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Non-directed highly para-selective C-H functionalization of TIPS-protected phenols promoted by a proton shuttle

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Abstract: Palladium-catalyzed non-directed C-H functionalization provides an efficient approach for direct functionalization of arenes, but it usually suffers from poor site selectivity, limiting its wide application. Herein, it is reported for the first time that the proton shuttle of 3,5-dimethyladamantane-1-carboxylic acid (1-DMAdCO₂H) can affect the site selectivity during the C-H activation step in palladium-catalyzed non-directed C-H functionalization, leading to highly para-selective C-H olefination of TIPS-protected phenols. This transformation displayed good generality in realizing various other para-selective C-H functionalization reactions such as hydroxylation, halogenation, and allylation reactions. A wide variety of phenol derivatives including bioactive molecules of triclosan, thymol, and propofol, were compatible substrates, leading to the corresponding para-selective products in moderate to good yields. A preliminary mechanism study revealed that the spatial repulsion factor between proton shuttle and bulky protecting group resulted in the selective C-H activation at the less sterically hindered para-position. This new model non-directed para-selective C-H functionalization can provide a straightforward route for remote site-selective C-H activations.

Introduction

Highly regioselective transformation of a C-H bond into carbon-carbon or carbon-heteroatom bond provides a direct route for fine chemical synthesis, because it can reduce the steps of prior functionalizations. Generally, the selective functionalization
of ortho\textsuperscript{1-5}, or meta\textsuperscript{6-11} position C-H bonds requires a suitable functional group (directing group/template) that can coordinate with transition-metals to form a stable cyclometalated intermediate (Figure 1a, 1). However, the stoichiometric introduction/removal of the directing group (template) involves additional steps, thus limiting its application in chemical synthesis. The non-directed C-H activation reaction\textsuperscript{12-15} provides a straightforward way for functionalization of arenes, especially for the remote position. However, it usually suffers from poor site selectivity, leading to the ortho, meta, and para regioomers. Recently, noncovalent interaction strategies have been employed to realize the direct C-H borylation\textsuperscript{16-19} at meta or para position with iridium as the catalyst. A bifunctional nitrile template that anchors heterocyclic compound to provide a weak coordination center to achieve palladium-catalyzed meta-selective C−H olefination was first reported by the group of Yu\textsuperscript{14} (Figure 1a, 2). Until now, there are only a few successful examples of para selective C-H olefinations via a non-directed approach. The para-selective olefination of anilines\textsuperscript{20} was accomplished with a palladium catalyst by taking advantage of the electronic effect of substrates. In another example, remote site-selective C-H olefination of arene was also achieved by utilizing the steric and electronic effects of 2-pyridone\textsuperscript{21}. However, only limited substrates could realize the site selective reaction (Figure 1a, 3). Non-directed para-selective C-H functionalization can not only avoid the requirement of additional directing group/template, but can also provide a new model to directly functionalize a specific C-H bond on arene. Here, it is reported for the first time that the proton shuttle of 1-DMAdCO\textsubscript{2}H enables para-selective C-H functionalization of TIPS-protected phenols (Figure 1b). This new protocol can tolerate a variety of TIPS-protected phenols, including bioactive compounds and drugs. The para-selective olefination was well explored and further successfully extended to para-selective C-H hydroxylation, halogenation, and allylation reactions. Preliminary mechanism study revealed that the para-selectivity of this non-directed C-H activation was regulated by steric effect. The protecting group of TIPS enhanced the steric hindrance at ortho and meta positions, while the bulky proton shuttle-assisted C-H activation tended to occur at less hindered position. This combined spatial effect of the proton shuttle and protecting group resulted in highly para-selective C-H functionalizations.
Since the early pioneering work of Fagnou\textsuperscript{22-24}, the carboxyl group was demonstrated to play an important role during the process of activation of a C-H bond, which is well known as the concerted-metalathion (CMD) mechanism. Based on our previous discovery\textsuperscript{25-27}, the steric effect of the ligand attached with transition metal can effectively adjust the site selectivity during the reaction between free radicals and aromatic rings. Thus, it was speculated that the position of C-H bond activation may be controllable by switching different sized proton shuttles in palladium non-directed C-H activation undergoing a CMD process. Phenol and its derivatives are ubiquitous in various natural products, materials, and pharmaceuticals. Several reports have demonstrated that the site selectivity between ortho and para positions can be modified with different protecting groups in the ligand to promote palladium-catalyzed olefination reactions. For example, the TIPS-protected phenol can provide a 1/4.4 (o/p) selectivity in the 2-pyridone-accelerated non-directed C-H olefination reaction\textsuperscript{13}, while anisole affords a much less selective olefination reaction\textsuperscript{28-31} (o:m:p = 1.8/1.0/3.7). In regard to these points, we envision that the combination of spatial factors between a proton shuttle and a bulk protecting group, a palladium-catalyzed...
non-direct para-selective C-H activation would be feasible (Scheme 1), which might offer an effective approach to highly para-selective C-H functionalizations. Based on this key point, TIPS-protected phenol (1a) was directly treated with ethyl acrylate (2a, 1.5 equiv.) in the presence of Pd(OAc)$_2$ (5 mol%), N-protected amino acids (30 mol%), and AgOAc (2 equiv.) in HFIP at 50 °C for 24 h. Several N-protected amino acids including N-Ac-Val-OH, N-Ac-Ile-OH, and N-Ac-Leu-OH were screened, and good yield of olefinated product 3a was observed. However, none of them provided good selectivity between the para- and ortho-olefinated products (para/ortho < 5:1; L1, L2). Next, 2, 6-disubstituted pyridines were further tested, but the site-selectivity was not improved and the yield was also poor (L3, L4). Oxalyl amides (L5, L6), which play an important role in the nickel-enabled para-selective alkylation, were also investigated, but they too displayed poor selectivity. When phosphates (L7) were used, slightly improved selectivity was obtained, and the yields were good too. Encouraged by these results, typical proton shuttles such as L8, L9, and 1-AdCO$_2$H (L10) were subjected to the standard reaction conditions. Reasonably good selectivity (para/ortho = 10:1) was achieved when 1-AdCO$_2$H was employed as the additive. Although the reason for high para-selectivity is unclear, it is likely that the rigid structure of adamantane enhanced the interaction with the protecting group, leading to the para-selectivity. Gratifyingly, 3,5-dimethyladamantane-1-carboxylic acid (L11) was most effective, leading to 81% yield of the product with high para selectivity (para/ortho = 13:1). Several silver salts were further explored. Among them, silver 2-ethylhexanoate slightly improved the selectivity (para/ortho = 16:1) and afforded product 3a in 81% yield. Control experiments show that palladium was indispensable for this transformation. It is worth noting that di-olefinated products were observed in less than 5 mol% yield, due to the steric hindrance effect between the proton shuttle and TIPS protecting group. Various protected phenols (S$_1$-S$_4$) were subjected to the standard reaction conditions, and it was evident that the selectivity decreased with less bulky protecting groups. These results further support the hypothesis that the high para-selectivity is influenced by the steric repulsion between the bulky proton shuttle and protecting group (see supporting information).
Scheme 1. Optimization of ligand

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Yield (%)</th>
<th>Site Selectivity</th>
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</thead>
<tbody>
<tr>
<td>3a</td>
<td>62%</td>
<td>1:3</td>
</tr>
<tr>
<td>3b</td>
<td>57%</td>
<td>1:3</td>
</tr>
<tr>
<td>3c</td>
<td>37%</td>
<td>1:4</td>
</tr>
<tr>
<td>3d</td>
<td>43%</td>
<td>1:5</td>
</tr>
<tr>
<td>3e</td>
<td>47%</td>
<td>1:5</td>
</tr>
<tr>
<td>3f</td>
<td>43%</td>
<td>1:6</td>
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</tbody>
</table>

Substrate scope. With the optimized reaction conditions, various ortho-substituted TIPS-protected phenols were subjected to the standard reaction conditions (Scheme 2). Substrates with electron-donating and electron-withdrawing functional groups such as ethyl, isobutyl, tert-butyl, cyclohexyl, chloride, bromide, OCF₃, and phenyl (3b-3j) were all well tolerated, leading to the corresponding products in good yields with high para-selectivity. Moreover, ortho-nitro-substituted phenol (3k) was compatible, leading to the corresponding product in acceptable yield. The meta chloride (3l) or fluoride (3m) substituted phenols all provided the olefinated products in good yields with high para-selectivity. When TIPS-protected 3-bromophenol (3n) was used, a slightly poor selectivity was observed, which might be due to the steric hindrance of bromide. A wide variety of di-substituted phenols (3o-3z) were further examined and all of them afforded the corresponding products in moderate to good yields with high site-selectivity, highlighting the synthetic importance of this non-directed para-selectivity olefination reaction. Both tetrahydro-1-naphthol (3aa) and inden-4-ol (3ab) were well tolerated.
generating the corresponding para-olefinated products in good yield.

**Scheme 2. Scope of phenols**
Encouraged by the success of 1-DMAdCO$_2$H enabled para-selective C-H olefination, the scope of olefin coupling partners was evaluated next (Scheme 3). Generally, unsaturated olefins are effective coupling partners for this transformation. Acrylate derivatives (4a-4f) all performed well, yielding the para-olefinated products in good yields. It is worth noting that fluorinated functional group can be indirectly introduced into the aromatic ring.

1,2-Disubstituted-unsaturated olefins such as methyl crotonoate (4g), ethyl crotonoate (4h), methyl pent-2-enoate (4i), and diethyl fumarate (4j) were all suitable coupling partners in this transformation. The steric effect of these substrates was likely responsible for the low transformation of 1a, leading to low yields of the corresponding olefinated products.

**Scheme 3. Scope of Olefins**

Synthetic application. Only one equivalent of arene was used in this non-directed para-selective C-H olefination reaction, which can guarantee its late-stage functionalization and scale-up of the bioactive compound (Scheme 4). For example, a gram scale reaction was performed with TIPS-protected thymol (5a), which is a drug molecule, and the olefinated product was isolated in 65% yield with high para-selectivity. The TIPS-protected amylmetacresol (5b), disoprofol (5c), and pyrocatechol (5d) all proceeded well in the reaction, affording the olefinated product in good yields with high para-selectivity. Importantly, the key structure of isoamyl 4-methoxycinnamate and octyl 4-methoxycinnamate (5e, 5f) could be synthesized in one step in good yields.
Scheme 4. Alkenylation of drug molecules

To demonstrate the potential generality of this proton-shuttle enabled non-directed para-selective C-H activation in affording various transformations, non-directed para-selective iodination, hydroxylation, and allylation reactions were explored (Scheme 5).

When NIS was used instead of ethyl acrylate, a highly para-selective iodinated product was isolated with substrate 1a. The ortho-, meta-, and multi-substituted TIPS-protected phenols all performed well, yielding the indoated products in good yields. Various pharmaceuticals such as thymol, amylnmetacresol, guaiacol, and triclosan derivatives were all compatible, leading to the indoated products in good yields (6a-6i). It was further revealed that cinnamyl bromide was also an effective coupling partner with cesium carbonate as the base. Several phenol derivatives were all compatible in this transformation, generating the acrylated products in good yields (7a-7d).

Furthermore, a highly para-selective hydroxylation was achieved when NFSI was used as the oxidant, Z-Nva-OH as the ligand, and DABCO as the base with 2 equiv. of water under oxygen atmosphere in HFIP at 50 °C for 24 h. A wide variety of substituted phenols were all tolerated well, providing the hydroxylated products in moderate to good yields (8a-8d).
Scheme 5. Types of para-selective C–H functionalizations

<table>
<thead>
<tr>
<th>Iodination&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Allylation&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Hydroxylation&lt;sup&gt;c&lt;/sup&gt;</th>
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<tr>
<td><img src="image.png" alt="Image" /></td>
<td><img src="image.png" alt="Image" /></td>
<td><img src="image.png" alt="Image" /></td>
</tr>
<tr>
<td>6a, 78%</td>
<td>7a, 62%</td>
<td>8a, 74%</td>
</tr>
<tr>
<td>6b, 75%</td>
<td>7b, 54%</td>
<td>8b, 70%</td>
</tr>
<tr>
<td>6c, 71%</td>
<td>7c, 47%</td>
<td>8c, 52%</td>
</tr>
<tr>
<td>6d, 62%</td>
<td>7d, 52%</td>
<td>8d, 60%</td>
</tr>
<tr>
<td>6e, 84%</td>
<td></td>
<td></td>
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</table>

[a]: 1 (0.1 mmol), NIS (1.1 equiv), Pd(OAc)<sub>2</sub> (5 mol%), 1-DMAdCO<sub>2</sub>H (50 mol%), HFIP (0.5 mL) at 60 °C for 24 h. [b]: 1 (0.1 mmol), Cinnamyl bromide (1.2 equiv), Pd(OAc)<sub>2</sub> (5 mol%), 1-DMAdCO<sub>2</sub>H (50 mol%), CsCO<sub>3</sub> (1.5 equiv), HFIP (0.5 mL) at 60 °C for 24 h. [c]: 1 (0.1 mmol), NFSI (4 equiv), Pd(OAc)<sub>2</sub> (5 mol%), Z-Nva-OH (30 mol%), DABCO (1.2 equiv), H<sub>2</sub>O (2 equiv) HFIP (0.5 mL) at 50 °C under O<sub>2</sub> atmosphere for 24 h.

Gratifyingly, a ten gram scale para-selective iodination reaction was also achieved with TIPS-protected triclosan, which is a well-known fungicide. To further demonstrate the synthetic importance of this new strategy, a variety of transformations were carried out through palladium cross-coupling<sup>32-34</sup> with iodinated-triclosan as the starting material (Scheme 6; 9b, 9c, 9d). In addition, the protecting group can be easily removed<sup>35</sup> under basic conditions in excellent yield (9a).
Mechanistic studies. To further understand the role of 1-DMAdCO₂H in this non-directed palladium-catalyzed C-H olefination reaction, different TIPS-protected phenols were tested with N-Ac-Gly-OH or acetic acid as the additive (Scheme 7a). The results clearly indicate that the site selectivity cannot be controlled without 1-DMAdCO₂H as the proton shuttle. The para-C-H bond of TIPS-protected 2-ethylphenol substrate was selectively deuterated under the catalysis of palladium acetate in D₄-acetic acid, generating the para-deuterated TIPS-protected 2-ethylphenol (Scheme 7b). This result suggests that spatial repulsion factor between the proton shuttle and the bulky protecting group resulted in the selective C-H activation at the para-position, which rules out the role of olefination coordination in the para-selectivity (Scheme 7c). A kinetic effect of 2.65 was obtained, indicating that C-H activation was the rate determining step and further supporting the above hypothesis. When acetic acid was used as the proton-shuttle, a kinetic effect of 3.45 was observed, suggesting that the additive 1-DMAdCO₂H was more conducive to assist C-H bond activation with a palladium catalyst (Scheme 7d).
In conclusion, this paper reveals for the first time that the bulky proton shuttle can affect the site selectivity during the C-H activation step when the non-directed C-H functionalizations undergo concerted-metalation deprotonation (CMD) mechanism with a palladium catalyst. Various phenol derivatives including the bioactive molecules of thymol, propofol, and triclosan, were all \textit{para}-selectively functionalized, leading to the corresponding olefinated, iodinated, hydroxylated, or allylated products in moderate to good yields. Moreover, the ten-gram scale \textit{para}-selective iodination reaction proceeded...
well with the bioactive compound of triclosan, facilitating its late-stage functionalization through cross-coupling reactions. Control experiments show that the use of a bulky proton shuttle (1-DMAHCO₂H) is the key factor to achieve $para$-selectivity. A preliminary mechanism study revealed that the spatial repulsion factor between proton shuttle and bulky protecting group resulted in the selective C-H activation at the sterically hindered $para$-position. This successful example of palladium-catalyzed non-directed $para$-selective C-H functionalization provides a straightforward route for remote site-selective C-H activation, which would open a new door for other remote site-selective C-H activation reactions.

References


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**Author contributions**

Y.Z. and J.G. conceived and designed the strategy. J.G. principally performed the experiments. Z.F., G.T. helped to conduct some experiments and collect data. Y.Z. provided overall supervision and wrote the manuscript.

**Competing interests**

The authors declare no competing interests.