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Rh(I)-Catalyzed Olefin Hydroarylation with Electron-Deficient Perfluoroarenes

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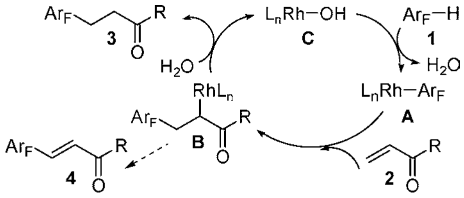
Transition-metal-catalyzed olefin hydroarylation has become an important strategy for alkylarene synthesis.[1] These atom-economic processes have been shown to proceed through aromatic C−H bond activation and subsequent olefin insertion.[2] Such a metal-mediated pathway is distinct from the conventional Friedel−Crafts mechanism and can promote anti-Markovnikov selectivity.[1] Recent advancements in catalytic C−H activation with or without neighboring directing groups[3] have led to significant progress in olefin hydroarylation with electron-neutral or electron-rich arenes and heteroarenes.[3b,4,5] However, reports on undirected olefin hydroarylation with electron-deficient arenes are rare.[6] Nakao and Hiyama have recently reported Ni-catalyzed couplings of pentafluorobenzene (**1a**) with 2-vinylnaphthalene or buta-1,3-dienylbenzene to afford Markovnikov hydroarylation products.[7] More recently, Yu and coworkers reported a Pd(II)-catalyzed direct alkenylation of electron-poor arenes that proceeds with highly unusual *meta*-selectivities and indirectly generates hydroarylation products upon further hydrogenation.[8,9] Herein, we report the first example of undirected olefin hydroarylation with electron-deficient perfluoroarenes. This Rh(I) catalysis proceeds with good catalyst efficiency and useful functional group tolerance. The current catalyst system is operationally simple and can be easily adjusted to selectively generate alkylation (*hydroarylation*) or olefination (*oxidative arylation*) products.

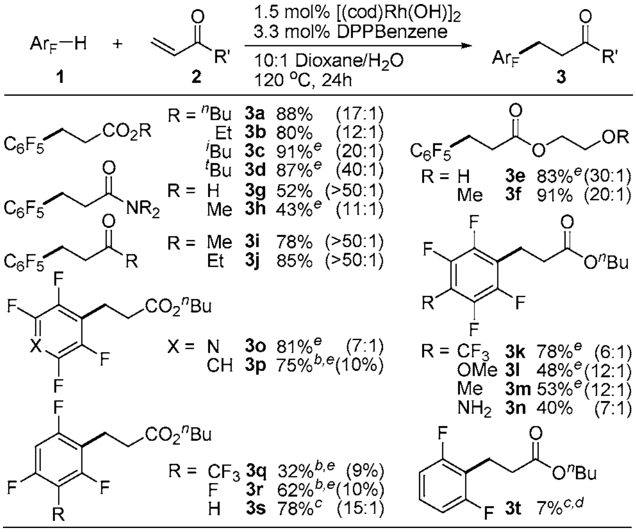
We have previously reported a Rh(I)-catalyzed decarboxylative conjugate addition with polyfluorinated benzoic acids in a partially aqueous solvent system.[10] This method provides a rare example of catalytic conjugate addition by polyfluoroaryl nucleophiles.[11,12] Prompted by this study and by the recent progress in perfluoroarene C−H functionalization,[7,9,13] we aimed to develop a Rh(I)-catalyzed hydroarylation process with a proposed catalytic cycle as described below (Scheme 1):[14] Aromatic C−H activation of a perfluoroarene substrate (**1**) generates a perfluoroarylrhodium(I) intermediate (**A**). Subsequent insertion with an activated olefin substrate (**2**) forms a Rh(I) enolate (**B**),[15] which releases the desired hydroarylation product (**3**) upon protonation. By including H_2O in the solvent system, hydrolysis of **B** can be promoted over β-H elimination to inhibit the formation of oxidative arylation product **4**.[10,16] Meanwhile, a Rh(I) hydroxide (**C**) will be formed, which undergoes C−H activation with **1** and completes the proposed catalytic cycle.[17,18]

Scheme 1



We began our study with Rh(I)-catalyzed reactions between pentafluorobenzene (**1a**) and *n*-butyl acrylate (**2a**). An extensive survey of reaction conditions led to an optimized catalyst system of 1.5 mol % $[(cod)Rh(OH)]_2$, 3.3 mol % DPPBenzene ligand,[19] and a mixed solvent of 10% H_2O/dioxane. Under these conditions, a 1.4:1 mixture of **1a** and **2a** was heated at 120 °C for 24 h to generate the anti-Markovnikov hydroarylation product *n*-butyl 3-pentafluoro-phenylpropionate (**3a**) in high yield and high selectivity over the oxidative arylation product **4a**[20] (93% combined yield, 17:1 selectivity of **3a**/**4a**). The overall reactivity and **3a**/**4a** selectivity were highly dependent on the conditions of phosphine ligand, reaction media, and the ratio of **1a**/**2a** (see Table S1 in the Supporting Information for details). In particular, removing water cosolvent led to slower reactions and reversed selectivities favoring oxidative arylation.[21] Thus, selective formation of **4a** could be optimized using *cis*-DPPEthylene ligand,[22] anhydrous dioxane solvent, and a 1:4 ratio of **1a**/**2a**. This direct alkenylation process consumes excess **2a** as a sacrificial hydrogen acceptor,[14b,16] providing a useful alternative to a recently reported Pd-based catalysis using excess Ag_2CO_3 as the oxidant.[9]

Table 1. Rh(I)-Catalyzed Hydroarylation with Perfluoroarenes[a]



R = ⁿBu **3a** 88% (17:1)
Et **3b** 80% (12:1)
ⁱBu **3c** 91%[e] (20:1)
ᵗBu **3d** 87%[e] (40:1)
R = H **3g** 52% (>50:1)
Me **3h** 43%[e] (11:1)
R = Me **3i** 78% (>50:1)
Et **3j** 85% (>50:1)
X = N **3o** 81%[e] (7:1)
CH **3p** 75%[b,e](10%)
R = CF_3 **3q** 32%[b,e] (9%)
F **3r** 62%[b,e](10%)
H **3s** 78%[c] (15:1)
R = H **3e** 83%[e](30:1)
Me **3f** 91% (20:1)
R = CF_3 **3k** 78%[e] (6:1)
OMe **3l** 48%[e](12:1)
Me **3m** 53%[e](12:1)
NH_2 **3n** 40% (7:1)
3t 7%[c,d]

[a] Conditions: **1** (0.70 mmol, 1.4 equiv), **2** (0.50 mmol, 1.0 equiv), $[(cod)Rh(OH)]_2$ (0.015 equiv), DPPBenzene (0.033 equiv), dioxane/H_2O (1.5/0.15 mL), 120 °C, 24 h; average isolated yields from two runs; ratio of **3**:**4** in parentheses. [b] GC yield of dialkylation product in parentheses; other byproducts detected in <5% yields. [c] 10 equiv of **1** was used in reaction. [d] GC yield. [e] Containing 2−4% byproduct **4**.

Under the optimized conditions for hydroarylation, **1a** was effectively coupled with various acryl esters in high yields and high selectivities over oxidative arylation (Table 1, products **3a**−**f**). The relatively mild conditions and the absence of base additives allowed selective hydroarylation for a hydroxy-functionalized acryl ester without dehydrogenation or hydroalkoxylation (**3e**),[23] providing a useful handle for further transformations. Acrylamide and *N*,*N*-dimethylacrylamide gave hydroarylation products in high selectivi-

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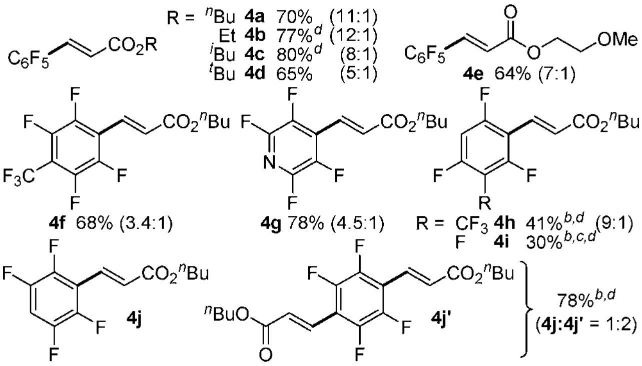
ties but moderate yields (**3g**, **3h**). In contrast, α,*β*-unsaturated ketones reacted smoothly with **1a** in good yields and >50:1 selectivities (**3i**, **3j**). No reaction occurred with less reactive olefins such as 2-cyclohexenone, styrene, or 1-hexene, and further catalyst development is needed to address this limitation.

Various perfluoroarenes in addition to **1a** also reacted with **2a** to form hydroarylation products in good selectivities (Table 1, **3k**−**t**). Lower reactivity was displayed by substrates with less fluoro substituents (**3p**, **3r**−**t**) or with electron-donating *para*-substituents (**3l**−**n**). A *para*-aniline derivative (**3n**) could be generated in 40% yield without N-protection, but the analogous *para*-phenol substrate was unreactive. When multiple aromatic C−H bonds were available, a mixture of mono- and dialkylation products was formed, with monoalkylated arene being the major product (**3p**−**r**). The low reactivity of 1,3,5-trifluorobenzene required a 10:1 ratio of arene/olefin to generate the monoalkylation product in 78% yield (**3s**). Notably, 1,3-difluorobenzene reacted exclusively at the 2-position, albeit with very low reactivity (**3t**). These substituent effects supported a rate-limiting arene C−H activation step, which appeared to be assisted by *ortho*-F substituents and by the overall electron deficiency of the aromatic system.[24,25] A concerted C−H activation pathway, such as internal electrophilic substitution (IES),[18] is likely involved, although other possibilities[17a] cannot be excluded without further mechanistic investigation.

Table 2. Examples of Oxidative Arylation with Perfluoroarenes[a]



[a] Conditions: **1** (0.50 mmol, 1.0 equiv), **2** (2.0 mmol, 4.0 equiv), $[(cod)Rh(OH)]_2$ (0.015 equiv), *cis*-DPPethylene (0.033 equiv), dioxane (1.5 mL), 120 °C, 24 h; *E*-isomers only; average isolated yields from two runs; ratio of **4**:**3** in parentheses. [b] DPPBenzene ligand (0.033 equiv) and 6.0 equiv of **2a** were used. [c] 14% of dialkenylation product was also detected; total yield of other byproducts <5%. [d] Containing 4−8% byproduct **3**; further purification attempts were not successful.

Examples of oxidative arylation were provided in Table 2 to evaluate its utility as a simple protocol for perfluoroarene alkenylation.[9] **1a** reacted with various acryl esters to give the desired olefin products in good yields and good selectivities (**4a**−**e**). Several other perfluoroarenes also reacted with **2a** to selectively form the oxidative arylation products in moderate to good yields (**4f**−**j**). However, the reactivity and functional group tolerance were generally lower than those for the corresponding hydroarylation,[26] and DPPBenzene ligand was used in place of *cis*-DPPEthylene to improve the yields with less reactive perfluorarenes (**4h**−**j**). Due to the higher olefin/arene ratios needed for selective oxidative arylation, dialkenylation became more competitive and could take over as the major process (e.g., **4j**, **4j′**).

In summary, we have developed a Rh(I)-based catalyst system for the effective couplings between perfluoroarenes and α,*β*-unsaturated carbonyl derivatives. Selective formation of hydroarylation and oxidative arylation products was achieved via a proposed tandem sequence of C−H activation and competitive conjugate addition vs Heck−Mizoroki olefination. Current efforts are focused on mechanism studies and further catalyst development for broader synthetic applications.

Acknowledgment. This work is dedicated to the memory of Keith Fagnou. Financial support for this work was provided by ND EPSCoR seed grant and NDSU startup fund.

Supporting Information Available: Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(19) DPPBenzene: 1,2-bis(diphenylphosphino)benzene.

(20) **4a**: (*E*)-*n*-butyl-3-pentafluorophenylacrylate. The Z isomers did not form in detectable amounts for oxidative arylations throughout the current study.

(21) (a) Too much water content also slowed down the reaction, presumably due to solubility problems and inhibition of arene C−H activation which generates H_2O (Scheme 1, **C**→**A**). (b) In a D_2O reaction media, mono D-incorporation was detected at the α-position of product **3d** (see Supporting Information).

(22) *cis*-DPPEthylene: *cis*-1,2-bis(diphenylphosphino)ethylene.

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(25) 1,3-Dimethoxybenzene, a common reactive substrate for Friedel−Crafts alkylation, did not show any hydroarylation reactivity in this study.

(26) For example, the acrylate analogue of **3e** could not be generated in acceptable yields, presumably due to competitive aldehyde formation by dehydrogenation.

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