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Asymmetric transfer hydrogenation of *gem*-difluoro-cyclopropenyl esters. Access to enantio-enriched *gem*-difluorocyclopropanes

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Abstract: A catalytic enantioselective access to disubstituted functionalized *gem*-difluorocyclopropanes, which lie among emerging fluorinated motifs, was developed by asymmetric transfer hydrogenation of *gem*-difluorocyclopropenyl esters, catalyzed by Noyori-Ikariya (*p*-cymene)-ruthenium(II) complex, with (*N*-tosyl-1,2-diphenylethylenediamine) as chiral ligand and isopropanol as hydrogen donor. The resulting *cis*-*gem*-difluorocyclopropyl esters were obtained with moderate to high enantiomeric purities (ee = 66-99%) and post-functionalization reactions enable access to valuable building blocks incorporating a *cis*- or *trans*-*gem*-difluorocyclopropyl motif.

gem-Difluorocyclopropanes have aroused considerable interest both from a structural standpoint and because of their ability to participate in various ring-opening reactions.[1,2] Considering the increasing use of the cyclopropyl fragment in the development of drug candidates[3] and the unarguable importance of fluorinated compounds in medicinal chemistry and agrochemistry,[4] it is not surprising that *gem*-difluorocyclopropanes are encountered into bioactive compounds[5] and currently lie among "emerging fluorinated motifs".[6] Notorious examples include α-amino acid **I**, a selective metabotropic glutamate receptor 2 antagonist,[7] the lysophosphatidic acid receptor 2 antagonist **II**,[8] the serotonin 2C receptor antagonist **III**[9] and zosuquidar,[10] which reached phase III clinical trials to treat acute myeloid leukemia (Figure 1).

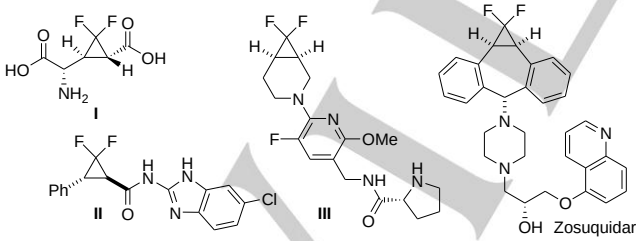
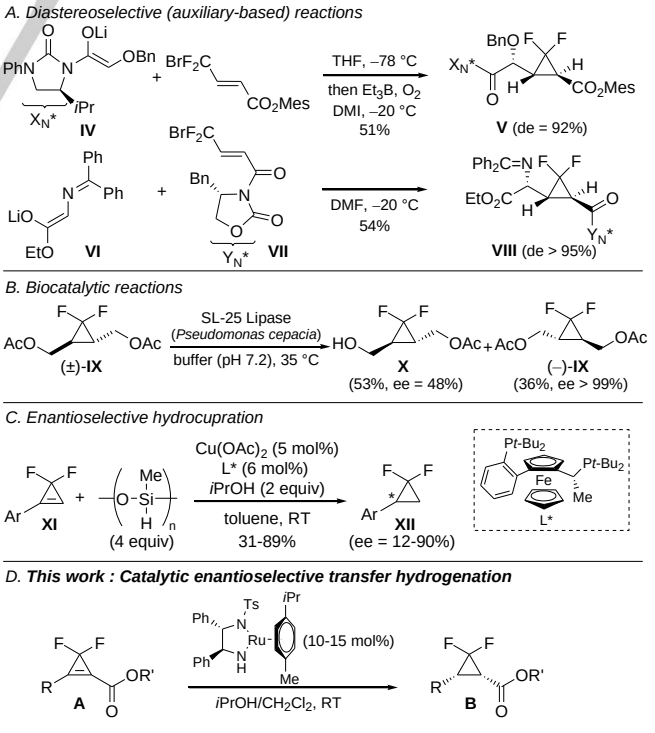


Figure 1. Examples of bioactive *gem*-difluorocyclopropanes.

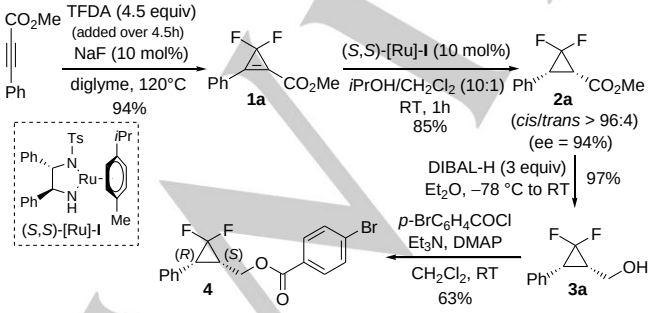
gem-Difluorocyclopropanes are classically synthesized by cyclopropanation of alkenes with difluorocarbene, which can be generated from various precursors.[6,11,12] Examples of diastereo-selective difluorocyclopropanations of alkenes possessing adjacent stereocenters have been reported,[13] but to date only a few methods are available for the synthesis of enantio-enriched *gem*-difluorocyclopropanes. Diastereoselective auxiliary-based approaches involve Michael addition of lithium enolate **IV** (derived from a chiral *N*-acyl imidazolidinone) to mesityl 4-bromo-4,4-difluorocrotonate, followed by radical-induced ring closure, to afford difluorocyclopropane **V**.[14] Ring-closure induced by Michael addition of glycine-derived enolate **VI** to *N*-(difluorobromocrotonyl)oxazolidinone **VII** was also disclosed to access α-amino acid derivative **VIII**[15] (Scheme 1A). Alternatively, chemo-enzymatic processes can be used, as illustrated by the kinetic resolution of racemic diacetate **IX**, which afforded optically active alcohol **X** and diacetate (–)-**IX** through a lipase-catalyzed ester hydrolysis.[16,17] Very recently, the enantioselective reduction of aryl *gem*-difluorocyclopropenes **XI** into aryl *gem*-difluorocyclopropanes **XII** by hydrocupration was disclosed (Scheme 1C).[18] Herein, we report a catalytic enantioselective approach toward disubstituted functionalized *gem*-difluorocyclopropanes, capitalizing on the asymmetric transfer hydrogenation of *gem*-difluorocyclopropenyl carboxylates **A** into *gem*-difluorocyclopropyl esters **B** in the presence of Noyori-Ikariya ruthenium(II) complex and isopropanol as hydrogen donor (Scheme 1D).



Scheme 1. Synthesis of enantio-enriched *gem*-difluorocyclopropanes. Mes = 2,4,6-trimethylphenyl, DMI = 1,3-dimethylimidazolidin-2-one.

Although hydrogenation of difluorocyclopropenes may appear as an appealing entry toward difluorocyclopropanes, those latter strained compounds are prone to ring-cleavage in the presence of transition metal catalysts,[1,2] in particular under standard Pd-catalyzed heterogeneous conditions.[19] Nevertheless, the conjugate reduction of *gem*-difluorocyclopropenyl ketones into diastereomeric mixtures of *cis*- and *trans*-*gem*-difluorocyclopropyl ketones was previously accomplished by hydride transfer from a Hantzsch ester in the presence of an acid catalyst.[20] Enantioselective transfer hydrogenation of C=O and C=N bonds, catalyzed by ruthenium complexes possessing a chiral *N*-sulfonyl-1,2-diphenylethylenediamine ligand (or related rhodium and iridium complexes), is a powerful method to access optically enriched alcohols and amines, respectively.[21] However, examples of enantioselective transfer hydrogenation of β,β-disubstituted electron-deficient olefins with those latter catalysts are scarce and so far limited to alkylidene-malononitriles or nitroalkenes.[22] We hypothesized that the high ring-strain of difluorocyclopropenylcarbonyl compounds could provide the driving force to achieve the catalytic transfer hydrogenation of the C=C bond under mild conditions without jeopardizing the three-membered ring.[24] To test this hypothesis, *gem*-difluorocyclopropenyl esters **A** were selected as substrates to avoid potential competitive reduction of the carbonyl group and hence circumvent chemoselectivity issues.

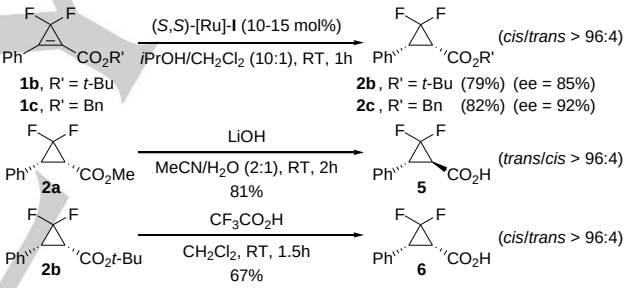
In our initial studies, *gem*-difluorocyclopropenyl methyl ester **1a**, prepared by slow addition (*via* syringe pump) of trimethylsilyl fluorosulfonyldifluoroacetate (TFDA) to methyl phenylpropiolate (cat. NaF, diglyme, 120°C, 4.5h, 94% yield), was selected as the test substrate.[23] Cyclopropenyl ester **1a** underwent an efficient hydrogen transfer upon treatment with catalyst (*S*,*S*)-[Ru]-**I**[21a-c] (10 mol%) in *i*PrOH/CH_2Cl_2 (10:1) (RT, 1h), which afforded the 3,3-difluorocyclopropyl ester **2a** as a single *cis* detectable diastereomer (*cis*/*trans* > 96:4, by analysis of the crude product by ^{1}H and ^{19}F NMR spectroscopy) in 85% yield (4.3 mmol scale experiment).[25] The enantiomer, *ent*-**2a** (83%), was obtained similarly from **1a** using (*R*,*R*)-[Ru]-**I** as the catalyst and an enantiomeric excess of 94% was determined for **2a** by supercritical fluid chromatography (SFC) on a chiral stationary phase.[26] Reduction of **2a** with DIBAL-H and condensation of the resulting primary alcohol **3a** with *p*-bromobenzoyl chloride afforded the crystalline *p*-bromobenzoate **4** (61%, two steps from **2a**), the absolute configuration of which was assigned by X-ray diffraction analysis (Scheme 2).



Scheme 2. Asymmetric transfer hydrogenation of **1a**. DIBAL-H = Diisobutyl-aluminum hydride, DMAP = 4-(Dimethylamino)pyridine.

Worthy of note was the slightly higher enantiomeric purity determined for *ent*-**2a** (ee = 98%) compared to that of **2a** (ee = 94%). Although in this case, the difference lies within an acceptable error range,[26] a phenomenon of self-disproportionation of enantiomers, already reported for scalemic fluorine-containing compounds, could be suspected.[27] Transfer hydrogenation of **1a** was repeated several times at different scales and optical purities of 94-96% were consistently determined for difluorocyclopropane **2a**.

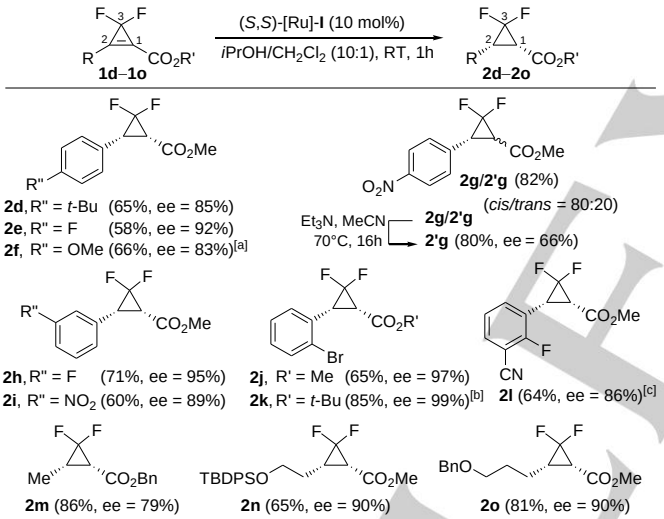
The substrate scope of this asymmetric transfer hydrogenation was examined and variation of the ester substituent was first studied. Transfer hydrogenation of *tert*-butyl ester **1b** and benzyl ester **1c** afforded *gem*-difluorocyclopropanes **2b** (79%, ee = 85%) and **2c** (82%, ee = 92%), respectively. The interest of having esters cleavable under different conditions was highlighted by the fact that saponification of methyl ester **2a** with LiOH occurred with concomitant epimerization and led to the *trans*-*gem*-difluorocyclopropanecarboxylic acid **5** (81%).[17] The vicinal fluorine atoms presumably increase the acidity of the proton at the α position of the carbonyl group thereby resulting in an easy epimerization under alkaline conditions (LiOH), although no competitive β-elimination of fluorine took place.[28] As a complementary method, *tert*-butyl ester **2b** was cleaved under acidic conditions (CF_3CO_2H, CH_2Cl_2, RT) to provide the *cis*-*gem*-difluorocyclopropanecarboxylic acid **6** (67%) (Scheme 3).



Scheme 3. Influence of the ester substituent.

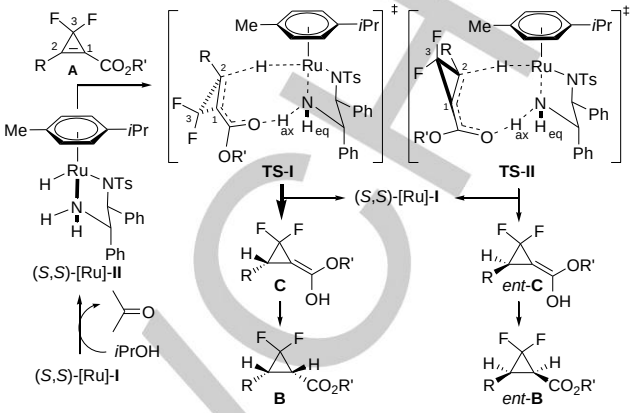
The substituent on the cyclopropene (at C2) was next varied. The presence of a substituent at the *para* position on the aromatic ring in substrates **1d–1g** resulted in a slight drop of enantioselectivity compared to **1a**, regardless of the steric or electronic properties of the substituent, as indicated by the formation of difluorocyclopropyl esters **2d** (ee = 85%), **2e** (ee = 92%) and **2f** (ee = 83%) possessing a *tert*-butyl, a fluorine atom and a methoxy group, respectively. For substrate **1f**, a higher catalyst loading (15 mol%) was required to reach full conversion presumably because the mesomeric donor *p*-methoxyphenyl group attenuates the electrophilicity of C2 and resulted in a slower reaction compared to **1a**. Whereas **2a–2f** were formed with high *cis* diastereoselectivity, transfer hydrogenation of **1g** possessing an electron-withdrawing *p*-nitrophenyl group at C2 led to a diastereomeric mixture of *cis*- and *trans*-difluoro-cyclopropanes **2g** and **2'g** (*cis*/*trans* = 80:20) both possessing the same optical purity.[26] Epimerization of the mixture of **2g**/**2'g** was purposely achieved by heating in the presence of Et_3N (MeCN, 70 °C, 1h) to produce selectively the more stable *trans* diastereomer **2'g** (80%, ee = 66%) under thermodynamic control.

Introduction of a fluorine atom or a nitro group at the *meta* position of the aromatic ring in substrates **1h** and **1i** had little impact on the enantioselectivity compared to **1a**, as illustrated with the isolation of difluorocyclopropanes **2h** (71%, ee = 95%) and **2i** (60%, ee = 89%), respectively. The highest enantioselectivities were observed for substrates **1j** and **1k** possessing a bromine atom at the *ortho* position which afforded *gem*-difluorocyclopropyl esters **2j** (65%, ee = 97%) and **2k** (85%, ee = 99%). The aromatic ring could also be disubstituted, as shown with substrate **1l** containing a fluorine atom and a cyano group at the *ortho* and *meta* positions, respectively, which led to cyclopropane **2l** (64%, ee = 86%). In this case, the reaction was carried out in *i*PrOH/CH_2Cl_2 (1:1) to ensure complete solubility of substrate **1l**. Transfer hydrogenation of difluorocyclopropenyl esters substituted by alkyl groups at C2 also proceeded well. Reduction of substrate **1m**, possessing a methyl group at C2, afforded *cis*-*gem*-difluorocyclopropane **2m** (86%, ee = 79%) with lower enantioselection compared to the analogous benzyl ester **2c** with a phenyl group at C2 (ee = 92%). However, higher enantioselectivities were observed for substrates **1n** and **1o** possessing a 2-(*tert*-butyldiphenylsilyloxy)ethyl or a 3-benzyloxy-propyl group, as illustrated by the formation of difluoro-cyclopropanes **2n** (65%, ee = 90%) and **2o** (81%, ee = 90%), respectively (Scheme 4).[26,29]



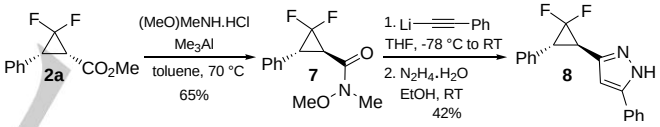
Scheme 4. Scope of the asymmetric transfer hydrogenation. TBDPS = Si*t*-BuPh$_2$. [a] (*S*,*S*)-[Ru]-**I** (15 mol%). [b] *i*PrOH/CH_2Cl_2 (8:1). [c] *i*PrOH/CH_2Cl_2 (1:1).

Although a detailed analysis of the enantioselectivities observed in the transfer hydrogenation of cyclopropenyl esters **A** deserves further studies, previous mechanistic investigations on the rhodium-catalyzed transfer hydrogenation of enones point toward a 1,4-addition mechanism rather than a concerted hydrogenation of the olefin, or migratory insertion of the latter into a Rh-H bond.[22d] Hence, dehydrogenation of *i*PrOH catalyzed by (*S*,*S*)-[Ru]-**I** would first generate hydride complex (*S*,*S*)-[Ru]-**II**.[30] Hydride transfer at C2 to Michael acceptors **A**,[31] with additional activation of the carbonyl by hydrogen bonding with the axial proton of the amino group on the ligand, may preferentially occur through transition state **TS-I** rather than **TS-II** to minimize steric interactions between the *gem*-difluorinated C3 atom and the *p*-cymene ligand. This would regenerate (*S*,*S*)-[Ru]-**I** and give rise to enols **C** and *ent*-**C** that would then tautomerize to *cis*-difluorocyclopropanes **B** (major enantiomer) and *ent*-**B** (with proton transfer at C1 on the less hindered face, opposite to the R group at C2, under kinetic control) (Scheme 5).



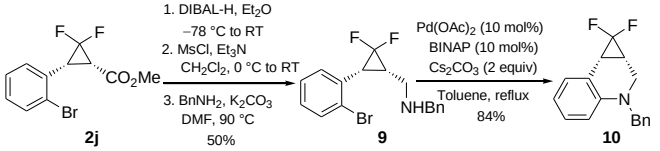
Scheme 5. Face selectivity of the transfer hydrogenation of substrates **A**.

To demonstrate the synthetic utility of *gem*-difluorocyclopropyl esters **B**, post-functionalization reactions were investigated with the particular goal of creating nitrogen heterocycles. Ester **2a** was treated with (MeO)MeNH•HCl in the presence of Me_3Al, (toluene, 70°C) to afford the *trans*-difluorocyclopropyl Weinreb amide **7** (65%). Subsequent addition of phenylethynyllithium and condensation of the resulting ynone with N_2H_4•H_2O delivered the (*gem*-difluorocyclopropyl)pyrazole **8**[32] (42%) (Scheme 6).



Scheme 6. Synthesis of *gem*-difluorocyclopropane **8**.

Construction of a nitrogen heterocycle fused to a difluoro-cyclopropane was also studied. After reduction of ester **2j**, the primary alcohol was converted into the corresponding mesylate which was displaced with benzylamine to afford secondary amine **9** (50%, three steps from **2j**). Compound **9** was involved in an intramolecular Hartwig-Buchwald amination[33] which provided the *gem*-difluorocyclopropa[*c*]quinoline **10** (84%) (Scheme 7).



Scheme 7. Synthesis of *gem*-difluorocyclopropa[c]quinoline **10**.

In conclusion, we have demonstrated that *gem*-difluoro-cyclopropenyl esters can undergo an efficient enantioselective transfer hydrogenation from isopropanol catalyzed by Noyori-Ikarya ruthenium(II) complex. This transformation opens a new access to enantio-enriched *gem*-difluorocyclopropyl esters and to diversely substituted *cis*- or *trans*-*gem*-difluorocyclopropyl building blocks of interest in medicinal chemistry.

Keywords: Transfer hydrogenation • Small ring systems • Difluorocyclopropanes • Difluorocyclopropenes • Enantioselectivity

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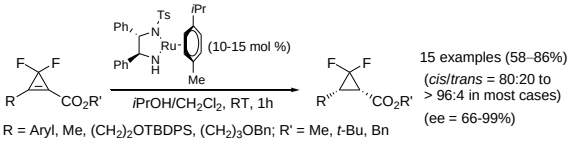

R = Aryl, Me, $(CH_2)_2OTBDPS$, $(CH_2)_3OBn$; R' = Me, *t*-Bu, Bn

Asymmetric transfer hydrogenation of *gem*-difluorocyclopropenyl esters using Noyori-Ikarya's catalyst and isopropanol as the hydrogen donor enables access to enantio-enriched *gem*-difluorocyclopropanes (ee = 66-99%) which are emerging fluorinated motifs of interest in medicinal chemistry.

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