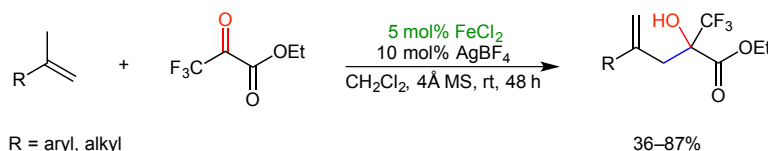


Fe(BF₄)₂ catalyzed inter- and intramolecular carbonyl-ene reaction of trifluoropyruvate

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Abstract Inter- and intramolecular carbonyl-ene reactions have been developed using 5 mol% Fe(BF₄)₂ as catalyst, affording homoallylic alcohols in 36 to 87% isolated yields. This catalyst, prepared from FeCl₂ and AgBF₄, 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.

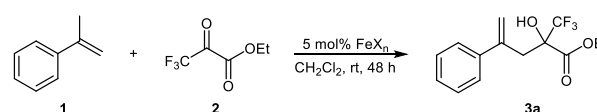
Key words ene reaction, Lewis acids, iron, trifluoropyruvate, cyclization.

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, 1c} 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 have been investigated as Lewis acid catalysts, such as AlMe₂Cl,² TiCl₄,³ SnCl₄,⁴ Sc(OTf)₃.⁵ 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 was focused on using trifluoropyruvates as activated ketones, since ketones were usually more difficult to react as an enophile,^{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} Metal Lewis acids, such as Ca,¹³ Pd,¹⁴ In,¹⁵ Ru¹⁶ complexes, and organocatalysts¹⁷ were proved to be efficient catalysts in the trifluoropyruvate-ene reaction. However, there is a need to develop a catalytic iron-mediated carbonyl-ene reaction. Indeed, a carbonyl-ene reaction catalyzed by an environmentally benign iron salt would be highly valuable. 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 in iron catalysis, such as in iron-catalyzed enantioselective Mukaiyama aldol, *meso*-epoxide opening, and aromatic sulfoxide oxidation reactions,¹⁹ this article describes the study of iron-catalyzed carbonyl-ene reaction of ethyl 3,3,3-trifluoropyruvate with various alkenes. The studies were

initiated by selecting the model reaction of α -methyl styrene **1** and ethyl trifluoropyruvate **2**, using various iron salts (Table 1). Fe^{III} catalysts only led to side reactions (Table 1, entries 1 and 2). Using Fe^{II} salts, the obtained products were a mixture of the ene-product and side products (Table 1, entries 3–7). Fe(BF₄)₂·6H₂O afforded homoallylic alcohol **3a** in a 75% yield, which encouraged us to further optimize the conditions (Table 1, entry 7). The yield decreased to 62% by 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 ra-

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}

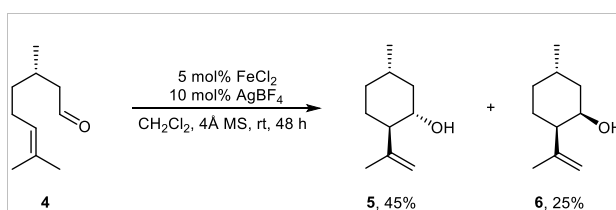
^a Isolated yield.

^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.

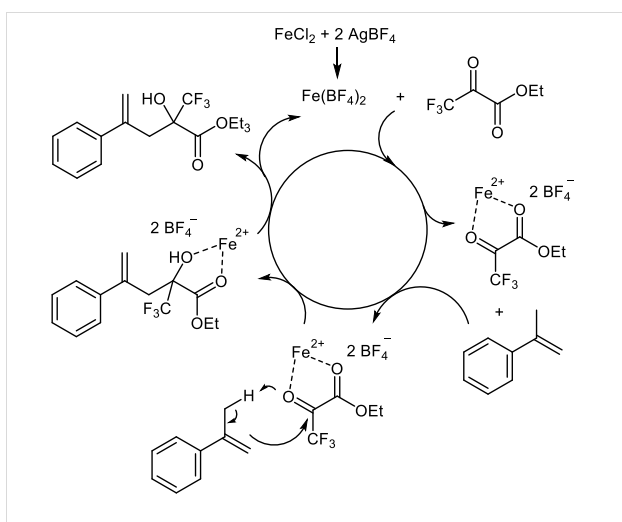
^d Using filtration on cotton and celite.

76:24 ratio of isopulegol **5** to other diastereomers was achieved.²⁴ Hence, it was still very valuable to test $\text{Fe}(\text{BF}_4)_2$ in the cyclization of citronellal, since iron salts were less explored compared to other metal salts. In this catalytic system of $\text{Fe}(\text{BF}_4)_2$, by using (*S*)-(-)-citronellal **4**, a total 70% yield 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%, and no (-)-*iso*-isopulegol or (-)-*neo*-*iso*-isopulegol was identified (Scheme 2).²⁵



Scheme 2 Intramolecular $\text{Fe}(\text{BF}_4)_2$ 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 studied reaction. Indeed, Fe^{III} salts, such as FeCl_3 and $\text{Fe}(\text{OTf})_3$, failed to catalyze the carbonyl-ene reaction of α -methyl styrene and trifluoropyruvate (Table 1, entries 1 and 2). Secondly, it was reported that a marked effect of the counterion existed on the conversion of Lewis acid-catalyzed reaction between methylene cyclohexane and ethyl trifluoropyruvate.²⁶ Anhydrous $\text{Fe}(\text{BF}_4)_2$, generated from FeCl_2 and AgBF_4 , led to higher yields than $\text{Fe}(\text{BF}_4)_2 \cdot 6\text{H}_2\text{O}$. Furthermore, a bidentate coordination can be postulated such that in the Cu^{II} catalyzed carbonyl-ene reaction of ethyl glyoxylate disclosed by Evans.^{12a} Fe^{II} coordinating with two carbonyl oxygens in one molecule of trifluoropyruvate was drawn in a bidentate manner in the proposed mechanism (Scheme 3). The Lewis acid-promoted ene reaction is usually discussed in terms of the continuum from concerted to cationic mechanism.^{1b,27} However, a stepwise radical pathway could also



Scheme 3 Postulated mechanism for the $\text{Fe}(\text{BF}_4)_2$ catalyzed carbonyl-ene reaction between ethyl trifluoropyruvate and α -methylstyrene

be envisioned.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 major decrease of the yield of **3a** (43% instead of 83%). The observation that the reaction still occurs in the presence of TEMPO does not indicate unambiguously that a radical process is not involved in the process, at least to some extent.

To sum up, we reported the first iron catalytic system for both inter- and intramolecular carbonyl-ene reactions. Using low catalytic loading of $\text{Fe}(\text{BF}_4)_2$, the reaction proceeds smoothly to afford ene products in 36 to 87% isolated yields.²⁹ The method was applied to 1,1-disubstituted alkenes with trifluoropyruvate and 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. Good yield and selectivity of isopulegol were obtained in the intramolecular carbonyl-ene reaction. Further development of iron catalysis in carbonyl-ene reaction will be reported in due course.

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Supporting Information

YES

Primary Data

NO

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- (29) **General procedure** for the carbonyl-ene reaction of alkenes with ethyl 3,3,3-trifluoropyruvate: FeCl₂ (1.7 mg, 0.0125 mmol) and AgBF₄ (5 mg, 0.025 mmol) were added into a flame-dried test tube. The test tube was put under high vacuum (pumped with argon three times). Afterwards, distilled THF (1 mL) was added and the resulting solution was stirred for 0.3 h. Then, using a pre-dried pipet plugged with cotton and celite to filter the precipitated AgCl under argon atmosphere. To the resulting solution was added 50 mg of 4 Å MS and the solution was then evaporated under reduced pressure. The test tube was then put under high-vacuum (1 Torr) for 0.3 h. Under argon atmosphere fresh-distilled CH₂Cl₂ (0.5 mL) was then added into the tube and stirred the solution 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 a syringe into the solution. The tube was put under argon protection and the solution was stirred for 48 h. Then, the crude reaction mixture was directly purified by silica flash chromatography (eluent: hexane/ethyl acetate). 63 mg of carbonyl-ene product **3a** was obtained (yield = 87%).
- Ethyl 2-hydroxy-4-phenyl-2-(trifluoromethyl)pent-4-enoate (3a)**:³⁰ ¹H NMR (400 MHz, CDCl₃) δ 7.35–7.26 (m, 5H), 5.39 (d, *J* = 1.3 Hz, 1H), 5.28 (d, *J* = 1.3 Hz, 1H), 4.03 (dq, *J* = 10.6, 7.2 Hz, 1H), 3.76 (d, *J* = 0.9 Hz, 1H), 3.64 (dq, *J* = 10.6, 7.2 Hz, 1H), 3.28 (d, *J* = 14.0 Hz, 1H), 3.04 (d, *J* = 14.0, 1.0 Hz, 1H), 1.11 (t, *J* = 7.2 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) 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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