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meta-Selective olefination of fluoroarenes with alkynes using CO_2 as a traceless directing group†

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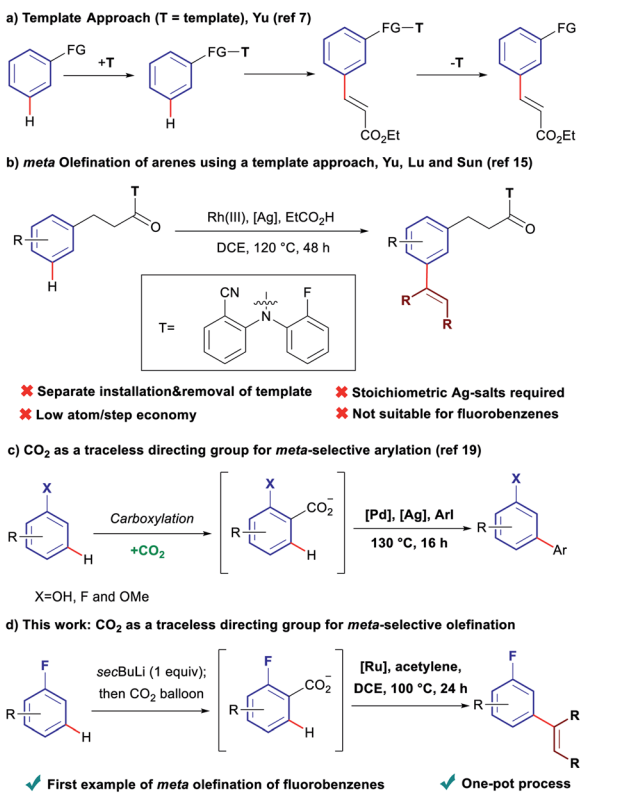
Over the last few decades C–H olefination has received significant interest, due to the importance and usefulness of aryl olefins both as synthetic targets and intermediates. While a wide range of *ortho*-olefination protocols have been developed, only a small number of *meta*-olefinations are currently available. Importantly, the most common approach to *meta*-olefination, using a large *meta*-directing template, is not suitable for substrates such as fluorobenzenes, which cannot be derivatised. We report that the *meta*-selective olefination of fluoroarenes can be achieved *via* the use of CO_2 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.[1] Aryl olefins are synthetically important motifs, as useful intermediates in synthesis,[2] and also due to their widespread presence in bioactive molecules and pharmaceuticals.[3] Consequently, large efforts have been devoted to the development of C–H olefination methodologies.[4] While a large number of strategies have been developed for the olefination of C–H bonds *ortho* to a directing group,[5] comparatively few exist for those in *meta* positions.[6] 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).[7] This approach has been used to perform *meta*-olefinations on derivatives of benzyl alcohols,[8] *N*-methyl anilines,[9] phenyl acetic acids,[10] benzyl sulfonyl esters,[11] benzoic acids,[12] aromatic carbonyls[13] and aryl boronic acids,[14] using alkenes 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).[15] 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.

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Fluoroarenes are recurring structural motifs in pharmaceuticals, agrochemicals, organic materials and other biologically relevant compounds.[16] Approximately 30% of pharmaceuticals and 40% of agrochemicals currently contain at least one fluorine atom, usually at the aromatic ring.[16] Thus, the direct C–H functionalisation of monofluorobenzenes can provide straightforward access to valuable materials (Fig. 1).[3b–d] 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.[17] 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.[18] 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 CO_2 can be used as a traceless directing group for the *meta*-selective arylation of phenols, fluorobenzenes and anisoles (Scheme 1c).[19] The process relies on the easy carboxylation of these aromatic substrates, to install a temporary carboxylate directing group. The carboxylate can then direct the arylation before it is cleaved, in a tandem process, thus allowing a one-pot *meta*-arylation to proceed. However, the CO_2 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 fluorobenzenes (Scheme 1d). This ruthenium-catalysed process involves the *in situ* installation and removal of a carboxylate, from CO_2, 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/protodecarboxylation, leading to the *meta*-arylation of fluoroarenes.[19c] In 2016, three methods for the Ru-catalysed tandem *ortho*-olefination/protodecarboxylation of benzoic acids by hydroarylation of alkynes were reported by Hartwig and Zhao,[20] Ackermann[21] and Gooβen.[22] Miura and co-workers have also reported numerous methods for the *ortho*-olefination/protodecarboxylation of benzoic acids using acrylates and styrenes as coupling partners.[23] We envisaged these methods could be ideally adapted to operate in combination with the directed *ortho*-metalation/carboxylation approach to furnish the desired *meta*-olefination of fluorarenes.

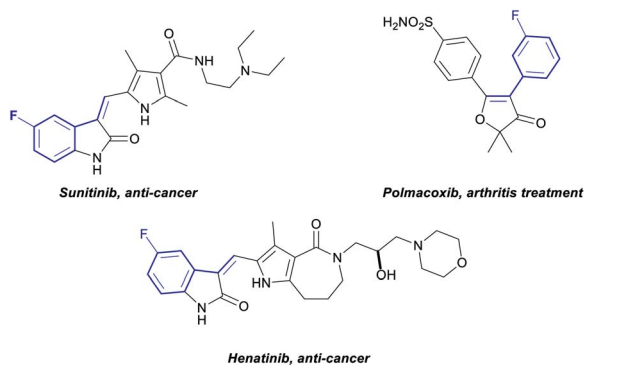
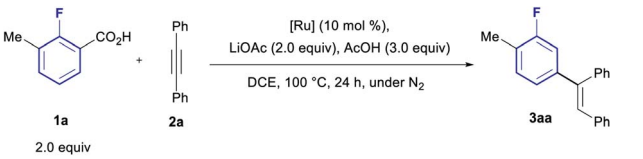


Fig. 1 Commercially available pharmaceuticals containing a *meta* alkenyl fluoroarene.

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



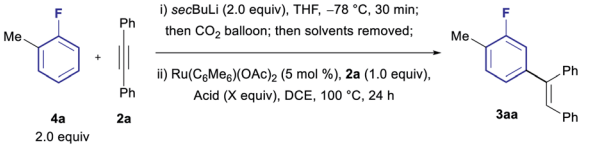
Entry	[Ru]	**3aa** (yield%)
1[a]	Ru(*p*-cymene)$(CO_2Mes)_2$	81
2[b]	Ru(*p*-cymene)$(CO_2Mes)_2$	60
3	Ru(*p*-cymene)$(CO_2Mes)_2$	86
4	$[Ru(t\text{BuCN})_6][BF_4]_2$	0
5	$[Ru(C_6H_6)(OPiv)_2]$	25
6	**$[Ru(C_6Me_6)(OAc)_2]$**	**93**

[a] Without LiOAc and AcOH. [b] Without AcOH.

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).[21] 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 polyfluorobenzenes we observed an inhibitory effect of coordinated *p*-cymene, leading to the development of the arene-free Ru-precatalyst $[Ru(t\text{BuCN})_6][BF_4]_2$.[24] However, the use of this catalyst in the olefination reaction led to no product formation (entry 4), suggesting the η^6-coordinated arene is essential for reactivity towards olefination. Accordingly, the weaker coordinating benzene-complex led to poor reactivity (entry 5), whereas the highly coordinating C_6Me_6-bearing Ru complex gave an improved yield, an effect which has previously been observed by Gooβen.[25]

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 *sec*BuLi at −78 °C for 30 min, followed by quenching with CO_2. Subsequent addition to the same flask of AcOH (3 equiv.), alkyne **2a** and 5 mol% $Ru(C_6Me_6)(OAc)_2$ 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 2 Optimisation of one-pot protocol. Yields were determined by ^{19}F NMR analysis using 1-bromo-4-fluorobenzene as an internal standard



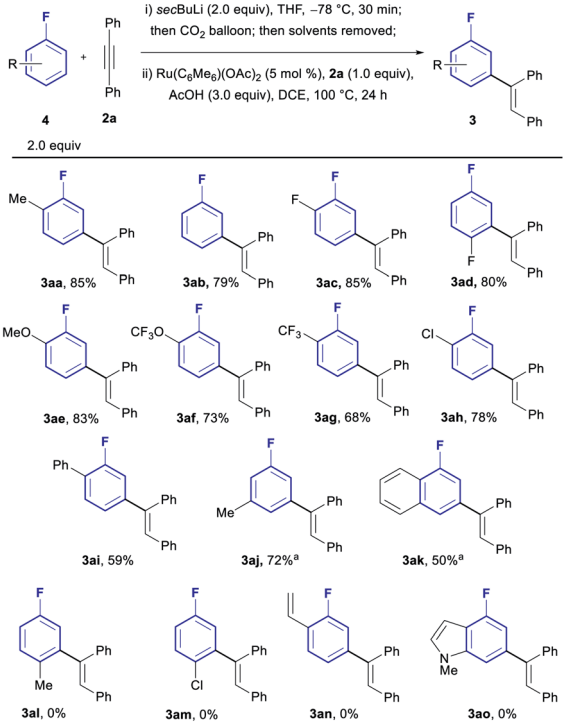
Entry	Acid (equiv.)	**4aa** (yield%)
1	**AcOH (3)**	**85**
2	AcOH (4)	75
3	AcOH (5)	72
4	PivOH (3)	1
5	*i*BuCOOH (3)	71
6	TFA (3)	5

revealing AcOH as the optimal acid to facilitate this one-pot process.

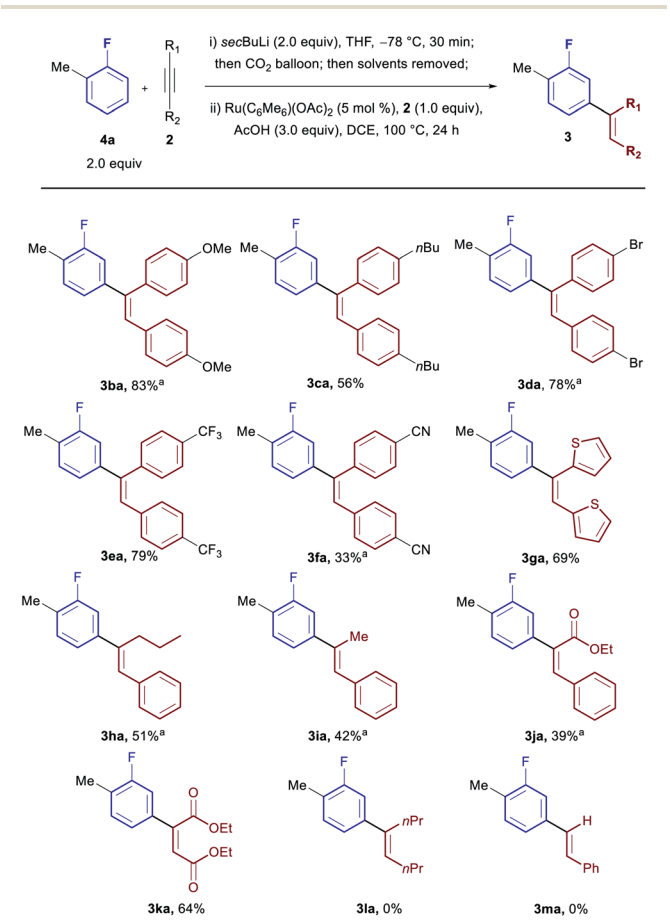
With the optimised conditions in hand, we investigated the generality of the process with regards to the fluoroarene core (Scheme 2). Substitution patterns in *ortho*, *meta* or *para* positions were all tolerated, albeit only the relatively small F-atom was compatible in *para* (**3ad**). When larger 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 bisalkyl acetylenes were incompatible with the procedure (**3la**), 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**).

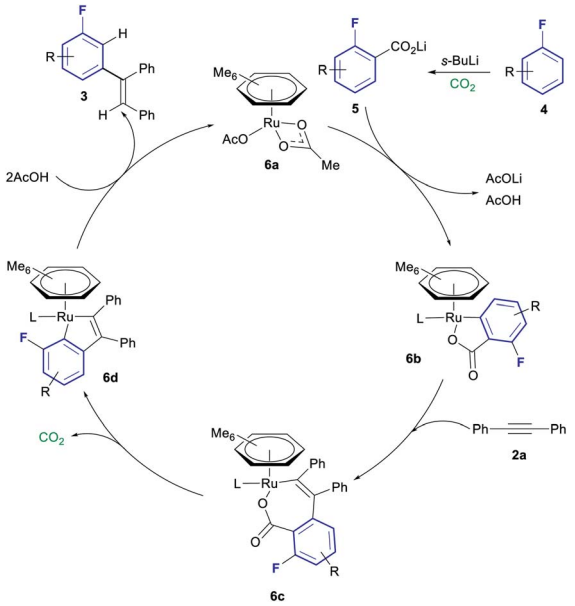
This new *meta*-olefination methodology can be easily scaled up with, for example, **3aa** being formed in 70% yield (1.10 g) without any changes to the protocol.



Scheme 2 Scope in fluoroarene core. [a]10 mol% catalyst used.



Scheme 3 Scope in acetylene. [a]10 mol% catalyst used.



Scheme 4 Plausible mechanism for the Ru catalysed *meta* olefination of fluoroarenes.

A plausible mechanism for this transformation is shown in Scheme 4, based on the mechanistic studies performed by Hartwig and Zhao.[20] *ortho*-Lithiation and carboxylation of fluoroarene **4** affords lithium benzoate **5**. *ortho*-C–H activation of lithium benzoate **5** with ruthenium complex **6a** affords cyclometallated 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 metallocycle 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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