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Palladium-catalyzed remote *para*-C–H activation of arenes assisted by a recyclable pyridine-based template†

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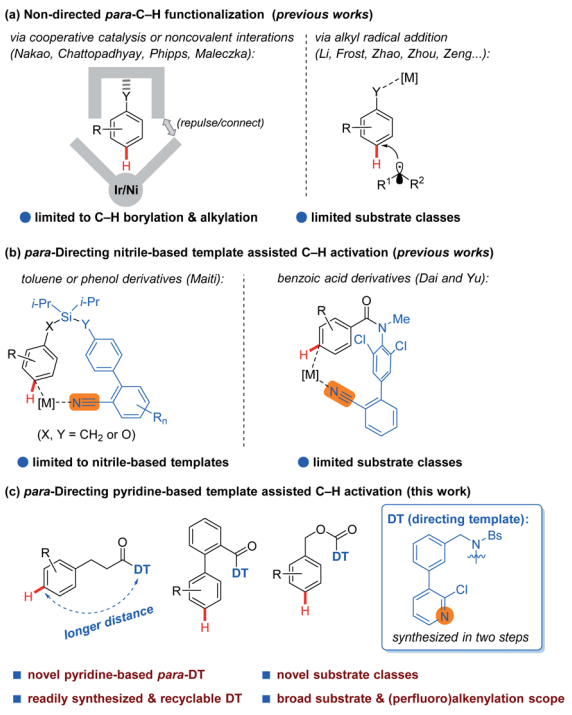
Direct *para*-selective C–H functionalization of arenes remains a daunting challenge and is still significantly restricted to a few scaffolds. Herein, we report an unprecedented pyridine-based *para*-directing template (DT) assisted, Pd-catalyzed *para*-C–H alkenylation of three classes of arenes, *i.e.* phenylpropanoic acids, 2-phenyl benzoic acids and benzyl alcohols, with a series of alkenes including perfluoroalkenes. Notably, the pyridine-based *para*-DT could be easily synthesized and readily recycled under mild conditions. These results may find application in rapid construction of *para*-substituted arenes and stimulate the exploration of novel methods for *para*-C–H functionalization of arenes.

Introduction

Transition-metal-catalyzed C–H activation assisted by directing groups (DGs) has proven to be a powerful strategy for achieving regioselective C–H functionalizations in a general manner, which is able to differentiate C–H bonds with similar electronic and steric properties in an organic molecule. The DG strategy has enabled the development of a large number of *ortho*-C–H and some *meta*-C–H transformations of arenes.[1,2] In contrast, although quite a few *para*-C–H transformations of arenes have been disclosed by making use of arene's electronic and steric biases,[3,4] the *para*-C–H transformation beyond the control of such biases remains a daunting challenge and is still significantly restricted to a few scaffolds. In this endeavor, Nakao and co-workers reported a breakthrough in *para*-C–H alkylation and borylation of arenes by cooperative nickel/aluminum and iridium/aluminum catalysis (Scheme 1a, left).[5] Chattopadhyay,[6] Phipps[7a] and Maleczka[7b] also independently realized elegant Ir-catalyzed, noncovalent interactions assisted *para*-C–H borylation of arenes (Scheme 1a, left). A series of *para*-C–H alkylations of arenes through alkyl radical addition have also been developed by Li,[8a] Frost,[8b] Zhao,[8c–e,i] Zhou,[8f] Zeng,[8g] and others (Scheme 1a, right).[8] However, these non-directed *para*-C–H functionalizations are restricted in transformation patterns and substrate classes. Alternatively, Maiti and co-workers developed the first D-shaped nitrile-based *para*-directing template (DT) to assist several *para*-C–H functionalizations of toluene and phenol derivatives, demonstrating the possibility of using the DT strategy as a general means to achieve diverse *para*-C–H transformations (Scheme 1b, left).[9] Dai and Yu also reported a *para*-C–H acetoxylation of benzoic acid derivatives assisted by an amide linked DT (Scheme 1b, right).[10] Unfortunately, this DT



Scheme 1 *Para*-C–H activation beyond steric & electronic control.

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strategy is restricted to very limited substrate classes at present. Most recently, by using the cooperation of a *meta*-DT and norbornene relay palladation, Yu and Houk[11a] as well as Maiti[11b] independently reported two examples of *para*-C–H arylation of arenes such as the phenylpropanoic acids. However, 2,6-disubstitution of the substrate is unavoidable for this method to achieve the desired selectivity, making it not a general solution. Due to the aforementioned limitations and the good performance of pyridine-based DGs in promoting *ortho*-[1] and *meta*-C–H activations,[2d,12] the development of a versatile method for *para*-C–H activation of arenes by taking the advantage of the directing ability of pyridines is highly desirable.

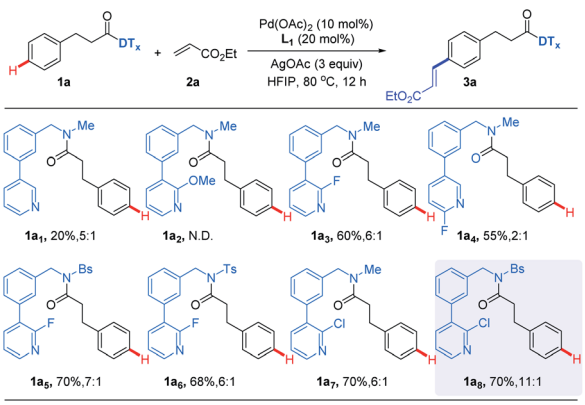
Herein, we report an unprecedented Pd-catalyzed *para*-selective C–H alkenylation of three classes of arenes, *i.e.* phenylpropanoic acids, 2-phenyl benzoic acids and benzyl alcohols, with a series of alkenes including perfluoroalkenes assisted by a novel pyridine-based *para*-DT (Scheme 1c). Notably, the distance between the DT and the target C–H bond is longer than previous examples using the nitrile-based *para*-DT,[9,10] and the pyridine-based *para*-DT could be easily synthesized in two steps and readily recycled under mild conditions.

Results and discussion

Phenylpropionic acids are highly important structural motifs in drug molecules such as baclofen, and *p*-phenylenedipropionic acids is a class of important molecular unit of functional materials such as the gelator molecule of nanofiber.[13] Therefore, phenylpropionic acid was selected as the model substrate for our investigation of *para*-C–H activation of arenes. Based on our recent work on *meta*-C–H activation of phenylpropionic acid[14] and inspired by recent research on *meta*-C–H activation assisted by pyridine-based DTs,[12] we designed a series of potential pyridine-based *para*-DTs with different substitutions to attach with phenylpropionic acid, leading to the amide substrates (Table 1, see ESI† for more DTs evaluated), where the nitrogen atom of pyridine could coordinate to the transition metal to induce site-selective C–H activation. The design of the structure of the template was also inspired by previous reported nitrile-based biphenyl containing *para*-directing template.[9,10] After selecting C–H alkenylation as the model reaction, it was found simple template without a substituent led to low yield and moderate selectivity (**1a$_1$**). Introducing an electron-donating methoxy group resulted in no desired product (**1a$_2$**). It was found an electron-withdrawing substituent, which could help to reduce the coordination ability of the pyridine group, was beneficial for the reaction to produce good yield of desired product (**1a$_3$**–**1a$_7$**). Since the amide group could coordinate with the Pd catalyst to possibly influence the efficiency and selectivity of the reaction, the templates bearing an electron-withdrawing protecting group of the amide linkage to reduce the coordination ability were prepared, leading to higher selectivities (**1a$_5$** *vs.* **1a$_3$** and **1a$_8$** *vs.* **1a$_7$**). Thus, the best preliminary results were obtained with substrate **1a$_8$** using $Pd(OAc)_2$ as the catalyst with 3-(trifluoromethyl)pyridin-2-ol (**L1**) as the ligand in HFIP (hexafluoroisopropanol) at 80 °C for 12 h, affording desired *para*-olefinated phenylpropionic acid derivative **3a$_8$** as the major product with good site-selectivity.

With the optimal pyridine-based *para*-DTs, we continued to optimize the reaction conditions. After extensive

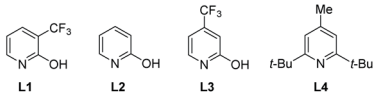
Table 1 Evaluation of pyridine-based *para*-DT[a]



[a] Reaction conditions: **1a** (0.1 mmol), **2a** (2 equiv.), $Pd(OAc)_2$ (0.01 mmol), 3-(trifluoromethyl)pyridin-2-ol (**L1**) (0.02 mmol), AgOAc (0.3 mmol), HFIP (1.0 mL), 80 °C, 12 h. Ratio = *p* : others; Ts: tosyl; Bs: phenylsulfonyl.

Table 2 Optimization of reaction conditions.[a,b]

Entry	Oxidant (equiv.)	Additive (equiv.)	Yield (%) (*p* : others)
1	**AgOAc (3)**	—	**90(79)[j]/15 : 1**
2[c]	AgOAc (3)	—	70/11 : 1
3[d]	AgOAc (3)	—	76/12 : 1
4[e]	$Cu(TFA)_2$ (3)	—	21/7 : 1
5[e]	$CuCl_2$ (3)	—	—
6[e]	CuI (3)	—	11/5 : 1
7[e]	$Cu(OAc)_2$ (3)	—	40/8 : 1
8[f]	$Cu(OAc)_2$ (0.5)	AcOH (2.0)	68/12 : 1
9[f,g]	$Cu(OAc)_2$ (0.5)	AcOH (2.0)	72/12 : 1
10[f,h]	**$Cu(OAc)_2$ (0.5)**	**AcOH (2.0)**	**80(72)[j]/12 : 1**
11[f,i]	$Cu(OAc)_2$ (0.5)	AcOH (2.0)	53/12 : 1
12[f,h]	$Cu(OAc)_2$ (0.5)	AcOH (1.0)	76/12 : 1
13[f,h]	$Cu(OAc)_2$ (0.5)	AcOH (5.0)	73/12 : 1



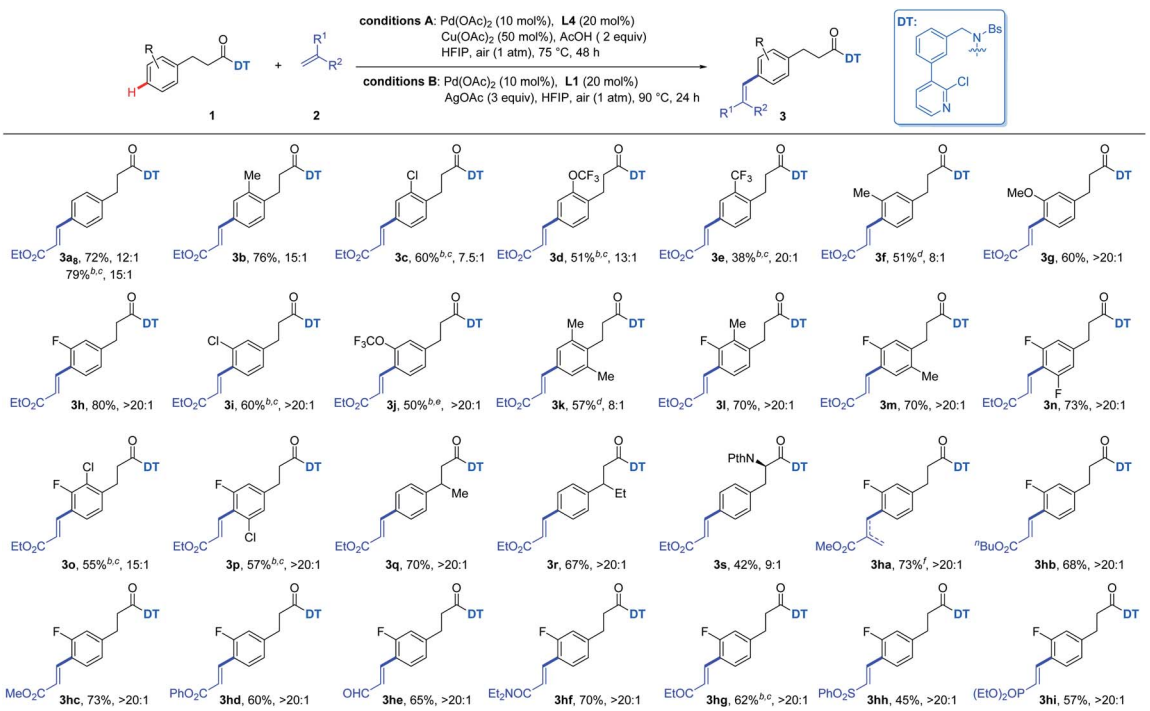
[a] **1a$_8$** (0.1 mmol), $Pd(OAc)_2$ (0.01 mmol), **2a** (2 equiv.), **L1** (0.02 mmol), oxidant, additive, HFIP (1.5 mL), 90 °C, air (1 atm), 12 h. [b] Yield was determined by ^{1}H NMR with CH_2Br_2 as internal standard; products ratios were determined from crude ^{1}H NMR, and products of others were mainly *m*- and *o*-isomers. [c] **L2** (20 mol%). [d] **L3** (20 mol%). [e] 18 h. [f] **2a** (3 equiv.), **L4** (20 mol%), 60 °C, 48 h. [g] 70 °C. [h] 75 °C. [i] 80 °C. [j] Isolated yield of desired product in parentheses.

investigation of the reaction conditions (see ESI† for details), desired product **3a$_8$** was produced in 79% isolated yield with elevated temperature at 90 °C and lowered concentration based on the preliminary reaction conditions (Table 2, entry 1), together with excellent site-selectivity. The yield was decreased when other pyridine-based ligands were tested (entries 2 and 3). We then tried to use a cheaper copper salt as the oxidant, and $Cu(OAc)_2$ was found to be promising (entries 4–7). Pleasingly, a substoichiometric amount of $Cu(OAc)_2$ could be enough to produce higher yields of **3a$_8$** with good site-selectivity (entries 8–11) in the presence of air as the terminal oxidant and two equivalents of AcOH as the additive (see ESI† for the evaluation of other acids) using **L4** as the ligand for 48 h, and the best results using $Cu(OAc)_2$ were obtained at 75 °C (entry 10). Notably, the mount of AcOH was also important, since slightly lower yields of **3a$_8$** would be received with lower (entry 12) of higher (entry 13) loading of this additive.

With the optimized reaction conditions in hand, the generality of this reaction was investigated with a range of phenylpropionic acids as well as some representative olefins (Table 3). It was found that a number of substituents that are electron-donating such as methyl and methoxy groups or electron-withdrawing such as choloro, trifluoromethoxy, trifluoromethyl and fluoro groups at the *ortho*- or *meta*-positions were tolerated in this reaction, delivering the target products in generally moderate to good yields with overall high *para*-selectivity (**3a–3j**). Notably, several di-substituted substrates were also viable in this reaction to afford generally good yields of desired products (**3k–3p**). Moreover, substitution at the benzylic position with a methyl (**3q**) or ethyl (**3r**) groups was tolerated. Interestingly, *para*-C–H functionalization of the phenylalanine derivative was also feasible (**3s**). Finally, a series of electron-deficient alkenes were examined to give generally good yields of the desired products with substrate **1h** (**3ha–3hi**), albeit electron-rich alkenes were not viable.

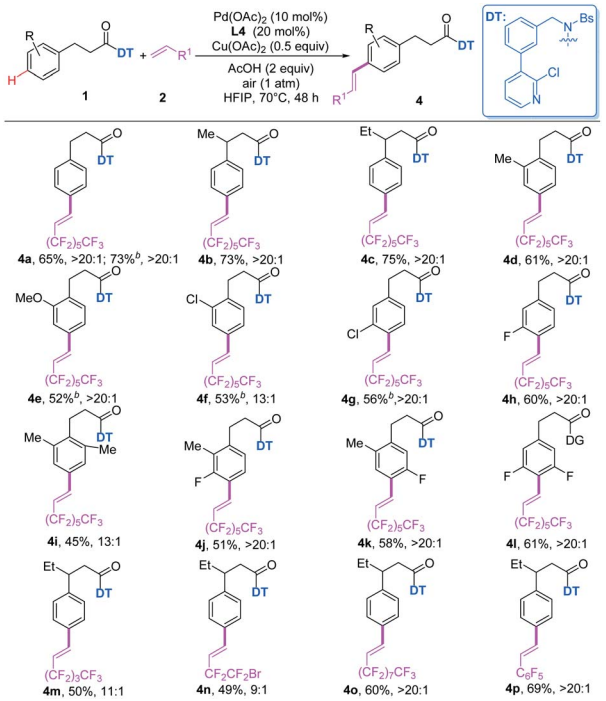
Subsequently, perfluoroalkenes were also evaluated in our study since fluorine-containing compounds play an important role in drug development and material sciences.[15] Although *meta*-C–H perfluoroalkenylation of arenes had been disclosed,[16] there was no report of *para*-C–H perfluoroalkenylation of arenes. We were glad to find that this reaction was compatible with several perfluoroalkenes including brominated perfluoroalkene (Table 4). Phenylpropionic acid derivatives bearing mono-substitution at the benzylic position or on the aryl group were well tolerated to react with tridecafluorooct-1-ene to give desired products with excellent *para*-selectivity (**4a–4h**). Di-substituted substrates were also feasible to produce desired products (**4i–4l**). In

Table 3 Scope of phenylpropionic acids and alkenes[a]



[a] Reaction conditions A: **1** (0.1 mmol), $Pd(OAc)_2$ (10 mol%), **2** (3 equiv.), $Cu(OAc)_2$ (50 mol%), **L4** (20 mol%), AcOH (2 equiv.), air (1 atm), HFIP (1.5 mL), 75 °C, 48 h. [b] Conditions B: Oxidant: AgOAc (3 equiv.), ligand: **L1** (20 mol%), 24 h; no AcOH added. [c] **2** (2 equiv.), 90 °C. [d] O_2 (1 atm). [e] **2** (3 equiv.), HFIP (1.0 mL), 100 °C. [f] **3ha$_1$** (51%, terminal alkene), **3ha$_2$** (22%, internal alkene). Ratio = *p* : others. Isolated yield of pure desired *para*-isomer was reported herein.

Table 4 Reaction with perfluoroalkenes[a]



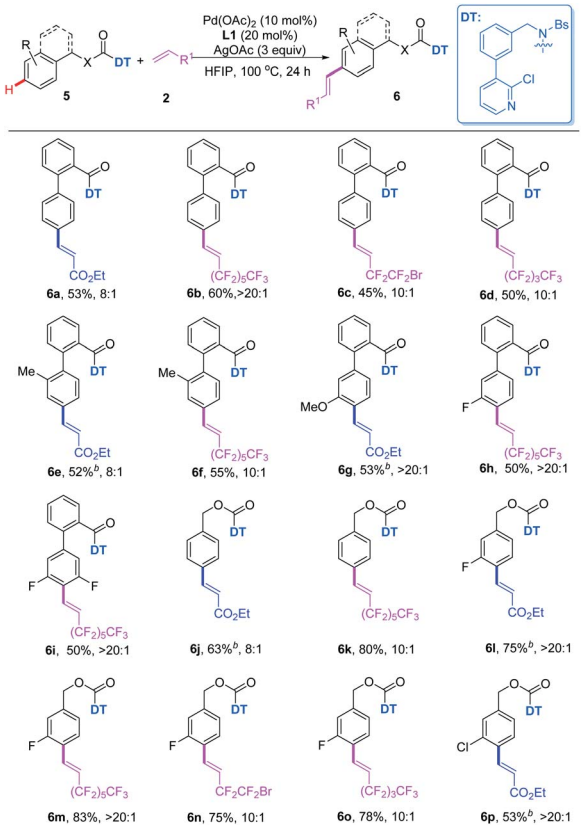
[a] Reaction conditions: **1** (0.1 mmol), $Pd(OAc)_2$ (10 mol%), **2** (3 equiv.), $Cu(OAc)_2$ (50 mol%), **L4** (20 mol%), AcOH (2 equiv.), HFIP (1.5 mL), air (1 atm), 70 °C, 48 h. [b] AgOAc (3 equiv.), **L1** (20 mol%), 80 °C, 24 h; no AcOH added. Ratio = *p* : others. Isolated yield of pure desired *para*-isomer was reported herein.

addition, other fluorinated alkenes were also evaluated to give moderate to good yields of the target molecules (**4m–4p**).

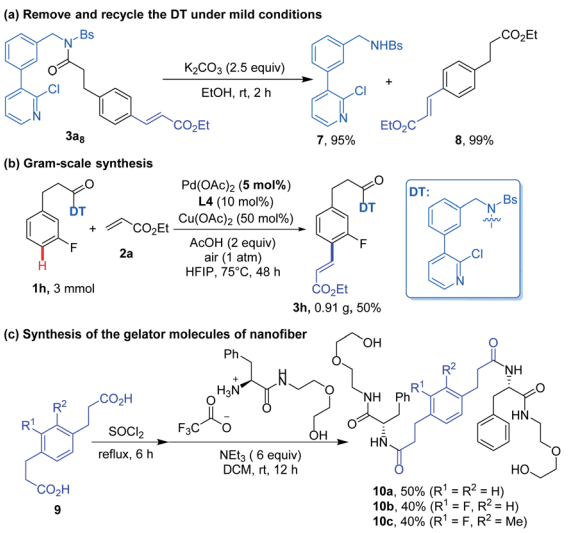
The generality of the newly designed pyridine-based *para*-DT was then tested with other types of molecular structures. Pleasingly, 2-phenyl benzoic acid derivatives bearing several substitution patterns were also smoothly alkenylated at the remote *para*-position with acrylate or fluorinated alkenes (Table 5, **6a–6i**). Moreover, several benzyl alcohol derivatives were also tested, and good yields of desired products could be produced with good to excellent *para*-selectivity (**6j–6p**). It should also be mentioned that the scopes of these two types substrates were not as good as that of phenylpropionic acids at current stage.

Finally, the synthetic potential of our method was investigated briefly. The DT could be readily removed and recycled with excellent yield of *para*-alkenylated phenylpropionic acid under mild reaction conditions (Scheme 2a). The recovered DT (**7**) was identical to that synthesized from Suzuki coupling reaction (see ESI†). The reaction was able to be scaled up to 3 mmol to give about one gram of **3h** using lower loading of $Pd(OAc)_2$ (5 mol%) (Scheme 2b). In addition, *p*-phenylenedipropionic acids, which could be synthesized from our *para*-alkenylated-products after hydrolysis and hydrogenation, were employed to synthesize gelator of nanofiber, including uncommon ones (Scheme 2c).[13a]

Table 5 Scope of 2-phenyl benzoic acids and benzyl alcohols[a]



[a] Reaction conditions: **5** (0.1 mmol), **2** (3 equiv.), $Pd(OAc)_2$ (10 mol%), **L1** (20 mol%), AgOAc (3 equiv.), HFIP (1.0 mL), 100 °C, 24 h. [b] **2** (2 equiv.), HFIP (1.5 mL), 90 °C. Ratio = *p* : others. Isolated yield of pure desired *para*-isomer was reported herein.



Scheme 2 Synthetic Potential Investigation.

Conclusions

In conclusion, we have developed an unprecedented pyridine-based *para*-DT assisted, Pd-catalyzed *para*-selective C–H alkenylation of phenylpropanoic acids with a series of alkenes including perfluoroalkenes. This protocol was also compatible with 2-phenyl benzoic acids and benzyl alcohols with high *para*-selectivity. Notably, air could be used as the terminal oxidant for this reaction and the pyridine-based *para*-DT could be easily synthesized and readily recycled under mild conditions. It is expected these results would find application in rapid construction of *para*-substituted arenes and stimulate the exploration of novel methods for *para*-C–H functionalization of arenes.

Author contributions

X. C. and G. L. conceived the project. X. C. performed the experiments and developed the method. S. F. and M. Z. prepared some of the substrates. S. F., Y. G. and S. L. repeated some of the reactions and checked the data. G. L. directed the project and wrote the manuscript with the feedback from other authors.

Conflicts of interest

There are no conflicts to declare.

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