Iron(III) 2-ethylhexanoate as a novel, stereoselective hetero-Diels–Alder catalyst

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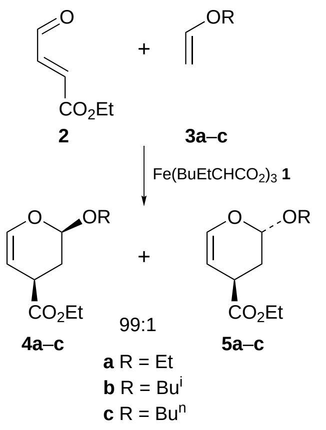
Iron(III) 2-ethylhexanoate has been used as a novel, mild Lewis acid catalyst for the stereoselective Diels–Alder reaction of ethyl (*E*)-4-oxobutenoate with alkyl vinyl ethers to stereoselectively produce *cis*-2-alkoxy-3,4-dihydro-2*H*-pyran-4-carboxylic acid, ethyl esters with diastereoisomeric excesses (de) as high as 98%.

Since its discovery over 65 years ago,[1] the Diels–Alder reaction has been one of the most versatile reactions for assembling six-membered rings. The use of Lewis acid catalysts has led to improved regio- and stereo-selectivity for many of these reactions. Lanthanide reagents have been used as very mild Lewis acid catalysts for the Diels–Alder reaction of α,β-unsaturated aldehydes or esters with vinyl ethers to give substituted dihydropyrans.[2] In a search for cost-effective alternative catalysts, we have discovered that iron(III) 2-ethylhexanoate **1** is a novel, mild and economical Lewis acid catalyst for carrying out highly stereoselective Diels–Alder reactions between ethyl (*E*)-4-oxobutenoate **2**[3] and alkyl vinyl ethers **3a**–**3c** to give 2,4-disubstituted pyrans **4a–c** and **5a–c** (Scheme 1).

Based on analogous Diels–Alder transformations to give 2,4-substituted tetrahydropyrans, the major products have been assigned as the *endo* isomers.[4] Effectively an inverse electron demand hetero-Diels–Alder reaction, cyclization occurs selectively through the *endo* transition state, regio- and stereo-selectively producing the *cis*-2,4-disubstituted pyrans **4**). This *endo* selectivity is enhanced using **1** as a catalyst (Table 1), giving diastereoisomeric excesses (de) as high as 98% based on relative product peak ratios obtained by gas chromatography. Similar yields and selectivities have been obtained when ethyl, isobutyl, and n-butyl vinyl ethers are used.

The reaction of **2** and **3b** has been examined with varying amounts of **1** at various temperatures (Table 2). Clearly, selectivity and reaction rate were enhanced by the addition of **1** (entry 6 *vs.* entries 7–10). The highest selectivity was seen at room temperature. Increasing reaction temperature shortened the reaction time from a few days to a few hours, but the de decreased from 98% at room temperature to 96% at 60 °C and 90% at 80 °C (entries 2–5 *vs.* entries 7–10 *vs.* entry 15). For reaction mixtures at elevated temperatures, yields could be improved by adding a trace amount of Et_3N as an inhibitor; at levels above 1 wt% Et_3N in the reaction of **2**, yields and selectivity began to decrease, indicating Et_3N was poisoning the catalyst (entries 15–19). Reaction times could also be shortened by adding additional catalyst, but optimal yields of ⩾80% were obtained using 0.20–0.25 equiv. of **1** (entries 3, 8 and 13). Modest yield increases also were realized by increasing the amount of vinyl ether from 6 to 10 equiv. (entries 12 and 14 *vs.* entries 11 and 13).



Scheme 1

To isolate gram quantities, the product was removed from the catalyst by selective precipitation followed by column chroma-

Table 1 Comparison of vinyl ethers[a]

Entry	Ether	*T*/°C	*t*/d	Yield (%)	De (%)
1	**3a**	23	14	78	98
2	**3b**	23	14	80	98
3	**3c**	23	14	79	98

[a] Each reaction mixture contained ethyl (*E*)-4-oxobutenoate, 6 equiv. of vinyl ether and 0.1 euqiv. of iron(III) 2-ethylhexanoate. Ethyl (*E*)-4-oxobutenoate was inhibited with a trace amount of hydroquinone. Reported yields are GLC yields based on an internal standard. Yields at 66 h were calculated to be 72, 79 and 71% for entries 1, 2 and 3, respectively.

Table 2 Optimization reactions[a]

Entry	*T*/°C	*t*/h	**1** (equiv.)	Yield[b] (%)	De (%)
1	23	96	0	2	—
2	23	96	0.10	66	98
3	23	96	0.25	81	98
4	23	96	0.50	78	98
5	23	96	1.00	70	98
6[c]	60	18	0	13	66
7[c]	60	18	0.10	72	96
8[c]	60	18	0.25	80	96
9[c]	60	18	0.50	79	98
10[c]	60	18	1.00	67	98
11	60	16	0.10	72	96
12[d]	60	16	0.10	75	96
13	60	16	0.20	80	96
14[d]	60	16	0.20	84	96
15[e]	80	20	0.10	64	90
16[e]	80	20	0.10	73	92
17[e]	80	20	0.10	67	90
18[e]	80	20	0.10	56	82
19[e]	80	20	0.10	47	78

[a] Each reaction mixture contained ethyl (*E*)-4-oxobutenoate, isobutyl vinyl ether and iron(III) 2-ethylhexanoate. Ethyl (*E*)-4-oxobutenoate was inhibited with a trace amount of hydroquinone. Unless otherwise specified, 6 equiv. of isobutyl vinyl ether were used. [b] Reported yields are GLC yields based on an internal standard. [c] The reaction mixtures were stirred at room temperature for 18 h before heating to 60 °C for 18 h. [d] 10 equiv. of isobutyl vinyl ether were added instead of 6 equiv. [e] Et_3N was added in the following weight percents relative to **2**: 0% for entry 15, 1% for entry 16, 5% for entry 17, 15% for entry 18 and 25% for entry 19.

Table 3 Comparison of Iron-Based Catalysts[a]

Entry	Catalyst	T °C	t/h	**2** (%)	Yield[b] (%)	De (%)
1	Iron(III) 2-ethylhexanoate	70	6	15	58	96
2	Iron(II) 2-ethylhexanoate	70	6	29	38	92
3	Iron(III) naphthenate	70	5	21	30	92
4	Iron(III) benzoate	70	5	44	29	86
5	Iron(II) stearate	70	4	59	18	86
6	Iron(III) stearate	70	4	71	14	80
7	—	70	6	71	10	64

[a] All reactions were carried out in sealed glass tubes containing **2**, 6 equiv. of ethyl vinyl ether and 0.1 equiv. of catalyst. [b] Reported yields are GLC yields based on an internal standard.

tography on silica gel which had been deactivated by mixing with Et_3N in CH_2Cl_2 and evaporating to dryness. For larger samples, the product was isolated either by chromatography or wiped-film evaporation.

Although the exact binding nature of the catalyst is unknown, the choice of metal ligands and metal oxidation state is critical to the success of the catalytic reaction. Similar catalysts containing lower metal oxidation states and/or ligands which are bulkier and/or more rigid give lower selectivity, as well as lower reaction yields (Table 3). The bulkier/more rigid ligands may cause steric interference with the ethyl (*E*)-4-oxobutenoate, where complexation is believed to take place. A lower oxidation state may decrease the catalyst electrophilicity enough that it does not coordinate well with any of the oxygens from **2**.

In summary, iron(III) 2-ethylhexanoate is a novel, mild and relatively inexpensive Lewis acid catalyst for the stereoselective Diels–Alder reaction of ethyl (*E*)-4-oxobutenoate with alkyl vinyl ethers to give *cis*-2,4-disubstituted pyrans, extending the range of known catalysts for these types of transformations.

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Footnotes and References

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† Iron(III) 2-ethylhexanoate was purchased as a 52% solution in mineral spirits from Johnson Matthey Alfa Aesar. Ethyl (*E*)- 4-oxobutenoate was purchased from Lonza. Representative experimental procedures. (*a*) Purification by chromatography: A mixture of ethyl (*E*)-4-oxobutenoate (2.56 g, 0.02 mol): *n*-butyl vinyl ether (8.65 g, 0.12 mol) and 52% iron(III) 2-ethylhexanoate (1.86 g, 0.002 mol) in mineral spirits was stirred at room temperature for 44 h. The catalyst precipitated after adding 20 ml of 20% MeCN in water. The slurry was filtered through filter agent, rinsing the cake with 20% MeCN in water. The filtrate was saturated with NaCl. The organic layer was separated and dried ($MgSO_4$). The solution was decanted and the MeCN evaporated. The remaining brown oil was flushed through a 0.75″ × 12″ deactivated silica gel column, eluting with hexane, followed by 20% EtOAc in hexane. After concentrating, a clear yellow oil (3.36 g) was obtained, assaying at 97% of **4a** as a single isomer for a calculated yield of 3.26 g (81%).

(*b*) purification by wiped-film evaporation: A mixture of of 52% iron(III) 2-ethylhexanoate (96.5 g) in mineral spirits and (±)-bis(2-ethylhexyl) sebacate (50.3 g) was dripped down a wiped-film still over 2 h operating at a vacuum of 0.05 mmHg, a heating temperature of 60 °C, a condensing temperature of 4 °C and a spinning rate of 300 rpm. The recovered bottoms (99.4 g) were assumed to be 50% catalyst by weight. A mixture of ethyl (*E*)-4-oxobutenoate (25.7 g, 0.20 mol) *n*-butyl vinyl ether (120.4 g, 1.20 mol) Et_3N (0.3 g), hydroquinone (0.026 g), and 50% iron(III) 2-ethylhexanoate in (±)-bis(2-ethylhexyl) sebacate (18.6 g, 0.02 mol) was heated at 60 °C for 12 h. After evaporating excess vinyl ether, the residue was dripped at 1 drop per second down a wiped-film still operating at a vacuum of 0.1 mmHg, a heating temperature of 90 °C, a condensing temperature of 2 °C and a spinning rate of 300 rpm. The overheads (30.2 g) assayed at 93% of **4a** for a calculated yield of 28 g (62%).

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