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Authors: Ning Jiao, Yuchao Zhu, Ziyao Zhang, Rui Jin, Jianzhong Liu, Guoquan Liu, and Bing Han

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COMMUNICATION

DMSO Enabled Selective Radical O-H Activation of 1,3(4)-Diols

Yuchao Zhu, [a] Ziyao Zhang, [a] Rui Jin, [a] Jianzhong Liu, [a] Guoquan Liu, [a] Bing Han, [b] and Ning Jiao*[a]

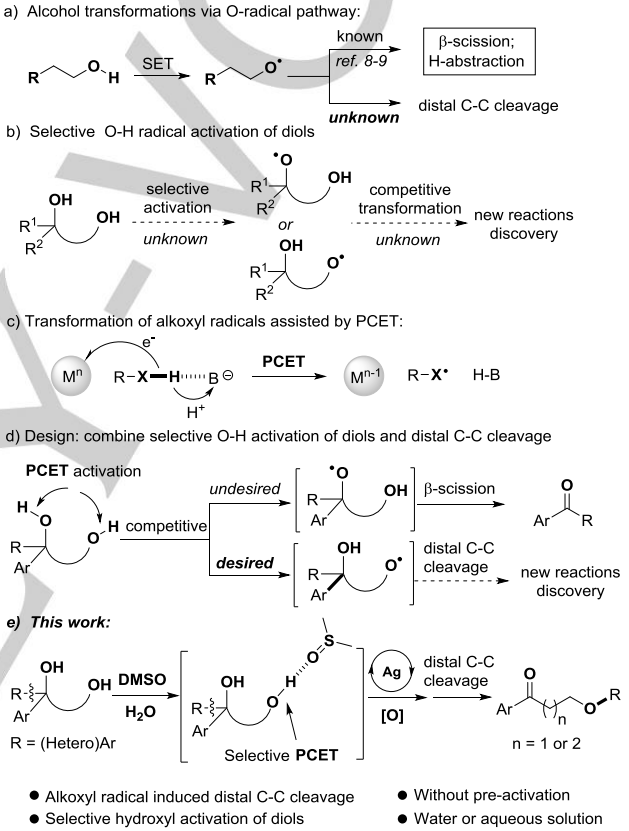
Dedicated to the 70th anniversary of Shanghai Institute of Organic Chemistry

Abstract: Selectivity control is one of the central topics in organic chemistry. Although the alkoxyl radical induced unprecedented transformations have drawn more attentions, compared to the booming selective C-H activation, the selective radical O-H activation remains less explored. Herein, we report a novel selective radical O-H activation strategy of diols by combining spatial effect with proton coupled electron transfer (PCET). We found the common molecule DMSO is an essential reagent that enables the regioselective transformation of diols. Mechanistic studies indicated the existence of the alkoxyl radical and the selective interaction between DMSO and hydroxyls. Moreover, the distal C-C cleavage is realized by this selective alkoxyl radical initiation protocol.

The selective transformation of hydroxyl (OH) groups in di- and polyols is a frequently encountered problem in organic synthesis, in contexts ranging from simple alcohol transformations to the preparation of highly functionalized natural products.[1] Despite the importance of this issue, strategies for the selective O-H activation are rare compared to the fast-growing studies on selective C-H activation.[2] The classic methods for selective activation of one hydroxyl in diols involve ionic transformations by steric regulation or based on special hydrocarbon structure.[3] Unlike traditional ionic alcohol transformations involving nucleophilic substitution/addition,[4] oxidation[5] and elimination[6] of hydroxyls, the alkoxyl radical induced transformations have drawn more attention with the discovery of unprecedented strategies for the generation of alkoxy radicals from alcohol without the need for pre-activation.[7] The O-H radical processes greatly enlarged the reaction types of alcohols either with alkoxyl radical induced β scission[8] or hydrogen abstraction.[9, 10] However, to the best of our knowledge, the general methods for the alkoxyl radical induced distal C-C cleavage remains unexplored (Scheme 1a). Moreover, the realized O-H radical transformations are limited to the activation of mono-ols, so far, there is a lack of selective radical O-H activation due to the almost identical bond-dissociation energy between two hydroxyls in diols (~105 kcal mol^{-1})[11] (Scheme 1b).

[a] Y. Zhu, Z. Zhang, R. Jin, J. Liu, G. Liu, Prof. N. Jiao
State Key Laboratory of Natural and Biomimetic Drugs
School of Pharmaceutical Sciences, Peking University
Xue Yuan Rd. 38, Beijing 100191 (China)
Prof. N. Jiao
State Key Laboratory of Organometallic Chemistry
Chinese Academy of Sciences, Shanghai 200032 (China)
E-mail: jiaoning@pku.edu.cn
Homepage: http://sklnbd.bjmu.edu.cn/nj
[b] Prof. B. Han
State Key Laboratory of Applied Organic Chemistry,
Lanzhou University, Lanzhou 730000 (China)

Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under.



Scheme 1. Selective hydroxyl activation of diols.

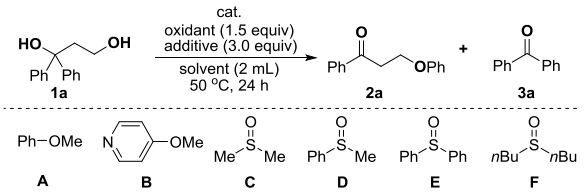
To address this problem, we paid our attention to the strategy of proton coupled electron transfer (PCET), which was reported that a Brønsted base and an oxidant can synergistically remove a proton and an electron from the substrate to afford a free radical (Scheme 1c).[12] Recently, Knowles and coworkers significantly achieved the O-H bond homolysis through PCET.[13] Inspired by these reports, we hypothesized that if we could find a proper Brønsted or Lewis base that can selectively form a hydrogen bond with one hydroxyl in diols, we would have a chance to selectively activate one O-H bond and realize the selective alkoxyl radical transformation of diols (Scheme 1d).

Taking this strategy in hand and based on our previous works,[14] we herein report an unprecedented Ag-catalyzed selective radical O-H activation of diols (Scheme 1e). We found the common molecule DMSO is an essential reagent to enable the high selective O-H activation under mild conditions by selectively forming hydrogen bonds with one hydroxyl in diols. Moreover, the alkoxyl radical induced distal C-C cleavage is realized, which is a formidable challenge in organic chemistry.[15,

10.1002/anie.202007187

16] This new strategy that combines the spatial effect with PCET would strategically enlarge the transformation of alcohols and can also promote the development of selective X-H radical activation reactions.

Table 1. Optimization of reaction conditions.[a]



entry	cat.(x mol%)	additive	oxidant	Solvent	2a	3a	2a/3a
1	$AgNO_3$ (20)	—	$K_2S_2O_8$	CH_3CN/H_2O(1:1)	33%	12%	3:1
2	$AgNO_3$ (20)	—	$K_2S_2O_8$	Acetone/H_2O(1:1)	23%	20%	1:1
3	$AgNO_3$ (20)	—	$K_2S_2O_8$	PhCl/H_2O(1:1)	40%	22%	2:1
4	$AgClO_4$ (20)	—	$K_2S_2O_8$	PhCl/H_2O(1:1)	52%	31%	1.7:1
5	$AgClO_4$ (20)	—	$K_2S_2O_8$	DMSO/H_2O(1:1)	33%	4%	8:1
6	$AgClO_4$ (20)	—	$K_2S_2O_8$	H_2O	31%	21%	1.5:1
7	$AgClO_4$ (20)	C[b]	$K_2S_2O_8$	H_2O	76%	6%	13:1
8	$AgClO_4$ (5)	C[b]	$K_2S_2O_8$	H_2O	77%	6%	13:1
9	**$AgClO_4$ (5)**	**C**	**$K_2S_2O_8$**	**H_2O**	**91%(80%)**[c]	**4%**	>20:1
10	$AgClO_4$ (5)	A	$K_2S_2O_8$	H_2O	34%	5%	7:1
11	$AgClO_4$ (5)	B	$K_2S_2O_8$	H_2O	17%	2%	9:1
12	$AgClO_4$ (5)	D	$K_2S_2O_8$	H_2O	82%	6%	14:1
13	$AgClO_4$ (5)	E	$K_2S_2O_8$	H_2O	40%	15%	2.7:1
14	$AgClO_4$ (5)	F	$K_2S_2O_8$	H_2O	35%	2%	17:1

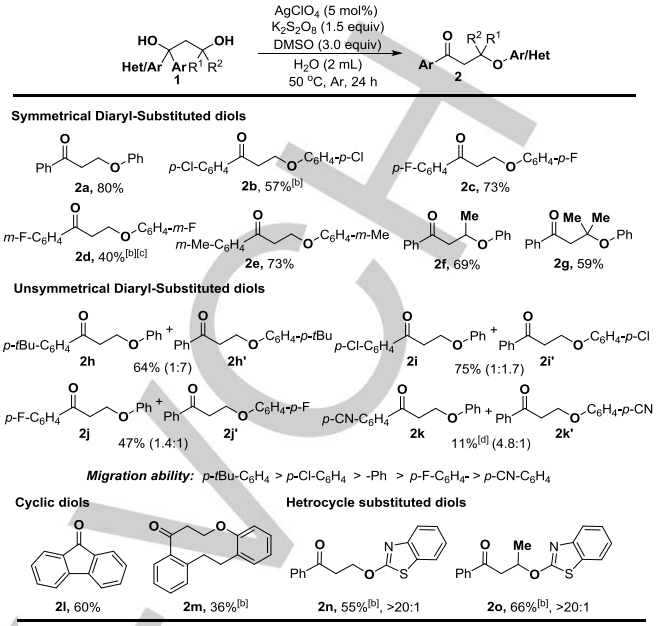
[a] Reaction conditions: **1a** (0.2 mmol), catalyst (x mol%), oxidant (1.5 equiv), additive (3.0 equiv), solvent (2 mL) under Ar at 50 °C for 24h. NMR yields with 1,1,2,2-Tetrachloroethane as standard. [b] 2.0 equiv DMSO was used. [c] The number in the parenthesis is isolated yield.

For proof-of-concept, we chose 1,1-diphenylpropane-1,3-diol (**1a**) as model substrate. Interestingly, when **1a** was treated with $AgNO_3$ catalyst in the presence of $K_2S_2O_8$ oxidant in different solvents, a novel phenyl migration product **2a** via alkoxyl radical induced distal C-C cleavage was obtained with the formation of β scission product **3a**, indicating the unselective activation of two hydroxyls (Table 1, entries 1-3). Of various silver salts, $AgClO_4$ showed the best catalytic efficiency (Entry 4). To improve the regio-selectivity by PCET, we turned to screening a series of lewis bases and found adding DMSO as a reagent can significantly improve the regioselectivity (Entries 5-9). Other lewis bases like pyridine derivatives and sulphones with larger steric hindrance are less effective compared to DMSO (Entries 9-14), indicating the spatial effect can significantly impact the interaction between hydroxyls and selected reagents.

With the optimum conditions in hand, we explored the scope of this reaction. For the symmetrical diaryl-substituted diols, the aryl bearing Cl, F, Me groups were tolerated (**2b**-**e**). Especially, the selective generation of secondary alkoxyl radical and tertiary alkoxyl radical was efficient to afford **2f** and **2g** in good yields. The unsymmetrical diaryl-substituted diols were also tested. **1h** worked well to afford **2h** and **2h'** in totally 64% yield in a ratio of 1:7. The migration ability of 4-chlorophenyl was stronger than phenyl to afford **2i** and **2i'** in 1:1.7 ratio. Furthermore, in F and CN substituted diols, phenyl migration products **2j** and **2k** were the main products. In general, the migration of electron-rich aryl groups is easier than electron-deficient groups to react with the electron deficient O-centered radicals.

We further applied this reaction to cyclic diols. Although the strained diol **1l** was favored to undergo β scission pathway (Scheme 1d) and afforded **2l** in 60% yield, to our delight, 10-membered cyclic ketone **2m** was high selectively obtained by the present protocol. Heteroaryl substituted diols were also investigated and we found the penzothiazolyl is a good migration group, affording **2n** and **2o** in 55% and 66% yields with excellent regioselectivity.

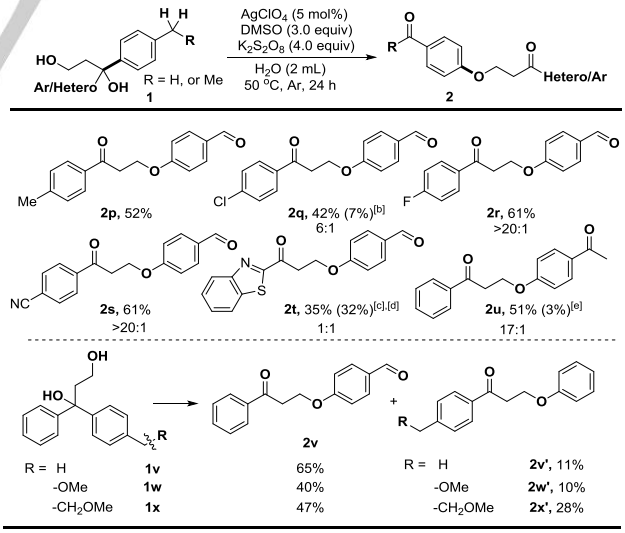
Table 2. Substrate scope of distal (hetero)aryl migration reaction.[a]



[a] Reaction conditions: see entry 9, Table 1. Isolated yields. [b] 0.5 mL CH_3CN was added. [c] Yield based on recovered alcohol. [d] 0.1 mL DMSO was used.

By increasing the loading of $K_2S_2O_8$ to 4.0 equiv, new migration-oxygenation products by a further alkyl substituents oxidation process were detected (Scheme 3). Under these conditions, various benzaldehyde derivatives were obtained in moderate yields (**2p**-**t**). It was noteworthy that we obtained **2r** and **2s** with excellent regioselectivity. The ketone product **2u** can also be isolated in 51% yield. Besides, the diols **1v**-**x** afforded the same oxygenation product **2v** in 47% to 65% yields via the oxidative oxygen element incorporation reaction.

Table 3. Substrate Scope of Migration-Oxygenation Reaction.[a]

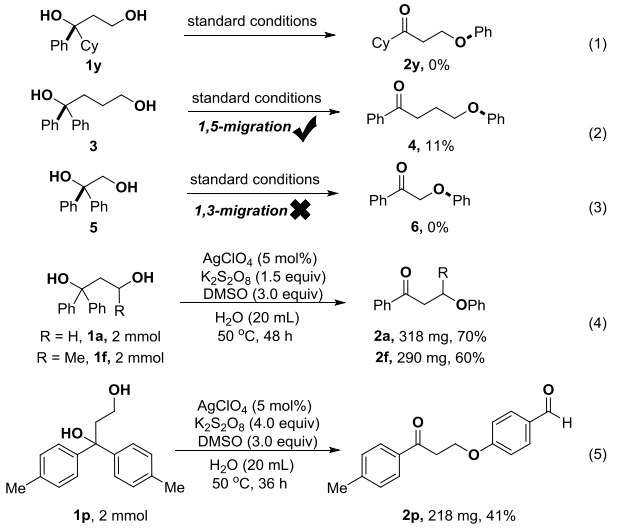


[a] Reaction conditions: see entry 9, Table 1. Isolated yields. [b] Yield of chlorophenyl migration product. [c] Yield of Heteroaryl migration product. [d] 0.5 mL CH_3CN was added. [e] Yield of phenyl migration product.

We further explored the generality of this distal (hetero) aryl migration reaction using aryl alkyl disubstituted diol **1y** as the substrate. Unfortunately, no **2y** was detected (eq 1). We also investigated 1,4-diol **4** under standard conditions and found the 1,5-aryl migration is compatible (eq 2). On the contrary, the 1,3-aryl migration is incompatible because of the strained and unstable four-membered ring transition state (eq 3). Also, we

10.1002/anie.202007187

tested the reaction activity by expanding the scale of several substrates to 2 mmol. As shown in eqs 4-5, **1a**, **1f** and **1p** could transform to the corresponding migration products in moderate to good yields.



In previous reports, the aryl radical cation could be involved in an intramolecular electron transfer leading to the alkoxyl radical,[13a] therefore we tested our catalyst system using alkanols as substrates. As shown in eqs 6-7, alkanols **7** and **10** can react to afford **9** and **11** either by alkoxyl radical induced 1,5-HAT or β-scission process under our conditions. These results support our assumption that the alkoxyl radicals are generated through PCET. Next, we carried out EPR experiments with DMPO as radical scavenger (Figure 1, A). To our delight, we detected the clear RO-DMPO signal at 60 minutes under standard conditions (Figure 1, A1).[17] However, in the absence of $AgClO_4$, the RO-DMPO signal became very weak and the signal of the oxidation product of DMPO, 5,5-dimethyl-2-oxopyrroline-1-oxyl (DMPOX)[18] was detected (Figure 1, A2). Besides, no signal was detected when the reaction conducted without $K_2S_2O_8$. These results suggest $K_2S_2O_8$ is necessary to initiate the alkoxyl radical and silver catalyst greatly increased reaction rate.

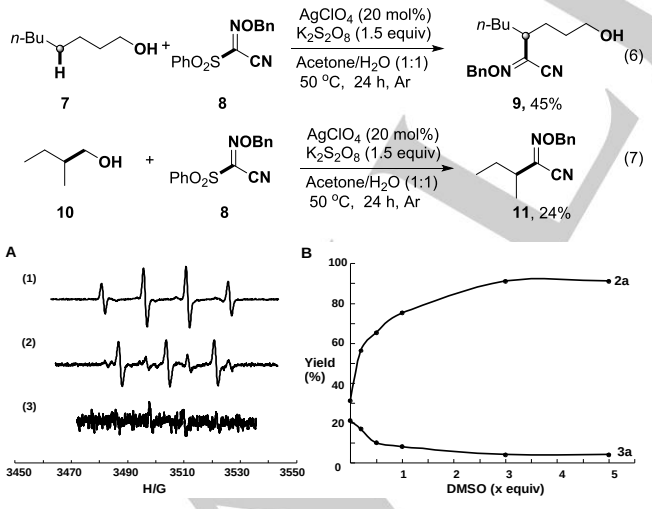
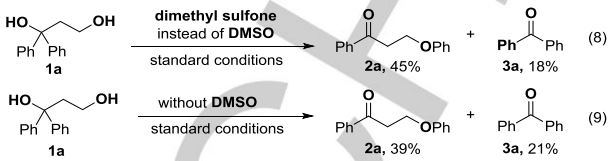
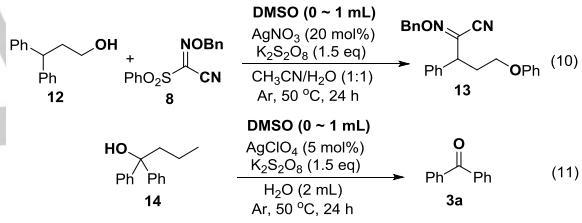


Figure 1. Mechanism studies. (A) Detected EPR signals at 60 minutes. (1) Standard conditions. (2) Without $AgClO_4$. (3) Without $K_2S_2O_8$. (B) DMSO is essential to the regioselectivity.

It is noteworthy that DMSO is essential to the regioselectivity. With the increase of DMSO loading, the regioselectivity improved. (Figure 1, B). DMSO may act as a ligand for the silver catalyst,[19] but the IR experiments (Figures S8-9, SI) indicate it has little influence in our case. We further investigated the selectivity of this reaction in the presence of dimethyl sulfone, as it could be produced by the oxidation of DMSO in this oxidative environment. However, the control experiments show the yields of **2a** and **3a** were similar when dimethyl sulfone was used or not, both regioselectivities were poor (eqs 8, 9). These results further support DMSO as the key additive for the high regioselectivity of this protocol.



Furthermore, we turned to study the interaction between DMSO and the hydroxyls of diols (Figure 2). We had hypothesized that DMSO can selectively form the hydrogen bonding with the hydroxyl. To prove this, we studied the reaction between 3,3-diphenylpropan-1-ol **12** and a radical acceptor **8**, which afforded phenyl migration product **13** in 18% yield via silver catalyzed O-H homolysis process.[15g, 20] Interestingly, the yield of **13** increased with the addition of DMSO, and then decreased when DMSO was added too much. In contrast, when **14** was used, the reaction efficiency was not significantly affected by DMSO. These results indicate that the diaryl substituted tertiary hydroxyl group may not interact with DMSO, probably due to the steric hindrance.



DMSO	0 equiv	0.5 equiv	1.0 equiv	3.0 equiv	5.0 equiv	1 mL
Yield of **13**	18%	45%	45%	39%	34%	14%
Yield of **3a**	23%	25%	25%	18%	15%	3%

Figure 2. The yields of **13** and **3a** with different amount of DMSO.

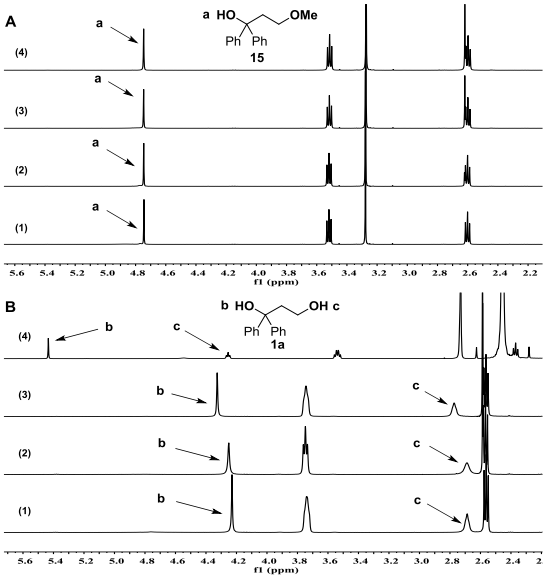


Figure 3. ^{1}H-NMR studies. (A) ^{1}H-NMR analysis of **15** with different amount of DMSO. (1) without DMSO (2) with 1.0 equiv DMSO (3) with 3.0 equiv DMSO (4)

with 5.0 equiv DMSO (B) ^{1}H-NMR analysis of **1a** with different amount of DMSO. (1) without DMSO. (2) with 3.0 equiv DMSO (3) with 5.0 equiv DMSO (4) with 1 mL DMSO.

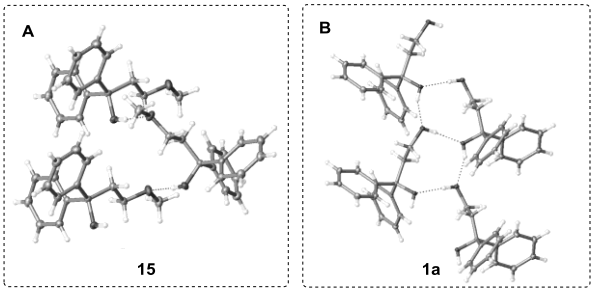
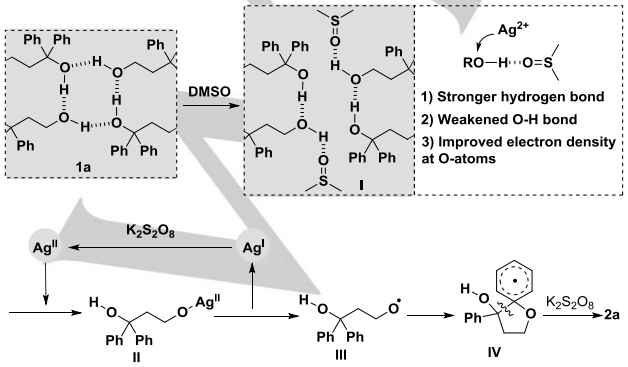


Figure 4. The crystal structure and the hydrogen bonds of **15** and **1a**.

We next conducted ^{1}H-NMR analysis. The results showed the hydrogen signal of the tertiary hydroxyl in **15** is not affected by DMSO (Figure 3, A), probably because the difficulty to break the internal hydrogen bonds between the tertiary hydroxyl and methoxy groups (See the crystal structure of **15** in Figure 4, A). However, the ^{1}H-NMR analysis of **1a** showed that the shifts of both hydroxyl hydrogen signals moved toward the low field with the increase of DMSO loading (Figure 3, B). According to the crystal structure of **1a** (Figure 4, B), we speculate that the less hindered hydrogen bonds between the primary hydroxyl and O atom in the tertiary hydroxyls were destroyed by the addition of DMSO, which caused the hydroxyls signals shift (Figure 3, B). These results indicated that the hydrogen bonds exist between DMSO and the primary hydroxyl.[21] Although it was not completely clear, we believed that the larger steric hindrance prevented the direct interaction between DMSO and the tertiary hydroxyl group.

On the basis of the above experiments and precedent reports,[13, 14, 15g-j] we proposed a plausible mechanism (Scheme 2). The addition of DMSO initially breaks the less hindered hydrogen bonds between the primary hydroxyl and O atoms in the tertiary hydroxyls, and yields stronger new hydrogen bonds. Subsequently, through the PCET effect, the activated Ag(II) catalyst selectively coordinates with the DMSO assisted hydroxyl to afford intermediate **II** which undergoes homolytic cleavage to afford alkoxyl radical **III** and Ag(I). Then, the intramolecular electrophilic radical addition of species **III** occurs giving a spiro intermediate **IV**, which undergoes the relay of oxidation, dealkyl aromatization via C-C cleavage, and deprotonation processes to afford **2a** (Scheme 2). Although the formation of aryl radical cation could interact with alcohols to afford the same inetrmediate **IV** after deprotonation, we didn't detect the nucleophilic addition products by adding benzylamine, TMSCN, or imidazole into our reaction system (Eqs S1-3, SI).[22] These results, combined with the EPR experiments, indicate that the formation of radical cation followed by deprotonation is not the main process in our transformations.



Scheme 2. Proposed mechanism.

In conclusion, we have disclosed a novel and efficient selective radical O-H activation strategy. The alkoxyl radicals were selectively generated from corresponding diols without pre-activation. Mechanistic studies indicate that the common molecule DMSO can selectively form hydrogen bonds with the less-hindered hydroxyls, which facilitates the site-selective alkoxyl radical initiation of alcohols via the combination of spatial effect and PCET process. Meanwhile, we addressed a long-standing problem to realize the distal (hetero)aryl migration from C to O via alkoxyl radical induced distal C-C cleavage. We hope this chemistry could inspire the development of selective X-H activation and controlled radical chemistry.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: Selectivity • Alkoxyl radical • DMSO • C-C cleavage • Silver

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Entry for the Table of Contents

Selective Radical Transformation

*Y. Zhu, Z. Zhang, R. Jin, J. Liu, G. Liu, B. Han, N. Jiao**

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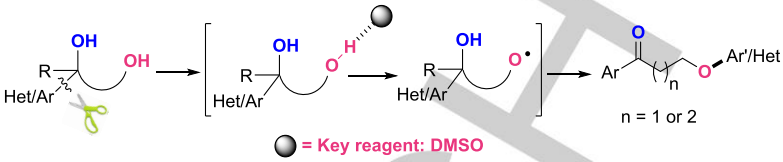
DMSO Enabled Selective Radical O-H Activation of 1,3(4)-Diols



- **New application of common chemical DMSO:** selective alkoxyl radical initiation
- Ag-catalyzed alkoxyl radical process for **distal (hetero)aryl migration from C to O atom**

This work discloses a new radical strategy for selective activation of one hydroxyl in diols, and thereby achieves the novel alkoxyl radical induced distal (hetero)aryl migration reactions through C-C cleavage.