ORGANIC PROCESS RESEARCH & DEVELOPMENT
OPR&D
Communication
Cite This: Org. Process Res. Dev. XXXX, XXX, XXX−XXX
pubs.acs.org/OPRD

Synthesis of Benzofurans and Benzoxazoles through a [3,3]-Sigmatropic Rearrangement: O−NHAc as a Multitasking Functional Group

Dingyuan Yan,[†,‡] Heming Jiang,[§] Wenxue Sun,[‡] Wei Wei,[‡] Jing Zhao,[*,†,∥] Xinhao Zhang,[*,§] and Yun-Dong Wu[§]

[†]State Key Laboratory of Coordination Chemistry, Institute of Chemistry and BioMedical Sciences, School of Chemistry and Chemical Engineering, Nanjing University, Nanjing 210093, China

[‡]State Key Laboratory of Pharmaceutical Biotechnology, School of Life Sciences, Nanjing University, Nanjing 210093, China

[§]Lab of Computational Chemistry and Drug Design, State Key Laboratory of Chemical Oncogenomics, Peking University Shenzhen Graduate School, Shenzhen 518055, China

[∥]Shenzhen Research Institute of Nanjing University, Shenzhen 518000, China

Supporting Information

ABSTRACT: The synthesis of heterocycles relies heavily on diverse sigmatropic rearrangements triggered by the cleavage of X−Y (X, Y = C, O, N, S, I) bonds. However, a unified rearrangement approach for constructing heterocyclic libraries is highly desirable. Encouraged by computational analysis of [3,3]-sigmatropic rearrangements, we can now rapidly synthesize oxa-heterocycles by treating *N*-phenoxyacetamides (Ph−ONHAc) with compounds containing an sp-hybridized carbon. The generality of the process is illustrated by the late-stage diversification of natural products, including estrone and an approved drug. A combination of experimental and computational studies revealed that the reactions proceed through a facile Claisen-like [3,3]-sigmatropic rearrangement/annulation process.

KEYWORDS: *sigmatropic rearrangements, oxa-heterocycles, O−N bond cleavage*

INTRODUCTION

One century after their discovery, [3,3]-sigmatropic rearrangements occupy an irreplaceable role in the synthesis of complex organic molecules and continue to be intensively investigated.[1] Although a wealth of protocols to obtain biologically active heterocycles have been reported,[2] many of them require harsh conditions[3] (such as high temperature, long reaction timed, and the need for strong oxidants). As an alternative, [3,3]-sigmatropic rearrangement reactions triggered by the cleavage of X−Y (X, Y = C, O, N, S, I) bonds have attracted much attention for the synthesis of those skeletons under relatively mild conditions. For example, the Fischer indole rearrangement, which is based on cleavage of the N−N bond in phenylhydrazines, remains among the most widely used approaches to indoles.[4] Recently, Maulide and co-workers made pivotal progress in Pummerer-type rearrangements to use the sulfoxide as an arylation/directing group through cleavage of the O−S bond.[5] Significantly, an extension of the Pummerer reaction to produce benzofurans in a practical and mild manner was discovered by Yorimitsu and co-workers.[6] The same strategy was used by Procter and co-workers to construct C3 functionalization of benzothiophenes.[7] Peng and co-workers subsequently reported an ingenious design to form α-arylated nitriles by an accelerated [3,3]-rearrangement, releasing steric congestion associated with the formation of an active S/I−ketenimine species.[8]

An intrinsically weak and highly polar O−N bond was found to promote sigmatropic rearrangements.[9] Substantial progress has been made in O−N-cleavage-assisted rearrangements by Tomkinson[10] and Ioffe[11] in the past several decades. Notably, Ngai[12] and Nakamura[13] recently reported the [1,3] rearrangement of OCF_3/OMe groups of *N*-aryl-*N*-hydroxylamine derivatives to afford various ortho-functionalized aniline derivatives, respectively. Very recently, an efficient synthesis of multisubstituted *o*-anisidines via N-heterocyclic carbene (NHC) Cu-catalyzed [1,3]/[1,2] domino rearrangement of *N*-methoxyanilines was developed by Nakamura (Figure 1a).[14]

Although high efficiency has been achieved in the synthesis of indoles[15] as well as benzofurans[16] under mild reaction conditions via cleavage of O−N bonds, a unified approach to access diverse oxa-heterocycles is highly desirable. The introduction of an O−N bond may encompass the elevated temperature accompanied by the classical Claisen [3,3]-sigmatropic rearrangement.[1b,2a,17] The other challenge is that the annulation/aromatization may not occur readily after the rearrangement step[18] (Figure 1b). Following our continued interest in the O−N bond,[19] we hypothesized that a facile [3,3]-sigmatropic rearrangement might be envisioned by installing an sp-hybridized carbon on the nitrogen in the oxyacetamide moiety (O−NHAc) to facilitate the subsequent annulation.[20] To confirm this hypothesis, density functional theory (DFT) calculations were first performed.[21] The free energy profiles of the [3,3]-sigmatropic rearrangement and the bond dissociation energies (BDEs) of the O−Y bonds (Y = C,

Special Issue: 25th Anniversary of the Buchwald-Hartwig Amination

Received: January 1, 2019

DOI: 10.1021/acs.oprd.9b00002
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

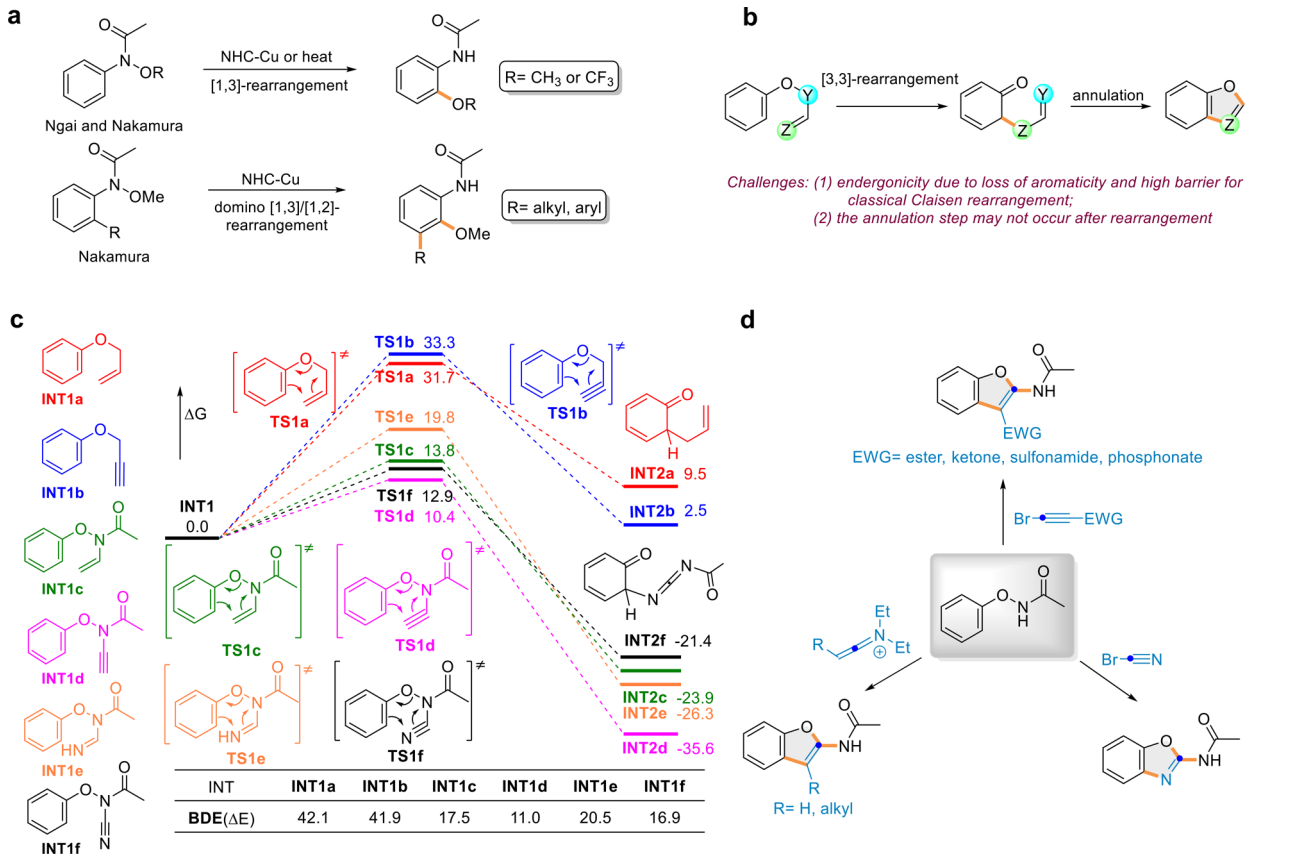


Figure 1. Protocol to construct heterocycles via [3,3]-sigmatropic rearrangement. (a) Recent works on the rearrangement of *N*-arylhydroxylamine derivatives. (b) Challenges to obtain diverse oxa-heterocycles via a [3,3]-sigmatropic rearrangement. (c) DFT calculations on the synthesis of heterocycles via a [3,3]-sigmatropic rearrangement by incorporation of an O−NHAc group. Relative free energies and energies are in kcal/mol. (d) Our approaches toward oxa-heterocycles by treating PhONHAc with compounds containing an sp-hybridized carbon.

N) in several model substrates are listed in Figure 1c. Aryl vinyl ether (**INT1a**) is regarded as the standard reference of a classical Claisen rearrangement. The barrier for O−N bond cleavage is indeed significantly lower than that for O−C bond cleavage, and this is well-correlated with the calculated BDEs. Furthermore, pericyclic processes with O−N bond cleavage become highly exergonic. Notably, incorporation of an sp-hybridized carbon in the migrating moiety indeed promotes the rearrangement (**TS1c** vs **TS1d** and **TS1e** vs **TS1f**). The N−C_{sp} bonds in **TS1d** and **TS1f** are much shorter than the N−C_{sp^2} bonds in **TS1c** and **TS1d**, suggesting that the lower barriers of **TS1d** and **TS1f** could be attributed to the delocalization resonance involving an sp-hybridized carbon (see Supplementary Figure 2 for details). Herein we report a unified rearrangement to synthesize oxa-heterocycles by treatment of *N*-phenoxyacetamides (Ph−ONHAc) with compounds containing an sp-hybridized carbon (Figure 1d).

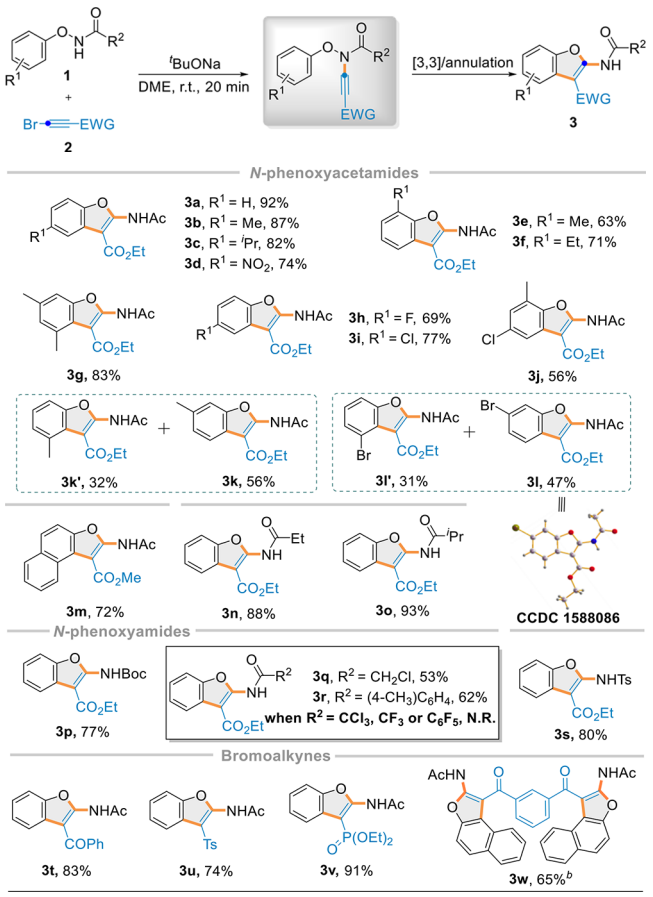
RESULTS AND DISCUSSION

As the first attempt, a solution of *N*-phenoxyacetamide (**1a**) and 2.0 equiv of ethyl 3-bromopropiolate (**2a**) in ethyl acetate was treated with 1.5 equiv of NaOH at ambient temperature over a period of 20 min. We were pleased to observe that ethyl 2-acetamidobenzofuran-3-carboxylate (**3a**) was obtained in 46% NMR yield (Supplementary Table 1, entry 1). Following this encouraging result, we screened a variety of other bases (Supplementary Table 1, entries 2−11). Sodium *tert*-butoxide was the best, and potassium methoxide gave slightly diminished yields, whereas DBU and DABCO provided no product. Subsequently, different solvents were screened, and the results indicated that 1,2-dimethoxyethane (DME) is efficient with a 94% yield, whereas other solvents, such as 1,2-dichloroethane, acetone, and tetrahydrofuran, afforded inferior yields (Supplementary Table 1, entries 12−22). Ultimately, the optimal reaction conditions employed 1.5 equiv of ^{t}BuONa in DME at room temperature for 20 min.

The scope of *N*-phenoxyacetamides was examined under standard reaction conditions (Table 1). Many *N*-phenoxyacetamides bearing electron-rich and electron-poor groups worked well, giving moderate to excellent yields (**3a**−**l**, 56−92% yield). Notably, when meta-substituted *N*-phenoxyacetamides **1k** and **1l** were used, the annulation occurred at the two ortho positions, and the yields of the products annulated at the less-hindered site were much higher (**3k′** and **3l**). We also examined substituents on the nitrogen atom of the *N*-phenoxyamide. Compounds **1n**−**r** afforded the desired products in 53−93% yield. Unfortunately, substrates bearing strongly electron-deficient groups such as −CCl_3, −CF_3, and −C_6F_5 as R^2 could not be used under the same reaction conditions, possibly because of the reduced nucleophilicity of the nitrogen in such compounds. After the acetamide in **1a** was changed to a sulfonamide, the desired product **3s** was formed in 80% yield. Suitable alkynyl electron-withdrawing groups included ketone (**3t**), sulfonamide (**3u**), and phosphonate (**3v**). Finally, we performed the synthesis of multisubstituted

DOI: 10.1021/acs.oprd.9b00002
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

Table 1. Substrate Scope of Type I Reaction[a]



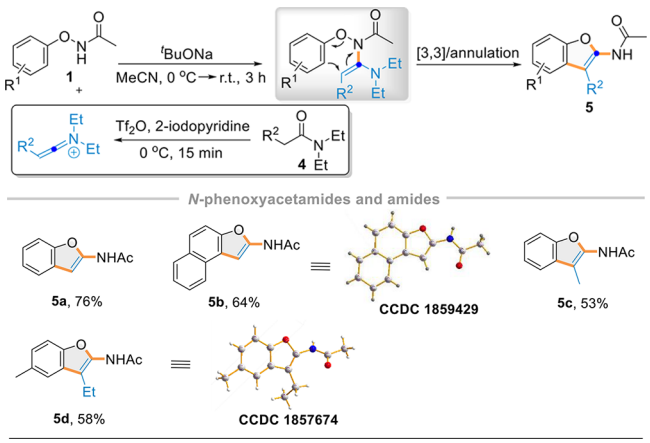
[a]Standard conditions: **1** (0.2 mmol), **2** (0.4 mmol), and ^{t}BuONa (0.3 mmol) in DME (2 mL) at ambient temperature for 20 min. EWG = electron-withdrawing group; N.R.= no reaction. [b]0.1 mmol of **1**, 0.1 mmol of **2**, and 0.15 mmol ^{t}BuONa were used.

difuran product **3w** when a dibromoalkyne substrate was subjected to our reaction conditions.

Keteniminium salts have exhibited great power in organic synthesis.[22] Recently, Maulide and co-workers have exploited this strategy extensively for the functionalization of amides.[5b,23] Inspired by those pioneering works, we thought that the electrophilic keteniminium generated from an amide might be used to trigger rearrangement of the O−N bond to construct benzofurans. To our delight, after screening the reaction conditions carefully, we obtained a 76% yield of *N*-(benzofuran-2-yl)acetamide (**5a**) when **1a** was treated with *N*,*N*-diethylacetamide (see Supplementary Table 2 for the optimization of the conditions). *N*-Phenoxyacetamides and *N*,*N*-disubstituted amides with different substituents were effectively converted to products in acceptable yields (Table 2, **5b**-**5e**, 53−64%).

Encouraged by the successful synthesis of benzofurans from *N*-phenoxyacetamides, we then tried to extend this transformation to obtain benzoxazoles. When **1a** and cyanogen bromide (BrCN) were subjected to the standard conditions, benzoxazole **6a** was successfully obtained in 79% NMR yield. When potassium *tert*-butoxide was used as the base and DME as the solvent, **6a** was formed in 89% NMR yield and 87% isolated yield within 30 min (for details, see Supplementary Table 3). With the optimized reaction conditions established, we next examined the versatility of the reaction with diversely

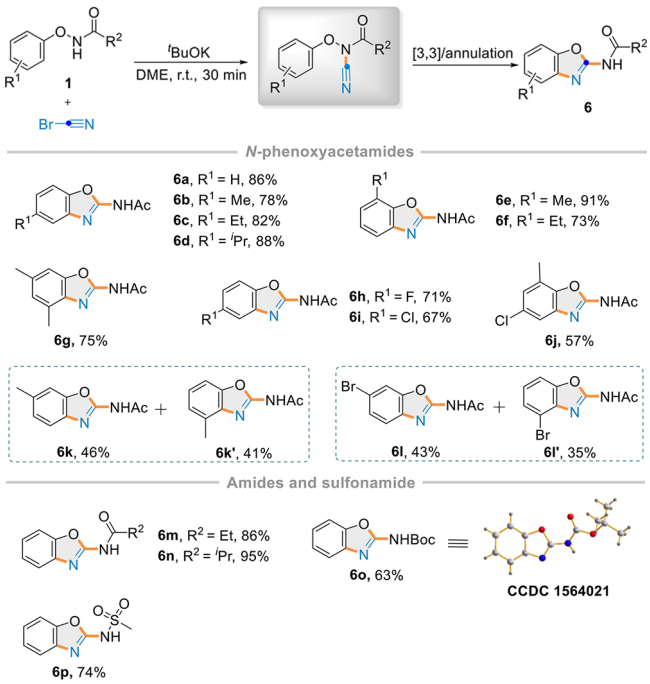
Table 2. Substrate Scope of Type II Reaction[a]



[a]Standard conditions: A mixture of **4** (0.6 mmol) and 2-iodopyridine (1.2 mmol) in MeCN (1.0 mL) was treated with Tf_2O (0.6 mmol) under N_2. The mixture was stirred at 0 °C for 15 min and then added to a solution of **1** (0.2 mmol) and ^{t}BuONa (0.3 mmol) in MeCN (1.0 mL) at 0 °C. The reaction mixture was allowed to warm to room temperature for 3 h.

substituted *N*-phenoxyacetamides (Table 3). *N*-Phenoxyacetamides with electron-donating groups on the aryl moiety

Table 3. Substrate Scope of Type III Reaction[a]



[a]Standard conditions: **1** (0.2 mmol), BrCN (0.4 mmol), and ^{t}BuOK (0.3 mmol) in DME (2.0 mL) at ambient temperature for 30 min.

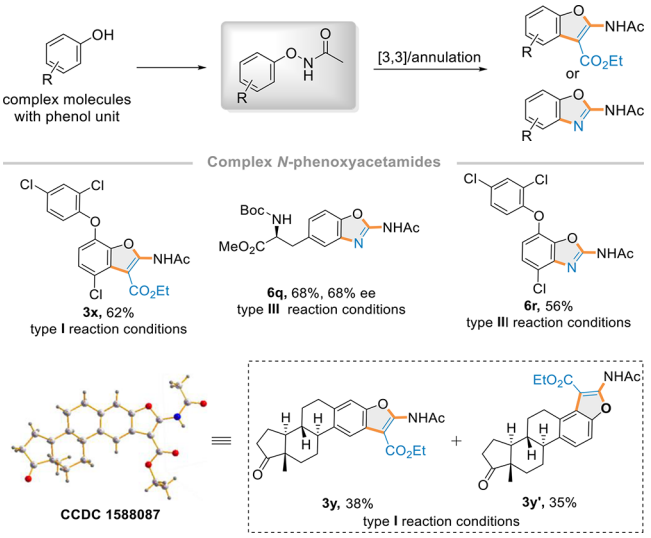
reacted smoothly with BrCN, and the corresponding products (**6a**−**g**) were isolated in 73−91% yield. This annulation reaction can tolerate reactive functional groups such as fluoro (**6h**) and chloro (**6i** and **6j**), which are useful for further synthetic transformations. When meta-substituted *N*-phenoxyacetamides were used, the annulation took place at two ortho sites. Therefore, for substrates **1k** and **1l**, two regioisomers with a ratio of almost 1:1 were obtained. Replacing the acetyl

DOI: 10.1021/acs.oprd.9b00002
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

group with other groups such as propionyl or isobutyryl led to smooth reactions, affording the desired products **6m** and **6n** in 86% and 95% yield, respectively. The *N*-phenoxyamide with a Boc-substituent on the nitrogen afforded the corresponding product **6o** in 63% yield. Moreover, the same reaction conditions could be used when the acetamide was replaced by a sulfonamide (**6p**).

Late-stage functionalization of natural products and synthetic drugs is important in the synthesis of bioactive compounds.[24] Hence, we were pleased to find that the outstanding versatility of our newly developed strategy provides a unique approach to the modification of complex molecules into oxyheterocyclic derivatives. *N*-Aryloxyamides derived from tyrosine, triclosan, and estrone were prepared and subjected to the optimized conditions (Table 4). The [3,3]-sigmatropic rearrangement took place smoothly, affording the corresponding 2-aminobenzofurans (**3x**–**y′**) and 2-aminobenzoxazoles (**6q** and **6r**) in acceptable yields. The structure of **3y** was unambiguously established by single-crystal X-ray diffraction.

Table 4. Late-Stage Manipulation of Complex Natural Products and an Approved Drug[a]



[a]Reaction conditions: type I reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), and ^{t}BuONa (0.3 mmol) in DME (2.0 mL) for 20 min at ambient temperature; type III reaction conditions: **1** (0.2 mmol), BrCN (0.4 mmol), and ^{t}BuOK (0.3 mmol) in DME (2 mL) for 30 min at ambient temperature.

Benzoxazole benzenesulfonamides have been identified as inhibitors of human fructose-1,6-bisphosphatase (hFBPase-1).[25] However, the reported approach to obtain such compounds requires high temperatures with the aid of microwave radiation. Here, benzoxazole benzenesulfonamides (**6s** and **6t**) were synthesized successfully under mild reaction conditions (Figure 2a). With a modification of the newly developed reaction type I, we also achieved the functionalization of tyrosine in phosphate-buffered saline (PBS) (Figure 2b). In order to further understand this reaction, we studied its kinetics. *N*-Phenoxyacetamide (**1a**) (0.5 mmol), ethyl 3-bromopropiolate (**2a**) (2.0 equiv), and ^{t}BuONa (1.5 equiv) were mixed in DME (5.0 mL) at 25 °C, and the reaction was monitored by ^{1}H NMR spectroscopy. We obtained a second-order rate constant of $(4.4 \pm 0.065) \times 10^{-2}$ M^{-1} s^{-1}, which

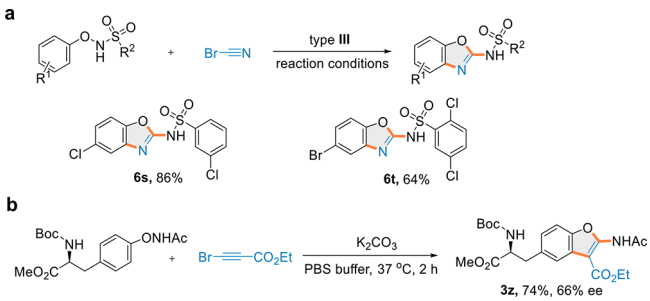


Figure 2. Further synthetic application of our strategy. (a) Rapid synthesis of an inhibitor of hFBPase-1. Type III reaction conditions: **1** (0.2 mmol), BrCN (0.4 mmol), and ^{t}BuOK (0.3 mmol) in solvent (2.0 mL) at ambient temperature for 30 min. (b) Modification of tyrosine in aqueous buffer. Reaction conditions: **1** (0.2 mmol), **3a** (0.4 mmol), and K_2CO_3 (0.3 mmol) in PBS (2.0 mL) at 37 °C for 2 h.

suggests that it is potentially a novel click reaction (Supplementary Figure 1).

Given the unique versatility of these annulation reactions, we delineated the mechanism of the reaction, and further experiments were conducted to investigate the mechanistic details. When the O–N bond was replaced by a N–N or S–N bond in either reaction type I or reaction type III, none of the desired products were detected. The calculated BDEs of the corresponding N–N or S–N bond in **INT1**, ranging from 35.7 to 44.1 kcal/mol, are as high as those of **INT1a** and **INT1b**, which are unreactive (Figure 1c). Furthermore, the free energy barrier for the [3,3]-sigmatropic rearrangement (**TS1**) was calculated to be at least 10.1 kcal/mol higher than that of **TS1d**, suggesting poor reactivity. The above experimental and computational results illustrated the indispensable role of the O–N bond (Figure 3a). For reaction type I, the protocol was found to be general for electron-withdrawing groups as substituents in **2**, but electron-donating substituents (–^{n}Bu, –TIPS, –Ph) were not beneficial in this transformation (Figure 3b). An intermolecular competition reaction between **1b** and **1i** under type I reaction conditions revealed that the aryl moiety with higher electron density facilitated the annulation (Figure 3c).

DFT calculations were performed to investigate the detailed free energy profiles for the reactions. Figure 4 shows the critical rearrangement steps for reaction type I leading to **3a** from **1a**. Other reaction types and the details of the overall profile are shown in Supplementary Figures 3–6. First, the amide (NH) of substrate **1a** was deprotonated[19c] in the presence of the base sodium *tert*-butoxide, forming intermediate **INT0**. Next, nucleophilic substitution of ethyl 3-bromopropiolate by **INT0** led to the formation of intermediate **INT1** via **TS0**. The computational results indicated that this step is the rate-determining step with a free energy barrier of 8.3 kcal/mol. The computations of the control experiment and competitive experiment in Figure 3b,c were consistent with the experimental observations and revealed that **TS0** is indeed the rate-determining step (see Supplementary Figures 3 and 5 for details). The subsequent [3,3]-sigmatropic rearrangement occurs through **TS1** to form **INT2**. Dearomatization takes place in this step, which is associated with a free energy barrier of 6.0 kcal/mol. Then the facile process of aromatization and cyclization leads to the final product **3a** (see Supplementary Figure 4 for details). This reaction is intensely exergonic with an overall reaction free energy of −133.1 kcal/mol. The type

DOI: 10.1021/acs.oprd.9b00002
Org. Process Res. Dev. XXXX, XXX, XXX–XXX

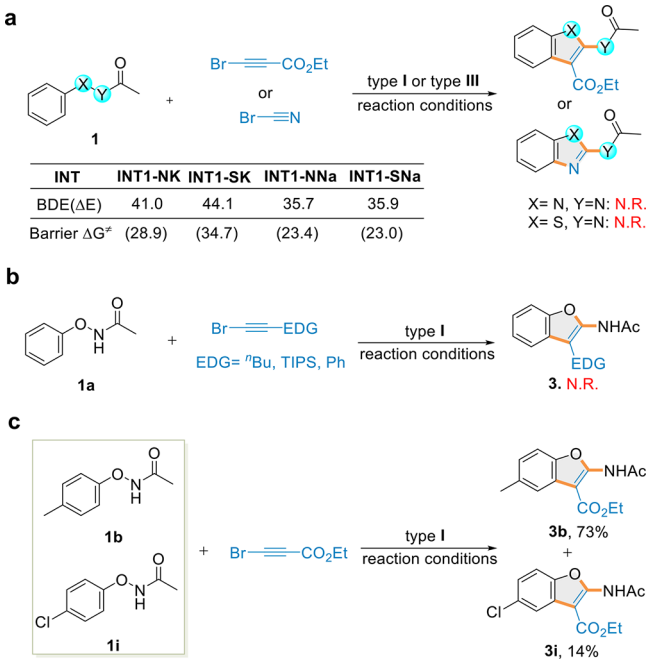


Figure 3. Mechanistic study. (a) Irreplaceability of the O−N bond. (b) Control experiments. (c) Competition experiment. Type I reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), and ^{t}BuONa (0.3 mmol) in DME (2 mL) for 20 min at ambient temperature. Type III reaction conditions: **1** (0.2 mmol), BrCN (0.4 mmol), and ^{t}BuOK (0.3 mmol) in DME (2.0 mL) for 30 min at ambient temperature. EDG = electron-donating group; N.R. = no reaction.

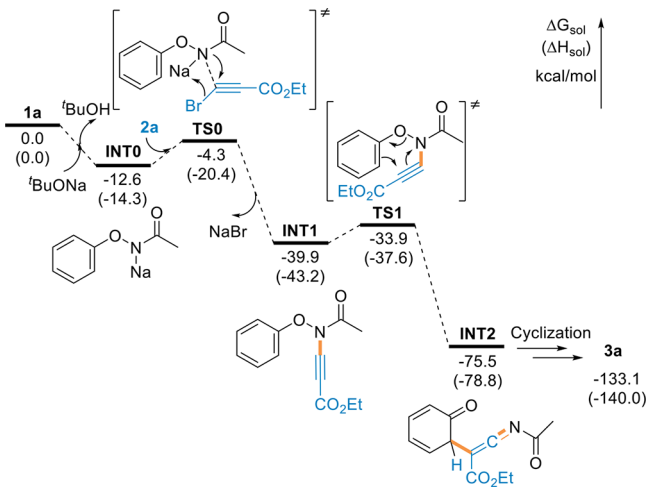


Figure 4. Free energy profile for the synthesis of **3a** from **1a** in solution, showing a plausible mechanism for the formation of **3a** via [3,3]-sigmatropic rearrangements.

III reaction proceeds by a process similar to that for type I (see Supplementary Figure 6 for details). For these reactions, the cleavage of the weak O−N bond and the reconstruction of aromaticity provide the driving force for the reaction.

CONCLUSION

We have reported that O−NHAc acts as a diverse functional group for the unified synthesis of benzofurans and benzoxazoles. This strategy was successfully applied to the late-stage modification of natural products as well as the rapid construction of hFBPase-1. A combination of experimental and computational studies suggests that the rearrangement/annulation process is intensely exothermic and that the O−N bond is indispensable. We are currently exploring more sigmatropic rearrangement reactions based on the O−N bond cleavage.

EXPERIMENTAL SECTION

General. Commercially available chemicals were obtained from Adamas, Energy, TCI, and Bide and used as received unless otherwise stated. Reactions were monitored with analytical thin-layer chromatography (TLC) on silica. ^{1}H and ^{13}C NMR data were recorded on Bruker NMR spectrometers (300, 400, and 500 MHz) unless otherwise specified. Chemical shifts (δ) are given in parts per million relative to TMS. The residual solvent signals were used as references, and the chemical shifts were converted to the TMS scale ($CDCl_3$, δ_H = 7.26 ppm and δ_C = 77.16 ppm; CD_2Cl_2, δ_H = 5.32 ppm and δ_C = 54.00 ppm; DMSO-d_6, δ_H = 2.50 ppm and δ_C = 39.52 ppm; MeOH-d_4, δ_H = 3.31 ppm and δ_C = 49.00 ppm; acetone-d_6, δ_H = 2.05 ppm and δ_C = 29.84 and 206.26 ppm). HRMS (ESI) analysis was performed by The Analytical Instrumentation Center at Peking University, Shenzhen Graduate School, and the HRMS data are reported with ion mass/charge (m/z) ratios as values in atomic mass units.

For NMR spectra of compounds in this Communication, see Supplementary Figures 13−74. For the crystallographic data for compounds **3l**, **3y**, **5b**, **5d**, and **6o**, see Supplementary Figures 6−10 and Supplementary Tables 4−36. For the representative experimental procedures and analytic data of compounds synthesized, see Supplementary Methods.

Standard Reaction Conditions of Reaction Type I. *N*-Phenoxyacetamide (**1a**) (30 mg, 0.20 mmol), **2a** (70.8 mg, 0.40 mmol), and DME (2.0 mL) were weighed into a 10 mL pressure tube, to which ^{t}BuONa (28.8 mg, 0.30 mmol) was added. The reaction vessel was stirred at room temperature for 20 min. Then the mixture was concentrated under vacuum, and the residue was purified by column chromatography on silica gel with a gradient eluent of petroleum ether and ethyl acetate to afford the product ethyl 2-acetamidobenzofuran-3-carboxylate (**3a**) (45.4 mg, 92% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.86 (s, 1H), 7.71 (d, J = 7.4 Hz, 1H), 7.44 (d, J = 8.0 Hz, 1H), 7.29−7.14 (m, 2H), 4.36 (q, J = 7.1 Hz, 2H), 2.33 (s, 3H), 1.41 (t, J = 7.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 166.80, 165.61, 156.09, 150.37, 124.55, 123.99, 123.66, 120.61, 111.11, 91.35, 60.70, 24.70, 14.35. HRMS (ESI): calcd for $C_{13}H_{13}NNaO_4$ $[M + Na]^+$, 270.0737; found, 270.0736.

Standard Reaction Conditions of Reaction Type II. To a mixture of *N*,*N*-diethylacetamide (65 μL, 0.6 mmol) and 2-iodopyridine (60 μL, 1.2 mmol) in MeCN was added triflic anhydride (40 μL, 0.6 mmol) dropwise at 0 °C under N_2. This mixture was stirred for 15 min and then added to a solution of **1a** (30 mg, 0.20 mmol) and ^{t}BuONa (28.8 mg, 0.3 mmol) at 0 °C, and the mixture was allowed to warm to room temperature. After 3 h, the reaction mixture was concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel to afford *N*-(benzofuran-2-yl)acetamide (**5a**) (26.6 mg, 76% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (s, 1H), 7.46 (d, J = 6.9 Hz, 1H), 7.31 (d, J = 7.0 Hz, 1H), 7.19 (d, J = 12.5 Hz, 2H), 6.76 (s, 1H), 2.24 (s, 3H). ^{13}C NMR (101 MHz, DMSO): δ 166.82, 149.56, 147.59, 129.48, 123.26, 122.83, 120.40, 110.18,

DOI: 10.1021/acs.oprd.9b00002
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

90.44, 23.80. HRMS (ESI): calcd for $C_{10}H_9NNaO_2$ $[M + Na]^+$, 198.0525; found, 198.0526.

Standard Reaction Conditions of Reaction Type III. **1a** (30 mg, 0.20 mmol), BrCN (42 mg, 0.40 mmol), and DME (2.0 mL) were weighed into a 10 mL pressure tube, to which ^{t}BuOK (34 mg, 0.30 mmol) was added. The reaction vessel was stirred at room temperature for 30 min in air. The mixture was then concentrated under vacuum, and the residue was purified by column chromatography on silica gel with a gradient eluent of petroleum ether and ethyl acetate to afford the product *N*-(benzo[*d*]oxazol-2-yl)acetamide (**6a**) (30.3 mg, 86% yield) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.10 (s, 1H), 7.63 (d, J = 7.6 Hz, 1H), 7.52 (d, J = 7.9 Hz, 1H), 7.37−7.25 (m, 2H), 2.52 (s, 3H). ^{13}C NMR (101 MHz, DMSO): δ 168.82, 155.63, 147.96, 141.05, 124.94, 123.94, 118.56, 110.38, 24.29. HRMS (ESI): calcd for $C_9H_8N_2NaO_2$ $[M + Na]^+$, 199.0477; found, 199.0477.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.9b00002.

^{1}H NMR spectra, ^{13}C NMR spectra, and high-resolution mass spectra for selected compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: jingzhao@nju.edu.cn.
*E-mail: zhangxh@pkusz.edu.cn.

ORCID

Jing Zhao: 0000-0001-5177-5699

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support was provided by the National Natural Science Foundation of China (21622103, 21571098, 21671099, and 91753121), the Natural Science Foundation of Jiangsu Province (BK20160022), the Fundamental Research Funds for the Central Universities (020514380139), the Shenzhen Basic Research Program (JCYJ20170413150538897), the Shenzhen STIC (JCYJ20170412150343516), and the Shenzhen San-Ming Project (SZSM201809085).

■ REFERENCES

(1) (a) Martín Castro, A. M. Claisen Rearrangement over the Past Nine Decades. *Chem. Rev.* **2004**, *104* (6), 2939−3002. (b) Sweeney, J. B. Sigmatropic Rearrangements of 'onium' Ylids. *Chem. Soc. Rev.* **2009**, *38* (4), 1027−1038. (c) Tejedor, D.; Méndez-Abt, G.; Cotos, L.; García-Tellado, F. Propargyl Claisen Rearrangement: Allene Synthesis and Beyond. *Chem. Soc. Rev.* **2013**, *42* (2), 458−471.

(2) (a) Hutchinson, S. A.; Luetjens, H.; Scammells, P. J. A New Synthesis of the Benzofuran Adenosine Antagonist XH-14. *Bioorg. Med. Chem. Lett.* **1997**, *7* (24), 3081−3084. (b) Liu, K. G.; Lo, J. R.; Comery, T. A.; Zhang, G. M.; Zhang, J. Y.; Kowal, D. M.; Smith, D. L.; Di, L.; Kerns, E. H.; Schechter, L. E.; Robichaud, A. J. Identification of A Series of Benzoxazoles as Potent 5-HT6 Ligands. *Bioorg. Med. Chem. Lett.* **2009**, *19* (4), 1115−1117. (c) Cox, C. D.; Breslin, M. J.; Whitman, D. B.; Schreier, J. D.; McGaughey, G. B.; Bogusky, M. J.; Roecker, A. J.; Mercer, S. P.; Bednar, R. A.; Lemaire, W.; Bruno, J. G.; Reiss, D. R.; Harrell, C. M.; Murphy, K. L.; Garson, S. L.; Doran, S. M.; Prueksaritanont, T.; Anderson, W. B.; Tang, C.; Roller, S.; Cabalu, T. D.; Cui, D.; Hartman, G. D.; Young, S. D.; Koblan, K. S.; Winrow, C. J.; Renger, J. J.; Coleman, P. J. Discovery of the Dual Orexin Receptor Antagonist [(7R)-4-(5-Chloro-1,3-benzoxazol-2-yl)-7-methyl-1,4-diazepan-1-yl][5-methyl-2-(2H-1,2,3-triazol-2-yl)phenyl]methanone (MK-4305) for the Treatment of Insomnia. *J. Med. Chem.* **2010**, *53* (14), 5320−5332. (d) Kobayashi, H.; Eickhoff, J. A.; Zakarian, A. Synthesis of 2-Aminoazoles from Thioesters via α-Heterosubstituted Ketones by Copper-Mediated Cross-Coupling. *J. Org. Chem.* **2015**, *80* (20), 9989−9999. (e) Alvarado, J.; Fournier, J.; Zakarian, A. Synthesis of Functionalized Dihydrobenzofurans by Direct Aryl C−O Bond Formation under Mild Conditions. *Angew. Chem., Int. Ed.* **2016**, *55* (38), 11625−11628.

(3) (a) Bates, C. G.; Saejueng, P.; Murphy, J. M.; Venkataraman, D. Synthesis of 2-Arylbenzo[b]furans via Copper(I)-Catalyzed Coupling of o-Iodophenols and Aryl Acetylenes. *Org. Lett.* **2002**, *4* (26), 4727−4729. (b) Zhao, B.; Lu, X. Cationic Palladium(II)-Catalyzed Addition of Arylboronic Acids to Nitriles. One-Step Synthesis of Benzofurans from Phenoxyacetonitriles. *Org. Lett.* **2006**, *8* (26), 5987−5990. (c) Ueda, S.; Nagasawa, H. Synthesis of 2-Arylbenzoxazoles by Copper-Catalyzed Intramolecular Oxidative C−O Coupling of Benzanilides. *Angew. Chem., Int. Ed.* **2008**, *47* (34), 6411−6413. (d) Guo, X.; Yu, R.; Li, H.; Li, Z. Iron-Catalyzed Tandem Oxidative Coupling and Annulation: An Efficient Approach to Construct Polysubstituted Benzofurans. *J. Am. Chem. Soc.* **2009**, *131* (47), 17387−17393. (e) Riadi, Y.; Mamouni, R.; Azzalou, R.; Haddad, M. E.; Routier, S.; Guillaumet, G.; Lazar, S. An Efficient and Reusable Heterogeneous Catalyst Animal Bone Meal for Facile Synthesis of Benzimidazoles, Benzoxazoles, and Benzothiazoles. *Tetrahedron Lett.* **2011**, *52* (27), 3492−3495. (f) Park, I.-K.; Park, J.; Cho, C.-G. Intramolecular Fischer Indole Synthesis and its Combination with an Aromatic [3,3]-Sigmatropic Rearrangement for the Preparation of Tricyclic Benzo[*cd*]indoles. *Angew. Chem., Int. Ed.* **2012**, *51* (10), 2496−2499. (g) Shimizu, S.; Ohori, K.; Arai, T.; Sasai, H.; Shibasaki, M. A Catalytic Asymmetric Synthesis of Tubifolidine. *J. Org. Chem.* **1998**, *63* (21), 7547−7551.

(4) (a) Hillier, M. C.; Marcoux, J.-F.; Zhao, D.; Grabowski, E. J. J.; McKeown, A. E.; Tillyer, R. D. Stereoselective Formation of Carbon−Carbon Bonds via SN_2-Displacement: Synthesis of Substituted Cycloalkyl[*b*]indoles. *J. Org. Chem.* **2005**, *70* (21), 8385−8394. (b) Humphrey, G. R.; Kuethe, J. T. Practical Methodologies for the Synthesis of Indoles. *Chem. Rev.* **2006**, *106* (7), 2875−2911.

(5) (a) Huang, X.; Maulide, N. Sulfoxide-Mediated α-Arylation of Carbonyl Compounds. *J. Am. Chem. Soc.* **2011**, *133* (22), 8510−8513. (b) Peng, B.; Geerdink, D.; Farès, C.; Maulide, N. Chemoselective Intermolecular α-Arylation of Amides. *Angew. Chem., Int. Ed.* **2014**, *53* (21), 5462−5466. (c) Peng, B.; Huang, X.; Xie, L.-G.; Maulide, N. A Brønsted Acid Catalyzed Redox Arylation. *Angew. Chem., Int. Ed.* **2014**, *53* (33), 8718−8721. (d) Kaiser, D.; Veiros, L. F.; Maulide, N. Brønsted Acid-Mediated Hydrative Arylation of Unactivated Alkynes. *Chem. - Eur. J.* **2016**, *22* (14), 4727−4732. (e) Kaldre, D.; Maryasin, B.; Kaiser, D.; Gajsek, O.; González, L.; Maulide, N. An Asymmetric Redox Arylation: Chirality Transfer from Sulfur to Carbon through a Sulfonium [3,3]-Sigmatropic Rearrangement. *Angew. Chem., Int. Ed.* **2017**, *56* (8), 2212−2215. (f) Kaldre, D.; Klose, I.; Maulide, N. Stereodivergent synthesis of 1,4-dicarbonyls by traceless charge−accelerated sulfonium rearrangement. *Science* **2018**, *361* (6403), 664.

(6) (a) Kobatake, T.; Fujino, D.; Yoshida, S.; Yorimitsu, H.; Oshima, K. Synthesis of 3-Trifluoromethylbenzo[*b*]furans from Phenols via Direct *Ortho* Functionalization by Extended Pummerer Reaction. *J. Am. Chem. Soc.* **2010**, *132* (34), 11838−11840. (b) Ookubo, Y.; Wakamiya, A.; Yorimitsu, H.; Osuka, A. Synthesis of a Library of Fluorescent 2-Aryl-3-trifluoromethylnaphthofurans from Naphthols by Using a Sequential Pummerer-Annulation/Cross-Coupling Strategy and their Photophysical Properties. *Chem. - Eur. J.* **2012**, *18* (40), 12690−12697. (c) Murakami, K.; Yorimitsu, H.; Osuka, A. Practical, Modular, and General Synthesis of Benzofurans through Extended Pummerer Annulation/Cross-Coupling Strategy. *Angew. Chem., Int. Ed.* **2014**, *53* (29), 7510−7513. (d) Yanagi, T.; Otsuka, S.; Kasuga, Y.;

DOI: 10.1021/acs.oprd.9b00002
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

Fujimoto, K.; Murakami, K.; Nogi, K.; Yorimitsu, H.; Osuka, A. Metal-Free Approach to Biaryls from Phenols and Aryl Sulfoxides by Temporarily Sulfur-Tethered Regioselective C−H/C−H Coupling. *J. Am. Chem. Soc.* **2016**, *138* (44), 14582−14585.

(7) Shrives, H. J.; Fernández-Salas, J. A.; Hedtke, C.; Pulis, A. P.; Procter, D. J. Regioselective Synthesis of C3 Alkylated and Arylated Benzothiophenes. *Nat. Commun.* **2017**, *8*, 14801.

(8) (a) Shang, L.; Chang, Y.; Luo, F.; He, J.-N.; Huang, X.; Zhang, L.; Kong, L.; Li, K.; Peng, B. Redox-Neutral α-Arylation of Alkyl Nitriles with Aryl Sulfoxides: A Rapid Electrophilic Rearrangement. *J. Am. Chem. Soc.* **2017**, *139* (11), 4211−4217. (b) Tian, J.; Luo, F.; Zhang, C.; Huang, X.; Zhang, Y.; Zhang, L.; Kong, L.; Hu, X.; Wang, Z.-X.; Peng, B. Selective *Ortho* C−H Cyanoalkylation of (Diacetoxyiodo)arenes through [3,3]-Sigmatropic Rearrangement. *Angew. Chem., Int. Ed.* **2018**, *57* (29), 9078−9082. (c) Luo, F.; Lu, Y.; Hu, M.; Tian, J.; Zhang, L.; Bao, W.; Yan, C.; Huang, X.; Wang, Z.-X.; Peng, B. Reductive *Ortho* C−H Cyanoalkylation of Aryl-(heteroaryl) Sulfoxides: A General Approach to α-Aryl(heteroaryl) Nitriles. *Org. Chem. Front.* **2018**, *5* (11), 1756−1762.

(9) (a) Tabolin, A. A.; Ioffe, S. L. Rearrangement of *N*-Oxyenamines and Related Reactions. *Chem. Rev.* **2014**, *114* (10), 5426−5476. (b) Luo, Y.-R. *Comprehensive Handbook of Chemical Bond Energies*; CRC Press: Boca Raton, FL, 2007; p 353.

(10) (a) Beshara, C. S.; Hall, A.; Jenkins, R. L.; Jones, T. C.; Parry, R. T.; Thomas, S. P.; Tomkinson, N. C. O. A Simple Method for the α-Oxygenation of Aldehydes. *Chem. Commun.* **2005**, *41* (11), 1478−1480. (b) Porzelle, A.; Woodrow, M. D.; Tomkinson, N. C. O. Palladium-Catalyzed Coupling of Hydroxylamines with Aryl Bromides, Chlorides, and Iodides. *Org. Lett.* **2009**, *11* (1), 233−236. (c) Porzelle, A.; Woodrow, M. D.; Tomkinson, N. C. O. Synthesis of Benzoxazolones from Nitroarenes or Aryl Halides. *Org. Lett.* **2010**, *12* (4), 812−815. (d) Smithen, D. A.; Mathews, C. J.; Tomkinson, N. C. O. Asymmetric α-Oxyacylation of Cyclic Ketones. *Org. Biomol. Chem.* **2012**, *10* (18), 3756−3762.

(11) (a) Tishkov, A. A.; Lesiv, A. V.; Khomutova, Y. A.; Strelenko, Y. A.; Nesterov, I. D.; Antipin, M. Y.; Ioffe, S. L.; Denmark, S. E. 2-Silyloxy-1,2-oxazines, a New Type of Acetals of Conjugated Nitroso Alkenes. *J. Org. Chem.* **2003**, *68* (24), 9477−9480. (b) Tabolin, A. A.; Lesiv, A. V.; Khomutova, Y. A.; Nelyubina, Y. V.; Ioffe, S. L. Rearrangement of 3-Alkylidene-2-siloxy-tetrahydro-1,2-oxazines (ASENA). A New Approach toward the Synthesis of 3-α-Hydroxyalkyl-5,6-dihydro-4H-1,2-oxazines. *Tetrahedron* **2009**, *65* (23), 4578−4592.

(12) Hojczyk, K. N.; Feng, P.; Zhan, C.; Ngai, M.-Y. Trifluoromethoxylation of Arenes: Synthesis of *Ortho*-Trifluoromethoxylated Aniline Derivatives by OCF_3 Migration. *Angew. Chem., Int. Ed.* **2014**, *53* (52), 14559−14563.

(13) Nakamura, I.; Jo, T.; Ishida, Y.; Tashiro, H.; Terada, M. Cationic *N*-Heterocyclic Carbene Copper-Catalyzed [1,3]-Alkoxy Rearrangement of *N*-Alkoxyanilines. *Org. Lett.* **2017**, *19* (12), 3059−3062.

(14) Ishida, Y.; Nakamura, I.; Terada, M. Copper-Catalyzed Domino [1,3]/[1,2] Rearrangement for the Efficient Synthesis of Multisubstituted ortho-Anisidines. *J. Am. Chem. Soc.* **2018**, *140* (28), 8629−8633.

(15) (a) Wang, Y.; Ye, L.; Zhang, L. Au-catalyzed Synthesis of 2-Alkylindoles from *N*-arylhydroxylamines and Terminal Alkynes. *Chem. Commun.* **2011**, *47* (27), 7815−7817. (b) Wang, Y.; Liu, L.; Zhang, L. Combining Zn Ion Catalysis with Homogeneous Gold Catalysis: An Efficient Annulation Approach to *N*-protected Indoles. *Chem. Sci.* **2013**, *4* (2), 739−746.

(16) (a) Guzzo, P. R.; Buckle, R. N.; Chou, M.; Dinn, S. R.; Flaugh, M. E.; Kiefer, A. D., Jr.; Ryter, K. T.; Sampognaro, A. J.; Tregay, S. W.; Xu, Y.-C. Preparation of 8-Amido-2-dimethylamino-1,2,3,4-tetrahydro-2-dibenzofurans and Several Fluorinated Derivatives via [3,3]-Sigmatropic Rearrangement of O-Aryloximes. *J. Org. Chem.* **2003**, *68* (3), 770−778. (b) Miyata, O.; Takeda, N.; Naito, T. Highly Effective Synthetic Methods for Substituted 2-Arylbenzofurans Using [3,3]-Sigmatropic Rearrangement: Short Syntheses of Stemofuran A and Eupomatenoid 6. *Org. Lett.* **2004**, *6* (11), 1761−1763. (c) Ghosh, R.; Stridfeldt, E.; Olofsson, B. Metal-Free One-Pot Synthesis of Benzofurans. *Chem. - Eur. J.* **2014**, *20* (29), 8888−8892. (d) Gao, H.; Xu, Q.-L.; Keene, C.; Kürti, L. Scalable, Transition-Metal-Free Direct Oxime O-Arylation: Rapid Access to *O*-Arylhydroxylamines and Substituted Benzo[*b*]furans. *Chem. - Eur. J.* **2014**, *20* (29), 8883−8887.

(17) (a) Fukuyama, T.; Li, T.; Peng, G. Use of 1,1,1,3,3,3-hexamethyldisilazane and N,O-bis-(trimethylsilyl)acetamide in aromatic Claisen rearrangement: An Efficient Method for Preventing Abnormal Claisen Rearrangement. *Tetrahedron Lett.* **1994**, *35* (14), 2145−2148. (b) Nicolaou, K. C.; Li, J. Biomimetic" Cascade Reactions in Organic Synthesis: Construction of 4-Oxatricyclo[4.3.1.0]decan-2-one Systems and Total Synthesis of 1-O-Methylforbesione via Tandem Claisen Rearrangement/Diels−Alder Reactions. *Angew. Chem., Int. Ed.* **2001**, *40* (22), 4264−4268. (c) Jana, A. K.; Mal, D. A Rapid Entry to C-prenylcarbazoles: Total Synthesis of Clausamine C−D, Clausevatine D and Clausine F. *Chem. Commun.* **2010**, *46* (24), 4411−4413.

(18) (a) Sheradsky, T.; Salemnick, G. Thermal Rearrangement of O-(2-pyridyl)oximes. *J. Org. Chem.* **1971**, *36* (8), 1061−1063. (b) Sheradsky, T.; Nov, E.; Segal, S.; Frank, A. Cope Rearrangements of Arylvinylhydroxylamines. *J. Chem. Soc., Perkin Trans. 1* **1977**, *1* (16), 1827−1831. (c) Çelebi-Ölçüm, N.; Boal, B. W.; Huters, A. D.; Garg, N. K.; Houk, K. N. Why Do Some Fischer Indolizations Fail? *J. Am. Chem. Soc.* **2011**, *133* (15), 5752−5755.

(19) (a) Wu, Q.; Chen, Y.; Yan, D.; Zhang, M.; Lu, Y.; Sun, W.-Y.; Zhao, J. Unified Synthesis of Mono/bis-arylated Phenols via RhIII-catalyzed Dehydrogenative Coupling. *Chem. Sci.* **2017**, *8* (1), 169−173. (b) Wu, Q.; Yan, D.; Chen, Y.; Wang, T.; Xiong, F.; Wei, W.; Lu, Y.; Sun, W.-Y.; Li, J. J.; Zhao, J. A Redox-neutral Catechol Synthesis. *Nat. Commun.* **2017**, *8*, 14227. (c) Xiong, F.; Lu, L.; Sun, T.-Y.; Wu, Q.; Yan, D.; Chen, Y.; Zhang, X.; Wei, W.; Lu, Y.; Sun, W.-Y.; Li, J. J.; Zhao, J. A Bioinspired and Biocompatible *Ortho*-sulfiliminyl phenol Synthesis. *Nat. Commun.* **2017**, *8*, 15912. (d) Hu, S.; Lu, L.; Zhu, T.; Wu, Q.; Chen, Y.; Li, J. J.; Zhao, J. Rh(iii)-Catalyzed *Ortho*-C−H Alkynylation of *N*-phenoxyacetamides with Hypervalent Iodine-Alkyne Reagents at Room Temperature. *Org. Biomol. Chem.* **2018**, *16* (1), 43−47. (e) Yan, D.; Wang, G.; Xiong, F.; Sun, W. Y.; Shi, Z.; Lu, Y.; Li, S.; Zhao, J. A Selenium-catalysed *para*-Amination of Phenols. *Nat. Commun.* **2018**, *9* (1), 4293.

(20) (a) Larraufie, M.-H.; Ollivier, C.; Fensterbank, L.; Malacria, M.; Lacôte, E. Radical Synthesis of Guanidines from *N*-Acyl Cyanamides. *Angew. Chem., Int. Ed.* **2010**, *49* (12), 2178−2181. (b) Zheng, J.; Zhang, Y.; Wang, D.; Cui, S. Silver(I)-Mediated Phosphorylation/Cyclization Cascade of *N*-Cyanamide Alkenes for Divergent Access to Quinazolinones and Dihydroisoquinolinones. *Org. Lett.* **2016**, *18* (8), 1768−1771.

(21) All of the DFT calculations were conducted using the B3LYP-D3 functional with the 6-311++G(d,p) basis set for C, H, O, and N and the cc-pVTZ-pp basis set for Br. Solvent effects were taken into account with the SMD method, and 1,4-dioxane was chosen as the solvent. Gibbs free energies at 298.15 K are presented for discussion. All of the calculations were performed with Gaussian 09: Frisch, M. J.; et al.*Gaussian 09*; Gaussian, Inc.: Wallingford, CT, 2009. More details are included in the Supporting Information.

(22) (a) Snider, B. B. Intramolecular Cycloaddition Reactions of Ketenes and Keteniminium Salts with Alkenes. *Chem. Rev.* **1988**, *88* (5), 793−811. (b) Madelaine, C.; Valerio, V.; Maulide, N. Revisiting Keteniminium Salts: More than the Nitrogen Analogs of Ketenes. *Chem. - Asian J.* **2011**, *6* (9), 2224−2239. (c) Kaiser, D.; Maulide, N. Making the Least Reactive Electrophile the First in Class: Domino Electrophilic Activation of Amides. *J. Org. Chem.* **2016**, *81* (11), 4421−4428.

(23) (a) Tona, V.; de la Torre, A.; Padmanaban, M.; Ruider, S.; González, L.; Maulide, N. Chemo- and Stereoselective Transition-Metal-Free Amination of Amides with Azides. *J. Am. Chem. Soc.* **2016**, *138* (27), 8348−8351. (b) de la Torre, A.; Kaiser, D.; Maulide, N. Flexible and Chemoselective Oxidation of Amides to α-Keto Amides

DOI: 10.1021/acs.oprd.9b00002
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

and α-Hydroxy Amides. *J. Am. Chem. Soc.* **2017**, *139* (19), 6578−6581. (c) Kaiser, D.; Teskey, C. J.; Adler, P.; Maulide, N. Chemoselective Intermolecular Cross-Enolate-Type Coupling of Amides. *J. Am. Chem. Soc.* **2017**, *139* (45), 16040−16043. (d) Kaiser, D.; de la Torre, A.; Shaaban, S.; Maulide, N. Metal-Free Formal Oxidative C−C Coupling by In Situ Generation of an Enolonium Species. *Angew. Chem., Int. Ed.* **2017**, *56* (21), 5921−5925. (e) Kaiser, D.; Bauer, A.; Lemmerer, M.; Maulide, N. Amide Activation: An Emerging Tool for Chemoselective Synthesis. *Chem. Soc. Rev.* **2018**, *47* (21), 7899−7925.

(24) Cernak, T.; Dykstra, K. D.; Tyagarajan, S.; Vachal, P.; Krska, S. W. The Medicinal Chemist's Toolbox for Late Stage Functionalization of Drug-like Molecules. *Chem. Soc. Rev.* **2016**, *45* (3), 546−576.

(25) Lai, C.; Gum, R. J.; Daly, M.; Fry, E. H.; Hutchins, C.; Abad-Zapatero, C.; von Geldern, T. W. Benzoxazole Benzenesulfonamides as Allosteric Inhibitors of Fructose-1,6-bisphosphatase. *Bioorg. Med. Chem. Lett.* **2006**, *16* (7), 1807−1810.

DOI: 10.1021/acs.oprd.9b00002
Org. Process Res. Dev. XXXX, XXX, XXX−XXX