

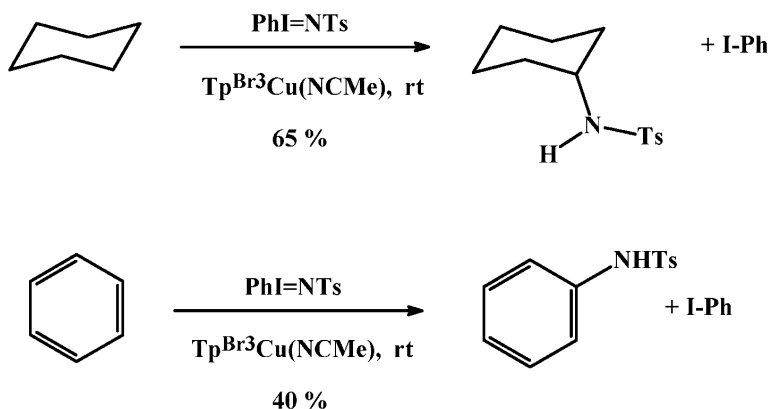
Communication

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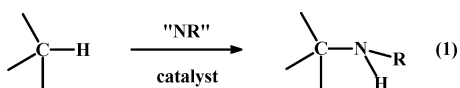
Cyclohexane and Benzene Amination by Catalytic Nitrene Insertion into C–H Bonds with the Copper-Homoscorpionate Catalyst $\text{Tp}^{\text{Br}_3}\text{Cu}(\text{NCMe})$

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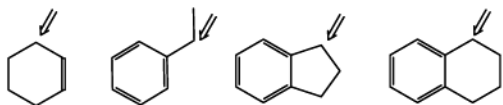
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One of the most interesting reactions to functionalize a carbon–hydrogen bond consists of the catalytic formation of an amine by means of the formal insertion of a nitrene group into such unit, in the so-called amination reaction (eq 1). This methodology has been



known for years since the seminal work by Breslow and co-workers,¹ that demonstrated the capabilities of the Cytochrome P450 for the tosylamidation of cyclohexane, that is, the insertion of a NTs fragment ($\text{Ts} = p\text{-tolylsulfonyl}$) into a C–H bond. Motherwell et al.² later reported the use of ferrous chloride as the catalyst for this transformation. The yields in both cases were low, but these reactions heralded the opening of a new field in the area of C–N bond formation. In recent years, impressive results have been obtained by Che and co-workers,³ showing the capabilities of ruthenium porphyrins for the tosylamination reaction. Other manganese-,⁴ cobalt-,⁵ rhodium-⁶ or copper-based⁷ systems have also been reported to induce this insertion reaction. However, most of these results supposed the transfer of a nitrene group from iminoidanes of formula $\text{PhI}=\text{NR}$ to substrates that contain a somewhat activated carbon–hydrogen bond (Scheme 1): allylic or benzylic C–H bonds have been the preferred reaction sites for the above catalytic systems, whereas very few examples of the tosylamidation of unactivated C–H bonds have been reported to date. Thus, the conversion of cyclohexane into *N*-(*p*-tolylsulfonyl)-aminocyclohexane has been reported only in a few cases, and has never been achieved in yields higher than 20%, based in the nitrene

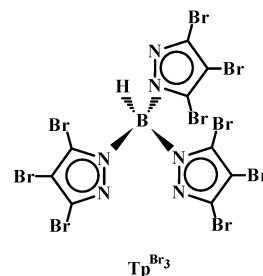
Scheme 1. Usual Substrates Employed in the Metal-Catalyzed Tosylamidation Reaction by Nitrene Insertion; Arrow Indicates the Reaction Site



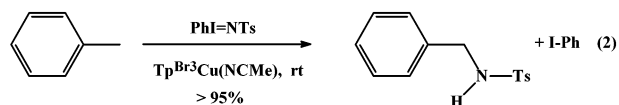
source.^{1–3h} Another representative example is toluene: in contrast with the common use of ethylbenzene as a probe molecule for this transformation, and the ease with which its secondary sites have been activated, the primary C–H bonds of toluene have remained unreactive by this method for the majority of catalysts reported, with just a few exceptions.^{3h,5} The extreme case of a molecule of considerable interest to be converted into an amine is benzene: aniline is currently obtained by indirect methods that require the

conversion of benzene into other derivatives such as nitro- or chlorobenzene, or into phenol as an intermediate step. Despite that interest, very few examples for the amination of benzene have been reported to date.⁸

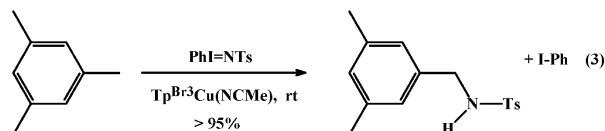
In recent years we have studied the use of copper(I)–homoscorpionate⁹ complexes as catalysts for the carbene,¹⁰ nitrene,¹¹ and oxo¹² transfer reactions to a variety of substrates. Now we have turned our attention toward the amination of C–H bonds, and we have tested the catalytic capabilities of this type of complex toward such transformation. We have chosen $\text{Tp}^{\text{Br}_3}\text{Cu}(\text{NCMe})$ (**1**), a



compound that is readily prepared by direct reaction of $\text{TiTp}^{\text{Br}_3}$ and CuI to carry out this preliminary study.^{10h} When PhINTs^{13} (0.5 mmol) was added to a solution of **1** (0.025 mmol) in neat toluene (10 mL), the initial suspension gradually converted into a solution. After 1 h of stirring, a clear, greenish solution was obtained. GC and NMR studies revealed the quantitative conversion of toluene into *N*-(*p*-tolylsulfonyl)aminotoluene (eq 2). As mentioned above,



other authors have reported related transformations in low yields. Thus, Che et al.^{3h} reported a 11% yield for the stoichiometric transfer from a ruthenium complex, whereas Cenini and co-workers⁵ obtained even lower conversions of such amines when using cobalt–porphyrin catalysts and azides as the nitrene source. The related reaction with mesitylene has also been investigated, with very similar results: quantitative conversion of the nitrene source into the corresponding amine (eq 3) has been observed. To our

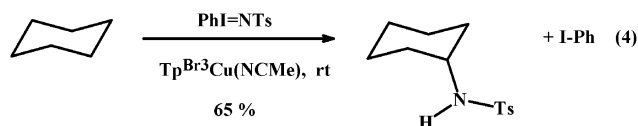


knowledge, the activation of such primary C–H bonds of toluene

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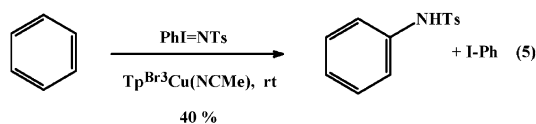
and mesitylene by this methodology and with these degrees of conversion finds no precedent in the literature.

Having demonstrated the exceptional catalytic activity of the complex $\text{Tp}^{\text{Br}^3}\text{Cu}(\text{NCMe})$ toward the tosylamidation of those primary C–H bonds, we wondered about its behavior when facing secondary carbon–hydrogen sites. However, instead of using ethylbenzene, we have employed the less reactive cyclohexane.



Under conditions similar¹⁴ to those employed for toluene and mesitylene, cyclohexane has been converted into *N*-(*p*-tolylsulfonyl)aminocyclohexane in 65% yield, based in PhINTs. *p*-Toluene-sulfonamide, TsNH_2 , was also obtained, accounting for 100% of the initial PhINTs, resulting from the presence of adventitious water. Therefore, experimental work must be carried out with special precaution to avoid the presence of water in the reaction mixture. As pointed out above, very few examples for this reaction have appeared in the literature. The initial report by Breslow gave a 3% yield,¹ whereas Che^{3h} has reported a 10% yield for a stoichiometric nitrene transfer with Ru–porphyrins. Regarding the use of copper for these transformations, only reports by Katsuki^{4b} and Taylor^{4a} refer to the use of this metal, and only with the aforementioned activated substrates: the use of copper for the tosylamidation of cyclohexane seems to be restricted to the system we present herein.

We have also carried out the reaction of PhINTs and benzene in the presence of catalytic amounts of **1** following an identical procedure. After the complete dissolution of the nitrene precursor, the resulting solution was analyzed by GC as well as by NMR. A mixture of TsNH_2 and *N*-(*p*-tolylsulfonyl)aminobenzene in a 60:40 ratio was observed (eq 5), the latter compound being formed as



the result of the formal insertion of the nitrene group into the carbon–hydrogen bond of the benzene ring. A noncatalytic method for the synthesis of such amine was reported by Ayyangar et al.^{8c} in low yield and as part of a mixture of compounds. Ingresso later reported^{8d} the reaction of benzene and diethylamine in the presence of a complex Ir/Hg system, that gave diethylaniline in ca. 20% yield at 130 °C. Heterogeneous catalysts under drastic conditions have been employed for the direct reaction of benzene and ammonia,^{8a,c} but with low conversions. Similar results have been obtained when using several transition metals as catalysts for the reaction of benzene and hydroxylamine. On the basis of these data, the procedure reported in this contribution for the amidation of benzene constitutes, to our knowledge, the first example of such transformation that provides the aniline derivative in acceptable yields, under very mild conditions and with a simple catalyst.

In conclusion, we have discovered that the complex $\text{Tp}^{\text{Br}^3}\text{Cu}(\text{NCMe})$ catalyzes the insertion of a nitrene group into the carbon–hydrogen bond of cyclohexane and benzene, as well as into the primary C–H bonds of the methyl groups of toluene and mesitylene, in moderate to high yield, respectively. We believe

that these findings will allow the design of new catalysts that will lead to the achievement of higher conversions as well as to the control of the selectivity with the use of the appropriate ligands around copper.

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- (14) General catalytic procedure: inside a drybox, 0.025 mmol of **1** was dissolved in neat toluene or mesitylene (10 mL). Molecular sieves were added to diminish the presence of water. PhINTs (0.5 mmol) were added in one portion to the solution. After 1 h stirring, no solid PhINTs was observed. The greenish solution was filtered to retire the sieves and was investigated by GC. Volatiles were removed under vacuum, and the residue was investigated by NMR. Spectroscopic data were similar to those reported by Che for related compounds (ref 3h). In the case of the less reactive cyclohexane and benzene, a 1:20 ratio of **1** and PhINTs was employed, and the reaction times were up to 12–18 h. The cyclohexane derivative was identified by NMR, the spectra being identical to those reported by Che (ref 3h). The benzene derivative was characterized by comparison with an authentic sample prepared by reaction of aniline and tosyl chloride in the presence of base.

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