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Solvent-Switched Benzylic Methylene Functionalization: Addition, Ring-Opening, Cyclization, and Unexpected Cleavage of C−O and C−C Bonds

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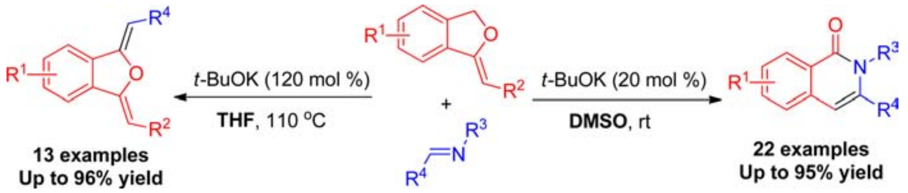
ABSTRACT



Intermolecular benzylic methylene functionalization of *exo*-cyclic enol ethers has been achieved using imines as reagents and potassium *tert*-butoxide as the catalyst. Depending on the solvent used, the reaction proceeds by two pathways. In THF, an addition/elimination reaction of *exo*-cyclic enol ethers with imines provides dihydroisobenzofuran derivatives in good yield. In DMSO, an addition/ring-opening/cyclization cascade reaction occurs with unexpected cleavage of C−O and C−C bonds, affording isoquinolin-1(2*H*)-one products in high yield under ambient reaction conditions.

The direct functionalization of the benzylic methylene group has attracted increasing attention in recent years, which usually involves transition metal salts or complexes as catalysts.[1] Some examples of transition-metal-free functionalization at the benzylic methylene group have been reported.[2−5] In particular, diphenyl phosphate,[3] MsOH,[4] and chiral phosphoric acids[5] have been described as efficient catalysts for such transformations, in which the key step is 1,5-hydride transfer. In 2012, Walsh et al. reported that $LiN(SiMe_3)_2$ could deprotonate the acidic hydrogen of benzylic methylene in $[(\eta^6\text{-benzylamine})Cr(CO)_3]$. The resulting anion can be stabilized by delocalizing the negative charge to $Cr(CO)_3$, and undergo palladium-catalyzed cross-coupling with aryl triflate.[6]

Recent years have seen increased interest in the direct functionalization of *endo*-cyclic enol ethers, which has furnished important, complex synthetic intermediates with high efficiency.[7] Functionalization of *exo*-cyclic enol ethers, however, has rarely been investigated.[8] Here we

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[1] (a) Wang, H.; Li, G.; Engle, K. M.; Yu, J.-Q.; Davies, H. M. L. *J. Am. Chem. Soc.* **2013**, *135*, 6774. (b) Chen, H.; Sanjaya, S.; Wang, Y.-F.; Chiba, S. *Org. Lett.* **2013**, *15*, 212. (c) Nörder, A.; Warren, S. A.; Herdtweck, E.; Huber, S. M.; Bach, T. *J. Am. Chem. Soc.* **2012**, *134*, 13524. (d) Zhang, G.; Ma, Y.; Wang, S.; Zhang, Y.; Wang, R. *J. Am. Chem. Soc.* **2012**, *134*, 12334. (e) Xie, P.; Xie, Y.; Qian, B.; Zhou, H.; Xia, C.; Huang, H. *J. Am. Chem. Soc.* **2012**, *134*, 9902.

[2] (a) Tanoue, A.; Yoo, W.-J.; Kobayashi, S. *Adv. Synth. Catal.* **2013**, *355*, 269. (b) Hari, D. P.; König, B. *Org. Lett.* **2011**, *13*, 3852. (c) Zhang, B.; Xiang, S.-K.; Zhang, L.-H.; Cui, Y.; Jiao, N. *Org. Lett.* **2011**, *13*, 5212. (d) Pintér, Á.; Sud, A.; Sureshkumar, D.; Klussmann, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 5004.

[3] Haibach, M. C.; Deb, I.; De, C. K.; Seidel, D. *J. Am. Chem. Soc.* **2011**, *133*, 2100.

[4] Chen, D.-F.; Han, Z.-Y.; He, Y.-P.; Yu, J.; Gong, L.-Z. *Angew. Chem., Int. Ed.* **2012**, *51*, 12307.

[5] Mori, K.; Ehara, K.; Kurihara, K.; Akiyama, T. *J. Am. Chem. Soc.* **2011**, *133*, 6166.

[6] McGrew, G. I.; Stanciu, C.; Zhang, J.; Carroll, P. J.; Dreher, S. D.; Walsh, P. J. *Angew. Chem., Int. Ed.* **2012**, *51*, 11510.

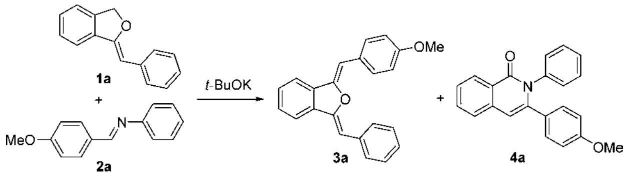
[7] (a) Sun, Z.; Winschel, G. A.; Borovika, A.; Nagorny, P. *J. Am. Chem. Soc.* **2012**, *134*, 8074. (b) Balmond, E. I.; Coe, D. M.; Galan, M. C.; McGarrigle, E. M. *Angew. Chem., Int. Ed.* **2012**, *51*, 9152. (c) Xu, H.; Zuend, S. J.; Woll, M. G.; Tao, Y.; Jacobsen, E. N. *Science* **2010**, *327*, 986. (d) Rueping, M.; Lin, M.-Y. *Chem.—Eur. J.* **2010**, *16*, 4169. (e) Akiyama, T.; Morita, H.; Fuchibe, K. *J. Am. Chem. Soc.* **2006**, *128*, 13070. (f) Boglio, C.; Lemière, G.; Hasenknopf, B.; Thorimbert, S.; Lacôte, E.; Malacria, M. *Angew. Chem., Int. Ed.* **2006**, *45*, 3324. (g) Sundararajan, G.; Prabagaran, N.; Varghese, B. *Org. Lett.* **2001**, *3*, 1973.

10.1021/ol401470y

report the solvent-switched, direct benzylic methylene functionalization of *exo*-cyclic enol ethers via addition to imines using a potassium *tert*-butoxide (*t*-BuOK) catalyst. In THF, the reaction proceeds via an addition/elimination pathway; in DMSO, it proceeds via an addition/ring-opening/cyclization cascade reaction with unexpected cleavage of C–O and C–C bonds.

First we focused on developing the intermolecular addition of *exo*-cyclic enol ether **1a** to imine **2a** (Table 1). In the presence of commercially available *t*-BuOK as the catalyst, reaction of **1a** and **2a** in THF at 80 °C afforded the addition/elimination product **3a** in 85% yield, as well as the unexpected addition/ring-opening/cyclization cascade reaction product **4a** in 15% yield (entry 1). When the reaction was carried out in a sealed tube at 110 °C and the dosage of *t*-BuOK was increased to 1.2 equiv of **1a**, product **3a** was obtained in up to 95% yield after 3 h (entries 2 and 3). If the reaction was performed under rt in THF, only an 11% yield was observed even after 12 h (entry 4). To our surprise, when **1a** and **2a** were reacted in the polar aprotic solvent DMF or DMSO with 20 mol % *t*-BuOK as the catalyst, the yield of **3a** decreased dramatically and the yield of addition/ring-opening/cyclization cascade product **4a** increased to 28% or 58% (entries 5 and 6). These results indicate that the solvent plays a crucial role in controlling the reaction pathway, allowing the same starting materials to generate different types of products.

Table 1. Investigation of the Reactions of **1a** and **2a** under Various Conditions[a]



entry	temp (°C)	time (h)	solvent	yield (**3a**, %)[b]	yield (**4a**, %)[b]
1	80	3	THF	85	15
2	110	3	THF	88	10
3[c]	110	3	THF	95	trace
4[c]	rt	12	THF	11	23
5	80	3	DMF	8	28
6	80	3	DMSO	40	58
7	60	6	DMSO	35	65
8	rt	6	DMSO	trace	90
9[d]	rt	6	DMSO	trace	74

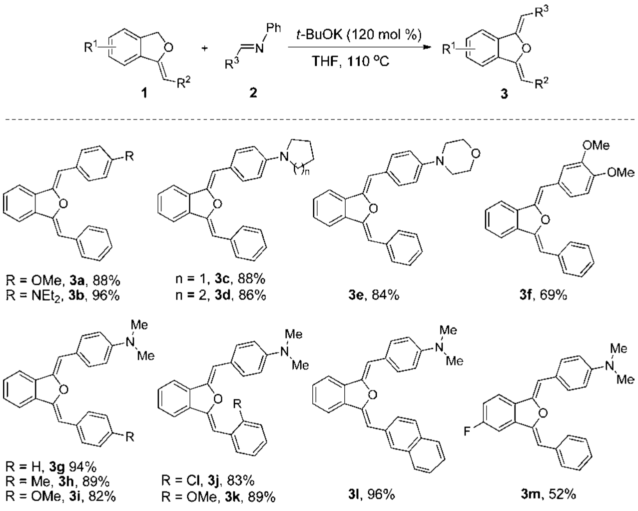
[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.24 mmol), *t*-BuOK (0.04 mmol), solvent (1.0 mL), unless otherwise noted. [b] Determined by ^{1}H NMR integration. [c] *t*-BuOK (0.24 mmol) was used. [d] *t*-BuOK (0.02 mmol) was used.

Encouraged by these results, we examined the reaction of **1a** and **2a** in DMSO at lower temperature. At rt, the reaction produced **4a** in 90% yield in the presence of 20 mol % *t*-BuOK (entries 7 and 8). Decreasing catalyst loading of *t*-BuOK to 10 mol % substantially reduced the yield of **4a** (entry 9).

Addition/elimination reactions of *exo*-cyclic enol ethers with imines provide access to a new class of vinylogous analogues of 3-arylideneisobenzofuran-1(3*H*)-one compounds possessing antianxiety and anti-HIV activity.[9] To explore whether our solvent-switched approach might be useful for synthesizing such analogues, we reacted *exo*-cyclic enol ethers and substituted *N*-phenylmethanimines in the presence of 1.2 equiv of *t*-BuOK for 3 h in THF in sealed tubes at 110 °C. Products **3a**–**3m** were obtained exclusively in the *Z*-configuration at both the 1 and 3 positions, as indicated by single-crystal X-ray diffraction analysis of **3d** (see Supporting Information) and by comparison of ^{1}H NMR spectra of the products. When the R^3 substituent on the *N*-phenylmethanimine was a phenyl group incorporating electron-donating moieties such as OMe, NEt_2, pyrrolidinyl, piperidinyl, or morpholinyl, the addition/elimination reactions with *exo*-cyclic enol ether **1a** gave the corresponding products **3a**–**3e** in 84–96% yield, while product **3f** was obtained in only 69% yield (Scheme 1).

We also examined addition/elimination reactions between *N*-phenylmethanimine substituted with *N*,*N*-dimethylaniline and the *exo*-cyclic enol ether **1a** or derivatives of **1a** containing 4-Me, 4-MeO, 2-Cl, 2-MeO or naphthyl at position R^2. These reactions produced **3g-3l** in 82–96% yield. In contrast, reaction of the same imine with the *exo*-cyclic enol ether derivative of **1a** containing 6-F at position R^1 gave product **3m** in only 52% yield.

Scheme 1. Addition/Elimination Reaction of *exo*-Cyclic Enol Ethers **1** with Imines **2**[a]



[a] Reaction conditions: **1** (0.2 mmol), **2** (0.24 mmol), *t*-BuOk (0.24 mmol), THF (1.0 mL), 110 °C, 3 h; isolated yields are shown.

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(8) (a) Smith, J. G.; Dibble, P. W. *J. Org. Chem.* **1988**, *53*, 1841. (b) Smith, J. G.; Welankiwar, S. S.; Chu, N. G.; Lai, E. H.; Sondheimer, S. J. *J. Org. Chem.* **1981**, *46*, 4658. (c) Smith, J. G.; Welankiwar, S. S.; Shantz, B. S.; Lai, E. H.; Chu, N. G. *J. Org. Chem.* **1980**, *45*, 1817.

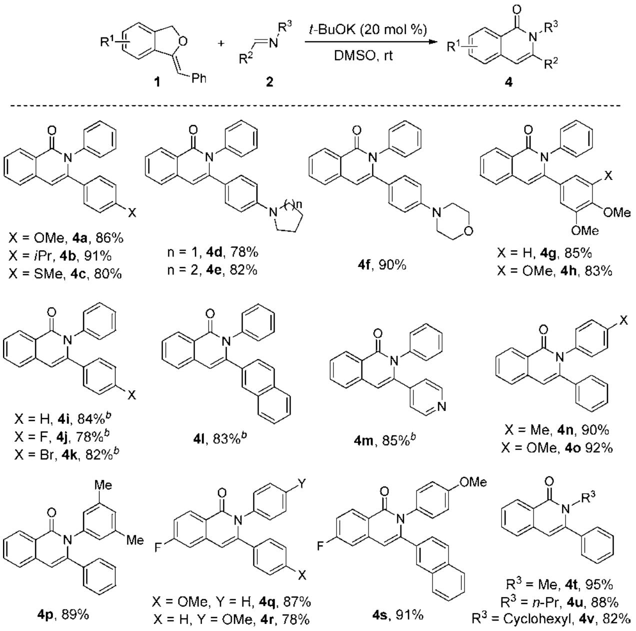
(9) Zamilpa, A.; Herrera-Ruiz, M.; del Olmo, E.; López-Pérez, J. L.; Tortoriello, J.; San Feliciano, A. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3483.

Changing the reaction solvent from THF to DMSO caused the *t*-BuOK-catalyzed reactions of *exo*-cyclic enol ethers with imines to proceed via an interesting addition/ring-opening/cyclization cascade reaction. The result was isoquinolin-1(2*H*)-one products, which have become increasingly attractive synthetic targets because of their antihypertensive[10] and antitumor[11] activity. Usually they are synthesized through the cycloaddition of benzamides and alkynes in the presence of transition metal catalysts such as Ni,[12] Cu,[13] Rh,[14] and Ru[15] To explore our solvent-switched system in greater detail, we first examined the reactions of *exo*-cyclic enol ether **1a** with *N*-phenylmethanimines substituted at position R^2 with an unsubstituted Ph or substituted phenyl groups. When the phenyl group carried electron-donating substituents such as OMe, *i*-Pr, SMe, pyrrolidinyl, piperidinyl, or morpholinyl, the *N*-phenylmethanimines reacted with **1a** to afford products **4a**–**4h** in 78–91% yield (Scheme 2). In contrast, if position R^2 was occupied by unsubstituted Ph, a phenyl group with electron-withdrawing fluoro or bromo substituents, or naphthyl or pyridyl groups, the *N*-phenylmethanimine reacted with **1a** in THF to give single products **4i**–**4m** in 78–85% yield, although the reactions could also proceed smoothly in DMSO at lower yields.

When these reactions were carried out in DMSO using 1-phenylmethanimine substituted at position R^3 with 4-Me-Ph, 4-MeO-Ph, or 3,5-Me$_2$-Ph, the reaction with **1a** gave products **4n**–**4p** in 89–92% yield. Note that product structures were confirmed by single-crystal X-ray diffraction analysis of **4o** and the comparison of the ^{1}H NMR spectra (see Supporting Information). However, attaching phenyl groups bearing electron-withdrawing substituents to position R^3 of 1-phenylmethanimine led to unsatisfactory reactions with **1a**.

At the same time, we also obtained good yields by inserting an electron-withdrawing substituent on the enol ether: a 6-fluoro-substituted *exo*-cyclic enol ether reacted with various imines to give products **4q**–**4s** in 78–91% yield. Finally, we examined the reactivity of alkyl-substituted imines in this reaction. *N*-Methyl, *N*-propyl, and *N*-cyclohexyl substitutions on 1-phenylmethanimine allowed the imine to react smoothly with **1a** and generate products **4t**–**4v** in 82–95% yield. This suggests that alkyl substituents on the imine exert minimal steric effects on reaction efficiency.

Scheme 2. Addition/Ring-Opening/Cyclization Cascade Reactions of *exo*-Cyclic Enol Ethers and Imines[a]



[a] Reaction conditions: **1** (0.2 mmol), **2** (0.24 mmol), *t*-BuOk (0.04 mmol), DMSO (1.0 mL), room temperature, 6 h, unless otherwise noted; isolated yields are shown. [b] THF was used as solvent at 80 °C for 3 h.

In the next phase of our study, we performed detailed investigations of the mechanism of the solvent-switched intermolecular benzylic methylene functionalization of the *exo*-cyclic enol ethers. We obtained 75% deuteration of the benzylic methylene in the presence of 4 equiv of *t*-BuOD and 10 mol % *t*-BuOK (eq 1, Scheme 3), revealing the acidity of the benzylic C–H bond. When **1a** and imine **2b** were reacted in DMSO with 20 mol % *t*-BuOK as the catalyst, the addition product **5** was isolated after 2 h, together with the isoquinolin-1(2*H*)-one **4i**. Under similar catalytic reaction conditions, isolated addition product **5** converted smoothly to isoquinolin-1(2*H*)-one **4i** after 6 h (eq 2, Scheme 3). These results clearly demonstrate that addition product **5** is an intermediate in the cascade reactions. A similar addition reaction seemed to occur in the addition/elimination reaction of **1a** and **2a**, in which the formal C=N bond was cleaved and the byproduct phenylamine was detected as the result of elimination. To clarify the ring-opening step of the cascade reaction, we reacted imine **2c** with *exo*-cyclic enol ether **1b** substituted with a methyl group on the benzylic carbon. The only product generated was **4w**, and no addition/elimination product was detected (eq 3, Scheme 3). This indicates that the ring opening occurs selectively through sp^3 C–O cleavage. In the reaction of **1a** with **2a**, volatile toluene was detected in the reaction mixture by GC-MS. In addition, when the *exo*-cyclic enol ether **1c** bearing a naphthyl group reacted with imine **2d**, the nonvolatile byproduct 2-methylnaphthalene was isolated (eq 4, Scheme 3). These results indicate formal cleavage of the C=C bond in the *exo*-cyclic enol ether moiety and the unusual release of Ar–CH$_3$.

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(10) Saeed, A.; Ashraf, Z. *Pharm. Chem. J.* **2008**, *42*, 277.

(11) Cushman, M.; Jayaraman, M.; Vroman, J. A.; Fukunaga, A. K.; Fox, B. M.; Kohlhagen, G.; Strumberg, D.; Pommier, Y. *J. Med. Chem.* **2000**, *43*, 3688.

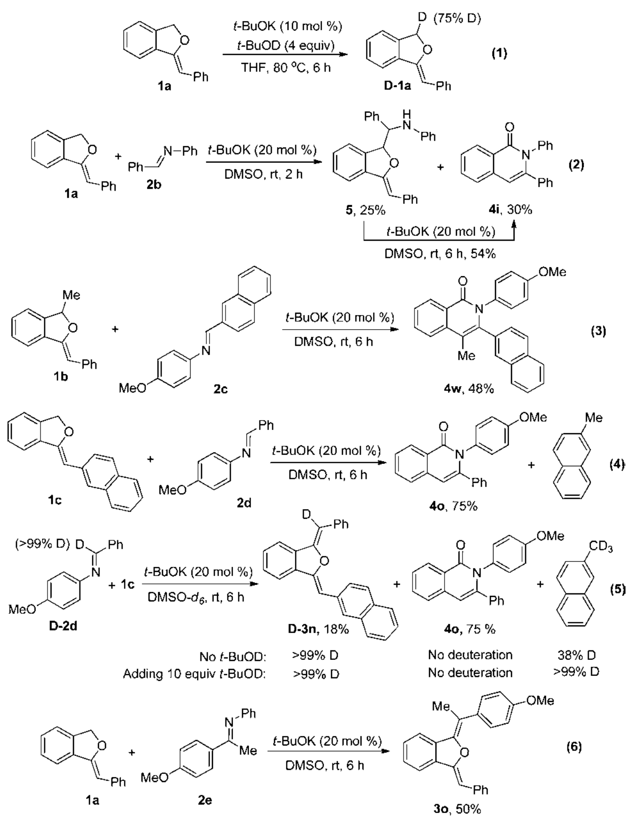
(12) (a) Kajita, Y.; Matsubara, S.; Kurahashi, T. *J. Am. Chem. Soc.* **2008**, *130*, 6058. (b) Liu, C.-C.; Parthasarathy, K.; Cheng, C.-H. *Org. Lett.* **2010**, *12*, 3518. (c) Miura, T.; Yamauchi, M.; Murakami, M. *Org. Lett.* **2008**, *10*, 3085.

(13) (a) Too, P. C.; Chiba, S. *Chem. Commun.* **2012**, *48*, 7634. (b) Wang, F.; Liu, H.; Fu, H.; Jiang, Y.; Zhao, Y. *Org. Lett.* **2009**, *11*, 2469.

(14) (a) Guimond, N.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2011**, *133*, 6449. (b) Hyster, T. K.; Rovis, T. *J. Am. Chem. Soc.* **2010**, *132*, 10565. (c) Guimond, N.; Gouliaras, C.; Fagnou, K. *J. Am. Chem. Soc.* **2010**, *132*, 6908.

(15) (a) Ackermann, L.; Lygin, A. V.; Hofmann, N. *Angew. Chem., Int. Ed.* **2011**, *50*, 6379. (b) Ackermann, L.; Fenner, S. *Org. Lett.* **2011**, *13*, 6548. (c) Li, B.; Feng, H.; Xu, S.; Wang, B. *Chem.—Eur. J.* **2011**, *17*, 12573.

Scheme 3. Mechanism Investigations of the Solvent-Switched Reactions

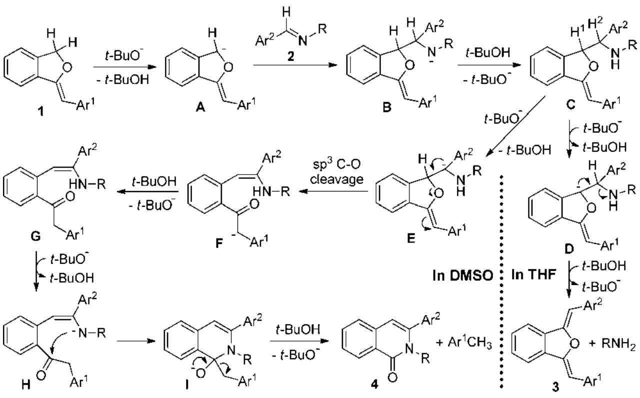


When **1c** and deuterated imine **D-2d** reacted in the absence of *t*-BuOD or the presence of 10 equiv of *t*-BuOD, the undeuterated product **4o** was obtained in 75% yield, as well as **D-3n** and deuterated 2-methylnaphthalene in 18% yield (eq 5, Scheme 3). Under both sets of reaction conditions, the deuteration ratio on the sole deuteron in **D-3n** was >99%, indicating that no C–D bond cleavage or exchange occurred in the addition/elimination reaction forming **D-3n**. Interestingly, the deuteration ratio on 2-methylnaphthalene was 38% in the absence of *t*-BuOD and >99% in the presence of 10 equiv of *t*-BuOD, indicating intermolecular proton migration rather than intramolecular transfer.

When **1a** was reacted with the methyl-substituted imine **2e**, only the addition/elimination product **3o** was formed, without any isoquinolin-1(2*H*)-one product (eq 6, Scheme 3). This shows that C–H cleavage in the N=C–H moiety is crucial in the formation of the isoquinolin-1(2*H*)-one product but not in the formation of **3o**.

Based on these experimental results, we propose mechanisms for the solvent-switched reactions in Scheme 4. First, deprotonation of *exo*-cyclic enol ethers **1** in the presence of *t*-BuOK affords intermediate **A**, which adds to imines **2** to produce **B**. The nitrogen anion **B** traps a proton, leading to the key intermediate **C**. When the solvent is THF, proton H^1 of intermediate **C** is selectively removed to generate intermediate **D**, which undergoes amine elimination to afford product **3**. When the solvent is DMSO, however, proton H^2 of intermediate **C** is selectively deprotonated to produce the intermediate **E**. Selective intramolecular sp^3 C–O bond cleavage then leads to **F**. Proton exchange generates intermediate **H**, which undergoes intramolecular nucleophilic addition to form intermediate **I**. Unusual C–C cleavage releases Ar^1–CH_3 and generates the isoquinolin-1(2*H*)-one product **4**.

Scheme 4. Proposed Mechanism of the Solvent-Switched Reactions



In summary, concise, solvent-switched transition-metal-free benzylic methylene functionalization of *exo*-cyclic enol ethers has been achieved using imines and a *t*-BuOK catalyst. Notably, the solvent acts as a switch to trigger different reaction pathways, affording two types of products from the same starting materials. In THF, addition/elimination reactions of *exo*-cyclic enol ethers with imines provide dihydroisobenzofuran derivatives in good to excellent yields. In DMSO, a novel addition/ring-opening/cyclization cascade reaction of the same reactants leads to unexpected cleavage of C–O and C–C bonds, generating high yields of isoquinolin-1(2*H*)-one products under ambient reaction conditions. These results provide new insights into the functionalization of benzylic sp^3 C–H and support the development of new strategies for constructing organic skeletons via functionalization of *exo*-cyclic enol ethers.

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Supporting Information Available. Experimental procedures, analysis data of the products, and crystallographic data (CIF) of **3d** and **4o**. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.