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An unusual formal migrative cycloaddition of aurone-derived azadienes: synthesis of benzofuran-fused nitrogen heterocycles†

Qiang Feng,‡[a] An Wu,‡[a] Xinhao Zhang,[b] Lijuan Song*[c] and Jianwei Sun*[ad]

Aurone-derived azadienes are well-known four-atom synthons for direct [4 + *n*] cycloadditions owing to their s-*cis* conformation as well as the thermodynamically favored aromatization nature of these processes. However, distinct from this common reactivity, herein we report an unusual formal migrative annulation with siloxy alkynes initiated by [2 + 2] cycloaddition. Unexpectedly, this process generates benzofuran-fused nitrogen heterocyclic products with formal substituent migration. This observation is rationalized by less common [2 + 2] cycloaddition followed by 4π and 6π electrocyclic events. DFT calculations provided support to the proposed mechanism.

Benzofuran is an important scaffold in biologically important natural molecules and therapeutic agents.[1] Among them, benzofuran-fused nitrogen heterocycles are particularly noteworthy owing to their broad spectrum of bioactivities for the treatment of various diseases (Fig. 1).[2] Consequently, the development of efficient methods for their assembly has been a topic receiving enthusiastic attention from synthetic chemists.[3] Notably, aurone-derived azadienes (*e.g.*, **1**) have been extensively employed as precursors toward these skeletons owing to their easy availability and versatile reactivity (Scheme 1a).[3] The polarized conjugation system, combined with the preexisting s-*cis* conformation, has enabled them to serve as ideal annulation partners for the synthesis of nitrogen heterocycles of variable ring sizes. Moreover, the aromatization nature of these processes by forming a benzofuran ring provides additional driving force for them to behave as a perfect four-atom synthon for [4 + *n*] cycloaddition.[3] In contrast, the use of such species as a two-atom partner for [2 + *n*] cycloaddition has been less developed.[3c,k,4] Herein, we report a new migrative annulation leading to benzofuran-fused dihydropyridines of unexpected topology (Scheme 1b, with formal R^2 migration), which is initiated by the less common [2 + 2] cycloaddition.

Siloxy alkynes are another important family of building blocks in organic synthesis.[5–8] The presence of a highly polarized C–C triple bond enables such molecules to serve as versatile two-carbon cycloaddition partners in various annulation reactions.[5–7] In the above context and in continuation of our interest in the study of such electron-rich alkynes,[7] we envisioned that the reaction between aurone-derived azadienes **1**

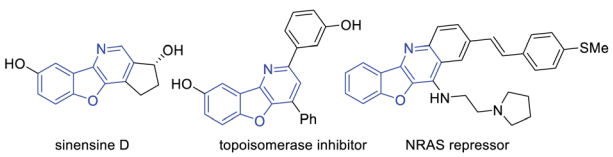
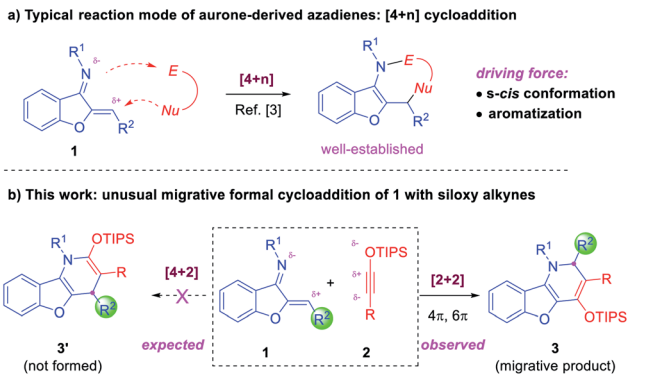


Fig. 1 Benzofuran-fused N-heterocyclic natural and bioactive molecules.



Scheme 1 Synthesis of benzofuran-fused nitrogen heterocycles.

[a]*Department of Chemistry, Shenzhen Research Institute, The Hong Kong University of Science and Technology, Clear Water Bay, Kowloon, Hong Kong SAR, China. E-mail: sunjw@ust.hk*

[b]*Shenzhen Bay Laboratory, State Key Laboratory of Chemical Oncogenomics, Peking University Shenzhen Graduate School, Shenzhen, China*

[c]*School of Science, Harbin Institute of Technology (Shenzhen), Shenzhen, 518055, China. E-mail: songlijuan@hit.edu.cn*

[d]*The Hong Kong Branch of Chinese National Engineering Research Centre for Tissue Restoration & Reconstruction, Clear, Water Bay, Kowloon, Hong Kong SAR, China*

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‡ These authors contributed equally to this work.

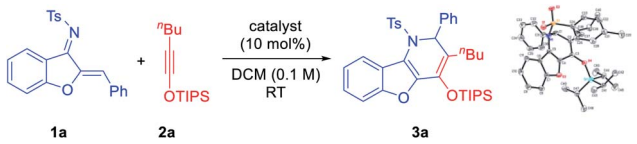
and siloxy alkynes **2** should lead to facile electron-inversed [4 + 2] cycloaddition to form benzofuran-fused dihydropyridine products (Scheme 1b). Interestingly, the expected product **3′** from direct [4 + 2] cycloaddition was not observed. Instead, a dihydropyridine product **3** with formal R^2 migration was observed. Careful analysis of the mechanism suggested that a [2 + 2] cycloaddition followed by 4π and 6π electrocyclic steps might be responsible for this unexpected product topology (*vide infra*).

We began our investigation with the model substrates **1a** and **2a**, which were easily prepared in one step from aurone and 1-hexyne, respectively.[8] Various Lewis acids were initially examined as potential catalysts for this cycloaddition (Table 1). Unfortunately, common Lewis acids (*e.g.*, $TiCl_4$, $BF_3{\cdot}OEt_2$, $Sc(OTf)_3$, $In(OTf)_3$, and AgOTf) were all ineffective (entries 1–5). Substrate decomposition into an unidentifiable mixture was typically observed. However, further screening indicated that $AgNTf_2$ served as an effective catalyst, leading to benzofuran-fused dihydropyridine **3a** in 44% yield (entry 6). Careful analysis by X-ray crystallography confirmed that it was not formed by simple [4 + 2] cycloaddition, as the positions of the phenyl and the siloxy groups were switched (*vs.* the expected topology). The distinct catalytic performance of $AgNTf_2$ (*vs.* AgOTf) suggested that the triflimide counter anion Tf_2N^- might be important. However, further screening of various metal triflimide salts did not improve the reaction efficiency (entry 7). Instead, we were delighted to find that the corresponding Brønsted acid $HNTf_2$ served as a better catalyst (57% yield, entry 8). However, triflic acid (TfOH) led to no desired product in spite of complete conversion (entry 9). After considerable efforts in the optimization of other reaction parameters, an improved yield of 75% was obtained with 2.5 mol% of $HNTf_2$ and 2.5 equivalents of **2a** at 60 °C (entry 10). Solvent screening indicated that the reaction proceeded faster in DCE with comparable yield (entry 11). However, other solvents were all inferior (entries 12–15). Finally, with a reversed order of addition of the two reactants, the yield was slightly improved (entry 16). We believe that this might be related to the relative decomposition rates of the substrates.

With the optimized conditions, we examined the reaction scope. A range of aurone-derived azadienes with different electron-donating and electron-withdrawing substituents at various positions smoothly participated in this formal migrative cycloaddition process with siloxy alkyne **2a** (Scheme 2). The corresponding benzofuran-fused dihydropyridine products **3** were formed with excellent selectivity and moderate to good efficiency. A thiophene unit was also successfully incorporated into the product (**3h**). However, substitution with a pyridinyl group shut down the reactivity, even with 1.1 equivalents of $HNTf_2$. Other siloxy alkynes bearing different alkyl substituents on the triple bond were also good reaction partners, except that these reactions were more efficient when the catalyst loading was increased to 10 mol% (Table 2). Unfortunately, direct aryl substitution on the alkyne triple bond resulted in essentially no reaction (entry 7). Notably, in spite of the strong acidic conditions, various functional groups, such as TIPS-protected alcohol (**3p**) and acetal (**3c**), were tolerated. Moreover, increasing steric hindrance in close proximity to the reaction centers (*e.g.*, ^{t}Bu group in **3i** and **3r**) did not obviously affect the reaction efficiency.

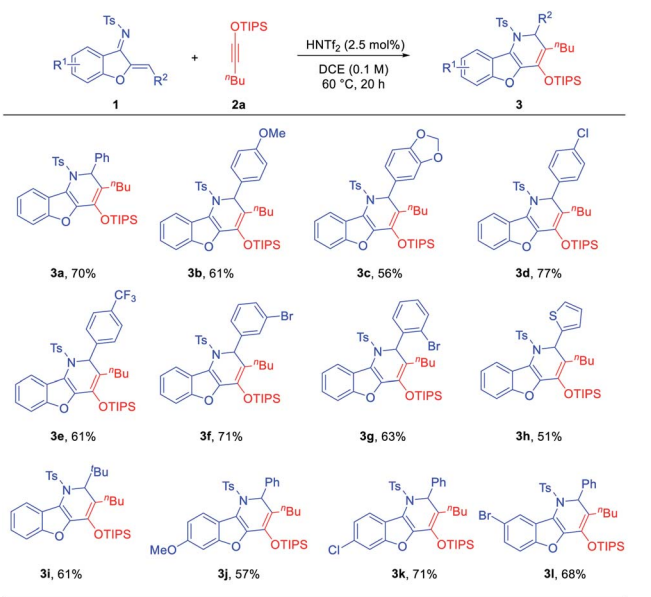
Owing to the electron-rich silyl enol ether motif, the benzofuran-fused dihydropyridine products can be transformed into

Table 1 Reaction conditions[a]



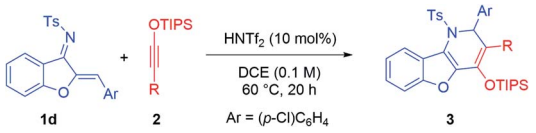
Entry	Catalyst	Solvent	Time (h)	Yield (%)
1	$TiCl_4$	DCM	9	0
2	$BF_3{\cdot}OEt_2$	DCM	9	0
3	$Sc(OTf)_3$	DCM	9	0
4	$In(OTf)_3$	DCM	9	0
5	AgOTf	DCM	9	0
6	$AgNTf_2$	DCM	9	44
7	$Sc(NTf_2)_3$	DCM	9	0
8	$HNTf_2$	DCM	9	57
9	HOTf	DCM	9	0
10[b]	$HNTf_2$	DCM	42	75
11[b]	$HNTf_2$	DCE	18	72
12[b]	$HNTf_2$	$CHCl_3$	18	20
13[b]	$HNTf_2$	THF	18	0
14[b]	$HNTf_2$	MeCN	18	0
15[b]	$HNTf_2$	EtOAc	18	0
16[b,c]	$HNTf_2$	DCE	18	81 (76)[d]

[a] **2a** (0.06 mmol) was added to the solution of **1a** (0.05 mol) and the catalyst (10 mol%). Yield was determined by analysis of the ^{1}H NMR spectrum of the crude mixture using CH_2Br_2 as an internal standard. [b] Run with 2.5 mol% catalyst and 2.5 equiv. of **2a** at 60 °C. [c] **1a** was added into the solution of **2a** and the catalyst. [d] Yield in parentheses was isolated yield.



Scheme 2 Scope of aurone-derived azadienes. Conditions: **1** (0.3 mmol), **2a** (0.75 mmol), $HNTf_2$ (2.5 mol%), DCE (3.0 mL), 60 °C. Isolated yield.

Table 2 Scope of siloxyl alkynes[a]

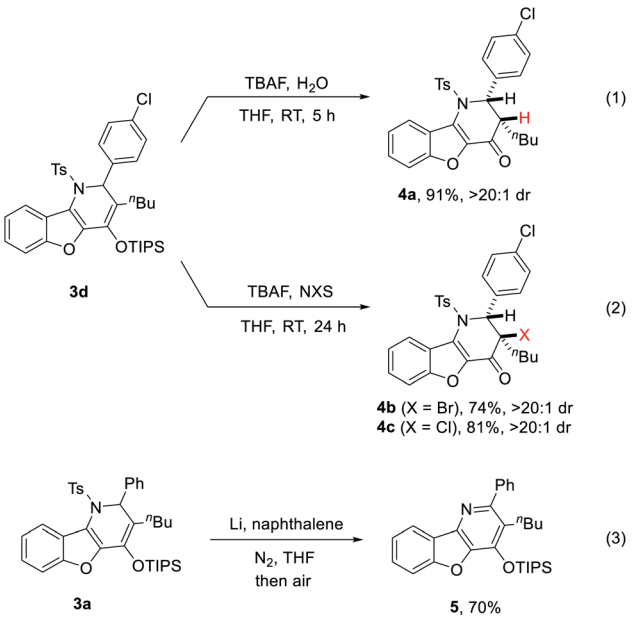


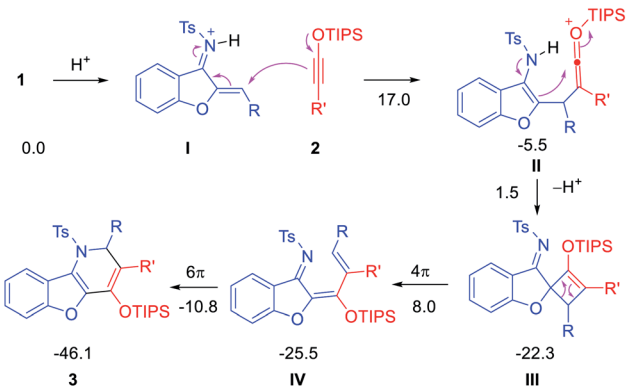
Entry	R	3	Yield (%)
1	^{n}Oct	**3m**	66
2	Bn	**3n**	74
3	Ph	**3o**	53[b]
4	OTIPS	**3p**	64
5		**3q**	58
6	^{t}Bu	**3r**	62
7	Ph	**3s**	<5

[a] Conditions: **1d** (0.3 mmol), **2** (0.75 mmol), $HNTf_2$ (10 mol%), DCE (3 mL), 60 °C. Isolated yield. [b] Run with 2.5 mol% of $HNTf_2$.

other related heterocycles upon treatment with electrophiles. For example, deprotection of the silyl group in **3d** with TBAF in the presence of water produced ketone **4a** (eqn (1)). In the presence of NBS or NCS, the corresponding bromoketone **4b** and chloroketone **4c** were obtained, respectively (eqn (2)). These reactions were both efficient and highly diastereoselective. The structures of **4b** and **4c** were also confirmed by X-ray crystallography. Moreover, deprotection of the *N*-tosyl group with Li/naphthalene followed by air oxidation led to the highly-substituted benzofuran-fused pyridine **5**, the core structure of a family of bioactive molecules (eqn (3)).[2]

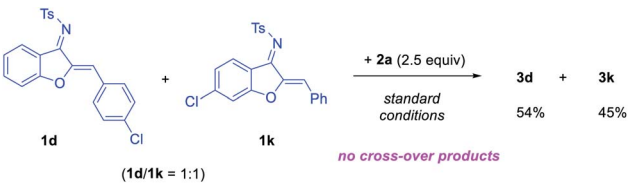
A possible mechanism is proposed to rationalize the unusual formal migrative process (Scheme 3). The reaction begins with LUMO-lowering protonation of the aurone-derived azadiene **1** by $HNTf_2$.[9] Then, the electron-rich alkyne attacks the resulting activated iminium intermediate **I**, leading to ketenium ion **II** after intermolecular C–C bond formation. Subsequent intramolecular cyclization from the electron-rich enamine motif to the electrophilic ketenium unit forms oxetene **III**. The formation of this oxetene can also be considered as a [2 + 2] cycloaddition of the two reactants.[6a–d,11] Subsequent 4π-electrocyclic opening of oxetene **III** affords azatriene **IV**. Further 6π-electrocyclic closing leads to the observed product **3**. This observed product topology is fully consistent with this pathway. It is worth noting that the excellent performance with $HNTf_2$ might be attributed to the low nucleophilicity and good compatibility of its counter anion with the highly electrophilic cationic intermediates (*e.g.*, ketenium **II**) in this process. We have also carried out DFT studies. The results indicated that the proposed pathway is energetically viable and consistent with the experimental data (Scheme 3 and Fig. S1†). Moreover, some other possible pathways that engage the nitrogen atom in intermediate **II** to directly attack the ketenium in a [4 + 2] mode were explored. However, no reasonable transition state could be located (Fig. S2†). Thus, the origin of preference toward [2 + 2] cycloaddition remains unclear.





Scheme 3 Proposed mechanism and free energies (in kcal mol^{-1}) computed at the M06-2X(D3)/6-311G(d,p)-SMD//M06-2X/6-31G(d) level of theory.

We also prepared $TIPSNTf_2$ and examined its catalytic activity in this reaction since it is known that such a Lewis acid might be generated *in situ*.[10] However, no reaction was observed when $TIPSNTf_2$ was used in place of $HNTf_2$, suggesting that it is unlikely the actual catalyst. Finally, in order to probe the nature of the substituent migration (intermolecular *vs.* intramolecular), we carried out a cross-over experiment (Scheme 4). Under the standard conditions, the reaction using a 1 : 1 mixture of **1d** and **1k** led to exclusive formation of **3d** and **3k**,



Scheme 4 Cross-over experiment.

without detection of any cross-over products. This result is consistent with the proposed intramolecular migration pathway.

In conclusion, we have discovered an unusual formal migrative cycloaddition of aurone-derived azadienes with siloxy alkynes. In the presence of a catalytic amount of $HNTf_2$, this reaction provided expedient access to a range of useful benzofuran-fused dihydropyridine products with unexpected topology, distinct from normal [4 + 2] cycloaddition. Although aurone-derived azadienes are ideal four-atom synthons for direct [4 + *n*] cycloaddition, the present process is initiated by less common [2 + 2] cycloaddition, which is critical for the observed product formation. Subsequent electrocyclic opening and cyclization steps provide a reasonable rationale. The heterocyclic products generated from this process are precursors toward other useful structures, such as benzofuran-fused pyridines.

Author contributions

Q. F. and A. W. conceived and performed the experiments and wrote the paper. X. Z. and L. S. performed DFT calculations. J. S. conceived and directed the project and wrote the paper. All the authors discussed the results and commented on the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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