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Communication

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Palladium–Catalyzed Asymmetric Allylic Fluoroalkylation/Trifluoromethylation

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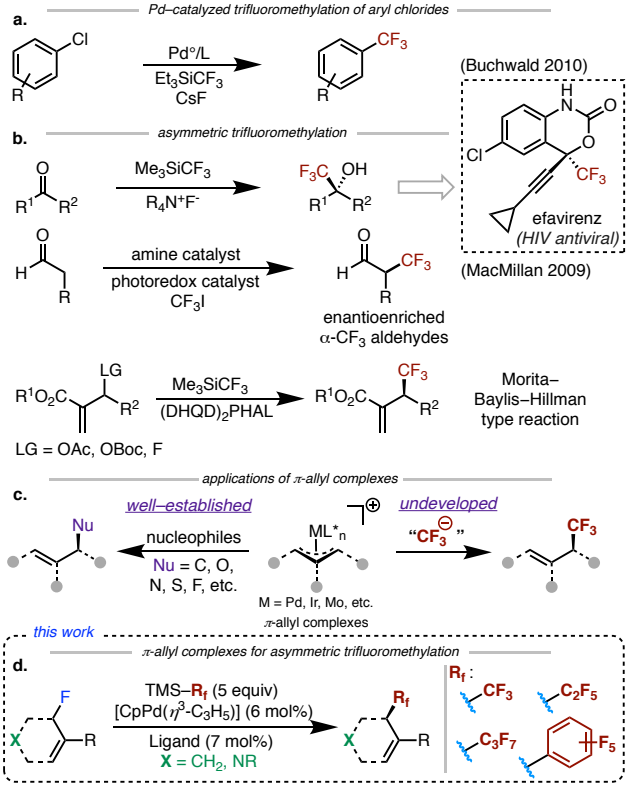
Supporting Information Placeholder

ABSTRACT: The first palladium-catalyzed asymmetric allylic trifluoromethylation is disclosed. The methodology evokes a fundamental principle by which the synergistic interplay of a leaving group and its subsequent activation of the nucleophilic trifluoromethyl group enabled the reaction. Allyl fluorides have been shown to be superior precursors for generation of π–allyl complexes, which lead to trifluoromethylated products with high selectivities and functional group tolerance. This study highlights the unique role of a bidentate diamidophosphite ligand class in palladium-catalyzed reactions that allow a challenging transformation to proceed.

Introduction of fluorine into organic molecules is of paramount interest, due to the unique properties that fluorine offers and its broad application in pharmaceutical products and in agrochemical ingredients.[1] Fluoroalkyl groups in general and the trifluoromethyl group in particular are among the privileged fluorinated groups that appear frequently in numerous pharmaceutically relevant chemicals.[1e] The effect of fluorinated alkyl groups is surmised to adjust the acidity or basicity, to increase metabolite stability, and to modulate lipophilicity of a compound.[1f, 2] With the underlined importance of this strategic motif, there have been an increasing number of methods that are developed in the past decades to access molecules bearing the trifluoromethyl group.[3a-d, 1d, 3e, 1f, 2, 3f] However, a vast majority of reports are focused on approaches for trifluoromethylation of aromatic frameworks utilizing various transition-metal catalytic systems.[4a-f, 3e, 4g, 4h] As an example, a very elegant palladium-catalyzed trifluoromethylation of aryl chlorides was disclosed by the Buchwald group (Scheme 1-a).[4b]

In stark contrast, direct aliphatic trifluoromethylation has received less attention. More importantly, performing the latter transformation in an asymmetric fashion with high enantioselectivity is utterly undeveloped.[1f, 2] Presumably, the challenges in carrying out such a task has hampered the availability of methods for asymmetric aliphatic trifluoromethylations. One of the early discoveries in this line is the addition of a nucleophilic trifluoromethyl group to carbonyl compounds (Scheme 1-b).[5] The requisite effect of a catalytic fluoride source to initiate the reaction has led to the development of chiral quaternary ammonium salts to induce asymmetry in the addition reaction.[6, 1f] The latter approach has been utilized as one of the synthetic routes to access efavirenz (dashed box, Scheme 1), a HIV drug molecule containing a CF_3 group, in moderate enantioselectivity.[7] In a different approach, the MacMillan group has developed an asymmetric radical based α-trifluoromethylation of aldehydes using organo-catalysis merged with photoredox catalysis.[8] Apart from these seminal reports, the asymmetric introduction of nucleophilic trifluoromethyl group into

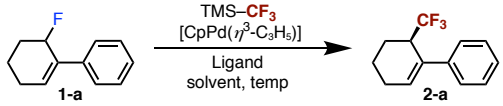
Scheme 1. Trifluoromethylation reactions; The asymmetic allylic trifluoromethylation.



electrophilic carbon centers is extremely rare. To the best of our knowledge, a Baylis-Hillman type reaction stands as the only example in this regard (Scheme 1b).[9]

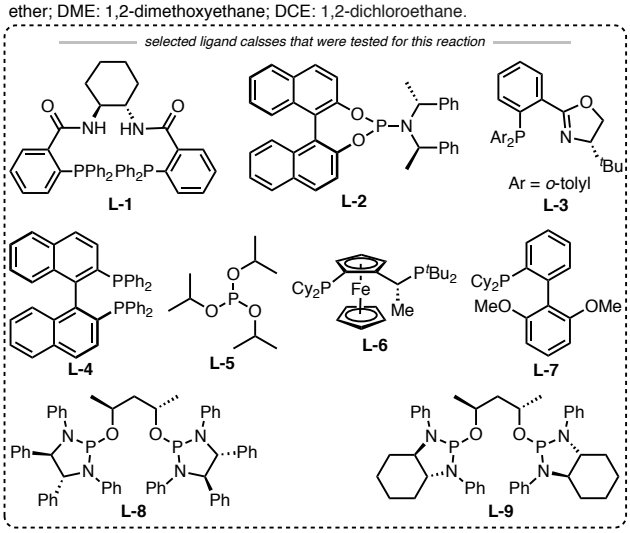
Given the tremendous success of electrophilic π-allyl complexes with different metals to incorporate various carbon or heteroatom nucleophiles into organic molecules, we aimed to use this platform to implement an elusive asymmetric allylic trifluoromethylation (Scheme 1-c).[10] Due to the abundance of cyclic frameworks, especially six-membered ring motifs, in the skeletons of pharmaceutically relevant compounds, we chose to utilize this scaffold as the model substrate (Scheme 1-d).

Table 1. Selected optimization conditions for the asymmetric allylic trilfuormethylation.



entry[a]	ligand	solvent	temp (°C)	yield[b]	*er*[c]
1	**L-1** to **L-5**	MTBE	50	n.d.[d]	-
2	**L-6**	MTBE	50	<5%[d]	-
3	**L-7**	MTBE	50	20%	-
4	**L-8**	$PhCH_3$	50	35%	91:9
5	**L-9**	$PhCH_3$	75	40%	92:8
6	**L-9**	DME	75	<5%[d]	-
7	**L-9**	DCE	75	<5%[d]	-
8	**L-9**	1,4-dioxane	75	60%	90:10
9	**L-9**	MTBE	75	80%	90:10
10	**L-9**	MTBE	r.t.	30%	96:4
11	**L-9**	MTBE	50	67%	95:5
12[e]	**L-9**	MTBE	50	>95%	95.5:4.5
13[e]	**L-9**	MTBE	50	n.d.[d,f]	-
14[e]	**L-9**	MTBE	50	22%[g]	-
15[h]	**L-9**	**MTBE**	**50**	**>90%**[i]	**96:4**

[a]Reactions on 0.05 mmol scale (~0.2 M) using [CpPd(η^3-C_3H_5)] (5 mol%), ligand (5 –15 mol%), and $TMSCF_3$ (5.0 equiv) after 14 h. [b]Determined by ^{1}H-NMR using 1,3,5-trimethoxy benzene as an internal standard. [c]*e.r.* are determined using chiral GC analysis. [d]>90% of the starting material was recovered.[e]10 mol% [CpPd(η^3-C_3H_5)], 15 mol% **L-9** was employed. [f]Allyl chloride. [g]Allyl–OBoc. [h]0.25 mmol of the allyl fluoride (0.4 M), [CpPd(η^3-C_3H_5)] (6 mol%), **L-9** (7 mol%) was used. [i]79% isolated yield. MTBE: methyl *tert*-butyl ether; DME: 1,2-dimethoxyethane; DCE: 1,2-dichloroethane.

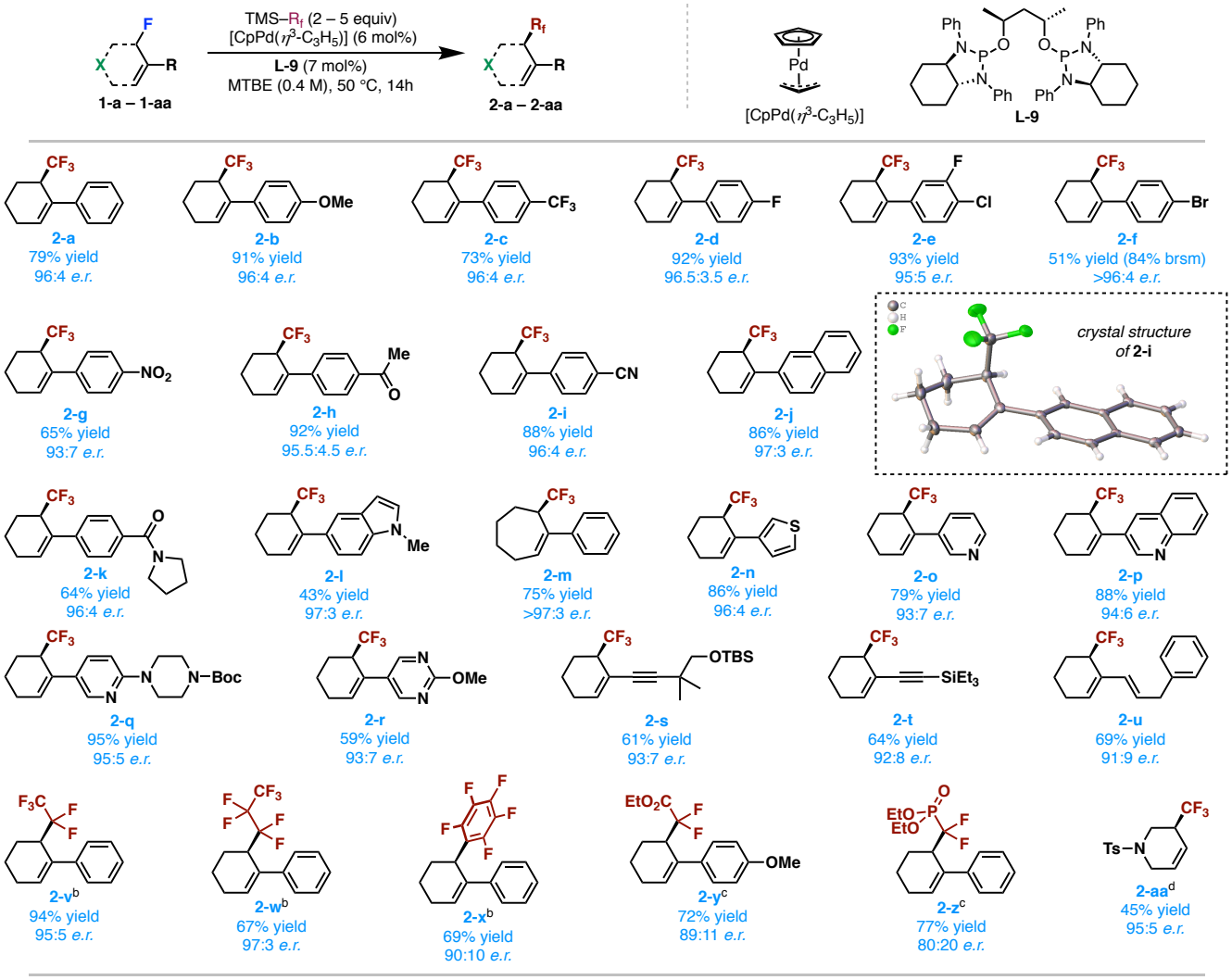


Herein, we report the first palladium-catalyzed asymmetric allylic trifluoromethylation and more importantly, fluoroalkylation reactions.

We began our endeavor by looking into the typical leaving groups to generate the π-allyl complex and intercept this electrophilic species with the nucleophilic trifluoromethyl anion. Our initial foray of experiments indicated that the proposed allylic trifluoromethylation using trimethyl(trifluoromethyl)silane ($TMSCF_3$) could not be accomplished efficiently using prototypical leaving groups (carbonates, acetate, chloride, etc.). This observation was presumably due to the incompetency of $TMSCF_3$ to engage as a pronucleophile in the proposed reaction under the tested conditions. A possible rationale was that, the oxygen-based leaving groups in this reaction are insufficiently silylophilic to liberate a nucleophilic trifluoromethyl anion. In light of this notion, fluoride was chosen as a leaving group because its high silylophilicity should enhance the polarization of the C–Si bond presumably via a hypervalent silicon species. Since a naked trifluoromethyl group can undergo α-elimination and carbene formation,[11, 4b] by using allyl fluorides as substrate, this nucleophile would be generated alongside the catalytic process and would be consumed by the *in situ* generated electrophilic π-allyl complexes. Furthermore, the ionization of the allyl fluoride would be facilitated by its interaction with $TMSCF_3$ and a synergistic interplay can be invoked in this reaction paradigm.[12, 9c] In line with our conceptual view, utilization of substrate's fluoride in reactions involve acyl fluorides, has been demonstrated to offer a unique reactivity pattern in various transition-metal catalyzed reactions.[13]

Optimization studies revealed that no reaction could be detected when using ligands typically developed for allylic alkylation (Table 1, entries 1 and 2).[10a-c, 10f-h] When S-Phos (**L-7**) was utilized as a ligand, the trifluoromethylated product could be detected in low yield (Table 1, entry 3). This result is significant since **L-7** is structurally similar to the ligands that are utilized by the Buchwald group for the palladium-catalyzed trifluoromethylation of aryl chlorides (Scheme 1-a).[4b] To our delight, diamidophosphite ligands **L-8** and **L-9** delivered the desired product with moderate yield and high enantioselectivity (entries 4 and 5).[14] Ligand **L-9** that showed slightly better results was chosen as the optimized ligand, and further optimization showed that methyl *tert*-butyl ether as solvent could deliver the product **2** in 80% yield at elevated temperature with good *e.r.* (Table 1, entry 9). Performing the reaction at lower temperature led to the improvement of *e.r.*, albeit with decreasing the yield of **2** due to lower conversion of the allyl fluoride (Table 1, entries 10 and 11). Increasing the catalyst and ligand loadings led to complete consumption of the allyl fluoride and the **2** was formed in >95% NMR yield (Table 1, entry 12). Of note, under these optimized conditions, allyl chloride and allyl–OBoc (O–*tert*-butyloxycarbonyl) did

Scheme 2. Scope of the palladium-catalyzed asymmetric allylic fluoroalkylation.[a]



[a]Reactions were carried out using 0.25 mmol of allyl fluorides. *e.r.* of the products were determined using GC or HPLC analysis. [b]2.5 equivalents of TMS–R_f was utilized. [c]1.5 equivalents of TMS–R_f was utilized. [d]The reaction was carried out on 0.1 mmol of allyl fluoride **1-aa**.

not deliver the product **2** with satisfactory results (Table 1, entries 13 and 14). Ultimately, increase in the concentration by carrying out the reaction on 0.25 mmol scale allowed to lowering the catalyst and ligand loadings to 6 mol% and 7 mol% respectively, to give product **2** in 79% isolated yield and 96:4 *e.r.* (Table 1, entry 15).

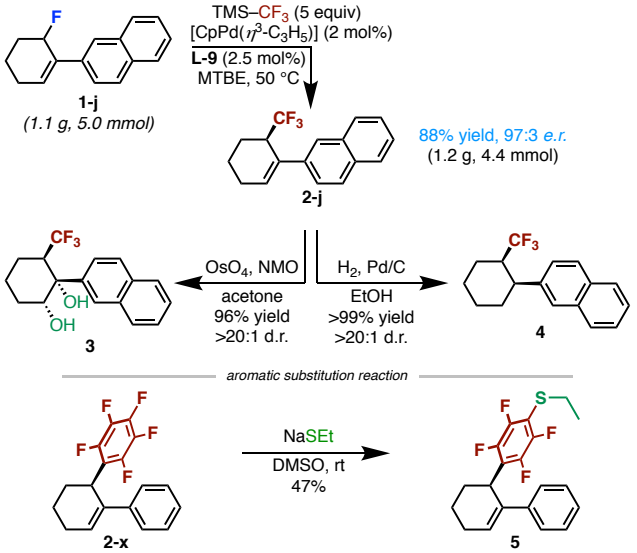
With this optimized set of conditions in hand, we explored the generality of the reaction (Scheme 2). The reaction showed good tolerance with respect to the substituents directly attached to the π–allyl moiety. Electron-rich as well as electron-deficient aromatic rings were well tolerated and resulted in the trifluoromethylated products **2** in good yields and high enantioselectivities. Different substitution patterns on the aromatic ring were also tolerated and delivered the functionalized product in good yield and selectivity. Aromatic rings bearing different halogen atoms could be used under these palladium-catalyzed conditions. Nonetheless, *para*-bromo phenyl group showed lower reactivity and complete consumption of allyl fluoride could not be achieved (**2-f**), which is presumably due to the competing oxidative addition of palladium into C–Br bond. The tolerance of the ketone group in **2-h** is noteworthy, as the reaction showed complete chemoselectivity for the allylic trifluoromethylation. We have demonstrated the reaction with cyclic six membered ring systems as the main substrates; however, the reaction could be carried out on a seven-membered ring system with comparable results (**2-m**). On the other hand, π–allyl complexes from five-membered rings did not give satisfactory results under these conditions. Heteroaromatic moieties on the allyl group were also well tolerated and the desired products were obtained in good yields and selectivities (**2-n** to **2-r**). In this line, **2-q** is of particular interest since it contains an aminopyridine core that is a key structural feature in many drug molecules. Of particular note, alkyne and alkene groups attached to

the allyl fluoride core could also be engaged in this reaction (**2-s** to **2-u**). Nevertheless, the enantioselectivity in these cases was slightly lower than the aryl-substituted substrates. We realized that the reaction is not limited to the trifluoromethyl group. Indeed, perfluoroalkyl groups such as pentafluoro ethyl, heptafluoro propyl and pentafluorophenyl were excellent reaction partners in this allylic functionalization, leading to **2-v**, **2-w**, and **2x**, respectively in good yields and with excellent enantioselectivity. Nevertheless, the enantioselectivity of the reaction with pentafluorophenyl as a nucleophile is slightly lower than the sp^3–hybridized fluoroalkyl nucleophiles. We further explored the feasibility of the reaction with α,α–difluoroester and α,α–difluorophosphate as nucleophiles. Thus, products **2-y** and **2-z** were obtained in good yield although with diminished enantioselectivity as compared with the perfluoroalkyl nucleophiles. Additionally, nitrogen containing cyclic allyl fluorides could be used in the reaction to access trifluoromethylated heterocycle **2-aa** in moderate yield and high enantioselectivity. By obtaining a crystal structure of **2-j**, the absolute configuration was readily determined, and all other products were assigned by analogy (Scheme 2).

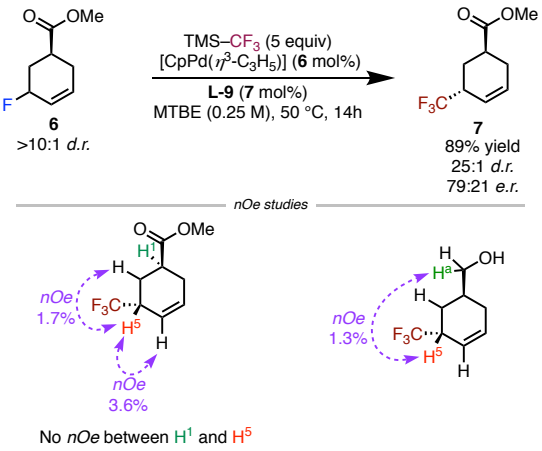
The reaction could be carried out on gram scale with some benefits (Scheme 3). Performing the reaction on a larger scale allowed us to lower the palladium loading to 2 mol% and the ligand loading to 2.5 mol%. The concentration of the reaction for the large scale reaction was increased to compensate for lower catalyst loading, resulting in the formation of **2-j** in 88% yield and 97:3 *e.r.*, a slight improvement compared to the smaller scale reaction. Our method gives access to variable chiral cyclic compounds with a trifluoromethyl group vicinal to a double bound. The double bond in these products can be utilized to further access molecular diversity using known transformations of olefins. As illustrated in Scheme 3, the double bond in **2-j** could readily undergo dihydroxylation to deliver **3** in excellent yield and high diastereoselectivity. In addition, hydrogenation of this motif delivered the disubstituted cyclohexane **4** in quantitative yield and high *d.r.*. Additionally, the pentafluoro group in **2-x** could provide a path for aromatic substitution to access **5**.[15] This transformation is noteworthy since the perfluoroaryl rings have been utilized in various bioconjugate strategies, thus pentafluorophenyl motif in **2-x** could be exploited in a distinctive interaction with biologically important targets.

With these results in hand, we turned our attention to the mechanism of the reaction. We first sought to establish the overall stereochemical outcome of the reaction. For this purpose, the known allyl fluoride **6**,[10d, 16] which possesses a *trans* disubstituted core can be used to probe the retention or inversion mechanism of the trifluoromethylation process. To this end, **6** was subjected to the optimized reaction conditions and the trifluoromethylated product **7** was obtained in high yield, high diastereoselectivity and moderate *e.r.*. The *nOe* studies were then employed to determine the relative stereochemistry of the stereocenters in the product. No *nOe* was observed between the hydrogen atoms on the stereocenters in **7**. The latter could potentially suggest a *trans* configuration of these two hydrogens. We further reduced the ester group to the primary alcohol. A positive *nOe* between the carbinol hydrogens and the hydrogen atom on the carbon bearing the trifluoromethyl group places these hydrogens *cis* to each other which confirmed the *trans* configuration of the substituents. This analysis indicates an overall retention of the stereochemistry during the trifluoromethylation process. The latter could point to a double inversion (ionization and nucleophilic addition) or a double retention mechanism. The clear scenario of this reaction is not known; however, the results from Gouverneur, Brown, and coworkers that have elucidated the stereochemical outcome of allyl fluorides with a series of nucleophiles, suggests an inversion mechanism during the

Scheme 3. Gram scale reaction and utilization of the fluoroalkylated products.



Scheme 4. Elucidation of the stereochemical outcome of the trifluoromethylation reaction.



ionization event of allyl fluorides.[12, 16] Thus, a double inversion mechanism should be involved in our methodology to deliver an overall retention.

In summary, we report the first palladium-catalyzed asymmetric allylic trifluoromethylation reaction empowered by a unique ligand class. The role of allyl fluorides as a superior precursor for generation of π-allyl complexes suggests a synergistic interplay of the fluoride leaving group and TMS–CF_3 in ionization and nucleophilic activation. This methodology gives access to various fluoroalkylated carbo- and heterocycles with high functional group tolerance and excellent enantioselectivities. Our mechanistic studies indicate an overall retention of the stereochemistry during this unprecedented trifluoromethylation reaction.

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, analytical data (^{1}H-NMR, ^{13}C-NMR, MS, IR, and $[\alpha]_D$) for all new compounds, crystal structure data (PDF)

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