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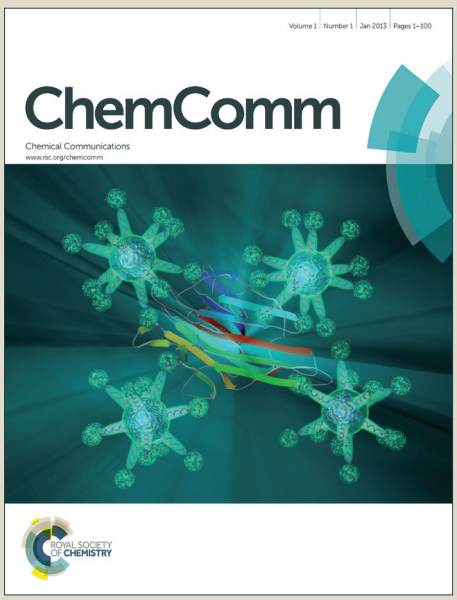

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Cite this: DOI: 10.1039/c0xx00000x

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ARTICLE TYPE

Intramolecular Annulation of Aromatic Rings with *N*-Sulfonyl 1,2,3-triazoles: Divergent Synthesis of 3-Methylene-2,3-dihydrobenzofurans and 3-Methylene-2,3-dihydroindoles

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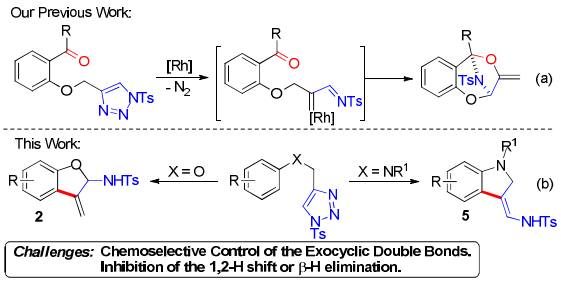
Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

The controllable synthesis of 3-methylene-2,3-dihydrobenzofurans 2 and 3-methylene-2,3-dihydroindoles 5 has been developed through Rh-catalyzed intramolecular annulation of aromatic rings with azavinyl carbenes.

Benzofuran and indole containing molecules are very important heterocycles which can serve as versatile building blocks and spread in a number of natural products with a wide range of biological activities.[1,2] Not surprisingly, numerous efforts have been made to synthesize such compounds.[3,4] On the other hand, less attention has been paid on the chemoselective synthesis of 3-methylene-2,3-dihydrobenzofurans and 3-methylene-2,3-dihydroindoles, which are also very important due to that the exocyclic double bonds can be easily transformed to other useful functional groups for rapid construction of molecular complexity. The challenge relies on the 1,3-H shift driven by aromatization process. Therefore, many reported synthetic methods showed no chemoselectivity in the synthesis of such *exo*-methylene heterocyclic compounds, or suffered from very limited substrate scopes.[5] Only one selective synthesis of both 3-methylene-2,3-dihydrobenzofurans and 3-methylene-2,3-dihydroindoles was accomplished by means of the cycloisomerization of dienes in the presence of Ru complex and trimethylsilyl vinyl ether.[6] Therefore, developing new methodologies to chemoselectively construct such compounds are highly desirable and urgent.

Recently, the Rh(II) catalyzed ring-opening reactions of *N*-sulfonyl 1,2,3-triazoles[7] have immerged as a powerful tool for many useful transformations, including annulation with unsaturated compounds,[8] X-H bonds insertion or functionalization (X = heteroatoms or carbon),[9] ring expansion or carbene induced other transformations.[10] Previously, we also developed the intramolecular annulation of carbonyl-triazoles for the facile construction of 8-aza bridged benzodioxepines through Rh azavinyl carbene intermediates (Scheme 1, a).[11] Herein, we wish to report the substrate-dependent divergent synthesis of 3-methylene-2,3-dihydrobenzofurans and 3-methylene-2,3-dihydroindoles (Scheme 1, b).

Scheme 1. Intramolecualr annulations of triazoles.



Our initial work started with the annulation reaction of 4-(phenyloxymethyl)-1-tosyl-1,2,3-triazole **1a**, which was readily available from Cu(I)-catalyzed azide-alkyne cycloaddition (CuAAC),[12] in the presence of $Rh_2(Piv)_4$ catalyst. To our delight and surprise, an unprecedented 3-methylene-2,3-dihydrobenzofuran **2a** was obtained and unequivocally confirmed by X-ray diffraction.[13] Moreover, when nitrogen tethered substrates **4** were employed as the substrate, the reaction gave indole derivatives (see Tables 3).

After evaluation of the catalysts, solvent effect, temperature and reaction time, we found that **2a** could be formed in 95% yields in DCE upon heating at 90 °C for 3 h (see Supporting Information, Table S1).

With the optimized reaction conditions in hand, we next investigated the generality of this method with respect to various 4-(aryloxymethyl)-1-tosyl-1,2,3-triazoles **1** (Table 1). As for substrates **1b-1d** with electron-withdrawing Cl and Br atoms on the benzene ring, the corresponding products **2b-2d** were isolated in 43-72% yields (Table 1, entries 1-3). On the other hand, upon variation of the substituents by different electron-donating groups, the reactions also proceeded smoothly to give the corresponding 2-aminobenzofuran derivatives **2e-2j** in moderate to excellent yields (65-99%) (Table 1, entries 4-9). However, when a strongly electron-withdrawing CN group was introduced at the *para* position of phenyl ring, the reaction became sluggish to give complex product mixtures, and no desired product **2k** was observed (Table 1, entry 10). Next, several substrates with 4-naphthyloxymethyl substituted **1l-1o** were investigated under the

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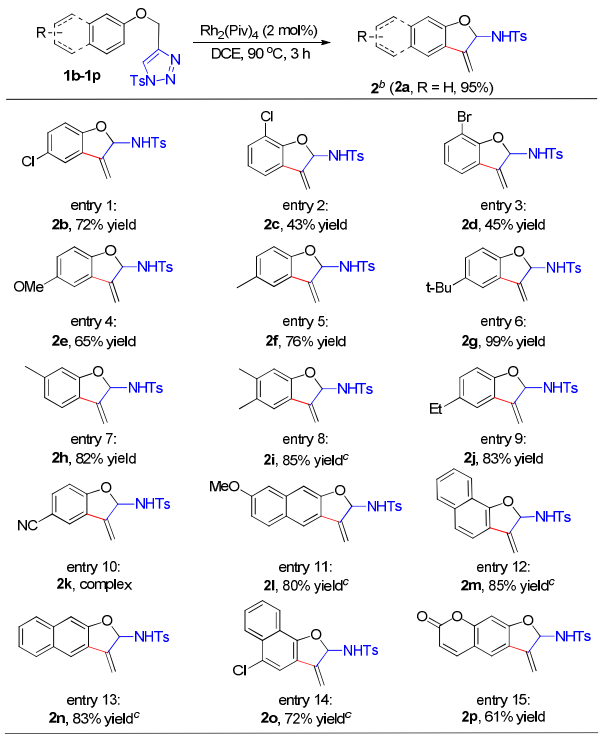
† Electronic Supplementary Information (ESI) available: Experimental procedures, characterization data of new compounds, and CCDC 966827, 969393, 969179, 1012006 and 989483. See DOI: 10.1039/b000000x

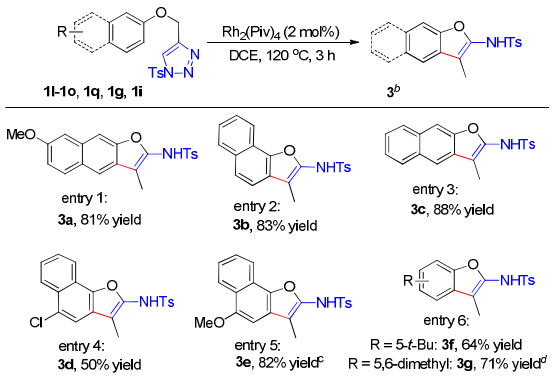
standard reaction conditions, delivering the corresponding 3-methylenenaphthofuran derivatives **2l-2o** in 72-85% yields (Table 1, entries 11-14). For 7-hydroxycoumarin derived *N*-sulfonyl triazole **1p**, the reaction also proceeded smoothly to give the desired product **2p** in 61% yield (Table 1, entry 15).

Table 1. Scope of the Reaction for Synthesis of **2**.[a]



[a] 0.2 mmol scale. Reaction conditions: under Ar, triazole, $Rh_2(Piv)_4$ and DCE (2.0 mL) were stirred in a sealed tube at 90 °C for 3 h. [b] Isolated yields. [c] The reaction temperature was decreased to 80 °C to avoid formation of 1,3-H shift product **3**.

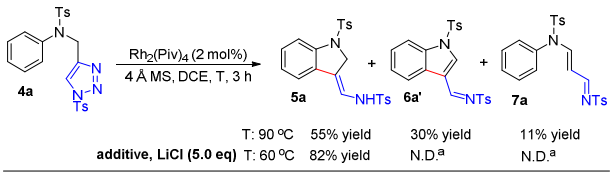
Table 2. Rearrangement of **1** at High Temperature.[a]



[a] 0.2 mmol scale. Procedure: under Ar, triazole, $Rh_2(Piv)_4$ and DCE (2.0 mL) were stirred in a sealed tube at 120 °C for 3 h. [b] Isolated yields. [c] Starting material is **1q**.

During the reaction scope investigation, we found that in some cases (see Table 1, substrates **1i** and **1l-1o**), the temperature need to be decreased to 80 °C to get pure product **2**, higher temperature (90 °C) resulted in the 1,3-H shift relevant **3**, which could not be isolated from **2**. The structure was also confirmed by X-ray diffraction of **3e**.[13] We were pleased to find that products **3a-3e** could be exclusively formed at 120 °C in moderate to good yields (50-88%) (Table 2, entries 1-5). However, for most of 4-aryloxymethyl-1,2,3-triazoles, conducting the reaction at 120 °C led to the formation of both **2** and **3** together with increased β-H elimination byproduct acrolein imines, suggesting that temperature significantly affects the reaction pathways. Fortunately, by carefully tuning the temperature, the reactions of **1g** and **1i** proceeded smoothly at 120 °C and 90 °C, furnishing the corresponding products **3f** and **3g** in 64% and 71% yields, respectively (Table 2, entry 6).

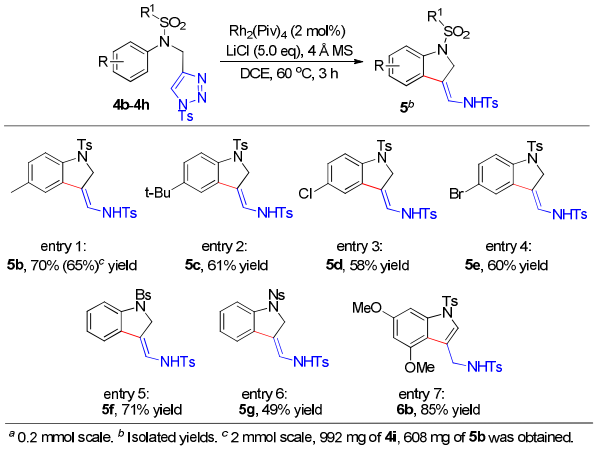
Scheme 2. Inhibition of β-H Elimination/1,2-H shift.



[a] N.D.: Not determined.

Next, we also turned our effort to study the reaction of *N*-tethered substrate **4**. However, upon treatment of *N*-tosyl tethered substrate **4a** with $Rh_2(Piv)_4$ at 90 °C in DCE for 3 h, product **5a**[14] was obtained in 55% yield, together with the formation of indolyl imine product **6a′** (β-H elimination) and acrolein imine **7a** (carbene induced 1,2-H shift) in 30% and 11% yields, respectively (Scheme 2). The identification of **6a′**[13] and **7a**[13] were established by single-crystal X-ray analysis. It is reported that LiCl could suppress β-H elimination by coordination with metal catalyst.[15] Therefore, 5 eq. of LiCl was used in the reaction. As conducting the reaction at 60 °C, we were glad to find that **5a** was exclusively formed in 82% yield (Scheme 2).

Table 3. Scope of the Reaction for the Synthesis of **5**.[a]

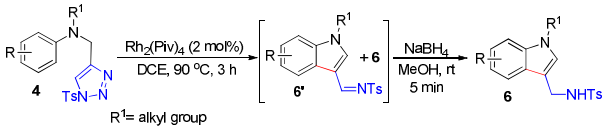


[a] 0.2 mmol scale. [b] Isolated yields. [c] 2 mmol scale, 992 mg of **4i**, 608 mg of **5b** was obtained.

As we successfully solved the problem of β-H elimination and 1,2-H shift, various *N*-sulfonyl tethered triazoles were synthesized to test the generality of this reaction (Table 3). All substrates employed were suitable for this cyclization reaction, giving the corresponding products **5** in 41%-71% yields (Table 3, entries 1-6). Interestingly, when substrate **4h** with 3,5-dimethoxy substituents was treated under the standard reaction conditions, indolyl methanamine product **6a** was obtained in 85% yield after aromatization (Table 3, entry 7). It is worth mentioning that gram scale reaction of **4b** also gives **5b** in 65% yield (608 mg) (Table 3, entry 1).

For *N*-alkyl group tethered triazoles, the reactions gave 3-indolylimines **6'** and 3-indolylmethanamines **6** together, and finally, the mixture could be converted 3-indolylmethanamines **6** after a one-pot reduction (Scheme 3) (for substrate scope study, see Table S2 in the Supporting Information).[16]

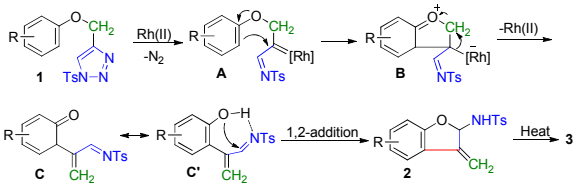
Scheme 3. One-pot Synthesis of **6**.



Several control experiments were conducted and carbene induced 1,2-H shift or 1,2-phenyl migration were observed (for detail, see Scheme S1 in the Supporting Information). The deuterium labeling isotopic experiments revealed that the alkyl methylene carbon migrates to the terminal alkene in the final products (for detail, see Scheme S2 in Supporting Information).

The deuterium kinetic isotope effects were also investigated. The obtained intra- and intermolecular k_H/k_Ds were 0.89 and 0.77 (for detail, see Supporting Information), respectively, suggesting that C-H functionalization is a Friedel-Crafts type reaction.[17] This result is also consistent with the electronic effect observed in substrate scope study.

Scheme 4. Proposed Catalytic Cycle for the Synthesis of **2** and **3**.

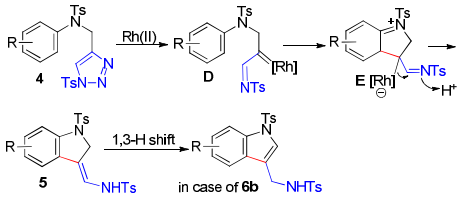


In view of the control experiments and kinetic studies, an explanation of the reaction sequence is depicted in Scheme 4. First, in the presence of Rh(II) catalyst, an azavinyl carbene intermediate **A** is formed after denitrogenation, followed by a Friedel-Crafts type nucleophilic attack of aryl ring to the Rh azavinyl carbenoid gives a zwitterionic intermediate **B**. The elimination of the Rh(II) catalyst together with the cleavage of C-O bond delivers an acrolein imine **C** and its resonance structure **C'**. Finally, product **2** is formed via a 1,2-addition, which is more favored than 1,4-addition probably due to that the intramolecular H bonding can pull the imine group more closely to the oxygen atom. Upon heating, the thermodynamically more stable product **3** is formed after 1,3-H shift.

A plausible mechanism for the synthesis of **5** is also outlined in Scheme 5. First, in the presence of Rh(II) complex, compound **4** generates an azavinyl carbene intermediate **D**, then the Rh imino carbenoid accepts a nucleophilic attack from aryl ring to give zwitterionic intermediate **E**. After aromatization and protonation, product **5** is formed. In the case of substrate **4h** with two strongly electron-donating groups on the benzene ring, **6b** is obtained after the 1,3-H shift.

According to the DFT calculation, the 1,3-H shift process of **5a** needs a relatively high energy barrier of 67.1 kcal/mol, indicating that this 1,3-H shift process is hard to take place under normal reaction conditions, which may account for why only product **5a** is obtained (for detail, see Figure S1 in Supporting Information).

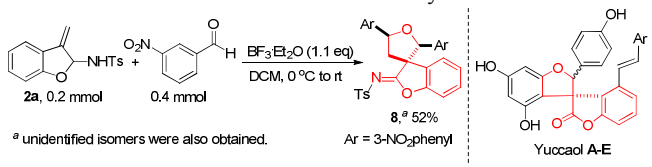
Scheme 5. Proposed Catalytic Cycle for the Formation of **5**.



The gram scale reaction of **1a** was conducted and **2a** was obtained in 90% yield (for detail, see Scheme S3 in the Supporting Information). It was also found that **2a** could be readily converted to the corresponding ketone and indoline after ozonization and hydrogenation (for detail, see Scheme S4 in the Supporting Information). Other aromatic system, such as indoles and pyroles, will be investigated and reported in due course.

Furthermore, upon treatment of **2a** with 2 equiv. of *m*-nitrobenzaldehyde in the presence of $BF_3{\cdot}Et_2O$ (1.1 equiv), a 3,3'-spirobi[benzofuran]2-one derived imine **8**[18] was isolated in 52% yield (Scheme 6) and its structure was confirmed by X-ray diffraction.[13] Notably, the 3,3'-spirobi[benzofuran]-2-one structure is found existing in a natural product family of phenolics (Yuccaol **A-E** and Larixinol), which are extracted from yucca schidigera roezl and have been used in folk medicine, food and pharmaceutical industries.[19]

Scheme 6. Further Derivatization of **2a** to Synthesize Imine **8**.



In conclusion, the controllable and chemoselective synthesis of 3-methylene-2,3-dihydrobenzofurans and 3-methylene-2,3-dihydroindoles has been established through two types of annulations of aromatic rings with *N*-sulfonyl 1,2,3-triazoles. For benzofuran synthesis, temperature plays an important role to control the exocyclic double bond and intramolecular hydrogen bonding facilitates the 1,2-addition. While in indole synthesis, the big challenges are the β-H elimination and 1,2-H shift, which are successfully solved by the combination of additive (LiCl) and temperature, and this finding may be helpful for those reactions in which the triazole ring has adjacent beta-protons. Several derivatizations of **2a** were conducted to access biologically and medicinally valuable molecules, such as the analogs phenolics. Further investigations to examine the mechanistic details more extensively are currently underway in our laboratory.

We are grateful for the financial support from the National Basic Research Program of China (973)-2015CB856603, Shanghai Municipal Committee of Science and Technology (11JC1402600), and the National Natural Science Foundation of China (20472096, 21372241, 21361140350, 20672127, 21102166, 21121062, 21302203 and 20732008).

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[16] The results are similar as a previously reported work, see: B. Rajagopal, C.-H. Chou, C.-C. Chung, P.-C. Lin, *Org. Lett.* **2014**, *16*, 3752.

[17] Most of the Friedel-Crafts reactions exhibit inverse isotope effects (k_H/k_D < 1, ~ 0.8~0.9), see: a) Melander, L. *Isotope Effect on Reaction Rates*; Ronald Press: New York, **1960**; pp 107-123; b) E. V. Anslyn, D. A. Dougherty, *Modern Physical Organic Chemistry. University Science Books*; **2006** pp. 428.

[18] Proposed mechanism for the formation of **8** is presented in the Supporting Information.

[19] a) S. Piacente, C. Pizza, W. Oleszek, *Phytochem. Rev.* **2005**, *4*, 177; b) C. Balestrieri, F. Felice, S. Piacente, C. Pizza, P. Montoro, W. Oleszek, V. Visciano, M. L. Balestrieri, *Biochem. Pharmacol*. **2006**, *71*, 1479; c) S. Marzocco, S. Piacente, C. Pizza, W. Oleszek, A. Stochmal, A. Pinto, R. Sorrentino, G. Autore, *Life Sci.* **2004**, *75*, 1491; d) E. M. Wenzig, W. Oleszek, A. Stochmal, O. Kunert, R. Bauer, *J. Agric. Food Chem.* **2008**, *56*, 8885.

_N_-Heterocycles

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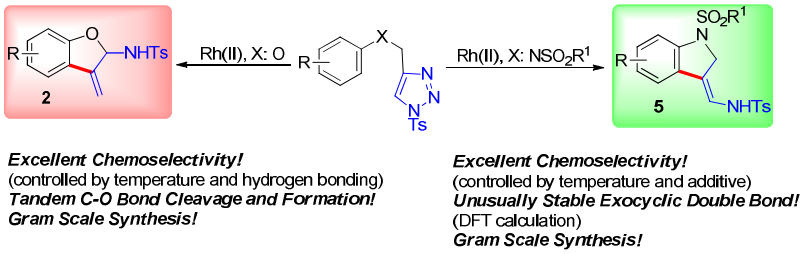

Intramolecular Annulation ofAromatic Rings with 1-Sulfonyl 1,2,3-triazoles: Divergent Synthesis of 3-Methylene-2,3-dihydrobenzofurans and 3-Methylene-2,3-dihydroindoles

The controllable synthesis of 3-methylene-2,3-dihydrobenzofurans **2** and 3-methylene-2,3-dihydroindoles **5** has been developed. The high chemoselectivity in synthesis of exocyclic benzofuran was controlled by temperature and intramolecular hydrogen bonding, while the combination of temperature and additive (LiCl) facilitated the formation of exocyclic indoline.