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Copper-Catalyzed Nitrene Transfer as a Tool for the Synthesis of N-Substituted 1,2-Dihydro- and 1,2,3,4-Tetrahydropyridines

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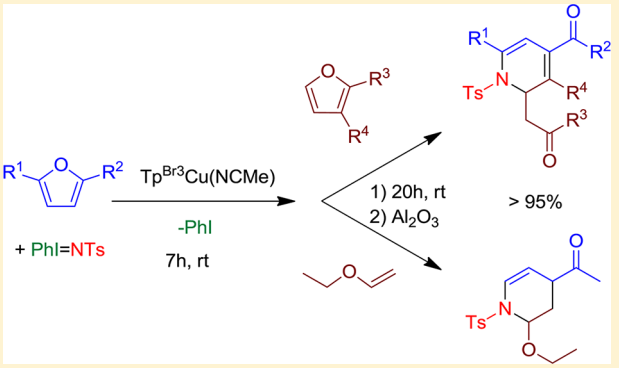
ABSTRACT: The sequential reaction of two different furans and PhI=NTs produces 1,2-dihydropyridines in a quantitative manner in the presence of $Tp^{Br3}Cu(NCMe)$ (Tp^{Br3} = hydrotris(3,4,5-tribromopyrazolyl)borate) as the catalyst under very mild conditions. The use of a furan and ethyl vinyl ether with PhI=NTs has led to the corresponding 1,2,3,4-tetrahydropyridine.

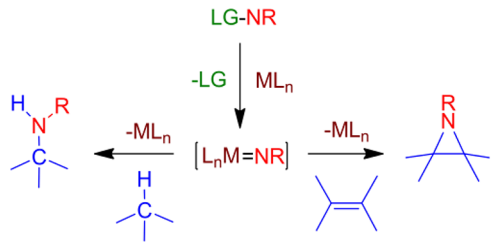


INTRODUCTION

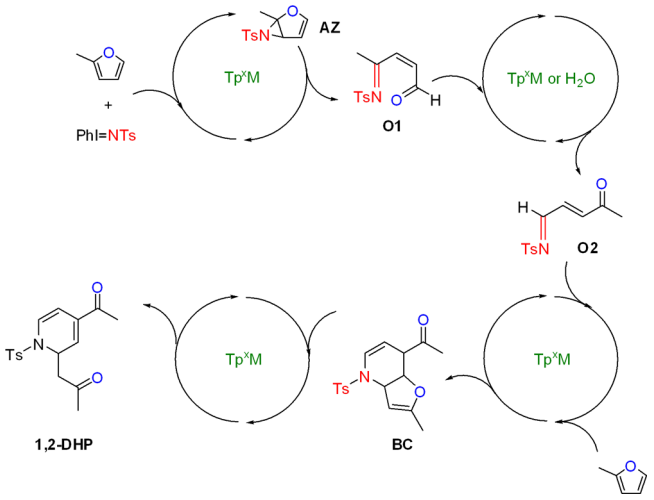
The metal-mediated catalytic transfer of nitrene (NR) groups to saturated or unsaturated substrates constitutes a useful tool in organic synthesis, in both inter- and intramolecular fashions, the main transformations being the C−H amination or the C=C aziridination reactions (Scheme 1).[1] During the course of our investigations in this area, we found a novel reaction[2] in which alkyl-substituted furans could be selectively converted into 1,2-dihydropyridines, in a process involving two molecules of the heterocycle and one molecule of PhI=NTs (Ts = *p*-toluenesulfonyl) and with Tp^xM complexes (Tp^x = hydrotris(x-substituted-pyrazolyl)borate ligand; M = Cu, Ag) as the catalyst. Mechanistic studies showed that this transformation takes place along four consecutive catalytic cycles, in which at least three of them were metal-mediated. The first step consisted of the aziridination of the furan (2-methylfuran in Scheme 2) and subsequent spontaneous opening of the aziridine AZ to give the aldehyde O1. This aldehyde was converted into the imine O2 throughout a transimination catalytic step (either metal- or water-induced). The third cycle involved in this transformation was a metal-induced aza-Diels−Alder reaction (ADAR) that afforded the bicyclic compound BC, which finally converted into the 1,2-dihydropyridine upon a metal-catalyzed H-elimination−migration process.

Dihydropyridines (DHPs) are essential intermediates in the synthetic routes of organic compounds with important biological activity.[3] 1,4-Dihydropyridines are starting materials for a variety of drugs such as Nifedipine[4] and AK-2-38[5] as

Scheme 1. Metal-Mediated C−H Amination and Olefin Aziridination Reactions by Nitrene Transfer



Scheme 2. Synthesis of 1,2-Dihydropyridines from Furans and PhINTs Catalyzed by Tp^xM Complexes (M = Cu, Ag)



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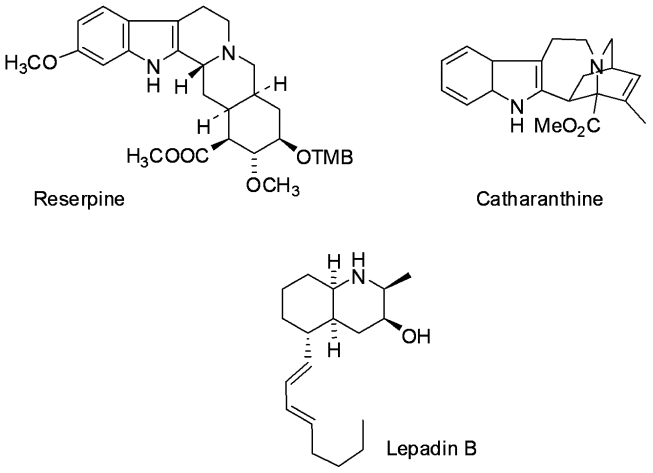
cardiovascular agents and Nimodipine[6] for the treatment of Alzheimer's disease, all them displaying a 1,4-DHP core in their structures. 1,2-DHPs also find application in the synthetic routes of numerous natural products (Scheme 3) with medical

Scheme 3. Some Drugs Produced with the Intermediacy of 1,2-Dihydropyridine Cores



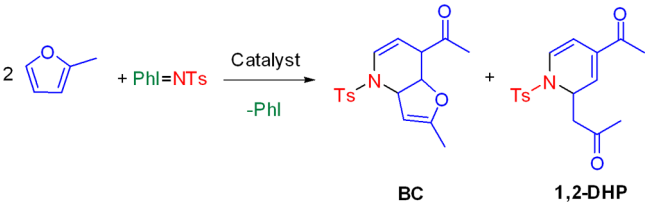
applications, such as Reserpine[7] (hypertension and mental disorders), the alkaloids Catharanthine[8] (precursor of the anticancer agent vinblastine), and (+)-Lepadin B[9] (treatment of viral infection and cancer metastasis). In spite of the interest in 1,2-DHPs, there have been few described procedures for their synthesis,[10] particularly in a regioselective manner, 1,4-DHPs being far more developed to date.[11]

Our previous work[2] was performed using a large excess of furan to be reacted with PhI=NTs in the presence of the copper- or silver-based catalyst. Therefore, the product contained two molecules of the starting furan. We wondered about the possibility of coupling two different furans in the final 1,2-dihydropyridines. Under the appropriate conditions, it has been possible to obtain novel 1,2-DHPs, demonstrating the potential of certain copper catalysts to induce their quantitative synthesis, providing a tool for future, more specific applications.

RESULTS AND DISCUSSION

Catalyst Screening. We have first carried out a preliminary catalyst screening to compare the activity of several simple copper salts and precatalysts with the well-established catalytic capabilities of the complex $Tp^{Br3}Cu(NCMe)$. As a model reaction we have reproduced that with 2-methylfuran in our previous work, using an excess of the heterocycle. Thus, when a 1:20:100 mixture of the catalyst source, PhI=NTs, and 2-methylfuran were stirred at room temperature for 20 h, all the catalyst precursors employed provided a mixture of both the bicyclic compound (BC) and the 1,2-dihydropyridine (1,2-DHP), in a variable ratio, as shown in Table 1. Simple copper(I) halides (Table 1, entries 1 and 2) gave 1:1 to 3:1 mixtures of those compounds. However, the addition of a donor ligand such as PPh_3 or bipy led to the enhancement of the yields in 1,2-DHP (Table 1, entries 3 and 4), the former providing the desired product in quantitative yield. The $Tp^{Br3}Cu(NCMe)$ complex gave the dihydropyridine in 95% yield, with a minor amount of the bicyclic precursor (Table 1, entry 7). It is worth mentioning that the mixtures of BC and

Table 1. Catalyst Screening for the Reaction of 2-Methylfuran and PhINTs[a]



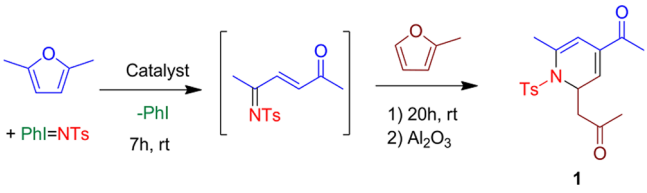
entry	cat. precursor	yield of BC, %[b]	yield of 1,2-DHP, %[b]
1	CuI	25	75
2	CuCl	50	50
3	CuI + PPh_3	0	>99
4	CuI + bipy	20	80
5	CuOTf C_6H_6	50	50
6	$[Cu(NCMe)_4]PF_6$	50	50
7	$Tp^{Br3}Cu(NCMe)$	5	95

[a]Reaction conditions: 0.025 mmol of catalyst; 0.5 mmol of PhI=NTs; 2.5 mmol of 2-methylfuran; 5 mL of CH_2Cl_2 as solvent; at room temperature; reaction time 20 h. [b]Based on initial PhI=NTs. $TsNH_2$ was not detected after complete consumption of PhI=NTs.

1,2-DHP were quantitatively converted into the latter by treatment with alumina.

After the above screening of a series of catalyst precursors, we turned to the targeted reaction involving two different furans. In this case, an equimolar mixture of 2,5-dimethylfuran was reacted with PhI=NTs in the presence of catalytic amounts of the catalyst source (5 mol % with respect to reactants). After 7 h of stirring the reactants were consumed, providing the imine intermediate (Scheme 4), and 5 equiv of 2-methylfuran

Scheme 4. Synthesis of 1,2-Dihydropyridines from Two Different Furans



was added to the mixture. Workup (see the Experimental Section) consisted of elimination of volatiles and filtration through alumina to drive the reaction mixture to the desired dihydropyridine **1** (Scheme 4). In this case we have found a marked difference among the group of catalyst precursors employed (Table 2). With no doubt, the $Tp^{Br3}Cu(NCMe)$ complex provided the best conversion by far into the 1,2-dihydropyridine **1**. This is explained as the consequence of furan aziridination as the first step of this transformation (as shown in Scheme 2). Although most of the catalyst precursors shown in Table 2 have been described to induce the olefin aziridination reaction,[1] usually such a transformation takes place with an excess of the olefin with respect to the nitrene source. The use of equimolar amounts in this system significantly decreases the yield in the starting aziridine and subsequent products. Only $Tp^{Br3}Cu(NCMe)$ seems to overcome this drawback, due to its already described capability to catalyze the olefin aziridination reaction with equimolar amounts of the reactants.[12] Therefore, for the purpose of

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Table 2. Catalyst Screening for the Synthesis of 1,2-Dihydropyridine 1 (see Scheme 4)[a]

entry	cat. precursor	yield of **1**, %[b]
1	CuI	65
2	CuCl	30
3	CuI + PPh_3	50
4	CuI + bipy	5
5	CuOTf C_6H_6	<5
6	$[Cu(NCMe)_4]PF_6$	65
7	$Tp^{Br3}Cu(NCMe)$	94

[a]Reaction conditions: 0.025 mmol of catalyst; 0.5 mmol of PhI=NTs; 0.5 mmol of 2,5-dimethylfuran; 2.5 mmol of 2-methylfuran; 5 mL of CH_2Cl_2 as solvent; at room temperature; overall reaction time 27 h. [b]The remainder of the initial PhI=NTs up to 100% was converted into $TsNH_2$.

affording novel DHPs from two different furans, the complex $Tp^{Br3}Cu(NCMe)$ was chosen to develop the reaction scope.

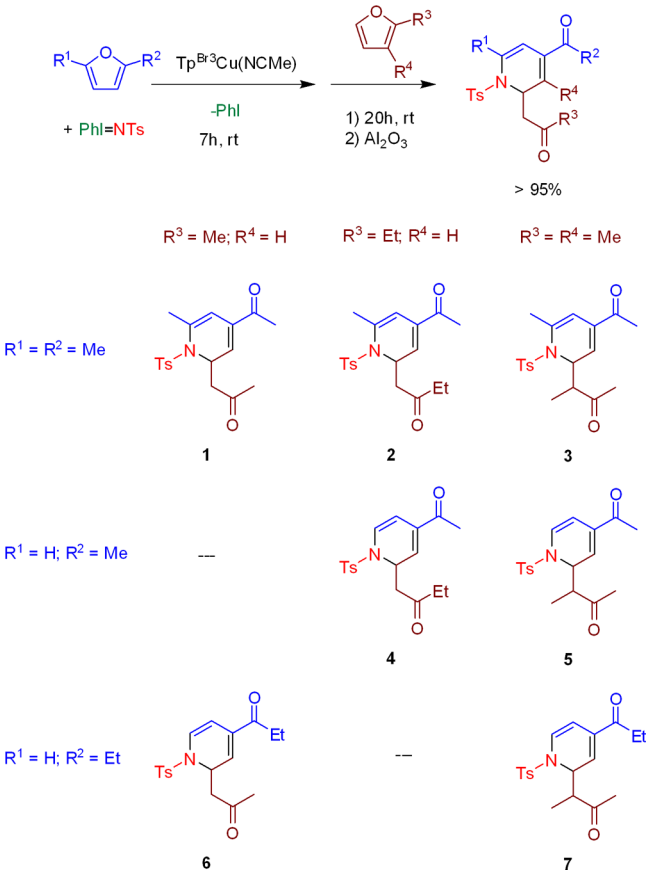
General Procedure for the Synthesis of 1,2-Dihydropyridines from Two Different Furans. After the above results, we ran a series of seven crossed experiments using four different furans (Scheme 5), following a similar procedure: a 5 mol % catalyst loading was employed with an equimolar mixture of an alkyl-substituted furan and PhI=NTs. After 7 h, the second furan (5 equiv) was added and finally the reaction mixture was treated with alumina to give the expected dihydropyridines in very high yield (>95% in all cases). Overall, this is a very efficient transformation in which a NTs fragment and two different furans are assembled to give a more complex structure with a pyridine skeleton. Interestingly, it is possible to control the position of the substituents at the end of the reaction: for instance, 2-methylfuran and 2-ethylfuran led to two different products, **4** and **6**, depending on the order in which they are employed in the reaction protocol.

An interesting feature was observed in the NMR spectra of the compounds derived from the use of 2,3-dimethylfuran. The dihydropyridines **3**, **5**, and **7** contain two stereogenic centers, and as a result of this, mixtures of two diastereomers have been detected by NMR spectroscopy. A small diastereomeric excess of ca. 10% was induced in two cases.

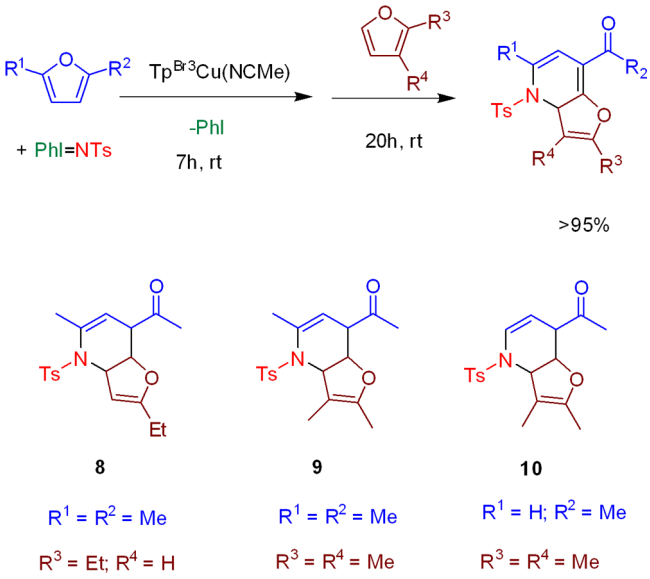
As mentioned above, the formation of the 1,2-DHP by this procedure takes place through the intermediacy of a bicyclic compound derived from an aza-Diels–Alder reaction of an imine and the second molecule of furan (Scheme 2). Although we were interested in the synthesis of 1,2-DHPs, for the sake of completeness we focused on the detection of those intermediates. Therefore, we ran the same protocol with the exception of the final treatment with alumina. After removal of volatiles and removal of the metal by quick filtration throughout a plug of silica gel, we observed by NMR the nearly quantitative formation of the bicyclic products in the three representative examples studied (Scheme 6). Compounds **8**–**10** were characterized by means of their ^1H NMR spectra and comparison with our previous work. However, they smoothly transform in solution into the corresponding 1,2-DHPs, precluding the acquisition of $^{13}C\{^1H\}$ NMR data. In any case, the interpretation of the available data is unambiguous in comparison with our previous work[2] (see the Experimental Section), and we propose a bicyclic structure for these three compounds.

Vinyl Ethyl Ether As Substrate: Synthesis of a Tetrahydropyridine. Since the generation of the imine from the copper-catalyzed reaction of a furan and PhI=NTs seems to be a clean process, we wondered about the addition of a dienophile distinct to furan in the second step of this transformation. On the basis of the initial use of 2-methylfuran, we first tried styrene and 3-hexyne as representative examples

Scheme 5. General Synthesis of 1,2-Dihydropyridines from Two Different Furans



Scheme 6. Preparation of the Intermediate Bicyclic Compounds 8–10



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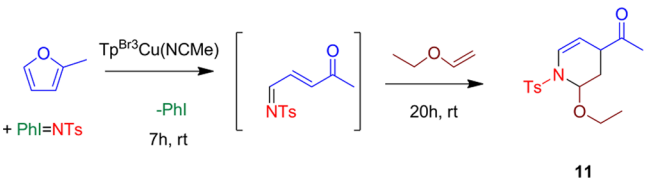
of alkenes and alkynes, respectively. Unfortunately, we observed no reaction at all with these substrates. However, when we employed ethyl vinyl ether, we observed the formation of compound **11**, a tetrahydropyridine derived from the aza-Diels–Alder reaction of the imine and the unsaturated ether shown in Scheme 7. The synthesis of chiral tetrahydropyridines

Scheme 7. Synthesis of the Tetrahydropyridine 11



11

is an area of interest. A recent work by Carretero and co-workers[13] with chiral nickel-based catalysts has proven the validity of the aza-Diels–Alder reaction to generate those molecules.

CONCLUSIONS

In summary, we have employed the complex $Tp^{Br3}Cu(NCMe)$ as a catalyst for a transformation in which two different furans and PhI=NTs react to produce 1,2-dihydropyridines. The procedure also applies to a furan and ethyl vinyl ether to give a 1,2,3,4-tetrahydropyridine. All the reactions took place in quantitative yields and under very mild conditions. The generation of stereocenters opens a window for the future development of the asymmetric catalytic version of this transformation.

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. The copper salts, substituted furans, and other reagents were purchased from Aldrich and were rigorously dried previously to their use. Solvents were dried and degassed before use with a MBRAUN SPS system. The $Tp^{Br3}Cu(NCMe)$ complex[14] and PhI=NTs[15] were prepared according to literature methods. NMR experiments were run in a Varian Mercury 400 MHz spectrometer. ESI-MS analyses were carried out at CITIUS (Universidad de Sevilla, Spain).

General Catalytic Experiment for the Synthesis of Dihydropyridines 1–7. The catalyst precursor (0.025 mmol) was dissolved in 5 mL of CH_2Cl_2, and 0.5 mmol of the first alkylfuran (see Scheme 5) was added. To the resulting colorless solution was added PhI=NTs (0.5 mmol, 186 mg) as yellow crystals. The mixture turned greenish within a few seconds, and the color slowly changed to orange with time. After 7 h of stirring, 5 equiv (2.5 mmol) of the second alkylfuran was added, and the mixture was stirred for an additional 20 h. Volatiles were then removed under vacuum, 2 mL of methylene chloride was added, and the solution was passed throughout a plug of neutral alumina. The solution was evaporated, and the resulting reddish solids corresponded to pure dihydropyridines **1**–**7**. Isolated yields: >95%.

*1-(4-Acetyl-6-methyl-1-tosyl-1,2-dihydropyridin-2-yl)propan-2-one (**1**).* ^1H NMR ($CDCl_3$, 400 MHz): δ 7.52 (d, 2H, J = 8 Hz), 7.12 (d, 2H, J = 8 Hz), 6.09 (s, 1H), 6.17, 5.21, 2.73, 2.61 (ABMX spin system, δ_A 2.61, δ_B 3.09, δ_M 5.21, δ_X 6.17, J_{AB} = 18 Hz, J_{AM} = 4 Hz, J_{BM} = 8 Hz, J_{MX} = 6 Hz), 2.29 (s, 3H), 2.19 (s, 3H), 2.08 (s, 3H), 1.85 (s, 3H). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 204.2 (CO), 194.2 (CO), 143.0 (C_q), 134.9 (C_q), 134.7 (C_q), 132.4 (C_q), 130.8 (olefinic CH), 128.3 (aromatic CH), 126.2 (aromatic CH), 111.5 (olefinic CH), 50.3 (CH), 46.0 (CH_2), 29.0 ($COCH_3$), 23.8 ($COCH_3$), 22.1 (CH_3), 20.4 (CH_3). ESI-MS analysis: calcd for $C_{18}H_{21}NO_4S$, 347.43; found, 348.12.

*1-(4-Acetyl-6-methyl-1-tosyl-1,2-dihydropyridin-2-yl)butan-2-one (**2**).* ^1H NMR ($CDCl_3$, 400 MHz): δ 7.51 (d, 2H, J = 8 Hz), 7.12 (d, 2H, J = 8 Hz), 6.09 (s, 1H), 6.15, 5.22, 2.68, 2.58 (ABMX spin system, δ_A 2.58, δ_B 2.68, δ_M 5.22, δ_X 6.15, J_{AB} = 18 Hz, J_{AM} = 4 Hz, J_{BM} = 8 Hz, J_{MX} = 6 Hz), 2.37 (2H, J = 7.5 Hz), 2.28 (s, 3H), 2.18 (s, 3H), 1.85 (s, 3H), 0.97 (s, 3H, J = 7.5 Hz). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 207.9 (CO), 195.3 (CO), 144.0 (C_q), 135.9 (C_q), 135.6 (C_q), 132.3 (C_q), 132.0 (olefinic CH), 129.6 (aromatic CH), 127.2 (aromatic CH), 112.4 (olefinic CH), 51.3 (CH), 45.7 (CH_2), 36.0 (CH_2), 24.8 (CH_3), 23.2 ($COCH_3$), 21.4 (CH_3), 7.5 (CH_3). ESI-MS analysis: calcd for $C_{19}H_{23}NO_4S$, 361.45; found, 362.14.

*3-(4-Acetyl-6-methyl-1-tosyl-1,2-dihydropyridin-2-yl)butan-2-one (**3**).* Two diastereomers, 1:1 mixture. Data for diastereomer A are as follows. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.51 (d, 2H, J = 8 Hz), 7.10 (d, 2H, J = 8 Hz), 6.11 (s, 1H), 6.10 (d, 1H, J = 6 Hz), 4.93 (dd, 1H, J = 6, 10 Hz), 2.62 (dq, 1H, J = 7.5, 10 Hz), 2.29 (s, 3H), 2.15 (s, 3H), 2.05 (s, 3H), 1.82 (s, 3H), 1.04 (d, 3H, J = 7.5 Hz). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 208.9 (CO), 194.8 (CO), 143.9 (C_q), 135.0 (C_q), 132.8 (C_q), 131.1 (C_q), 129.9 (olefinic CH), 129.6 (aromatic CH), 126.6 (aromatic CH), 105.6 (olefinic CH), 54.1 (CH), 49.4 (CH), 29.7 ($COCH_3$), 24.7 (CH_3), 23.0 ($COCH_3$), 21.3 (CH_3), 14.1 (CH_3). Data for diastereomer B are as follows. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.51 (d, 2H, J = 8 Hz), 7.10 (d, 2H, J = 8 Hz), 6.10 (s, 1H), 6.02 (d, 1H, J = 6 Hz), 5.0 (dd, 1H, J = 6, 10 Hz), 2.62 (dq, 1H, J = 7.5, 10 Hz), 2.29 (s, 3H), 2.21 (s, 3H), 2.18 (s, 3H), 1.85 (s, 1H), 1.22 (d, 3H, J = 7.5 Hz). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 209.6 (CO), 195.4 (CO), 144.1 (C_q), 133.6 (C_q), 130.6 (olefinic CH), 129.8 (aromatic CH), 126.7 (aromatic CH), 135.6 (C_q), 131.6 (C_q), 109.3 (olefinic CH), 54.3 (CH), 49.7 (CH), 28.6 ($COCH_3$), 24.6 (CH_3), 24.1 ($COCH_3$), 21.5 (CH_3), 13.4 (CH_3).

*1-(4-Acetyl-1-tosyl-1,2-dihydropyridin-2-yl)butan-2-one (**4**).* ^1H NMR ($CDCl_3$, 400 MHz): δ 7.59 (d, 2H, J = 8 Hz), 7.20 (d, 2H, J = 8 Hz), 6.66 (d, 1H, J = 7.5 Hz), 5.91 (d, 1H, J = 7.5 Hz), 6.30, 5.04, 3.01, 2.72 (ABMX spin system, δ_A 2.72, δ_B 3.01, δ_M 5.04, δ_X 6.30, J_{AB} = 18 Hz, J_{AM} = 4 Hz, J_{BM} = 8 Hz, J_{MX} = 6 Hz), 2.37 (q, 2H, J = 7.5 Hz), 2.38 (s, 3H), 2.08 (s, 3H), 0.98 (t, 3H, J = 7.5 Hz). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 208.3 (CO), 195.4 (CO), 144.3 (C_q), 136.2 (C_q), 133.1 (C_q), 129.9 (aromatic CH), 129.7 (olefinic CH), 126.7 (aromatic CH), 126.1 (olefinic CH), 104.8 (olefinic CH), 49.8 (CH), 48.2 (CH_2), 36.3 (CH_2), 25.2 ($COCH_3$), 21.6 (CH_3), 7.5 (CH_3). ESI-MS analysis: calcd for $C_{18}H_{21}NO_4S$, 347.43; found, 346.11.

*3-(4-Acetyl-1-tosyl-1,2-dihydropyridin-2-yl)butan-2-one (**5**).* Data for the major diastereomer (55%) are as follows. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.55 (d, 2H, J = 8 Hz), 7.15 (d, 2H, J = 8 Hz), 6.57 (d, 1H, J = 7.5 Hz), 6.17 (d, 1H, J = 6 Hz), 6.10 (d, 1H, J = 7.5 Hz) 4.88 (dd, 1H, J = 6, 10 Hz), 2.81 (dq, 1H J = 7.5, 10 Hz), 2.31 (s, 3H), 2.10 (s, 3H), 1.99 (s, 3H), 1.22 (d, 3H, J = 7.5 Hz).$^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 209.4 (CO), 195.1 (CO), 144.1 (C_q), 135.5 (C_q), 133.2 (C_q), 129.6 (aromatic CH), 127.9 (olefinic CH), 126.8 (aromatic CH), 126.2 (olefinic CH), 104.7 (olefinic CH), 54.9 (CH), 54.6 (CH), 28.5 ($COCH_3$), 25.0 ($COCH_3$), 21.5 (CH_3), 10.9 (CH_3). Data for the minor diastereomer (45%) are as follows. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.58 (d, 2H, J = 8 Hz), 7.21 (d, 2H, J = 8 Hz), 6.68 (d, 1H, J = 7.5 Hz), 6.10 (d, 1H, J = 6 Hz), 5.82 (d, 1H, J = 7.5 Hz), 5.04 (dd, 1H, J = 6, 10 Hz), 2.98 (dq, 1H, J = 7.5, 10 Hz), 2.34 (s, 3H), 2.14 (s, 3H), 2.09 (s, 3H), 1.22 (d, 3H, J = 7.5 Hz). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 209.9 (CO), 195.4 (CO), 144.4 (C_q), 137.4 (C_q), 134.4 (C_q), 129.9 (olefinic CH), 129.9 (aromatic CH), 127.3 (olefinic CH), 126.8 (aromatic CH), 109.1 (olefinic CH), 55.0 (CH), 49.8 (CH), 29.8 ($COCH_3$), 25.1 ($COCH_3$), 21.6 (CH_3), 14.1 (CH_3). ESI-MS analysis (mixture of diastereomers): calcd for $C_{18}H_{21}NO_4S$, 347.43; found, 346.11.

*1-(2-(2-Oxopropyl)-1-tosyl-1,2-dihydropyridin-4-yl)propan-1-one (**6**).* ^1H NMR ($CDCl_3$, 400 MHz): δ 7.67 (d, 2H, J = 8 Hz), 7.28 (d, 2H, J = 8 Hz), 6.65 (d, 1H, J = 7.5 Hz), 5.92 (d, 1H, J = 7.5 Hz), 6.29, 5.00, 3.04, 2.72 (ABMX spin system, δ_A 2.72, δ_B 3.04, δ_M 5.00, δ_X 6.29, J_{AB} = 18 Hz, J_{AM} = 4 Hz, J_{BM} = 8 Hz, J_{MX} = 6 Hz), 2.40 (q, 2H, J = 7.5 Hz), 2.35 (s, 3H), 2.07 (s, 3H), 0.91 (t, 3H, J = 7.5 Hz). $^{13}C\{^1H\}$

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NMR ($CDCl_3$, 100 MHz): 205.7 (CO), 198.4 (CO), 144.3 (C_q), 136.2 (C_q), 132.5 (C_q), 129.8 (aromatic CH), 128.5 (olefinic CH), 126.7 (aromatic CH), 126.1 (olefinic CH), 105.4 (olefinic CH), 49.5 (CH), 30.4 (CH_2), 30.3 ($COCH_3$), 21.6 (CH_3), 8.0 (CH_3). ESI-MS analysis: calcd for $C_{18}H_{21}NO_4S$, 347.43; found, 346.11.

*3-(4-Propionyl-1-tosyl-1,2-dihydropyridin-2-yl)butan-2-one (**7**).* Data for the major diastereomer (55%) are as follows. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.66 (d, 2H, J = 8 Hz), 7.27 (d, 2H, J = 8 Hz), 6.57 (d, 1H, J = 8 Hz), 6.15 (d, 1H, J = 6 Hz), 6.09 (d, 1H, J = 8 Hz) 4.84 (dd, 1H, J = 6, 10 Hz), 2.81 (dq, 1H, J = 7.5, 10 Hz), 2.39 (q, 2H, J = 7.5 Hz), 2.07 (s, 3H), 1.18 (d, 1H, J = 7 Hz), 0.85 (t, 3H, J = 7.5 Hz). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 209.4 (CO), 197.9 (CO), 144.1 (C_q), 135.6 (C_q), 132.5 (C_q), 129.6 (aromatic CH), 126.6 (aromatic CH), 126.5 (olefinic CH), 126.1 (olefinic CH), 109.6 (olefinic CH), 54.7 (CH), 49.7 (CH), 30.4 (CH_2), 29.8 ($COCH_3$), 21.5 (CH_3), 10.9 (CH_3), 8.1 (CH_3). Data for the minor diastereomer (45%) are as follows. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.67 (d, 2H, J = 8 Hz), 7.28 (d, 2H, J = 8 Hz), 6.67 (d, 1H, J = 7 Hz), 6.09 (d, 1H, J = 6 Hz), 5.83 (d, 1H, J = 8 Hz), 5.02 (dd, 1H, J = 6, 10 Hz), 2.97 (dq, 1H, J = 7.5, 10 Hz), 2.40 (q, 2H, J = 7.5 Hz), 2.15 (s, 3H), 1.20 (d, 1H, 7 Hz), 0.92 (t, 3H, J = 7 Hz). $C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 209.9 (CO), 198.3 (CO), 144.3 (C_q), 136.5 (C_q), 133.8 (C_q), 129.9 (aromatic CH), 128.8 (olefinic CH), 127.2 (olefinic CH), 126.8 (aromatic CH), 105.3 (olefinic CH), 54.9 (CH), 54.6 (CH), 30.4 (CH_2), 28.5 ($COCH_3$), 21.5 (CH_3), 14.1 (CH_3), 8.1 (CH_3). ESI-MS analysis: calcd for $C_{19}H_{23}NO_4S$, 361.45; found, 360.12.

General Catalytic Experiment for the Synthesis of the Bicyclic Compounds 8−10. Following a procedure identical with that detailed above, the final reaction mixture, using the furans shown in Scheme 6, was filtered through a plug of silica gel to retain the catalyst. Solvent removal led to the isolation of reddish orange oils that were identified by NMR as the bicyclic compounds **8**−**10** (vide infra). Isolated yields: >95%. Samples converted into dihydropyridines on standing for several hours in solution, precluding the acquisition of $^{13}C\{^1H\}$ NMR spectra.

*1-(2-Ethyl-3a,4,7,7a-tetrahydro-5-methyl-4-tosylfuro[3,2-b]-pyridine-7-yl)ethanone (**8**).* ^1H NMR ($CDCl_3$, 400 MHz): δ 7.57 (d, 2H, J = 8 Hz), 7.20 (d, 2H, J = 8 Hz), 5.41 (d, 1H, J = 8 Hz), 5.40 (m, 1H), 5.30 (m, 1H), 4.48 (br s, 1H), 3.23 (dd, 1H, J = 8, 1.2 Hz), 2.34 (s, 3H), 1.98 (m, 2H), 1.93 (s, 3H), 1.84 (s, 3H), 0.93 (t, 3H, J = 7.5 Hz).

*1-(3a,4,7,7a-tTetrahydro-2,3,5-trimethyl-4-tosylfuro[3,2-b]-pyridine-7-yl)ethanone (**9**).* ^1H NMR ($CDCl_3$, 400 MHz): δ 7.58 (d, 2H, J = 8 Hz), 7.25 (d, 2H, J = 8 Hz), 5.45 (d, 1H, J = 8.5 Hz), 5.32 (d, 1H, J = 9 Hz), 5.21 (dd, 1H, J = 1.5, 8.5 Hz), 3.17 (dd, 1H, J = 1.5, 8.5 Hz), 2.34 (s, 3H), 2.05 (s, 3H), 1.62 (s, 3H), 1.61 (s, 3H), 1.48 (s, 3H).

*1-(3a,4,7,7a-Tetrahydro-2,3-dimethyl-4-tosylfuro[3,2-b]pyridine-7-yl)ethanone (**10**).* ^1H NMR ($CDCl_3$, 400 MHz): δ 7.58 (d, 2H, J = 8 Hz), 7.23 (d, 2H, J = 8 Hz), 6.54 (d, 1H, J = 7.5 Hz), 5.39 (dd, 1H, J = 7.5 Hz), 5.00 (dd, 1H, J = 9, 1.5 Hz), 4.88 (d, 1H, J = 9 Hz), 3.18 (dd, 1H, J = 1.5, 7.5 Hz), 2.4 (s, 3H), 1.73 (s, 3H), 1.70 (s, 3H), 1.64 (s, 3H).

General Catalytic Experiment for the Synthesis of 1-(2-Ethoxy-6-methyl-1-tosyl-1,2,3,4-tetrahydropyridin-4-yl)-ethanone (11). This compound was prepared following a procedure identical with that detailed above, using 2-methylfuran as the starting material. After the initial 7 h of stirring, 5 equiv of ethyl vinyl ether (2.5 mmol) was added, and the final reaction mixture was treated with silica to yield, after removal of volatiles, 90% isolated yield of compound **11** as a brown-orange oil.

^1H NMR ($CDCl_3$, 400 MHz): δ 7.58 (d, 2H, J = 8 Hz), 7.23 (d, 2H, J = 8 Hz), 6.60 (d, 1H, J = 8 Hz), 5.25 (dd, 1H, J = 8, 1.5 Hz), 5.14 (br s, 1H), 3.58 (dt, 1H, J = 7, 1.5 Hz), 3.40 (dt, 1H, J = 7, 1.5 Hz), 2.57 (m, 1H), 2.49 (m, 1H), 2.37 (s, 3H), 2.07 (s, 3H), 1.26 (m, 1H), 0.96 (t, 3H, J = 7 Hz). $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz): δ 209 (CO), 143.9 (C_q), 137.4 (C_q), 129.8 (aromatic CH), 126.7 (aromatic CH), 123.3 (olefinic CH), 107.7 (olefinic CH), 80.0 (CH), 63.1 (CH_2), 41.6 (CH), 28.7 (CH_2), 28.5 ($COCH_3$), 21.6 (CH_3), 14.6 (CH_3). ESI-MS analysis: calcd for $C_{16}H_{19}NO_4S$, 321.39; found, 320.09.

AUTHOR INFORMATION

Notes

The authors declare no competing financial interest.

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