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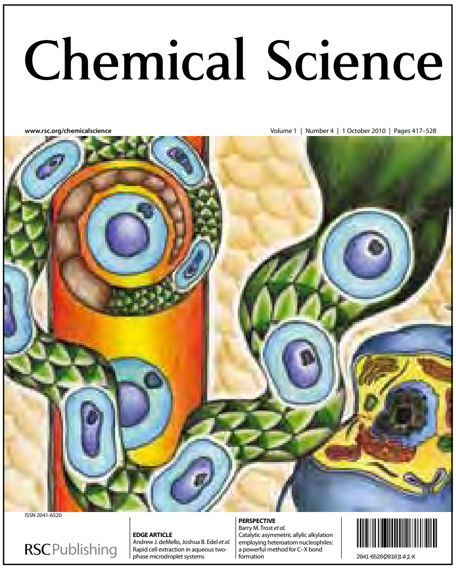

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EDGE ARTICLE
Andrew J. deMello, Joshua B. Edel *et al.*
Rapid cell extraction in aqueous two-phase microdroplet systems

PERSPECTIVE
Barry M. Trost *et al.*
Catalytic asymmetric allylic alkylation employing heteroatom nucleophiles: a powerful method for C–X bond formation

2041-6520(2010)1:4;1-X

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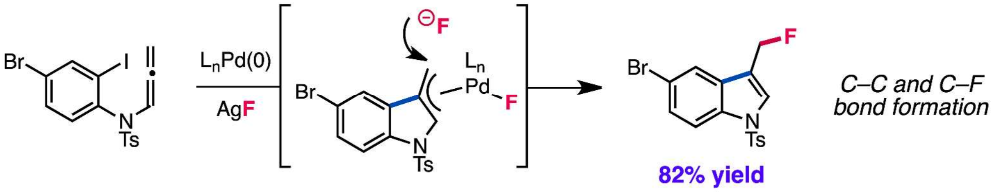
Br
I
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AgF
Br
N
Ts
F
L_n
Pd
F
Br
F
N
Ts
82% yield
C–C and C–F
bond formation

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EDGE ARTICLE

Carbofluorination via a Palladium-Catalyzed Cascade Reaction

Marie-Gabrielle Braun,[‡a] Matthew H. Katcher[‡a] and Abigail G. Doyle*[a]

Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
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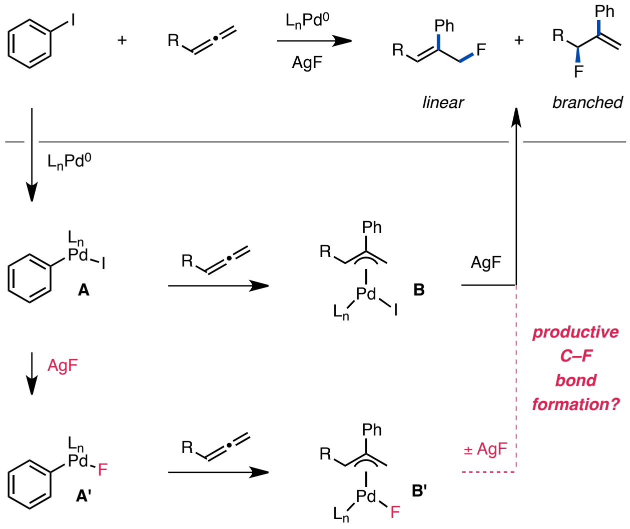
This article demonstrates the first examples of tandem C–C and C–F bond formation for the palladium-catalyzed carbofluorination of allenes. The intramolecular Heck-fluorination cascade provides monofluoromethylated heteroarenes, an important class of products in medicinal chemistry. We also describe an intermolecular variant for the three-component coupling of allenes, aryl iodides, and AgF. Mechanistic studies indicate that C–F bond formation occurs by outer sphere attack of fluoride on an allylpalladium fluoride intermediate.

Introduction

Palladium-catalyzed cascade reactions are valuable transformations in chemical synthesis that enable rapid and efficient access to molecular complexity.[1] Among these, cascades initiated by the coupling of an aryl or vinyl halide with an olefin (Heck reaction) have been used extensively to achieve olefin difunctionalization,[2] including recent examples of carbochlorination, carbobromination,[3] and carboiodination.[4] Notably, related carbofluorination reactions have yet to be described.[5] Since organofluorine derivatives have found widespread application in nearly every facet of the chemical industry,[6] such a cascade reaction would be of great value as it would permit access to these compounds by the modular combination of an aryl halide, olefin, and fluoride source. Herein, we report the development of an intramolecular Pd^0-catalyzed carbofluorination of allenes for the preparation of monofluoromethylated heterocycles. Although the CH_2F unit is important to isostere-based drug discovery,[7] current strategies for the preparation of monofluoromethylated heterocycles suffer from significant limitations in functional group compatibility or starting material preparation.[8] The intramolecular carbofluorination reported in this article offers a functional group tolerant and flexible method for the synthesis of these motifs via simultaneous heterocycle and C–F bond formation. Furthermore, an intermolecular variant of the carbofluorination is described, which delivers 2-substituted allylic fluorides in an efficient three-component coupling reaction.[9] Based on stoichiometric experiments conducted on this intermolecular reaction, we report a key role for a Pd^{II}(allyl)(F) intermediate in the carbofluorination.



Scheme 1 Proposed carbofluorination of allenes

Prior work has demonstrated that reductive elimination of a C–F bond from Pd^{II} is challenging.[10] For the synthesis of aryl fluorides, inner-sphere C–F bond formation from Pd^{II}(Ar)(F) complexes has only been demonstrated at temperatures near 100 ºC and with specialized ligands.[11] By contrast, our laboratory has reported mild conditions for Pd^0-catalyzed allylic fluorination using AgF, and stoichiometric studies with a Pd(allyl)(Cl) complex support an outer-sphere mechanism for C–F bond formation.[12,13] Recently, we questioned whether this mechanism could enable the design of a carbofluorination reaction between readily available allenes and aryl iodides. As outlined in Scheme 1, it was envisioned that exposure of an aryl iodide to Pd^0 would afford Pd(Ar)(I) **A**, which could readily engage an allene in a Heck insertion.[14] In accord with our earlier studies, we anticipated that the resulting Pd(allyl)(I) intermediate **B** would then undergo outer-sphere C–F bond formation with AgF to deliver the desired carbofluorinated product. As an alternative pathway, it is well-known that AgF readily reacts with Pd(Ar)(I) complexes to give Pd(Ar)(F) species (**A'**) by halide metathesis,[15] and **A'** could also participate in Heck insertion with the allene to furnish Pd(allyl)(F) **B'**. At the outset of our studies it was unclear whether this neutral intermediate could participate in productive C–F bond formation since most Pd-catalyzed allylic alkylations with outer-sphere nucleophiles undergo reaction from cationic

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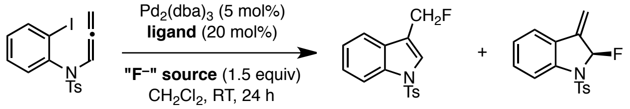
Table 1 Optimization of intramolecular carbofluorination



1a **2a** (+/–)-**3a**

Entry	Ligand	"F⁻" source	Yield (%)[a]	**2a**:**3a**[b]
1[c]	Trost DACH-naphthyl	AgF	7	nd[d]
2	PPh$_3$	AgF	20	1:1
3	P(4-OMe-C$_6$H$_4$)$_3$	AgF	9	nd[d]
4	XPhos	AgF	36	>20:1
5	P(2-furyl)$_3$	AgF	53	>20:1
6	P(3,5-CF$_3$-C$_6$H$_3$)$_3$	AgF	80	>20:1
7	P(3,5-CF$_3$-C$_6$H$_3$)$_3$	CsF	0	nd[d]
8	P(3,5-CF$_3$-C$_6$H$_3$)$_3$	Et$_3$N•3HF	0	nd[d]
9	P(3,5-CF$_3$-C$_6$H$_3$)$_3$	TBAT[e]	0	nd[d]

[a] Combined yield of **2a** and **3a**, determined by HPLC using naphthalene as a quantitative internal standard. [b] Determined by ^{19}F NMR. [c] 10 mol% ligand. [d] Not determined. [e] Tetrabutylammonium difluorotriphenylsilicate.

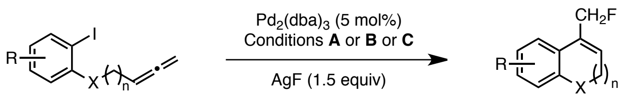
allyl complexes[16] and ionization of a Pd–F bond is unfavorable compared to that of a Pd–Cl or Pd–I bond.[17]

Results and discussion

With these concerns in mind, we began our investigation by examining the intramolecular carbofluorination of allene **1a** with a tethered aryl iodide (Table 1). Recognizing that ligand effects would play an important role in achieving the desired reactivity and regioselectivity (**2a**:**3a**), we initially surveyed ligands that had been effective for allylic fluorination.[12] With AgF as fluoride source, carbofluorinations conducted with both the Trost DACH-naphthyl ligand and triphenylphosphine provided the desired product, albeit with low yield and regioselectivity. Although reactions with electron-rich phosphines also resulted in poor yields (entries 3–4), the use of electron-deficient monophosphines led to improvements in reactivity and selectivity (entries 5–6). The best outcome was obtained with P(3,5-CF$_3$-C$_6$H$_3$)$_3$, which afforded **2a** in 80% yield (entry 6).[18] Notably, these conditions (conditions **A**, Table 2) also provided complete regioselectivity for the linear isomer presumably due in part to the preference for aromaticity over cross-conjugation. As observed in our previous studies, AgF was uniquely effective as a fluoride source (entries 7–9).

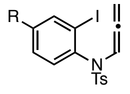
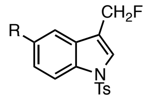
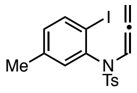
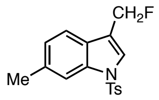
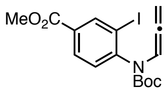
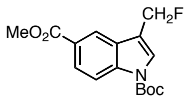
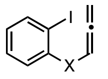
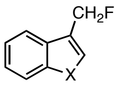
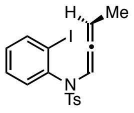
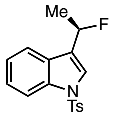
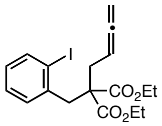
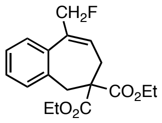
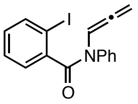
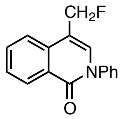
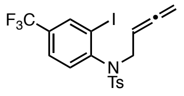
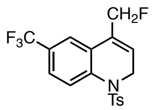
Following this optimization, we investigated the scope of the intramolecular carbofluorination for the preparation of monofluoromethylated heterocycles (Table 2). From easily accessible allenes,[19] various five-membered nitrogen-, oxygen-, and sulfur-containing heteroarenes were synthesized. Using conditions **A**, good to moderate yields were obtained for indoles with a range of substitution patterns and functional groups, including trifluoromethyl (**2c**), methoxy (**2d**), methyl (**2e**), *N*-Boc (**2f**), and ester (**2f**). An aryl bromide (**2b**) was also well-tolerated, potentially allowing for subsequent derivatization via distinct cross-coupling protocols.[20] Allene substrates bearing ether and thioether tethers furnished benzofuran **2g** and benzothiophene **2h** in slightly lower yields; for these substrates, the use of XPhos as ligand was required to avoid competitive degradation of the allene. XPhos was also optimal to minimize diene formation (*vide infra*) in the conversion of a disubstituted allene into 1-fluoroethyl indole **2i**.[21,22]

Table 2 Scope of intramolecular carbofluorination



1: n= 0, 1, 2 **2**

A: P(3,5-CF$_3$-C$_6$H$_3$)$_3$ (20 mol%), CH$_2$Cl$_2$, RT, 24 h
B: XPhos (20 mol%), toluene, 60 °C, 2–3 h
C: PPh$_3$ (30 mol%), toluene, 40 °C, 48 h

Substrate	Product	Conditions	Yield (%)[a]
 **1a–d**	 **2a–d**	**A**	**2a** R=H, 71 **2b** R=Br, 82[b] **2c** R=CF$_3$, 67 **2d** R=OMe, 76
 **1e**	 **2e**	**A**	77
 **1f**	 **2f**	**A**	69
 **1g–h**	 **2g–h**	**B**	**2g** X = O, 57 **2h** X=S, 58
 (+/–)-**1i**	 (+/–)-**2i**	**A**	72[c]
 **1j**	 **2j**	**C**	62
 **1k**	 **2k**	**C**	40
 **1l**	 **2l**	**C**	53

[a] Isolated yields for reactions carried out on 0.3–1.0 mmol scale (average of two runs). [b] [η^3-C$_3$H$_5$PdCl]$_2$ (5 mol%) was used as catalyst, 12 h. [c] With [η^3-C$_3$H$_5$PdCl]$_2$ (5 mol%), XPhos (20 mol%).

Given the importance of monofluoromethylated heterocycles in medicinal chemistry,[7] we sought to extend the scope of the carbofluorination to the synthesis of 6- and 7-membered ring products (Table 2). In these cases, higher temperatures were required to induce cyclization. However, for the preparation of **2j**,

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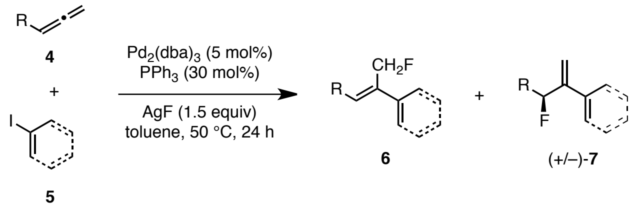
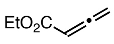
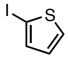
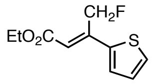
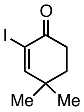
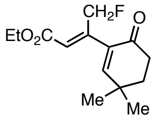
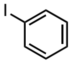
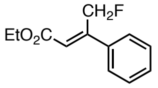
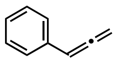
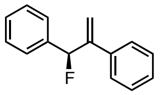
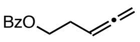
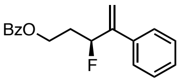
Table 3 Scope of intermolecular carbofluorination

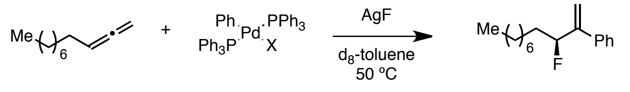


Allene	Iodide	Product	Yield (%)[a]
 **4a**	 **5a**	 **6a**	63
4a	 **5b**	 **6b**	60[b]
4a	 **5c**	 **6c**	62
 **4b**	**5c**	 **7d**:**6d** = 1.5:1.0	76
 **4c**	**5c**	 **7e**:**6e** = 2.0:1.0	71[c]

[a] Product ratios were determined by ^{19}F and ^{1}H NMR. Combined isolated yields of all isomers for reactions carried out on 0.5–1.0 mmol scale, average of two runs. Ratio of olefin isomers > 20:1, linear:branched > 20:1, except where noted. [b] With Pd(dmdba)$_2$ (10 mol%) and Xantphos (10 mol%), *Z*:*E* = 1.3:1.0. [c] With Pd(dmdba)$_2$ (10 mol%) as catalyst.

reactions under conditions **B** (60 °C, XPhos as ligand) afforded mainly diene (80%) via elimination, a common pathway in nucleophilic fluorinations with substrates bearing β-hydrogens.[23] We were pleased to find that use of PPh$_3$ as ligand at 40 °C reduced the formation of this undesired byproduct to 20%, allowing for isolation of carbocycle **2j** in 62% yield.[22] With these conditions, the reaction also provided access to isoquinolinone **2k** and 1,2-dihydroquinoline **2l**. Despite their seeming simplicity, none of the fluorinated products in Table 2 has been previously reported,[24] underscoring the lack of efficient strategies for the preparation of these motifs in comparison with methods for the synthesis of fluoro-[25] trifluoromethyl-,[26] and difluoromethyl-[27] heterocycles.

We next pursued an intermolecular carbofluorination cascade for the three-component coupling of commercial or readily accessible aryl iodides, allenes, and AgF. Importantly, this method allows access to allylic fluorides with 2-substitution,[28] products that were difficult to access via our previous method due to limitations in preparing the corresponding allylic chloride substrates.[12] In addition to aryl iodides (**5c**), heteroaryl (**5a**) and vinyl (**5b**) iodides were also competent coupling partners (Table 3). Notably, the regioselectivity of fluoride attack varied with the structure of the allene. For products **6a**, **6b**, and **6c**, the linear isomer was observed due to the preference for conjugation with the ester. In contrast, other substrates (**4b**, **4c**) afforded products with a slight excess of the branched isomer; this regiochemical outcome is in accord with our previous work on allylic fluorination.[12b]



4d

8-F: X = F
8-I: X = I

(+/−)-**7f**
8-F: 23%[a]
8-I: 50%[a]
8-F, without AgF: 34%[b]

Scheme 2 Mechanistic studies with stoichiometric Pd complexes. Reactions conducted in the presence of dimethyl fumarate (1 equiv) to complex Pd(0). Yield determined by ^{1}H NMR, using methyl benzoate as a quantitative internal standard. Branched:linear ratio >20:1 by ^{19}F NMR. [a] **4d** (1 equiv), **8-I** or **8-F** (1 equiv), AgF (3 equiv), 12 h. [b] **4d** (1 equiv), **8-F** (1 equiv), 24 h.

The success of this intermolecular reaction provides a unique opportunity to interrogate the intermediacy of a Pd^{II}(allyl)(F) (**B'**, Scheme 1) in Pd-catalyzed allylic fluorinations. To this end, we prepared known Pd^{II}(Ph)(F) **8-F**[15] and subjected it to allene **4d** in the presence of AgF (Scheme 2).[29] After 12 h at 50 ºC, the desired carbofluorination product **7f** was produced in 23% yield, with the major byproduct of the reaction resulting from elimination. Notably, when the analogous iodide complex **8-I** was subjected to the same conditions, carbofluorination also required 12 h to reach full conversion of **4d** and 50% yield of **7f**,[30] but the only Pd^{II} species detectable by ^{31}P NMR after 30 min was **8-F**.[31] Furthermore, at temperatures below those required for carbofluorination, halide exchange between **8-I** and AgF occurred readily. These findings demonstrate that **A'** is a kinetically viable intermediate in the catalytic cycle and that allylic C–F bond formation can proceed via Pd^{II}(allyl)(F) **B'** (Scheme 1).[32]

Surprisingly, a control experiment showed that AgF is not required for stoichiometric carbofluorination, as the reaction of **8-F** with **4d** in the *absence* of AgF also afforded **7f** (34% yield, Scheme 2). Taking into account our previous stereochemical studies on allylic fluorination and the fact that a Pd^{II}–F bond is unlikely to undergo inner-sphere C–F reductive elimination under these conditions (*vide supra*), this stoichiometric reaction likely proceeds via an outer-sphere pathway. "Naked" fluoride generated from ionization of Pd–F **B'** could serve as the outer-sphere nucleophile. However, this mechanism seems unlikely given that the reactions are conducted in non-polar solvents in which the concentration of free fluoride will be low.[33] A more likely possibility is that the outer-sphere nucleophile is a palladium fluoride complex (**A'** or **B'**) that delivers fluoride to a distinct allylpalladium intermediate in a bimetallic mechanism.[34] Mechanistic studies are underway in order to distinguish these two scenarios; however, preliminary rate data suggest that the Ag-free mechanism may not be relevant to the catalytic system.[35] The result nevertheless highlights the attractive possibility that a transition metal fluoride other than AgF can be identified for the catalytic reaction.

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Conclusions

In summary, we have demonstrated the first examples of palladium-catalyzed intra- and intermolecular carbofluorination of olefins. Valuable fluorinated motifs, including monofluoromethylated heterocycles, can be efficiently synthesized. Based on stoichiometric experiments, we propose that a palladium fluoride, resulting from halide exchange with AgF, is a key intermediate in the reaction. The implications of this unexpected observation on the mechanism of C–F bond formation are the subject of further investigations in our laboratory.

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† Electronic Supplementary Information (ESI) available: Experimental procedures, additional reaction optimization, details for stoichiometric reactions, and spectroscopic data for all new compounds. See DOI: 10.1039/b000000x/

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