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Ligand free palladium-catalyzed synthesis of α-trifluoromethylacrylic acids and related acrylates by three-component reaction

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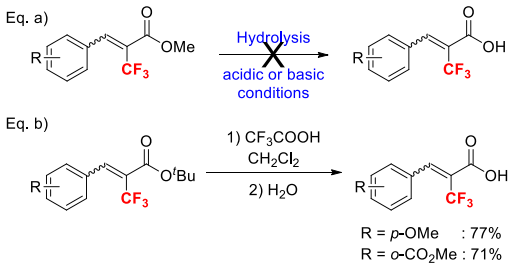
Abstract: Aryl iodides and 2-(trifluoromethyl)acrylic acid reacted together in ligand-free Mizoroki-Heck reaction furnishing a quick and efficient access to highly valuable α-trifluoromethylacrylic acids. The useful transformation was independent with regard to the electronic nature of the aryl group substituent. A three-component one-pot version was also developed to give diverse substituted acrylates. The versatility of α-trifluoromethylacrylic acids was demonstrated by quick access to 3-CF_3-coumarins as well as fluorinated analogues of therapeutic or cosmetic agents. Finally, we proposed a catalytic cycle based on the silver carboxylate salt, identified as a key intermediate in the reaction.

Keywords: Fluoroalkenes; trifluoromethyl; acrylates; palladium; silver

Nowadays, due to the unique properties of the fluorine atom, fluorinated organic compounds are found in many fields such as pharmacy, agrochemistry or materials.[1] Among the numerous fluoroorganic compounds, we are particularly interested by those containing a trifluoromethylalkene moiety. Indeed, this highly attractive group is known as an efficient peptide bond surrogate and can also be incorporated in many bio-relevant molecules.[2] More specifically, in a current ongoing research project, we have targeted the synthesis of α-trifluoromethylacrylic acids and their use in subsequent transformations. In the literature, α-trifluoromethylacrylic acids exhibited relevant applications in medicinal chemistry[3] and materials science[4] and have emerged as key intermediates for the production of valuable α-trifluoromethyl asymmetric compounds[5] as well as a high variety of polymers.[6]

As we recently reported the synthesis of alkyl α-trifluoromethylacrylates,[7] we first thought to simply hydrolyze the esters to the corresponding acids. Unfortunately, the various basic and acidic conditions which were tried were unsuccessful from the methyl α-trifluoromethylacrylate (Scheme 1, Eq. a)). To circumvent this problem, we then decided to hydrolyze a *tert*-butyl α-trifluoromethylacrylate in acidic condition with the generation of a stable *tert*-butyl carbocation and the recovery of the acid at the end of the reaction. Two examples were studied and good yields were obtained (Scheme 1, Eq. b)).



Scheme 1. Hydrolysis of alkyl α-trifluoromethylacrylates.

At the same time, a literature survey of the methods reported to directly give α-trifluoromethylacrylic acids was performed and we were surprised that, to our knowledge, only a few reactions were reported to give access to these valuable targets. In the early seventies, England and Krespan published the first synthesis of α-trifluoromethylacrylic acid starting from perfluoro-methacryloyl fluoride and *p*-(*N*,*N*-dimethylamino) benzaldehyde in a two-step reaction with a global yield of 50%. No indication was given about the ratio of the *E*/*Z* isomers of the acid (Scheme 2, Eq. a)).[8] Several years later, Kunyants *et al.* reported the reaction between three different Grignard reagents with 3,3,3-trifluoro-2-(trifluoromethyl)propionic acid to give a mixture of α-trifluoromethylacrylic acids in moderate yields (Scheme 2, Eq. b)).[9] Finally, the most efficient method to date was published in 2011 by Fang *et al.*.[10] They reported a Knoevenagel-type reaction, mediated by $TiCl_4$, between aldehydes and 3,3,3-trifluoropropionic acid (Scheme 2, Eq. c)). The

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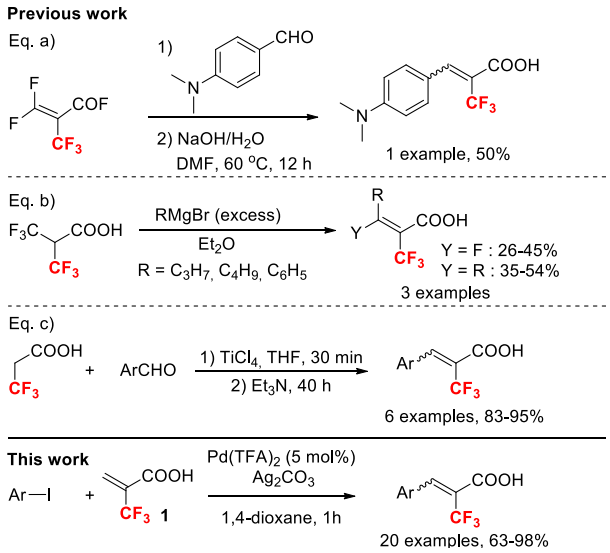
reaction has good stereoselectivity but only six examples were described and the reaction time was rather long (almost two days).

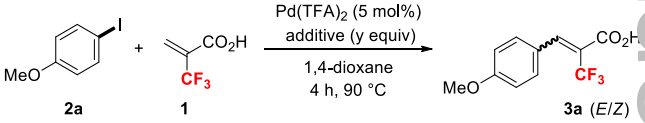


Scheme 2. Reported access to α-trifluoromethylacrylic acids

Due to the lack of rapid, efficient and general methods to obtain α-trifluoromethylacrylic acids, combined with the difficulty of hydrolysis of alkyl α-trifluoromethylacrylates, we wondered if we could apply a Mizoroki-Heck reaction directly to the commercially available α-(trifluoromethyl)acrylic acid **1** as a coupling partner, and avoid a decarboxylation process. Indeed, this acid **1** has already been used in olefination reactions but via a decarboxylative process giving access to 2-aryl-1-trifluoromethylvinyl derivatives.[11] What also prompted us to study a new Mizoroki-Heck reaction with this substrate was the effective low cost of α-(trifluoromethyl)acrylic acid (0.70$/mmol) five to six times cheaper than the corresponding methyl or *tert*-butyl α-(trifluoromethyl)acrylate. This last fact shows that our first envisioned two-step strategy to synthesize the α-trifluoromethylacrylic acid through acrylate formation and subsequent hydrolysis was not economically viable. So, we present here an efficient and quick access to highly valuable α-trifluoromethylacrylic acids by ligand-free Mizoroki-Heck reaction starting from inexpensive and commercially available reagent, the α-(trifluoromethyl)acrylic acid **1**.

We started to optimize the process with 4-iodoanisole **2a** and α-(trifluoromethyl)acrylic acid **1** (Table 1). The use of silver triflate was ineffective giving only a low 35% ^{19}F NMR yield (Table 1, entry 1). The use of silver carbonate allowed us to reach a good 91% yield of the desired product whereas the absence of additive or the use of potassium carbonate did only afford traces of product, proving that the silver is essential for the reaction (Table 1, entries 2-4). Silver carbonate was more efficient because of the basic character of this additive in comparison to silver triflate. As discussed further on the reaction mechanism, a stronger base was needed to deprotonate the acid **1**. A decrease in catalyst loading resulted in a lower yield (Table 1, entry 5) whereas an increase in catalyst loading did not improve it.[12] A catalyst screening showed that the $Pd(TFA)_2$ was the best one for this reaction.[12] Decreasing the amount of silver carbonate was still effective (Table 1, entry 6) whereas the yield dropped with a sub-stoichiometric amount (Table 1, entry 7). Increasing the concentration to 0.4 M allowed a maximum yield of 95% of product **3a** (Table 1, entry 8). A decrease in the temperature to 70 °C decreased the yield to 89% with a slightly worse stereoselectivity (Table 1, entry 9). Finally, one hour of reaction proved to be enough to get excellent 93% yield of **3a** with no change in stereoselectivity (Table 1, entry 10). It should be noted that the best molar ratio of **2a**/**1** was 1/1.5. The use of stoichiometric molar ratio 1/1 of **2a**/**1** or a reverse molecular ratio 1.5/1 of **2a**/**1** significantly decreased the reaction yield.[12] We would like to point out that no side-product resulting from a decarboxylative reaction with the fluorinated substrate **1** was detected in any of our trials with silver carbonate. The reaction did not require inert atmosphere, or the use of dry vials or molecular sieves to succeed. The only drawback encountered was the low stereoselectivity obtained with a *E*/*Z* ratio of 64/36. Optimisation of other reaction parameters has been done in an attempt to improve the stereoselectivity (use of ligand, screening of solvent, concentration, equivalent, temperature…), unfortunately, without success.[12] Interestingly, the compound **3a** is a fluorinated analogue of *p* methoxycinnamic acid which is biologically active as an antidiabetic, hepatoprotective, or antihyperglycemic agent.[13]

Table 1. Optimisation of the trifluoromethylalkenylation reaction.[a]



Entry	[**2a**] (M)	Additive (y equiv)	Yield of **3a** (%)[b]	*E*/*Z* ratio
1	0.2	AgOTf (2.0)	35	66/34
2	0.2	-	traces	-
3	0.2	K_2CO_3 (2.0)	traces	-
4	0.2	Ag_2CO_3 (2.0)	91	66/34
5[c]	0.2	Ag_2CO_3 (2.0)	80	68/32
6	0.2	Ag_2CO_3 (1.1)	85	64/36
7	0.2	Ag_2CO_3 (0.5)	61	64/36
8	0.4	Ag_2CO_3 (1.1)	95	64/36
9[d]	0.4	Ag_2CO_3 (1.1)	89	61/39

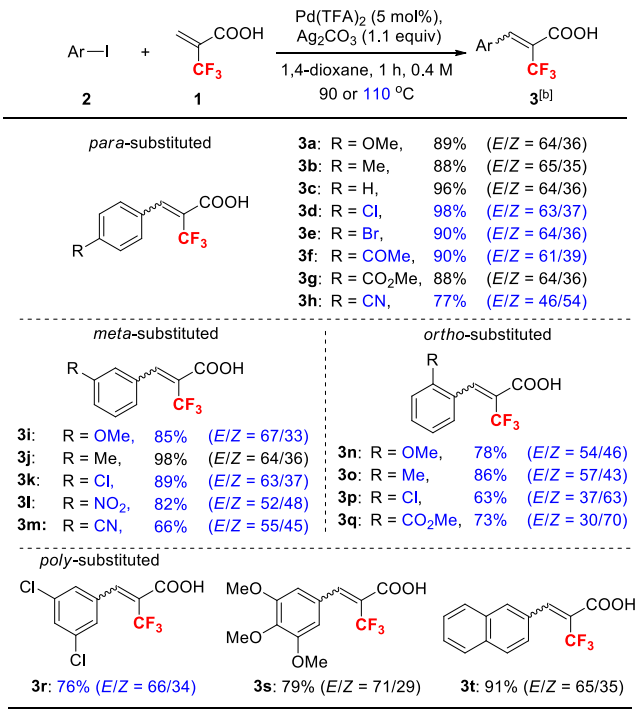
10[e]	0.4	Ag_2CO_3 (1.1)	93	64/36

[a] Reaction conditions: **1** (0.3 mmol, 1.5 equiv), **2a** (0.2 mmol, 1.0 equiv), $Pd(TFA)_2$ (5 mol%), additive (y equiv), 1,4-dioxane (0.5 or 1.0 mL), 4 h, 90 °C.
[b] ^{19}F NMR yields were obtained by using $PhCOCF_3$ as an internal standard.
[c] 1.5 mol% of catalyst.
[d] Reaction carried out at 70 °C.
[e] 1 h of reaction time.

With our optimal conditions in hand, we studied the scope of the reaction (Table 2). A temperature increase to 110 °C was necessary for some substrates to get better yields. Whatever the position (*ortho*, *meta* or *para*) and electronic effect of the substituent on the aryl iodide, *i.e.* electron-donating or electron-withdrawing group, good to excellent yields were obtained in the range from 63% to 98%. The reaction was chemoselective reacting only on the carbon-iodide bond in the presence of other halogens, such as chlorine (**2d**, **2k**, **2p**, **2r**) or bromine (**2e**), furnishing reactive sites for further chemical modifications. Post-functionnalizable moieties, such as ketone (**2f**), ester (**2g**, **2q**), nitro (**2l**) or nitrile (**2h**, **2m**) were also compatible with the reaction. The stereoselectivity decreased in the presence of highly electron-withdrawing groups such as nitrile or nitro or in the presence of an *ortho*-substituent, probably because of steric hindrance, in the latter cases. The stereoselectivity was even reversed for the *ortho*-electron-withdrawing moieties in substrates **2p** and **2q**.

Two reactions on a larger scale (2.0 mmol instead of 0.2 mmol) were done with success starting from **2a** and **2h**, furnishing the desired products **3a** and **3h** in 89% and 79% yield, respectively.[12]

Table 2. Scope of the reaction.[a]



[a] Reaction conditions: **1** (0.3 mmol, 1.5 equiv), **2** (0.2 mmol, 1.0 equiv), $Pd(TFA)_2$ (5 mol%), Ag_2CO_3 (0.22 mmol, 1.1 equiv), 1,4-dioxane (0.5 mL), 1 h, 0.4 M, 90 or 110 °C.
[b] Yield based on isolated product after flash column chromatography.

The stereoselectivity of the reaction was unconditionally assigned by NMR spectroscopy (^{19}F NMR and HOESY experiments)[12] and X-ray diffraction analysis (Figure 1).[14] The less constrained *E*-product was, most of the time, the major isomer obtained.

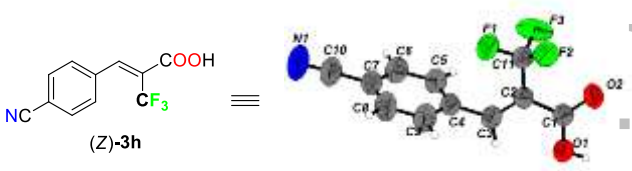
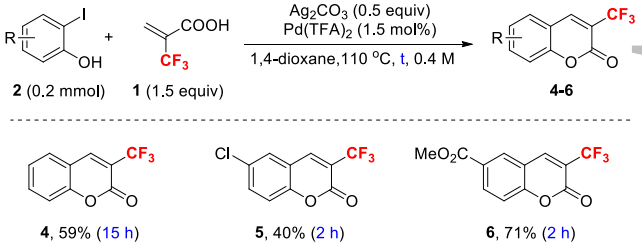


Figure 1. X-ray of product (*Z*)-**3h**.

Starting from 2-iodophenol substrates, it was also possible to produce highly valuable 3-CF_3-coumarins **4-6** in fair to good yields with less palladium and silver reagents (Scheme 3),[12] offering a rapid and effective alternative to the usual procedures for the preparation of these fluorinated coumarins.[15]

Scheme 3. Direct access to 3-CF_3-coumarins **4-6**



Thanks to the free acid function of our products **3**, we could easily envision the preparation of various 3-substituted-2-trifluoromethylacrylates, molecules rarely studied in the literature in spite of their potential as fluorinated analogues of bioactive cinnamates, which have numerous applications.[13],[16] Indeed, alkyl 2-trifluoromethylacrylate reagents are hardly ever commercially available (except for methyl and *tert*-butyl) and quite expensive which is not the case of reagent **1**. So we developed a simple and effective three-component reaction to directly obtain the desired acrylates. We thought that adding alkyl iodide in our experimental media, should result in the *in situ* transformation of acid to ester via a carboxylate nucleophilic substitution mediated by silver carbonate. Indeed, as expected in our reaction (without Pd catalyst), replacing the aryl iodide **2a** by

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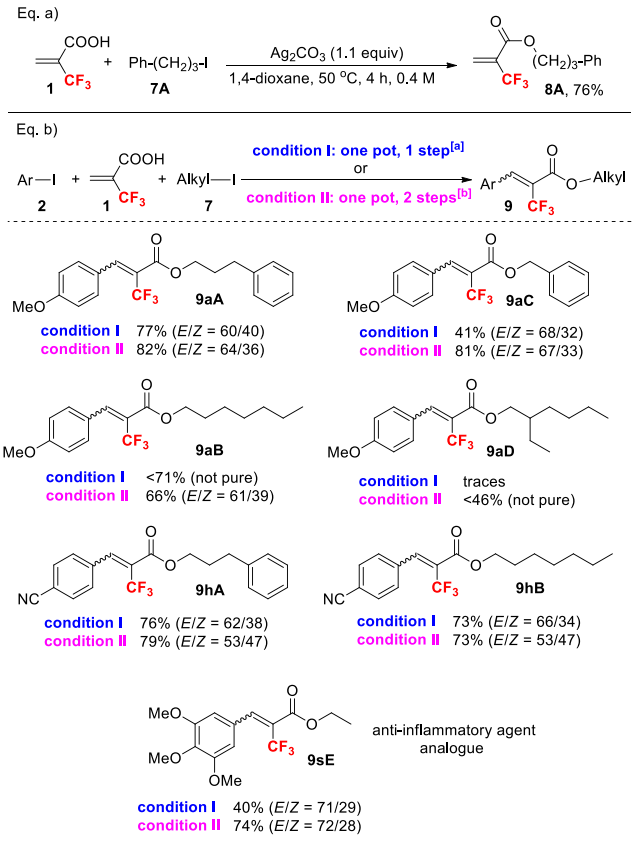
the alkyl iodide (3-iodopropyl)benzene **7A** furnished only the corresponding 3-phenylpropyl 2-trifluoromethyl-acrylate **8A** in 76% yield (Table 3, Eq. a)).[12]

Carrying out the reaction with a mixture of α-(trifluoromethyl)acrylic acid **1**, aryl iodide **2** and alkyl iodide **7** can give a mixture of **3** (acid), **9** (β-substituted acrylate) as well as unsubstituted acrylate **8**. In order to prepare compound **9** as the major product, we optimized the three-component process[12] and found two different procedures that could be applied to produce the desired compound **9** (Table 3, Eq. b)). Obtaining the final acrylates was facilitated with the one-pot procedures and avoided the purification of highly polar acid intermediates. Following conditions I or II, we were able to propose an efficient access to various products **9**, including the anti-inflammatoy fluoroanalogue **9sE**,[17] containing a benzyl, a 3-phenylpropyl, a heptyl, an ethyl or an ethylhexyl carbon chains in good yields. Disappointingly, product **9aD**, a UV-B screen fluorinated analogue,[18] was only produced in fair yields.

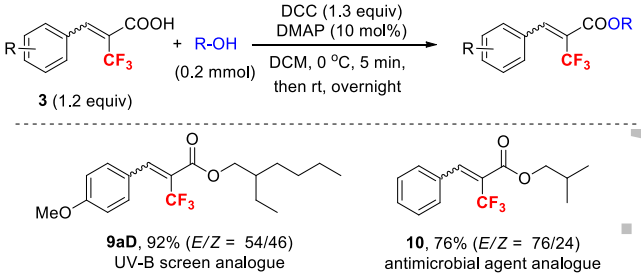
Table 3. Three-component reaction to obtain 3-substituted-2-trifluoromethylacrylates **9**.[a],[b]



[a] Condition I: **2** (0.2 mmol, 1.0 equiv), **1** (0.4 mmol, 2.0 equiv), **7** (0.8 mmol, 4.0 equiv), Ag_2CO_3 (0.8 mmol, 4.0 equiv), $Pd(TFA)_2$ (10 mol%), 1,4-dioxane (1.0 mL), 0.2 M, 50 °C, 4 h; then 90 °C, 2 h.

[b] Condition II: **2** (0.2 mmol, 1.0 equiv), **1** (0.3 mmol, 1.5 equiv), Ag_2CO_3 (0.22 mmol, 1.1 equiv), $Pd(TFA)_2$ (5 mol%), 1,4-dioxane (0.5 mL), 0.4 M, 90 or 110 °C, 1 h; then **7** (0.4 mmol, 2.0 equiv), Ag_2CO_3 (0.3 mmol, 1.5 equiv), 90 °C, 4 h.

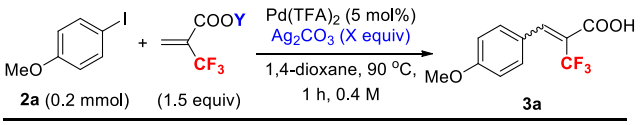
We therefore decided to produce it using a classical coupling reaction and compound **9aD** was obtained in excellent yield. We also produced the fluorinated compound **10**, an analogue of an antimicrobial agent (Scheme 4).[19]



Scheme 4. Synthesis of relevant alkyl 3-substituted-2-trifluoromethylacrylates **9aD**,**10**

Concerning the mechanism of the reaction and in light of the different procedures described in this manuscript, we propose the silver carboxylate salt as a key intermediate in our reaction. Indeed, the three-component reaction highlighted the easy deprotonation of trifluoromethylated acid **1**, so we thought that the first reaction was probably an acid-base reaction between silver carbonate and **1** generating the silver carboxylate salt **11**. To confirm this hypothesis, we synthesized two salts, the silver **11** and the potassium **12** carboxylates.[12],[20] The reaction carried out with **11** in the presence of $Pd(TFA)_2$ led to a similar yield of **3a** compared to the optimal experimental procedure starting with acid **1** and silver carbonate (Table 4, entries 1-2). As expected, the potassium salt **12** was almost unreactive, proving the importance of the silver cation in the media (Table 4, entry 3). No side-reaction from decarboxylation of the silver salt **11** was observed.

Table 4. Use of carboxylate salt in reaction.[a]



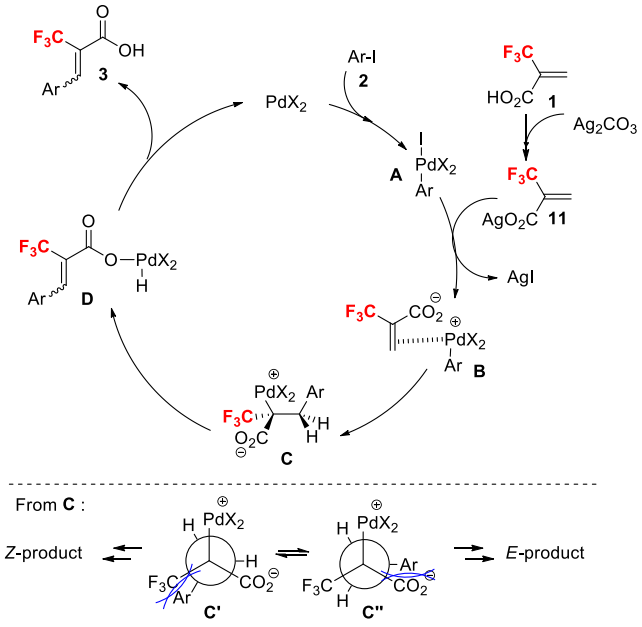
Entry	Y (reactant)	X	Yield of **3a** (%)[b]	*E*/*Z* ratio
1	H (**1**)	1.1	89	64/36
2	Ag (**11**)	0	93	64/36
3	K (**12**)	0	< 10	42/58

[a] Reaction conditions: reactant (0.3 mmol, 1.5 equiv), **2a** (0.2 mmol, 1.0 equiv), $Pd(TFA)_2$ (5 mol%), Ag_2CO_3 (X equiv), 1,4-dioxane (0.5 mL), 1 h, 90 °C.

[b] Yield based on isolated product after flash column chromatography.

In light of our observations, we propose the following catalytic cycle (Scheme 5). After an oxidative addition, the complex **A** reacted with silver carboxylate **11** to give the neutral complex **B**. The silver plays an important role as halide abstracter during this step.[7],[21] Then an insertion of the aryl group in the double bond furnishs the complex **C**. From **C**, β-H elimination, a syn-process, can proceed either towards the formation of *Z* or *E*-compound, taking into account that neither intermediate **C'** or **C''** seems more stable than the other one because of steric hindrance in both cases. Finally, the complex **D** is formed by β-H elimination, and reductive elimination ends the catalytic cycle to give the desired acid **3** and regenerated catalyst.

To summarize, we have developed a new relevant access to α-CF_3-acrylic acids, scarcely studied in the literature despite their great potential. The ligand-free Mizoroki-Heck reaction gave good to excellent yields of fluorinated acrylic acids and tolerated the presence of many organic functional groups. Nevertheless, the stereoselectivity of the reaction was quite low and the various attempts to increase it were unsuccessful to date. Based on further experiments, a hypothetic catalytic cycle involving a silver carboxylate salt as a key intermediate was proposed. This mechanism also gave an explanation as to the observed stereo-selectivity. We also demonstrated the high versatility of the α-CF_3 acrylic acids, which give α-CF_3-coumarins or acrylates, via a three-component or a classical esterification reaction. The latters give access to fluorinated analogues of numerous bioactive compounds, such as various analogues of therapeutic and cosmetic agents.



Scheme 5. Proposed catalytic cycle and explanation for stereoselectivity.

Experimental Section

General procedure for the synthesis of α-trifluoromethylacrylic acids (3).

To a vial (2 mL) were added 2-(trifluoromethyl)acrylic acid **1** (0.3 mmol, 1.5 equiv), iodoarene **2** (0.2 mmol, 1.0 equiv), Ag_2CO_3 (0.22 mmol, 1.1 equiv), $Pd(TFA)_2$ (0.01 mmol, 5 mol%), and 1,4-dioxane (0.5 mL, 0.4 M of iodoarene). The vial was then sealed. The reaction mixture was stirred at 90 or 110 °C for 1 hour and was then cooled to room temperature. The resulted reaction mixture was purified directly by silica gel column chromatography (TLC: CH_2Cl_2/MeOH (AcOH), 20/1 (1%)).

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UPDATE

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