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Communication

Ruthenium(II)-catalyzed para-selective C—H difluoroalkylation of aromatic aldehydes and ketones using transient directing groups

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ABSTRACT

A Ru(II)-catalyzed *para*-difluoroalkylation of aromatic aldehydes and ketones with a transient directing group has been developed. It utilizes less expensive ruthenium catalysts and allows facile access to challenging difluoroalkylated aldehydes. The mechanism studies suggest that the distinct coordination mode of ruthenium complex with imine moieties is responsible for *para*-selectivity.

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Fluorinated arenes, especially difluoroalkylated arenes, remain privileged moieties for drug discovery and development owing to *gem*-difluoromethylene group's unique stability, and isosteric properties as an ethereal oxygen atom or a carbonyl group, as well as a lipophilic hydrogen-bond donor [1]. Accordingly, various approaches to direct difluoroalkylation of aromatic rings have been explored extensively in the last few decades [2]. Although heteroarenes can afford site-selective products due to their intrinsic electronic effects and photo-redox-catalyzed *ortho*-difluoroalkylation of anilines have been achieved [3], general aromatic compounds usually suffer from poor site selectivity for remote C—H difluoroalkylation. Until recently, *meta*-selective C—H difluoroalkylation of 2-arylpyridine derivatives [4] and purine [5] has successfully been achieved by groups of Ackermann and Wang. Following these remote C—H difluoroalkylations, *para*-selective counterparts have been demonstrated viable to several aromatic rings, such as aniline derivatives [6], oximes [7], ketones [8], aldehydes [9] and benzoate derivatives [10] (Scheme 1). However, given that the formation of cycloruthenation between oxygen-containing directing group and ruthenium is sluggish owing to the weak coordination of oxygen and ruthenium, the direct *para*-selective difluoroalkylation of aromatic aldehydes, ketones or benzoate derivatives employing less expensive ruthenium catalysts still remains unsolved and challenging [11].

Aldehydes as the directing group (DG) in the C—H activation normally suffer from their weak coordinating ability, susceptibility toward oxidation, and undesired metal insertion into acyl C—H bond. To overcome these limitations, Yu and others recently introduced the transient directing group (TDG) concept and successfully achieved diverse *ortho*-C–H functionalization of aromatic aldehydes using amines as TDGs [12]. We envisioned that introduction of TDG in *para*-difluoroalkylation of aromatic aldehydes would enable the formation of strong coordinating imine moiety which can benefit substrate-ruthenium coordination. Herein, we report the first transient directing group promoted *para*-difluoroalkylation of aromatic aldehydes. This protocol employs less expensive ruthenium catalysts and allows the rapid access to both difluoroalkylated aromatic aldehydes and ketones.

We commenced our initial investigation by the reaction of benzaldehyde **1a** and bromodifluoroacetate **2a** using [Ru(*p*-cymene)Cl_2]$_2$ as catalyst with diverse TDGs (Scheme 2, Table S1 in Supporting information). When subjected to the model reactions, the reported bidentate TDGs previously employed for *ortho*-C–H functionalization of aldehydes afforded low yields in this remote C–H difluoroalkylation (**TDG1-TDG7**) [12b–e,12k,12l]. Aniline type monodentate TDGs did not improve the reaction efficiency (**TDG8** and **TDG9**) [12h,12m]. To our delight, aliphatic primary amine **TDG10** could significantly enhanced the reaction

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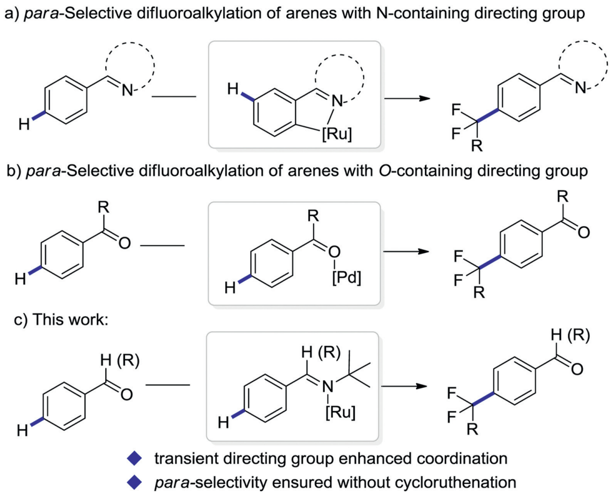
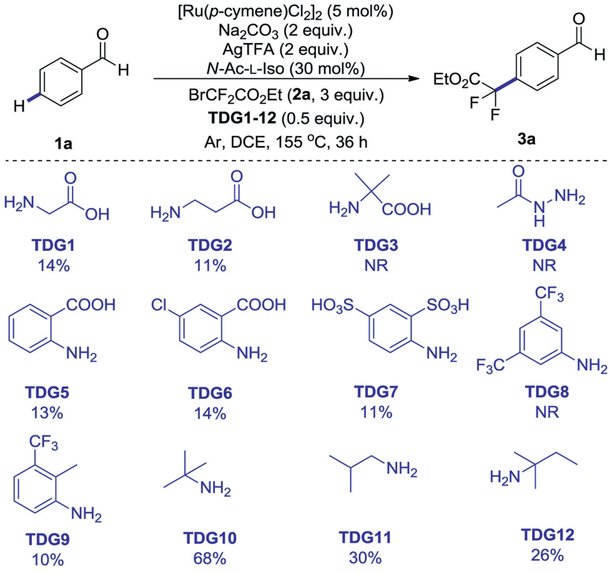


Scheme 1. The remote C—H difluoroalkylation of arenes.

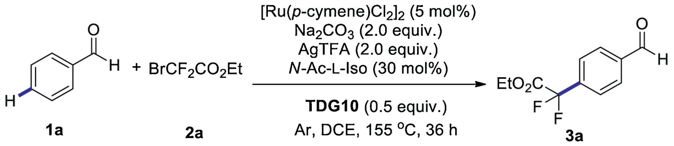


Scheme 2. Transient directing group screening. Standard conditions: **1a** (0.2 mmol), **2a** (0.6 mmol), $[Ru(p\text{-cymene})Cl_2]_2$ (5 mol%), Na_2CO_3 (2 equiv.), AgTFA (2 equiv.), *N*-acetyl-L-isoleucine (30 mol%), TDG (0.5 equiv.), DCE (1 mL), 155 °C, 36 h, under Ar. Isolated yields.

outcome, delivering the *para*-product **3a** in 68% (Table 1, entry 1). Other amines, such as 2-methylpropan-1-amine and 2-methylbutan-2-amine, gave lower chemical yields.

Further survey of other ruthenium catalysts [7] and previous employed $Pd(PPh_3)_4$ [8] showed lower catalytic efficiency (Table 1, entries 2–6). Besides, the use of *N*-acetylglycine, 1-adamantane carboxylic acid (1-Ad-OH), pivalic acid (*t*-BuCOOH) and 2,4,6-trimethylbenzoic acid (MesCOOH) instead of *N*-acetyl-L-isoleucine decreased the efficiency of difluoroalkylation and regioselectivity (Table 1, entries 7–10). Further screening of diverse silver salts demonstrated AgTFA as the optimal choice (Table 1, entries 11–17). A thorough investigation of bases and solvents revealed the combination of Na_2CO_3 and 1,2-dichloroethane (DCE) led to the best chemical yields (Table 1, entries 18–23).

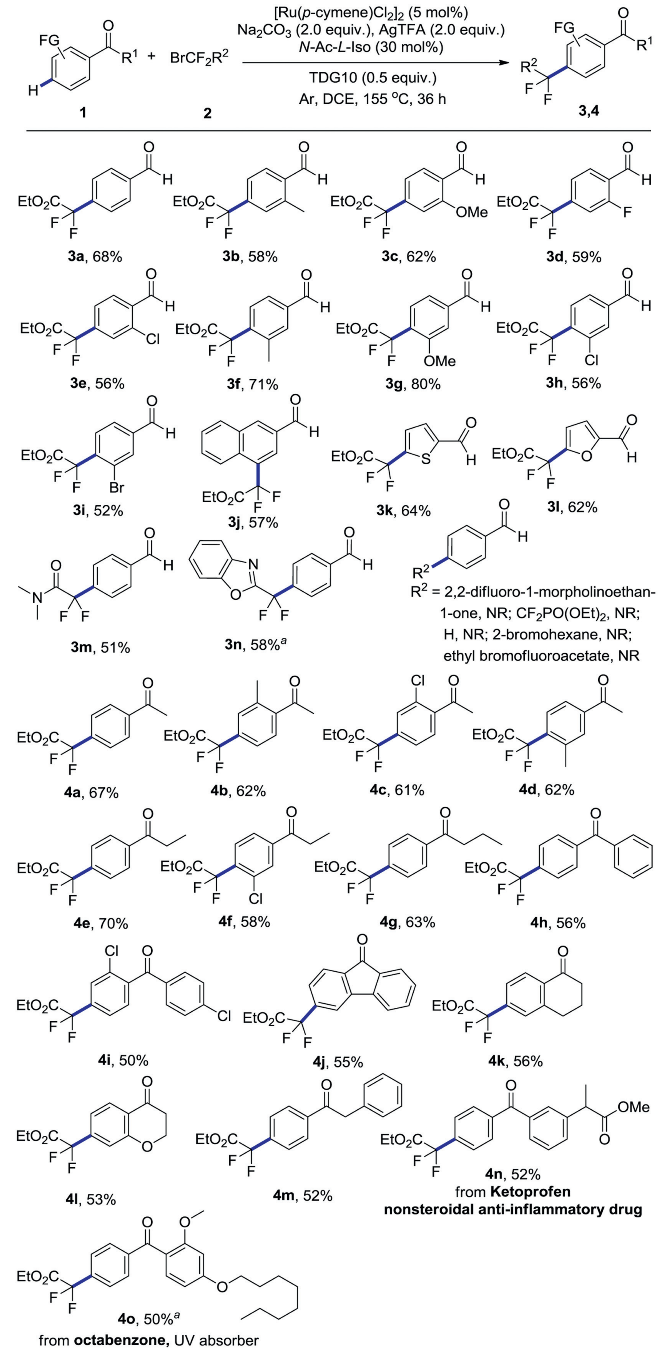
Table 1
Optimization of reaction conditions.[a]



Entry	Deviation from the standard conditions	Yield (%)[b]
1	–	68
2	$Pd(PPh_3)_4$ instead of $[Ru(p\text{-cymene})Cl_2]_2$	0
3	$Ru_3(CO)_{12}$ instead of $[Ru(p\text{-cymene})Cl_2]_2$	33
4	$Ru(DMSO)_4Cl_2$ instead of $[Ru(p\text{-cymene})Cl_2]_2$	12
5	$RuCl_3$ instead of $[Ru(p\text{-cymene})Cl_2]_2$	15
6	$Ru(bpy)_3(PF_6)_2$ instead of $[Ru(p\text{-cymene})Cl_2]_2$	15
7	*N*-Acetylglycine instead of *N*-Ac-L-Iso	33
8	1-Ad-OH instead of *N*-Ac-L-Iso	43
9	*t*-BuCOOH instead of *N*-Ac-L-Iso	38
10	MesCOOH instead of *N*-Ac-L-Iso	40
11	$AgNTf_2$ instead of AgTFA	60
12	Ag_2O instead of AgTFA	54
13	AgF instead of AgTFA	58
14	$AgSbF_6$ instead of AgTFA	42
15	AgOAc instead of AgTFA	30
16	$AgNO_3$ instead of AgTFA	28
17	$AgBF_4$ instead of AgTFA	32
18	NaH_2PO_4 instead of Na_2CO_3	57
19	$NaHCO_3$ instead of Na_2CO_3	50
20	NaOAc instead of Na_2CO_3	43
21	K_2CO_3 instead of Na_2CO_3	51
22	Dioxane instead of DCE	9
23	H_2O instead of DCE	30

[a] Standard conditions: **1a** (0.2 mmol, 1.0 equiv.), **2a** (0.6 mmol, 3.0 equiv.), $[Ru(p\text{-cymene})Cl_2]_2$ (5 mol%), Na_2CO_3 (0.4 mmol, 2.0 equiv.), AgTFA (0.4 mmol, 2.0 equiv.), *N*-acetyl-L-isoleucine (30 mol%), **TDG10** (0.1 mmol, 0.5 equiv.), DCE (1.0 mL), 155 °C, 36 h, under Ar.
[b] Isolated yields.

With optimal conditions, we treated different benzaldehydes with **2a** to examine the functional-group tolerance (Scheme 3). Difluoroalkylation of benzaldehyde derivatives with *ortho* substituents proceeded smoothly to furnish the corresponding *para*-difluoroalkylated products **3b**-**3e**. Pleasingly, *meta*-substituted benzaldehyde derivatives provided the corresponding products **3f**-**3i** difluoroalkylated at the sterically hindered *para*-position in moderate to good yield. This reactivity is different to that observed in previous *meta*-selective alkylation and difluoroalkylation reactions [8], in which *meta*-substituted substrates are less



Scheme 3. Reaction scope. Standard conditions: **1** (0.2 mmol, 1.0 equiv.), **2** (0.6 mmol, 3.0 equiv.), [Ru(*p*-cymene)Cl$_2$]$_2$ (5 mol%), Na$_2$CO$_3$ (0.4 mmol, 2.0 equiv.), AgTFA (0.4 mmol, 2.0 equiv.), *N*-acetyl-L-isoleucine (30 mol%), **TDG10** (0.1 mmol, 0.5 equiv.), DCE (1.0 mL), 155 °C, 36 h, under Ar; Isolated yields. [a]Cannot be separated from aryl impurities.

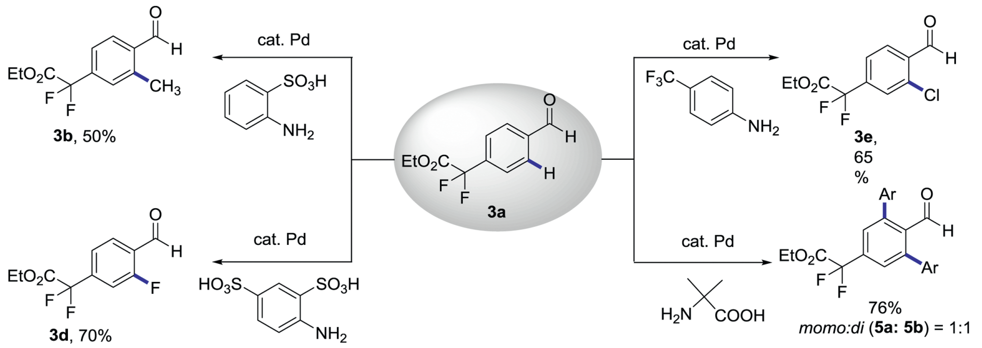
reactive than their *ortho*- or *para*-substituted analogues. Notably, previous uninvestigated 2-naphthaldehyde only generated the *meta*-difluoroalkylated product **3j**. Heteroarenes, such as furan-2-carbaldehyde and thiophene-2-carbaldehyde, are also viable substrates, providing **3k** and **3l** in moderate yields. The current methodology can be easily extended to the coupling of BrCF$_2$CONMe$_2$ (**2b**) and heteroaryl difluoromethyl bromide (**2d**) with benzaldehyde, providing **3m** and **3n** in good yields. Although ^{1}H and ^{19}F NMR of **3n** is in agreement with literature [13], it was containment with aryl impurities and cannot be further purified. Unfortunately, cyclic amides, difluoromethyl halides (HCF$_2$X), difluoroalkyl halides, BrCF$_2$PO(OEt)$_2$ and BrCFHCO$_2$Et didnot react with aldehydes to provide desired products. Further extension of this protocol to aromatic ketones successfully furnished corresponding *para*-difluoroalkylated products as well (Scheme 3). The acetophenone derivatives performed well under the optimal conditions (**4a**-**4d**). Other alkyl aromatic ketones were compatible with the difluoroalkylation, providing the corresponding products **4e**-**4g** in moderate to good yields. The diphenyl ketones afforded monodifluoromethylation products **4h** and **4i**. 9-Fluorenone, the important intermediate for organic synthesis and materials science, also provided the mono-*para*-difluoroalkylated product **4j**. 1-Tetralone and chromanone reacted smoothly with bromodifluoroacetate to afford the corresponding *para*-difluoroalkylated products **4k** and **4l** in 56% and 53% yields, respectively. Substrates of **4m** provided single difluoroalkylated products with high selectivity at the *para*-position of the benzoyl ring rather than the electronically rich aromatic ring. Directly introducing fluorine-containing functional groups into bioactive compounds is an effective method for new drug development. To our delight, the difluoroalkylated ketoprofen derivative (**4n**) and octabenzone derivative (**4o**) were successfully obtained by this transformation. Although ^{1}H and ^{19}F NMR of **4o** is in agreement with literature [9a], it was containment with aryl impurities and can not be further purified.

Further conversion of difluoralkylated products can also be achieved *via* transient directing group strategy. *ortho*-C–H methylation [12e], fluorination [12e], chlorination [12i] and arylation [12k] were successfully applied to functionalize **3a**. In contrast to methylation, fluorination and chlorination, mono- and diarylation of **3a** provided **5a** and **5b** with 1:1 ratio (Scheme 4).

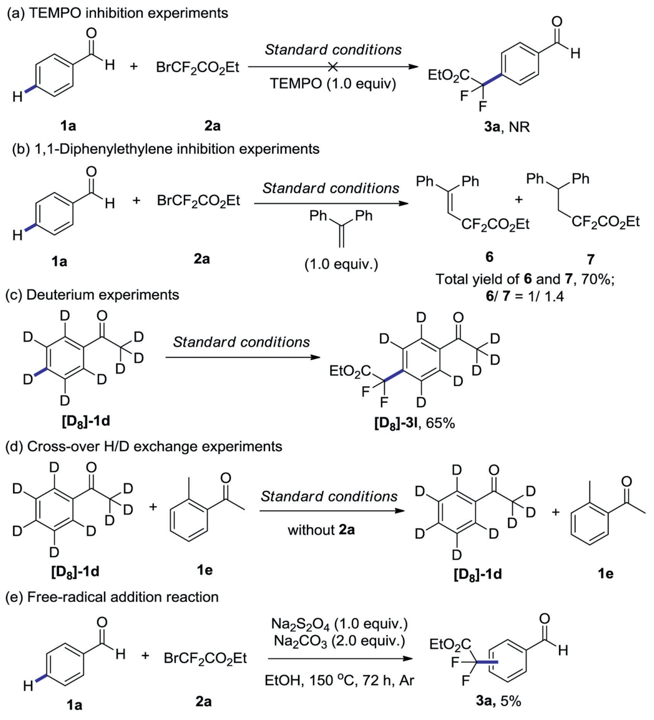
To explore the mechanism and the explanation for the *para*-selectivity, a series of control experiments were carried out. Addition of TEMPO as radical inhibitor completely suppressed difluoroalkylation, implying a plausible radical pathway (Scheme 5a). Trapping of difluoroalkyl radical using 1,1-diphenylethylene under the standard conditions was detected *via* ^{19}F NMR, affording a mixture of **6** and **7** (Scheme 5b) [14]. This result suggests a difluroalkyl radical is involved in the *para*-selective reaction. As formation of chelation-assisted cycloruthenation is normally the key factor that controls the regioselectivity of *meta*- or *para*-C–H difluroakylation, we subjected the deuterated substrate **[D8]-1d** for investigation of cycloruthenation. The product **[D8]-3l** without any D/H exchange by NMR analysis implies a distinct coordination mode from previous cycloruthenation (Scheme 5c) [7].

Another plausible pathway without D/H exchange would be formation of complex **9** (Scheme 6) [15]. To elucidate this possibility, cross-over H/D exchange experiment was carried out, which substrates **[D8]-1d** and **1e** were recovered without H/D exchange (Scheme 5d). These results indicate the cycloruthenation cannot be obtained from coordination of **A** with Ru catalysts under our conditions and is not responsible for *para*-selectivity. When substrate **1a** was subjected to the difluoroalkyl radical generated conditions without Ru catalysts [16], a mixture of *para*- and *meta*-difluoroalkylated products was obtained in 5% yield (Scheme 5e). Therefore, we hypothesized *para*-selectivity could be controlled by the steric and electronic feature of complex **B**, which is similar to Zhou's reports [17].

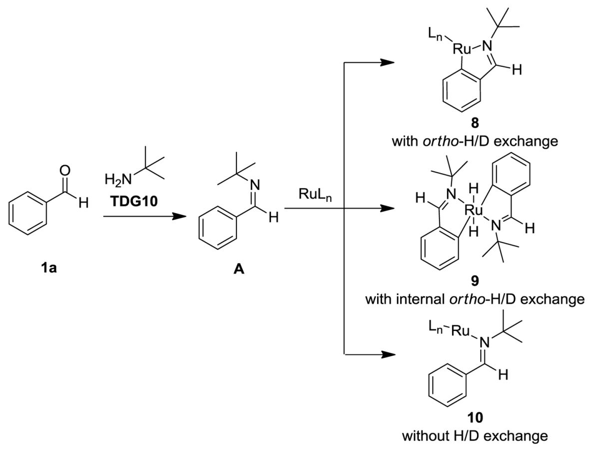
Based on these experiments, a mechanism is proposed for *para*-selective difluoroalkylation of aromatic aldehydes and ketones (Scheme 7). First, the **TDG10** reacts with the **1a** to form imine intermediate **A**. Subsequent coordination of **A** and **F** affords complex **B**. A radical **C**, derived from 2-bromo-2,2-difluoroacetate *via* a single-electron-transfer process [7], is trapped by **B** to



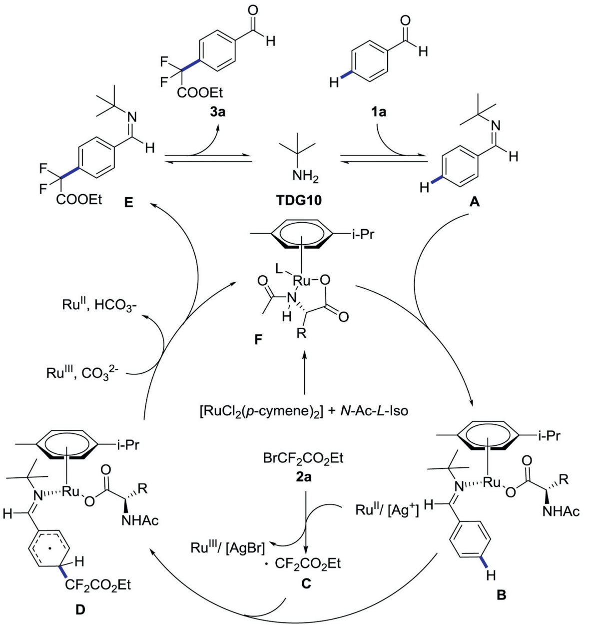
Scheme 4. Transformations of **3a**.



Scheme 5. Preliminary mechanistic study.



Scheme 6. Plausible coordination mode of ruthenium complex with imine moieties.



Scheme 7. Proposed catalytic cycle.

generate **D**, which releases product **3a**, **TDG10** and catalysis species **F**.

In summary, we have developed a general transient directing group strategy for *para*-selective C—H difluoroalkylation of aromatic aldehydes and ketones. The protocol can be performed by using an inexpensive ruthenium catalyst, and allows the rapid access to challenging *para*-difluoroalkylated aldehydes. Mechanism investigation suggests that the distinct coordination of ruthenium complex with imine moieties is responsible for *para*-selectivity.

Declaration of competing interest

The authors report no declarations of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.cclet.2020.09.044.

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