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Synthesis of Enantioenriched α,α-Difluoro-β-arylbutanoic Esters by Pd-Catalyzed Asymmetric Hydrogenation

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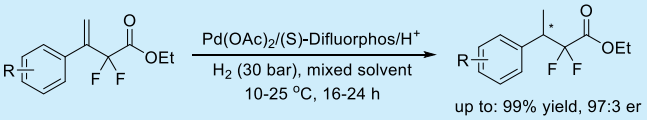
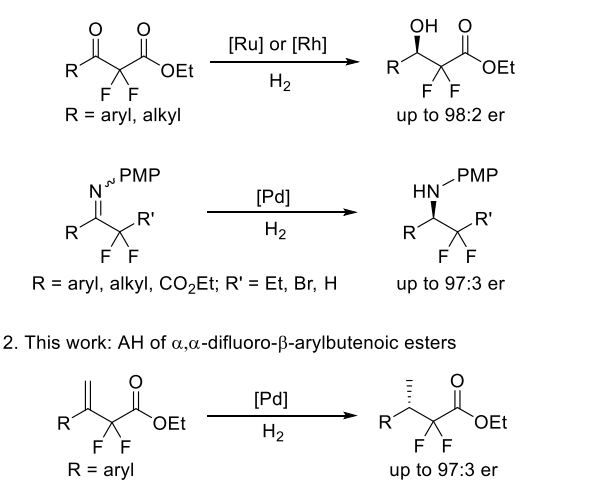
ABSTRACT: Synthesis of optically active *gem*-difluorinated organic molecules attracts a great deal of interest due to their unique properties in pharmaceutical and agrochemical areas. Herein, a series of enantioenriched α,α-difluoro-β-arylbutanoic esters were prepared in high yields (83−99%) with moderate to excellent enantioselectivities (≤97:3 er) by palladium-catalyzed asymmetric hydrogenation.



Optically active fluorine-containing compounds have received an increasing amount of attention in the fields of pharmaceuticals and agrochemicals since the introduction of the most electronegative fluorine atom with a small atomic radius into organic molecules has been demonstrated to be a powerful strategy for modulating their physical, chemical, and biological properties.[1] Among these fluoroalkyl moieties, the geminal difluoromethylene group has showcased its beneficial properties as an isostere of carbonyl and other polar functional groups.[2] Therefore, the development of methods for the synthesis of enantioenriched difluoroalkylated organic molecules is of considerable interest, and significant progress has been made toward this direction.[3] In addition to chiral induction with stoichiometric optically active substrates and/or reagents,[4] a catalytic asymmetric approach has attracted an increasing amount of consideration, and representative examples include difluorination[5] or aminodifluoromethylation[6] of alkenes, difluoroalkylation of aldehydes,[7] β-ketoesters,[8] and allylic bromides,[9] and other transformations[10] involving difluorinated silyl enol ethers[11] or ketones and/or imines.[12] Transition metal-catalyzed asymmetric hydrogenation (AH) of unsaturated bonds featured with a difluoromethyl group provides efficient and convenient access to optically active fluorine-containing molecules as hydrogenation constitutes the most fundamental and atom-economical process.[13] In fact, the synthesis of chiral α,α-difluorinated alcohols and amines via enantioselective reduction of the corresponding ketones and imines with ruthenium or rhodium complexes was reported by Iseki, Genet, Zhou, and Uneyama (Scheme 1).[14]

Despite the fact that a couple of chiral catalysts have been successfully developed for the enantioselective hydrogenation of various nonfluorinated β,γ-unsaturated acids/esters,[15] the reduction of the corresponding α,α-difluorinated butenoates has yet to be established probably due to the highly electron-withdrawing nature of the difluoromethylene group in the olefinic substrates. Herein, we reported an asymmetric hydrogenation of α,α-difluoro-β-arylbutenoic esters by using a palladium−diphosphine−acid catalyst system, providing enantioenriched carboxylic esters bearing a difluoromethylene group in high yields and moderate to good enantioselectivities.

Scheme 1. Synthesis of Enantioenriched *gem*-Difluorinated Molecules via Asymmetric Hydrogenation



We initiated this study by choosing ethyl α,α-difluoro-β-phenylbutenoate (**1a**) as the model substrate to examine the performance of chiral transition metal catalysts in 1,2-dichloroethane (DCE) under an atmosphere of 30 bar of H_2 at 25 °C for 16 h (Table 1). No promising results were detected with the commonly used catalysts, including palladium/**L1**, rhodium/**L1**, iridium-(*S*)-PHOX, and nickel/

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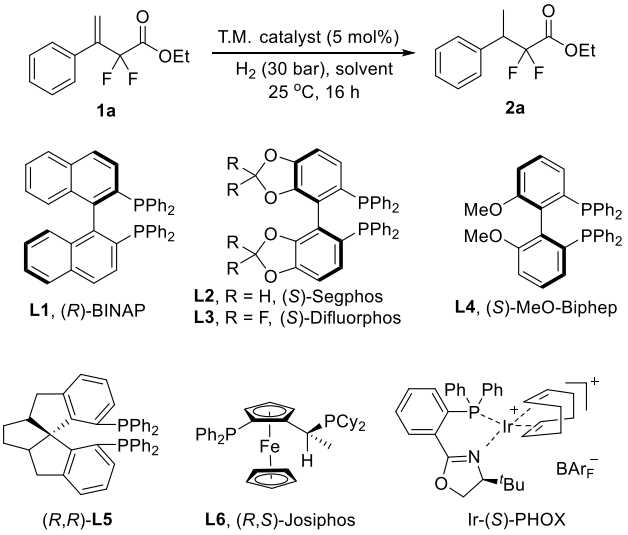
Table 1. Optimization of Reaction Conditions[a]



entry	TM	L	solvent	conversion (%)[b]	er (%)[c]
1	$Pd(OAc)_2$	**L1**	DCE	0	–
2	$Rh(COD)BF_4$	**L1**	DCE	80	53:47
3	Ir-(*S*)-PHOX	–	DCE	>99	0
4	$Ni(OAc)_2{\cdot}4H_2O$	**L1**	DCE	0	–
5[d]	$Pd(OAc)_2$	**L1**	DCE	>99	88:12
6[d]	$Pd(OAc)_2$	**L1**	THF	17	–
7[d]	$Pd(OAc)_2$	**L1**	toluene	14	–
8[d]	$Pd(OAc)_2$	**L1**	^{i}PrOH	>99	53:47
9[d]	$Pd(OAc)_2$	**L1**	TFE	>99	89:11
10[d]	$Pd(OAc)_2$	**L2**	TFE	>99	91:9
11[d]	$Pd_2(dba)_3$	**L2**	TFE	>99	52:48
12[d]	$Pd(CH_3CN)_2Cl_2$	**L2**	TFE	0	–
13[d]	$Pd(OAc)_2$	**L3**	TFE	>99	92:8
14[d]	$Pd(OAc)_2$	**L4**	TFE	99	0
15[d]	$Pd(OAc)_2$	**L5**	TFE	60	65:35
16[d]	$Pd(OAc)_2$	**L6**	TFE	>99	58:42
17[d,e]	$Pd(OAc)_2$	**L3**	TFE/DCE	>99 (99)	95:5
18[d,f]	$Pd(OAc)_2$	**L3**	TFE/DCE	>99 (90)	90:10

[a]Reaction conditions: **1a** (0.2 mmol), transition metal (5 mol %), ligand (6 mol %), H_2 (30 bar), solvent (1 mL), 25 °C, 16 h. DCE = 1,2-dichloroethane; TFE = trifluoroethanol; THF = tetrahydrofuran. [b]Determined by GC analysis using isooctane as the internal standard. [c]Determined by HPLC analysis on a chiral stationary phase using an OJ-3 column. [d]PTSA·H_2O (25 mol %) was added. [e]Reaction carried out at 10 °C in DCE/TFE mixed solvent (1/1 mL) for 24 h; isolated yield given in parentheses. [f]**1a** (452 mg, 2 mmol), (*S*)-Difluorphos (82 mg, 6 mol %), PTSA·H_2O (95 mg, 25 mol %), TFE/DCE (5/5 mL), 10 °C, 24 h.

L1, indicating the unbeneficial influence of the difluoromethylene moiety on such alkene enantioselective hydrogenation (entries 1–4). Protonic acid has been reported to promote the generation of active palladium–hydride species in palladium-catalyzed hydrogenation and hydrofunctionalization.[13h] Thus, a catalytic amount of *p*-toluenesulfonic acid monohydrate (PTSA·H_2O) was added to the reaction system consisting of $Pd(OAc)_2$ and **L1**, and to our delight, full conversion and an 88:12 enantiomeric ratio (er) of **2a** were observed (entry 5; for details of the effects of different acids, see Table S1). Variation of the solvent indicated that trifluoroethanol (TFE) slightly improved the er value of the product while other solvents gave lower yields and/or enantioselectivities (entries 6–9). Using ligand **L2** instead of **L1** slightly improved the enantioselectivity of the reaction (entry 10). When metal precursor $Pd_2(dba)_3$ or $Pd(CH_3CN)_2Cl_2$ was used under identical reaction conditions, significantly inferior effects were discovered (entries 11 and 12). After systematic investigation of commercially available chiral phosphine ligands, including **L3**–**L6** (for details, see Table S2), the er value was increased to 92:8 with **L3** (entry 13). Finally, when the reaction was performed at 10 °C in a DCM/TFE mixed solvent (1/1) for 24 h, **2a** was afforded with 95:5 er and 99% isolated yield (entry 17).

The scale-up asymmetric hydrogenation of **1a** under optimized reaction conditions was then attempted. For a 2 mmol reaction scale, the product was obtained with 90% yield and 90:10 er (entry 18). When the scale was further increased to 3 mmol, although the substrate was quantitatively converted to **2a**, the er value dropped to 83:17.

With the optimized $Pd(OAc)_2$/(*S*)-Difluorphos/H^+ catalyst system in hand, the scope and compatibility for the enantioselective hydrogenation of α,α-difluorobutenoic esters were explored with 30 bar of H_2 in a TFE/DCE mixed solvent at 10 °C for 24 h (Scheme 2). Various electron-drawing substituents on the phenyl ring of the substrates, such as fluoro, chloro, bromo, and trifluoromethyl groups, were well tolerated and afforded **2b**–**2d**, **2i**, **2l**, and **2m** in high yields (90–99%) and enantioselectivities (91:9–97:3 er). Difluorinated butenoic esters **2e**–**2h** containing electron-rich substituents, including methyl and methoxy groups, were hydrogenated with similar activity with slightly lower er values. The absolute configuration of **2f** was determined to be (*S*) by single-crystal X-ray diffraction analysis. No significant effect of the position of the substituent on the phenyl ring was observed upon such a transformation. Asymmetric hydrogenation of **1n** with a 1-naphthyl group proceeded with high activity and moderate selectivity. When the corresponding *N*,*N*-diethyl amide of **1a** was subjected to the standard reaction conditions, no conversion of the starting material was observed. α,α-Difluoro-β-thienyl and -phenylethyl butenoic esters were also prepared and applied in such asymmetric hydrogenation under standard reaction conditions, giving the desired products **2p** and **2q** in high yields with 53:47 and 84:16 er, respectively. Trisubstituted substrate **1r** (*E*/*Z* = 5/1) exhibited no conversion with this protocol, regardless of whether the reaction was carried out at 10 or 60 °C.

To understand this palladium-catalyzed asymmetric hydrogenation of α,α-difluoro-β-arylbutenoates, control experiments were conducted under standard reaction conditions (Scheme 3). Using the nonfluorinated **1a** structure analogues (**3** and **4**) as the substrates under otherwise identical reaction conditions led to the corresponding hydrogenated products in high yield but almost without enantioselectivity (Scheme 3a). Furthermore, substituting the ethoxycarbonyl group in **1a** with a fluoro atom or phenylacetyl group resulted in a drastic decrease in enantioselectivity (Scheme 3b,c). These results indicated the unique role of the difluoromethylene moiety and implied the complicated structure–enantioselectivity relationship, which was difficult to elucidate at this stage.

Inspired by these results and recent elegant work on nonprecious metal-catalyzed asymmetric reduction of functionalized alkenes,[16] we explored the application of a nickel catalyst in such an enantioselective hydrogenation. After the investigation of chiral diphosphine ligands and other reaction parameters, **1a** was hydrogenated in quantitative yield and 8:92

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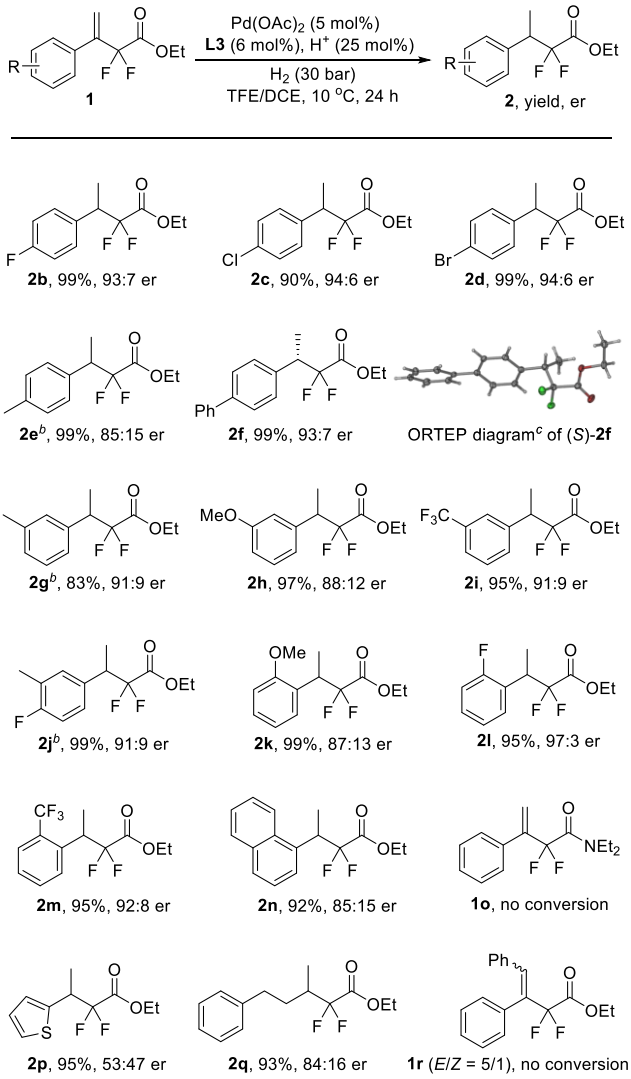
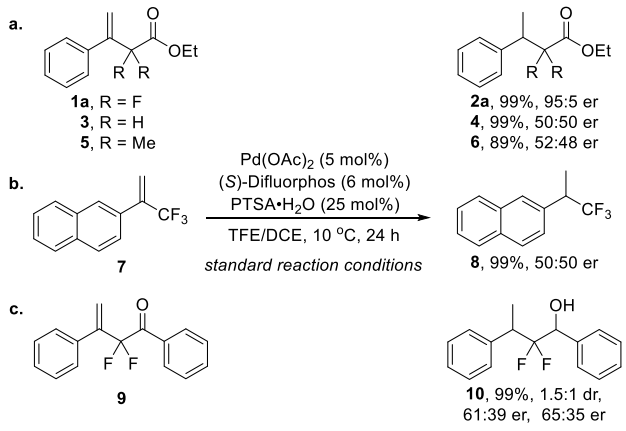
Scheme 2. Substrate Scope[a]



[a]Reaction conditions: **1** (0.2 mmol), $Pd(OAc)_2$ (5 mol %), **L3** (Difluorphos, 6 mol %), PTSA·H_2O (25 mol %), H_2 (30 bar), TFE/DCE mixed solvent (0.5/0.5 mL), 10 °C, 24 h. Isolated yields. er values were determined by HPLC analysis on a chiral stationary phase. [b]Temperature of 25 °C. [c]Thermal ellipsoids set at the 50% probability level.

Scheme 3. Control Experiments



er using $Ni(OAc)_2·4H_2O$/(*S*)-Binapine as the catalyst in the TFE/toluene mixed solvent at rt for 16 h (for details, see Tables S3 and S4). Further experiments to improve the enantioselectivity were underway in our laboratory.

In conclusion, an asymmetric hydrogenation of *α*,*α*-difluoro-*β*-arylbutenoates was developed with an in situ-generated palladium/diphosphine/H^+ catalyst, yielding a class of optically active *α*,*α*-difluorinated carboxylic acids in high yields with moderate to good er values. The indispensability of the fluoro atom to reactivity and enantioselectivity in this asymmetric hydrogenation was indicated with the designed control experiments.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c02700.

Additional data (PDF)

Accession Codes

CCDC 1978406 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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