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Published on Web 08/19/2006

Facile Amine Formation by Intermolecular Catalytic Amidation of Carbon−Hydrogen Bonds

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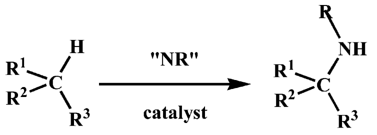
Abstract: A simple copper-based catalytic system has been developed for the carbon−hydrogen amidation reaction. The copper−homoscorpionate complex $Tp^{Br3}Cu(NCMe)$ catalyzes the transfer of the nitrene unit NTs (Ts = *p*-toluenesulfonyl) and its subsequent insertion into the sp^3 C−H bonds of alkyl aromatic and cyclic ethers or the sp^2 C−H bonds of benzene using PhI=NTs as the nitrene source, affording the corresponding trisubstitued NR^{1}HTs amines in moderate to high yields. The use of the environmentally friendly chloramine-T has also proven effective, with the advantage that sodium chloride is formed as the only byproduct. A tandem, one-pot consecutive nitrene−carbene insertion system has been developed to yield amino acid derivatives.

Introduction

The formation of carbon−nitrogen bonds is a topic of current interest in the field of homogeneous catalysis.[1,2] Several strategies have been developed in the past decade using late metal-based catalysts, most of them employing an already existing amine as the reagent. Therefore, these systems usually represent the formation of one amine by modification of another. In contrast, very few examples of the different approach of metal-catalyzed nitrene insertion into C−H bonds are known (eq 1).[3] This is in spite of the fact that two decades have passed since the initial discovery by Breslow and co-workers of the utility of manganese− and iron−tetraphenylporphyrin complexes[4a] or cytochrome P450[4b] to catalyze the tosylamidation of cyclohexane (eq 2), a process in which an NTs group (Ts = *p*-toluenesulfonyl) is inserted into the C−H bond of the cycloalkane. These, and the later report by Motherwell et al.[5] describing a similar behavior with iron(II) chloride, opened the way to search for new catalysts for this reaction. Mansuy and co-workers employed[6] a manganese−porphyrin complex to promote the allylic amination of alkanes, a metal later used by Katsuki.[7] Rhodium-based catalysts of composition Rh$_2$(L)$_4$ were independently described by Breslow[8] and Mueller,[9] the latter inducing for the first time a certain asymmetric induction in the reaction with indane. The intramolecular version has been developed by Du Bois et al.[10] in a multireagent reaction using PhI(OAc)$_2$, MgO, and Rh$_2$(OAc)$_4$ as the catalyst, which has also been applied to cyclooctane.[10c] More recently, Hashimito[11] has described the use of new Rh complexes for the amidation of benzylic C−H bonds. In recent years, ruthenium has been



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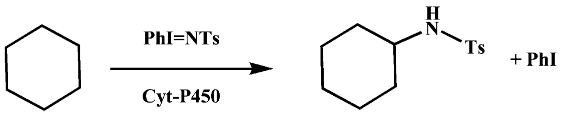

(2)

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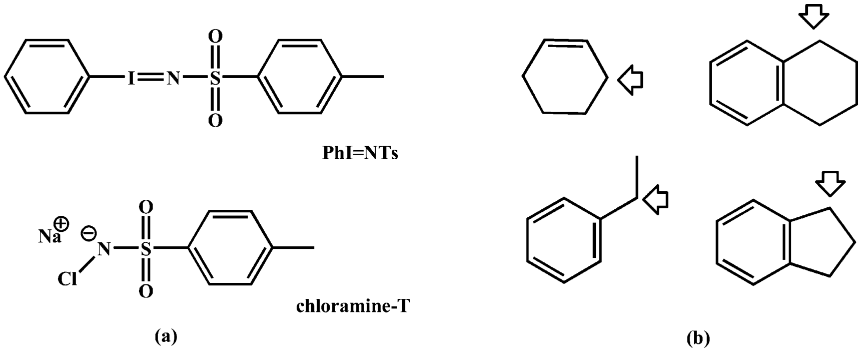
10.1021/ja0627850 CCC: $33.50 © 2006 American Chemical Society

Scheme 1. Nitrene Sources (a) and Substrates (b) Commonly Employed for the C−H Functionalization by Nitrene Insertion[a]

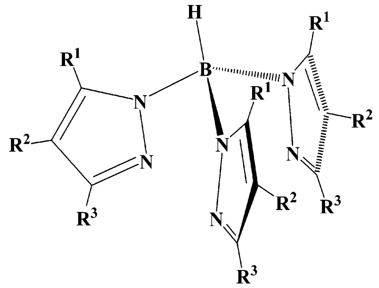


[a] Arrows indicate the insertion site.

proposed as an alternative to rhodium, after the report by Che et al.[12] on interesting mechanistic studies using ruthenium−porphyrins as the catalyst. Since that report, an extensive and exhaustive nitrene-transfer amidation procedure, either stoichiometric[13] or catalytic,[14] has been developed by this group in recent years. It is also worth mentioning the use of cobalt-based catalysts by Cenini and co-workers for the amination of the benzylic C−H bond with aryl azides.[15]

It is quite surprising that, considering the importance of the formation of carbon−nitrogen bonds, only the few systems mentioned above have been reported to date. This is also in contrast with the considerable number of contributions appearing in the literature describing metal-based catalysts for nitrene addition to olefins, in the well-known aziridination reaction.[3a,16] A closer look at the literature leads to the following conclusions: (i) most of these results involve the transfer of a nitrene group from iminoiodanes of formula PhI═NR, with some exceptions that employs chloramine-T or aryl azides (Scheme 1a); (ii) the substrates studied very often undergo nitrene insertion into allylic or benzylic C−H bonds, and usually at secondary carbons (Scheme 1b), examples with less reactive carbon−hydrogen bonds such as cyclohexane being rare; and (iii) the conversions into the desired products ranged from low to moderate. Thus, work in this area to improve the current state of the art should be focused on the development of an active catalyst for the general nitrene-transfer reaction from several sources to the C−H bond of a given substrate. With this aim in mind, we decided to study the catalytic potential of copper−homoscorpionate[17] complexes $Tp^xCu(L)$ for this transformation (Table 1). These studies have led to the discovery of an outstanding catalytic activity of the complex $Tp^{Br3}Cu(NCMe)$ (**1**) for the insertion of NTs units (Ts = *p*-toluenesulfonyl) into a variety of substrates, with either PhI═NTs or chloramine-T as the nitrene source and under mild conditions.

Table 1. Trispyrazolylborate Ligands Tp^x Employed in This Work



Tp^x	R^1	R^2	R^3
Tp^{Br3}	Br	Br	Br
Tp^{Ms}	H	H	2,4,6-$Me_3C_6H_2$
Tp^{Cy}	H	H	C_6H_{11}
Tp*	CH_3	H	CH_3

Results and Discussion

Amination of Cyclohexane, Benzene, and Other Aromatics with PhI═NTs. In a preliminary report,[18] we described the functionalization of the carbon−hydrogen bonds of benzene (eq 3) and cyclohexane (eq 4) by direct reaction with PhI═NTs in the presence of catalytic amounts of $Tp^{Br3}Cu(NCMe)$ (**1**) at room temperature. We later learned that an increase in the reaction temperature does not alter the conversion in the cyclohexane case but nearly doubles that of benzene. These degrees of conversion for the two substrates are, to the best of our knowledge, the highest described to date for these transformations, the formal insertion of the nitrene NTs unit into the sp^2 and sp^3 C−H bonds of benzene and cyclohexane, respectively. The yields correspond to the amount of the initial nitrene source incorporated into the hydrocarbon, the remainder being converted into $TsNH_2$ due to the presence of adventitious water. As mentioned above, the catalytic tosylamidation of cyclohexane by nitrene insertion has been known for years, since the seminal work by Breslow.[4] However, the conversions reported to

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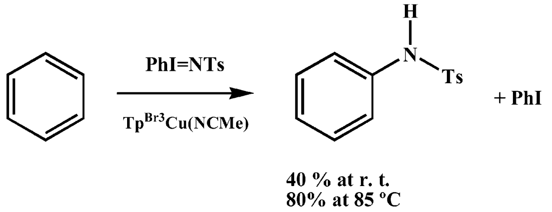

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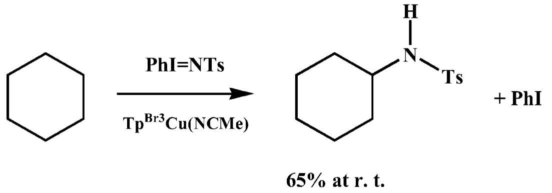

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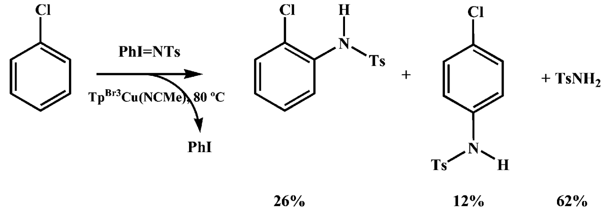

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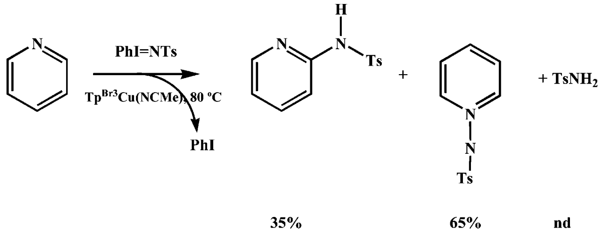

(6)

date[4,13d] are substantially lower (<10%) than the 65% value obtained with **1** and PhI═NTs.

Examples of the direct amination of benzene are sparse. The reaction of NH_3 and benzene under heterogeneous conditions has proven ineffective,[19] as has the use of transition metal-based systems for the reaction of benzene and other amines;[20] again, the conversions remained below the 20% limit. Regarding the use of nitrene sources, an earlier work by Ayyangar et al.[21] reported the stoichiometric reaction of tosyl azide with benzene at 160 °C. A mixture of compounds was obtained, with a very low yield of the insertion product. In the present system, the reaction of PhI═NTs in neat benzene in the presence of 5% of **1** as the catalyst has led to the formation of 80% of the aniline derivative, as shown in eq 3. After our initial report, a phenantroline-containing copper catalyst was reported to insert NTs fragments into the sp^2 C−H bonds of only electron-rich arenes of formula $(MeO)_2C_6H_4$ in moderate yield.[22]

After the functionalization of the C−H bond of benzene, we tried two substituted derivatives, chlorobenzene and (trifluoromethyl)benzene. No H-containing derivatives could be employed, since insertion into the corresponding C−H bond of the substituent was observed in such cases (as in $MeOC_6H_5$). The use of Tp^{Br3}Cu(NCMe) in catalytic amounts at 80 °C did not induce any detectable formation of the insertion product in the case of (trifluoromethyl)benzene; only complete conversion of PhI═NTs into tosylamine was observed. However, the use of chlorobenzene as the substrate led to the formation of a mixture of the two possible isomers, the ortho and para derivatives (eq 5), in addition to tosylamine. The conversion into the insertion products was lower (38%) than for benzene, whereas the ortho and para isomers were obtained in nearly statistical ratios. The use of pyridine as a substrate has also accomplished this transformation (eq 6), with no tosylamine being observed. However, the major product was not that of the formal insertion of the nitrene moiety into the ortho position of the pyridine but C_6H_5N−NTs, a zwitterionic compound already described in this type of transformation.[22b] Therefore, we have found that the insertion of the nitrene unit NTs from PhI═NTs, catalyzed by **1**, can be achieved with several aromatic compounds, although in moderate yields, and in the absence of strong deactivating substituents.

Amination of Alkyl Aromatics with PhI═NTs. Toluene and mesitylene were also studied in our initial report, leading to nearly quantitative conversions into the corresponding amines upon reaction with PhI═NTs in the presence of **1** at room temperature. The observed yields are higher than those reported with rhodium-,[11] ruthenium-,[13a] and cobalt-based[15b] catalysts, which fall in the range 9−22% for the toluene case. A series of other alkyl aromatic substrates has been studied, and the results are shown in Table 2. Ethylbenzene was converted into a mixture of two products as the result of the insertion of the nitrene group into the primary and the secondary C−H bonds of the ethyl fragment, in 80% overall yield (20% of $TsNH_2$ after initial 100% of PhI═NTs). This is a quite singular result, since in spite of the common use of this substrate by other groups,[11,12,13a,14c] due to the easiness of functionalization of the benzylic sites, we have found no other example of the activation of the primary C−H bonds of ethylbenzene; the insertion at primary sites not directly bonded to the aromatic ring seems to be unprecedented. This behavior is not limited to ethylbenzene, since other mono- and bis-alkyl aromatic substrates also show a similar reactivity. Thus, the use of *p*-ethyltoluene (Table 2, entry 4) led to a mixture of three products due to the insertion into the three distinct sp^3 C−H bonds. Cumene (entry 5) and *p*-cymene (entry 6) were also studied, showing the expected mixture of products derived from the activation of *all* the alkylic carbon−hydrogen bonds. All the reactions were performed at room temperature, and PhI═NTs was completely consumed after several hours. The yields varied from high to moderate with increasing steric bulk of the substrate, the lowest yields being obtained with those substrates containing the isopropyl group. The use of cumene with other reported catalysts led to the exclusive formation of the product derived from the insertion of the nitrene unit into the tertiary sites.[13a,14c]

The data in Table 2 refer to the distribution of products. In order to establish an order of reactivity, these values should be normalized with the number of hydrogens of each type. Table 3 displays such values, from which a direct comparison between

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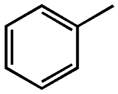
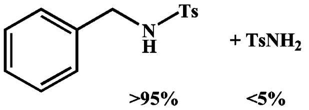
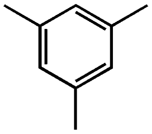
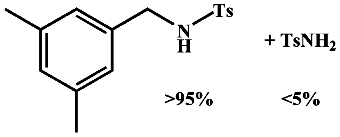
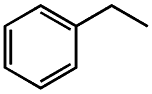
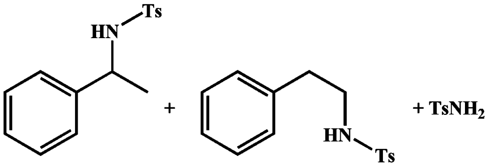
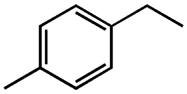
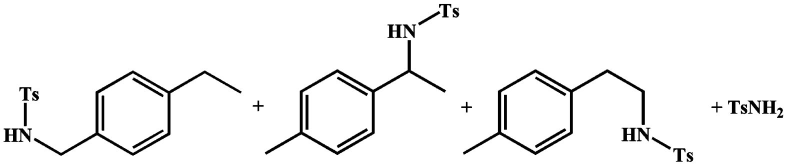
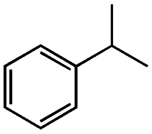
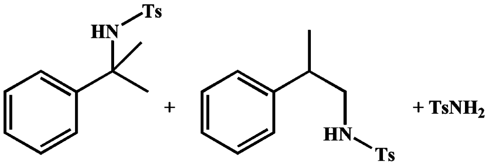
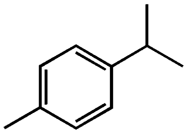
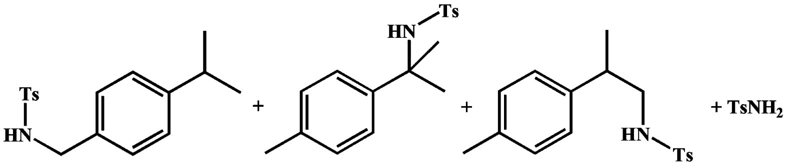
Table 2. Reaction of PhI=NTs and Alkyl Aromatics in the Presence of **1** as the Catalyst[a]

Entry	Substrate	Distribution of Products[b]
1		 >95% <5%
2		 >95% <5%
3		 56% 14% 30%
4		 9% 58% 19% 14%
5		 30% 20% 50%
6		 20% 20% 10% 50%

[a] Reactions were performed at room temperature; see Experimental Section for details. [b] Determined by GC and NMR at the end of the reaction after total consumption of PhI=NTs. Iodobenzene was also obtained as a byproduct.

different sites can now be obtained. In all cases, the secondary and tertiary sites in position B display the highest reactivity, followed by the position C methyl groups. The toluene-like methyl group at position A seems to be the least reactive, although in the case of *p*-cymene its reactivity is comparable to that at position B. The regioselectivity follows the general trend tertiary sites > secondary sites > C primary sites ≥ A primary sites. It is worth mentioning that previous work from this laboratory has shown that the use of complex **1** as the catalyst for the reaction of ethyl diazoacetate (EDA) and these alkyl aromatic substrates did not induce the insertion of the carbene **:**$CHCO_2Et$ group into the primary sites when secondary sites were available: for ethylbenzene and *p*-ethyltoluene, only the CH_2 bonds were modified.[23] However, in the case of the reaction of alkanes and EDA, a similar trend, tertiary > secondary ≫ primary, was observed.[24] Although this tendency is parallel to the trend in the bond energies and opposite to the steric effect, the decrease in the conversion into amines with increasing bulk of the substrates, clearly observable by comparing ethylbenzene and cumene (Table 2, entries 3 and 5) or *p*-ethyltoluene and *p*-cymene (entries 4 and 6), seems to indicate that sterics play a certain role in this transformation.

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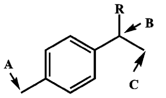
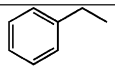
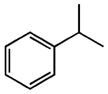
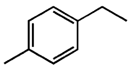
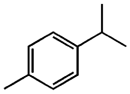
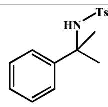
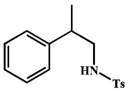
Table 3. Observed Regioselectivity[a] in the Reaction of PhI═NTs and Alkyl Aromatics in the Presence of **1** as the Catalyst

	Substrate	A	B	C
		---	3.5	1
		---	9	1
		0.5	4.6	1
		2	6	1

[a] Values normalized for the relative number of C−H bonds of each type.

Table 4. Reaction of PhI═NTs and Cumene in the Presence of Tp^{x}Cu as the Catalyst[a]

Catalyst			TsNH$_2$
Tp*Cu	13 (57)	9 (43)	78
Tp^{Cy}Cu	11 (36)	19 (64)	70
Tp^{Ms}Cu	1 (5)	16 (95)	83
Tp^{Br3}Cu(NCMe)	30 (59)	20 (41)	50

[a] Reactions were performed at room temperature; see Experimental Section for details. Yields were determined by GC and NMR at the end of the reaction, after total consumption of PhI═NTs. Values correspond to distribution of products; regioselectivities are given in parentheses.

Since the Tp^{x}Cu system has been reported to catalyze several transformations involving carbene transfer from ethyl diazoacetate, being markedly influenced by the structure of the Tp^x ligand,[25] we have performed a series of experiments with a somewhat bulky substrate, cumene, and four Tp^{x}Cu complexes as the catalyst (Table 4), with complex **1** inducing the highest conversion into amines. There is not a simple explanation for the observed sequence of the conversion values in this set of experiments. Previous studies with this family of complexes, regarding the olefin aziridination reaction, have shown that this transformation differs from the carbene-transfer reaction[26] and that the participation of metalloradical species could be invoked. The Tp*- and the Tp^{Br3}-containing catalysts gave similar amounts of the two products. This is in good accord with previous work that demonstrated these two ligands to be isosteric.[17,27] The other two catalysts, containing the more sterically demanding Tp^{Cy} and Tp^{Ms},[17] provided higher amounts of the product derived from the insertion into the less hindered position, i.e., the primary sites.

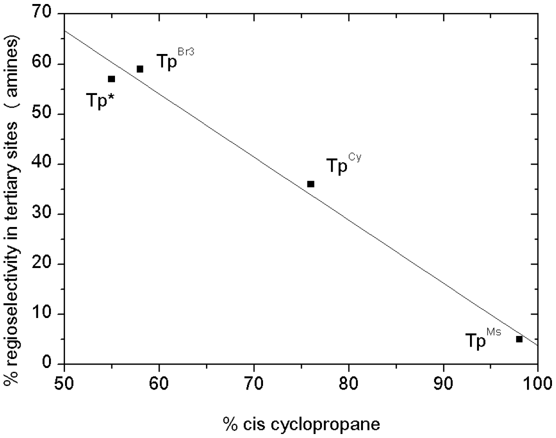


Figure 1. Correlation of the regioselectivity in the amination of tertiary sites of cumene with PhI═NTs and the cyclopropanation of styrene with EDA with Tp^{x}Cu as the catalyst.

We interpret these results in the following manner: the nitrene-transfer process, *whatever its nature* (radical or not), takes place in such a way that the transition metal catalyst influences the distribution of products. We have compared the data shown in Table 4 with those obtained with the same group of catalyst in the styrene cyclopropanation reaction with EDA.[28] A plot of the percent regioselectivity of the most hindered product (tertiary activation) in Table 4 vs the percentage of the *cis*-cyclopropane with the same catalyst is shown in Figure 1, where a linear correlation is observed. The Tp^{Ms}Cu complex gave ca. 98% of the *cis*-cyclopropane, which was explained as the consequence of a small catalytic pocket. In good accord with this, the most hindered position in cumene is less favored with this catalyst. The largest catalytic pocket is assigned to Tp* and Tp^{Br3}, which gave similar amounts of the *cis*-cyclopropanes (55 and 58%, respectively), matching the regioselectivities of the amines obtained by nitrene insertion (57 and 59%, respectively). There is only one possible explanation for this behavior: in both cases (carbene transfer from EDA and nitrene transfer from PhI═NTs), the catalytic pocket is largely defined by the geometry of the Tp^{x}Cu core, and the relative increase or decrease in the volume of such a pocket when moving from one ligand to another is similar in the two cases.

Amination of Cyclic Ethers with PhI═NTs. In the related carbene-transfer reaction from EDA catalyzed by Tp^{x}Cu complexes, we have found that cyclic ethers are easily transformed into products derived from insertion into the C−H bond located at the α-carbon vicinal to oxygen.[24b,29] We have now evaluated the reactivity of this class of substrates toward the nitrene insertion reaction, using PhI═NTs as the NTs source. Following a procedure similar to that employed in the previous section, a series of cyclic ethers has been converted in the corresponding amines, in moderate to high yield. As shown in Table 5, the four ethers employed were functionalized and converted into amines by insertion of the NTs fragment into the α-C−H bond, similar to the above-mentioned carbene insertion reaction. This nitrene-selective insertion has been also observed in the case

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(25) For a review, see: Díaz-Requejo, M. M.; Pérez, P. J. *J. Organomet. Chem.* **2005**, *690*, 5441.

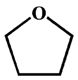
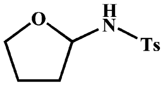
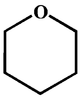
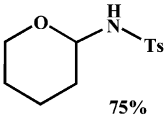
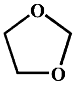
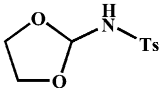
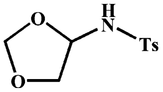
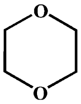
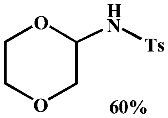
(26) Díaz-Requejo, M. M.; Pérez, P. J.; Brookhart, M.; Templeton, J. L. *Organometallics* **1997**, *16*, 4399.

(27) Rodríguez, P.; Díaz-Requejo, M. M.; Belderrain, T. R.; Trofimenko, S.; Nicasio, M. C.; Pérez, P. J. *Organometallics* **2004**, *23*, 2162.

(28) (a) Díaz-Requejo, M. M.; Caballero, A.; Belderrain, T. R.; Nicasio, M. C.; Trofimenko, S.; Pérez, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 978. (b) Díaz-Requejo, M. M.; Belderrain, T. R.; Trofimenko, S.; Pérez, P. J. *J. Am. Chem. Soc.* **2001**, *123*, 3167.

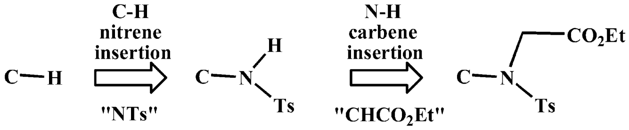
(29) Díaz-Requejo, M. M.; Belderrain, T. R.; Nicasio, M. C.; Trofimenko, S.; Pérez, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 896.

Table 5. Reaction of PhI=NTs and Cyclic Ethers in the Presence of **1** as the Catalyst[a]

Entry	Substrate	Distribution of Products[b]
1		 + TsNH$_2$ >98% <2%
2		 + TsNH$_2$ 75% 25%
3		 +  + TsNH$_2$ 15% 45% 40%
4		 + TsNH$_2$ 60% 40%

[a] Reactions were performed at room temperature; see Experimental Section for details. [b] Determined by GC and NMR at the end of the reaction, after total consumption of PhI=NTs. Iodobenzene was also obtained as a byproduct.

Scheme 2. Strategy for the Formation of Secondary and Tertiary Amines



of tetrahydrofuran by Che and co-workers, who reported 93% conversion with a Ru-based catalyst.[14h] We have found no previous reports for the other cyclic ethers shown in Table 5 using PhI=NTs as the nitrene source. In our case, the use of substrates with two ether functionalities, where all the C−H bonds are vicinal to oxygen, gave moderate conversions (60% for dioxolane and dioxane). In the case of dioxolane, a mixture of two products, with a nearly statistical distribution, was obtained.

Toward Green Chemistry: Use of Chloramine-T as Nitrene Source. The catalytic activity displayed by complex **1** for nitrene transfer from PhI=NTs presented in the previous sections constitutes, in our opinion, an important advance in the area of the catalytic formation of carbon−nitrogen bonds and the subsequent generation of amines. As pointed out above, the use of PhI=NTs generates stoichiometric amounts of iodobenzene. In order to eliminate this byproduct, we have studied the use of the inexpensive, commercially available chloramine-T (Scheme 1) in this transformation. Thus, a series of experiments with several substrates, such as cyclic ethers or alkyl aromatics, was carried out in the presence of complex **1** as the catalyst, and the results are shown in Table 6.

There are very few reports of the use of this nitrene source for the intermolecular amidation of carbon−hydrogen bonds. Sharpless and co-workers described a bromine-induced aziridination, with minor amounts of the allylic amidation products, using chloramine-T.[30] Later, Taylor et al. described the copper-induced amination of activated hydrocarbons[31a] and ethers.[31b] The use of the related bromamine-T in the benzylic amination with a rhodium-based catalyst was reported by Bedekar.[32] The direct comparison of the conversions shown in Table 6 and these previous examples in the literature is quite straightforward. The quantitative conversion observed for tetrahydrofuran is higher than that already reported.[32] The use of this methodology for toluene, mesitylene, and tetrahydropyran is, to the best of our knowledge, yet unknown, these results being the first examples for such molecules.

Consecutive Nitrene and Carbene Insertions: One-Pot Synthesis of Glycine Derivatives. On the basis of our results reported above, we decided to take advantage of the catalytic capabilities of complex **1** toward both the nitrene transfer (from PhI=NTs or chloramine-T) and the decomposition of EDA and subsequent carbene transfer. Since the insertion of the NTs fragment into a C−H bond results in the formation of a secondary amine, we wondered if the addition of EDA to that amine, with **1** in the reaction mixture, would lead to the formation of the corresponding tertiary amine due to the insertion of the **:**CHCO$_2$Et group into the amine N−H bond (Scheme 2).[33] We have chosen toluene as a representative example. As described in the previous sections, this hydrocarbon can be converted into the corresponding amine using either chloramine-T or PhI=NTs as the nitrene surce, in moderate

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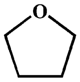
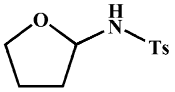
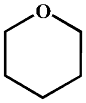
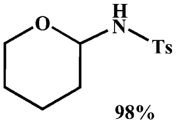
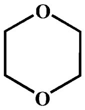
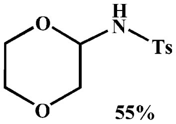
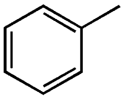
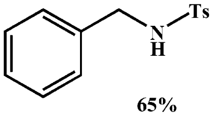
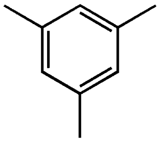
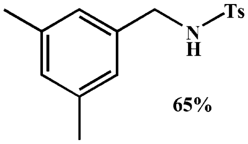
(30) Jeong, J. U.; Tao, B.; Sagasser, I.; Henniges, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1998**, *120*, 6844.

(31) (a) Albone, D. P.; Aujla, P. S.; Taylor, P. C. *J. Org. Chem.* **1998**, *63*, 9569. (b) Albone, D. P.; Challenger, S.; Derrick, A. M.; Fillery, S. M.; Irwin, J. L.; Parsons C. M.; Takada, H.; Taylor, P. C.; Wilson, D. J. *Org. Biomol. Chem.* **2005**, *3*, 107.

(32) Chanda, B. M.; Vyas, R.; Bedekar, A. V. *J. Org. Chem.* **2001**, *66*, 30.

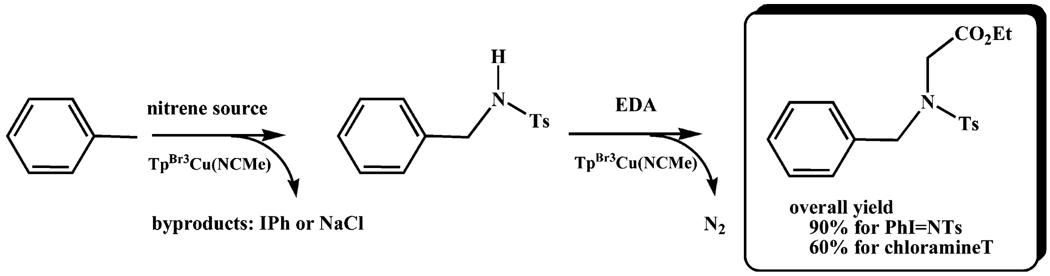
(33) For metal-catalyzed carbene insertion into N−H bonds, see: Morilla, M. E.; Díaz-Requejo, M. M.; Belderrain, T. R.; Nicasio, M. C.; Trofimenko, S.; Pérez, P. J. *Chem. Commun.* **2002**, 2998 and references cited therein.

Table 6. Amidation of C–H Bonds with Chloramine-T in the Presence of **1** as the Catalyst[a]

Entry	Substrate	Distribution of Products[b]
1		 + $TsNH_2$ >98% <2%
2		 + $TsNH_2$ 98% <2%
3		 + $TsNH_2$ 55% 45%
4		 + $TsNH_2$ 65% 35%
5		 + $TsNH_2$ 65% 35%

[a] Reactions were performed at room temperature; see Experimental Section for details. [b] Determined by GC and NMR at the end of the reaction, after total consumption of chloramine-T.

Scheme 3. Consecutive Nitrene and Carbene Insertions



(65%) to high (>95%) yield, respectively. Once this transformation took place, and after removal of the volatiles, the residue was dissolved in methylene chloride and the mixture was treated with a slight excess of EDA (1.2 equiv referred to the initial nitrene source, see Experimental Section). Conversion of the secondary into the tertiary amine was complete (Scheme 3), with some diethyl fumarate and maleate, accounting for the excess of EDA. This reaction constitutes, to our knowledge, the first example of the synthesis, in a one-pot, two-step transformation, of an amino acid derivative using a hydrocarbon as the starting material. It is worth mentioning that the use of chloramine-T leads to the formation of NaCl and molecular dinitrogen as the sole byproducts in this transformation, and thus it could be considered a *green* process. We are currently exploring this strategy with the aim of ensuring quantitative conversions in the two steps when using chloramine-T, a goal that has already been achieved with PhI=NTs.

Conclusions

We have found that the complex $Tp^{Br3}Cu(NCMe)$ displays a singular catalytic activity toward the nitrene-transfer reaction and the subsequent insertion of such units into the carbon–hydrogen bond of a series of substrates, including benzene, cyclohexane, alkyl aromatics, and cyclic ethers. The conversions found are usually higher than those reported in the literature, and the wide number and nature of the substrates studied in this work clearly evidences a general behavior of this catalyst in this reaction. The use of the environmentally friendly chloramine-T as the nitrene source has also been studied, with results similar to those observed with PhI=NTs. A very interesting transformation for the direct synthesis of amino acids has been developed, in what can be envisaged as a new strategy for the synthesis of these very useful molecules.

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 prior to their use. The presence of adventitious water in the reaction mixture dramatically decreased the conversions, due to the formation of tosylamine. The complex $Tp^xCu(NCMe)$ and the other Tp^xCu complexes were prepared according to the literature. PhI═NTs was also prepared following the already reported methods, whereas chloramine-T trihydrate was purchased from Aldrich and dried under vacuum before use. NMR experiments were run in a Varian Mercury 400 MHz spectrometer. GC data were collected with a Varian GC-3900 with a TSD detector.

General Catalytic Procedure for Nitrene Insertion. Inside the drybox, 0.025 mmol of **1** was dissolved in neat substrate (10 mL). Molecular sieves were added to absorb the remaining water (if any). PhI═NTs (0.5 mmol) was added in one portion to the solution, which was stirred until complete dissolution of PhI═NTs (time varied from 1 to 18 h, depending on the substrate). The greenish solution was filtered to remove the sieves and was investigated by GC, with a specific detector (TSD) for N-containing compounds. Volatiles were then removed under vacuum, and the residue was investigated by NMR. Most of the products have previously been described in the literature (see Supporting Information) and were directly characterized by comparison of their NMR data. Those yet unknown were characterized (see Supporting Information). In all cases, a mixture of the insertion product(s) and tosylamine was obtained, the conversions being easily measured by relative ^1H NMR integral. The procedure employed in the case of chloramine-T was nearly identical. Only in the cases of toluene and mesitylene was the reagent added dissolved in 5 mL of acetonitrile, instead of direct addition of the solid.

The products were isolated following already described methods.[14e,31b] The reaction mixture was filtered through Celite to remove the solid formed from the sieves due to the stirring, and the resulting clear solution was then passed through a plug of silica before the final silica gel chromatography. In the case of the hydrocarbons, a mixture of *n*-hexane/ethyl acetate (6:1, v/v) was employed as the elutant, whereas for the cyclic ethers, 10% ethyl acetate in methylene chloride was used instead. The isolated yields corresponded to ca. 80−90% of the conversions quantified by GC and NMR.

Consecutive Nitrene and Carbene Insertions. A 0.025 mmol portion of **1** was dissolved in toluene (10 mL), and the nitrene source, PhI═NTs or chloramine-T, was added (0.5 mmol) in the presence of molecular sieves. After complete dissolution of the nitrene source (30 min), the mixture was filtered and the filtrate was taken to dryness. The residue was dissolved in petroleum ether, and the volatiles were again removed. This procedure was performed twice to ensure the complete removal of toluene. The final residue was dissolved in methylene chloride. A solution of EDA (0.7 mmol) in CH_2Cl_2 (10 mL) was slowly added over that solution for 8 h. After that time, the volatiles were removed, and the residue was investigated by NMR, showing quantitative formation of the desired product (Scheme 3). The product was isolated by the previous procedure in 57% and 88% yields for chloramine-T or PhI═NTs, respectively.

Acknowledgment. MEC is acknowledged for financial support of this work (CTQ2005-00324/BQU). The Universidad de Huelva (NMR Service), MEC (M.R.F.), and the Ramon y Cajal Program (M.M.D.-R.) are also acknowledged. This paper is dedicated to Prof. Victor Riera on the occasion of his retirement.

Supporting Information Available: NMR data for the new compounds and reference data for the already reported compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

JA0627850