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Catalytic Asymmetric Synthesis of Tertiary Alcohols and Oxetenes Bearing a Difluoromethyl Group

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Supporting Information

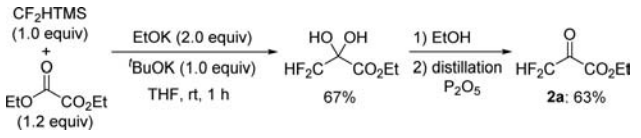
ABSTRACT: The catalytic asymmetric ene reaction with difluoropyruvate as an electrophile in the presence of a dicationic palladium complex is shown. This is the reliable and practical catalytic asymmetric synthesis for various α-CF_2H tertiary alcohols in high yields and enantioselectivities. The reaction with isobutene can be catalyzed efficiently under solvent-free conditions with low catalyst loading (up to S/C 2000). Furthermore, difluoropyruvate is applicable to the [2 + 2] cycloaddition reaction in high yields and enantioselectivities.

Fluorinated organic compounds have found increasing applications in a variety of fields, such as pharmaceuticals and agrochemicals, because incorporation of fluorine atom or fluoroalkyl functionality into small-molecule drugs, and these candidates frequently enhance metabolic stability, lipophilicity, bioavailability, and membrane permeability.[1] As a consequence, the development of trifluoromethylation with trifluoromethylating reagents has been an extreme topic of focus.[2] Compared to the direct method with trifluoromethylating reagents,[3] the building block method using CF_3-containing substrates has made a more important contribution to asymmetric synthesis of optically active α-CF_3 alcohols and amines by chiral transition-metal catalysts or organocatalysts.[4] In particular, trifluoropyruvate is readily available and valuable as a versatile CF_3-containing substrate, and thus, its application to various catalytic asymmetric carbon−carbon bond-forming reactions has been successfully developed.[5]

Among various fluoroalkyl groups, the difluoromethyl (CF_2H) group has appeared as an intriguing structural motif in medicinal chemistry.[6] The reason is that the CF_2H group can function as a lipophilic hydrogen donor via hydrogen bonding, namely a bioisostere of alcohol and thiol groups. The CF_2H group is actually found in a variety of biologically active compounds.[6] Classically, CF_2H-containing compounds can be synthesized through deoxyfluorination of aldehydes with SF_4, Et_2NSF_3 (DAST), and DAST derivatives.[7] The fundamental drawbacks of these reactions are the harsh conditions and poor functional group compatibility. Recently, some progress has thus been accomplished on the direct difluoromethylation of not only aliphatic but also aromatic systems in a straightforward synthetic manner.[6,8,9] However, the catalytic enantioselective approach via direct difluoromethylation is a challenging and undeveloped area of research.[3a,10] Even in the case of the building block method, several examples of the catalytic asymmetric synthesis based on α-difluorinated ketones and ketimines have been reported, but the substrate scope is extremely limited.[11,12] Herein, we disclose the Pd-catalyzed asymmetric carbonyl−ene reaction with difluoropyruvate as an electrophile that has never been utilized for catalytic asymmetric synthesis. This is a reliable and practical catalytic asymmetric synthesis for various α-CF_2H tertiary alcohols in high yields and enantioselectivities. The highly enantioselective [2 + 2] cycloaddition reaction with difluoropyruvate is also disclosed.

Three synthetic methods for ethyl difluoropyruvate **2a** have been reported, but they required more than three steps from starting materials containing a CF_3 group.[13] Therefore, we initially investigated the simple synthetic method based on shorter steps from a commercially available starting material. As a consequence of extensive examinations, we found that the reaction using diethyl oxalate by treatment of (difluoromethyl)-trimethylsilane (CF_2HTMS) in the presence of ^{t}BuOK and EtOK provided the hydrated difluoropyruvate in 67% yield (Scheme 1).

Scheme 1. Synthesis of Ethyl Difluoropyruvate



Hemiacetalization of the hydrate followed by distillation employing P_2O_5 led to ethyl difluoropyruvate **2a** in 63% yield. Under the reaction conditions without addition of EtOK, it was found that the hydrated *tert*-butyl difluoropyruvate was obtained as a major product, which readily caused decomposition under the heating conditions.

With this practical synthesis in hand, our initial research was focused on the ene reaction of difluoropyruvate **2a** with isobutene **3a** in the presence of dicationic Pd catalysts[14] (Table 1). We were delighted to find that the desired reaction using **1a** proceeded smoothly in CH_2Cl_2 at 0 °C, providing the ene product **4aa** in 95%

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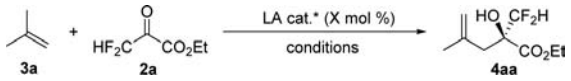
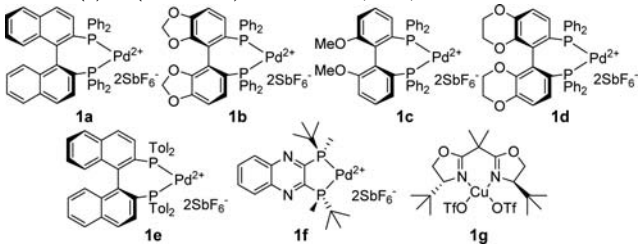
Table 1. Catalytic Asymmetric Ene Reaction[a]



3a 2a 4aa

entry	LA cat.* (X mol %)	conditions	yield[b] (%)	ee (%)
1	(*S*)-**1a** (5 mol %)	CH_2Cl_2, 0 °C, 2 h	95	97
2	(*S*)-**1b** (5 mol %)	CH_2Cl_2, 0 °C, 2 h	58	97
3	(*S*)-**1c** (5 mol %)	CH_2Cl_2, 0 °C, 2 h	59	94
4	(*S*)-**1d** (5 mol %)	CH_2Cl_2, 0 °C, 2 h	31	96
5	(*S*)-**1e** (5 mol %)	CH_2Cl_2, 0 °C, 2 h	37	96
6	(*S,S*)-**1f** (5 mol %)	CH_2Cl_2, 0 °C, 2 h	52	83
7	(*S*)-**1g** (10 mol %)	CH_2Cl_2, 0 °C, 2 h	trace	
8[c]	(*S*)-**1a** (5 mol %)	CH_2Cl_2, 0 °C, 24 h	15	78
9[d]	(*S*)-**1a** (5 mol %)	CH_2Cl_2, 0 °C, 24 h	47	94
10	(*S*)-**1a** (5 mol %)	CH_2Cl_2, −20 °C, 2 h	48	98
11	(*S*)-**1a** (5 mol %)	CH_2Cl_2/toluene,[e] −20 °C, 2 h	42	98
12	(*S*)-**1a** (5 mol %)	CH_2Cl_2/Et_2O,[e] −20 °C, 2 h	48	98
13[f]	(*S*)-**1a** (0.05 mol %)	solvent-free, 0 °C, 24 h	77	96



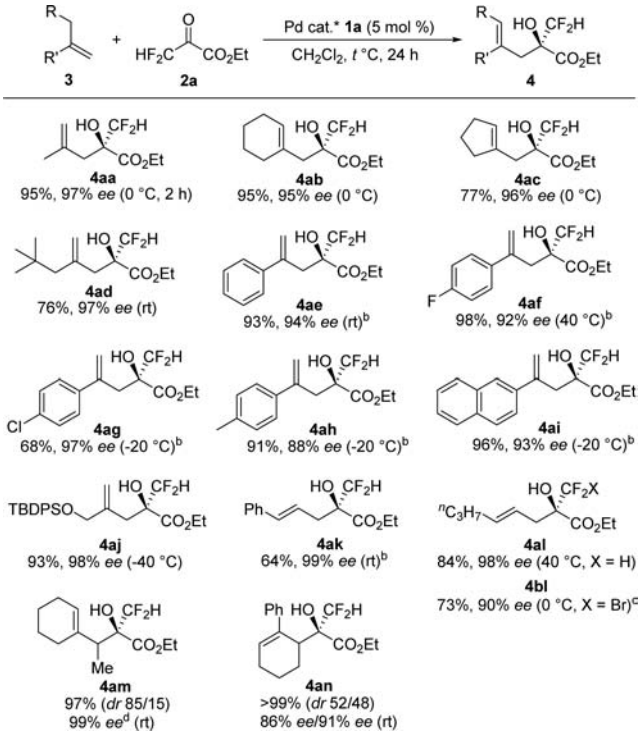
1a 1b 1c 1d 1e 1f 1g

[a]Conditions: LA cat.* **1** (0.01 mmol), difluoropyruvate **2** (0.2 mmol), and isobutene **3a** (0.4 mmol) in CH_2Cl_2 (2.0 mL). [b]Isolated yields. [c]$AgBF_4$ instead of $AgSbF_6$ was used. [d]$AgNTf_2$ instead of $AgSbF_6$ was used. [e]CH_2Cl_2/cosolvent = 1.0 mL/1.0 mL. [f]Conditions: LA cat.* **1a** (0.005 mmol), difluoropyruvate **2a** (10 mmol), and isobutene **3a** (25 mmol) without solvent.

yield with 97% ee (entry 1). The effect of chiral diphosphine ligands was clarified to be decisive on yields of the reaction. Chiral diphosphines, such as SEGPHOS, MeO-BIPHEP, SYNPHOS, and Tol-BINAP, could not exceed the level attained by BINAP (entries 1 vs 2−5). No improvement of yields was observed even with elongated reaction time. QuinoxP* with central chirality on phosphorus atom[15] also decreased the yield and enantioselectivity (entry 6). The reaction using bis(oxazoline)−copper complex did not proceed (entry 7). Exchange of counteranions and lowering reaction temperatures led to a decrease in yields (entries 8−10). Toluene or diethyl ether as a cosolvent did not enhance the reactivity (entries 11 and 12). To reveal the practicality of the present reaction, a gram-scale experiment under the solvent-free conditions was explored to demonstrate that **1a** of lower catalyst loading (S/C 2000) can efficiently promote the reaction in 77% yield and 96% ee (entry 13).

Next, the substrate scope was investigated with **1a** (5 mol %) in CH_2Cl_2 (Scheme 2). 1,1′-Disubstituted cyclic and acyclic olefins with an aliphatic group were transformed into the desired tertiary alcohols (**4ab**−**ad**) with high enantioselectivities. The reaction of α-methylstyrenes with electron-donating and -withdrawing substituents also gave high asymmetric inductions (**4ae**−**ai**). The oxygen atom on the alkyl chain was compatible with this transformation (**4aj**). Monosubstituted olefins with lower nucleophilicity also resulted in the formation of the desired products (**4ak**−**al**) in excellent enantioselectivities, respectively, but higher reaction temperature was needed to afford a good yield

Scheme 2. Scope of Olefin Substrates[a]



[a]Conditions: (a) Pd cat.* **1a** (0.01 mmol), difluoropyruvate **2a** (0.2 mmol), and olefin **3** (0.4 mmol) in CH_2Cl_2 (2.0 mL), isolated yields; (b) CH_2Cl_2/Et_2O (1.0 mL/1.0 mL) instead of CH_2Cl_2 was used as a solvent; (c) bromodifluoropyruvate **2b** instead of **2a** was used; (d) enantiomeric excess of major diastereomer.

(**4al**). Bromodifluoropyruvate **2b**[13b] instead of **2a** underwent the reaction even at 0 °C (**4bl**), while the enantioselectivity was decreased. Likewise, 1,1′,2-trisubstituted olefins gave the products **4am**−**an** in high enantioselectivities and low diastereoselectivities.

The absolute configuration of **4aa** was determined to be *R* by X-ray crystallographic analysis of ammonium salt **5**, which was obtained by the combination of (*S*)-1-(1-naphthyl)ethylamine and carboxylic acid **4′aa** prepared by hydrosis of **4aa** (Scheme 3a). Furthermore, the most stable 1,2-chelating fashion to the palladium center of difluoropyruvate was calculated by the computational study (B3LYP-D3BJ/6-31G(d)/IEFPCM-(CH_2Cl_2) level calculations) (Scheme 3b). The structures **B** and **C** coordinating on an oxygen atom of ether and a fluorine atom of CF_2H group were found to be destabilized in 6.50 and 6.51 kcal/mol than **A**, respectively. The six-membered metal chelate ring **D** was also unstable. Among the complexes with trifluoropyruvate **6**, the structure **A′** was also the most stable compared to other structures **B′**, **C′**, and **D′**. On the basis of their results, a plausible model for asymmetric induction can be proposed (Scheme 3c). Difluoropyruvate **2a** would be activated by **1a** via 1,2-chelation of two carbonyl oxygen atoms to a palladium complex. The *Re*-face attack of nucleophile **3a** to the ketone moiety would be prevented by the equatorial phenyl group on phosphorus atom, and consequently, the *Si*-face attack from the less sterically hindered site would be favored to provide the corresponding *R* product **4aa**.

Various fluoroalkylated pyruvates were also applied to this transformation (Scheme 4). Bromodifluoropyruvate **2b** and difluoroiodopyruvate **2c**[13b] underwent the reactions in good

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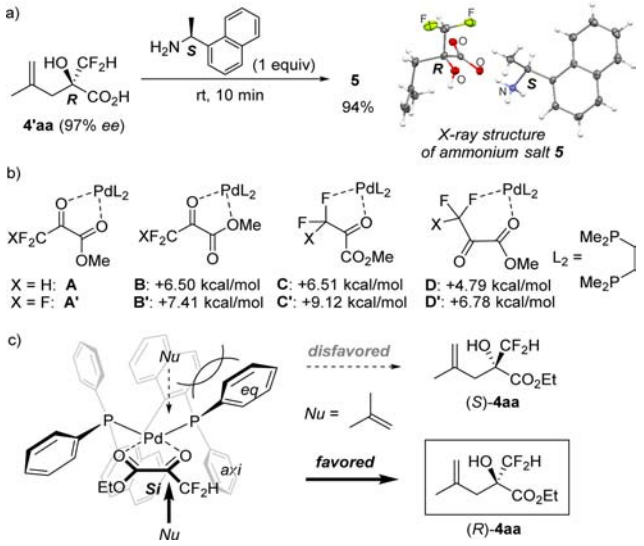
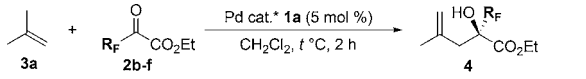
Scheme 3. Sense of Enantioselectivity and Coordination Patterns[a]



[a]Calculated energies of chelating structures at B3LYP-D3BJ/6-31G(d)/IEFPCM(CH_2Cl_2) (Pd: LANL2DZ)

Scheme 4. Ene Reaction with Fluoroalkylpyruvate

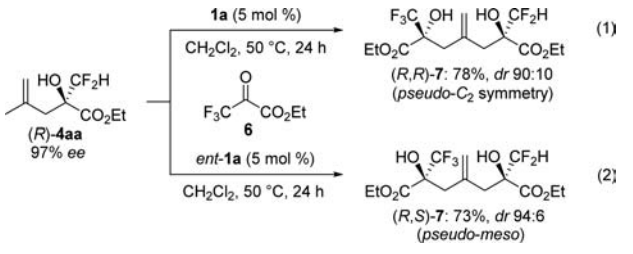


[a](*S*)-DTBM-SEGPHOS instead of (*S*)-BINAP was used.

yields with high enantioselectivities, regardless of the large steric hindrance of CF_2X group. In the case of **2c**, the Pd catalyst bearing (*S*)-DTBM-SEGPHOS could improve the enantioselectivity from 81% to 98% ee. Perfluoropyruvates **2d**−**e** also promoted the reaction in high enantioselectivities, respectively.

The Pd-catalyzed ene reaction was then expanded to the two-directional catalytic ene reaction (Scheme 5). Trifluoropyruvate **6**

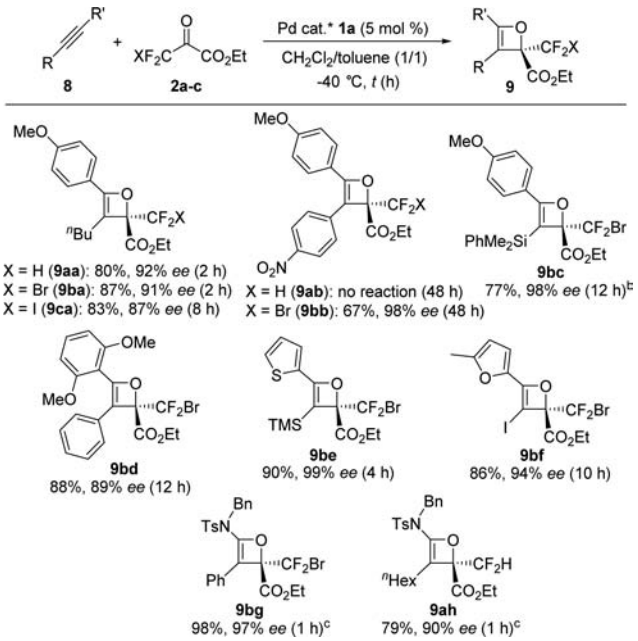
Scheme 5. Catalytic Two-Directional Ene Reaction



in the presence of **1a** was allowed to react with (*R*)-**4aa** (97% ee) to yield pseudo-C_2 symmetrical product (*R*,*R*)-**7** as a major isomer where only one fluorine is replaced by one hydrogen, along with high diastereoselectivity (dr 90:10) (eq 1). In contrast, employment of *ent*-**1a** led to pseudo-*meso* product (*R*,*S*)-**7** as a major isomer with high diastereoselectivity (dr 94:6) (eq 2).

To expand the utilization of the building block method using fluoroalkylpyruvates, we next conducted the catalytic asymmetric [2 + 2] cycloaddition reactions of **2a**−**c** and alkynes **8**, affording enantiomerically enriched oxetenes[14c] bearing a CF_2H moiety (Scheme 6). The reactions of electron-rich alkyne **8a** with **2a**−**c** proceeded smoothly to produce the corresponding products

Scheme 6. Application to [2 + 2] Cycloaddition Reaction[a]

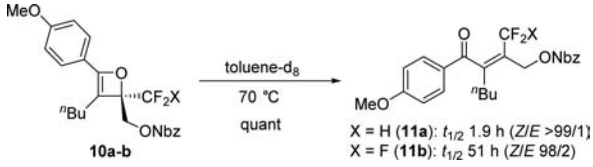


[a]Conditions: (a) Pd cat.* **1a** (0.005 mmol), difluoropyruvate derivatives **2a**−**c** (0.2 mmol), and alkyne **8** (0.1 mmol) in CH_2Cl_2/toluene (0.5 mL/0.5 mL); isolated yields; (b) reaction temp −30 °C; (c) reaction temp −78 °C.

(**9aa**, **9ba**, and **9ca**) in high yields and enantioselectivities, respectively. However, alkyne **8b** bearing an electron-withdrawing substituent did not react with **2a** bearing lower electrophilicity than **2b**, which underwent the reaction with **8b** to give the product **9bb** in high enantioselectivity. Therefore, the reactions employing **2b** under the optimized reaction conditions were compatible with silyl (**8c** and **8e**), phenyl **8d**, iodide **8f**, and amide **8g** substituents. Ynamide **8h** was found to possess higher nucleophilicity by which the reaction even with difluoropyruvate **2a** can proceed smoothly.

Finally, the effects of the difluoromethyl group on oxetene were examined in ring-opening reactions (Scheme 7).[16] The CF_2H group has been found to be C−F σ*-accepting and a less sterically demanding group that should exhibit higher inward torquoselectivity.[16b] Difluoromethyl oxetene **10a** at 70 °C in toluene-d_8 gave (*Z*)-α,β-unsaturated ketone **11a** with higher (virtually complete) inward selectivity than **10b** with a CF_3 group. Furthermore, a half-life of **10a** with the more σ-electron-donating CF_2H group was found to be shorter than **10b**.

Scheme 7. Effect of Difluoromethyl Group on Oxetene



In summary, we have succeeded in performing the highly enantioselective ene and [2 + 2] cycloaddition reactions with a dicationic palladium catalyst with difluoropyruvate as an

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electrophile, which have never been applied to catalytic asymmetric synthesis. This is a reliable and practical catalytic asymmetric synthesis for α-CF_2H tertiary alcohols and oxetenes with an ester group as a convenient platform for further functionalization. Development of novel catalytic asymmetric reactions with fluoroalkyl ketones to provide versatile chiral fluoroalkylated compounds is ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02617.

Experimental procedures and compound characterization data (PDF)

X-ray crystallographic data (CIF)

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Notes

The authors declare no competing financial interest.

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