A Journal of the Gesellschaft Deutscher Chemiker

Angewandte International Edition GDCh Chemie

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Accepted Article

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201711221
Angew. Chem. 10.1002/ange.201711221

Link to VoR: http://dx.doi.org/10.1002/anie.201711221
http://dx.doi.org/10.1002/ange.201711221

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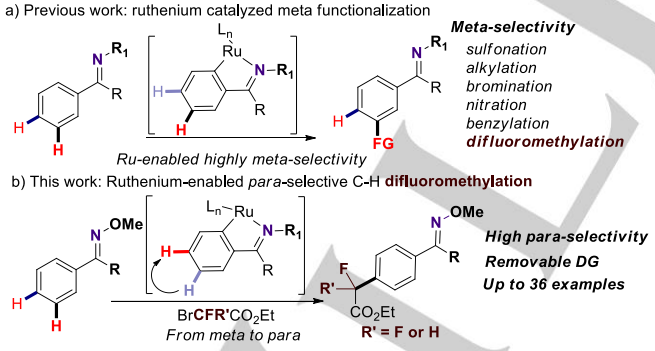
Ruthenium(II)-catalyzed C-H Difluoromethylation of Ketoxime: Tuning the Regioselectivity from *meta* to *para* Position

Chunchen Yuan,[+] Lei Zhu,[+] Runsheng Zeng, Yu Lan* and Yingsheng Zhao*

Abstract: A highly *para*-selective C_{Ar}-H difluoromethylation of ketoxime ether using a ruthenium catalyst has been developed. A wide variety of ketoxime ethers are compatible in the reaction, leading to the corresponding *para*-selective difluorometylated products in moderate to good yield. A mechanistic study clearly shows that chelation-assisted cycloruthenation is the key factor in achieving the *para*-selective difluoromethylation of ketoxime ethers. The density functional theory (DFT) method was used to gain a theoretical understanding of the *para*-selectivity.

Recently, *para*-selective C_{Ar}-H functionalization has undergone groundbreaking development.[1-6] For example, electronic-controlled,[1] bulky substituted arenes[2] or arenes with a D-shaped directing group[3] can be selectively functionalized at the *para*-position. A major breakthrough was realized by of Zhang[4], Nakao[5] and Ye[6] groups, respectively, who developed a *para*-selective alkylation, arylation and borylation of *mono*-substituted arenes, including alkyl benzenes, alkoxylbenzenes, halobenzenes, benzamides and aromatic ketones. Despite these important accomplishments, these methodologies usually suffer from a narrow substrate scope and poor regioselectivity, which greatly hinder their application in pharmaceutical and natural product synthesis. Herein, we report the development of a ruthenium(II)-induced reaction of ketoxime ethers with bromodifluoroacetate to provide difluoromethylated ketoxime ether derivatives with high *para*-selectivity (Scheme 1, b).

Scheme 1. The ruthenium-enabled difluoromethylation reaction.



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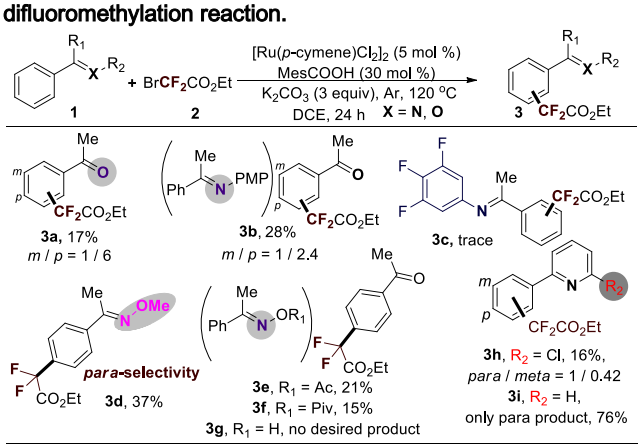
Because fluorine-containing compounds, especially those containing difluoromethylene (CF_2) groups, have great application in agrochemicals, pharmaceuticals, and life science, we set out to expand the difluoromethylation reactions to the acetophenone-containing structural units. Inspired by the previously reported ruthenium complex enabled *meta*-selective C-H functionalization reactions (Scheme 1a),[7-11] we initially treated PMP protected acetophenone imine or acetophenone with bromodifluoroacetate in the presence of a ruthenium catalyst and potassium carbonate. A mixture of the *meta*- and *para*-difluoromethylated ketone products was obtained (Scheme 2, **3a**-**b**). When substrate **1c** was subjected to the standard reaction conditions, only a trace amount of the desired difluoromethyalted product was obtained. To our great delight, when phenyl ketoxime ether was used, the *para*-selective difluoromethylated product **3d** was isolated in 37% yield, along with recovered 55% starting material. When substrates **1e**, **1f** and **1g** were further tested, the *para*-difluoromethylated ketone products were observed. It is highly likely that an ester will not be stable under the reaction conditions and will lead to the decomposed ketone product. To get insight into these results, substrates bearing a chloride substituent on the pyridine were tested. As expected, a mixture of *meta*- and *para*-difluoromethylated products were obtained (**3h**, For more details see SI.), which was different from the ruthenium enabled meta selective C-H difluoromethylation reaction (**3i**). The clear reason for this *para*-selectivity result was unclear, however, we could speculate that the weak coordination ability of the oxime may greatly reduce the *para*-directing ability of the Ru-C sigma bond, leading to the reaction center changing to the position meta to the Ru-C bond.

Scheme 2. Preliminary study of the Ru(II)-catalyzed difluoromethylation reaction.



Further studies showed that a satisfactory yield of **3d** was achieved when Na_2CO_3 was used as the base and N-Ac-L-Iso as the ligand (See SI, Scheme 2S). With the optimized reaction conditions in hand, a wide range of ketone oximes were treated with **2** to examine the functional group tolerance of this ruthenium-enabled *para*-selective C_{Ar}-H difluoromethylation reaction.

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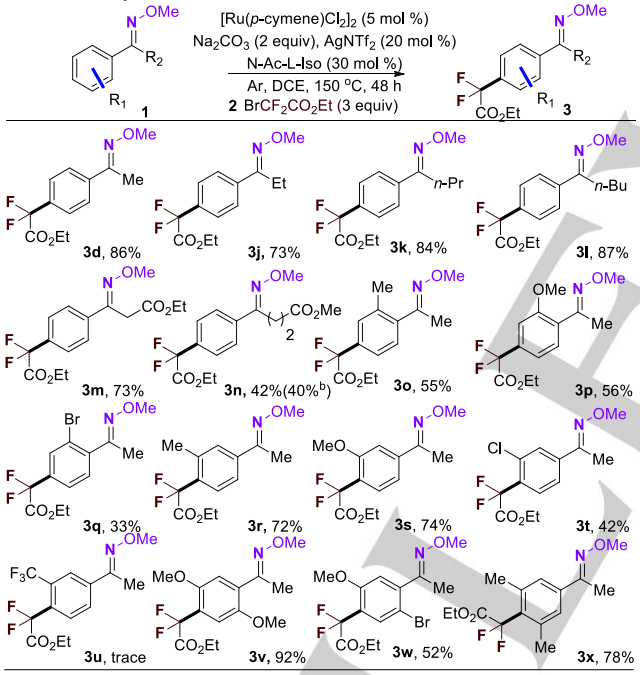
Oxime-protected phenones were all well tolerated, providing the *para*-difluoromethylated products in moderate to good yield (**3d, j-n**). Substrate **1n** was decomposed to the corresponding ketone, resulting in a lower yield of the difluoromethylated product **3n**. *Ortho*-substituted acetophenone oxime derivatives gave the corresponding *para*-difluoromethylated products in moderate to good yield (**3o–q**). To our great delight, *meta*-substituted acetophenone oxime derivatives provided their corresponding difluoromethylated products at the sterically hindered *para*-position in moderate to good yield (**3r–t**). These results are different to the ruthenium-catalyzed *meta*-selective alkylation and difluoromethylation reactions where the *meta*-substituted substrates are less reactive than their *ortho* or *para*-substituted analogues. It is worth mentioning that *ortho*- or *meta*-methoxy-substituted acetophenone oxime derivatives only generated the *para*-difluoromethylated products (**3p, s**) while the other difluoromethylated regioisomer was not observed. However, *meta*-trifluoro-substituted acetophenone was unreactive with only trace amounts of the difluoromethylated product observed in the reaction (**3u**). Disubstituted acetophenone oxime derivatives all performed well in the reaction, affording the corresponding products in good yield (**3v-x**).

Table 1. Scope of the ketoxime ethers.[a]

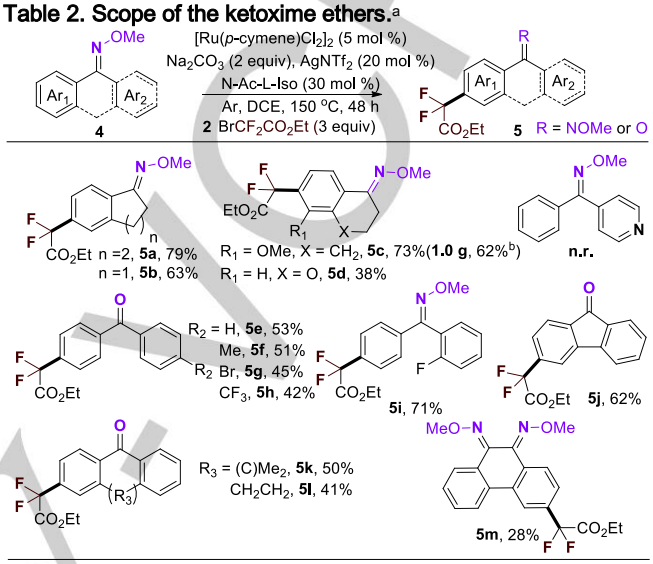


[a] **1** (0.20 mmol, 1.0 equiv) was used. Isolated yield after chromatography. [b] Recovered 4-oxo-4-phenylbutanoate.

We next surveyed the scope and limitation of the aromatic ketones using the oxime as the coordination center. Benzoquinone and diphenylketone all proceed smoothly under the standard reaction conditions to provide the *para*-difluoromethylated products in moderate to good yields (**5a-m**). However, *oxime*-protected 4-benzoylpyridine was totally unreactive, with only starting material recovered. It is probable that the pyridine can directly coordinate with the ruthenium catalyst, shutting down the reaction completely.

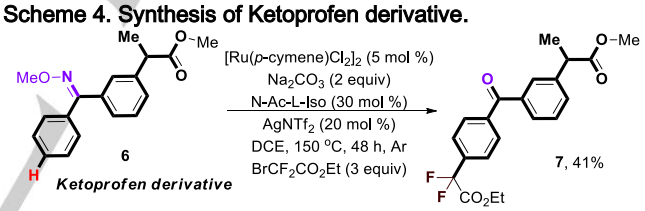
The synthetic importance of this newly developed *para*-selective difluoromethylation reaction can be demonstrated by the synthesis of a fluorine-containing ketoprofen derivative[12]. Ketoprofen was first protected as the oxime and then subjected to the standard reaction conditions. Gratifyingly, the *para*-selective difluoromethylation selective happened at the less hindered phenyl ring, providing the difluoromethylated ketoprofen product **7** in 41% yield, along with deprotected ketoprofen in 35% yield (Scheme 4). Moreover, *para*-C-H monofluoromethylation was also compatible under otherwise identical reaction conditions (Scheme 5), highlighting the synthetic utility of this new protocol.

Table 2. Scope of the ketoxime ethers.[a]

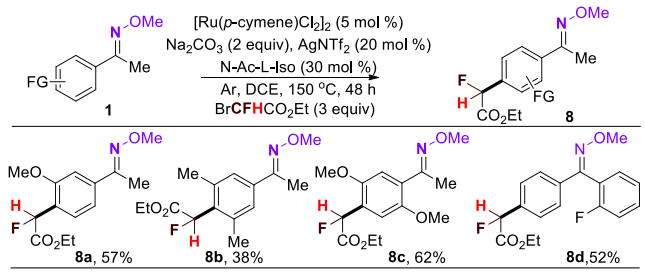


[a] **4** (0.20 mmol, 1.0 equiv) was used. Isolated yield after chromatography. [b] Gram scale reaction.

Scheme 4. Synthesis of Ketoprofen derivative.



Scheme 5. Ru-enabled *para*-C-H monofluoromethylation.



To further understand the pathway of this ruthenium-enabled *para*-selective difluoromethylation reaction, several reactions were performed (Scheme 6). For example, when oxime protected 2, 6-dimethyl-substituted acetophenone was subjected to the standard reaction conditions, only the starting material **1y** was recovered (Scheme 6a). This result may indicate that the initial *ortho*-cycloruthenation is a key intermediate in achieving *para*-C-H functionalization. Oxime protected **1z** was further investigated under the standard reaction condition. The result clearly reveals the *para*-difluoromethylation reaction selectively occurred on the benzoyl group rather than the non-activated phenyl ring. This shows that the arylruthmuim complex[13] was more inclined to react with the difluoromethyl radical than the arene ring itself (Scheme

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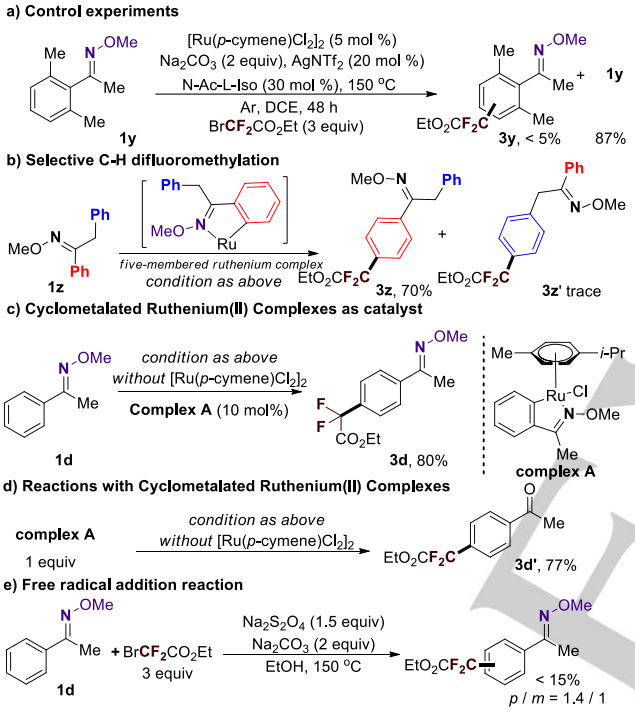
6b). A variety of known-ruthenium(II) complexes were further prepared according to Jeganmohan's procedure[14]. Complex **A** can be used as the catalyst instead of $[Ru(p\text{-cymene})Cl_2]_2$, affording the difluoromethylated product **3a** in 80% yield (Scheme 6c). Next, complex **A** was directly treated with bromodifluoroacetate **2** and difluoromethylated acetophenone was obtained with high *para*-selectivity (Scheme 6 d). In contrast, when substrate **1a** was subjected to the reaction conditions in which a difluoromethyl free radical can be generated, a mixture of *para*- and *meta*-difluoromethylated products was obtained in less than 15% yield[15] (Scheme 6e). Based on these experimental results, we can speculate that reaction intermediates bearing Ru-C bonds are responsible for the *para*-C-H functionalization reaction.

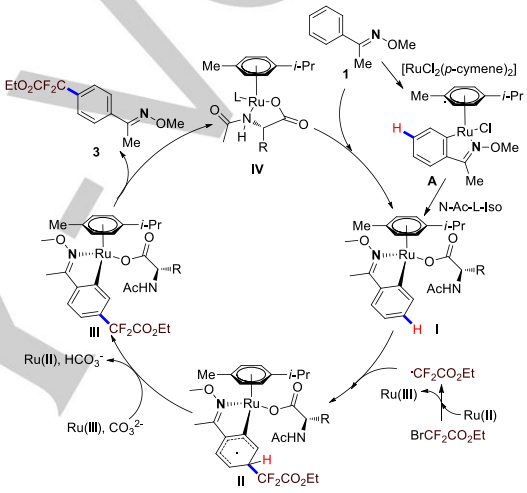
Scheme 6. Mechanistic studies.



A series of deuterated experiments were performed to gain insight into the reaction pathway (See SI, Scheme 3s). An isotopic labeling experiment suggested that the *ortho*-C-H cycloruthenation step was reversible, whereas the *para*-C-H activation was not. A kinetic isotope effect of 1.74 was obtained, implying that the *ortho*-C_{Ar}-H activation step was the kinetically relevant step. This result also explained why the amino acid type ligand, which is usually applied in accelerating C-H activation, was needed in the reaction. No product **3a** was obtained in the reaction mixture when a radical scavenger TEMPO was employed in the reaction which was similar to that disclosed by Ackermann.[10a] This result suggests a free radical pathway was involved in this *para*-selective difluoromethylation reaction.

To understand the regioselectivity for the ruthenium catalyzed C_{Ar}-H difluoromethylation reaction, the density functional theory (DFT) method was employed to investigate the mechanism and regioselectivity of this reaction.[16] Based on the aforementioned experimental observations, aryl ruthenium(II) complex **I** was verified to be an active intermediate. Thus, we focused on the subsequent radical addition step, which is considered to be the step that determines the regioselectivity of this transformation. As depicted in Figure 1, two possible transition states **TS-*para*** and **TS-*meta*** were located by the DFT calculations, which lead to the formation of the corresponding *para*- and *meta*-difluoromethylated products, respectively. Meanwhile, the intermolecular radical addition of $\cdot CF_2CO_2Et$ to the C3 position of intermediate **I** via transition state **TS-*para*** leads to the generation of the *para*-difluoromethylated product with a free energy barrier of 15.2 kcal/mol. Alternatively, radical addition to the C4 position of intermediate **I** via transition state **TS-*meta*** could afford the *meta*-substituted isomer. The computational results showed that the relative free energy of transition state **TS-*meta*** was 1.7 kcal/mol higher than that of transition state **TS-*para***. This energetic discrepancy indicates that the *para*-difluoromethylated product will be observed as the major product formed in this system, which is consistent with the experimental results.

Scheme 7. Plausible catalytic cycle.



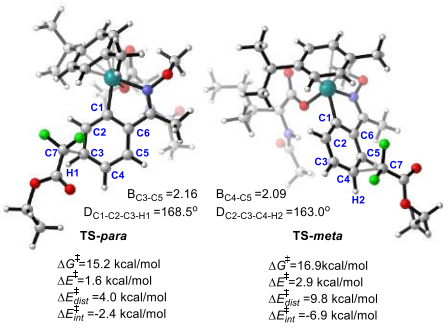


Figure 1. Energetics and geometry information of transition states **TS-*para*** and **TS-*meta*** for the radical addition step. The bond lengths are given in angstroms.

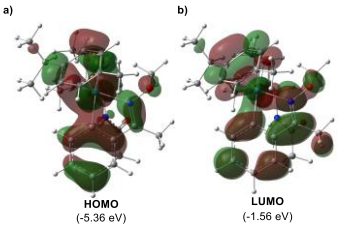


Figure 2. Calculated frontier molecular orbital (FMO) diagram for intermediate **I**.

In order to understand the intrinsic preference for the regioselectivity in this difluoromethylation reaction, we initially considered the electronic effect of the benzene ring moiety in

intermediate **I**. We calculated the electrostatic potential (ESP) of intermediate **I** (Figure S2). The results indicate the electronic density distribution at the C3 and C4 position is nearly identical, which proved that the ·CF_2CO_2Et radical addition position was independent of the electron density in this case. Furthermore, we calculated the frontier molecular orbitals (FMOs) of intermediate **I** (Figure 2b). The lowest unoccupied molecular orbital (LUMO) of intermediate **I** mainly locates at the C1, C3 and C5 positions in the reacting phenyl moiety. On the contrary, the corresponding HOMO majorly appears at C2, C4 and C6 carbons. The calculated HOMO and LUMO energy levels of intermediate **I** are -5.36 and -1.56 eV, respectively, while the SOMO energy level of ·CF_2CO_2Et radical is determined to be -2.91 eV. The computational energy level of molecular orbitals clearly showed that the energy level of·CF_2CO_2Et radical SOMO is closed to that of the LUMO of intermediate **I**, which suggests that SOMO/LUMO interaction would be more predominant than SOMO/HOMO interaction in this case. Therefore, the distribution of the LUMO of intermediate **I** revealed that C3 position should exhibit enhanced reactivity for the radical addition reaction. Moreover, a distortion/interaction model was also employed to clarify the origin of the regioselectivity.[17] For each reaction, the transition state was separated into two distorted fragments followed by singlepoint energy calculations on each fragment. The difference in energy between the distorted fragments and the optimized groundstate geometries was the distortion energy ($\Delta E_{dist}^{\ddagger}$). The TS interaction energy ($\Delta E_{int}^{\ddagger}$) was the difference between the activation energy and the distortion energy ($\Delta E_{int}^{\ddagger} = \Delta E^{\ddagger} - \Delta E_{dist}^{\ddagger}$). The results in Figure 1 show that the distortion energy controlled the reactivity because of the same trend in the activation free energy. The calculated geometry information revealed a larger distortion of reacting carbon in **TS-*meta*** ($D_{C2\text{-}C3\text{-}C4\text{-}H2}$, from 180° to 163.0°) compared with **TS-*para*** ($D_{C1\text{-}C2\text{-}C3\text{-}H1}$, from 180° to 168.5°). It means, when the radical addition takes place at C4 position, the phenyl moiety should distorted further to capture the radical, which leads to a late transition state. This is also in accordance the length of forming C-C bond: The C4-C7 bond in transition state **TS-*meta*** is 2.09 Å, which is 0.07 Å shorter than the correspond value (C3-C7) in transition state **TS-*para***. All these results lead to the higher activation free energy of transition state **TS-*meta***, indicating the subdued reactivity of C4 position. Based on our experimental results and a previous report[7l-n], a plausible reaction pathway was proposed. Complex **I** will be formed via the combination of $[Ru(p\text{-cymene})Cl_2]_2$ and substrate **1** in the presence of Na_2CO_3 and N-Ac-L-Iso. A free radical of ·CF_2CO_2Et derived from 2-bromo-2,2-difluoroacetate was formed via a single-electron-transfer process with the ruthenium catalyst. The ·CF_2CO_2Et radical may be trapped by complex **I**, followed by oxidation, aromatization and generation of the product (Scheme 7).

In conclusion, we have developed a ruthenium-enabled *para*-selective C-H difluoromethylation reaction of ketoxime ethers. The site selectivity can be altered from the *meta*- to the *para*-position by modifying the coupling partners, which gives an insight into the ruthenium-enabled remote C-H activation process. Our mechanistic study clearly implies that chelation-assisted cycloruthenation is the key factor in achieving the *para*-selective difluoromethylation of ketoxime ethers. The DFT calculation results reveal that the *para*-selectivity was controlled by the differences in the frontier molecular orbital contributions. In addition, distortion/interaction analysis showed that the distortion energy differences between **TS-*para*** and **TS-*meta*** result in the *para*-selectivity.

Acknowledgements

We gratefully acknowledge financial support from the Natural Science Foundation of China (NO. 21772139, 21572149, 21372266, and 21772020), Young National Natural Science Foundation of China (NO. 21402133, 21403148) and the Prospective Study Program of Jiangsu (BY2015039-08). The PAPD Project are also gratefully acknowledged.

Keywords: ketoxime ethers • difluoromethylated • ruthenium • *para*-selectivity • DFT calculation

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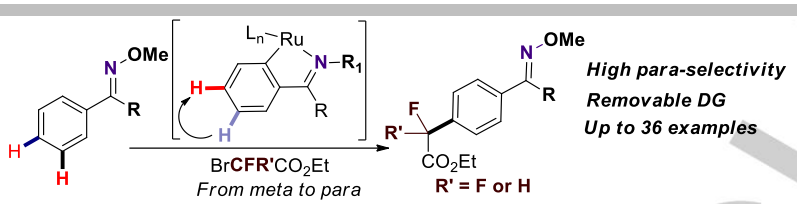

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