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Catalytic enantioselective Diels–Alder reactions of furans and 1,1,1-trifluoroethyl acrylate

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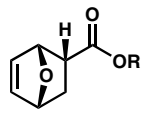
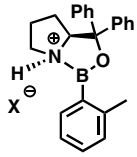
Abstract—Catalytic enantioselective Diels–Alder reactions of furans and 1,1,1-trifluoroethyl acrylate in the presence of oxazaborolidium catalysts **2** or **3** provide 7-oxabicyclo[2.2.1]hept-5-enes with high *endo*-selectivity and excellent enantioselectivity.

Chiral 7-oxabicyclo[2.2.1]hept-5-enes, **1** are attractive precursors for the synthesis of various important natural products such as pseudo-sugars,[1] shikimic acid,[2] *trans*-kumausyne,[3] and epoxyquinols.[4] Although these products can in principle be prepared by enantioselective Diels–Alder reactions of furan and acrylate derivatives, the low reactivity of furan, poor conversions and the occurrence of side reactions have made this approach problematic. In fact, only a few examples of catalytic asymmetric Diels–Alder reactions of furans and acrylate derivatives have been reported.[2,5]



1



2, X=TfO
3, Tf_2N

The cationic chiral oxazaborolidium catalysts **2** or **3** generated from the corresponding oxazaborolidines by protonation by trifluoromethanesulfonic acid or trifluoromethanesulfonimide are excellent catalysts for enantioselective Diels–Alder reactions with a variety of dienes and dienophiles, for example, α,β-enones, esters, and quinones.[6] We found that these catalysts also provide excellent results in the Diels–Alder reaction of trifluoroethyl acrylate with furans.

Initially, the Diels–Alder reactions of furan and ethyl, benzyl, and 1,1,1-trifluoroethyl acrylates with oxazaborolidium cation catalyst **2**, were attempted (Table 1). Among the three acrylate esters, we found that 1,1,1-trifluoroethyl acrylate is the best dienophile in terms of rate and yield.[6a] The reaction was generally carried out at −20 °C by stirring 1,1,1-trifluoroethyl acrylate with furan in the presence of oxazaborolidinium salt of **3** (20 mol %) in CH_2Cl_2 under 1 atm nitrogen. The reaction reached completion after 2 h. The cycloadduct **1** was generated in 98% yield but a 44:55 mixture of *endo*- and *exo*-diastereomers was obtained (Table 1, entry 1). Although the diastereomeric ratio was low, the enantiomeric excesses of *endo* and *exo* products were high, 86%, 94%, respectively. However, when the reaction was performed at −78 °C, the *endo*:*exo* ratio reversed to 80:20, and each adduct was obtained in 98% ee (entry 1). Still higher *endo*:*exo* ratio (88:12) was obtained at −95 °C, but the yield dropped to 24%. This observation can be explained by thermodynamic equilibration at higher temperature in favor of *exo*-isomer. High *endo* selectivity can be achieved under kinetic control at low temperature. In order to increase the yield and diastereomeric ratio, we tried the reaction with more reactive oxazaborolidium cation **2** (20 mol %). Although the oxazaborolidium salt **3** is more stable than **2**,[6c] catalyst **2** is more efficient in terms of the diastereomer ratio (*endo*:*exo* = 91:9) and reaction rate (4 h). To the best of our knowledge, this was the first highly

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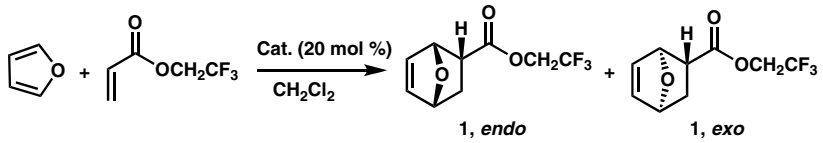
Table 1. Enantioselective Diels–Alder reaction of furan and trifluoroethyl acrylate



Entry	Catalyst	Conditions	% Yield[a]	% *endo*:*exo*[b]	% ee (*endo*, *exo*)[c]
1	3	−20 °C, 2 h	98	44:55	86, 94
2	3	−78 °C, 16 h	96	80:20	98, 98
3	3	−95 °C, 5 h	24	88:12	98, 98
4	2	−78 °C, 4 h	94	91:9	99, 99

[a] Yield of isolated product.
[b] The ratio was determined by ^{1}H NMR analysis (500 MHz) and GC analysis.
[c] The enantioselectivity was determined after hydrogenation with H_2 in the presence of 10% Pd/C and GC analysis.

endo-selective Diels–Alder reaction of furan with an acrylate derivative.

Next, substituted furans were employed in the catalytic enantioselective Diels–Alder reaction as diene (Table 2). Because of higher HOMO levels of all methyl substituted furans relative to those of the parent, the reactions proceed much faster and provide the Diels–Alder adducts with very high *endo*:*exo* diastereomeric ratios and excellent enantioselectivity.[7] Toluene also can be used as solvent, but the diastereomeric ratio was inferior to that with dichloromethane (entries 1 and 3).

The absolute configuration of the *endo*-adduct was established by comparison of its optical rotation with the literature value after conversion into the corresponding iodolactone.[8] This absolute configuration is exactly that which is predicted from the mechanistic model[6c,d] (Fig. 1).

In summary, the enantioselective Diels–Alder reaction of furans and 1,1,1-trifluoroethyl acrylate is efficiently promoted by catalysts **2** or **3** to afford cycloadducts with high *endo*-selectivity and excellent enantioselectivity.

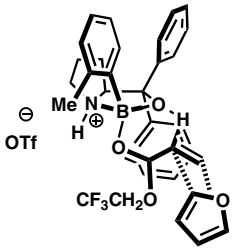


Figure 1. The transition-state assembly of Diels–Alder reaction of furan and trifluoro acrylate in the presence of **2**.

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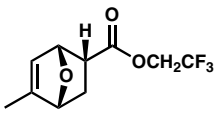
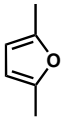
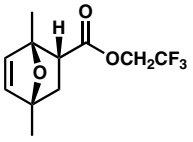
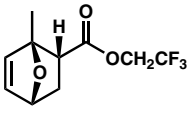
Table 2. Enantioselective Diels–Alder reactions of methyl substituted furans and trifluoroethyl acrylate

Entry	Diene	Product	Catalyst	Conditions	% Yield[a]	% *endo*:*exo*[b]	% ee (*endo*)[c]
1			3	$PhCH_3$, −78 °C, 16 h	99	67:33	96
2			3	CH_2Cl_2, −95 °C, 2 h	99	96:4	99
3			3	$PhCH_3$, −78 °C, 40 h	98	94:6	95
4			2	CH_2Cl_2, −78 °C, 3 h	98	97:3	97
			2	CH_2Cl_2, −78 °C, 6 h	74	94:6	98

[a] Yield of isolated product.
[b] The ratio was determined by ^{1}H NMR analysis (500 MHz) and GC analysis.
[c] The enantioselectivity was determined by double bond reduction with H_2 in the presence of 10% Pd/C and GC analysis.

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7. Typical procedure (Table 1, entry 4): To a stirred solution of oxazaborolidium catalyst **2** (0.133 mmol)[6d] in dichloromethane (1.0 mL) were added sequentially at −78 °C 1,1,1-trifluoroethyl acrylate (85 μL, 0.665 mmol) and furan (242 μL, 3.325 mmol). The reaction mixture was stirred for 4 h and then quenched with triethylamine (20 μL) and water. After the mixture was warmed to 23 °C, the solvent was removed by rotary evaporation and the residue was purified by silica gel chromatography (ethyl acetate–hexane, 1:3) to afford 139 mg (94%) of Diels–Alder adduct **1** (*endo*:*exo* = 91:9). *(1R,2R,4R)-2,2,2-trifluoroethyl 5-methyl-7-oxa-bicyclo[2.2.1]hept-5-ene-2-carboxylate (Table 2 entry 2)*. FT-IR 2360, 2342, 1755, 1279, 1150 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 5.73 (m, 1H), 5.10 (d, 1H, $J = 4.0$ Hz), 4.76 (d, 1H, $J = 4.8$ Hz), 4.49 (dq, 1H, $J = 8.4$, 12.4 Hz), 4.37 (dq, 1H, $J = 8.4$, 12.4 Hz), 3.22 (dt, 1H, $J = 4.4$, 9.2 Hz), 2.10 (ddd, 1H, $J = 4.8$, 9.2, 11.6 Hz), 1.84 (d, 3H, $J = 1.2$ Hz), 1.60 (dd, 1H, $J = 4.0$, 11.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 148.2, 125.4, 122.8 (q, 1C, $J = 278$ Hz), 82.3, 79.7, 60.1 (q, 1C, $J = 36.7$ Hz), 44.7, 28.0, 12.3. LRMS calcd for $C_{10}H_{12}F_3O_3$: 237.0; found 237.0. Diastereoselectivity (*endo*:*exo* ratio)—^1H NMR δ 5.86 (m, 1H, *exo* minor), 5.73 (m, 1H, *endo* major). *(1R,2R,4R)-2,2,2-trifluoroethyl 1-methyl-7-oxa-bicyclo-[2.2.1]hept-5-ene-2-carboxylate (Table 2, entry 5)*. FT-IR 2974, 1755, 1281, 1172, 976 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 6.45 (dd, 1H, $J = 1.5$, 5.7 Hz), 6.01 (d, 1H, $J = 5.7$ Hz), 4.95 (dd, 1H, $J = 1.8$, 4.8 Hz), 4.56 (dq, 2H, $J = 8.4$, 12.6 Hz), 2.85 (dd, 1H, $J = 3.6$, 9.3 Hz), 2.31 (m, 1H), 1.7 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.1, 137.9, 135.6, 125.6 (q, 1C, $J = 278$ Hz), 87.7, 77.5, 60.7 (q, 1C, $J = 36.7$ Hz), 48.1, 31.8, 18.3 LRMS calcd for $C_{10}H_{11}F_3O_3$: 236.1; found 236.1 Diastereoselectivity (*endo*:*exo* ratio)—^1H NMR δ 6.19 (d, 1H, *exo* minor), 6.01 (d, 1H, *endo* major).
8. Pure (1*R*,4*R*,5*R*,6*R*,8*S*)-5-iodo-3,7-dioxatricyclo[4,2,1,$0^{4,8}$]-nonan-2-one iodolactone was prepared from 7-oxabicyclo[2.2.1]hept-5-ene, **1** (*endo*:*exo* = 91:9) by saponification of **1** and iodination of the sodium salt (I_2, CH_3CN/H_2O = 3/1, rt, 85% yield) $[\alpha]_D^{23}$ −116 (*c* 1.00, $CHCl_3$) [lit. $[\alpha]_D^{23}$ −113 (*c* 1.04, $CHCl_3$). Ogawa, S.; Yoshikawa, M.; Taki, T.; Yokoi, S.; Chida, N. *Carbohydr. Res.* **1995**, *269*, 53].