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Journal Name

COMMUNICATION

Cascade Rh(II) and Yb(III) Catalyzed Synthesis of Substituted Naphthofurans via Transannulation of *N*-Sulfonyl-1,2,3-triazoles with β-naphthols

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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An efficient cascade Rh(II) and Yb(III) catalyzed transannulation of *N*-sulfonyl-1,2,3-triazoles with *β* -naphthols have been accomplished for the synthesis of substituted naphthofurans in good yields. The reaction involves the initial rhodium catalyzed insertion of azavinyl carbene into O-H bond followed by ytterbium catalyzed annulative C-C bond formation and concomitant aerial oxidation. The developed reaction was successfully extended to the phenols to afford substituted benzofurans. Furthermore, synthetic utility of the method was demonstrated through the synthesis of important polyhetero aromatic compounds.

Naphthofurans are vital heterocyclic motifs found in various pharmacological drugs and natural products and also employed as promising building blocks in organic synthesis.[1] Representative examples of napththofurans are shown in Figure 1. Due to the importance of naphthofuran frameworks, various strategies were documented for the synthesis of substituted naphthofurans.[2] Most these strategies utilize either *β* -naphthols or naphthoquinones as starting materials and involve initial C-C bond formation followed by C-O bond formation. However, these methods require synthesis of prefunctionalized starting materials and harsh conditions. Thus, development of new method for the construction of substituted naphthofurans from readily accessible starting material is highly desirable.

On the other hand, rhodium azavinyl carbene, a highly reactive intermediate generated from readily accessible *N*-sulfonyl 1,2,3-triazole, has gained significant attention in recent years due to its valuable contribution in the synthesis of diverse polyheterocyclic compounds.[3] Most of these methods were focused on the synthesis of nitrogen based heterocycles[4] and only selected oxygen based heterocycles[5] were demonstrated. Particularly, constructions of substituted/fused furans are rather limited.

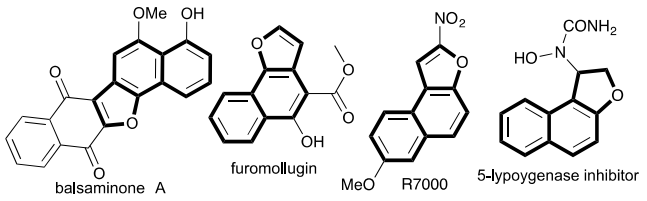
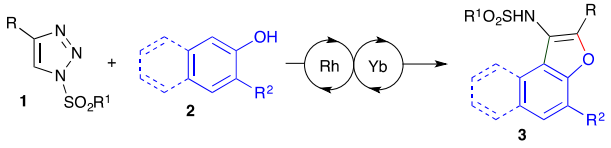


Figure 1. Biologically important naphthofurans.

For instance, Chen and co-workers reported the two-step synthesis of benzofuran via initial C-H insertion followed by oxidation.[6] The similar approach was accomplished by Kang and co-workes in single step employing the combination of Rh(II) and Cu(I) catalysts.[7] On the other hand, carbonyl tethered triazole was utilized by Li and co-workers for the synthesis of substituted furans.[8] Substituted 3-aminofurans were achieved from triazoles and propargyl alcohols by Huang and co-workers via rhodium catalyzed insertion, thermal Claisen rearrangement and gold catalyzed cyclization.[9]



Scheme 1. Synthesis of naphthofurans.

However, synthesis of naphtho/benzofurans from corresponding phenol derivatives and *N*-sulfonyl-1,2,3-triazoles was not documented. In continuation of our interest in the development of efficient strategy for the synthesis of various heterocycles utilizing rhodium azavinyl carbenes,[10] we herein disclose the Rh(II) and Yb(III) catalyzed synthesis of naphthofurans from *β*-naphthols and *N*-sulfonyl-1,2,3-triazoles via rhodium catalyzed insertion followed by ytterbium catalyzed cyclization and oxidation (Scheme 1). In addition, this method also demonstrates the efficiency of the cascade catalysis employing more than one catalyst in one-pot.

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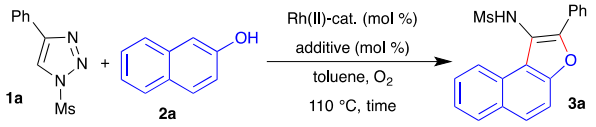
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

We commenced our studies employing *N*-sulfonyl triazoles **1a** with *β*-naphthol **2** as model substrates. Initial reaction of 1 equiv of **1a** with 1 equiv of **2a** in the presence of 2 mol % of $Rh_2(OAc)_4$ under N_2 atmosphere in the absence of additive didn't afford the expected product **3a**. Subsequently, we were pleased to find that the above reaction under O_2 atmosphere in the presence of 10 mol% of CuTC as an additive furnished the desired product **3a** in 45% along with significant amount of BINOL (50%) (Table 1, entry 1). Further investigation with various additives such as $Cu(OAc)_2$ and Cu_2O were failed to improve the yield of **3a** (Table 1, entry 2 and 3). Next, reactions were screened with AgOTf, $Sc(OTf)_3$ and $Yb(OTf)_3$ as additive, which afforded **3a** in 30, 31 and 40% yield, respectively (Table 1, entries 4-6).

Table 1. Transannulation of **1a** with **2a**: Optimization.[a]

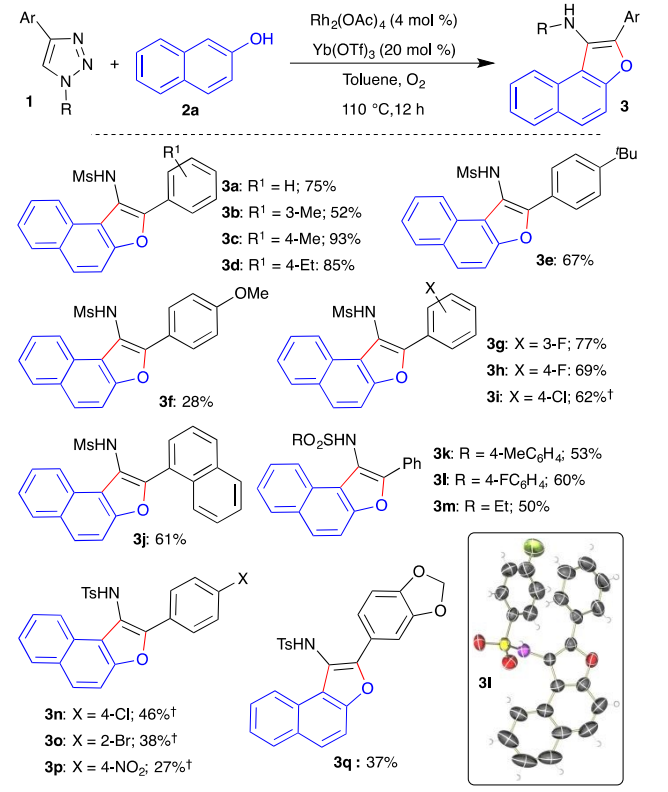


Entry	Catalyst (mol %)	Additive (mol %)	Time (h)	Yield (%)[b]
1	$Rh_2(OAc)_4$ (2)	CuTC (10)	14	45
2	$Rh_2(OAc)_4$ (2)	$Cu(OAc)_2$ (10)	14	20
3	$Rh_2(OAc)_4$ (2)	Cu_2O (10)	12	36
4	$Rh_2(OAc)_4$ (2)	AgOTf (10)	10	30
5	$Rh_2(OAc)_4$ (2)	$Sc(OTf)_3$ (10)	12	31
6	$Rh_2(OAc)_4$ (2)	$Yb(OTf)_3$ (10)	12	40
7	$Rh_2(OAc)_4$ (2)	$Yb(OTf)_3$ (20)	12	61
8	$Rh_2(OAc)_4$ (4)	$Yb(OTf)_3$ (20)	12	65
9	$Rh_2(OAc)_4$ (4)	$Ni(OTf)_2$ (20)	12	44
10	$Rh_2(OAc)_4$ (4)	$Hf(OTf)_3$ (20)	12	60
11	$Rh_2(OAc)_4$ (4)	$In(OTf)_3$ (20)	12	48
12	$Rh_2(OAc)_4$ (4)	$Cu(OTf)_2$ (20)	12	32
13[c]	$Rh_2(OAc)_4$ (4)	$Yb(OTf)_3$ (20)	12	75
14[c]	$Rh_2(Oct)_4$ (4)	$Yb(OTf)_3$ (20)	12	28
15[c]	$Rh_2(Piv)_4$ (4)	$Yb(OTf)_3$ (20)	12	39
16[c]	$Rh_2(esp)_4$ (4)	$Yb(OTf)_3$ (20)	12	43

[a] Reaction conditions: **1a** (0.35 mmol, 1 equiv), **2a** (0.35 mmol, 1 equiv), Rh(II)-cat., additive, toluene 110 °C, time. [b] All are isolated yields. [c] 2 equiv of **1a**.

Increasing the catalyst loading to 4 mol% and additive loading to 20 mol% further improved the yield of the naphthofuran **3a** (Table 1, entry 7 and 8). In attempt to further tune the reaction condition with other metal triflates were unsuccessful (Table 1, entries 9-12). To suppress the formation of BINOL, the equivalence of triazole was increased to 2 equiv and the formation of product was observed in 75% yield (Table 1, entry 13). Furthermore, various rhodium catalysts such as $Rh_2(Oct)_4$, $Rh_2(Piv)_4$, and $Rh_2(esp)_4$ were also tested and gave the product **3a** in 28% , 39% and 43% yield, respectively (Table 1, entries 14-16). Thus, entry 13 was chosen as optimal conditions for the transannulation of **1a** with **2a**.

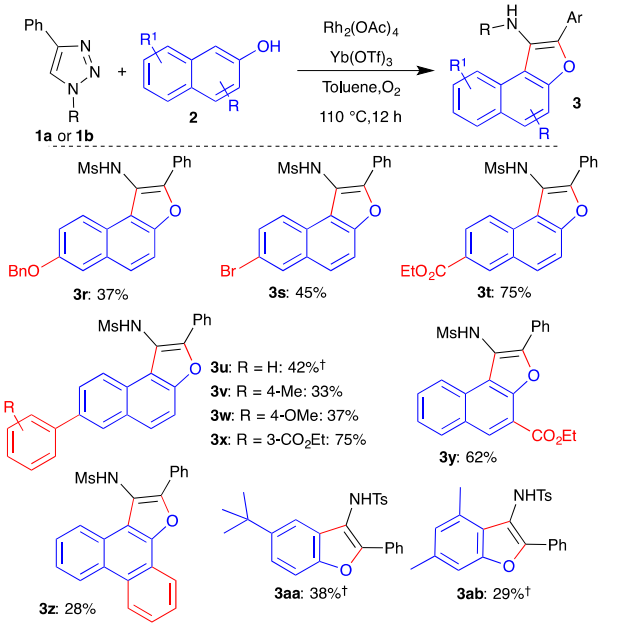
With the optimized conditions in hand, we next investigated the scope and generality of this reaction with substituted triazoles. Alkyl substituted aryl containing *N*-sulfonyl-1,2,3-triazoles gave the corresponding naphthofuran derivatives (**3a**-**3e**) in good to excellent yields (Scheme 2). Halides (F and Cl) and methoxy substituents were well tolerated to afford the corresponding naphthofurans **3f**-**3i** and **3n**-**3o**. Formation of naphthyl substituted naphthofuran **3j** was achieved in 61% yield from corresponding substituted triazole. Next, substitution on the nitrogen was examined. Changing the sulfonyl group at the N1 position of triazole moiety furnished the corresponding naphthofurans **3k**-**3m** in ~55% yield. The structure of the naphthofuran **3l** was unambiguously confirmed by single crystal X-ray analysis.[11] The present method also works with less efficiency for the electron withdrawing nitro and sensitive dioxolane substituted triazoles and let to the formation of products **3o** and **3p** in low yield. The low yield issue was address by introducing the $Yb(OTf)_3$ after 3 h, where the formation of **3i**, **3n**-**p** was observed in the improved yield.



Scheme 2. Scope of triazoles. † $Yb(OTf)_3$ was added after 3 h.

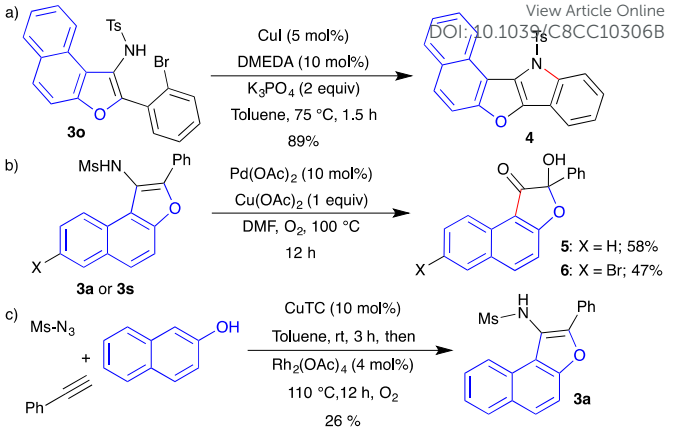
To further expand the scope of the developed method, the reaction of diverse substituted *β*-naphthols with mesyl triazole **1a** were investigated (Scheme 3). 6-Benzyloxy and 6-bromo *β*-naphthols on reaction with **1a** under the optimized conditions afforded the products **3r** and **3s** in 37 and 45% yield. Importantly, ethoxycarbonyl group substituted *β*-naphthols underwent smooth reaction to give the products **3t** and **3y** in 75% and 62% yield, respectively. Similarly, substituted aryl containing *β*-naphthols also furnished the corresponding

naphthofurans **3u**-**3x** in moderate to good yield. Formation of furan annulated phenanthrene was achieved in 28% yield from 9-phenanthrol and **1b**. Consequently, the efficiency of this method was successfully extended to the synthesis of benzofuran derivatives employing simple substituted phenols. Thus, the reaction of 4-*tert*-butylphenol and **1a** in the presence of $Rh_2(OAc)_4$ in toluene at 110 °C followed by addition of $Yb(OTf)_3$ after 12 h furnished the benzofuran derivative **3aa** in 38% yield. Similarly, formation of 4,7-dimethyl substituted benzofuran **3ab** was achieved in appreciable yield from 2,5-dimethylphenol.



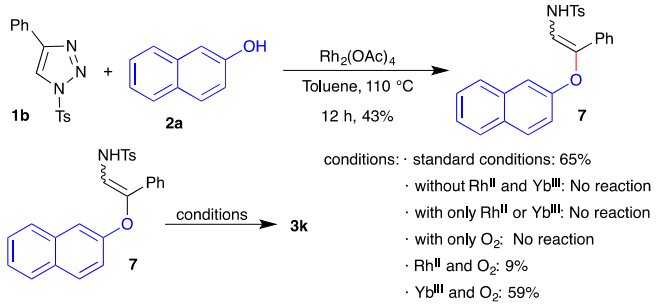
Scheme 3. Scope of *β*-naphthols and phenols. †$Yb(OTf)_3$ was added after 3 h.

Next, to demonstrate the synthetic utility of the developed method, we envisaged the conversion of naphthofurans to biologically important polycyclic heteroaromatic compound. For instance, construction of naphthofuroindole **4** was achieved in 89% yield *via* copper-catalyzed C-N bond cross coupling[12] of *ortho* brominated naphthofuran **3o** in the presence of 5 mol % of CuI, 10 mol % of DMEDA, and K_3PO_4 at 70 °C in toluene (Scheme 4a). In addition, we successfully established an unusual oxidative functionalization of **3a** to naphtho[2,1-*b*]furan-1(2*H*)-ones **5**[13] in the presence of 10 mol % of $Pd(OAc)_2$, 1 equiv of $Cu(OAc)_2$ in DMF at 100 °C for 12 h in 58% of yield (Scheme 4b). Reaction of naphthofuran **3s** under the similar conditions also furnished **6** in 47% yield, demonstrating the general applicability of the oxidative functionalization. Next, the one-pot conversion of alkyne to naphthofuran was envisioned, since the CuTC was also effective for the oxidative cyclization. Thus, the reaction of phenylacetylene and mesylazide in presence of 10 mol% of CuTC in toluene at room temperature for 3 h followed by addition of *β*-naphthol **2a** and $Rh_2(OAc)_4$ and heating reaction mixture at 110 °C under oxygen atmosphere gave the product **3a** in appreciable yield (Scheme 4c).



Scheme 4. Synthetic applications.

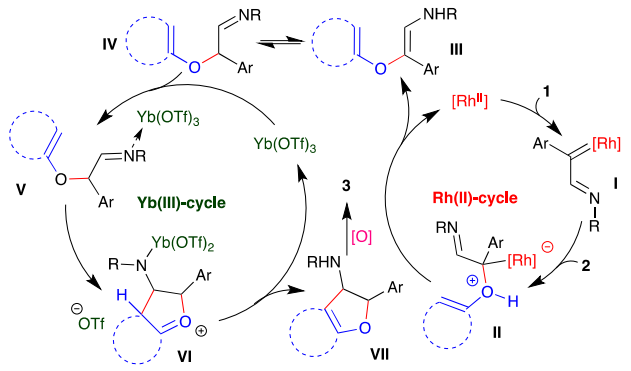
To understand the plausible mechanism, few control experiments were performed. 4-Phenyl-1-tosyl-1*H*-1,2,3-triazole **1b** and *β*-naphthol **2** was treated with $Rh_2(OAc)_4$ in toluene at 110 °C in the absence of additive and oxygen. Interestingly, formation of O-H insertion product **7** was observed in 43% yield (Scheme 5).[14] To further prove **7** as potential intermediate, various conditions were screened employing **7** as starting point. Treatment of **7** under the optimized conditions afforded the **3k** in 65% yield. Thermal heating of **7** under nitrogen atmosphere in the absence of both Rh- and Yb-catalysts did not afford the expected transformation and **7** was recovered. Similar observations were made when thermal heating of **7** at 110 °C under nitrogen atmosphere in the presence of Rh- or Yb-catalysts as well as thermal heating of **7** under oxygen atmosphere in the absence of Rh- and Yb-catalysts. Next, reaction of **7** with rhodium catalyst under oxygen atmosphere led to the formation of **3k** in 9% yield. On the other hand, 59% of **3k** was isolated when **7** was treated with Yb-catalyst under the oxygen atmosphere. These experiments clearly suggested the promising formation of insertion product **12** as potential intermediate and importance of $Yb(OTf)_3$ under O_2 atmosphere for the successive oxidative cyclization.



Scheme 5. Control experiments.

Based on the control experiments, we postulated the plausible mechanism for the cascade Rh and Yb-catalyzed transannulation of **1** with **2**, which occurs in a sequential manner. Reaction of active Rh(II) catalyst with **1** would form reactive rhodium carbenoid **I** through the generation of

diazoimine from ring-chain isomerism **1** (Scheme 6). Insertion of **I** into O-H bond of *β*-naphthol would afford the inserted product **III** via the formation ylide **II**, along with the regeneration of rhodium catalyst for the subsequent cycle. Next, the formed insertion product **III** gets in to the Yb-catalytic cycle. Tautomerization of enamide **III** would give imine **IV**, which on activation by $Yb(OTf)_3$ would provide the intermediate **V**. Intramolecular cyclization in **V** from electron rich *ortho*-position would form the cation **VI**. Formation of fused-dihydrofuran **VII** and regeneration of Yb-catalyst could be rationalized *via* aromatization of **VI** by loss of proton and ion exchange. Finally, aerial oxidation of **VII** would furnish the expected fused-furan products **3**.



Scheme 6. Plausible mechanism.

In conclusion, we have successfully developed a cascade Rh(II) and Yb(III) catalysis for the transannulation of *N*-sulfonyl-1,2,3-triazoles with substituted *β*-naphthol. The reaction involves the initial rhodium catalyzed insertion of azavinyl carbene into O-H bond followed by ytterbium catalyzed annulative C-C bond formation and concomitant aerial oxidation. The developed methodology tolerates various functional groups and offers access to diverse substituted naphthofurans in moderate to good yield. In addition, this methodology was successfully extended to the synthesis of benzofurans employing phenols. O-H inserted product, potential intermediate of the transformation was isolated to postulate the possible mechanism. Furthermore, the synthetic utility of this method was demonstrated through the synthesis of polyhetero aromatic system.

We thank DST-SERB, New Delhi, India (Project No. EMR/2016/003677/OC) for funding this work. SK and MK thanks DST-SERB for the NPDF fellowship.

Conflicts of interest

"There are no conflicts to declare".

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