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Selective Synthesis of N-Substituted 1,2-Dihydropyridines from Furans by Copper-Induced Concurrent Tandem Catalysis

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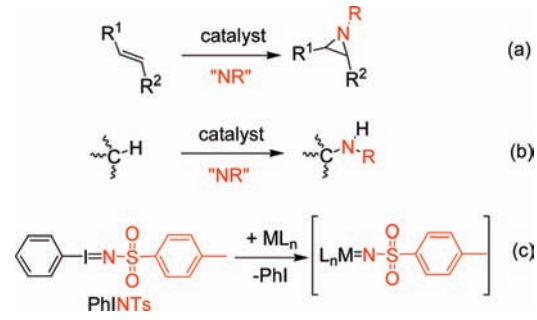
Abstract: A novel transformation in which mono- or dialkyl-substituted furans are converted into 1,2-dihydropyridines upon reaction with PhI=NTs at room temperature is reported. The reaction is catalyzed by complexes of general formula Tp^xM (M = Cu, Ag) and consists of a one-pot procedure with four consecutive catalytic cycles. Furan aziridination is followed by aziridine ring-opening, transimination reaction, inverse-electronic-demand aza-Diels−Alder reaction, and a final hydrogen elimination reaction. The mechanism of the overall transformation is proposed where the metal complex displays a crucial role along the reaction pathway.

Introduction

The metal-catalyzed nitrene transfer reaction to saturated or unsaturated substrates constitutes an emerging methodology in organic synthesis.[1,2] Thus, the addition of a nitrene moiety NR to an olefin leads to the formation of aziridine rings (Scheme 1a). In the case of saturated substrates, the insertion of such unit into a C−H bond affords a new carbon−nitrogen bond (Scheme 1b), a reaction of enormous current interest.[3] The role of the catalyst in these transformations is the generation of transient metallonitrene species (Scheme 1c) from nitrene precursors, PhI=NTs being by far the most employed to date. Such intermediates have scarcely been detected or isolated due to their high reactivity.[4]

We have been interested in the development of group 11 metal-based catalysts for the above transformations[5] and have previously found that complexes of formulas Tp^xCu (Tp^x = hydrotrispyrazolylborate ligand)[6] efficiently catalyze the olefin aziridination reaction.[7] On the other hand, we have also described the use of Tp^xM (M = Cu, Ag) complexes as catalysts for the insertion of NTs groups into the C−H bond of several substrates, including benzene, alkylaromatics, and plain alkanes.[8,9] As a follow up of these findings, we thought it would be

Scheme 1. Nitrene Transfer Reactions



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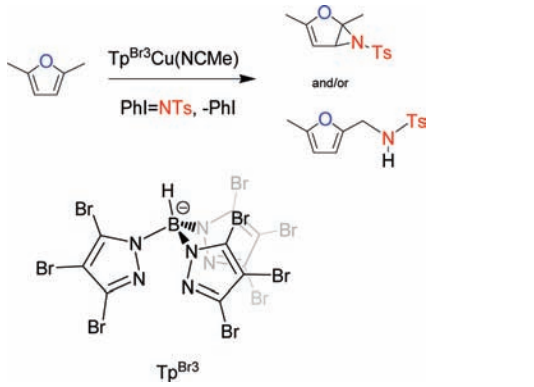
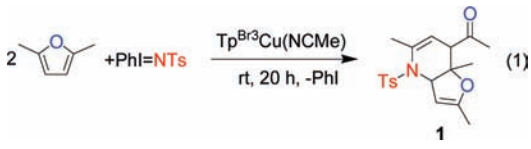
Scheme 2. Expected Products Derived from the Reaction of 2,5-Dimethylfuran and PhI=NTs



interesting to study the effect that the presence of a heteroatom in the substrate (the above systems were applied to saturated of unsaturated hydrocarbons without any substituent) would exert in these transformations, when both insertion or aziridination routes could be, in principle, accessible. With this idea in mind, we screened the use of furans as substrates and found an unexpected, novel transformation: the formation of 1,2-dihydropyridine rings. In this paper, we describe this novel process, which could be classified in the area of concurrent tandem catalysis,[10] the metal catalyst being crucial in several steps of the overall transformation.

Results and Discussion

Reaction of 2,5-Dimethylfuran with PhI=NTs. We first studied the reaction of 2,5-dimethylfuran with PhI=NTs in the presence of the complex $Tp^{Br3}Cu(NCMe)$ as the catalyst, expecting the formation of the aziridine and/or the tosylamide (Scheme 2) derived from the addition or the insertion of the nitrene group in that substrate, respectively. This copper complex has been already described as a good catalyst for both transformations.[7,8] The reaction was carried out in CH_2Cl_2 as the solvent, at room temperature, with a 1:20:400 ratio of [Cu]/[PhI=NTs]/[2,5-dimethylfuran] being employed. The nitrene precursor dissolved within 1 h to give a yellow solution that turned reddish-orange with time. After 20 h of stirring, volatiles were removed to give a reddish oil that was investigated by NMR, showing the existence of one unique set of resonances. Isolation of this new compound **1** as an off-white solid was achieved by silica gel chromatography. Extensive multinuclear, 1D, and 2D NMR studies have led to the proposal of a bicyclic structure that has been characterized as 1-(3a,4,7,7a-tetrahydro-2,5-dimethyl-4-tosylfuro[3,2-*b*]pyridin-7-yl)ethanone. Such composition formally derives from two molecules of 2,5-dimethylfuran and one NTs unit (eq 1):



Interestingly, during the process of purification, we unexpectedly observed that when neutral alumina was employed instead of silica gel, a clean, quantitative transformation of the bicyclic **1** into another compound took place. The NMR spectrum of this compound was deceptively simple in terms of the number of resonances: four singlets with integrals of 3 H each appeared in the 2.0−1.5 ppm range, a AX spin system for two protons (5.36, 3.31 ppm, $J = 8$ Hz), two broad singlets (5.08, 4.57 ppm), accounting for one proton each, and the set of resonances typical for a tosyl group. Again, the overall 23 proton NMR spectrum was in agreement with the formation of a product formed from two molecules of 2,5-dimethylfuran and one NTs unit, but different from **1**. Single crystals were obtained by slow evaporation of methylene chloride solutions, some of them being suitable for a X-ray study.[11] The structure of the molecule of **2** is shown in Figure 1 and has led to the identification of this compound as the 1,2-dihydropyridine derivative 1-(4-acetyl-1,2-dihydro-3,6-dimethyl-1-tosylpyridin-2-yl)propan-2-one), being consistent with the spectroscopic data available. In this structure, the C4′ is a stereogenic carbon, showing the enantiomer R in the asymmetric unit, but the enantiomer S is also present in the unit cell for symmetry of the inversion center of the spatial group $P1^-$, appearing this compound in the crystal as a racemate as expected. The transformation of **1** into **2** (eq 2) formally consists of the elimination of a hydrogen atom vicinal to the acetyl group. This step will be discussed in more detail in the mechanistic proposal.

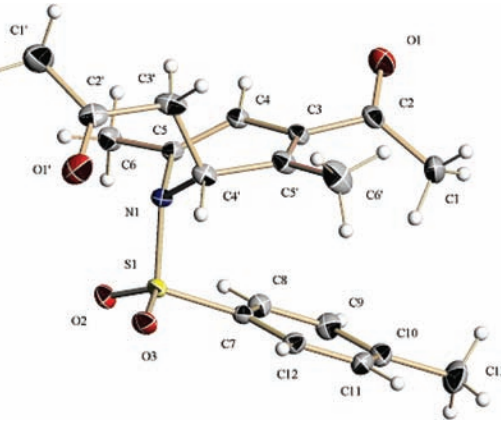
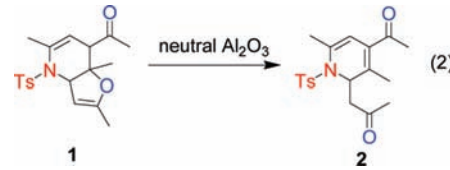


Figure 1. X-ray structure of **2**. Thermal ellipsoids are drawn at the 30% probability level.



Catalyst Screening. After the observation of the formation of dihydropyridine derivatives from 2,5-dimethylfuran and PhI=NTs in the presence of $Tp^{Br3}Cu(NCMe)$, we evaluated the effect of the transition metal complex in this transformation. A series of complexes of formula Tp^xM (Scheme 3) were employed following the above procedure, with 2,5-dimethylfuran as the substrate. In all cases, the bicyclic compound **1** was obtained upon stirring at room temperature for 20 h. However, the use of the asymmetric 2-methylfuran as the

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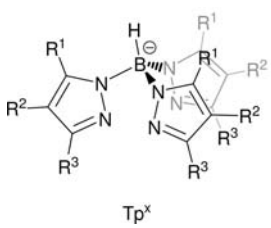
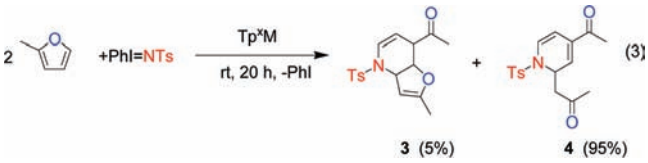
Scheme 3. Ligands Employed in This Work



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

substrate has provided very interesting information. In a manner similar to that for the disubstituted furan, two compounds have been obtained from the reaction of 2-methylfuran and PhI=NTs (eq 3), the bicyclic **3** and the 1,2-dihydropyridine **4**, i.e., the analogues to **1** and **2**, respectively. But at variance with that, after 20 h of stirring at room temperature, mixtures of **3** and **4** were obtained in a variable ratio depending of the catalyst employed (Table 1). Thus, Tp^{Ms}Cu(NCMe) induced the quantitative formation of **4**, whereas in the case of the Tp*−, Tp^{Br3}−, or $Tp^{*,Br}$−copper catalysts, a certain, although minor (5−10%), amount of **3** could be detected. More interestingly, this selectivity could be reversed by using silver instead of copper: the complex $Tp^{*,Br}$Ag provided a 90:10 ratio of **3** and **4**, respectively, allowing the full characterization of the former. It is worth mentioning that these values correspond to identical reaction times (20 h) and that when prolonged for several days, the dihydropyridine **4** was the sole product isolated. In addition, any uncompleted reaction after those 20 h could be instantaneously completed toward **4** by treatment with neutral alumina, similar to the aforementioned **1**→**2** conversion. Reaction times can be dramatically diminished by increasing the temperature. Thus, the reaction of 2-methylfuran with PhI=NTs in the presence of Tp^{Br3}Cu(NCMe) as the catalyst carried out at 60 °C was completed in 2 h, with quantitative conversion into **4**. On the other hand, when the reaction was performed at 5−10 °C, a mixture of **3** and **4** with **3** as the major product (ca. 75%) was obtained.



Extension to Other Furans and Heterocycles. Since the previous results were obtained with substrates bearing methyl substituents at the position vicinal to oxygen, we wondered if that would be a restriction of the system. Therefore, a series of different furans, shown in Scheme 4, were employed as starting materials, under identical reaction conditions, with Tp^{Br3}Cu(NCMe) as the catalyst and at room temperature. The use of unsubstituted, plain furan as the substrate led to intractable mixtures of compounds, not only at room temperature but also at −10 °C. At this temperature, in addition to other species, a minor set of signals similar to those observed for the dihydropyridines **2** and **4** were observed in the ^{1}H NMR spectrum, but accounting for less than 10% of the overall mixture.

Table 1. Selectivity of the Reaction of 2-Methylfuran and PhI=NTs in the Presence of Tp^xM Complexes As Catalysts[a]

catalyst	**3** (%)	**4** (%)
Tp^{Br3}Cu(NCMe)	5	95
Tp*Cu	5	95
Tp^{Ms}Cu(NCMe)	<1	>99
$Tp^{*,Br}$Cu(NCMe)	10	90
$Tp^{*,Br}$Ag	90	10

[a] Reaction conditions: 0.0125 mmol of the catalyst, 0.25 mmol of PhI=NTs, 10 mmol of 2-methylfurane, 2 mL in CH_2Cl_2. Temperature: 20 °C. Reaction time: 20 h.

2-Ethylfuran provided very interesting information, since the presence of methylenic protons (CH_2) could offer a reaction site for the insertion of the NTs moiety to occur. However, a clean transformation took place, and a mixture of the bicyclic and dihydropyridine compounds **5** and **6** was obtained, favoring the latter in a ratio similar to that previously observed with 2-methylfuran. Therefore, this result shows that the system is not restricted to furans with methyl groups as substituents but also is compatible with more reactive methylenic groups.

As already discussed, 2,5-dimethylfuran gave only the bicyclic compound **1**, further transformed into the dihydropyridine **2** with the aid of neutral alumina. Another disubstituted furan has also been investigated, that with two methyl groups located at positions 2 and 3. Again, only the related bicyclic compound **7** was quantitatively obtained. However, at variance with **1**, all attempts to convert **7** into a dihydropyridine skeleton failed (prolonged heating or treatment with alumina).

Two more furans were studied, ethyl furan-2-carboxylate and benzofuran. In both cases, the reaction did not take place toward the expected products. In contrast, all of the PhI=NTs reagent decomposed into $TsNH_2$. Several *N*-Me-pyrrolidines and methylthiophenes have been also screened under similar conditions, but a distinct reactivity has been observed. Pyrrolydines underwent insertion into the C−H bond of the N-Me moiety, whereas in the case of 2-methylthiophene or 2,5-dimethylthiophene, products derived from the insertion into the methyl groups were obtained. This is in agreement with the strong delocalization in the pyrrol- and thiophene rings, in contrast with that of furans. The transformation reported herein requires loss of aromaticity of the starting heterocycle, and therefore, those with strong delocalization (pyrrole, thiophene) are less prone to undergo this reaction.

Compounds **2**, **4**, and **6** are 1,2-dihydropyridine derivatives and have not been previously described. The 1,4-dihydropyridine skeleton is found in a large number of pharmaceuticals and therefore has been largely studied.[12] In contrast, the related 1,2-dihydropyridines have not been so far developed in the same manner. The number of synthetic procedures reported to date is small,[13,14] with only a few being known to generate 1,2-dihydropyridines in a regioselective manner.[15] Compared to them, the method described in this contribution is quite simple and is performed under very mild conditions. The synthetic potential of this system is yet to be developed, although it is important to note at this point that the existence of acetyl groups in the easily accessible compounds **2**, **4**, and **6** provides an additional entry for further derivatization.

Mechanistic Studies. In order to gain useful information about the mechanism that governs this novel transformation, we first monitored by ^{1}H NMR the reaction of 2,5-dimethylfuran with

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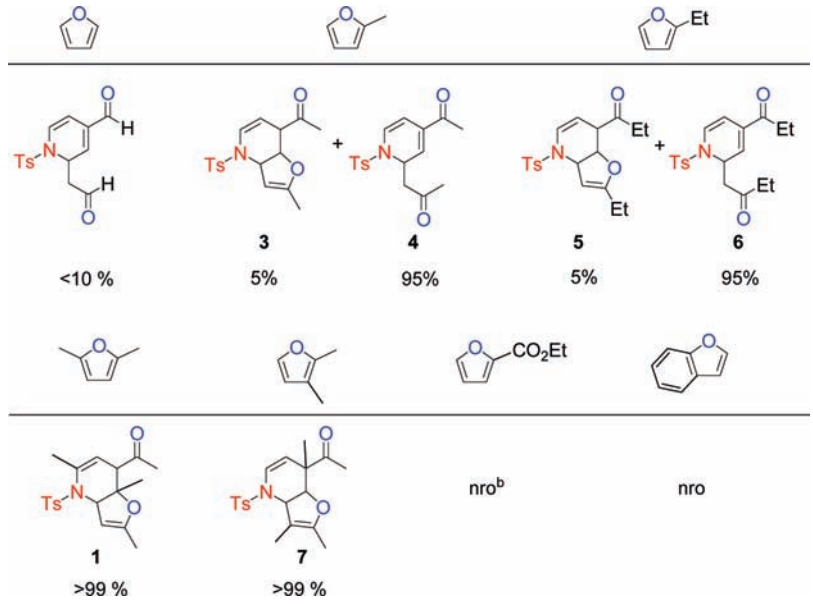
Scheme 4. Reactivity of Several Furans with PhI=NTs in the Presence of $Tp^{Br3}Cu(NCMe)$ as the Catalyst[a,b]



[a] Reaction conditions: 0.0125 mmol of the catalyst, 0.25 mmol of PhI=NTs, 10 mmol of the furan, 2 mL in CH_2Cl_2. Temperature: 20 °C. Reaction time: 20 h. All PhI=NTs was converted into products; percentages correspond to distribution of products. [b] nro: no reaction observed. All PhINTs decomposed into $TsNH_2$.

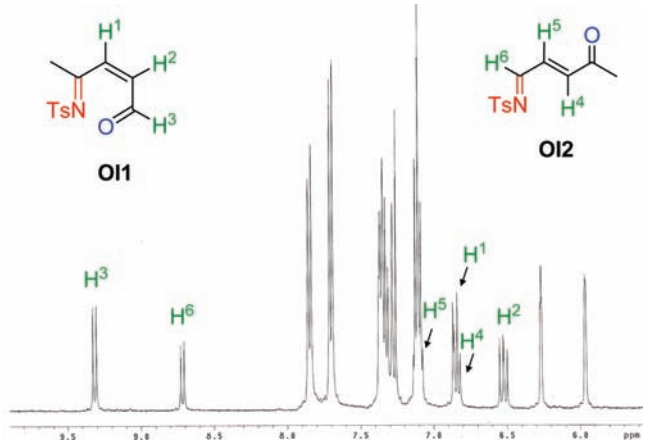


Figure 2. ^1H NMR spectrum ($CDCl_3$, 400 MHz) of the reaction of 2-methylfuran and PhI=NTs (equimolar ratio) using $Tp^{Br3}Cu(NCMe)$ as the catalyst after 10 min of stirring at room temperature.

PhI=NTs, using $Tp^{Br3}Cu(NCMe)$ as the catalyst. Unfortunately, only the resonances of **1** were observed along the reaction time, with no other intermediate being clearly detected (the aromatic region is crowded in this chemical system). We were more fortunate when moving to 2-methylfuran as the substrate. In this case, an NMR-scaled reaction (0.0125 mmol of the catalyst, 0.25 mmol of PhI=NTs, 0.25 mmol of 2-methylfuran, 1 mL of $CDCl_3$) with equimolar amounts (eq 4) of the furan and PhI=NTs showed that upon dissolution of PhI=NTs (10 min) the reaction mixture was constituted by two major species, (2*Z*)-4-tosyliminopent-2-enal (**OI1**) and (3*E*)-5-tosyliminopent-3-en-2-one (**OI2**), the exact geometry being assigned from the values of the coupling constants (see the Experimental Section). Figure 2 shows the NMR spectrum of the reaction mixture after 10 min of reaction. Some residual 2-methylfuran was also observed, along with PhI derived from PhI=NTs. Monitoring of the reaction mixture showed a smooth transformation of the aldehyde **OI1** into the imine **OI2** (Figure 3), the latter being the unique species detected after 3 h at room temperature (the initial mixture was constituted by equimolar amounts of 2-methylfuran and PhI=NTs).

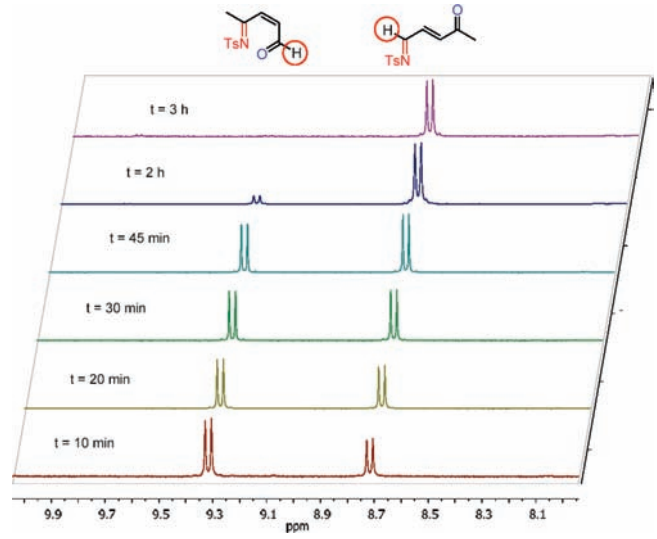
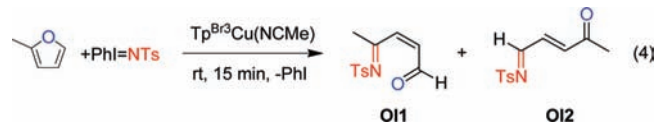


Figure 3. Monitoring of the reaction mixture of 2-methylfuran and PhI=NTs (equimolar ratio) using $Tp^{Br3}Cu(NCMe)$ as the catalyst with time (downfield region).



Once demonstrated that the aldehyde **OI1** and the imine **OI2** are intermediates in this transformation, we decided to investigate the next step, i.e., the reaction of the imine with a second equivalent of 2-methylfuran that was added to the reaction mixture. However, the reaction was extremely slow. After some experiments in which a 5- or 10-fold excess of 2-methylfuran was added to the imine solution, we found that at least 20 equiv

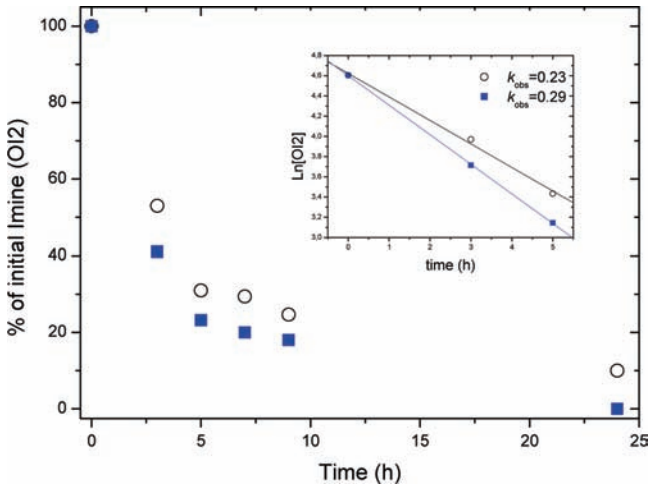


Figure 4. Monitoring of the disappearance of the imine **OI2** with (square) and without (circle) additional catalyst. Inset: plot of Ln[**OI2**] vs time (three half-lifes).

of the furan should be added in order to induce the transformation at an acceptable reaction rate. Under those conditions, complete transformation of the imine into the final product **4** was observed, with a steady-state concentration of the bicyclic **3** detected along the reaction time. In the case of the silver catalyst $Tp^{*,Br}Ag$, accumulation of **3** was observed, the **3**→**4** conversion being significantly lower than for the copper-based catalysts (see Table 1).

A question that arises from these observations is the role of the metal center in this step, which could be mediated by the $Tp^{Br3}Cu$ moiety, a 16-electron fragment that would display a certain degree of Lewis acidity. We have tried to isolate the imine **OI2** from the reaction mixture of 2-methylfuran and PhI═NTs, with no success: decomposition was observed in all cases. Independent synthesis[16] has also failed, and therefore, the direct reaction of a pure sample of the imine with 2-methylfuran in the presence and in the absence of the catalyst could not be performed. However, we have done a related experiment in the following manner (see the Experimental Section). The imine **OI2** was generated as above (2-methylfuran + PhI═NTs, in the presence of $Tp^{Br3}Cu$(NCMe) as the catalyst), and the solution was divided in two identical parts. Additional $Tp^{Br3}Cu$(NCMe) was added to one of the aliquots, and then 40 equiv of 2-methylfuran was added to both solutions. The disappearance of the imine resonance (and the concomitant appearance of the dihydropyridine **4**) was monitored by ^{1}H NMR. Figure 4 shows the decrease of the concentration of imine with time, where it is clearly observable that the concentration of the catalyst seems crucial: the reaction with a higher concentration of the copper complex consumed the imine at a higher rate (25% increase). We interpret these results as a proof of the involvement of the copper complex in the formation of the bicyclic compound **3**.

Mechanistic Proposal. (a) Step 1: Formation of the Aldehyde OI1 and the Imine OI2. The intermediate (2Z)-4-tosyliminopent-2-enal (**OI1**) corresponds to the addition of a molecule of 2-methylfuran and the NTs unit, although there is no obvious, direct reaction that could explain the formation of such molecule. In spite of the lack of observation of any intermediate previous to **OI1** in the catalytic cycle, we believe that aziridination occurred as the first step in this transformation. This proposal is based in the reactivity already described for the oxidation of furan with TS1−H_2O_2,[16] peracids,[17] or dioxiranes,[18] for which the mechanism shown in Scheme 5a has been proposed. In these cases, an epoxide intermediate, which has not been detected, undergoes a rearrangement to yield unsaturated dicarbonylic species.[16−18] In our system, the addition of the nitrene moiety would lead to the formation of a bicyclic aziridine that could be also unstable. However, given the asymmetry of the 2-methylfuran molecule, aziridination could in principle take place in both double bonds of the ring, leading to **AZ1** and **AZ2** (Scheme 5b). Subsequent, spontaneous ring opening, similar to the aforementioned epoxide, would lead to the open intermediates **OI1** and **OI2**, respectively. It is worth mentioning that **OI1** would form from the more sterically hindered but also more electron-rich substituted double bond. This could explain that at the early stages of the reaction, **OI1** predominates. Unfortunately, the picture in Scheme 5b cannot explain the experimentally observed conversion of **OI1** into **OI2**, unless an additional process arises. This could be a transimination reaction,[19] shown in Scheme 6, in which the presence of adventitious water should be responsible for such conversion in a catalytic manner. Alternatively, the acid nature of the Tp^xM active catalyst could also induce this transformation. We cannot rule out that coordination of the intermediate **OI1** to the metal center could also have a certain influence to activate **OI1** and trigger this transformation.

(b) Step 2: Formation of the Bicyclic Compound 3. The second step of this transformation can be explained as an aza-Diels−Alder reaction (ADAR) with inverse-electron-demand[20,21] between the intermediate **OI2** and a second molecule of 2-methylfuran (Scheme 7). The exclusive formation of 1-(3a,4,7,7a-tetrahydro-2-methyl-4-tosylfuro[3,2-*b*]pyridin-7-yl)ethanone (**3**), along with the lack of observance of the product derived from the ADAR reaction with the more hindered double bond of the furan, evidence the existence of a certain steric effect in this step. The same behavior was found when 2-ethylfuran or 2,3-dimethylfuran were employed as the substrates, the substituents occupying the external double bond in the final bicyclic products **5** and **7**, respectively. As inferred from the results shown in Figure 4, this step seems to be affected by the presence of the metal-center, the Tp^xM fragments displaying a certain degree of Lewis basicity. As a precedent for this metal-induced ADAR, very recently, Carretero and co-workers have reported[22] the use of a nickel-mediated ADAR with inverse-electron-demand in which the metal catalyst also displays such acidic behavior.

(c) Step 3: Generation of the Dihydropyridine 4. The use of 2-methyl- or 2-ethylfuran as substrates has provided dihydro-

(16) We have employed a procedure similar to that reported for the synthesis of unsaturated 1,4-diketones. See: Whalen, J.; Moens, B.; De Vos, D. E.; Alsters, P. L.; Jacobs, P. A. *Adv. Synth. Catal* **2004**, *346*, 333.

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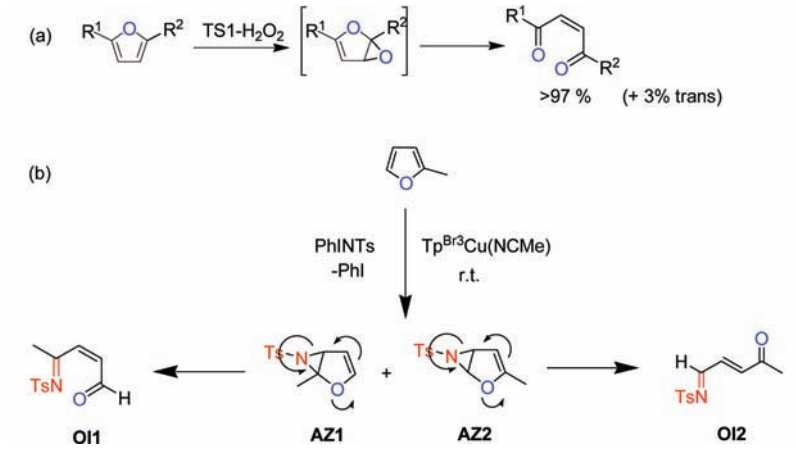
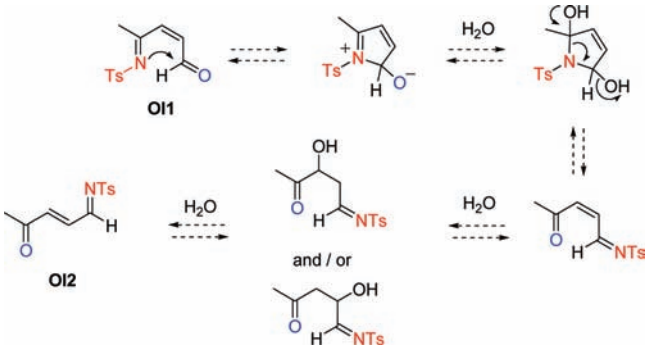
Scheme 5. (a) Instability of Epoxides Derived from Furans. (b) Formation of **OI1** and **OI2** through Aziridine Intermediates



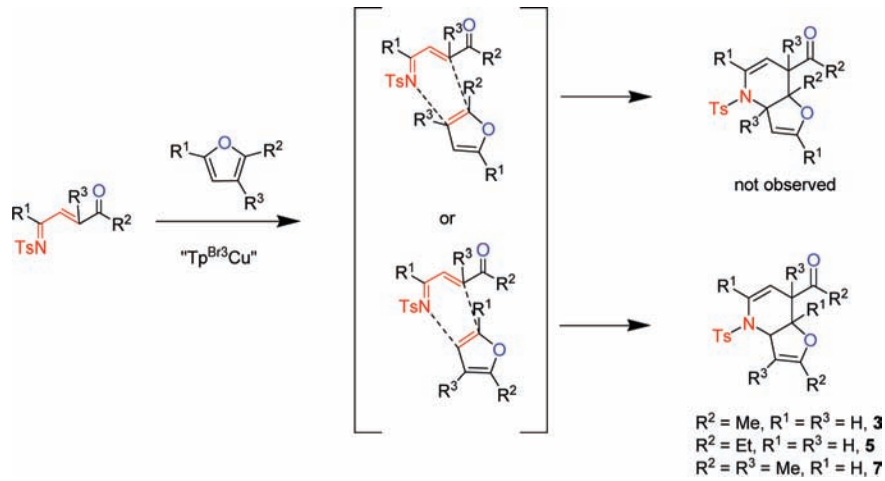
Scheme 6. Transimination Pathway That Converts **OI1** into **OI2**



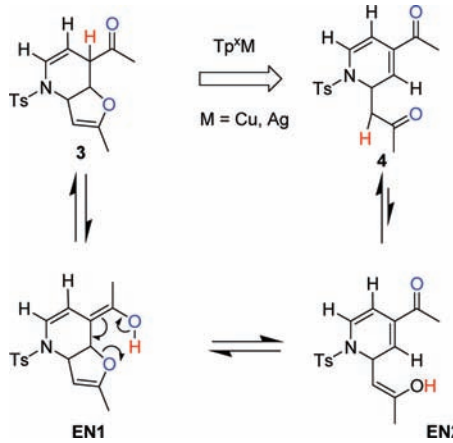
pyridines **4** and **6** as the final products. The related compound **1**, derived from 2,5-dimethylfuran, was converted into the six-membered ring with the aid of neutral alumina. On the other hand, the bicylic compound **7**, formed from 2,3-dimethylfuran as the substrate, has not been converted into a dihydropyridine derivative in any case. The only difference in this case is the existence of a methyl group instead of a hydrogen as R^3, vicinal to the acetyl group. Therefore, a plausible explanation for the formation of the dihydropyridines should invoke the participation of that H atom at R^3, in the form of an elimination reaction. Scheme 8 shows a possible reaction pathway for this step. An enol (**EN1**) would form at the first stage, followed by a β-elimination ring-opening mechanism that would end into a new enol (**EN2**) which further tautomerizes to the more stable ketone **4**. This would be in good agreement with the lack of reactivity of **7**, due to the presence of a methyl group as R^3. Interestingly, the use of copper- or silver-based catalysts has provided a different selectivity at the end of the reaction, the silver one leading to the bicyclic compound **3** as the major product. Since the unique difference between the experiments was the catalyst, we believe that the metal center is affecting this last elimination step. Elimination reactions are easily induced by acids. Therefore, the differences must stand on the distinct acidic nature of the metal center, i.e., Cu(I) or Ag(I) ions in a tetrahedral environment. A simple estimation of the acidity based in Z^2/r values[23] ($r_{Cu(I)} = 74$ pm, $r_{Ag(I)} = 114$ pm)[24] allows us to propose a higher acidity for the copper center, with the corresponding effect in the conversion **3** → **4**. On the other hand, the acidity of Ag(I), moderate compared with that of Cu(I), was not enough to promote such conversion at a significant rate, compound **3** remaining as the major component of the reaction mixture after 24 h. The need of neutral alumina to promote the conversion of **1** into **2** also favors the proposal of an acid-catalyzed elimination step: in this case, the presence of the additional methyl groups probably provides additional stability to the bicyclic compound **1**.

The Global Mechanism. On the basis of the above, the general mechanism for the reaction of 2-methylfuran and PhI═NTs in the presence of Tp^xM (M = Cu, Ag) complexes is shown in Scheme 9. Four consecutive catalytic cycles **I**−**IV** take place,

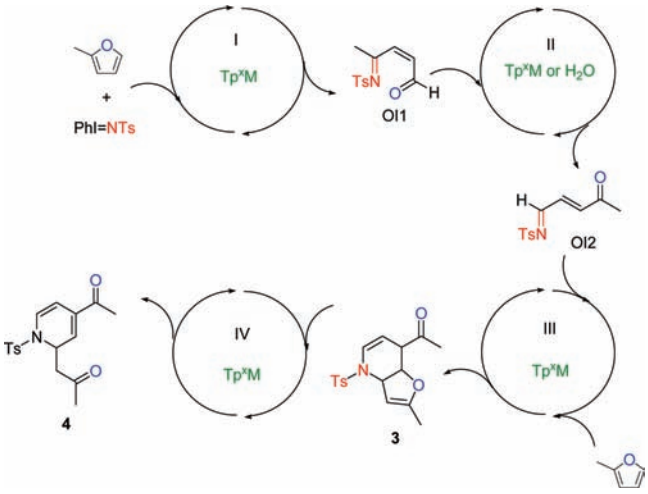
Scheme 7. Proposal for the Conversion of the Imine Intermediates into the Bicyclic Compounds **3**, **5**, and **7**



Scheme 8. Final Elimination Step to Convert **3** into **4**



Scheme 9. Overall Mechanism for the Concurrent Tandem Catalytic System to Convert 2-Methaylfuran and PhI=NTs into Dihydropyridine **4**



at least three of them promoted by the metal catalyst. Cycle (I) corresponds to furan aziridination and ring-opening to yield aldehyde **OI1**. Cycle II, for which either adventitious water or the metal complex could act as the catalyst, converts **OI1** into the imine **OI2**. Cycle III corresponds to a metal-catalyzed aza-Diels−Alder reaction with inverse electronic demand, which yields the bicyclic compound **3**. Finally, the latter undergoes a metal-catalyzed elimination reaction to afford the 1,2-dihydropyridine **4**. According to Baker, Bazan, and co-workers,[10] the overall mechanism can be designed under the term "concurrent tandem catalysis" on the basis of the existence of cooperative action of four catalytic cycles in a single reactor. The mechanism can be applied with success to the series of furans discussed in the previous sections.

Conclusions

We have discovered that complexes $Tp^xCu(NCMe)$ or related Tp^xM (M = Cu, Ag) catalyze the reaction of several mono- or disubstituted dialkylfurans with PhI=NTs, at room temperature, to provide novel 1,2-dihydropyridines derived from a series of four concurrent catalytic cycles in a completely unprecedented transformation. Work aimed to expand the scope of this transformation is currently underway in our laboratory.

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. The copper and silver complexes employed as catalysts were prepared according to the literature.[7−9] PhI=NTs was also prepared following the previously reported methods.[25] NMR experiments were run in a Varian Mercury 400 MHz spectrometer. GC data were collected with a Varian GC-3900 with a TSD detector.

Reaction of 2,5-Dimethylfuran with PhI=NTs in the Presence of $Tp^{Br3}Cu(NCMe)$. Synthesis of 1-(3a,4,7,7a-Tetrahydro-2,5,7a-trimethyl-4-tosylfuro[3,2-*b*]pyridin-7-yl)ethanone (1). A 0.025 mmol (25.6 mg) portion of the copper complex was dissolved in 2.0 mL of 2,5-dimethylfuran and 2 mL of CH_2Cl_2. To the colorless stirred solution was added 186 mg (0.5 mmol) of PhI=NTs as yellow crystals. The mixture became greenish in a few seconds, and the color slowly turned orange while the nitrene precursor dissolved into the solution. After 2 h of stirring at room temperature, a homogeneous, red solution was obtained. Volatiles were removed after 20 h of stirring under vacuum, and the residue was washed several times with petroleum ether to give compound **1** as a reddish, somewhat oily solid in 78% yield. This procedure was employed for the catalyst screening set of experiments showed in Table 1. ^{1}H NMR ($CDCl_3$, 400 MHz): 7.70 (d, 2H, J = 8 Hz), 7.30 (d, 2H, J = 8 Hz), 5.36 (d, 1H, J = 8 Hz), 5.08 (br s, 1 H), 4.57 (br s, 1H), 3.31 (d, 1 H, J = 8 Hz), 2.41 (s, 3H, Me), 2.0 (s, 3H, Me), 1.92 (s, 3H, Me), 1.70 (s, 3H, Me), 1.50 (s, 3H, Me). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): 143.4, 137.6, 130.5 (quaternary), 129.7, 127.7, (aromatic, C−H), 113.0, 55.8 (olefinic C-H), 69.4 (C-H), 55.8 (C-H), 29.7 ($COCH_3$), 22.2, 21.7, 13.9 (CH_3). Anal. Calcd for $C_{19}H_{23}SO_4N$: C, 63.13; H, 6.41; N, 3.88; S, 8.87. Found: C, 63.18; H, 6.49; N, 3.81; S, 8.89.

Conversion of 1-(3a,4,7,7a-Tetrahydro-2,5,7a-trimethyl-4-tosylfuro[3,2-*b*]pyridin-7-yl)ethanone (1) into 1-(4-Acetyl-1,2-dihydro-3,6-dimethyl-1-tosylpyridin-2-yl)propan-2-one (2). The product obtained in the previous reaction (0.4 mmol) was dissolved in methylene chloride and passed through a column filled with neutral alumina. The resulting red solution was concentrated and cooled at −20 °C to give off-white crystals of 1-(4-acetyl-1,2-dihydro-3,6-dimethyl-1-tosylpyridin-2-yl)propan-2-one (**2**). Slow evaporation of a CH_2Cl_2/petroleum ether solutions gave single crystals suitable for a X-ray study. ^{1}H NMR ($CDCl_3$, 400 MHz): 7.57 (d, 2H, J = 8 Hz), 7.21 (d, 2H, J = 8 Hz), 5.93 (s, 1H), 4.96, 2.52, 2.41 (ABM spin system, δ_A = 2.41, δ_B = 2.52, δ_M = 4.96, J_{AB} = 15 Hz, J_{AM}= 10 Hz, J_{BM} = 5 Hz), 2.36 (s, 3H, CH_3), 2.25 (s, 3H, $COCH_3$), 2.25 (s, 3H, $COCH_3$), 1.83 (s, 3H, CH_3), 1.56 (s, 3H, CH_3). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): 144.3, 138.3, 135.5, 132.9, 129.9 (quaternary C), 127.3, 127.1 (aromatic, C-H), 116.4 (olefinic C-H), 58.2 (C-H), 43.9 (CH_2), 30.4, 29.9 ($COCH_3$), 22.9, 21.7, 19.3 (CH_3). Anal. Calcd for $C_{19}H_{23}SO_4N$: C, 63.13; H, 6.41; N, 3.88; S, 8.87. Found: C, 63.27; H, 6.51; N, 3.81; S, 9.05.

CCDC 713086 contains the supplementary crystallographic data for compound **2**. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Reaction of 2-methylfuran with PhI=NTs in the Presence of $Tp^{Br3}Cu(NCMe)$. A 0.025 mmol (25.6 mg) portion of the copper complex was dissolved in 1.85 mL of 2-methylfuran and 2 mL of CH_2Cl_2. To the colorless stirred solution was added 186 mg (0.5 mmol) of PhI=NTs as yellow crystals. The mixture became

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greenish in a few seconds, and the color slowly turned orange while the nitrene precursor entered the solution in a few minutes. The mixture was stirred for 20 h. Volatiles were removed under vacuum, and the residue was investigated by NMR showing the formation of 1-(3a,4,7,7a-tetrahydro-2-methyl-4-tosylfuro[3,2-*b*]pyridin-7-yl)-ethanone (**3**) and 1-(4-acetyl-1,2-dihydro-1-tosylpyridin-2-yl)propan-2-one (**4**) (ratio **3**/**4** 5:95). Attempts to separate both compounds failed, both by crystallization or chromatography. In fact, passing the mixture through silica gel or neutral alumina led to the quantitative conversion of **3** into **4**. The same result was achieved by stirring the reaction mixture for 3−4 days at room temperature. However, the use of the silver complex $Tp^{*,Br}Ag$ as the catalyst provided a 90:10 mixture of **3** and **4**, respectively, from which **3** could be completely characterized by NMR spectroscopy.

1-(3a,4,7,7a-Tetrahydro-2-methyl-4-tosylfuro[3,2-*b*]pyridin-7-yl)ethanone (**3**). ^{1}H NMR ($CDCl_3$, 400 MHz): 7.8 (d, 2H, J = 8 Hz), 7.26 (d, 2H, J = 8 Hz), 6.75 (d, 1H, J = 8 Hz), 5.25 (d, 1H, J = 8 Hz), 4.98 (d, 1H, J = 8 Hz), 4.78 (d, 1H, J = 8 Hz), 3.4 (dd, 1H, J = 8 Hz), 2.3 (s, 3H, CH_3), 1.95 (s, 3H, $COCH_3$), 1.78 (s, 3H, $COCH_3$). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): 204.1 (carbonylic CO), 158.5, 144.1, 136.2 (quaternary C), 129.8, 128.7 (aromatic, C-H), 127, 104.8, 81.4 (olefinic C-H), 100.5 (C-H), 60.4 (C−H), 48.7 (CH), 28.4 ($COCH_3$), 21.8 (CH_3), 13.7 (CH_3).

1-(4-Acetyl-1,2-dihydro-1-tosylpyridin-2-yl)propan-2-one (**4**). ^{1}H NMR ($CDCl_3$, 400 MHz): 7.67 (d, 2H, J = 8 Hz), 7.28 (d, 2H, J = 8 Hz), 6.72 (d, 1H, J = 8 Hz), 5.98 (d, 1H, J = 8 Hz), 6.36, 5.10, 3.09, 2.82 (ABMX spin system, δ_A = 2.82, δ_B = 3.09, δ_M = 5.10, δ_X = 6.36, J_{AB} = 18 Hz, J_{AM} = 4 Hz, J_{BM} = 8 Hz, J_{MX} = 6 Hz), 2.41 (s, 3H, CH_3), 2.15 (s, 3H, $COCH_3$), 2.15 (s, 3H, $COCH_3$). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): 205.6, 195.5 (carbonylic CO), 144.3, 136.2, 133.1 (quaternary C), 129.7, 126.4 (aromatic, C-H), 129.6, 126.1, 105.0 (olefinic C-H), 49.7 (C-H), 49.4 (CH_2), 30.2, 25.1 ($COCH_3$), 21.5 (CH_3). Mass spectrum (FAB): m/z [M^+ + 1] 334, [M^+ + Na] 356, [M^+ + K] 372.

Reaction of 2-Ethylfuran with PhI═NTs in the Presence of Tp^{Br3}Cu(NCMe). The procedure was analogous to that previously described for 2-methylfuran. Again, two products were obtained after 20 h of stirring, in a 95:5 ratio. The major product **6** was identified as 1-(1,2-dihydro-4-propionyl-1-tosylpyridin-2-yl)butan-2-one. Minor amounts of the bicylic intermediate 1-(2-ethyl-3a,4,7,7a-tetrahydro-4-tosylfuro[3,2-*b*]pyridin-7-yl)propan-1-one (**5**) could be identified on the basis of a set of resonances similar to those of compound **3**.

1-(1,2-Dihydro-4-propionyl-1-tosylpyridin-2-yl)butan-2-one (**6**). ^{1}H NMR ($CDCl_3$, 400 MHz), 7.67 (d, 2H, J = 8 Hz), 7.28 (d, 2H, J = 8 Hz), 6.72 (d, 1H, J = 8 Hz), 5.98 (d, 1H, J = 8 Hz), 6.36, 5.10, 3.09, 2.82 (ABMX spin system, δ_A = 2.82, δ_B = 3.09, δ_M = 5.10, δ_X = 6.36, J_{AB} = 18 Hz, J_{AM}= 4 Hz, J_{BM} = 8 Hz, J_{MX} = 6 Hz), 2.38 (s, 3H, CH_3), 2.40 (q, 2H, $CO\mathit{CH}_2CH_3$, J = 7.8 Hz), 2.35 (q, 2H, $CO\mathit{CH}_2CH_3$), 1.02 (t, 3H, $COCH_2\mathit{CH}_3$, J = 7.8 Hz), 0.98 (t, 3H, $COCH_2\mathit{CH}_3$, J = 7.8 Hz). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): 208.5, 198.5 (carbonylic CO), 144.5, 136.5, 132.7 (quaternary C), 130.0, 126.9 (aromatic, C-H), 128.8, 126.3, 105.7 (olefinic C-H), 50.0 (C-H), 48.3 (CH_2), 36.5, 30.6 ($COCH_3$), 8.3, 7.7 (CH_3). Mass spectrum (CI): m/z calcd for $C_{19}H_{23}NO_4S$ 362.1426, found 362.1419.

Reaction of 2,3-Dimethylfuran with PhI═NTs in the Presence of Tp^{Br3}Cu(NCMe). With the above procedure, the reaction was performed with 2,3-dimethylfuran, leading to the isolation of an oily residue that has been identified as 1-(3a,4,7,7a-tetrahydro-2,3,7-trimethyl-4-tosylfuro[3,2-*b*]pyridin-7-yl)ethanone (**7**). This bicyclic compound could not be further transformed into a dihydropyridine by treatment with alumina or by prolonged heating. ^{1}H NMR ($CDCl_3$, 400 MHz): 7.8 (d, 2H, J = 8 Hz), 7.26 (d, 2H, J = 8 Hz), 6.50 (d, 1H, J = 8 Hz), 5.18 (d, 1H, J = 8 Hz), 5.08 (d, 1H, J = 8 Hz), 4.95 (d, 1H, J = 8 Hz), 2.4 (s, 3H, CH_3), 1.75 (s, CH_3), 1.71 (s, CH_3), 1.35 (s, CH_3), 1.27 (s, CH_3). ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz): 208.0 (carbonylic CO),151.4, 148.2, 143.5, 139.6, 132.7 (quaternary C), 130.0, 126.9 (aromatic, C-H), 128.5, 118.6, (olefinic C-H), 85.6, 65.9 (C-H), 27.8, 21.6, 11.6, 11.4, 10.5 (CH_3). Mass spectrum (CI): m/z calcd for $C_{19}H_{23}NO_4S$ 362.1426, found 362.1440.

NMR Monitoring Experiments. A 0.0125 mmol portion of the Tp^{Br3}Cu(NCMe), 0.25 mmol of PhI═NTs, and 0.25 mmol of 2-methylfuran were dissolved, inside of a drybox, in 1 mL of $CDCl_3$ in a vial. After 5 min of stirring, a orange solution was obtained that was transferred into an NMR tube. The reaction was monitored by ^{1}H NMR (Figures 2 and 3). From the first spectrum, 10 min after the beginning of the reaction, **OI1** and **OI2** could be detected. Selected ^{1}H NMR resonances for (2*Z*)-4-tosyliminopent-2-enal (**OI1**): δ 9.32 (d, H^3, J = 9.3 Hz), 6.52 (dd, H^2, J = 11.3, 9.3 Hz), 6.83 (d, H^1, J = 11.3 Hz). See Figure 2 for labeling. Selected ^{1}H NMR resonances for (3*E*)-5-tosyliminopent-3-en-2-one (**OI2**): δ 8.71 (d, H^6, J = 9 Hz), 6.81 (d, H^4, J = 15 Hz). H^5 is obscured by aromatic resonances. See Figure 2 for labeling.

Effect of the Metal Catalyst in the Reaction of OI2 with 2-Methylfuran. A solution identical to that described in the previous paragraph was prepared and strred until only **OI1** was present. At that point, the solution was divided in two identical aliquots of 0.5 mL each, and 0.5 mL of $CDCl_3$ was added to re-establish the initial concentration values in both samples. Additional Tp^{Br3}Cu(NCMe) (0.0125 mmol) was added to one of the aliquots. Both samples were monitored by ^{1}H NMR as shown in Figure 4.

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Supporting Information Available: Crystallographic data for compound **2** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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