**meta-Selective olefination of fluoroarenes with alkynes using CO₂ as a traceless directing group†**

Andrew R. A. Spencer, Rishi Korde, Marc Font and Igor Larrosa

Over the last few decades C–H olefination has received significant interest, due to the importance and usefulness of aryl olefins both as synthetic targets and intermediates. While a wide range of ortho-olefination protocols have been developed, only a small number of meta-olefinations are currently available. Importantly, the most common approach to meta-olefination, using a large meta-directing template, is not suitable for substrates such as fluoroarenes, which cannot be derivatised. We report that the meta-selective olefination of fluoroarenes can be achieved via the use of CO₂ as a traceless directing group, which can be easily installed and removed in a one-pot process. Furthermore, this approach avoids the use of stoichiometric Ag(i)-salts, commonly used in C–H olefinations, and affords complete meta-over ortho/para-regioselectivity.

**Introduction**

Over the last decades, direct C–H bond activation has emerged as a powerful tool providing a wide variety of novel disconnections simplifying access to, and accelerating the synthesis of complex molecules. Aryl olefins are synthetically important motifs, as useful intermediates in synthesis, and also due to their widespread presence in bioactive molecules and pharmaceuticals. Consequently, large efforts have been devoted to the development of C–H olefination methodologies. While a large number of strategies have been developed for the olefination of C–H bonds ortho to a directing group, comparatively few exist for those in meta positions. To date, the only available ‘direct’ strategy for meta-olefination, involves the use of the U-shaped directing groups pioneered by the group of Yu (Scheme 1a). This approach has been used to perform meta-olefinations on derivatives of benzyl alcohols, N-methyl anilines, phenyl acetic acids, benzyl sulfonylesters, benzoic acids, aromatic carbonyls and aryl boronic acids, using alkynes as coupling partners. The major drawback of this approach arises from the need to install the large U-shaped directing group covalently bound, and its subsequent removal after the C–H olefination, as separate synthetic steps. In addition, stoichiometric toxic Ag(i)-salts are required as terminal oxidants in these oxidative couplings. A recent report has expanded the applicability of this strategy to the Rh(III)-catalysed meta-olefination of hydrocinnamic acid derivatives using alkynes as coupling partners (Scheme 1b). However, despite it being a redox neutral process, it still requires over three equivalents of Ag(i)-salts as an additive. Furthermore, in addition to the main meta-olefination product, 5–10% of the sometimes difficult to separate ortho and para olefination products are typically obtained. Additionally, the U-shaped directing group strategy is only applicable to aromatics containing a group that can be easily derivatised.

**Scheme 1** Comparison of the template approach and the traceless directing group relay strategy for the meta olefination of arenes.
Fluoroarenes are recurring structural motifs in pharmaceuticals, agrochemicals, organic materials and other biologically relevant compounds. Approximately 30% of pharmaceuticals and 40% of agrochemicals currently contain at least one fluorine atom, usually at the aromatic ring. Thus, the direct C–H functionalisation of monofluoroarenes can provide straightforward access to valuable materials (Fig. 1). While monofluoroarenes generally present low reactivity towards direct C–H olefination, a number of examples have been reported that use the arene as cosolvent to achieve ortho, para-selective olefination. Some pioneering methods for direct olefination using the fluoroarene as the limiting reagent have been reported by Yu et al., but mixtures of ortho, meta and para substitution are obtained. However, meta-selective olefination has never been achieved. Importantly, the U-shaped directing group strategy cannot be applied to this class of substrates. We have previously shown that CO2 can be used as a traceless directing group for the meta-selective arylation of phenols, fluoroarenes and anisoles (Scheme 1c). The process relies on the easy carboxylation of these aromatic substrates, to install a temporary carboxylate directing group. The carboxylate can then directly the arylation before it is cleaved, in a tandem process, thus allowing a one-pot meta-arylation to proceed. However, the CO2 traceless directing group approach has never been demonstrated on any other type of functionalisation. Herein we report the first example of a meta-olefination of fluoroarenes (Scheme 1d). This ruthenium-catalysed process involves the in situ installation and removal of a carboxylate, from CO2, uses alkynes as coupling partners and avoids the need for stoichiometric use of Ag(i)-salts.

Results and discussion

We have previously developed an optimised protocol for the lithiation/carboxylation of fluoroarenes suitable for combination in a one-pot process with a Pd-catalysed tandem arylation/protondecarboxylation, leading to the meta-arylation of fluoroarenes. In 2016, three methods for the Ru-catalysed tandem ortho-olefination/protondecarboxylation of benzoic acids by hydroarylation of alkynes were reported by Hartwig and Zhao, Ackermann and Gooßen. Miura and co-workers have also reported numerous methods for the ortho-olefination/protodecarboxylation of benzoic acids using acrylates and styrenes as coupling partners. We envisaged these methods could be ideally adapted to operate in combination with the directed ortho-metallation/carboxylation approach to furnish the desired meta-olefination of fluoroarenes.

We started our investigation by probing the decarboxylative olefination of the fluorotoluic acid 1a with diphenyl acetylene (2a), using Ackermann’s protocol (Table 1, entry 1). To evaluate the effect of the installation of the carboxylic acid using ortho-lithiation during the desired one-pot process we tested the addition of 2 equiv. of LiOAc (entry 2), revealing a significant negative effect in reactivity. Gratifyingly, addition of 3 equiv. of AcOH efficiently reversed the effect of the presence of the Li-salt (entry 3), providing a method to ensure compatibility of the protocol with the carboxylation step. In previous work on Ru-catalysed ortho-arylation of polyfluoroarenes we observed an inhibitory effect of coordinated p-cymene, leading to the development of the arenne-free Ru-precatalyst [Ru(BuCN)6] [BF4]2. However, the use of this catalyst in the olefination reaction led to no product formation (entry 4), suggesting the η5-coordinated arene is essential for reactivity towards olefination. Accordingly, the weaker coordinating benzene-complex led to poor reactivity (entry 5), whereas the highly coordinating C6Me6-bearing Ru complex gave an improved yield, an effect which has previously been observed by Gooßen.

We then moved to optimize the full one-pot protocol, starting from ortho-fluorotoluene (4a, Table 2). Carboxylation of the fluoroarene was observed to occur in nearly quantitative conversion using secBuLi at −78 °C for 30 min, followed by quenching with CO2. Subsequent addition to the same flask of AcOH (3 equiv.), alkyne 2a and 5 mol% Ru(C6Me6)(OAc)2 in DCE led to the formation of the meta-olefinated product 3aa in an excellent 85% yield (entry 1). The use of 4 equiv. or 5 equiv. of AcOH led to reduced yields (entries 2 and 3). Examination of other organic acids also led to lower yields (entries 4–6),

Table 1  Optimisation of catalyst. Yields were determined by 19F NMR analysis using 1-bromo-4-fluorobenzene as an internal standard

<table>
<thead>
<tr>
<th>Entry</th>
<th>[Ru]</th>
<th>3aa (yield%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td></td>
<td>81</td>
</tr>
<tr>
<td>2b</td>
<td></td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>86</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>25</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>93</td>
</tr>
</tbody>
</table>

a Without LiOAc and AcOH. b Without AcOH.

Fig. 1  Commercially available pharmaceuticals containing a meta alkynyl fluoroarene.
revealing AcOH as the optimal acid to facilitate this one-pot process.

With the optimised conditions in hand, we investigated the generality of the process with regards to the fluoroarene core (Scheme 2). Substitution patterns in ortho, meta or para positions were all tolerated, albeit only the relatively small F-atom was compatible in para (3ad). When larger groups were installed in the para position such as Me and Cl, no reactivity could be observed (3al and 3am). Furthermore, the reaction is in all cases completely selective towards mono-olefination and towards the meta position, with no traces of neither bisolefination nor other regioisomers observed by NMR and GCMS analysis of the reactions, even for simple fluorobenzene (3ab). Both electron withdrawing groups (3ac, 3ad, 3ag and 3ah) and donating groups (3aa, 3ae, 3af and 3aj) were compatible with the procedure. Chloroarenes (3ah) were also tolerated with no traces of de-halogenated products. Biaryl and naphthyl-based aromatic systems were also suitable substrates (3ai and 3ak).

Subsequently we investigated the scope with respect to the alkyne coupling partner (Scheme 3). Both electron donating (3ba and 3ca) and electron withdrawing groups (3da, 3ea and 3fa) were reactive giving excellent yields. Heterocyclic moieties were also tolerated (3ga). While bisallyl acetylenes were incompatible with the procedure (3ia), unsymmetrical alkyl, aryl-acetylenes led to completely regioselective addition at the carbon adjacent to the alkyl group (3ha and 3ia). Diesters and unsymmetrical ester, aryl-acetylenes were also tolerated offering a handle for further functionalisation (3ja and 3ka) with ethyl phenyl propiolate preferentially forming the α-aryl ester (3ja). No product was observed when terminal acetylenes were used (3ma).

This new meta-olefination methodology can be easily scaled up with, for example, 3aa being formed in 70% yield (1.10 g) without any changes to the protocol.

### Table 2

<table>
<thead>
<tr>
<th>Entry</th>
<th>Acid (equiv.)</th>
<th>4aa (yield%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AcOH (3)</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>AcOH (4)</td>
<td>75</td>
</tr>
<tr>
<td>3</td>
<td>AcOH (5)</td>
<td>72</td>
</tr>
<tr>
<td>4</td>
<td>PivOH (3)</td>
<td>71</td>
</tr>
<tr>
<td>5</td>
<td>iBuCOOH (3)</td>
<td>1</td>
</tr>
<tr>
<td>6</td>
<td>TFA (3)</td>
<td>5</td>
</tr>
</tbody>
</table>

This new meta-olefination methodology can be easily scaled up with, for example, 3aa being formed in 70% yield (1.10 g) without any changes to the protocol.
A plausible mechanism for this transformation is shown in Scheme 4, based on the mechanistic studies performed by Hartwig and Zhao.\(^{39}\) ortho-Lithiation and carboxylation of fluoroarene 4 affords lithium benzoate 5. ortho-C–H activation of lithium benzoate 5 with ruthenium complex 6a affords cyclo-metallated complex 6b. Insertion of alkyne 2a into the Ru–C of 6b forms complex 6c, which can in turn decarboxylate to from the 5-membered metalloccycle in complex 6d. Protonation of this complex with 2 equiv. of AcOH liberates the final product 3 and reforms complex 6a, thus closing the catalytic cycle.

Conclusions

In conclusion, we have developed the first example of a methodology for the meta-selective olefination of fluoroarenes. The natural ortho, para-reactivity of this class of substrates has been overcome by employing CO\(_2\) as a traceless directing group, that can be installed, used to control reactivity and then seamlessly removed in a one-pot process. Good to excellent yields can be obtained with a variety of functional groups and substitution patterns in both fluoroarene and alkyne, and in all cases complete meta-regioselectivity is observed.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references


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