Tsuji–Trost Allylations

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Palladium-Catalyzed Substitution of Allylic Fluorides**

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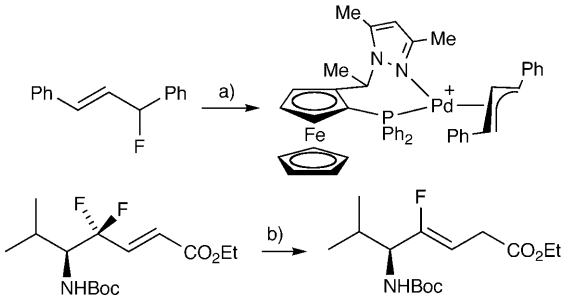
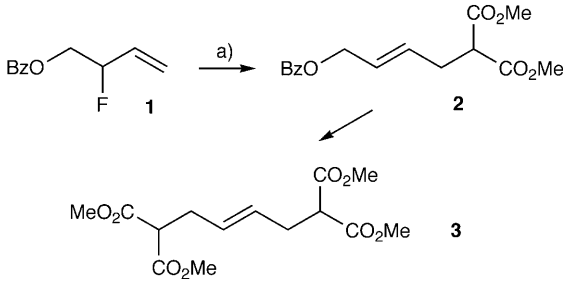
The chemistry of allylic fluorides has been intensively studied in recent years,[1] with some emphasis on the preparation and reactions of enantiomerically pure examples.[2] However, few cases of their participation in metal-catalyzed reactions are known. In pioneering work, Togni and co-workers explored the reactions of a model allyl fluoride with Pd and Pt complexes, and of cationic complexes of the same metals with desolvated fluoride ions.[3] In the first case, they demonstrated metal-promoted C–F activation, but were not able to create C–F bonds by the reverse process. Elimination from the ligand to form a diene, with F^- acting as a base, or simple displacement of the counterion occurred instead. They concluded that the attack of fluoride on a π-allyl Pd complex was thermodynamically unfavorable, making catalytic allylic fluorination a difficult objective. The ability of allylic fluoride to engage as a leaving group in palladium catalysis was endorsed in a recent demonstration of the selective reductive monodefluorination of allylic bifluorides, catalyzed by palladium diphosphine complexes.[4] In a closely related copper complex catalyzed reaction, the allyl intermediate was trapped by carbon electrophiles, leading to an overall S_N2' reaction[5] (Scheme 1).

Given stereocontrolled access to novel allylic fluorides, developed in previous work,[6] our intention was to develop their application in catalytic syntheses. Preliminary experiments with the simple reactant **1** provided useful basic information. On subjecting this compound to allylic alkylation with excess diethyl malonate activated by *N*,*O*-bis(trimethylsilyl)acetamide (BSA),[7] the doubly alkylated product **3** was isolated in 56% yield (Scheme 2).[8a] Furthermore, allylic alkylation of **1** with <1.5 equivalents of dimethyl malonate afforded the expected intermediate **2** (**2**/**3** = 62:38),[8b] which indicates that the rate of the first stage involving fluoride displacement is at least comparable with that of the second stage, where benzoate is the leaving group.



Scheme 1. Examples of C–F activation by Pd complexes: a) $[Pd(dba)_2]$ (dba = dibenzylideneacetone), 3-*tert*-butyl-1-{(*R*)-1-[(S_P)-2-(diphenylphosphanyl)ferrocenyl]ethyl}-1*H*-pyrazole;[3] b) $PhSiH_3$, Et_3N, $[\{Pd(\eta^3\text{-}C_3H_5)Cl\}_2]$, 1,3-bis(diphenylphosphanyl)propane, 50 °C. Boc = *tert*-butoxycarbonyl.[4]



Scheme 2. Allylic alkylation of allylic fluoride **1**: a) $CH_2(CO_2Me)_2$ (3 equivalents), BSA (3 equivalents), $[\{Pd(\eta^3\text{-}C_3H_5)Cl\}_2]$ (10 mol%), PPh_3 (40 mol%), CH_2Cl_2, room temperature, 56%.

This successful demonstration of catalytic alkylation of an allyl fluoride encouraged further work. 4-Carboxycyclohexenyl derivatives act as a classic stereochemical probe. Diastereoisomerically pure (±)-*syn*-**4**,[9] was treated with (diethylamino)sulfur trifluoride (DAST) under standard conditions giving allylic fluoride **5** as an inseparable mixture of diastereoisomers in 40:60 *syn*/*anti* ratio. Because this reaction was disappointingly unselective, an alternative approach was employed, which entailed synthesis of an allylsilane intermediate *anti*-**6** (Scheme 3).[10] Fluorodesilylation of compound **6** proceeded with inversion to give fluoride **5** with 87:13 *syn*/*anti* ratio. Alcohol *anti*-**4** was prepared by Mitsunobu inversion, and when treated as before gave allylsilane *syn*-**6** as the precursor of fluoride **5**, but in this case in a 10:90 *syn*/*anti* ratio. With three isomeric mixtures of fluoride **5** in hand, allylic alkylation was conducted as described in Table 1. All three stereoisomers gave product **7** with comparable isomer ratios, close to 3:1 *syn*/*anti* irrespective of the starting ratio. Solvent variation did not affect the outcome significantly (Table 1, entries 4 and 5). The slower reaction in THF was incomplete, but confirmed that the reactant allyl fluoride did not epimerize during the reaction.

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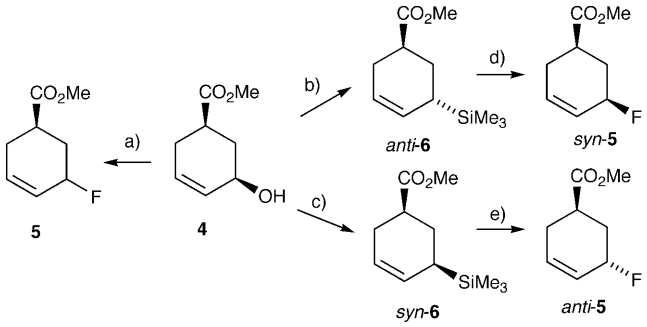
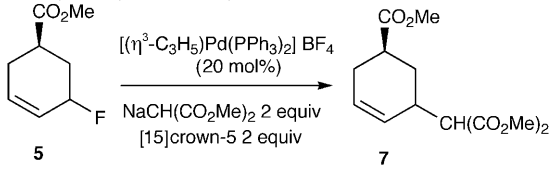


Scheme 3. Synthesis of racemic allylic fluoride **5** (for further details see the Supporting Information): a) DAST, CH_2Cl_2, −78 °C→room temperature, *syn*/*anti* 40:60, 59%; b) trifluoroacetic anhydride, pyridine, then Pd-catalyzed silylation with $(Me_3Si)_2$; c) Mitsunobu inversion, then as (b); d) Selectfluor (1-chloromethyl-4-fluorodiazoniabicyclo-[2.2.2]octane bis(tetrafluoroborate)), $NaHCO_3$, CH_3CN, *syn*/*anti* 87:13; 72%; e) as (d), *syn*/*anti* 10:90, 74%.

Table 1: Allylic alkylation of allyl fluoride **5** with malonate ion.[a]



Entry	*Syn*/*anti* ratio in **5**	Solvent	*t* [h]	*Syn*/*anti* ratio in **7**
1	40:60	CH_2Cl_2	0.25	76:24
2	10:90	CH_2Cl_2	0.25	72:28
3	87:13	CH_2Cl_2	0.25	73:27
4	40:60	CH_3CN	18	73:27
5	40:60	THF	24	72:28[a]
6[b]	40:60	CH_2Cl_2	0.25	37:63
7[b]	40:60	THF	24	32:68[a]

[a] 10 mol% catalyst was used in the absence of [15]crown-5, approximately 50% conversion was detected; *syn*/*anti* ratio in recovered **5** was not significantly altered. [b] Catalyst was $[\{(\eta^3\text{-}C_3H_5)PdCl\}_2]$, biphep.

When 2,2′-bis(diphenylphosphanyl)biphenyl (biphep) replaced PPh_3 as the ligand, the *syn*/*anti* ratio in product **7** changed to 1:2 and, again, the reactant recovered from an incomplete reaction in THF was not epimerized (Table 1, entries 6 and 7), reinforcing the observations regarding allyl fluoride reactivity, but also demonstrating an unusual mechanistic pathway; under optimized reaction conditions, the corresponding allyl acetates give ≥98% retention of configuration.[11]

Treatment of related allyl chlorides with $[Pd(PPh_3)_4]$ in $CDCl_3$ gives the corresponding η^3-allyl complex.[12] When **5** (40:60 *syn*/*anti*) was treated with $[Pd(dba)_2]$ (dba = dibenzylideneacetone) and PPh_3 in $CDCl_3$ and monitored by NMR spectroscopy, complex changes occurred, with initial broadening and then disappearance of the C*H*F signal (faster for *anti*-**5**). The known allyl cation,[13] derived from C–F ionization, was not detected in the NMR spectrum, but ES-MS analysis of the reaction mixture showed a strong signal for that cation (*m*/*z* calcd: 769.1611; found: 769.1574, with correct isotope pattern) as the only strong signal in the region *m*/*z* 500–1000.[14]

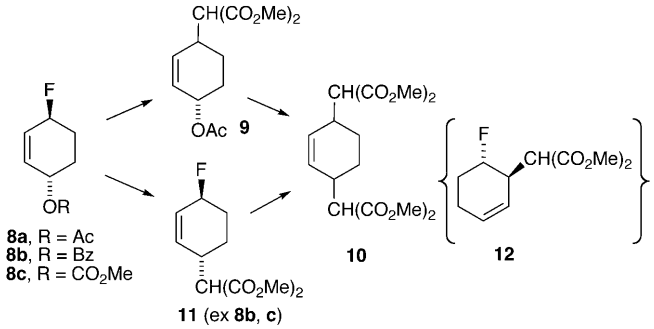
These results demonstrate the viability of fluoride as a leaving group in catalytic allylic alkylation, but do not quantify its reactivity as a leaving group. The availability of racemic fluoroesters **8a** and **8b**,[15] and ready access to the related fluorocarbonate **8c** informed the ensuing strategy. Initial reactions were carried out using acetate **8a**. Rapid loss of allylic fluoride was attested by direct detection by ^{19}F NMR spectroscopy of Me_3SiF, which formed rapidly under BSA-promoted conditions.[7] In the most revealing experiments (Table 2, entries 1–8) some intermediate species **9** was retained. The more reactive isomer *syn*-**9** was only detected under reagent-limited conditions (Table 2, entry 3). ^{19}F NMR indicated the absence of organofluorine species. In separate reactions with independently synthesized isomers,[16] *syn*-**9** gave 76:24 *syn*/*anti*-**10** under the conditions of entry 2, but *anti*-**9** was unreactive. When a chelating diphosphine, biphep or 1,3-bis(diphenylphosphanyl)propane (dppp), was employed as a ligand in place of PPh_3 (Table 2, entries 4–8), more *anti*-isomer was detected in total, but the reaction remained unselective. Entries 7 and 8 in particular indicated a higher tendency to form *anti*-**9** in the first step.

Allyl benzoates are far more reactive than allyl acetates towards alkylation.[17] With substrate **8b**, both leaving groups were displaced under standard conditions, with selective formation of the monoinverted product *syn*-**10** (Table 2, entries 9 and 10). However, with the chelating ligand biphep in place of PPh_3, overall retention to give *anti*-**10** was preferred by a ratio of 2:1. Further ^1H NMR experiments revealed the order of the two allylic alkylation steps. In addition to doubly alkylated products, intermediate **11** was formed with predominant retention of configuration (87% *anti*) with C*H*F resonating at $\delta = 5.1$ ppm in ^1H NMR spectroscopy. The minor product is tentatively assigned as the isomeric *anti*-homoallylic fluoride **12** ($\delta(CHF) = 4.78$ ppm), indicating that benzoate is a superior leaving group to fluoride, and the subsequent fluoride-substitution step occurs with predominant inversion of configuration (Table 2, entries 9 and 10).

Carbonates are known to be significantly more reactive than benzoates and other carboxylates in allylic alkylation reactions.[18] Synthesis of **8c** (2:98 *syn*/*anti* ratio) was accomplished by the previously described method. On subjecting **8c** to standard conditions, pure *anti*-**11** was isolable in 40% yield after relatively short reaction times, (Scheme 4). Crude *anti*-**11** contained 10% of **12**, but *syn*-**11** was not detected. In this case, an unambiguous preference is demonstrated for retention of configuration, with carbonate as the leaving group in the first step, and inversion of configuration with fluoride as leaving group in the second step.

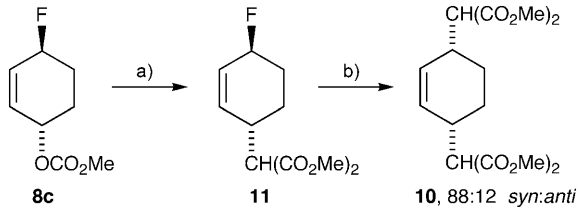
The data demonstrate unequivocally that allyl fluorides are active in palladium-catalyzed allylic alkylations. The leaving group propensity is $OCO_2Me > OBz \gg F \gg OAc$. More surprisingly, the stereochemical course of displacement of F^- is not governed by the normal double-inversion retention mechanism. In contrast, palladium-catalyzed reaction of the malonate ion with the allyl chloride analogue of fluoride **5** occurs with complete retention of configuration.[19]

Table 2: Allylic alkylation of allyl fluorides **8a** and **8b** with malonate ion.



Entry	Catalyst (mol%)	Reactant[a]	Reagent (equivalents)	Product ratio	
				syn-**9**/*anti*-**9**	*syn*-**10**/*anti*-**10**
1	$[\{Pd(\eta^3\text{-}C_3H_5)Cl\}_2]$, $2PPh_3$ (10)	**8a**	$CH_2(CO_2Me)_2$/BSA (3)	0:40	51:9
2[b]	$[(\eta^3\text{-}C_3H_5)Pd(PPh_3)_2]BF_4$ (20)	**8a**	$NaCH(CO_2Me)_2$/[15]crown-5 (3)	0:54	38:8
3	$[(\eta^3\text{-}C_3H_5)Pd(PPh_3)_2]BF_4$ (20)	**8a**	$NaCH(CO_2Me)_2$/[15]crown-5 (1.2)	44:44	9:3
4	$[\{Pd(\eta^3\text{-}C_3H_5)Cl\}_2]$, biphep (10)	**8a**	$CH_2(CO_2Me)_2$/BSA (3)	0:21	26:53
5	$[\{Pd(\eta^3\text{-}C_3H_5)Cl\}_2]$, biphep (10)	**8a**	$NaCH(CO_2Me)_2$/[15]crown-5 (3)	0:52	22:26
6	$[\{Pd(\eta^3\text{-}C_3H_5)Cl\}_2]$, dppp (10)	**8a**	$CH_2(CO_2Me)_2$/BSA (3)	0:59	16:25
7	$[\{Pd(\eta^3\text{-}C_3H_5)Cl\}_2]$, dppp (10)	**8a**	$NaCH(CO_2Me)_2$/[15]crown-5 (3)	0:65	27:8
8[c]	$[\{Pd(\eta^3\text{-}C_3H_5)Cl\}_2]$, dppp (2.5)	**8a**	$NaCH(CO_2Me)_2$/[15]crown-5 (3)	0:74	24:2
9	$[(\eta^3\text{-}C_3H_5)Pd(PPh_3)_2]BF_4$ (20)	**8b**	$CH_2(CO_2Me)_2$/BSA (3)	–	87:13
10	$[(\eta^3\text{-}C_3H_5)Pd(PPh_3)_2]BF_4$ (20)	**8b**	$CH_2(CO_2Me)_2$/BSA (3)	–	89:11
11	$[\{Pd(\eta^3\text{-}C_3H_5)Cl\}_2]$, biphep (10)	**8b**	$CH_2(CO_2Me)_2$/BSA (3)	–	32:68

[a] *syn*/*anti*(**8a**) 8:92, *syn*/*anti*(**8b**) 2:98. [b] With 100 mol% of catalyst, product ratio *anti*-**9**/*syn*-**10**/*anti*-**10** 42:20:38. [c] *anti*-**9** isolated in 53% yield.



Scheme 4. Selective displacement of carbonate in preference to fluoride a) $[\{Pd(\eta^3\text{-}C_3H_5)Cl\}_2]$ (2.5 mol%), $NaCH(CO_2Me)_2$, [15]crown-5, THF, 3 h, 40% isolated yield; b) $[(\eta^3\text{-}C_3H_5)Pd(PPh_3)_2]BF_4$ (20 mol%), $CH_2(CO_2Me)_2$, BSA, CH_2Cl_2, 16 h (see Supporting Information for further details).

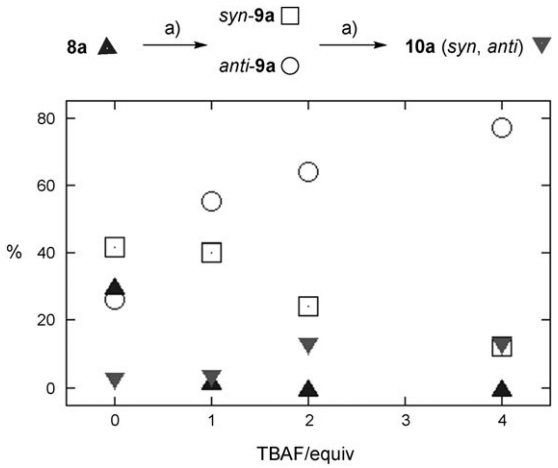
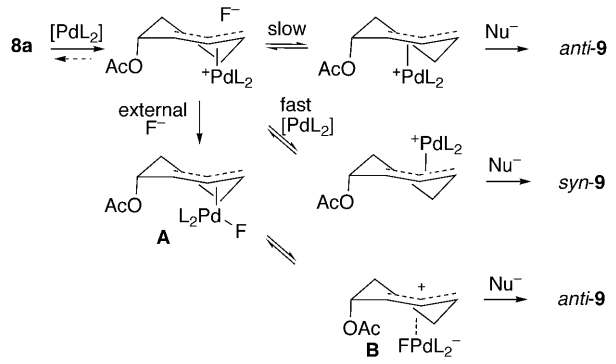


Figure 1. The effect of added $Bu_4NF{\cdot}3H_2O$ (TBAF, 1 M in THF) on the stereoselectivity of the alkylation of **8a**. Conditions: a) **8a** (0.024 g, 0.152 mmol), $[(\eta^3\text{-}C_3H_5)Pd(PPh_3)_2]BF_4$ (5 mol%), $NaCH(CO_2Me)_2$ (2 equivalents), [15]crown-5 (2.4 equivalents), TBAF, CH_2Cl_2 (2 mL), room temperature. Data shown are for ^1H NMR assay of aliquot taken after ten minutes of each run.[14]

In earlier work, it was demonstrated that Pd–F bonding is feasible.[20] Togni and co-workers demonstrated that added fluoride ion enhanced the enantioselectivity of asymmetric allylic amination, whereas noncoordinating anions, such as PF_6^-, were detrimental.[21] We thus carried out alkylation of **8a** in the presence of added tetrabutylammonium fluoride (TBAF, Figure 1). The reaction was monitored under the specified conditions, and aliquots were removed after 2, 4, 10 and 20 minutes for ^1H and/or ^{19}F NMR spectroscopic analysis. This led us to several notable observations; the reaction rate increases with increasing $[F^-]$, stereochemical retention becomes increasingly favored as $[F^-]$ increases, and the rate of the first step is more significantly enhanced than that of the second step. Added sodium tetrakis(3,5-bis(trifluoromethyl)-phenyl)borate ($NaBAr^F$), at comparable concentrations to those used for added F^-, had an inhibitory effect on the reaction rate, in accord with the precedent for noncoordinating anions described above. Recent work from Lloyd-Jones and co-workers showed that, at lower concentrations with acetate as the leaving group, $NaBAr^F$ can markedly enhance both rate and enantioselectivity of allylic alkylation.[22]

The accepted mechanism for stereochemical leakage was elucidated by Backväll and co-workers.[23,24] A coordinatively unsaturated $[L_2Pd^0]$ (L = phosphine ligand) nucleophile attacks the cationic allyl intermediate, resulting in displacement of the original ligated Pd fragment and an inversion of configuration. In complexes related to the cationic intermediate, depicted in Scheme 5, the reaction is fast even below



Scheme 5. A postulated model for the stereochemical course of allyl fluoride alkylation.

ambient temperature. The inhibitory effect of BAr^F anions locates the allyl fluoride effect at the ion-pair stage.

For allylic alkylation of allyl fluorides, we propose that the initial π-allyl intermediate is a tight ion pair, with fluoride as a counterion. If that reacts reversibly and more readily with a neutral $[L_2Pd^0]$ nucleophile than with the malonate anion, owing to the influence of coulombic repulsion, the standard double-inversion pathway would no longer operate (Scheme 5). This step would be expected to be more significant with twofold PPh_3 ligation than with a *cis*-chelating diphosphine; the preferred geometry for X-ray-characterized cases of isolable $\{P_2Pd\}$ complexes is near-linear, disfavoring *cis*-chelate ligands.[25] The effect of added fluoride in encouraging the retention pathway requires a further step involving reversible covalent Pd–F bond formation. This new intermediate **A** (or its η^1 analogue) could undergo ionic dissociation to form **B** (similar to the Amatore–Jutand anionic halopalladium intermediate).[26] The process naturally leads to retentive allylic alkylation. More conventionally, the known effects of Cl^- in suppressing reversal of oxidative addition and slowing *syn–anti* isomerization of the Pd–allyl complex,[12,27] would suffice to explain the effects of F^- in the present case.

In conclusion, this work has demonstrated, for the first time, that the role of allyl fluorides in catalytic allylic alkylation involves C–F displacement, which occurs by an unusual stereochemical course.

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