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Pyrrole functionalization by copper-catalyzed nitrene transfer reactions

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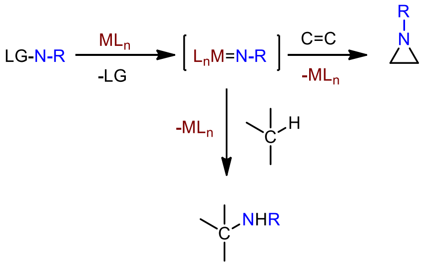
Dedicated to Professors Steve L. Buchwald and John F. Hartwig, always inspiring to those building up carbon-nitrogen bonds.

Abstract: The catalytic functionalization of pyrroles by incorporation of a nitrene group is reported. The Cα-H bond of 1H-pyrrole is amidated upon the formal insertion of the NTs (Ts =p-toluenesulfonyl) group catalyzed by $Tp^{Br3}Cu(NCMe)$ (Tp^{Br3} = hydrotris(3,4,5-tribromo-pyrazolyl)borate). N-protected pyrroles also verify the same transformation. The mechanism proposal is similar to that previously described for benzene amidation with the same catalyst and PhI=NTs, which takes place through aziridine formation, ring opening and 1,2-hydrogen shift. Also, a cascade reaction involving the coupling of 2,5-dimethylfuran, 1,2,3-trimethyl-pyrrole and a nitrene NTs group is also described, leading to a 1,2dihydropyridine-imine compound.

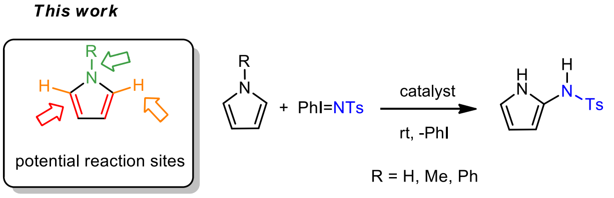
Keywords: nitrene transfer – pyrrole functionalization – C-H amidation – copper catalysis- copper nitrene

1. Introduction

The formation of C_{sp2}-N bonds in a catalytic manner is probably one of the most frequent processes nowadays in catalytic organic synthesis. After decades of development of Goldberg-Ullman protocols, [1] Buchwald-Hartwig methodology emerged to dominate the current panorama.[2] At a lower, but with increasing interest, the metal-catalyzed transfer of nitrene groups from azides or hypervalent iodine reagents also constitutes a strategy toward such goal, which has been crucial in the area of olefin aziridination of C-H amidation, among others, both inter- and intramolecularly.[3] The substrates modified upon addition or insertion of a nitrene group also include arenes, allenes, or heterocycles such as pyridine or furans. In spite of the continuous development in this area, we noticed that literature reports of the use of pyrroles as substrates for the incorporation of nitrenes in a catalytic manner are scarce. [4] This is despite the existence of several potential reaction sites in this molecule capable of interacting with the electrophilic metal-nitrene intermediate[5] responsible for the transfer step. Thus, pyrrole displays two olefinic sites, which may add the nitrene leading to aziridine rings, as well as C_{sp2}-H and N-H bonds also susceptible of being modified. In view of our experience in the use of group 11 metal-based catalysts for nitrene transfer[6] from PhI=NTs (Ts = p-toluensulfonyl) and the lack of reports on the use of pyrrole as the substrate in this context, we have focused on this goal. Herein we report the first example of the modification of 1H-pyrrole as well as several N- and ring-substituted pyrroles upon



Scheme 1. Most common C-N bond formation by metal catalysed nitrene insertion: olefin aziridination and C-H amidation.



Scheme 2. Left: potential reaction sites toward attack by the metal-nitrene species. This work: the reaction with 1H- or N-substituted pyrroles takes place onto the C_{sp2}-H bond in an exclusive manner.

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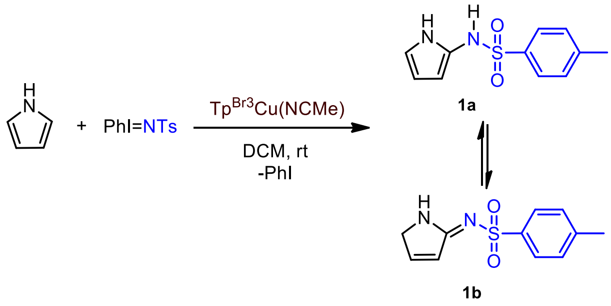
incorporating the NTs group to the C_{sp2}-H bonds or, when available, the C_{sp3}-H bonds of alkyl groups available in the pyrrole substrate.

2. Results and Discussion

2.1. Metal-catalyzed 1H-pyrrole functionalization by nitrene incorporation from PhI=NTs.

In view of the lack of examples for the nitrene transfer reaction to 1H-pyrrole, we first investigated the use of the complex $Tp^{Br3}Cu(NCMe)$ (Tp^{Br3} = hydrotris(3,4,5-tribromopyrazolyl)borate) as the catalyst for the tranfer of a NTs (Ts = p-toluensulfonyl) from PhI=NTs to 1H-pyrrole, in view of the previously described capabilitites of such copper complex to functionalize unsaturated substrates such as arenes, olefins, furanes or alkynes.[7] A 1:20:200 mixture of [Cu]:[PhI=NTs]:[pyrrole] was stirred at room temperature until all the nitrene precursor was dissolved. After elimination of volatiles, the reaction crude was investigated by NMR, showing the formation of pyrrole derivatives as inferred from the number of resonances due to several C_{sp2}-H bonds. After column chromatographic purification, a solid was obtained for which NMR studies revealed the presence of one pure compound, **1a** (Scheme 3), derived from the formal insertion of the nitrene NTs group into the C_α-H bond of pyrrole. However, when dissolved, it rapidly equilibrates with its imine isomer until a ca. 1:1 mixture is reached. Fortunately, both compounds could be characterized from extensive NMR studies (see Supporting Information). We noticed that such mixture was already present at the end of the catalytic reaction, allowing the determination of their yield with an internal standard. Unfortunately, **1b** could not be isolated from chromatography experiments. We are not aware of any literature precedent for the incorporation of a nitrene unit onto 1H-pyrrole by this methodology.



Scheme 3. Catalytic incorporation of nitrene units to 1H-pyrrole.

2.2. Catalyst screening and optimization of reaction conditions.

We next screened a number of catalysts previously described for nitrene transfer reactions,[3,6,7] as well as several Lewis acids, since they have also been reported toward that end. Figure 1 displays the results, showing that our first election ($Tp^{Br3}Cu(NCMe)$ was in fact the most appropriate catalyst, reaching ca. 45% yield (PhI=NTs-based) into the mixture of **1a:1b**. The remaining of the initial nitrene precursor was converted into $TsNH_2$, a common byproduct in these transformations. Other copper complexes were also effective in the incorporaion of the NTs group into the pyrrole ring, within the 12-25% yield range. $Cu(acac)_2$ provided the second best result, whereas Cu(OTf) led to the lowest value for the series of copper catalysts. At variance with this metal, the use of silver or rhodium was not effective toward this transformation, in the same way that Lewis acids such as $Sc(OTf)_3$ or $Fe(OTf)_2$. Only $AlCl_3$ gave ca. 10% yield into the **1a**:**1b** mixture.

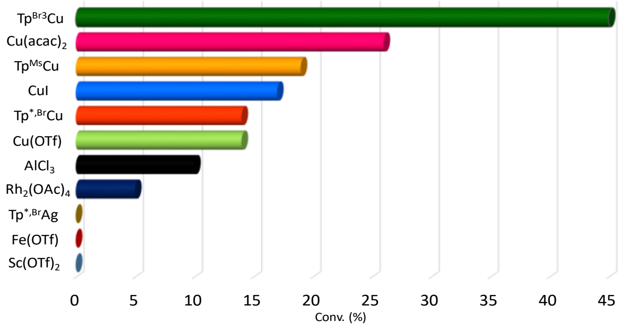
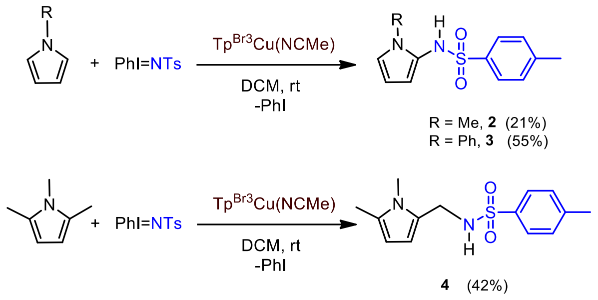


Figure 1. Catalyst screening for the reaction of pyrrole and PhN=NTs. [Cat]:[PhINTs]:[pyrrole] = 1:20:200, rt, 15 min in DCM. Yields based on PhI=NTs, corresponding to the mixture of **1a** and **1b**.

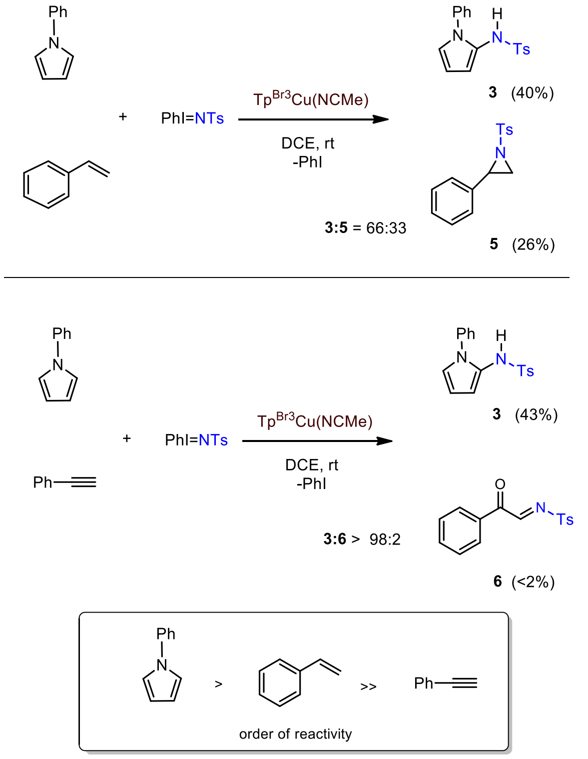
Optimization of reaction conditions (see Supporting Information) included screening of solvents (DCM, DCE, MeCN), temperature (0, 20, 60 ºC), catalyst loading (2, 5, 10, 20 mol% relative to PhI=NTs) and ratio of PhI=NTs;pyrrole (1:1.5; 1:5; 1:10; 1:20). From these experiments, DCE was found as the most appropriate solvent with room temperature providing the best results. A 1:10:100 ratio of catalysts:PhI=NTs:pyrrole led to the best conversions into the mixture of **1a**+**1b**, corresponding to 10% catalyst loading and 1:10 PhI=NTs:pyrrole ratio.

2.3. Functionalization of substituted pyrroles

We have chosen two N-substituted pyrroles and one N-substituted-C-substituted pyrrole to evaluate the influence of additional groups in the heterocycle in the reaction otucome. With N-methyl or N-phenyl pyrrole the reaction took place in a selective manner, leading to the formation of the products derived from the insertion of the NTs unit into the C_α–H bonds (Scheme 4) At variance with 1H-pyrrole, in this case no tautomerism was observed, products **2** and **3** being characterized from their spectroscopic data. However, all these compounds undergo partial decomposition during column chromatography purification, therefore the yields being obtained from the reaction crude with an internal standard. Thus, the presence of a substituent at N does not infer any change in the reaction site at the pyrrole. At variance with that, the use of 1,2,5-trimethylpyrrole originates as the only isolated product that derived from the insertion of the nitrene group into the C_{sp3}-H bond located at C_α, in line with previous reports from this laboratory with alkylbenzene derivatives.[7a,c] Thus, the C_β position seems to be unreactive when C_{sp3}-H bonds are available. The lack of reactivity of the N-Me C-H bonds must be related to steric factors, since bond dissociation energies of C-H bonds in N-Me moieties are lower than the corresponding C-Me units. [8] It is worth mentioning that when electron-withdrawing groups were attached to C_α (2-formyl-1H-pyrrole) or N (N-Boc-pyrrole), no functionalization was observed, showing the limit of this methodology.



Scheme 4. Substituted pyrroles as substrates



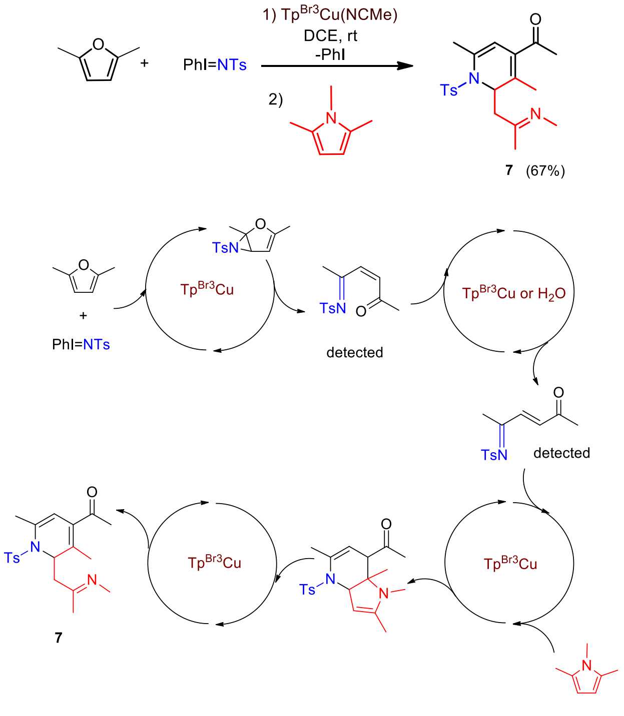
Scheme 5. Competition experiments toward relative reactivity. Yields in brackets, $TsNH_2$ accounting for initial PhI=NTs).

2.4. Relative reactivity experiments.

Given the complete absence of examples of pyrroles incorporating nitrene units by this methodology, we decided to perform several competition experiments with substrates being functionalized with the copper catalyst Tp^{Br3}Cu(NCMe). Two experiments between N-phenyl pyrrole and a second nitrene receptor such as styrene or phenylacetylene were carried out (Scheme 5). Previous work from our laboratories have shown that catalyst inducing the incorporation of NTs units (from PhI=NTs) to styrene or phenyl acetylene affording aziridine **5** or imine **6**.[7b,e] NMR studies of the reaction mixtures provided an estimation of the relative reactivities. Thus, the styrene:N-phenyl pyrrole competition gave a 1:2 mixture of the products **3**:**5**, whereas for 1-phenylacetylene: N-phenyl pyrrole the former was not detected. These experiments demonstrate that pyrrole is more reactive toward the electrophilic copper-nitrene intermediate than olefins or alkynes, a fact that could be related to both its nucleophilicity and its capability to stabilize positive charges (vide infra).

2.5. The furane-nitrene-pyrrole cascade reaction: synthesis of the dihydropyridine-pyrrole 7.

In a previous work from our laboratory we demonstrated that the copper catalyst Tp^{Br3}Cu(NCMe) induces the assembly of two molecules of furans and one NTs unit (from PhI=NTs) leading to the formation of 1,2-dihydropyridines.[7d, 9] We have now found the related transformation in which we employ one furan and one pyrrole along with PhI=NTs en route to the isolation of a



Scheme 6. Top: Synthesis of the 1,2-dihydropyridine-imine compound **7**. Bottom: the four cycles explaining the formation of such compound.

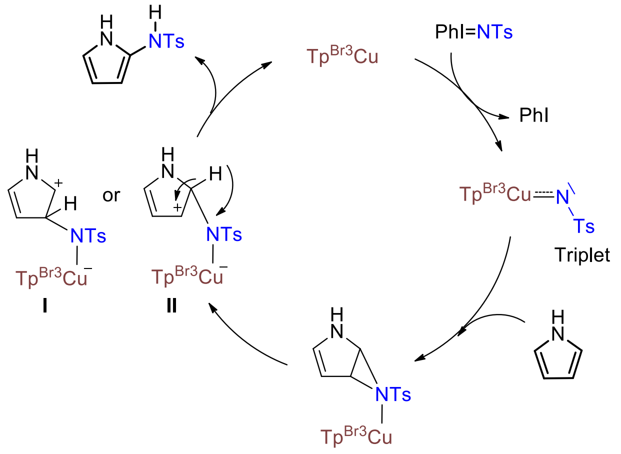
1,2-dihydropyridine-imine compound (Scheme 6). The reaction takes place in a sequential manner (Scheme 6) where PhI=NTs and 2,5-dimethylfuran are reacted in the presence of the copper catalyst, followed by the addition of 1,2,5-trimethylpyrrole (see SI for spectroscopic characterization), in a mechanism identical to that already proposed for the furan case.[7d] Attempts to induce the formation of **7** mixing the furan and the pyrrole at the beginning were not productive, thus the sequential procedure being more favorable.

2.6. Mechanistic interpretation.

As mentioned above, the Tp^{Br3}Cu(NCMe) complex also catalyze the direct benzene amination by reaction with PhI=NTs.[7a,c] This transformation has been studied by Bao and co-workers from a theoretical point of view.[10] In line with other studies from our group, .[11] the interaction of the copper complex with PhI=NTs afford a transient copper-nitrene intermediate in the triplet ground state. Based on these precedents, we propose a similar reaction pathway (Scheme 7), in which the interaction of such copper-nitrene species with pyrrole takes place through the C=C double bond en route to an aziridine intermediate. From here the C-N bond undergoes cleavage, a 1,2 H-shift generating the final product **1a**. This is the step in which the final functionalization at the α or β position is decided. The two possible intermediates **I** and **II** display carbocations which stability would govern the reaction outcome. We believe that secondary carbocation in **II** is more stable due to resonance stabilization, compared to that in **I**, for which the adjacent lone pair of N would not balance such effect, mainly due to the electron withdrawing effect of the Ts group. In the case of C_{sp3}-H bonds, Bao proposed for toluene that the mechanism takes place through the more favored, well-known hydrogen atom abstraction followed by a radical rebound step. This is very likely also occurring with pyrrole bearing methyl groups, thus explaining the formation of compound **4**.

3. Conclusions

We have found that the complex Tp^{Br3}Cu(NCMe) complex catalyze the transfer of the NTs group from PhI=NTs to 1H-pyrrole, in a rare example of the effective amidation of the C-H bonds of this heterocycle. The reaction is selective toward the C_α position, whereas the other ring C-H bonds as well as the NH moiety remain unmodified. When C_{sp3}-H bonds are available as substituents at the pyrrole ring they are selectively functionalized over the C_{sp3}-H bonds. Competition experiments demonstrate that pyrrole is more prone toward nitrene incorporation than styrene or phenylacetylene. We believe that this finding will pave the way toward other catalytic systems to improve and expand this new tool for carbon-nitrogen bond formation with pyrroles as substrates.



Scheme 7. Mechanistic proposal for the amidation of the C-H bond of 1H-pyrrole.

4. Materials and methods

General Information

All air– and moisture–sensitive manipulations were carried out with standard Schlenck techniques under nitrogen atmosphere or in a glovebox (MBRAUN UNILAB). Solvents were purchased from commercial sources, dried by distillation under nitrogen atmosphere using the suitable drying agent and deoxygenated immediately before their use. Reagents were acquired from Aldrich. Pyrroles were purified by distillation or sublimation before their use and were stored over activated molecular sieves (liquid pyrroles). The catalysts[7] and the nitrene precursor (PhI=NTs) [12] were synthesized following literature procedures. NMR spectra were recorded on the Agilent 400MR and Agilent 500DD2 spectrometers.

General Catalytic Experiment for compounds 1-4.

In a Schlenk tube under inert atmosphere, the catalyst (0.01 mmol) was dissolved in deoxygenated solvent (6 mL) before the pyrrole (1 mmol) was added. PhI=NTs (0.2 mmol) was added in one portion, and the mixture was stirred for 1 h. The solvent was removed under reduced pressure and the crude was analyzed by NMR spectroscopy. Purification was achieved by column chromatography (petroleum ether:EtOAc, 1:1). Partial decomposition was observed during purification, thus yields were determined with an internal standard with the reaction crude. See Supporting Information for product characterization.

Competition Experiments

In a Schlenk tube under inert atmosphere, the catalyst (0.01 mmol) was dissolved in deoxygenated solvent (6 mL). Pyrrole:styrene or pyrrole:phenylacetylene mixtures (1 mmol each) were added. PhI=NTs (0.2 mmol) was introduced in one portion, and the mixture was stirred for 1 h. The solvent was removed under reduced pressure and the crude was analyzed by NMR spectroscopy.

Synthesis of the dihydropyridine compound 7.

In a Schlenk tube under inert atmosphere, the catalyst (0.01 mmol) was dissolved in deoxygenated solvent (6 mL). 2,5-dimethylfurane (0.25 mmol) was added, followed by addition of PhI=NTs (0.2 mmol) in one portion. After stirring for 7 h, 1,2,5-trimethylpyrrole (2.5 mmol) was added. The mixture was further stirred for 24 h and the solvent was removed under reduced pressure. Purification was achieved by column chromatography (petroleum ether:EtOAc, 1:1).

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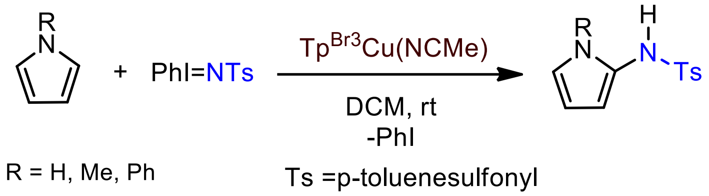
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PhI=NTs
$Tp^{Br3}Cu(NCMe)$
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R = H, Me, Ph
Ts =p-toluenesulfonyl