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Ligand-Dependent Regiodivergent Enantioselective Allylic Alkylations of α-Trifluoromethylated Ketones

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Cite This: *Org. Lett.* 2021, 23, 2443−2448 Read Online

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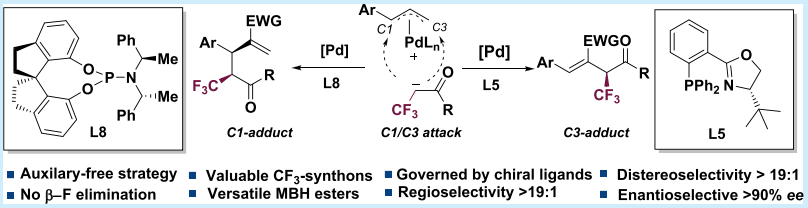

ABSTRACT: The asymmetric introduction of the CF_3 unit is a powerful tool for modifying pharmacokinetic properties and slowing metabolic degradation in medicinal chemistry. A catalytic and enantioselective addition of α-CF_3 enolates allows for expeditious access to functionalized chiral building blocks with CF_3-containing stereogenicity. The computational studies reveal that the choice of ligand in a designed palladium-complex system regulates the regioselectivity and stereoselectivity of the asymmetric allylic alkyation of α-CF_3 ketones and Morita−Baylis−Hillman adducts.

The wide application of fluorinated compounds in agrochemicals, pharmaceuticals, and materials science has triggered every endeavor to develop efficient methods for selective incorporation of a trifluoromethyl group into organic molecules.[1] The reliable methodology to access CF_3-containing stereogenicity is still underdeveloped in the context of matured asymmetric synthesis.[2] The electrophilic trifluoromethylation of ketones has shown low reactivity and enantioselectivity, even with the aid of a chiral auxiliary (Figure 1a).[3] Meanwhile, the exploitation of α-CF_3 enolate as an active nucleophile for enantioselective C−C bond-forming reactions is a viable strategy for pursuing this end, allowing rapid access to densely functionalized chiral building blocks.[4] Despite the significant advances in enolate-based chemistry over the past decades,[5] α-CF_3 enolates have only been scarcely explored because of the M−F elimination of their metal enolates.[6] Electrophilic alkylation of prefunctionalized α-CF_3 ketones provided remarkable outcomes by the use of chiral auxiliaries or directing groups (Figure 1b).[7] In contrast, the direct asymmetric alkylation of naked α-CF_3 ketones represents unmet challenges in terms of reactivity and selectivity that has not been addressed.[8]

Despite the broad application of Morita−Baylis−Hillman (MBH) adducts as functionalized allylic synthons, good regio- and enantiocontrol of metal-catalyzed C1-selective adducts has not yet been realized.[9,10] The comprehensive studies on palladium-catalyzed AAA reactions by Trost and co-workers revealed that the regioselectivity can be modulated by both sterics and electronics of the ligand.[10] The nucleophilic attack of α-CF_3 enolate from the *Re*/*Si* faces to either terminal of the π-allylmetal complexes would result in a number of stereo-

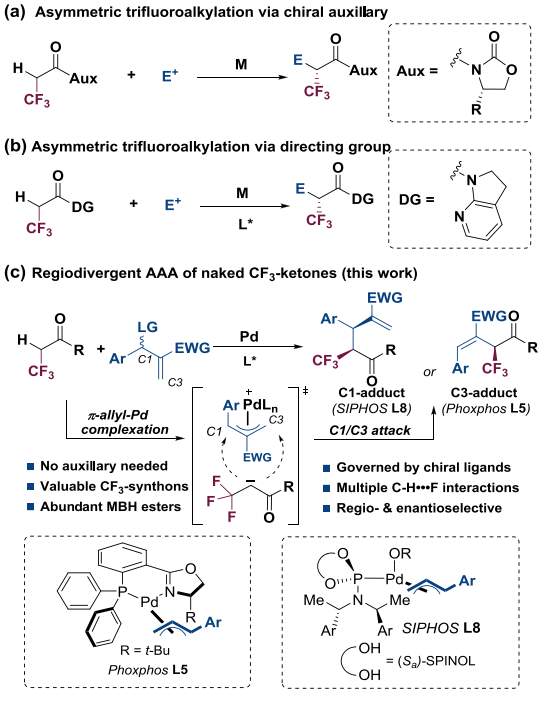

Figure 1. Overview of α-CF_3 enolate chemistry.

Received: January 28, 2021
Published: March 11, 2021

https://dx.doi.org/10.1021/acs.orglett.1c00329
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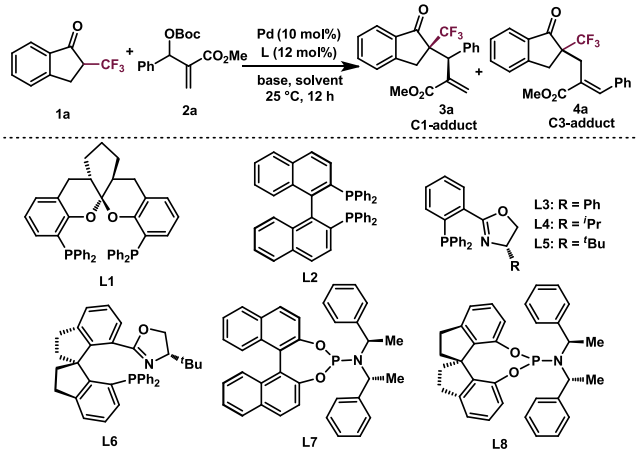
isomers. To overcome the above issues, we have designed a regiodivergent enantioselective allylic allylation of auxiliary-free α-CF_3 ketones with MBH adducts. By only switching the chiral ligands of the palladium complexes, excellent regio- and stereocontrol can be achieved on both C1 and C3 adducts for the construction of CF_3-bearing quaternary centers (Figure 1c).

To determine the suitable conditions for C1-selective allylic alkylation of α-CF_3 ketone **1**, we first studied the reaction of dihydroindenone **1a** and MBH ester **2a** (1.2 equiv) in the presence of Pd_2dba_3 (5 mol %) with a survey of chiral ligand (12 mol %) in THF at room temperature (Table 1). Spiro-type

Table 1. Optimization of the C1-Selective Reaction Conditions[a]



entry	base	ligand	solvent	yield[b] (%)	3a/4a	dr[c]	ee[d] (%)
1	none	L1	THF	85	7:93	>20:1	50
2	none	L2	THF	82	6:94	>20:1	25
3	none	L3	THF	75	12:88	>20:1	44
4	none	L4	THF	84	9:91	>20:1	51
5	none	L5	THF	93	4:96	>20:1	60
6	none	L6	THF	84	6:94	>20:1	−90
7	none	L7	THF	87	35:65	>20:1	−60
8	none	L8	THF	89	85:15	>20:1	97
9	none	L8	DCM	67	48:52	>20:1	85
10	none	L8	toluene	92	87:13	>20:1	98
11	NEt_3	L8	toluene	93	93:7	>20:1	99
12	**DIPEA**	**L8**	**toluene**	**96**	95:5	>20:1	**>99**

[a]Unless otherwise noted, all reactions were performed in solvent (1 mL) at room temperature for 12 h in the presence of **1a** (0.05 mmol), **2a** (0.06 mmol), [Pd] (0.005 mmol), ligand (0.006 mmol), and base (0.10 mmol). [b]Yield of isolated **3a** and **4a**. [c]The values of **3a**/**4a** and diastereomeric ratios of **3a** were determined by ^{19}F NMR analysis of the crude products. [d]The ee values of **3a** were determined by chiral HPLC analysis.

ligand (**L1**) afforded the products in a total of 85% yield in which the C1-adduct **3a** was only 7% with 50% ee (entry 1). When using BINAP (**L2**) and Phoxphos (**L3**−**L5**), low regio- and enantioselectivities for **3a** were obtained (entries 2−5). The reverse of the absolute configuration was obtained with **L6** (entry 6). When switching to monodentate binaphthol-derived phosphoramidite **L7**,[11] an increased ratio of the C1 adduct **3a** was observed (entry 7, 35:65). SIPHOS **L8** resulted in good regioselectivity (85:15) and 97% ee (entry 8). This could due to the electron-withdrawing feature of **L8**. Hence, the reduced electron density on Pd center can lead to the higher contribution of the cationic allyl intermediate, which would lead to the preferred C3-attack.

Further optimization with **L8** showed that using dichloromethane as the solvent did not improve the reaction yield (entry 9). With toluene, the yield increased to 92% (entry 10). By adding 2 equiv of Et_3N, both reaction yields and selectivities were simultaneously improved (entry 11). The best results were obtained with DIPEA (entry 12, 96%, 95:5 for **3a**, > 20:1 dr, 99% ee). Thus, the optimized conditions were selected for further investigation of the C1-selective AAA reaction.

The reaction scope of C1-alkylation was explored using CF_3-ketones **1a** and different MBH esters **2** (Scheme 1). Phenyls bearing both electron-withdrawing and electron-donating

Scheme 1. C1-Selective Asymmetric Allylic Alkylation

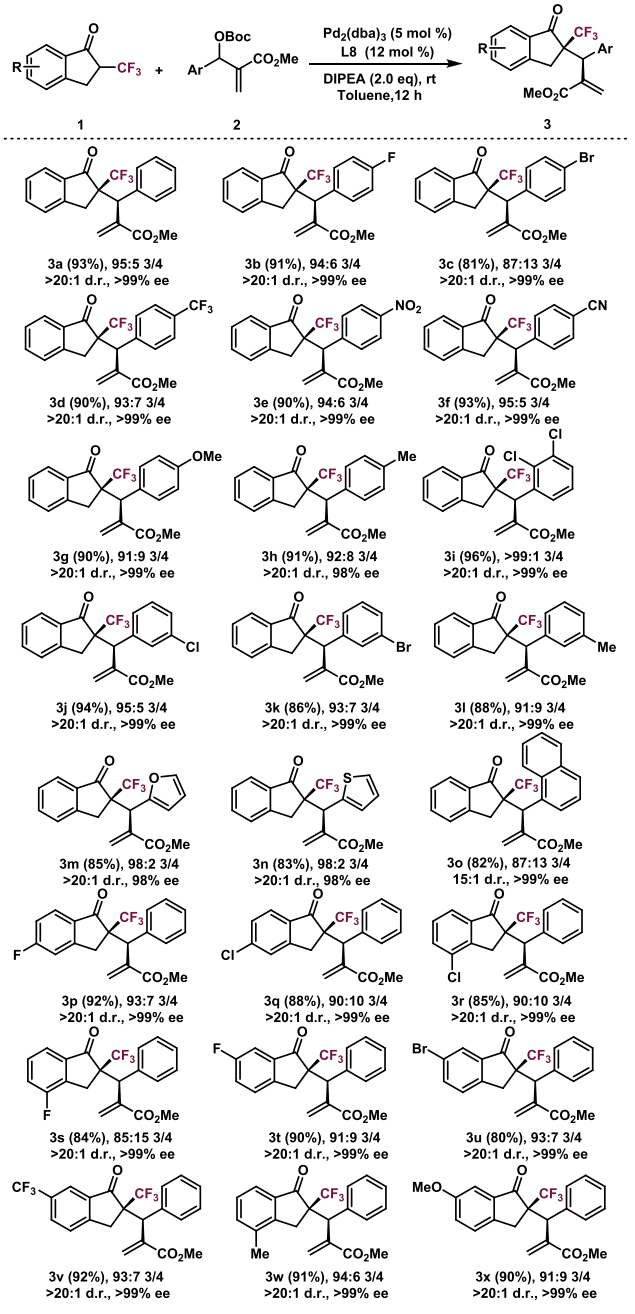


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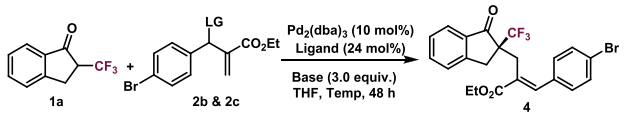
Table 2. Optimization of the C1-Selective Reactions[a]



entry	ligand	base	LG	T (°C)	yield[b] (%)	4/3	E/Z[c]	ee[d] (%)
1	**L1**	none	OBoc	25	85	93:7	8:1	10
2	**L3**	none	OBoc	25	75	88:12	10:1	44
3	**L4**	none	OBoc	25	84	91:9	8:1	0
4	**L5**	none	OBoc	25	93	96:4	13:1	60
5	**L7**	none	OBoc	25	87	65:35	1:6	−40
6	**L5**	none	OAc	25	52	95:5	8:1	80
7	**L5**	none	OAc	−10	40	92:8	15:1	85
8	**L5**	none	OAc	−30	27	95:5	13:1	95
9	**L5**	**Na_3PO_4**	**OAc**	**−30**	**50**	95:5	18:1	**93**
10	**L5**	K_2CO_3	OAc	−30	56	90:10	16:1	85
11	**L5**	NaOAc	OAc	−30	37	92:8	16:1	94
12	**L5**	KOH	OAc	−30	25	90:10	15:1	80

[a]Unless otherwise noted, all reactions were performed in solvent (1 mL) at a certain temperature for 48 h, in the presence of **1** (0.05 mmol), **2** (0.06 mmol), $Pd_2(dba)_3$ (0.005 mmol), **L5** (0.012 mmol), and base (0.15 mmol). [b]Yield of isolated **3** and **4**. [c]The ratios of **4**/**3** and E/Z ratio of 4 were determined by ^{19}F NMR analysis of the crude products. [d]The ee values of **4a** were determined by chiral HPLC analysis.

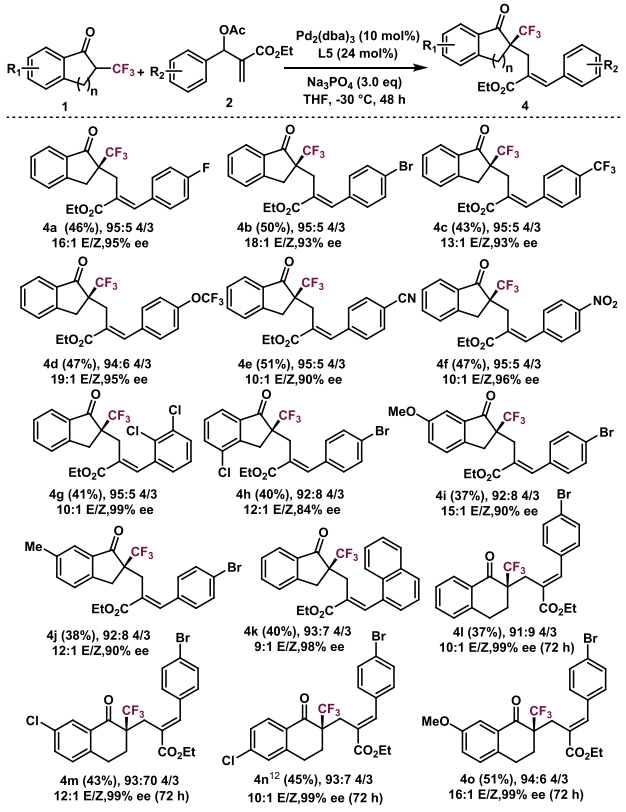
groups could be readily added to **1a** to furnish the CF_3-ketones in high yields with excellent diastereoselectivities and enantioselectivities (**3b**−**3l**). Furan-, thiophene-, and naphthyl-derived MBH esters were tolerated (**3n** and **3o**). Various substituted indenones on benzene ring could also afford the corresponding the C1-adducts (**3p**−**3x**).

For the optimization of C3-selective adduct (Table 2), we slightly modified the reaction conditions for substrate **1a** and MBH ester **2b** (LG = OBoc). With **L1** and **L4**, low ee's were obtained. For **L3** and **L7**, moderate regioselectivity and diastereoselectivity were achieved. **L5** gave high regioselectivity (96:4) and 60% ee (entry 6). Switching the temperature to −10 and −30 °C further improved the diastereoselectivity, affording the C3-selective adduct in 85% and 95% ee, respectively. However, the reaction yields decreased significantly (entries 8 and 9). By adding bases such as Na_3PO_4, K_2CO_3, and NaOAc, the reaction yields were improved and the enantioselectivities remained high. KOH was found to be detrimental both to the reaction efficiency and diastereoselectivity.

The reaction scope of asymmetric allylic alkylation is further extended to a range of MBH esters with **L5** to generate C3-selective adducts (Scheme 2). MBH esters **2** with an −OAc leaving group and phenyls bearing both electron-withdrawing groups could readily furnish the CF_3-ketones in good yields with high dr and ee's (**4a**−**4j**). Naphthalene-derived MBH esters were also tolerated (**4k**). Using CF_3-substituted tetralones, the corresponding adducts were also formed with equally high diastereoselectivity (**4l**−**4o**).

To gain insight into the regioselectivity, DFT calculations were carried out with M06L/6-311++G(2d,p)-SDD-SMD-(THF)//B3LYP/6-31G(d)-LANL2DZ-SMD (THF). For the Pd/**L5** system,[12] calculations suggest an outer-sphere S_N2-type attack is 3.6 kcal/mol lower than that for C1 attack, consistent with the experimental regioselectivity (Figure 2a). Interestingly, the calculated $\Delta\Delta G^{\ddagger}$ value of the nucleophilic addition TS parallels the calculated $\Delta\Delta G^{\ddagger}$ of their corresponding π-allyl-Pd precursor (Figure 2b) with 2.4 kcal/mol energy difference. Thus, the relative stability of the π-allyl-Pd complexes preserved in the subsequent nucleophilic addition

Scheme 2. C3-Selective Asymmetric Allylic Alkylation



TSs and thus dictates the regioselectivity of the Pd/**L5** system. A closer look at Pd−allyl complexes reveals longer C−Pd distances in C1-attack precursor, indicating a looser Pd−allyl binding. This is likely the result of the trans influence of phosphine on the PHOX ligand as well as the delocalization of positive charges on C1 by the conjugated phenyl group. As shown in Figure 2c, the back-donation interaction involving the d orbital of the Pd center and n−π orbital of the allyl moiety favors C3-attack precursor (−5.90 vs −5.79 eV on HOMOs). For more details, see the Supporting Information.

https://dx.doi.org/10.1021/acs.orglett.1c00329
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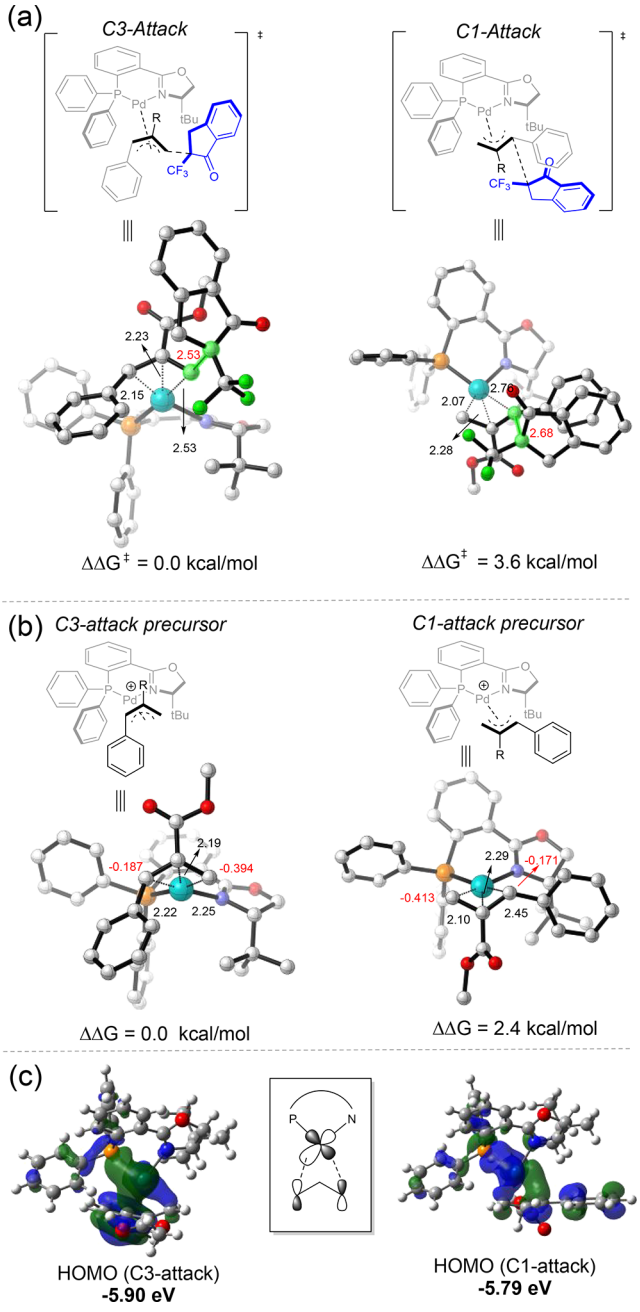
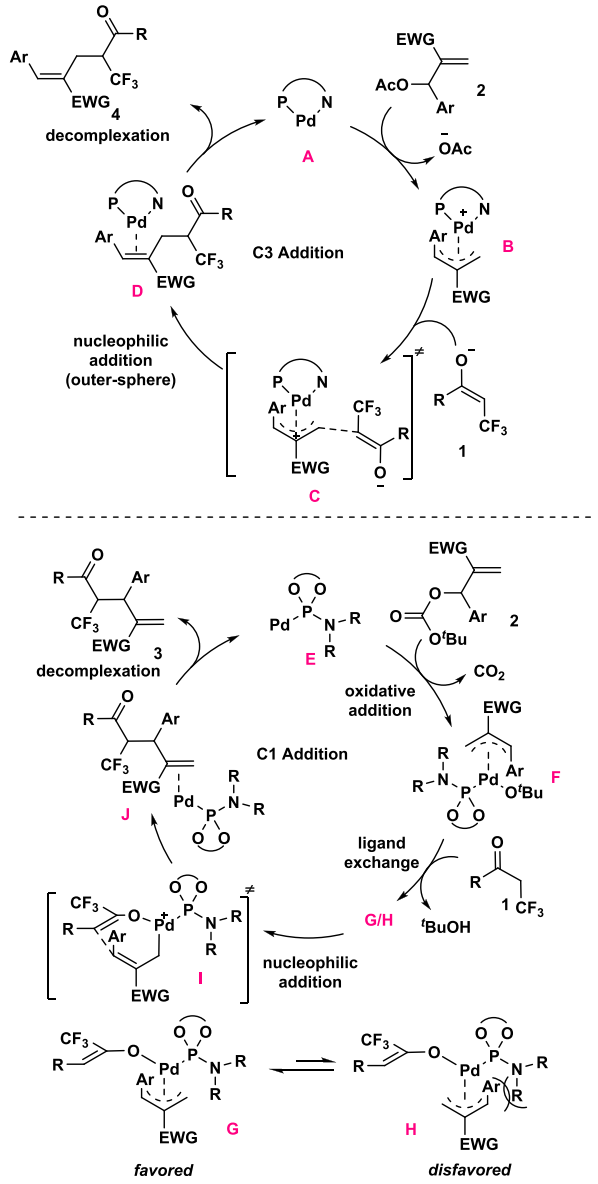


Figure 2. (a) Transition states and their relative free energy of C1/C3 attack of the Pd/**L5** system. (b) π-allyl-Pd precursors and their relative free energy. NBO charges on terminal carbons are marked in red. (c) HOMO of π-allyl-Pd precursors.

The plausible reaction pathways based on previous reports[13] and computational studies are illustrated in Scheme 3. The AAA process was initiated by the coordination of Pd−L* complex to the MBH ester followed by oxidative addition to generate Pd−π allyl species. Subsequent nucleophilic addition of α-CF_3 enolate to the Pd−π allyl species at the C1- or C3-position afforded trifluoromethylated ketones depending on the ligand-regulated process. The final decomplexation releases the corresponding product **3**/**4** and regenerate palladium catalysts. The key selectivity deviation is originated from each catalytic pathway using bidentate or monodentate ligand. For the bidentate Phoxphos **L5**, complexation of A with MBH ester and oxidative addition generated Pd−π allyl species **B** because

Scheme 3. Proposed Mechanism



B is stable enough and ligand exchange between the leaving group and substrate **1** in Pd/**L5** system is not likely to occur. Hence, nucleophilic addition of CF_3enolate to **B** from outer-sphere affords C3-selective intermediate **D**. For the monodentate SIPHOS ligand **L8**, only one phosphoramidite ligand can coordinate to the metal center of the allylpalladium complexes.[14] Thus, a similar oxidative addition process occurs first. The following decarboxylation of the Boc group releases ^{t}BuO, and the Pd−^{t}BuO complex **F** is obtained.[15] Here, an equilibrium of ligand exchange between the CF_3 enolate and ^{t}BuO controls the regioselectivity of the product. Configuration **G** with less steric hindrance against the Ar group of MBH ester is more favorable than H, which explains the C1 selectivity for SIPHOS **L8**.

In summary, we have developed a highly tunable ligand-regulated regiodivergent asymmetric allylic alkylation of fluorinated ketones with MBH adducts. The choices of ligand in the palladium catalytic systems turn out to be critical for both reactivity and selectivity for the construction of the CF_3-containing quaternary stereocenters. This protocol could

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access to a variety of fluorine-bearing motifs with high efficiency and selectivity.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00329.

Experimental procedures, compound characterization data, and NMR spectra (PDF)

Accession Codes

CCDC 1911158 and 2009810 contain 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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Author Contributions

#Y.Z. and Y.N. contributed equally to this work.

Notes

The authors declare no competing financial interest.

The preprint manuscript was deposited with Research Square. DOI: 10.21203/rs.3.rs-110638/v1.

■ ACKNOWLEDGMENTS

This work was funded by the National Natural Science Foundation of China (Nos. 21772085, 21971107, 22071101), the Fundamental Research Funds for the Central Universities (Nos. 020514380220, 020514380131, 020514913412, 020514913214), Natural Science Foundation of Jiangsu Province (BK20200610) and Postdoctoral Science Foundation of China (2019M661720). We also thank Jiangsu Provincial Key Laboratory of Photonic and Electronic Materials at Nanjing University for support. Professor Hon Wai Lam at University of Nottingham is gratefully acknowledged for helpful discussion.

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https://dx.doi.org/10.1021/acs.orglett.1c00329
Org. Lett. 2021, 23, 2443−2448