



Iron(III)-catalyzed hydroarylation of propiolic acid with activated arenes

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ABSTRACT

FeCl₃/AgOTf-catalyzed hydroarylation of propiolic acid with electron-rich arenes such as mesitylene, tetramethylbenzene, and pentamethylbenzene in trifluoroacetic acid proceeded to give 3-arylpropenoic acids in moderate to high yields. The same reactions with anisole and 1,4-dimethoxybenzene afforded double hydroarylation products, 3,3-diarylpropionic acids.

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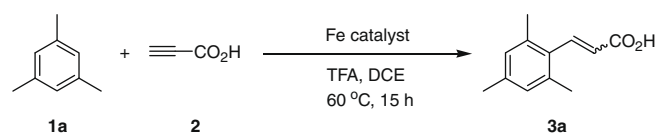
Recently much attention has been paid to direct C–H bond functionalization in organic chemistry because the direct functionalization has several advantages compared with conventional synthetic methods requiring prefunctionalization of C–H bonds.¹ As one of aromatic C–H bond functionalizations, hydroarylation of alkynes is an atom-economic and valuable reaction for preparing aromatic alkenes directly from arenes and alkynes.² Noble and rare metals such as palladium and platinum have been used as catalysts for the hydroarylation reaction.^{3–5} For example, we have reported that the hydroarylation reaction of propiolic acids proceeds effectively in the presence of palladium and platinum catalysts to give cinnamic acid derivatives. However, such noble metals are rare, expensive, and not economical. If the noble catalysts could be replaced by abundant and economical metals, the hydroarylation reactions would be a more valuable method for synthesis of aromatic alkenes.

Iron is one of the most abundant metals on earth, an inexpensive and environmentally benign metal, and has been applied to organic synthesis as catalysts.⁶ However, there are only two examples of the hydroarylation reaction of alkynes with the most versatile iron catalyst.⁷ The reported procedures include iron(III) chlorides (FeCl₃ and FeCl₃·6H₂O) as catalysts and electron-rich aromatic alkynes as substrates.⁷ In the hydroarylation of an electron-deficient propiolic acid, it is necessary to use a more reactive iron catalyst in order to cause the hydroarylation reaction effectively. Thus, we decided to use iron(III) chlorides activated with silver triflate (AgOTf). Here we report a convenient, simple, and more

reactive catalytic system consisting of FeCl₃ and AgOTf for the hydroarylation of propiolic acid.

Since we have found that trifluoroacetic acid (TFA) is a good solvent for hydroarylation reactions,^{4c–f} the iron-catalyzed hydroarylation of propiolic acid was carried out in a mixed solvent of TFA and 1,2-dichloroethane (DCE). First, we optimized the conditions of hydroarylation of propiolic acid (2) with mesitylene (1a) giving 3-(2,4,6-trimethylphenyl)propenoic acid (3a) (Scheme 1). For the iron catalyst, FeCl₃, FeCl₃·6H₂O, FeCl₃/AgOTf, and FeCl₃·6H₂O/AgOTf were examined. The results are given in Table 1.

Even in the case of FeCl₃ only, the hydroarylation reaction proceeded to afford 3a in 62% yield (entry 1). The addition of 3 equiv of AgOTf significantly improved the hydroarylation reaction, which proceeded almost quantitatively to give 3a in 99% yield (entry 2).⁸ However, a lower loading of the catalyst or AgOTf resulted in poor yields of 3a (entries 3 and 4). Interestingly, selective formation of the trans isomer of 3a was observed in the hydroarylation reaction with FeCl₃/AgOTf catalyst. This behavior is different from that of the hydroarylation reaction with Pd and Pt catalysts.⁵ We also examined the reaction with FeCl₃·6H₂O catalyst. However, it was found that FeCl₃·6H₂O catalyst was not effective under the present conditions even in the presence of AgOTf (entries 5–8).



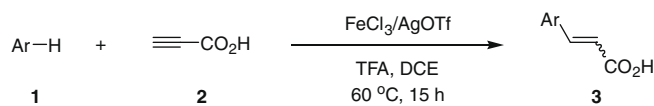
Scheme 1.

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Table 1Hydroarylation of propiolic acid (**2**) with mesitylene (**1a**) in the presence of iron catalysts^a

Entry	Catalyst	(mol %)	Yield ^b (%)	E/Z ^c
1	FeCl ₃	(20)	62	71/29
2	FeCl ₃ /AgOTf	(20/60)	99	66/34
3	FeCl ₃ /AgOTf	(10/30)	38	66/34
4	FeCl ₃ /AgOTf	(20/20)	46	72/28
5	FeCl ₃ ·6H ₂ O	(20)	15	10/90
6	FeCl ₃ ·6H ₂ O/AgOTf	(10/30)	12	16/84
7	FeCl ₃ ·6H ₂ O/AgOTf	(20/20)	22	11/89
8	FeCl ₃ ·6H ₂ O/AgOTf	(20/60)	32	14/86
9 ^d	FeCl ₃ ·6H ₂ O/AgOTf	(20/60)	3	12/88
10 ^e	FeCl ₃ /AgOTf	(20/60)	88	58/42
11 ^f	FeCl ₃ /AgOTf	(20/60)	0	—

^a Reaction conditions: catalyst, **1a** (4 mmol), **2** (2 mmol), TFA (0.5 mL), and DCE (0.5 mL) at 60 °C for 15 h.^b Isolated yield.^c Determined by ¹H NMR.^d Molecular sieves 4A (0.126 g) were added.^e TFA (0.5 mL) and nitromethane (0.5 mL) were used as solvents.^f Nitromethane (1 mL) was only used as a solvent.**Scheme 2.**

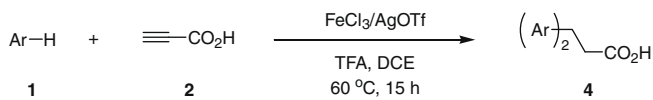
The addition of MS 4A retarded the reaction (entry 9). Since the reactions with AgOTf only and without any catalysts do not proceed efficiently,^{4e} FeCl₃ is considered to be an actual catalyst for hydroarylation. Replacement of DCE by nitromethane as the co-solvent decreased the product yield to 88% (entry 10). When the reaction was conducted in nitromethane only, no hydroarylation products were formed (entry 11). This result differs from the result reported by Lu and co-workers.^{7b}

On the basis of the optimization of the reaction conditions, the scope of this hydroarylation with various arenes was explored (Schemes 2 and 3).⁸ The results are given in Table 2. For electron-rich arenes such as pentamethylbenzene (**1b**) and 2,4,6-tri-

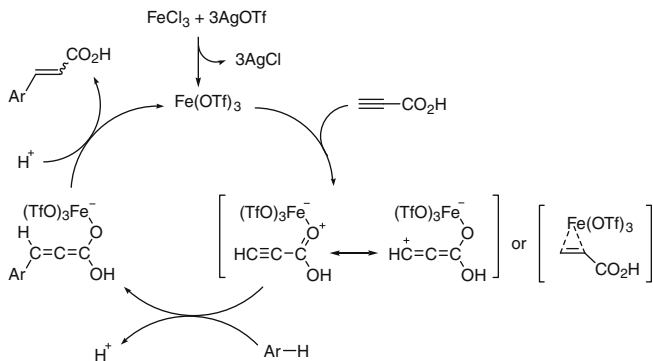
Table 2FeCl₃/AgOTf-catalyzed hydroarylation of propiolic acid (**2**) with various arenes^a

Entry	Arene 1	TFA (mL)	DCE (mL)	Product 3	Yield ^b (%)	E/Z ^c
1		1	2		92	70/30
2		0.5	0.5		28	69/31
3		0.5	0.5		7	68/32
4 ^d	1d	1	1	3d	11	69/31
5		1	0.5		9	63/37
6		0.5	0.5		48	70/30
7		0.5	0.5		17	72/28
8		0.5	0.5		22	—
9		0.5	0.5		76	—
10		0.5	0.5		58	—

^a Reaction conditions: FeCl₃ (0.4 mmol), AgOTf (1.2 mmol), **1** (4 mmol), **2** (2 mmol), TFA, and DCE at 60 °C for 15 h.^b Isolated yield.^c Determined by ¹H NMR.^d At refluxing temperature.



Scheme 3.



Scheme 4.

methylphenol (**1f**) the hydroarylation proceeded well (entries 1 and 6), but for moderately activated or unactivated arenes the reaction gave low yields of the hydroarylation products **3** (entries 2–5). On the other hand, anisole (**1g**), 1,4-dimethoxybenzene (**1h**), and 4-methoxytoluene (**1i**) underwent double hydroarylation to give 3,3-diarylpropionic acids **4** (entries 7–9).

In the $\text{FeCl}_3/\text{AgOTf}$ -catalyzed hydroarylation reaction of propiolic acid, there exist the following characteristic results to consider the reaction mechanism. (1) The hydroarylation reaction catalyzed by $\text{FeCl}_3/\text{AgOTf}$ in TFA provided *trans*-cinnamic acids as the major products. This strongly contrasts with the reaction catalyzed by platinum compounds where the *cis*-cinnamic acids are formed selectively.⁵ (2) In the present reaction, isomerization of *cis* to *trans*-cinnamic acids is not important because the hydroarylation with $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ under similar conditions gives *cis*-cinnamic acid **3a** as the major isomer. (3) Activated, electron-rich arenes show high reactivity.

A proposed mechanism is shown in Scheme 4. First, FeCl_3 reacts with AgOTf to generate a highly cationic, reactive $\text{Fe}(\text{OTf})_3$, which interacts with propiolic acid to form a vinyl cation. Since a primary open vinyl cation is very unstable and the formation is not possible,⁹ $\text{Fe}(\text{OTf})_3$ should coordinate with the oxygen atom acid and activate the propiolic acid. Formation of a bridged vinyl cation is possible but it may be ruled out by judging from the major formation of the *trans* isomer of cinnamic acids. The resulting vinyl cation undergoes electrophilic aromatic substitution with an electron-rich arene and finally generates a product by protonation. At the same time, regeneration of $\text{Fe}(\text{OTf})_3$ is concomitant and completes the catalytic cycle.

In conclusion, we have demonstrated that iron-catalyzed hydroarylation of propiolic acid with various arenes in TFA. The reaction proceeded efficiently in the presence of $\text{FeCl}_3/\text{AgOTf}$ cata-

lyst system. Especially, in the case of electron-rich arenes, the iron-catalyzed hydroarylation proceeded well and gave cinnamic acids in moderate to high yields. Even FeCl_3 only is capable of catalyzing the hydroarylation reaction, but the addition of AgOTf enhances the reactivity. Further investigation of the iron-catalyzed hydroarylation of alkynes is now in progress.

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- General procedure for $\text{FeCl}_3/\text{AgOTf}$ -catalyzed hydroarylation of propiolic acid*: After a mixture of FeCl_3 (0.4 mmol) and AgOTf (1.2 mmol) in TFA and DCE was stirred at room temperature for 10 min, arene (4 mmol) and propiolic acid (2 mmol) were added and then the mixture was stirred at 60 °C for 15 h. The reaction mixture was poured into water, neutralized with NaHCO_3 , and washed with ether. The ethereal layer was extracted with 2 M NaOH . The aqueous layer was washed with ether, acidified with HCl (ca. 36%), and extracted with CH_2Cl_2 . The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give cinnamic acids as solids. The products were identified by spectral data (^1H and ^{13}C NMR) and the data were compared with those in the literature. Representative spectral data are as follows: Compound **3a** (a mixture of *E* and *Z* isomers):^{4f} ^1H NMR (300 MHz, CDCl_3) δ 2.16 (s, CH_3), 2.26 (s, CH_3), 2.27 (s, CH_3), 2.31 (s, CH_3), 6.03 (d, $J = 16$ Hz, =CH), 6.10 (d, $J = 12$ Hz, =CH), 6.82 (s, ArH), 6.88 (s, ArH), 7.08 (d, $J = 12$ Hz, =CH), 7.91 (d, $J = 16$ Hz, =CH), 10.80 (br s, CO_2H); ^{13}C NMR (75 MHz, CDCl_3) δ 20.00, 20.89, 122.07, 127.89, 131.99, 134.44, 136.92, 146.28, 171.10. Compound **3b**:¹⁰ ^1H NMR (300 MHz, CDCl_3) δ 3.01 (d, $J = 7.5$ Hz, 2H, CH_2), 3.75 (s, 6H, OCH_3), 4.42 (t, $J = 7.5$ Hz, 1H, CH), 6.80 (d, $J = 9$ Hz, 2H, ArH), 7.11 (d, $J = 9$ Hz, 2H, ArH), 8.71 (br s, 1H, CO_2H); ^{13}C NMR (75 MHz, CDCl_3) δ 40.72, 45.10, 55.20, 113.99, 128.47, 135.78, 158.17, 177.94.
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