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C–H Activation

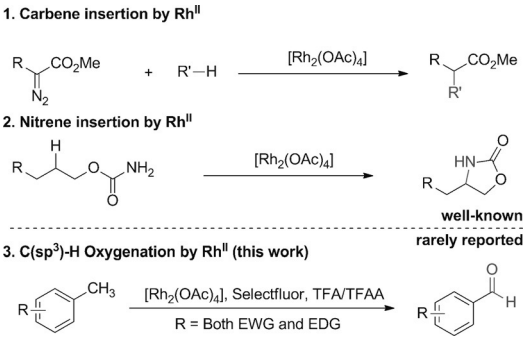
Development of a Rhodium(II)-Catalyzed Chemoselective C(sp^3)–H Oxygenation

Yun Lin,[a] Lei Zhu,[b] Yu Lan,*[b] and Yu Rao*[a]

Abstract: We report the first example of Rh^{II}-catalyzed chemoselective double C(sp^3)–H oxygenation, which can directly transform various toluene derivatives into highly valuable aromatic aldehydes with great chemoselectivity and practicality. The critical combination of catalyst $Rh(OAc)_2$, oxidant Selectfluor, and solvents of TFA/TFAA promises the successful delivery of the oxidation with satisfactory yields. A possible mechanism involving a unique carbene–Rh complex is proposed, and has been supported by both experiments and theoretical calculations.

Introduction

Rhodium(II) catalysts, such as $[Rh_2(OAc)_4]$, have been well studied in rhodium–carbene[1] and rhodium–nitrene[2] chemistry (Scheme 1). The use of $[Rh_2(OAc)_4]$ has also been reported in alkylation annulation reaction,[3] Claisen rearragement,[4] epoxide[5] and aziridine[2n,6] synthesis, and so forth. More recently, $[Rh_2(OAc)_4]$ was employed in sp^2 C–H arylation,[7] sp^2 C–H hydroxylation,[8] and sp^2 C–H vinylation.[9]. In comparison to the above achievements and advances, much less progress has been made in the field of Rh^{II}-catalyzed sp^3 C–H oxygenation.[10] Compared with Ru^{II} and Pd^{II} catalysts, $[Rh_2(OAc)_4]$ is less coordinating with the carbonyl oxygen atom of ketone group. In addition, Rh^{II} is stronger than Ru^{II} and Pd^{II} in terms of the potential oxidizing ability.[10d,11] We envisioned that certain fine-tuned oxidative conditions with the proper combination of Rh^{II} catalyst and oxidants may direct a sp^3 C–H oxygenation instead of a sp^2 C–H oxygenation to give aldyhyde derivatives. Over the past decade, transition-metal-catalyzed direct functionalization of benzylic C(sp^3)–H bonds has gradually emerged as a useful tool for the preparation of valuable chemicals.[2f,12] Among those successful discoveries of benzylic C(sp^3)–H bond activation, the majority of studies were focused on palladium- or copper-catalyzed C–H arylation,[13] halogenation,[14] acetoxylation,[15] or amidation.[13c,16] In contrast, other metals, like Ru and Rh, are rarely reported in this type of benzylic C–H transformation. To the best of our knowledge, Rh^{II}-catalyzed C(sp^3)–H oxygenation of benzylic positions has not been achieved yet. We are particularly interested in the possible new catalytic activity of rhodium catalysts and the substrate scope in the C(sp^3)–H oxygenation reaction. Moreover, expanding the catalyst and reaction scope will provide more choice and better control for its synthetic applications. Herein, we report the first example of Rh^{II}-catalyzed chemoselective double C(sp^3)–H oxygenation with Selectfluor as the key oxidant, which can readily transform a broad range of substrates into valuble aromatic aldehydes (Scheme 1).



Scheme 1. Rh^{II} catalysis for C(sp^3)–H oxygenation

Results and Disscusion

To test our hypothesis, a model study was initiated with di-*p*-tolylmethanone **1**. At the beginning of our investigations, a variety of oxidants, such as $PhI(OAc)_2$, $PhI(TFA)_2$, $K_2S_2O_8$ and $Na_2S_2O_8$, and so forth, were examined in the presence of $Rh_2(OAc)_4$ in trifluoroacetic acid/trifluoroacetic anhydride (TFA/TFAA; Table 1). Among them, only the condition using $K_2S_2O_8$ can provide the corresponding aldehyde **2** in a trace amount (Table 1, entry 1). We then turned our attention to electrophilic fluorinating reagents, including *N*-fluorobenzenesulfonimide (NFSI), *N*-fluoropyridinium triflate (NFPy) Selectfluor, and so

[a] *Y. Lin, Prof. Dr. Y. Rao*
MOE Key Laboratory of Protein Sciences
Department of Pharmacology and Pharmaceutical Sciences
School of Medicine and School of Life Sciences
Tsinghua University, Beijing, 100084 (P. R. China)
E-mail: yrao@mail.tsinghua.edu.cn

[b] *L. Zhu, Prof. Dr. Y. Lan*
School of Chemistry and Chemical Engineering
Chongqing University, Chongqing, 400030 (P. R. China)
E-mail: lanyu@cqu.edu.cn

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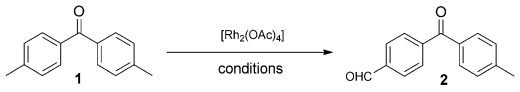
Table 1. Optimization of the reaction conditions.

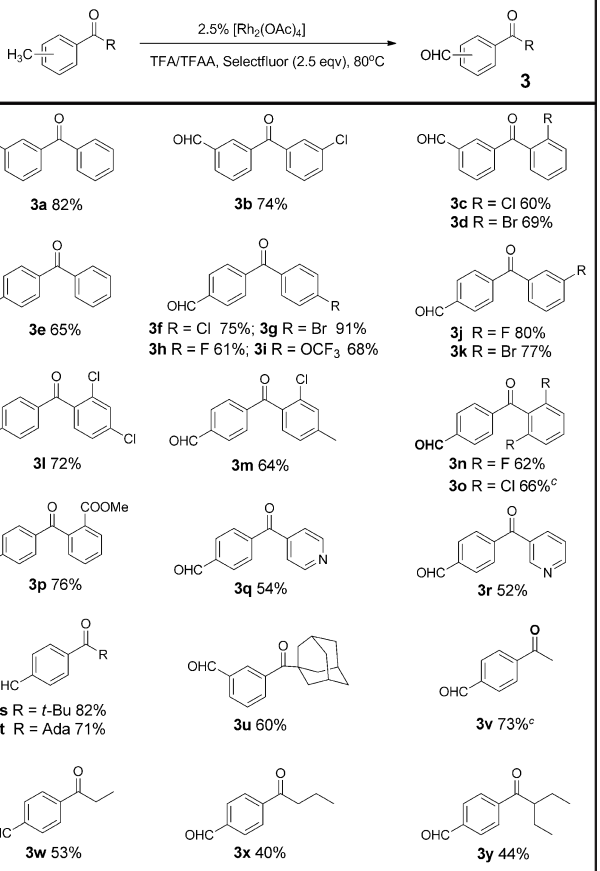


1 2

	Oxidant [2.5 equiv]	Conditions				C.R.[a] [%]
1	$K_2S_2O_8$	$Rh(OAc)_2$	TFA/TFAA(9:1)	80 °C	7 h	trace
2	$Na_2S_2O_8$	$Rh(OAc)_2$	TFA/TFAA(9:1)	80 °C	7 h	NR
3	$PhI(OAc)_2$	$Rh(OAc)_2$	TFA/TFAA(9:1)	80 °C	7 h	5%
4	NFPy[b]	$Rh(OAc)_2$	TFA/TFAA(9:1)	80 °C	7 h	NR
5	2,4,6-NFPy[c]	$Rh(OAc)_2$	TFA/TFAA(9:1)	80 °C	7 h	NR
6	NFSI	$Rh(OAc)_2$	TFA/TFAA(9:1)	80 °C	7 h	NR
7	Selectfluor	$Rh(OAc)_2$	TFA/TFAA(6:4)	80 °C	7 h	23%
8	Selectfluor	$Rh(OAc)_2$	TFA/TFAA(8:2)	80 °C	7 h	54%
9	Selectfluor	$Rh(OAc)_2$	TFA/TFAA(9:1)	80 °C	7 h	71%
10	Selectfluor	$Rh(OTFA)_2$	TFA/TFAA(9:1)	80 °C	5 h	80%
11	Selectfluor	$Rh(OAc)_2$	$AcOH/Ac_2O$(9:1)	80 °C	7 h	NR
12	Selectfluor	$Rh(OAc)_2$	TFA/TFAA(2:8)	80 °C	7 h	trace
13	Selectfluor	$Rh(OAc)_2$	TFA/TFAA(4:6)	80 °C	7 h	trace
14	Selectfluor	No Metal	TFA/TFAA(9:1)	80 °C	7 h	NR
15	PCC[d]	MeCN	reflux		3 h	NR
16	MnO_2	$AcOH/Ac_2O$(1:1)	H_2SO_4	0–80 °C	7 h	NR

[a] C.R. = conversion ratio; NR = No reaction. [b] NFPy = *N*-Fluoropyridinium triflate. [c] *N*-Fluoro-2,4,6-trimethylpyridinium triflate. [d] Pyridinium chlorochromate.

Table 2. $C(sp^3)$–H Oxygenation of benzoylated toluenes.



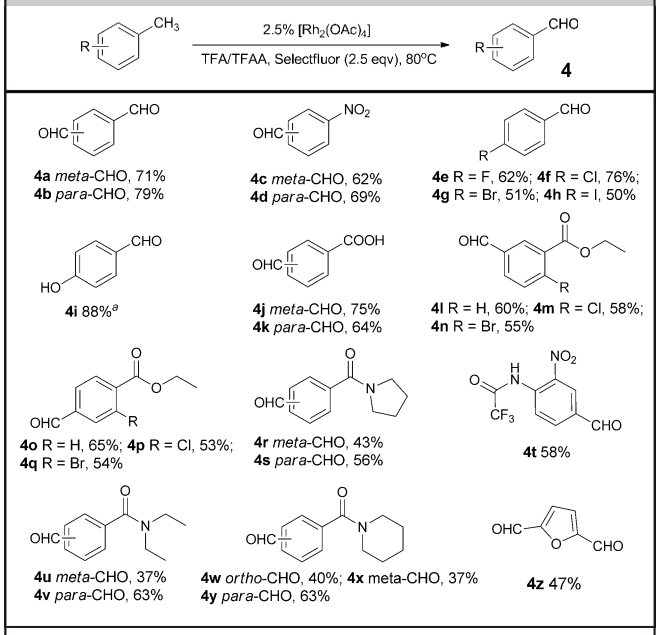
[a] Isolated yield. [b] *t*Bu: *tert*-butyl; Ada: 1-adamantyl. [c] Used $Rh(OTFA)_2$ instead of $Rh(OAc)_2$.

forth. To our delight, aldehyde **2** was obtained in 23% yield with Selectfluor (Table 1, entry 7). The following investigation revealed that a proper combination of temperature, ratio of TFA/TFAA, and oxidant stoichiometry could significantly affect the reaction yield. For instance, we found that the elevated temperature (at 100 °C) and 2.5 equivalents of the oxidant can provide **2** in 71% yield (Table 1, entry 9). Using $Rh(OTFA)_2$ can further improve the yield up to 80% (Table 1, entry 10). A variety of additives, including inorganic salts and ligands, were also examined, but no apparent effect was observed. A control reaction showed that, no reaction occurred in the absence of the Rh^{II} catalyst (Table 1, entry 14). Conventional oxidants, such as MnO_2 and PCC, were also unsuccessful (Table 1, entries 15 and 16). In general, 2.5 mol% of $[Rh_2(OAc)_4]$ was sufficient to catalyze the reaction, which could typically proceed to completion within 7 h with 2.5 equivalents of Selectfluor at 80 °C.

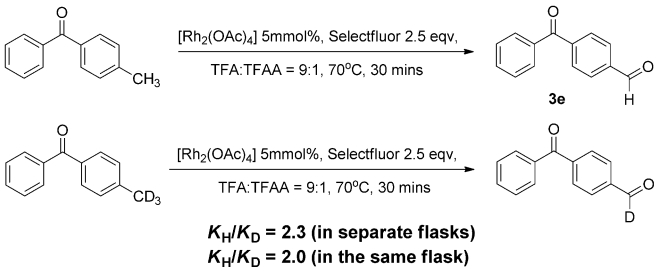
With the optimal condition in hand, we started to examine the scope for this transformation. As demonstrated in (Table 2), a broad range of benzoylated toluenes were readily converted to benzaldehyde products (**3a**–**3y**) in moderate to excellent yields. Various benzoyl groups, as well as different funcational groups (such as ester, halides, alkyl, trifluoromethoxyl, and heterocycle, etc.) were well tolerated. Both *meta*- (**3a**–**3d** and **3u**) and *para*-substituted aromatic aldehydes (like **3e**–**3i** and **3s**, etc.) can be prepared from the corresponding toluene substrates. It should be emphasized that some halogen-substituted aldehydes, such as **3c, 3f, 3g, 3l**, and **3o**, can be further modified to provide a wide variety of valuable derivatives through C–C, C–N, C–O cross-coupling reactions. For a diaryl ketone substrate containing two methyl groups, the electron-rich methyl was selectively oxidized (**3m**). Moreover, pyridyl groups were also found to be compatible in this reaction (**3q, 3r**). Delightfully, when substrates with easily oxidizable α-protons were attempted, the desired products (**3v–3y**) were obtained in satisfactory yields with remarkable chemoselectivity. These type of aromatic aldehydes are either difficult to access or need tedious steps to prepare through conventional methods.

Subsequently, the optimal condition was employed in the oxidation of other substrates. As shown in (Table 3), we were pleased to find that a wide range of different molecules can be successfully transformed to the corresponding benzaldehyde products in moderate to good yields. Various functional groups were found to be compatible with the reaction conditions. For instance, toluene derivatives containing nitro and halide groups can be efficiently converted to aldehydes **4c**–**4h**. Besides that, desired products can also be prepared with substrates including benzoates (**4l**–**4q**), benzamides (**4r, 4s, 4u**–**4y**), and acetanilides (**4t**). Interestingly, free aldehyde (**4a, 4b**), hydroxyl (**4i**), and carboxylic acid (**4j, 4k**) groups were tolerated in this reaction without the need of special protection. To our delight, the heterocycle 5-methylfuran-2-carbaldehyde can be oxidized as well to provide a symmetric molecule **4z** with two aldehyde groups.

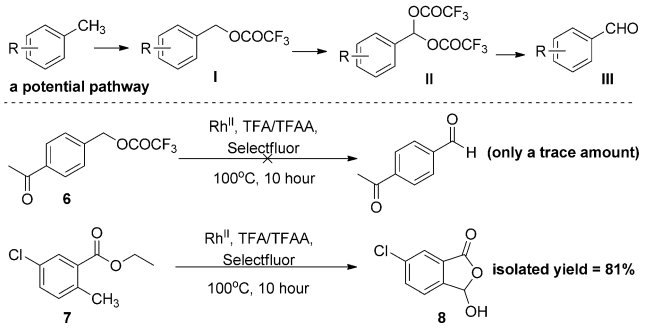
Table 3. Benzoates, benzamides, benzoic acids, toluenes, and others as substrates.



[a] $K_2HPO_43H_2O$ (0.2 equiv).

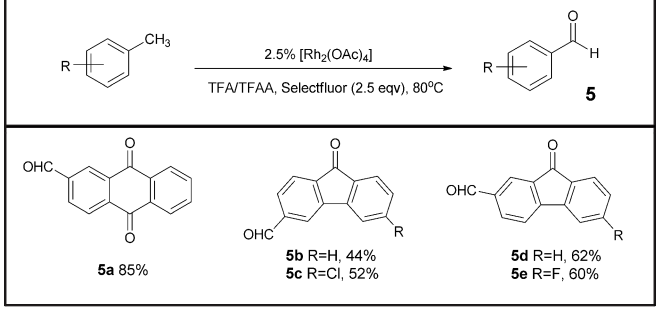


Scheme 2. KIE studies



Scheme 3. Investigation of the mechanistic pathway

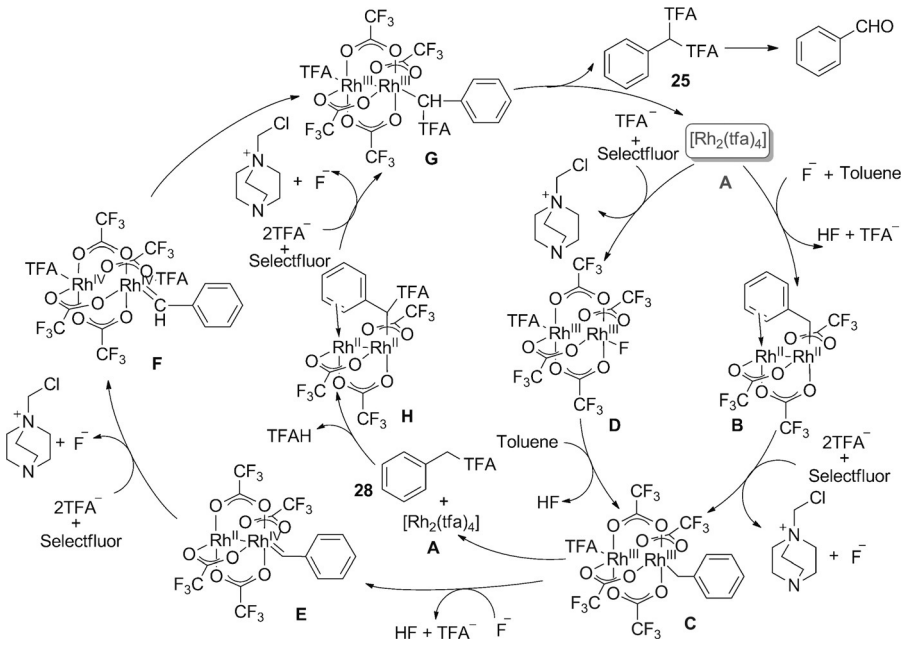
Table 4. 9-Fluorenones and anthraquinone as substrates.



To further demonstrate the usefulness and efficiency of this new reaction, 9-fluorenones and anthraquinones were chosen as the substrates. As shown in (Table 4), 2-methylanthracene-9,10-dione was readily converted to aldehyde **5a** in 85% yield. Gratifyingly, both 2-methyl-9*H*-fluoren-9-one and 3-methyl-9*H*-fluoren-9-one derivatives can also be transformed to the corresponding aldehydes (**5b–5e**). To the best of our knowledge, this represents the first example of aldehyde functional groups being directly installed on molecules like 9-fluorenones and anthraquinones by means of Rh^{II}-catalyzed C(sp^3)–H oxygenation. It is important to note that this late-stage C(sp^3)–H oxygenation reaction can provide a unique and convenient approach to aromatic aldehydes, which will serve as highly valuable synthetic intermediates.

Investigations were performed to gain some insight of the reaction mechanism, which is shown in Scheme 2. Consistant and significant kinetic isotopic effect (KIE) values were observed from both separate ($k_H/k_D = 2.30$) and mixed ($k_H/k_D = 2.00$) isotope effect studies, which indicated that the C–H bond cleavage step might be involved in the rate-limiting step of this transformation. As shown in Scheme 3, a potential pathway might involve the formation of intermediate **I**, which undergoes a second C–H oxidation to afford **II**. After aqueous workup, aldehyde **III** can be obtained. To prove this pathway, benzyl 2,2,2-trifluoroacetate **6** was prepared and subjected to optimal reaction conditions. However, to our surprise, only a trace amount of desired aldehyde products was observed. The above result strongly implied that the oxidation procedure would not go through intermediate **I**. When compound **7** was used as the substrate for the reaction, a five-membered benzolactone **8** was recovered as the product. This experiment suggested that the reaction intermediate can be trapped by the carbonyl oxygen atom of the ester functional group.

To further investigate the mechanism, a computational study was conducted. As shown in Scheme 4, some plausible pathways were taken into account during our computational modeling for this rhodium-catalyzed oxidation reaction of toluene. All these pathways begin with dimeric $[Rh_2(tfa)_4]$ **A**, which can be oxidized by Selectfluor to form dirhodium(III) complex **D**. The subsequent deprotonation of toluene gives dirhodium(III) complex **C**,[17] which is a common intermediate for the following pathways. Alternatively, benzylic deprotonation could take place first from complex **A** directly to generate dirhodium(III) complex **B**, which can then be oxidized to complex **C**. After the formation of complex **C**, a second benzylic deprotonation would lead to the formation of the carbene–Rh^{IV} species **E**. Subsequent oxidation may give dirhodium(IV) complex **F**, and the following carbene insertion into the Rh–O



Scheme 4. A Plausible mechanism

bond would generate Rh^{III} dimer **G**. The subsequent reductive elimination of benzylic carbon and one of the paddle-wheel TFAs on complex **G** would generate acetal ester **25** and the active catalyst $[Rh_2(tfa)_4]$ **A**. The final product benzaldehyde can be formed by the hydrolysis of acetal ester **25**. A possible competing alternative on complex **C** is the reductive elimination to afford benzyltrifluoroacetate **28** and complex **A**. Intermediate **G** could be also achieved from **28** via intermediate H, the formation of which includes the deprotonation of compound **28**. All these pathways have been evaluated in the current study using the density functional theory (DFT) method N12, which is newly reported by Truhlar group.[18]

As depicted in Figure 1, Rh^{II} dimer **9** is set to the relative zero value.[19] The oxidation of complex **9** takes place via transition state **10-ts** with a barrier of only 18.4 kcal mol^{-1} in the presence of Selectfluor, which leads to the formation of Rh^{II}–Rh^{IV} complex **11**. Subsequently, the generation of the Rh^{III} dimer **12**, by the coordination of trifluoroacetate, is exothermic (13.0 kcal mol^{-1}). Deprotonation with fluoride ions then takes place via transition state **13-ts** with a barrier of 22.3 kcal mol^{-1}, generating a benzyl–Rh^{III} complex **14** by an irreversible exothermic reaction (51.2 kcal mol^{-1}). The irreversible deprotonation indicates that, when toluene reacts with complex **12**, the formed intermediate **14** can not go back to **12** reversibly. When deuterated reactant is used, the reactivity of the C–D bond is lower than that of the corresponding C–H bond. Therefore, the kinetic isotope effect can be observed, which is consistent with experimental observation. Besides, complex **15** could be generated by ligand exchange of trifluoroacetate with intermediate **12** reversibly. Another deprotonation process with trifluoroacetate could occur through transition state **16-ts**, which also leads to the formation of complex **14**. However, the relative free energy of transition state **16-ts** is 6.8 kcal mol^{-1} higher than that of transition state **13-ts**. In addition, the pathway for direct deprotonation of Rh^{II} dimer **9** has also been considered. The calculated activation free energy for the deprotonation using fluoride ions is up to 35.6 kcal mol^{-1}, which indicates that the deprotonation–oxidation pathway is unfavorable (see Figure S1 in the Supporting Information for more details).

As shown in Figure 2, when intermediate **14** is formed, we first considered the benzylic deprotonation by trifluoroacetate. However, the barrier of this process via transition state **26-ts** is as high as 26.2 kcal mol^{-1}. We also found that the barrier of reductive elimination via transition state **27-ts** is 2.1 kcal mol^{-1} lower than that of deprotonation by trifluoroacetate. In an-

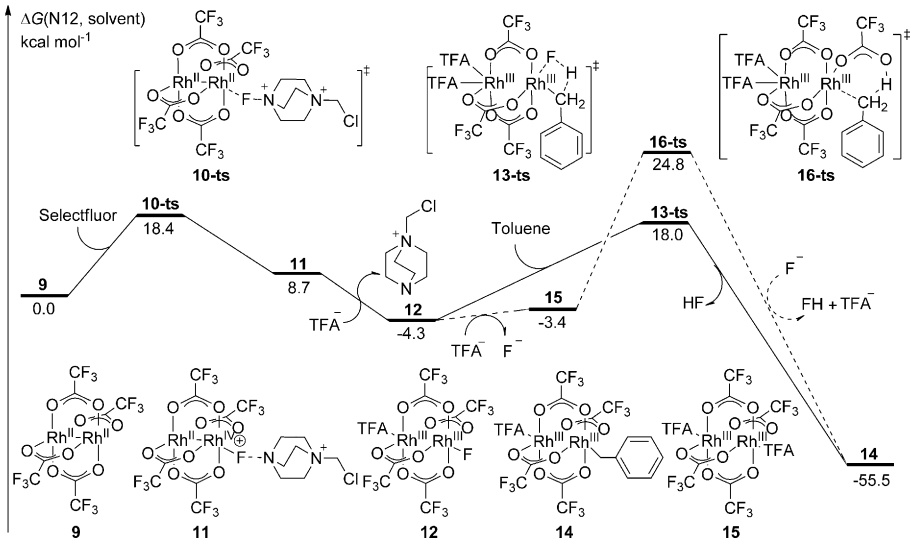


Figure 1. Free energy profiles for the toluene-loading steps of the rhodium-catalyzed oxidation reaction. The values have been given in the units of kcal mol^{-1} and represent the relative free energies calculated using the N12 method in acetic acid.

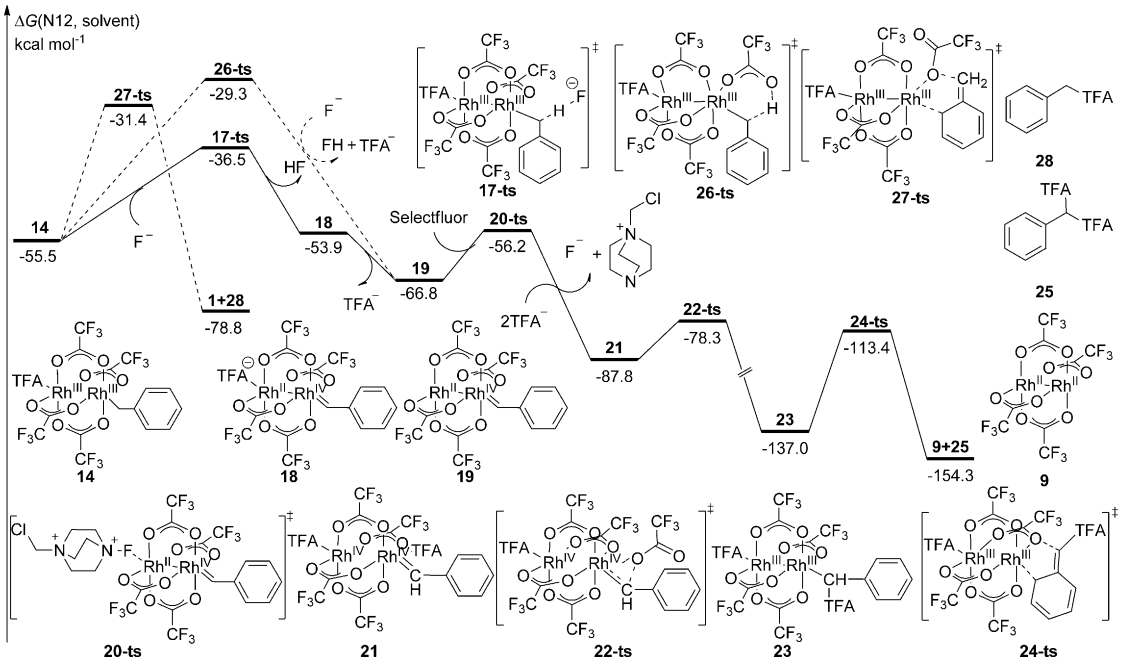


Figure 2. Free energy profiles for the rhodium-catalyzed oxidation of toluene. The values have been given in the units of kcal mol^{-1} and represent the relative free energies calculated using the N12 method in acetic acid.

other case, we found that the deprotonation by additional fluoride is faster via transition state **17-ts** with a barrier of only 19.0 kcal mol^{-1}. In this step, fluoride is necessary, which is consistent with experimental conditions. After releasing trifluoroacetate, carbene–Rh^{IV} intermediate **19** is formed irreversibly. The second oxidation by Selectfluor takes place via transition state **20-ts** with a barrierof only 10.6 kcal mol^{-1} to form dirhodium(IV) complex **21**. The following carbene insertion into the Rh–O bond takes place via transition state **22-ts** with a barrier of 9.6 kcal mol^{-1}, and Rh^{III} intermediate **23** is given irreversibly. The final reductive elimination regenerates the active catalyst [Rh_2(tfa)$_4$] complex **9**. The major product benzaldehyde can be obtained by the hydrolysis of acetal ester **25**.

As a summary of theoretical calculations, the mechanism for the rhodium-catalyzed oxidation of toluene includes the oxidation of [Rh_2(tfa)$_4$] (**A**) by Selectfluor, deprotonation of toluene, the second deprotonation by fluoride to form carbene–Rh complex (**E**), the second oxidation by Selectfluor, carbene insertion, and reductive elimination to regenerate the active catalyst [Rh_2(tfa)$_4$] (**A**).

Conclusion

In conclusion, a direct C(sp^3)–H benzylic formylation with a unique combination of catalyst Rh(OAc)$_2$, oxidant Selectfluor, and solvents of TFA/TFAA has been developed. Rh(OTFA)$_2$ has the same ability as Rh(OAc)$_2$, but other catalysts are unable to catalyze this reaction. Selectfluor as the key by standing oxidant is important because no other oxidants are effective. A variety of aromatic materials are smoothly transformed to the corresponding aldehyde products in moderate to excellent yields. A plausible mechanism involving carbene–Rh complex was proposed. The newly reported DFT method N12 is employed to study the mechanism. Theoretical calculations indicated that the initial step is the oxidation of Rh(OAc)$_2$ by Selectfluor and an electrophilic deprotonation to form a benzyl–Rh^{III} complex. The second deprotonation by fluoride formed carbene–Rh intermediate, which would be oxidized by another molecule of Selectfluor. The following TFA migration to carbene–Rh double bond and reductive elimination would generate an acetal ester complex **25** which would be hydrolyzed to form benzaldehyde. Further mechanistic study and application for this new reaction are currently ongoing in our laboratory.

Experimental Section

General procedures: In a 15 mL sealed tube, ketone **1** (21 mg, 0.1 mmol), [Rh_2(OAc)$_4$] (1.1 mg, 0.0025 mmol) and Selectflour (89 mg, 0.25 mmol) were dissolved in TFA/TFAA (0.9 mL/0.1 mL) under air. The reaction mixture was stirred for 1 min at room temperature for proper mixing of the reactants. The tube was sealed and heated to 80 °C to stir for 7 h. After the reaction, the system was cooled to room temperature and washed with CH_2Cl_2 (5 mL). Normal workup was conducted with CH_2Cl_2 (2×10 mL) and a saturated aqueous solution of $NaHCO_3$ (25 mL) After drying, filtration and evaporation of the combined organic layers, the crude product was purified by flash chromatography on silica gel with petroleum ether/EtOAc (10:1–8:1) to give the product 2 (16 mg, 71 % yield).

Acknowledgements

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Keywords: C(sp^3)–H oxygenation · chemoselective · rhodium(II) catalyst · carbene–Rh complex · oxidant

[1] a) D. F. Taber, E. H. Petty, K. Raman, *J. Am. Chem. Soc.* **1985**, *107*, 196; b) J. M. Hoover, S. S. Stahl, *J. Am. Chem. Soc.* **2011**, *133*, 16901; c) M. P. Doyle, *Chem. Rev.* **1986**, *86*, 919; d) H. M. L. Davies, J. R. Manning, *Nature* **2008**, *451*, 417; e) H. M. L. Davies, D. Morton, *Chem. Soc. Rev.* **2011**, *40*, 1857; f) H. B. Wang, G. Li, K. M. Engle, J. Q. Yu, H. M. L. Davies, *J. Am. Chem. Soc.* **2013**, *135*, 6774; g) J. R. Manning, H. M. L. Davies, *J. Am. Chem. Soc.* **2008**, *130*, 8602; h) J. R. Manning, H. M. L. Davies, *Tetrahedron* **2008**, *64*, 6901; i) J. Magano, J. R. Dunetz, *Chem. Rev.* **2011**, *111*, 2177; j) B. Saha, T. Ghatak, A. Sinha, S. M. W. Rahaman, J. K. Bera, *Organometallics* **2011**, *30*, 2051; k) E. Rodriguez-Cárdenas, R. Sabala, M. Romero-Ortega, A. Ortiz, H. F. Olivo, *Org. Lett.* **2012**, *14*, 238; l) A. DeAngelis, O. Dmitrenko, J. M. Fox, *J. Am. Chem. Soc.* **2012**, *134*, 11035; m) R. Liu, G. N. W. McPherson, Z. Y. Yang, X. Zhou, W. Song, I. A. Guzei, X. Xu, W. Tang, *J. Am. Chem. Soc.* **2013**, *135*, 8201; n) A. Padwa, Y. Zou, *J. Org. Chem.* **2015**, *80*, 1802; o) A. Archambeau, F. Miege, C. Meyer, J. Cossy, *Acc. Chem. Res.* **2015**, *48*, 1021; p) D. Chen, X. Zhang, W. Y. Qi, B. Xu, M. H. Xu, *J. Am. Chem. Soc.* **2015**, *137*, 5268.

[2] a) P. J. Reider, E. J. J. Grabowski, *Tetrahedron Lett.* **1982**, *23*, 2293; b) P. M. Wehn, J. Du Bois, *Org. Lett.* **2005**, *7*, 4685; c) M. Kim, J. V. Mulcahy, C. G. Espino, J. Du Bois, *Org. Lett.* **2006**, *8*, 1073; d) J. L. Roizen, M. E. Harvey, J. Du Bois, *Acc. Chem. Res.* **2012**, *45*, 911; e) D. N. Zalatan, J. Du Bois, *J. Am. Chem. Soc.* **2008**, *130*, 9220; f) H. M. L. Davies, R. E. Beckwith, *Chem. Rev.* **2003**, *103*, 2861; g) M. P. Doyle, R. Duffy, M. Ratnikov, L. Zhou, *Chem. Rev.* **2010**, *110*, 704; h) D. E. Olson, A. Maruniak, S. Malhotra, B. M. Trost, J. Du Bois, *Org. Lett.* **2011**, *13*, 3336; i) J. Du Bois, *Org. Process Res. Dev.* **2011**, *15*, 758; j) K. W. Fiori, C. G. Espino, B. H. Brodsky, J. Du Bois, *Tetrahedron* **2009**, *65*, 3042; k) X. Zhang, H. Xu, C. Zhao, *J. Org. Chem.* **2014**, *79*, 9799; l) M. Yamawaki, H. Tsutsui, S. Kitagaki, M. Anada, S. Hashimoto, *Tetrahedron Lett.* **2002**, *43*, 9561; m) H. Lebel, K. Huard, S. Lectard, *J. Am. Chem. Soc.* **2005**, *127*, 14198; n) C. Liang, F. Robert-Peillard, C. Fruit, P. Müller, R. H. Dodd, P. Dauban, *Angew. Chem. Int. Ed.* **2006**, *45*, 4641; o) R. P. Reddy, H. M. L. Davies, *Org. Lett.* **2006**, *8*, 5013; p) K. W. Fiori, J. Du Bois, *J. Am. Chem. Soc.* **2007**, *129*, 562; q) C. Liang, F. Collet, F. Robert-Peillard, P. Müller, R. H. Dodd, P. Dauban, *J. Am. Chem. Soc.* **2008**, *130*, 343; r) E. N. Bess, R. J. DeLuca, D. J. Tindall, M. S. Oderinde, J. L. Roizen, J. Du Bois, M. S. Sigman, *J. Am. Chem. Soc.* **2014**, *136*, 5783; s) M. E. Harvey, D. G. Musaev, J. Du Bois, *J. Am. Chem. Soc.* **2011**, *133*, 17207.

[3] Y. Kato, K. Miki, F. Nishino, K. Ohe, S. Uemura, *Org. Lett.* **2003**, *5*, 2619.

[4] J. A. May, B. M. Stoltz, *J. Am. Chem. Soc.* **2002**, *124*, 12426.

[5] V. K. Aggarwal, E. Alonso, G. Hynd, K. M. Lydon, M. J. Palmer, M. Porcelloni, J. R. Studley, *Angew. Chem. Int. Ed.* **2001**, *40*, 1430; *Angew. Chem.* **2001**, *113*, 1479.

[6] A. J. Catino, J. M. Nichols, R. E. Forslund, M. P. Doyle, *Org. Lett.* **2005**, *7*, 2787.

[7] J. Kwak, M. Kim, S. Chang, *J. Am. Chem. Soc.* **2011**, *133*, 3780.

[8] G. Shan, X. S. Han, Y. Lin, S. Y. Yua, Y. Rao, *Org. Biomol. Chem.* **2013**, *11*, 2318.

[9] H. U. Vora, A. P. Silvestri, C. J. Engelin, J. Q. Yu, *Angew. Chem. Int. Ed.* **2014**, *53*, 2683; *Angew. Chem.* **2014**, *126*, 2721.

[10] a) H. Choi, M. P. Doyle, *Org. Lett.* **2007**, *9*, 5349; b) J. A. S. Coelho, A. F. Trindade, R. Wanke, B. G. M. Rocha, L. F. Veiros, P. M. P. Gois, A. J. L. Pombeiro, C. A. M. Afonso, *Eur. J. Org. Chem.* **2013**, 1471; c) A. J. Catino, J. M. Nicols, H. Choi, S. Gottipamula, M. P. Doyle, *Org. Lett.* **2005**, *7*, 5167; d) Y. Wang, Y. Kuanga, Y. H. Wang, *Chem. Commun.* **2015**, *51*, 5852; e) A. F. Trindade, J. A. S. Coelho, C. A. M. Afonso, L. F. Veiros, P. M. P. Gois, *ACS Catal.* **2012**, *2*, 370.

[11] a) M. P. Doyle, *J. Org. Chem.* **2006**, *71*, 9253; b) A. J. Catino, R. E. Forslund, M. P. Doyle, *J. Am. Chem. Soc.* **2004**, *126*, 13622; c) T. P. Zhu, M. Q. Ahsan, T. Malinski, K. M. Kadish, J. L. Bear, *Inorg. Chem.* **1984**, *23*, 2.

[12] a) J. F. Hartwig, *Nature* **2008**, *455*, 314; b) S. M. Paradine, M. C. White, *J. Am. Chem. Soc.* **2012**, *134*, 2036; c) A. Sen, *Acc. Chem. Res.* **1998**, *31*, 550; d) A. E. Shilov, G. B. Shul'pin, *Chem. Rev.* **1997**, *97*, 2879;e) P. A. Vadola, I. Carrera, D. Sames, *J. Org. Chem.* **2012**, *77*, 6689.

[13] a) F. Pan, P. X. Shen, L. S. Zhang, X. Wang, Z. J. Shi, *Org. Lett.* **2013**, *15*, 4758; b) L. C. Campeau, D. J. Schipper, K. Fagnou, *J. Am. Chem. Soc.* **2008**, *130*, 3266; c) Á. Iglesias, R. Álvarez, Á. R. de Lera, K. Muńiz, *Angew. Chem. Int. Ed.* **2012**, *51*, 2225; d) V. G. Zaitsev, D. Shabashov, O. Daugulis, *J. Am. Chem. Soc.* **2005**, *127*, 13154; e) D. Shabashov, O. Daugulis, *J. Am. Chem. Soc.* **2010**, *132*, 3965; f) E. T. Nadres, O. Daugulis, *J. Am. Chem. Soc.* **2012**, *134*, 7; g) B. V. S. Reddy, L. R. Reddy, E. J. Corey, *Org. Lett.* **2006**, *8*, 3391; h) G. He, Y. Zhao, S. Zhang, C. Lu, G. Chen, *J. Am. Chem. Soc.* **2012**, *134*, 3; i) S. Y. Zhang, G. He, Y. Zhao, K. Wright, W. A. Nack, G. Chen, *J. Am. Chem. Soc.* **2012**, *134*, 7313; j) Y. Aihara, N. Chatani, *Chem. Sci.* **2013**, *4*, 664; k) Y. Ano, M. Tobisu, N. Chatani, *J. Am. Chem. Soc.* **2011**, *133*, 12984; l) R. K. Rit, M. R. Yadav, A. K. Sahoo, *Org. Lett.* **2012**, *14*, 3724; m) N. Rodríguez, J. A. Romero-Revilla, M. A. Fernández-Ibánez, J. C. Carretero, *Chem. Sci.* **2013**, *4*, 175.

[14] a) K. B. McMurtrey, J. M. Racowski, M. S. Sanford, *Org. Lett.* **2012**, *14*, 4094; b) K. L. Hull, A. Q. Waseem, M. S. Sanford, *J. Am. Chem. Soc.* **2006**, *128*, 7134; c) S. Bloom, C. R. Pitts, D. C. Miller, N. Haselton, M. G. Holl, E. Urheim, T. Lectka, *Angew. Chem. Int. Ed.* **2012**, *51*, 10580.

[15] a) L. Ju, J. Yao, Z. Wu, Z. Liu, Y. Zhang, *J. Org. Chem.* **2013**, *78*, 10821; b) T. Cheng, W. Yin, Y. Zhang, Y. Zhang, Y. Huang, *Org. Biomol. Chem.* **2014**, *12*, 1405.

[16] a) W. C. P. Tsang, N. Zheng, S. L. Buchwald, *J. Am. Chem. Soc.* **2005**, *127*, 14560; b) W. C. P. Tsang, R. H. Munday, G. Brasche, N. Zheng, S. L. Buchwald, *J. Org. Chem.* **2008**, *73*, 7603; c) Z. Ni, Q. Zhang, T. Xiong, Y. Zheng, Y. Li, H. Zhang, J. Zhang, Q. Liu, *Angew. Chem. Int. Ed.* **2012**, *51*, 1244; d) S. K. Y. Leung, W. M. Tsui, J. S. Huang, C. M. Che, J. L. Liang, N. Zhu, *J. Am. Chem. Soc.* **2005**, *127*, 16629; e) M. R. Fructos, S. Trofimenko, M. M. Diaz-Requejo, P. J. Perez, *J. Am. Chem. Soc.* **2006**, *128*, 11784; f) H. J. Kim, J. Kim, S. H. Cho, S. Chang, *J. Am. Chem. Soc.* **2011**, *133*, 16382.

[17] J. M. Nichols, J. Wolf, P. Zavalij, B. Varughese, M. P. Doyle, *J. Am. Chem. Soc.* **2007**, *129*, 3504.

[18] R. Peverati, D. G. Truhlar, *J. Chem. Theory Comput.* **2012**, *8*, 2310.

[19] The detailed computational methodology is listed in supporting information.

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