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Palladium-Catalyzed Stereoselective Hydrodefluorination of Tetrasubstituted *gem*-Difluoroalkenes

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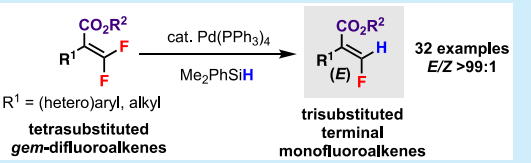
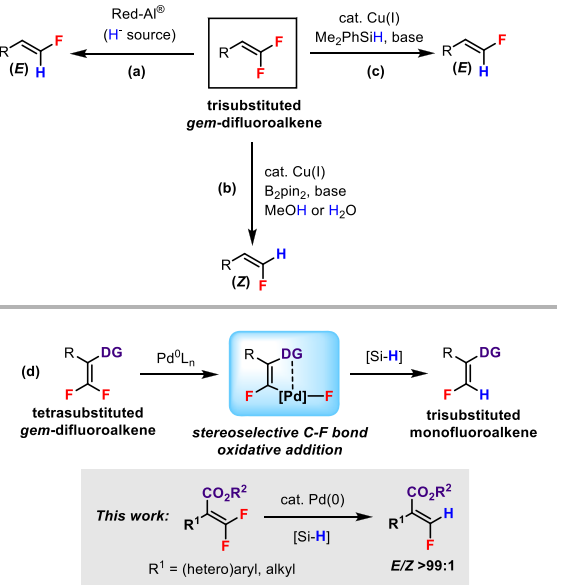
ABSTRACT: A highly stereoselective palladium(0)-catalyzed hydrodefluorination (HDF) of tetrasubstituted *gem*-difluoroalkenes is developed. By using catalytic $Pd(PPh_3)_4$ (2.5−5 mol %) and hydrosilane Me_2PhSiH, various trisubstituted terminal (*E*)-monofluoroalkenes can be synthesized with excellent *E*/*Z* selectivity (>99:1) and good functional group tolerability. The key stereocontrol should be exerted by an ester-directed C−F bond oxidative addition step in the catalytic cycle.



The growing demand for introducing fluorine into new materials, pharmaceuticals, and agrochemicals has inspired the development of diverse synthetic strategies.[1] To achieve the goal of efficient synthesis of fluorinated molecules, a dichotomy of approaches can be found: (1) formation of C−F bonds and (2) selective cleavage and functionalization of C−F bonds. The former approach has received tremendous attention culminating in the successful development of various electrophilic, nucleophilic, and radical fluorination techniques.[2] The latter approach, C−F bond activation, however, is considered a major challenge in organic synthesis.[3] Poly- or perfluorinated bulk chemicals are readily available on an industrial scale, and selective C−F bond functionalization can provide partially fluorinated products that may be difficult to obtain by direct fluorination methods.

Hydrodefluorination (HDF), the conversion of a C−F bond into a C−H bond, is the simplest form of C−F bond activation yet with unique mechanistic diversity.[4] While transition-metal-catalyzed HDF of polyfluoroarenes has been well-established with detailed mechanistic investigations, the corresponding HDF of *gem*-difluoroalkenes, which can provide valuable terminal *monofluoroalkenes*, has been much less explored. A key application of monofluoroalkenes is their potential as peptide bond isosteres in drug discovery.[1b,5] Literature reports have dealt with HDF of trisubstituted *gem*-difluoroalkenes[6] to address the important issue of stereoselectivity for obtaining either (*E*)- or (*Z*)-1,2-disubstituted monofluoroalkenes (Scheme 1).[7] In the transition-metal-free example, Red-Al has been employed as a hydride source to undergo an addition/elimination pathway with *gem*-difluoroalkenes resulting in the (*E*)-product (Scheme 1a).[7a,b,8] Examples of transition-metal-catalyzed HDF of *gem*-difluoroalkenes are very rare; Ito et al. and Shi et al. independently reported the copper(I)-catalyzed HDF for obtaining the (*Z*)-product (Scheme 1b).[7c,d] The reaction relies on the migratory insertion of double bond to the Cu−B bond followed by *β*-F elimination to give the (*Z*)-vinylboron intermediate. Analogously, insertion of a double bond in the

Scheme 1. Stereoselective Hydrodefluorination (HDF) of Trisubstituted versus Tetrasubstituted *gem*-Difluoroalkenes



Cu−H bond (H from hydrosilane) followed by *β*-F elimination affords the (*E*)-product directly, as reported by Ito et al. (Scheme 1c).[7c] The crucial stereocontrol in the *β*-F elimination step is based on either the *electronic repulsion* between the F and R group or the *steric repulsion* between Bpin and the R group.[9]

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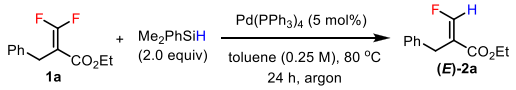
Despite the high carbon−fluorine bond dissociation energy (BDE) of approximately 500 ± 50 kJ/mol,[10] palladium-catalyzed HDF of polyfluoroarenes through *oxidative addition* of the C−F bond is known.[4,11] On the contrary, no report of Pd-catalyzed HDF of *gem*-difluoroalkenes exists in the literature to date. Zhang et al. described an intriguing *ortho*-selective Pd-catalyzed HDF of polyfluoroarenes using *N*-heterocycles as directing groups (DGs).[11a] We envisioned that a chelation-assisted C−F bond oxidative addition could be applied to tetrasubstituted *gem*-difluoroalkenes creating a stereodifferentiation in the two C−F bonds that would be difficult to achieve by electronic or steric repulsion (Scheme 1b).[12] We herein report the first Pd-catalyzed stereoselective HDF of tetrasubstituted *gem*-difluoroalkenes based on this hypothesis.

The tetrasubstituted *gem*-difluoroalkene **1a** containing a vinylic ester group as a potential directing group was conveniently synthesized from the corresponding diazo precursor.[13] By using dimethylphenylsilane as the "H source" with only 5 mol % of tetrakis(triphenylphosphine)palladium(0) catalyst upon heating at 80 °C, we were able to observe full conversion of **1a** to the hydrodefluorinated product **2a** as a single (*E*)-isomer (Table 1, entry 1). The reaction parameters

Table 1. Effects of Reaction Parameters



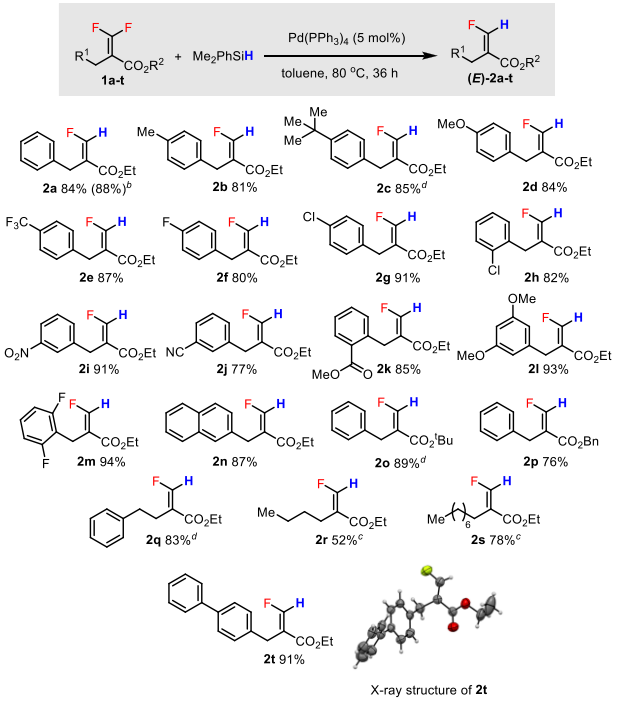
entry	variation from the "standard" conditions	yield[a] (%)
1	none	99[b]
2	Ph_2MeSiH or Et_2SiH_2, instead of Me_2PhSiH	99
3	Ph_3SiH, instead of Me_2PhSiH	94
4	Et_3SiH, instead of Me_2PhSiH	83
5	HBpin, instead of Me_2PhSiH	57[c]
6	2.5 mol % of $Pd(PPh_3)_4$	86
7	50 °C	10
8	1.2 equiv of Me_2PhSiH	77
9	no $Pd(PPh_3)_4$	0
10	$[PdCl(allyl)]_2$ (2.5 mol %), $Pd(OAc)_2$ (5 mol %), or $Pd(dba)_2$ (5 mol %), instead of $Pd(PPh_3)_4$	0
11	$[PdCl(allyl)]_2$ (2.5 mol %)/PPh_3 (20 mol %), $Pd(OAc)_2$ (5 mol %)/PPh_3 (20 mol %), or $Pd(dba)_2$ (5 mol %)/PPh_3 (20 mol %), instead of $Pd(PPh_3)_4$	99

[a]GC yield. [b]*E*/*Z* > 99:1 as determined by GC−MS and ^{19}F NMR analyses. [c]*E*/*Z* = 33:1.

were carefully screened, and some important trends are highlighted in Table 1.[14] Among the tested hydrosilanes, Ph_2MeSiH and Et_2SiH_2 were equally effective while Ph_3SiH and Et_3SiH were less reactive (Table 1, entries 2−4). On the other hand, using HBpin[11e] led to a significant decrease in yield (Table 1, entry 5). Lower catalyst loading, lower reaction temperature, and lower equivalents of hydrosilane all caused a decrease in yield (Table 1, entries 6−8). No reaction occurred without the Pd catalyst (Table 1, entry 9). Other Pd catalysts including Pd(II) complexes such as $[PdCl(allyl)]_2$ and $Pd(OAc)_2$ or a Pd(0) complex such as $Pd(dba)_2$ were completely unreactive (Table 1, entry 10). However, adding PPh_3 ligand to the above catalysts (Pd/P = 1:4) increased the reactivity dramatically (Table 1, entry 11). Apart from the result of using HBpin (Table 1, entry 5), we did not detect the formation of (*Z*)-isomer during the optimization studies.[14]

The reaction scope was subsequently investigated using alkyl-substituted substrates **1a−t** under standard conditions (Scheme 2). In all cases, only the (*E*)-product was obtained as a single

Scheme 2. Hydrodefluorination of Alkyl-Substituted *gem*-Difluoroalkenes[a]



[a]General conditions: **1** (0.2 mmol), Me_2PhSiH (0.4 mmol), toluene (0.8 mL), under argon. Isolated yields. *E*/*Z* > 99:1 as determined by GC−MS and ^{19}F NMR analyses. [b]2.4 mmol scale. [c]Reaction was run at 120 °C in DMF. [d]48 h.

diastereomer. The (*E*)-alkene geometry of compound **2b** was further confirmed by $^{19}F-^{1}H$ HOESY NMR experiments.[14] Benzyl-substituted products **2c−m** displayed excellent functional group tolerability. Substituents at the *para* position of the benzene ring including bulky *tert*-butyl (**2c**), electron-donating methoxy (**2d**), and electron-withdrawing trifluoromethyl (**2e**), fluoro (**2f**), and chloro (**2g**) were compatible. Other functional groups such as nitro (**2i**) and cyano (**2j**) at the *meta* position and ester (**2k**) at the *ortho* position were also shown to be compatible. Disubstituted aryl (**2l** and **2m**) and naphthyl (**2n**) systems gave good yields. Variations of the vinylic ester substituent group, including *tert*-butyl (**2o**) and benzyl (**2p**), did not lead to drastic changes in yield and *E*/*Z* selectivity. Longer chain linear alkyl-substituted products **2q−s** were also obtained; some required a higher reaction temperature in DMF (**2r−s**). The lower yield for product **2r** was due to its lower boiling point. Reaction at a larger scale (2.4 mmol) also provided product **2a** (0.44 g) in good yield. X-ray crystallography unambiguously confirmed the structure and (*E*)-alkene configuration of the biphenyl-containing product **2t**.

When the previous "standard" conditions were applied to the phenyl-substituted substrate **1u**, we only observed 58% GC yield of the desired product (*E*)-**2u**, along with unreacted starting materials and inseparable "over-reduced" side products **2u′** and **2u″** (Scheme 3). Extensive screenings of reaction parameters were subsequently carried out to reoptimize the conditions for improving the yield of **2u** while minimizing side-product

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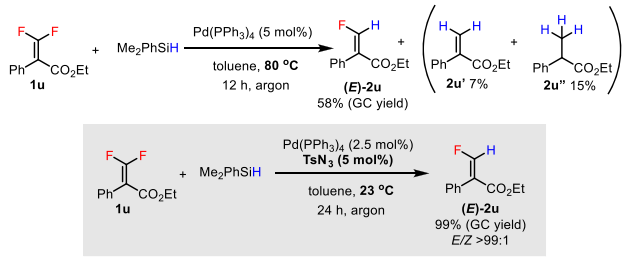
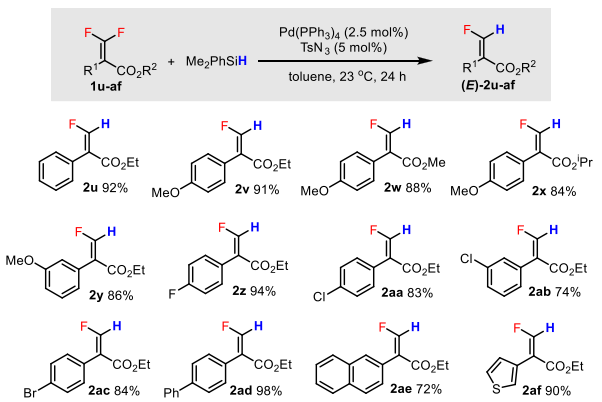
Scheme 3. Yield-Enhancing Effect of Adding Catalytic TsN_3 at Room Temperature



formation.[14] We found that the reactions gave significant amounts of over-reduction products at higher temperatures, yet the conversions were very poor at lower temperatures (e.g., 5% yield at 23 °C). The solution to this dilemma was narrowed down to the use of additives, in particular, an organic azide TsN_3 in catalytic amounts. A unique combination of as low as 2.5 mol % $Pd(PPh_3)_4$ and 5 mol % TsN_3 at room temperature allowed full conversion of **1u** to product **2u** as a single (*E*)-isomer with a clean reaction profile.

With the new set of conditions in hand, a variety of (hetero)aryl-substituted hydrodefluorinated products were successfully synthesized in good to excellent yields (Scheme 4). Electron-rich (**2v**) or -poor (**2z**) aryl substituents, biphenyl

Scheme 4. Hydrodefluorination of (Hetero)aryl-Substituted *gem*-Difluoroalkenes[a]

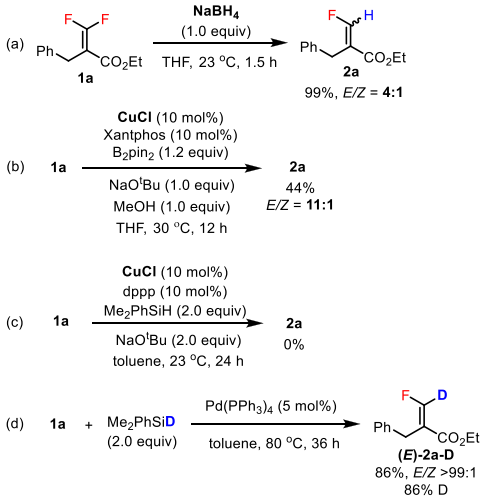


[a]General conditions: **1** (0.2 mmol), Me_2PhSiH (0.4 mmol), toluene (0.8 mL), under argon. Isolated yields. *E*/*Z* > 99:1 as determined by GC–MS and ^{19}F NMR analyses.

(**2ad**), naphthyl (**2ae**), and thienyl (**2af**) groups were tolerated. The results from products **2v–x** showed that the ester substituent group, including a sterically encumbering isopropyl group (**2x**), did not significantly affect the yield and *E*/*Z* selectivity. There was no sign of aryl C–F bond activation in **2z** (versus vinyl C–F bond). Furthermore, aryl bromide (**2ac**), a well-known cross-coupling partner in Pd(0) catalysis, remained intact, underscoring the orthogonal C(vinyl)–F bond vs C(aryl)–Br bond functionalization. The (*E*)-alkene geometry of compound **2u** was confirmed by $^{19}F-^{1}H$ HOESY NMR experiments.[14]

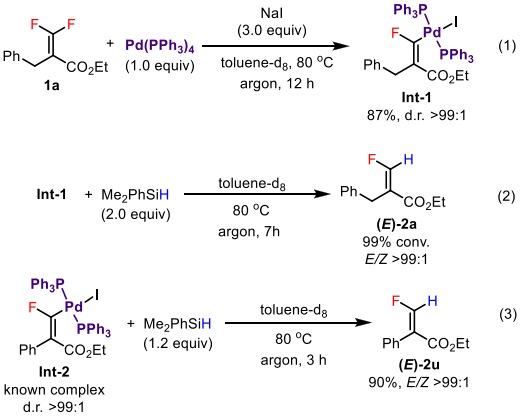
A series of experiments were conducted to shed light on mechanistic understanding of the Pd-catalyzed HDF reaction of **1** (Scheme 5). Under the Pd-free conditions using $NaBH_4$ as the hydride source (Scheme 5a), a mixture of *E*/*Z* products was obtained in 4:1 ratio. This result indicates that the intrinsic

Scheme 5. Further Studies



stereocontrol by tetrasubstituted *gem*-difluoroalkenes **1** based on electronic/steric repulsion[7a,b,8] is not sufficient compared to the stereocontrol exerted by the Pd-catalyzed pathway (*E*/*Z* > 99:1). Reported copper-catalyzed conditions[7c] were not applicable to **1a**, resulting in poor yields and inferior stereoselectivity (Scheme 5b,c). We suspect that the tetrasubstituted alkenes **1** are less reactive toward migratory insertion of Cu–B/H and the use of base might cause substrate decomposition. Using Me_2PhSiD led to deuterated (*E*)-**2a**, proving that hydrosilane is the H source (Scheme 5d).

Through NMR studies, we observed the formation of Pd(II) intermediate **Int-1** (^{19}F NMR: −25.34 ppm, broad triplet, J = 16.9 Hz; ^{31}P NMR: 19.55 ppm, doublet, J = 16.6 Hz) as a single diastereomer from the stoichiometric reaction between **1a** and $Pd(PPh_3)_4$ in the presence of NaI (eq 1).[14,15] Adding Me_2PhSiH to **Int-1** followed by heating at 80 °C provided full conversion to product (*E*)-**2a** (eq 2). Furthermore, we separately prepared a well-characterized Pd(II) complex **Int-2**[12] and added Me_2PhSiH to it, affording product (*E*)-**2u** in 90% yield (eq 3). These results show that a Pd(II) complex similar to **Int-1**/**Int-2**, which should be formed upon stereoselective C–F bond oxidative addition, is a viable intermediate for the product.



On the basis of the above studies and literature reports, the following plausible catalytic cycle for Pd-catalyzed stereoselective HDF of tetrasubstituted *gem*-difluoroalkene **1** is proposed (Scheme 6). The ester functionality of difluoroalkene **1** serves as a directing group (DG) by chelation to the Pd center (species **A**).[16] Stereodifferentiating C–F bond oxidative

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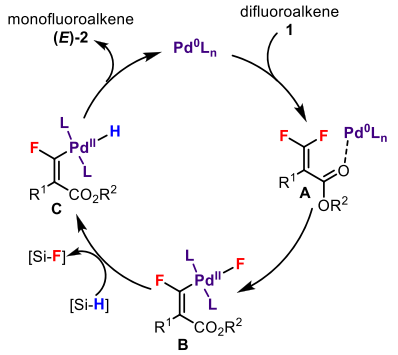
Scheme 6. Proposed Catalytic Cycle



addition to Pd(0) affords the monofluorovinylpalladium(II) fluoride intermediate **B** as a single diastereomer.[12] The existence of **B** is supported by the above NMR and complex studies (cf. eqs 1−3). Reaction of **B** with hydrosilane, a fluorophilic reductant, generates the Pd(II) hydrido complex **C**.[11a] The formation of thermostable Si−F bond provides the key driving force,[17] which also streamlines the reaction since no external bases are needed to activate the hydrosilane.[18] Finally, reductive elimination of **C** releases the monofluoroalkene product **2** in an *E*-configuration as well as regenerates the Pd(0) catalyst.

The yield-enhancing effect of adding an organic azide was worth investigating since it has been rarely described in Pd catalysis (cf. Schemes 3 and 4). We monitored the interaction between $Pd(PPh_3)_4$ and TsN_3 (Pd/azide = 1:2) by ^{31}P NMR over time (see the Supporting Information). The reaction quickly produced the *N*-tosyl iminophosphorane (TsN = PPh_3),[19a,b] presumably via a Staudinger-type reaction[19c] between TsN_3 and the ligand PPh_3 of $Pd(PPh_3)_4$. A new Pd−P signal was also observed, which was believed to be bis(triphenylphosphine)palladium(0) "$Pd(PPh_3)_2$".[20] The two-coordinate $Pd(PPh_3)_2$ was very reactive toward oxidative addition with iodobenzene to afford $PhPd(PPh_3)_2I$ quantitatively. It also reacted with *gem*-difluoroalkene **1u** to produce a characteristic side product α-trifluoromethyl ester, via C−F bond oxidative addition intermediate **B** (cf. Scheme 6). This evidence supported that, at room temperature, azide reacts with the triphenylphosphine ligand of $Pd(PPh_3)_4$ to create a coordinatively unsaturated $Pd(PPh_3)_2$, which is the active species for the C−F bond oxidative addition step. Such "activation" of Pd catalyst is important for (hetero)aryl-substituted substrates **1u**−**af** since at higher temperature (e.g., 80 °C) over-reduction products started to appear. On the other hand, alkyl-substituted substrates **1a**−**t** (cf. Scheme 2) were not prone to over-reduction at 80 °C, and $Pd(PPh_3)_4$ might be in equilibrium with $Pd(PPh_3)_2$ at this temperature, thus making azide additive unnecessary.

In conclusion, a Pd-catalyzed stereoselective hydrodefluorination of tetrasubstituted *gem*-difluoroalkenes using hydrosilane has been successfully developed for the first time. The excellent level of stereocontrol presumably stems from an ester-directed C−F bond oxidative addition process. Valuable trisubstituted terminal (*E*)-monofluoroalkenes can be synthesized by this method with well-defined alkene geometry. A novel yield-enhancing effect of adding catalytic organic azide is also revealed. Further exploration of C−C and C−heteroatom bond formations based on the stereoselective Pd-catalyzed C−F bond oxidative addition is ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01813.

Experimental procedures, detailed mechanistic studies, characterization data, crystallographic data, ^1H NMR, ^{13}C NMR, and ^{19}F NMR spectra for all new products (PDF)

Accession Codes

CCDC 1994409 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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