; (ii) the observation of the tertiary sites as the most reactive, in accordance with the comparatively easier formation and higher stability of free tertiary radicals with respect to primary and secondary radicals; and (iii) the formation of chloro derivatives when $CCl_4$ is the reaction medium.[13]

In conclusion, the direct, efficient conversion of linear and branched alkanes into amines has been achieved under mild, catalytic conditions using silver complexes as the catalysts. The complex Tp$^{*,Br}$Ag has been found to be the most active, inducing the formation of the amines in moderate to high yield. Tertiary sites are preferred for the functionalization reaction, followed by secondary and, to a lesser extent, primary C−H bonds. Available data has led to the finding that this reaction proceeds through the intermediacy of radical species, which serves as the basis for a mechanistic proposal.

## 3. Experimental Section

**General Methods.** All preparations and manipulations were carried out under an oxygen-free nitrogen atmosphere using conventional Schlenk techniques or inside a drybox. All the substrates were purchased from Aldrich. Substrates and solvents were rigorously dried previously to their use, since the presence of adventitious water in the reaction mixture dramatically decreased the conversions, due to the formation of tosylamine. The complexes Tp$^x$Ag (Tp$^x$ = Tp$^{Br3}$, Tp$^{Ms}$, Tp*) were prepared according to the literature.[15,20] PhI=NTs was also prepared following the already reported method.[21] NMR experiments were run in a Varian Mercury 400 MHz spectrometer.

**Synthesis of Tp$^{*,Br}$Ag.** A 0.5 mmol (0.37 g) portion of the TlTp$^{*,Br}$ salt[22] was suspended in 96% ethanol (30 mL), and $AgNO_3$ (0.5 mmol, 0.085 g) was added to the stirred suspension. The mixture was stirred for 4 h at room temperature. After that time, volatiles were removed under vacuum and the residue was extracted with 50 mL of methylene chloride. The colorless filtrate was taken to dryness to give a white solid of analytical composition Tp$^{*,Br}$Ag in 70% yield. Crystallization from methylene chloride gave white crystals upon cooling at −20 °C overnight. Anal. Calc for $BC_{15}H_{19}N_6Br_3Ag$: C, 28.08; H, 2.98; N, 13.1. Found: C, 27.46; H, 2.92; N, 12.11. IR (Nujol mull): $\nu$(B−H) = 2492 cm$^{-1}$. $^1$H NMR (400 MHz, $CDCl_3$): 2.28 (s, 6H, 2 $CH_3$), 1.89 (s, 6H, 2 $CH_3$). $^{13}$C{$^1$H} NMR (100 MHz, $CDCl_3$) 148.8 (3C, *C*-Me), 145.1 (3C, *C*-Me), 94.4 (3C, *C*-Br), 13.6 (3C, Me), 12.5 (3C, Me).

**General Catalytic Procedure.** Inside the drybox, a Teflon-capped ampule was charged with 0.35 mmol (0.13 g) of PhI=NTs, 5 mL of the alkane, and 0.0175 mmol of the corresponding Tp$^x$Ag catalyst. The ampule was removed from the drybox and placed into an oil bath at 80 °C, which was covered with aluminum foil to maintain the reaction mixture in the dark. After 4 h of stirring, volatiles were removed under vacuum and the residue was dissolved in DMSO-$d_6$ and studied by $^1$H NMR. The mixtures were formed by the amines derived from the insertion of the NTs unit in the C−H bonds of the starting alkanes and $TsNH_2$. Addition of an exact amount of styrene as internal standard provided mass balance and conversions. The amines were identified by comparison with the spectral data reported in the literature. Only the product derived from 2,3-dimethylbutane was not yet reported, being therefore characterized by spectroscopic procedures (see the Supporting Information).

The experiments with BHT as radical inhibitors were performed following the same procedure, with variable amounts of BHT being employed. The radical trapping experiment with $CCl_4$ was performed in the same manner, with the following amounts of catalyst and reagents: 0.005 mmol of Tp$^{*,Br}$Ag, 0.1 mmol of PhINTs, 2 mL of cyclohexane, and 2 mL of $CCl_4$. At the end of the reaction (80 °C, 4 h), volatiles were removed and the residue was investigated by NMR. A 1:4 mixture of $C_6H_{11}Cl$ and $C_6H_{11}NHTs$ was detected, as inferred from the relative ratios of the resonances of the hydrogen nuclei located

(20) For Tp*Ag see: Bruce, M. I.; Walsh, J. D. *Aust. J. Chem.* **1979**, *32*, 2753.
(21) Yamada, Y.; Yamamoto, T.; Okawara, M. *Chem. Lett.* **1975**, 361.
(22) Trofimenko, S. *Scorpionates, The Coordination Chemistry of Polypyrazolylborate Ligands*; Imperial College Press, 1999.

in the carbon supporting the Cl or NHTs substituent (the spectrum is provided in the Supporting Information).

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**Supporting Information Available:** Data for the characterization of the amines in Table 1 and NMR spectra of several experiments. This material is available free of charge via the Internet at http://pubs.acs.org.

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