Homogeneous Catalysis

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cis-Specific Hydrofluorination of Alkenylarenes under Palladium Catalysis through an Ionic Pathway**

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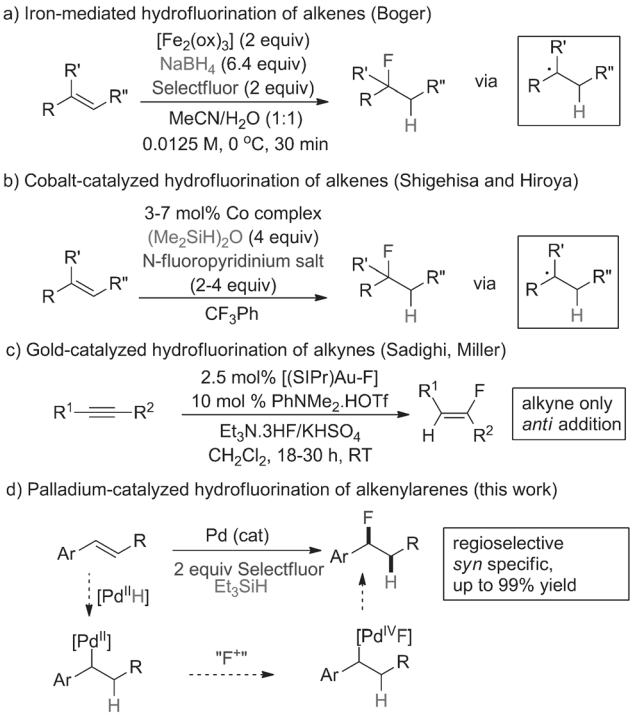
Dedicated to Professor Pier Giorgio Cozzi on the occasion of his 50th birthday

Abstract: *This paper describes the hydrofluorination of alkenes through sequential H^- and F^+ addition under palladium catalysis. The reaction is cis specific, thus providing access to benzylic fluorides. The mechanism of this reaction involves an ionic pathway and is distinct from known hydrofluorinations involving radical intermediates. The first catalytic enantioselective hydrofluorination is also disclosed.*

Catalytic hydrofunctionalization has become a topic of considerable interest as these reactions allow feedstock olefins to be transformed, regio- and stereoselectively, into high-value compounds. In this context, the hydrofluorination of alkenes has remained a challenging transformation. The addition of HF/pyridine or HF/SbF_5 across alkenes,[1] and free radical hydrofluorinations[2] have been studied. The harsh reaction conditions offer narrow substrate scope and restrict control over product selectivity. These limitations have encouraged us to develop metal-catalyzed hydrofluorinations that avoid such drawbacks. The importance of benzylic fluorides in agrochemical and medicinal chemistry provided a focus.[3] As a result the first successful catalytic method for the regiocontrolled addition of HF to styrenes, a reaction which involves electrophilic fluorination of an η^3-palladium benzyl compound, arises from the work described herein.

There are three examples of related metal-mediated reactions in the literature. Barker and Boger disclosed a powerful $Fe^{III}/NaBH_4$-mediated free radical hydrofluorination for unactivated alkenes using Selectfluor as the fluorine-atom donor.[4] This regioselective reaction is functional-group tolerant, but is not diastereospecific, an observation consistent with the free radical mechanism (Scheme 1a). Shigehisa, Hiroya, and co-workers reported a catalytic procedure which enhances this approach, and is general for mono- and α,α′-disubstituted alkenes. Hydrofluorination is achieved with *N*-fluorotrimethylpyridinium tetrafluoroborate and $(Me_2SiH)_2O$ under cobalt catalysis.[5,6] By using a substituted



Scheme 1. Hydrofluorination of alkynes and alkenes.

hepta-1,6-diene, cyclization occurred, and is consistent with the intermediacy of a 5-hexenyl radical (Scheme 1b). Sadighi and co-workers[7] reported a unique *trans* hydrofluorination of internal alkynes catalyzed by electrophilic (NHC)gold(I) complexes, a reaction which was further developed by Miller and co-workers,[8] and it is regio- and stereoselective, but is not applicable to alkenes (Scheme 1c).

In considering routes for catalytic hydrofluorination of olefins, we envisaged a palladium-catalyzed reaction for which the fluorine and hydrogen atoms stemmed from separate sources. This criteria led us to consider alkene hydropalladation with subsequent oxidative interception of the resulting organopalladium(II) species with an electrophilic fluorine source. Precedent suggests that the ensuing $Pd^{IV}F$ intermediate would readily undergo reductive elimination.[9] This important class of substrates is not amenable to hydrofluorination using known protocols.[4,5] The hydropalladation of styrenes is known to lead to η^3-benzyl complexes responsive to benzylic functionalization, but not to fluorination.[10] Ultimately, our successful route uses an excess of Selectfluor, which acts both as an electrophilic fluorinating

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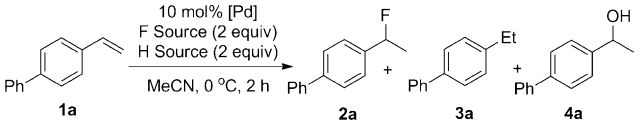
agent and an oxidant at different stages in the catalytic cycle (Scheme 1 d).

In our initial experiments,[11] we focused on the reactivity of 4-vinylbiphenyl (**1a**) and examined a range of palladium catalysts combined with various fluorine and hydride sources (Table 1). Selectfluor emerged as the most suitable fluorination reagent when used in the presence of iPr$_3$SiH and 10 mol% of [Pd(PPh$_3$)$_4$] in acetonitrile at 0°C (Table 1, entry 1). Selectfluor *bis*(triflate) was as efficient as Selectfluor *bis*(tetrafluoroborate) (Table 1, entry 2). *N*-Fluorobenzenesulfonimide, *N*-fluoropentachloropyridinium triflate, and XeF_2 were less effective fluorine sources as these reagents led preferentially to the reduced product 4-ethyl-1,1′-biphenyl (**3a**; Table 1, entries 3–5). The formation of **3a** was also observed when iPr$_3$SiH was replaced with PhSiH$_3$ or with NaBH$_4$ (Table 1, entries 6 and 7). Bu$_3$SnH gave mainly starting material with only trace amounts of **2a** (Table 1, entry 8). These results indicate that product formation is favored with the most reactive hydride source.[12] The reaction concentration and temperature were important parameters, with hydrofluorination best performed at 0°C and lower substrate concentration (0.025 M instead of 0.05 M; Table 1, entry 9). 4-Ethyl-1,1′-biphenyl (**3a**) was formed at room temperature along with traces of the benzylic alcohol **4a** (Table 1, entry 14). Pleasingly, the ratio of iPr$_3$SiH could be reduced to 1.5 equivalents with a beneficial effect on product formation (Table 1, entry 10). The conversion of **1a** into **2a** remained low with 1.5 equivalents of Selectfluor but was improved with an excess of N-F reagent (Table 1, entries 11 and 12). At this point, Et$_3$SiH was found to be better suited than iPr$_3$SiH (Table 1, entry 13). Amongst the palladium catalysts tested (Table 1, entries 15–17), [Pd(PPh$_3$)$_4$] was superior, thus allowing full conversion of **1a** into **2a**. Pd(OAc)$_2$, [PdCl$_2$(MeCN)$_2$], and [Pd(dba)$_2$] all led to **2a** along with **3a**. Benzylic chlorination was detectable (3%) with [PdCl$_2$(MeCN)$_2$] but acetoxylation was not observed with Pd(OAc)$_2$. In the absence of a catalyst or of Et$_3$SiH, **1a** was recovered along with trace amounts of **4a** (Table 1, entries 18 and 19). During the course of this study a vicinal fluoroamide, resulting from Ritter-type functionalization, was not typically detected.[12] Under the optimized reaction conditions the palladium-catalyzed reaction of **1a** with 3 equivalents of Selectfluor and 1.5 equivalents of Et$_3$SiH in MeCN (0.025 M) at 0°C afforded **2a** in 69% yield as a single regioisomer (Table 1, entry 13).

Table 1: Hydrofluorination of **1a**.[a]



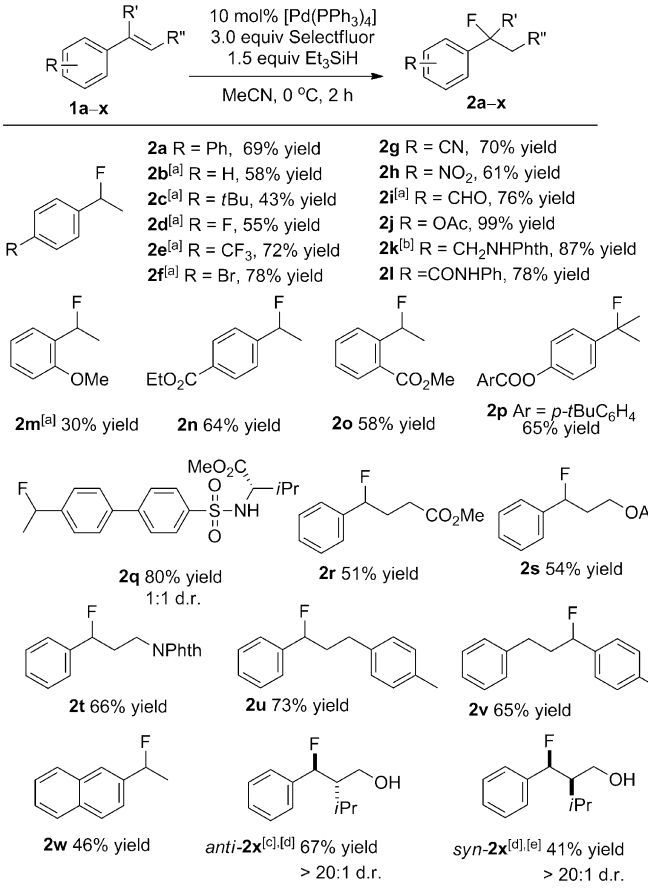
Entry	[Pd][b]	F Source[c]	H Source	Conv. [%][d]	Yield [%][d] 2a	3a
1	**I**	**A**	iPr$_3$SiH	>95	30	0
2	**I**	**B**	iPr$_3$SiH	>95	34	0
3	**I**	**C**	iPr$_3$SiH	25	11	12
4	**I**	**D**	iPr$_3$SiH	>95	0	23
5	**I**	**E**[e]	iPr$_3$SiH	72	16	28
6	**I**	**A**	PhSiH$_3$	>95	0	31
7	**I**	**A**	NaBH$_4$	>95	18	48
8	**I**	**A**	Bu$_3$SnH	9	<5	0
9[f]	**I**	**A**	iPr$_3$SiH	>95	35	0
10[f]	**I**	**A**	iPr$_3$SiH[g]	>95	41	0
11[f]	**I**	**A**[h]	iPr$_3$SiH[g]	37	22	0
12[f]	**I**	**A**[i]	iPr$_3$SiH[g]	>95	54	0
13[f]	**I**	**A**[i]	Et$_3$SiH[g]	>95	69	0
14[f,j]	**I**	**A**[i]	Et$_3$SiH[g]	>95	48	15
15[f]	**II**	**A**[i]	Et$_3$SiH[g]	>95	27	10
16[f]	**III**	**A**[i]	Et$_3$SiH[g]	>95	38	12
17[f]	**IV**	**A**[i]	Et$_3$SiH[g]	92	31	16
18[f]	–	**A**[i]	Et$_3$SiH[g]	10	0	0
19[f]	**I**	**A**[i]	–	<5	0	0

[a] Reaction conditions: **1a** (18 mg), MeCN (2 mL), fluorine source (2.0 equiv), hydride source (2.0 equiv), 0°C, 2 h. [b] **I** = [Pd(PPh$_3$)$_4$], **II** = Pd(OAc)$_2$, **III** = PdCl$_2$(MeCN)$_2$, **IV** = [Pd(dba)$_2$]. [c] **A** = Selectfluor bis(tetrafluoroborate) [(1-chloromethyl-4-fluoro-1,4-diazoniabicyclo-[2.2.2]octane bis(tetrafluoroborate), **B** = Selectfluor bis(triflate), **C** = *N*-fluorobenzenesulfonimide (NFSI), **D** = *N*-fluoropentachloropyridinium triflate, **E** = XeF_2. [d] Determined by ^{1}H NMR spectroscopy by peak integration using 1-fluoro-3-nitrobenzene as an internal reference. [e] Reaction performed in CH_2Cl_2 (2 mL). [f] 4 mL of solvent. [g] 1.5 equiv of iPr$_3$SiH (or with 1.5 equiv of Et$_3$SiH). [h] 1.5 equiv of Selectfluor bis(tetrafluoroborate). [i] 3 equiv of Selectfluor bis(tetrafluoroborate). [j] Reaction performed at RT.

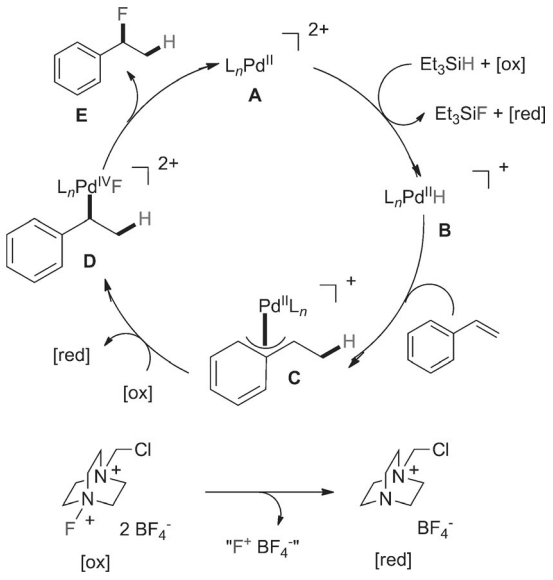
The substrate scope proved quite general, with various vinylarenes and disubstituted alkenylarenes participating effectively in the hydrofluorination reaction (Scheme 2). All the reactions of terminal as well as 1,1- and 1,2-disubstituted alkenylfluorides are regiospecific for benzyl fluoride formation. The electronic nature of the aryl motif is important with electron-neutral or electron-withdrawing groups leading to isolated benzylic fluorides with the highest yields (up to 99%). The method tolerates a wide range of functional groups including ether, amide, ester, sulfonamide, fluoro, bromo, alkyl, and trifluoromethyl groups. The method permits the installation of a fluorine substituent at a quaternary benzylic position as illustrated by the successful synthesis of **2p** (65%). However, the homologous but-1-en-2-ylbenzene gives approximately 10% yield.[11,14] The method gave access to **2u** and **2v**, two compounds that possess three benzylic positions, and are not accessible by direct benzylic C–H activation/fluorination[9] or by applying the iron(III)-mediated or cobalt-catalyzed hydrofluorinations previously reported.[4,5] Pleasingly, (*E*)- and (*Z*)-2-benzylidene-3-methylbutan-1-ol (**1x**) gave *anti*-**2x** and *syn*-**2x**, respectively, in good yields and with a d.r value of greater than 20:1. This result implies that the hydrofluorination is *cis* specific.[15]

A proposed catalytic cycle that explains the need for excess Selectfluor in the hydrofluorination reaction is presented in Scheme 3. Initial oxidation of the precatalyst gives the electrophilic Pd^{II} species **A** which activates the silane, thus giving access to the Pd^{II} hydride species **B**, which in turn effects reversible *syn* hydropalladation to the alkenylarene to afford the η^3-benzyl complex **C**. Electrophilic fluorination of **C** with Selectfluor affords the Pd^{IV}F dication **D** (or its η^3-complex). Reductive elimination then forms generic product **E**, and regenerates **A**.

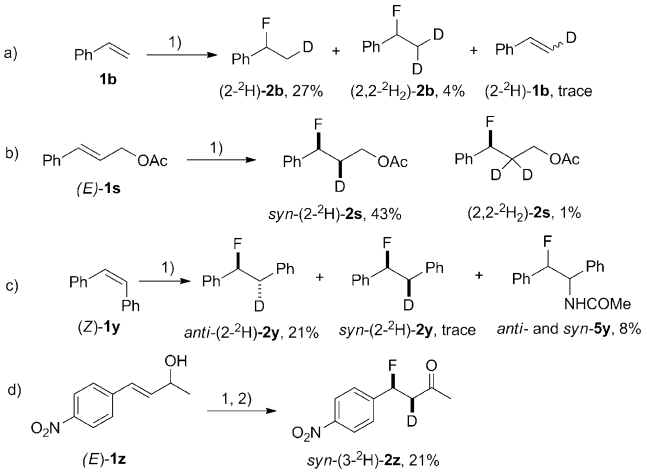
This mechanism is supported by the various experiments described in Scheme 4. The hydrofluorination of **1b** with Et$_3$SiD leads to (2-^{2}H)-**2b** and confirms that this reagent



Scheme 2. Hydrofluorination of alkenylarenes (**1a–x**). Regioselectivity >20:1. Phth = phtalimido. *i*Pr = isopropyl. [a] Yield determined by ^{19}F NMR spectroscopy with 1-fluoro-3-nitrobenzene as an internal reference. [b] Single-crystal diffraction data are available for **2k**.[11,13] [c] *anti*-**2x** was prepared from (*E*)-2-benzylidene-3-methylbutan-1-ol (**1x**). [d] The reaction time is 15 h. [e] *syn*-**2x** was prepared from (*Z*)-**1x**.



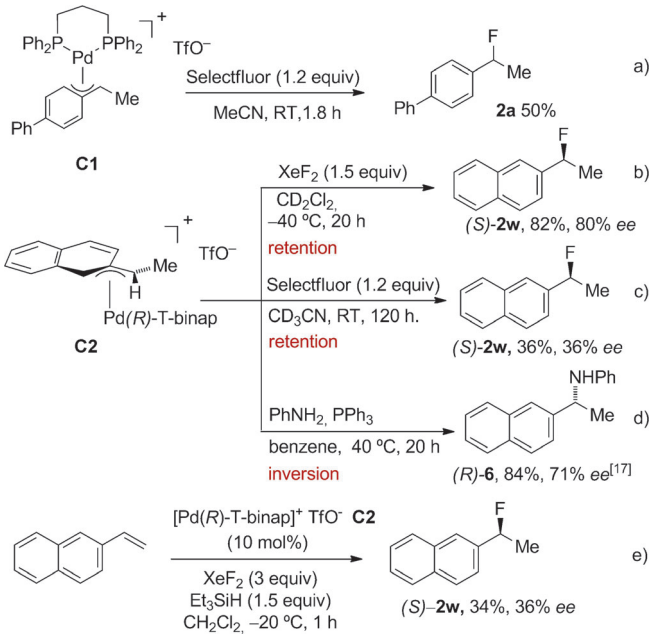
Scheme 3. Suggested catalytic cycle for hydrofluorination. Et_3SiF is formed upon hydrofluorination.[11]



Scheme 4. Regio- and stereochemical probes. Reaction conditions: 1) [Pd(PPh$_3$)$_4$] (10 mol%), Selectfluor (3.0 equiv) Et_3SiD (1.5 equiv), CH_3CN, 0 °C, 2 h. 2) PCC/alumina, benzene, RT, 12 h.

serves as the hydrogen atom source. The formation of the labeled alkene (2-^{2}H)-**1b** (<1%) and dideutero product (2,2-^{2}H$_2$)-**2b** indicates that the hydropalladation event is reversible during the course of the reaction (Scheme 4a). The product is not deuterated when the reaction is performed in CD_3CN, hence the solvent is not serving as a hydrogen donor. The substrate (*E*)-**1s** provided the single deuterated product *syn*-(2-^{2}H)-**2s**[16] with no detectable *anti*-(2-^{2}H)-**2s** upon deuterofluorination, thus implying that the addition of deuterium and fluorine across the double bond is *syn* stereospecific (Scheme 4b). For stereochemical assignment, the stilbenes (*E*)- and (*Z*)-**1y** were subjected to hydrofluorination using Et_3SiD because both *syn*- and *anti*-(2-^{2}H)-**2y** could be prepared through independent synthesis.[11,17] (*Z*)-Stilbene led to 21% of *anti*-(2-^{2}H)-**2y** along with trace amounts of *syn*-(2-^{2}H)-**2y** and the fluoroamide **5y**, resulting from Ritter-type functionalization (Scheme 4c). Conversely, (*E*)-**1y** led to a complex mixture of products, out of which *syn*-(2-^{2}H)-**2y** was detectable in trace amounts (2%) in addition to significant amounts of the *syn*- and *anti*-**5y** (18%). The synthesis of *syn*-(3-^{2}H)-**2z** provided additional evidence for *cis*-stereospecific hydrofluorination (Scheme 4d). Both *syn*-(3-^{2}H)-**2z** and *anti*-(3-^{2}H)-**2z** are known compounds.[18] Subjecting the allylic alcohol (*E*)-**1z** to deuterofluorination, by using our standard reaction conditions, with subsequent oxidation led exclusively to *syn*-(3-^{2}H)-**2z**, formed as a single stereoisomer.[11] The stereochemical course of hydrofluorination under palladium catalysis is consistent with the studies of Gagné and co-workers[19] who reported C(sp^3)–F bond formation with XeF_2 proceeding with retention of stereochemistry from putative Pt^{IV}F intermediates, and the work of Gary and Sanford[20] reporting on the first example of a C(sp^3)–F bond formation from a Pd^{IV} center.[20]

Additional experiments were carried out with isolated η^3-benzyl complexes (Scheme 5). We could not isolate either **C** or **D** (Scheme 3), or its η^3-analogue, but found that the η^3-benzyl complex **C1**[21] ligated with dppp (1,3-bis(diphenylphosphino)propane) led to **2a** in 50% yield upon treatment with Selectfluor in MeCN at room temperature (Scheme 5a).



Scheme 5. Reactivity of the complexes **C1** and **C2**.

Moreover, the enantioenriched naphtylethyl complex **C2**, prepared from (*R*)-T-binap according to the protocol of Hartwig et al.,[22] afforded (*S*)-2-(1-fluoroethyl)naphthalene (**2w**)[23] in 66% *ee* at room temperature and 80% *ee* at −40 °C (82% yield) in the presence of XeF_2[24] (Scheme 5b). By using 1.2 equivalents of Selectfluor at room temperature, **2w** was formed in 36% yield (^{19}F NMR spectroscopy) and a depleted *ee* value of 36%. The sense of enantiocontrol for the major enantiomer remained *S* (Scheme 5c). The stereochemical outcome of fluorination contrasts with the formation of (*R*)-*N*-(1-(naphthalen-2-yl)ethyl)aniline (**6**; 84% yield, 71% *ee*) arising from external attack of the amine on the **C2**, a reaction occurring with inversion of configuration (Scheme 5d).[11,25] These data indicate that the stereochemical outcome for the fluorination is consistent with coordination of F^+ leading to the $Pd^{IV}F$ complex and C–F bond-forming reductive elimination. The *cis* stereospecificity of this novel palladium-catalyzed reaction contrasts with the *anti* hydrofluorination of alkynes under gold catalysis and the iron(III)-mediated and cobalt-catalyzed hydrofluorinations which lead to a mixture of diastereomers. The sense of stereospecificity observed under palladium catalysis is consistent with the formation of a palladium(II) complex resulting from *syn* hydropalladation and subsequent oxidative fluorination to generate the $Pd^{IV}F$ complex **D**. Retention of configuration in the C–F coupling step can then afford a product resulting from net *syn* hydrofluorination. Notably, the reaction of 2-vinylnaphtalene with 10 mol% of **C2**, 3.0 equivalents of XeF_2, and 1.5 equivalents of Et_3SiH in CH_2Cl_2 at −20 °C delivered, within one hour, enantioenriched (*S*)-**2w** (34% yield, 36% *ee*). This transformation is the first catalytic enantioselective hydrofluorination (Scheme 5e).

Hence we have developed a novel catalytic hydrofluorination of alkenes, a reaction which is mechanistically distinct from known processes that all involve radical species. Hydrofluorination performed under palladium catalysis as described here is regioselective and characterized by the unique *cis* specificity. The methodology is best suited for alkenylarenes which can be transformed in a range of functionalized benzyl fluorides. The formation of (*S*)-2-(1-fluoroethyl)naphthalene (**2w**) from **C2**, used either as starting material or as catalyst, demonstrates the feasibility of enantioselective net HF addition to alkenes. We believe that the underlying principles, whereby HF addition is effected through sequential H^- and F^+ additions under palladium catalysis, are novel and may be applied to other catalytic reactions.

Experimental Section

General procedure for catalytic hydrofluorination: $[Pd(PPh_3)_4]$ (23.2 mg, 0.02 mmol), Selectfluor (213.0 mg, 0.60 mmol), and Et_3SiH (48 μL, 0.30 mmol) were added to a solution of 4-vinylbiphenyl **1a** (36.0 mg, 0.20 mmol) in dry MeCN (8 mL) in a 10 mL screw-top vial. The solution was stirred for 2 h at 0 °C before diluting with water (4 mL) and extracted with CH_2Cl_2 (3 × 6 mL). The combined organic layers were dried over $MgSO_4$ and evaporated under reduced pressure. Purification by column chromatography (SiO_2, EtOAc/petroleum ether = 1:15) afforded **2a** as a white solid (27.5 mg, 69% yield).

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[14] But-1-en-2-ylbenzene (**1aa**) gave 11 % of the product **2aa**, which results from hydrofluorination along with a mixture of (*E*)- and (*Z*)-but-2-en-2-ylbenzene (40 %). No starting material (**1aa**) was recovered.[11]

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[17] The independent synthesis of *syn*(2-^{2}H)-**2y** was performed by treating a racemic mixture of (2*R*,3*R*)- and (2*S*,3*S*)-2,3-diphenyloxirane with $LiAlD_4$ followed by fluorination of the deuterated benzylic alcohol. a*nti*-(2-^{2}H)-**2y** was obtained from (2*R*,3*S*)-2,3-diphenyloxirane.

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