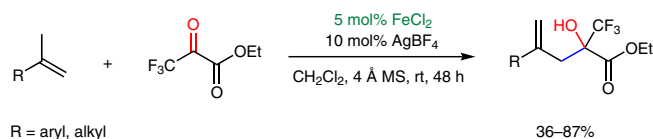D. Meng, T. Ollevier

Fe(BF$_4$)$_2$-Catalyzed Inter- and Intramolecular Carbonyl-Ene Reaction of Trifluoropyruvate

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R = aryl, alkyl

36–87%

Abstract Inter- and intramolecular carbonyl-ene reactions have been developed using 5 mol% Fe(BF$_4$)$_2$ as catalyst, affording homoallylic alcohols in 36–87% isolated yields. This catalyst, prepared from FeCl$_2$ and AgBF$_4$, is the first Fe^{II} Lewis acid reported for the carbonyl-ene reaction using ethyl trifluoropyruvate. The method was successfully applied to the reaction of various 1,1-disubstituted alkenes with ethyl trifluoropyruvate and to the cyclization of citronellal.
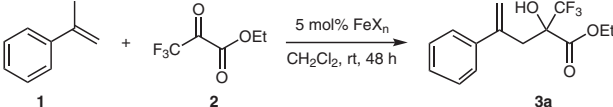
Key words ene reaction, Lewis acids, iron, trifluoropyruvate, cyclization

The carbonyl-ene reaction is a very powerful C–C bond-forming transformation.[1a] It readily converts available alkenes and carbonyl compounds into homoallylic alcohols via a synthetically economical route in an intra- or intermolecular fashion.[1b,c] The scope of the reaction has been studied extensively in terms of the aldehyde scope used in the carbonyl-ene reaction, and a variety of metal salts has been investigated including Lewis acid catalysts, such as AlMe$_2$Cl,[2] TiCl$_4$,[3] SnCl$_4$,[4] Sc(OTf)$_3$,[5] and chiral catalysts, such as BINOL-Ti,[6] BINAP-Pd/Pt,[7] BOX-Cu,[8] DPPF-Ni,[9] and Salen-Co,[10] have been disclosed in enantioselective versions. To the best of our knowledge, there are only two precedents of iron salts used in the carbonyl-ene reaction, but they have been employed in intramolecular cases and in a stoichiometric fashion.[11] In the past decade, research has focused on using trifluoropyruvates as activated ketones, since ketones were usually more difficult to react as enophiles,[12a] allowing the formation of chiral alcohols possessing tetrasubstituted stereogenic centers containing a trifluoromethyl group, which are important building blocks for pharmaceuticals and agrochemicals.[12b] Lewis acids, such as Ca,[13] Pd,[14] In,[15] Ru[16] complexes, and organocatalysts[17] have proved to be efficient catalysts in the trifluoropyruvate-ene reaction. However, there is a need to develop a catalytic iron-mediated carbonyl-ene reaction. From a green chemistry perspective, developing new synthetic methods using

iron, which is inexpensive, ubiquitous, and relatively less toxic in comparison with other metals, represents a major advantage.[18]

Following our studies on iron catalysis, such as in the iron-catalyzed enantioselective Mukaiyama aldol reaction, *meso*-epoxide opening, and aromatic sulfoxide oxidation reactions,[19] this article describes the study of the iron-catalyzed carbonyl-ene reaction of ethyl 3,3,3-trifluoropyruvate with various alkenes.

**Table 1** Screening of Iron Salts in Carbonyl-Ene Reaction

Entry	1/2	FeX$_n$	Yield (%)[a]
1	2:1	FeCl$_3$	–
2	2:1	Fe(OTf)$_3$	–
3	2:1	FeCl$_2$	58
4	2:1	Fe(OAc)$_2$	44
5	2:1	Fe(NTf)$_2$	63
6	2:1	Fe(ClO$_4$)$_2$·6H$_2$O	53[b]
7	2:1	Fe(BF$_4$)$_2$·6H$_2$O	75[b]
8	2:1	Fe(OTf)$_2$	62 (66)[c]
9	4:1	Fe(OTf)$_2$	68
10	1:1.5	Fe(OTf)$_2$	72
11	1:2	Fe(OTf)$_2$	73
12	1:1.2	Fe(OTf)$_2$	54
13	1:1.5	Fe(BF$_4$)$_2$·6H$_2$O	75[b]
14	1:1.5	FeCl$_2$ + 2 AgBF$_4$	83[b]
15	1:1.5	FeCl$_2$ + 2 AgBF$_4$	87[b,d]

[a] Isolated yield.
[b] With 4 Å molecular sieves (for entries 7 and 13, the yields were the same without 4 Å MS).
[c] 10 mol% iron salt, 60 h.
[d] Using filtration on cotton and Celite.

The studies were initiated by selecting the model reaction using α-methyl styrene (**1**) and ethyl trifluoropyruvate (**2**) with various iron salts (Table 1). Fe^{III} catalysts only led to side reactions (Table 1, entries 1 and 2). Using Fe^{II} salts, the products obtained were a mixture of the ene product and side products (Table 1, entries 3–7). $Fe(BF_4)_2 \cdot 6H_2O$ afforded homoallylic alcohol **3a** in a 75% yield, which encouraged us to optimize the conditions further (Table 1, entry 7). The yield decreased to 62% using $Fe(OTf)_2$, and a longer reaction time or an increased catalyst loading (10 mol%) had little effect on the reaction efficiency (Table 1, entry 8).

Optimization of the ratio of α-methyl styrene to ethyl trifluoropyruvate was performed in both ways (Table 1, entries 9–12). Using an excess of styrene (4 equivalents) did not lead to appreciable increase in yield (Table 1, entry 9); whereas using an excess of ethyl trifluoropyruvate afforded a better yield (Table 1, entries 10 and 11). However, using $Fe(BF_4)_2 \cdot 6H_2O$ and changing the ratio of **1/2** from 2:1 to 1:1.5 had no impact on the yield (Table 1, entries 7 and 13). When comparing $Fe(OTf)_2$ with $Fe(BF_4)_2 \cdot 6H_2O$, the latter exhibited a better catalytic activity (Table 1, entries 10 and 13). Anhydrous $Fe(BF_4)_2$, generated from $FeCl_2$ and $AgBF_4$, was also tested and showed better catalytic efficiency than $Fe(BF_4)_2 \cdot 6H_2O$ (Table 1, entry 14). In order to suppress any competing catalytic effect resulting from AgCl in the mixture of $FeCl_2$ and $AgBF_4$; a control experiment, after filtering off the AgCl, demonstrated that anhydrous $Fe(BF_4)_2$ in the absence of silver salt was a more efficient catalyst than $Fe(BF_4)_2$ in its presence, affording an 87% yield of **3a** (Table 1, entry 15). However, $Fe(BF_4)_2 \cdot 6H_2O$, being a commercial catalyst, was used for the screening of solvents (Table 2).

Table 2 Optimization of the Reaction Solvents
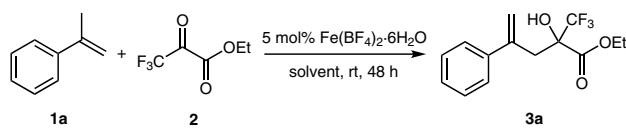
Entry	Solvent	Yield (%)[a]
1	MeCN	–
2	Et_2O	52
3	DCE	46
4	Toluene	71
5	CH_2Cl_2	75
6	THF	–
7	Me-THF	< 5[b]
8	CPME	72
9	TBME	42
10	DMC	59

[a] Isolated yield.
[b] Calculated by ^1H NMR spectroscopy.

In MeCN, the carbonyl-ene reaction did not proceed and starting materials were recovered (Table 2, entry 1). Et_2O and DCE gave moderate yields of **3a** (Table 2, entries 2 and 3). Toluene led to higher yield of **3a** (Table, entry 4). Both THF and Me-THF afforded only traces of the product, and ethyl trifluoropyruvate was recovered (Table 2, entries 6 and 7). Several 'green' solvents were considered (Table 2, entries 8–10). Cyclopentyl methyl ether (CPME) afforded a slightly lower yield than with dichloromethane (Table 2, entry 8). *tert*-Butyl methyl ether (TBME) and dimethyl carbonate (DMC) led to moderate yields (Table 2, entries 9 and 10). Among the list of selected solvents, CH_2Cl_2 provided the highest yield (Table 2, entry 5) and it was consequently chosen for studying the scope of the reaction using various alkene substrates.
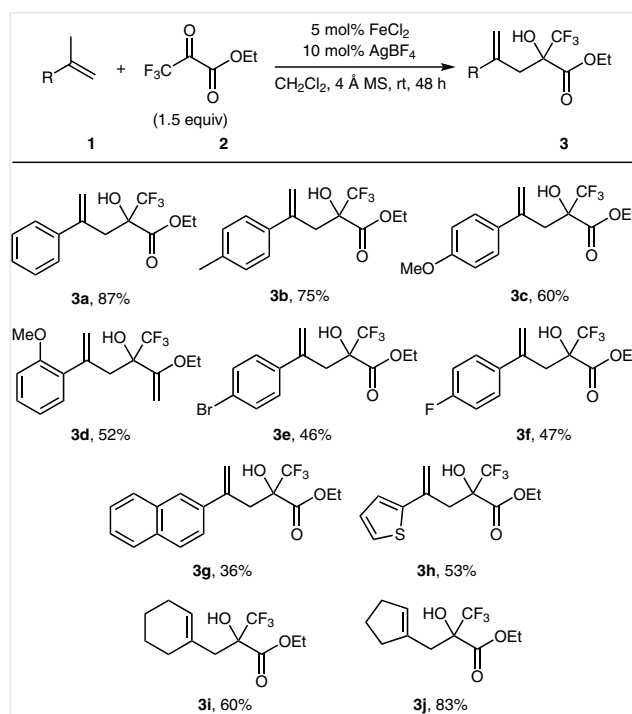

Scheme 1 Reaction scope of the $Fe(BF_4)_2$ catalyzed trifluoropyruvate carbonyl-ene reaction

However, cyclopentyl methyl ether, which is a green solvent, gave a very promising yield in the model reaction. In order to demonstrate the reaction scope, various substituted α-methyl styrenes were selected (Scheme 1), using the best conditions selected from Table 1 (5 mol% $FeCl_2$, 10 mol% $AgBF_4$, entry 15). Using substrates possessing an electron-donating group, such as a methyl group in the *para* position, the yield was good (**3b**). With a more electron-donating group such as *p*-MeO, side competing reactions of the alkene occurred and the yield of the adduct decreased to 60% (Scheme 1, **3c**). Steric hindrance was another factor influencing the reaction. A methoxy group in the *ortho* position led to further decrease of the yield (**3d**). Moreover,

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the presence of electron-withdrawing groups (Br, F) on the aryl ring of the styrene derivatives led to moderate yields (**3e,f**). Using less nucleophilic 2-isopropenylnaphthalene, the yield dropped further (**3g**). A moderate yield was obtained using 2-(prop-1-en-2-yl)thiophene as the nucleophile (**3h**). More nucleophilic methylenecyclopentane and methylenecyclohexane afforded the products in moderate to good yields (**3i,j**). Only traces of product were obtained when using 2-(1-methylethenyl)-pyridine as a heteroaromatic alkene, probably because the pyridine deactivated the catalyst.[20] Less nucleophilic noncyclic aliphatic alkenes, such as 1-hexene, led only to traces of the desired product. Indeed, 1-hexene has often been used in the literature with a large excess of the enophile.[12a] Overall, the developed catalytic system was efficient with 1,1-disubstituted aromatic and aliphatic alkenes.

The intramolecular carbonyl-ene reaction is a useful method for making C–C bonds in organic synthesis.[1,21] The cyclization of (R)-(+)-citronellal affording $(-)$-isopulegol (**5**) is a known reaction. The latter is a desirable precursor to a widely employed chemical $(-)$-menthol.[22] Several catalysts have been used for this process, including Sc(OTf)$_3$,[23a] SnCl$_4$,[23b] BiCl$_3$,[23c] and Bi(OTf)$_3$·xH$_2$O.[23d] FeCl$_3$ (10 mol%) has been reported in the literature but a low yield (20%) with a 76:24 ratio of isopulegol **5** to other diastereomers was achieved.[24] Hence, it was of interest to test Fe(BF$_4$)$_2$ in the cyclization of citronellal, since iron salts have been less explored compared to other metal salts. Using the Fe(BF$_4$)$_2$ catalytic system with (S)-(−)-citronellal (**4**), a total yield of 70% was obtained in a 70:30 *trans/cis* ratio of (+)-isopulegol to (−)-*neo*-isopulegol in the crude product while the isolated yields were: (+)-isopulegol **5**, 45%, (−)-*neo*-isopulegol **6**, 25%, with no (−)-*iso*-isopulegol or (−)-*neo-iso*-isopulegol being identified (Scheme 2).[25]
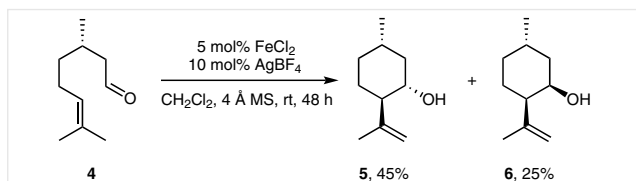
Scheme 2 Intramolecular Fe(BF$_4$)$_2$-catalyzed carbonyl-ene reaction of (S)-citronellal

Through the evaluation of a variety of iron salts, we have found that the Fe[II] salts were more appropriate to catalyze the carbonyl-ene reaction. Indeed, Fe[III] salts, such as FeCl$_3$ and Fe(OTf)$_3$, failed to catalyze the carbonyl-ene reaction of α-methyl styrene and trifluoropyruvate (Table 1, entries 1 and 2). Secondly, it was found that the counterion had a marked effect on the conversion of the Lewis acid catalyzed reaction between methylenecyclohexane and ethyl trifluoropyruvate.[26] Anhydrous Fe(BF$_4$)$_2$, generated from FeCl$_2$ and AgBF$_4$, led to higher yields than Fe(BF$_4$)$_2$·6H$_2$O. Furthermore, a bidentate coordination can be postulated

such as in the Cu[II]-catalyzed carbonyl-ene reaction of ethyl glyoxylate disclosed by Evans.[12a] Fe[II] can be considered to coordinate with the two carbonyl oxygens of the trifluoropyruvate in a bidentate manner as shown in the proposed mechanism (Scheme 3). The Lewis acid promoted ene reaction is usually discussed in terms of a continuum from a concerted to a cationic mechanism.[1b,27] However, a stepwise radical pathway could also be envisaged.[28] A control experiment using TEMPO as a radical scavenger [methylstyrene (**1**), 1.5 equiv trifluoromethyl pyruvate **2**, 5 mol% FeCl$_2$, 10 mol% AgBF$_4$, 5 mol% TEMPO] led to a signficant decrease in the yield of **3a** (43% instead of 83%).
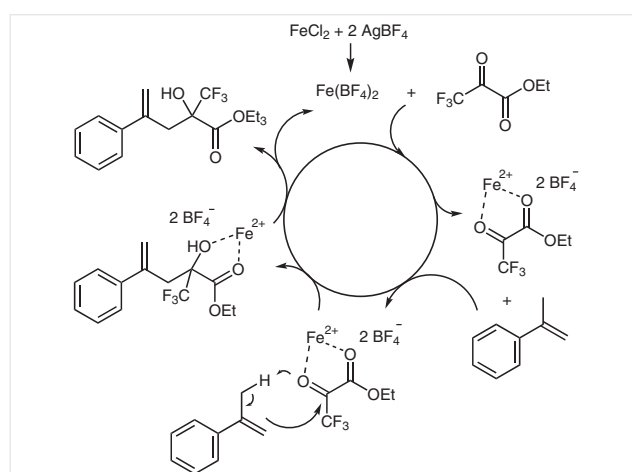
Scheme 3 Postulated mechanism for the Fe(BF$_4$)$_2$-catalyzed carbonyl-ene reaction between ethyl trifluoropyruvate and α-methylstyrene

The observation that the reaction still occurs, although less efficient, in the presence of TEMPO does not rule out unambiguously that a radical process is involved in the process, at least to some extent.

To sum up, we have reported the first iron catalytic system for both inter- and intramolecular carbonyl-ene reactions. Using a low catalytic loading of Fe(BF$_4$)$_2$, the reaction proceeds smoothly to afford ene products in 36–87% isolated yields.[29] The method was also applied to 1,1-disubstituted alkenes with trifluoropyruvate and to the cyclization of citronellal. The carbon–carbon bond-forming process was affected by the electronic and steric properties of the substituents on the arene ring in the intermolecular carbonyl-ene reaction. A good yield of and selectivity for isopulegol were obtained in the intramolecular carbonyl-ene reaction. Further development of iron catalysis in the carbonyl-ene reaction will be reported in due course.

Funding Information

Acknowledgment

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0036-1591858.

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(29) **General Procedure for the Carbonyl-Ene Reaction of Alkenes with Ethyl 3,3,3-Trifluoropyruvate**
FeCl$_2$ (1.7 mg, 0.0125 mmol) and AgBF$_4$ (5 mg, 0.025 mmol) were added into a flame-dried test tube. The test tube was placed under high vacuum and purged with argon three times. Afterwards, distilled THF (1 mL) was added, and the resulting solution was stirred for 0.3 h, then filtered under argon atmosphere through a pre-dried pipet plugged with cotton and Celite® to remove the precipitated AgCl. To the resulting solution was added 4 Å MS (50 mg), and the solution was then evaporated under reduced pressure. The test tube was then placed under high vacuum (1 Torr) for 0.3 h. Under an argon atmosphere freshly distilled CH$_2$Cl$_2$ (0.5 mL) was then added, and the solution stirred for 0.1 h. Then, α-methyl styrene (30 mg, 0.25 mmol) and ethyl 3,3,3-trifluoropyruvate (64 mg, 0.375 mmol) were added via syringe into the solution. The solution was then stirred for 48 h under an argon atmosphere. Then, the crude reaction mixture was directly purified by silica flash chromatography (eluent: hexane/ethyl acetate) to give pure carbonyl-ene product **3a** (63 mg, 87%).

Ethyl 2-Hydroxy-4-phenyl-2-(trifluoromethyl)pent-4-enoate (3a)[30]
¹H NMR (400 MHz, CDCl$_3$): δ = 7.35–7.26 (m, 5 H), 5.39 (d, *J* = 1.3 Hz, 1 H), 5.28 (d, *J* = 1.3 Hz, 1 H), 4.03 (dq, *J* = 10.6, 7.2 Hz, 1 H), 3.76 (d, *J* = 0.9 Hz, 1 H), 3.64 (dq, *J* = 10.6, 7.2 Hz, 1 H), 3.28

(d, J = 14.0 Hz, 1 H), 3.04 (d, J = 14.0, 1.0 Hz, 1 H), 1.11 (t, J = 7.2 Hz, 3 H). ^{13}C NMR (100 MHz, CDCl$_3$): δ = 168.9, 141.0, 128.1, 127.9, 126.8, 123.4 (q, J = 286.2 Hz), 119.4, 77.09 (q, J = 28.9 Hz), 63.5, 37.0, 13.5. IR (NaCl): 3491, 2985, 1741, 1629, 1446, 1370, 1312, 1227, 1184, 1136, 1050, 911, 778, 701 cm^{-1}.

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