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Pd(II)-catalyzed remote regiodivergent *ortho*- and *meta*-C–H functionalizations of phenylethylamines†

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Site selectivity control is of vital importance in the direct functionalization of inert C–H bonds. Reported here is a novel example of remote regiodivergent *ortho*- and *meta*-C–H bond functionalizations of phenylethylamine derivatives by using a novel 2-cyanobenzoyl group as the original directing functionality, where the regioselectivity was adjusted by a methylation. The potential of the method was exemplified by sequential functionalizations of both *ortho*- and *meta*-C–H bonds of a phenylethylamine derivative in a streamlined manner.

Introduction

Controlling site selectivity is an outstanding challenge in the direct functionalization of inert C–H bonds that are ubiquitous in organic molecules.¹ The increasing applications of these type of transformations in organic synthesis also demand accessibility to diverse site selectivities.² While numerous directing groups have been introduced to assist the cleavage of proximal *ortho*-C–H bonds in most cases with transition metals,^{1,3–10} directing group assisted *meta*-selective C–H functionalization of arenes has proved especially challenging and is still very rare.^{5,6,8,9} In 2009, a remarkable breakthrough was reported by Gaunt *et al.*, who developed a carbonyl group directed unprecedented *meta*-selective C–H arylation of anilides by using a Cu(II) catalyst and diaryliodonium salts.^{5a} This method was later extended to α -aryl carbonyl compounds by the same group.^{5b} Another impressive breakthrough came from the Frost group, who introduced an ingenious method of *meta*-selective C–H sulfonation of 2-phenylpyridines *via* cyclometalated ruthenium intermediates.^{6a,b} A similar strategy was then employed by Ackermann to realize a *meta*-selective C–H alkylation with secondary alkyl halides.^{6c} Recently, a small number of ground-breaking examples of Pd(II) catalyzed directed *meta*-selective C–H functionalizations of arenes that were attached with elegantly devised nitrile-based templates were disclosed, pioneered by Yu and then further

studied by Tan and Maiti.⁸ By using the above directing group assisted *meta*-selective C–H functionalization of arenes, elegant regiodivergent functionalizations of *ortho*- and *meta*-C–H bonds have been reported by Gaunt,^{4b,5b} Frost^{6b} and Yu,^{8b} and examples of reactions reported by Gaunt^{4b,5b} and Frost^{6b} could even be performed sequentially.^{8i,11,12} However, the use of analogous directing groups to achieve *remote-selective* regiodivergent activation of *ortho*- and *meta*-C–H bonds has not been examined and remains a significant challenge.^{13,14} We envision that such methodology is highly desirable for drug discovery and material sciences, since it only requires a single operation to achieve a different remote regioselectivity.^{2f} Herein, we report a novel strategy for regiodivergent *ortho*- and *meta*-C–H functionalizations of phenylethylamine derivatives.

To test our hypothesis of a regiodivergent C–H functionalization strategy by using analogous directing groups, we selected phenylethylamines as the testing compounds, since they are a class of aromatic compounds that are important core structures of numerous drug molecules (Fig. 1). Moreover, although *ortho*-C–H functionalizations have been reported for phenylethylamine derivatives, their *meta*-selective C–H functionalization remains elusive.¹⁵ Inspired by recent studies on directed *meta*-selective C–H functionalizations of arenes,⁸ we proposed that a 2-cyanobenzoyl group could act as the key directing functionality for both *ortho*- and *meta*-C–H functionalizations of phenylethylamines with a Pd(II) catalyst by taking advantage of the σ and π coordination ability of the nitrile group (Scheme 1).¹⁶ However, during our study we found that our proposed mode of *ortho*-selective C–H bond cleavage was not feasible and a novel remote-selective *ortho*-C–H bond cleavage was observed instead (*vide infra*).^{13,14}

Results and discussion

To examine our original hypothesis (Scheme 2), we chose olefination as the model reaction.^{16,17} After extensive condition

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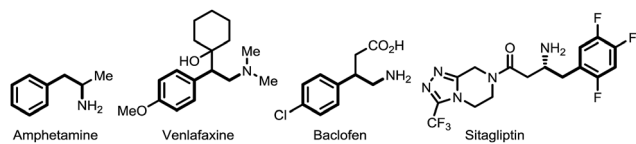
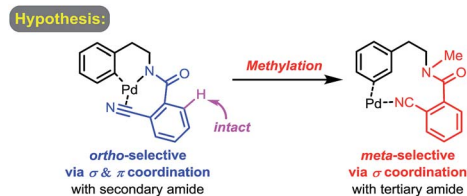


Fig. 1 Representative drugs containing a phenylethylamine core.

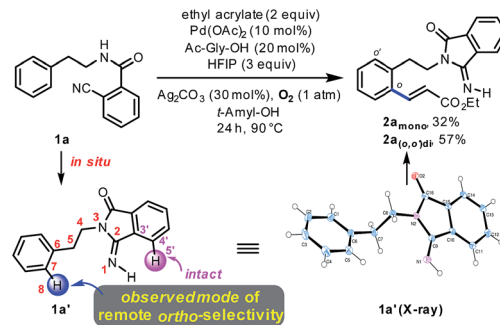


Scheme 1 Hypothesis of regioselectivity changed by a methylation.

screening with Pd(OAc)₂ as the catalyst (see ESI[†]), we were able to produce a high combined yield of *ortho*-olefinated products by treating **1a** with ethyl acrylate under oxygen with hexafluoroisopropanol (HFIP) as an additive and *N*-acetyl-glycine (Ac-Gly-OH) ligand.^{8a,18} Interestingly, the 2-cyanobenzoyl motif cyclized to an imidamide derivative in the products. To ascertain the mechanism of this olefination, **1a** was subjected to the above reaction conditions without adding ethyl acrylate, affording **1a'** that was believed to be the reactive substrate for the olefination. Indeed, after **1a'** was treated with the same olefination conditions, the desired products were generated in similar yields (see ESI[†]). Although this reaction pathway is not desired from our original hypothesis, the site selectivity of this reaction is surprisingly uncommon since the imino group of **1a'**, the most likely directing group on **1a'**, directed the cleavage of a remote *ortho*-C–H bond rather than a proximal *ortho*-C–H bond on the arene attached to the imidamide, which is in marked contrast to the *ortho*-C–H functionalizations of arylimine derivatives.¹⁹ The exact origin of the selectivity is unclear at present, and the study of the mechanism is under way.¹⁴

Several representative substrates were then surveyed briefly (Table 1). It was found that electron-withdrawing groups like chloride and fluoride were tolerated (**2b–c**), giving good yields of desired products. Good to excellent yields of products were also generated with substrates containing electron-donating groups such as methyl at the *meta*-position (**2d**) and methoxy at the *ortho*- (**2e**) and *para*-position (**2f**).

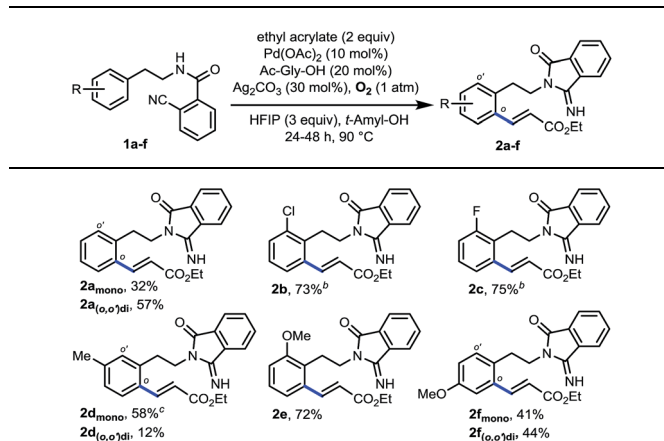
Having established the remote-selective *ortho*-C–H olefination of the secondary phenylethylamide, we were eager to test whether the selectivity could be switched to a remote-selective *meta*-C–H olefination after the secondary amide is methylated into a tertiary one (see the ESI[†] for methylation with MeI). Starting with the above *ortho*-olefination reaction conditions, we were very delighted to find that *N*-methyl amide **3a** could lead to a 10% yield of the desired product with a trace of other regioisomers (Table 2, entry 1). Inspired by the previous discovery that HFIP was a compatible solvent with nitrile-based templates,⁸ we switched the solvent to HFIP and found that the combined yield of desired products was increased dramatically



Scheme 2 A novel remote-selective *ortho*-C–H olefination.

to 58% with silver acetate as the sole oxidant (entry 2). Since when using weakly acidic HFIP as the sole solvent some substrate might decompose, DCE was added as the co-solvent, resulting in an increased yield of 73% (entry 3). To optimize the solvent system, we decreased the volume of HFIP to 15% and found that the combined yield was only slightly improved (entry 4). However, a further decreased volume of HFIP led to a much diminished yield (entry 5). Other solvents were also screened, but the combination of DCE and HFIP proved to be the best. The addition of a weak base, such as KHCO₃, to tune the acidity of the reaction system was not effective either (entry 6). Since a higher catalytic turnover of the Pd catalyst was observed with 50% volume of HFIP, we repeated the reaction with this solvent system at 80 °C and found that the combined yield was improved to 90% in 32 hours under nitrogen (entry 7), representing the highest catalytic turnover of the Pd catalyst. Finally, by adding 5 equivalents of DMF we were able to get more mono-olefinated product in 28 hours while maintaining the overall efficiency (entry 8, see the ESI[†] for more condition screenings). However, further screening of reaction conditions could not result in better mono- vs. di-olefination selectivity at present,

Table 1 Representative substrates of remote *ortho*-C–H olefination^a



^a Reaction conditions: **1** (0.2 mmol), ethyl acrylate (0.4 mmol), Pd(OAc)₂ (10 mol%), Ac-Gly-OH (20 mol%), HFIP (0.6 mmol), Ag₂CO₃ (0.06 mmol), O₂ (1 atm), *t*-amyl-OH (2 mL), 24–48 h, 90 °C. Isolated yields are reported, see the ESI for details. ^b 80 °C. ^c 70 °C.



Table 2 Screening of reaction conditions for *meta*-C–H olefination^a

| Entry | Solvents [v/v] | T (°C) | Yield (%) [4a _{mono} , 4a _{(m,m')di}] | 3a (%) |
|------------------|-------------------------|-----------|--|---------------|
| 1 ^b | <i>t</i> -Amyl-OH | 90 | 10 [10, 0] | 90 |
| 2 | HFIP | 90 | 58 [13, 45] | Trace |
| 3 | DCE/HFIP [50/50] | 90 | 71 [32, 39] | Trace |
| 4 | DCE/HFIP [85/15] | 90 | 73 [48, 25] | 10 |
| 5 | DCE/HFIP [95/5] | 90 | 39 [32, 7] | 44 |
| 6 ^c | DCE/HFIP [85/15] | 90 | 26 [26, 0] | 55 |
| 7 ^{d,e} | DCE/HFIP [50/50] | 80 | 90 [46, 44] | Trace |
| 8 ^{d,f} | DCE/HFIP [50/50] | 80 | 90 [58, 32] | Trace |

^a Reaction conditions: **3a** (0.2 mmol), ethyl acrylate (0.4 mmol), Pd(OAc)₂ (10 mol%), Ac-Gly-OH (20 mol%), AgOAc (0.6 mmol), solvent (2 mL), 24 h, 80–90 °C. Yield was determined by ¹H NMR analysis using CH₂Br₂ as the internal standard. ^b Using the same conditions as in Scheme 2. ^c KHCO₃ (2 equiv.) was added. ^d Under N₂. ^e 32 h. Isolated yields were 45% of **4a**_{mono} and 37% of **4a**_{(m,m')di}. ^f 28 h, DMF (5 equiv.) was added.

and a study on this issue is actively being carried out in our laboratory. The *meta*-selectivity was unambiguously verified by X-ray crystallographic analysis of a derivative obtained by hydrolyzing the ester group of **4a**_{mono} (see the ESI†).

With the optimized conditions at hand, we examined the scope of this remote *meta*-selective olefination protocol (Table 3). *Ortho*-substituted substrates with both electron-donating methyl and methoxy and electron-withdrawing bromo and chloro groups proved to be suitable substrates, producing good combined yields of *meta*-olefinated products (**4b–4e**). It is worth noting that arenes bearing bromo or chloro substituents (**4d** and **4e**) were compatible substrates, enabling further elaboration at the halogenated positions. Moreover, although we could not circumvent di-olefination (**4b**, **4d–e**), the fact that both *meta*-positions of 2-substituted substrates could be functionalized provides a great opportunity for synthesis of diversely substituted arenes, which is particularly beneficial for the drug discovery industry. The remaining *meta*-position of *meta*-substituted substrates was also selectively olefinated in high yields (**4f–4i**). *Para*-substituted compounds carrying methoxy or halide groups were also viable substrates for obtaining high yields of the desired products (**4j–4l**). Notably, despite the steric hindrance, the olefin partner could also be installed selectively at the *meta*-position with poly-substituted substrates (**4m–4n**), displaying an uncommon procedure for constructing new penta-substituted phenylethylamines. It is interesting to note that the reaction was not sensitive to the difference of steric hindrance and both *meta*-positions of **3n** could be olefinated. Finally, substituents at the benzylic position were also tolerated (**4o** and **4p**), presenting the potential utility of this protocol with a drug molecule (**4p**). The *meta*-selectivity of various substrates

was generally excellent with only minor amounts of other isomers whose amounts were hard to determine due to the presence of rotamers in the ¹H NMR spectra of the crude olefinated products. The exceptional substrate is **3g**, which also generated around 10% of other isomeric products owing to the electron-donating methoxy substituent. However, it is notable that the intrinsic electronic biases of the molecules were overall successfully overridden (**4d–4f**, **4k–4n**). Moreover, removal of the directing group was smoothly realized by hydrolysis with HCl to afford high yields of new *meta*-substituted phenylethylamines (see the ESI†).

To further expand the scope of this reaction, we examined various olefin coupling partners and found olefination of **3f** with α,β -unsaturated ketone, amide and phosphonate afforded desired products in good yields (Table 4, **6a–6c**). We were also pleased to find *trans*-2-butenate reacted stereoselectively with **3f** to give **6d** in moderate yield. It is noteworthy that this reaction was also compatible with cyclic tri-substituted olefin to give high yield of allylated product (**6e**). Finally, electron deficient

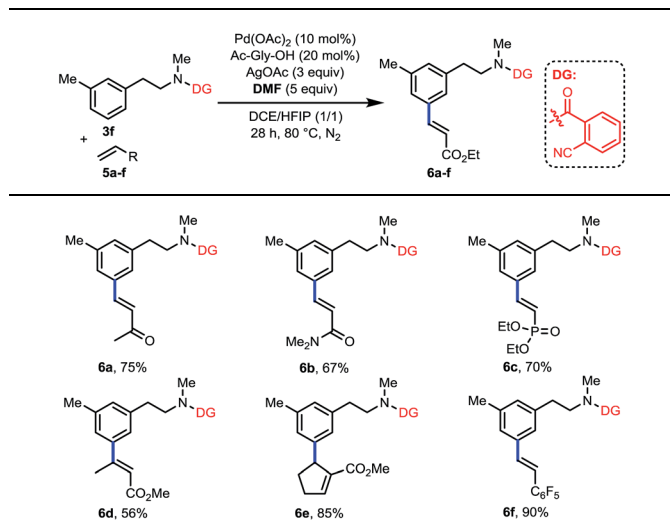
Table 3 *meta*-Olefination of phenylethylamine derivatives^a

| Substrate | Yield (%) |
|--------------------------------|--------------------|
| 4a _{mono} | 45% |
| 4a _{(m,m')di} | 37% |
| 4b _{mono} | 59% ^{b,c} |
| 4b _{(m,m')di} | 15% |
| 4c | 61% ^c |
| 4d _{mono (m)} | 11% ^{b,d} |
| 4d _{mono (m')} | 39% |
| 4d _{(m,m')di} | 29% |
| 4e _{mono (m)} | 13% ^{b,d} |
| 4e _{mono (m')} | 28% |
| 4e _{(m,m')di} | 41% |
| 4f | 76% ^c |
| 4g | 63% ^{c,e} |
| 4h | 78% ^c |
| 4i | 78% ^{b,d} |
| 4j | 74% ^c |
| 4k _{mono} | 61% ^b |
| 4k _{(m,m')di} | 19% |
| 4l _{mono} | 59% ^b |
| 4l _{(m,m')di} | 27% |
| 4m _{mono} | 50% ^{b,d} |
| 4m _{(m,m')di} | 24% |
| 4n _{mono (m)} | 24% ^{b,d} |
| 4n _{mono (m')} | 20% |
| 4n _{(m,m')di} | 29% |
| 4o _{mono} | 59% ^c |
| 4o _{(m,m')di} | 19% |
| 4p _{mono} | 37% ^b |
| 4p _{(m,m')di} | 35% |

Baclofen Derivatives

^a Reaction conditions: **3** (0.2 mmol), ethyl acrylate (0.4 mmol), Pd(OAc)₂ (10 mol%), Ac-Gly-OH (20 mol%), AgOAc (0.6 mmol), DCE (1 mL), HFIP (1 mL), 24–48 h, 80 °C, N₂. Isolated yields are reported, see the ESI† for details. ^b 90 °C. ^c DMF (1 mmol) was added. ^d DCE (0 mL)/HFIP (2 mL). ^e Around 10% of other isomers detected by ¹H NMR.

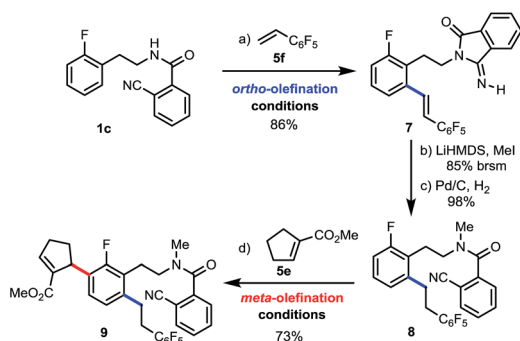


Table 4 Scope of olefin coupling partners^a

^a Reaction conditions: **3f** (0.1 mmol), **5** (0.2 mmol), Pd(OAc)₂ (10 mol%), Ac-Gly-OH (20 mol%), AgOAc (0.3 mmol), DMF (0.5 mmol), DCE (0.5 mL), HFIP (0.5 mL), 28 h, 80 °C, N₂. Isolated yields are reported.

styrene such as pentafluorostyrene **5f** was also effective with this method to produce excellent yield of product (**6f**), albeit electron-rich styrenes were not applicable coupling partners.

Finally, to demonstrate the potential of our method for streamlined synthesis of highly substituted arenes, we first subjected **1c** to our standard *ortho*-olefination conditions with **5f** and obtained *ortho*-olefinated **7** in 86% yield (Scheme 3). Then, much to our delight, we were able to convert **7** to the desired amide **8** with the required nitrile group which was reconstructed simultaneously with methylation by using LiHMDS, followed by hydrogenation of the double bond.²⁰ Lastly, the *meta*-selective allylation proceeded efficiently with tri-substituted olefin **5e** to afford tetrasubstituted arene **9** in good yield, enabling the building of complexity in a concise manner.



Scheme 3 Sequential *ortho*- and *meta*-C–H functionalizations. (a) **5f** (2 equiv.), Pd(OAc)₂ (10 mol%), Ac-Gly-OH (20 mol%), HFIP (3 equiv.), Ag₂CO₃ (30 mol%), O₂ (1 atm), *t*-amyl-OH, 24 h, 90 °C, 86% yield; (b) LiHMDS (2.5 equiv.), MeI (3 equiv.), THF, –15 °C, 58% yield (85% yield based on recovered starting material [brsm]); (c) Pd/C (12 mol%), H₂ (1 atm), MeOH, 98%; (d) **5e** (2 equiv.), Pd(OAc)₂ (10 mol%), Ac-Gly-OH (20 mol%), AgOAc (3 equiv.), DCE (1 mL)/HFIP (1 mL), 48 h, 90 °C, N₂, 73%.

Conclusions

In summary, a novel example of remote regiodivergent *ortho*- and *meta*-C–H functionalizations has been developed with phenylethylamine derivatives by introducing a novel 2-cyanobenzoyl group as the original directing functionality. A single methylation was sufficient to switch the remote regioselectivity. This method also enabled the novel sequential functionalizations of *ortho*- and *meta*-C–H bonds of a phenylethylamine derivative. Further development of this strategy will improve C–H functionalization to become a more versatile synthetic tool.

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