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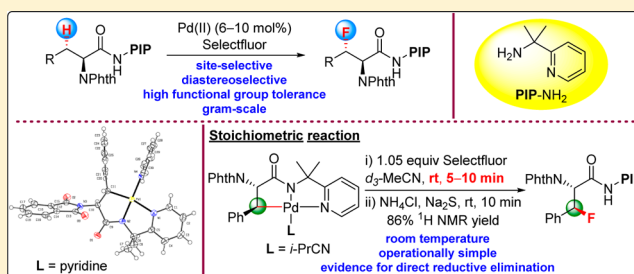
Stereoselective Synthesis of Chiral β -Fluoro α -Amino Acids via Pd(II)-Catalyzed Fluorination of Unactivated Methylene C(sp³)–H Bonds: Scope and Mechanistic Studies

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S Supporting Information

ABSTRACT: The synthesis of fluorinated complex molecules via direct C(sp³)–H fluorination is attractive yet remains challenging. Here we describe the Pd(II)-catalyzed fluorination of unactivated methylene C(sp³)–H bonds by an inner-sphere mechanism. This method allows the site- and diastereoselective fluorination of β -methylene C(sp³)–H bonds of α -amino acid derivatives. A range of substrates containing both aliphatic and benzylic C(sp³)–H bonds were compatible with this protocol, leading to an array of β -fluorinated α -amino acids. Stoichiometric fluorination of an isolated palladacycle intermediate takes place rapidly under very mild reaction conditions (room temperature, 5–10 min). Data from preliminary mechanistic studies are consistent with direct C–F reductive elimination from a high-valent intermediate.



1. INTRODUCTION

The incorporation of fluorine into organic molecules can dramatically affect their physicochemical and biological properties and is now a common strategy for modulating the properties of chemical leads in drug discovery.¹ Roughly 20% of pharmaceuticals and 40% of agrochemicals contain at least one fluorine atom.^{1f} As an important class of fluorinated compounds, β -fluoro α -amino acids (β F-AAs) are of particular importance because of their potential applications as enzyme inhibitors, drugs, and probes.² In addition, ¹⁸F-labeled amino acids are important radiotracers in positron emission tomography (PET) that target the increased rates of amino acid transport that occurs in numerous tumor cells.^{2c} Given these promising applications in medicine and biology, the synthesis of β F-AAs has been the subject of intense research efforts.³ However, the majority of methods require multiple synthetic steps and purifications, exhibit limited substrate scope and poor functional group tolerance, or employ expensive chiral auxiliaries or catalysts. In this context, an attractive and straightforward strategy would be direct C(sp³)–H fluorination of readily available, optically active α -amino acids.⁴

Although there are many methods for the incorporation of a fluorine atom through functional groups transformation,⁵ direct fluorination of aliphatic C(sp³)–H bonds remains undeveloped.⁶ Historically, electrophilic C–H fluorination of hydrocarbons with elemental fluorine has been extensively studied by Rozen, Sandford, and Chambers.⁷ Although useful in certain contexts, these methods suffer from limitations: requiring toxic F₂ gas, demonstrating poor functional group tolerance and site-selectivity, and being operationally inconvenient to execute. Recently, the seminal contributions of Groves^{8a} and Lectka^{8b} have inspired a number reports on site-selective fluorination of

C(sp³)–H bonds using a free-radical strategy (Figure 1a).⁸ In general, these strategies were proposed to proceed through the outer-sphere mechanism,⁹ in which stabilized alkyl radicals were generated by the employment of metal catalysts, organic photocatalysts, or photosensitizers. Among these examples, several challenges have persisted, including narrow substrate scope, poor selectivity, and low yields, which have hampered synthetic applications in complex molecules. As a consequence, these established methods are unsuitable for the stereoselective synthesis of chiral β F-AAs.¹⁰

In 2006, Sanford and co-workers reported a pioneering study on Pd(II)-catalyzed *ortho*-C–H fluorination directed by pyridyl groups using electrophilic fluorinating reagents (F⁺ sources).¹¹ Further experimental and mechanistic studies revealed that C–F reductive elimination from high-valent Pd(IV) intermediates may be involved in the catalytic cycle.¹² Subsequently, the Yu group reported the Pd(II)-catalyzed fluorination of aromatic C(sp²)–H bonds of triflamide-protected benzylamines and *N*-perfluoroaryl benzamides.¹³ Recently, Xu reported the nitrate-promoted fluorination of aromatic and olefinic C(sp²)–H bonds directed by oximes.¹⁴ Daugulis has demonstrated the copper-catalyzed fluorination of C(sp²)–H bonds assisted by 8-aminoquinoline and picolinic acid auxiliaries.¹⁵ Among these examples, reactions are generally limited to C(sp²)–H bonds.^{11,13–15} Sanford and co-workers reported an example of Pd-catalyzed benzylic C(sp³)–H fluorination.¹¹ However, the scope was limited to primary benzylic C(sp³)–H bonds in 8-aminoquinoline substrates (Figure 1b). A broadly applicable, mild approach to achieve site- and diastereoselective fluorina-

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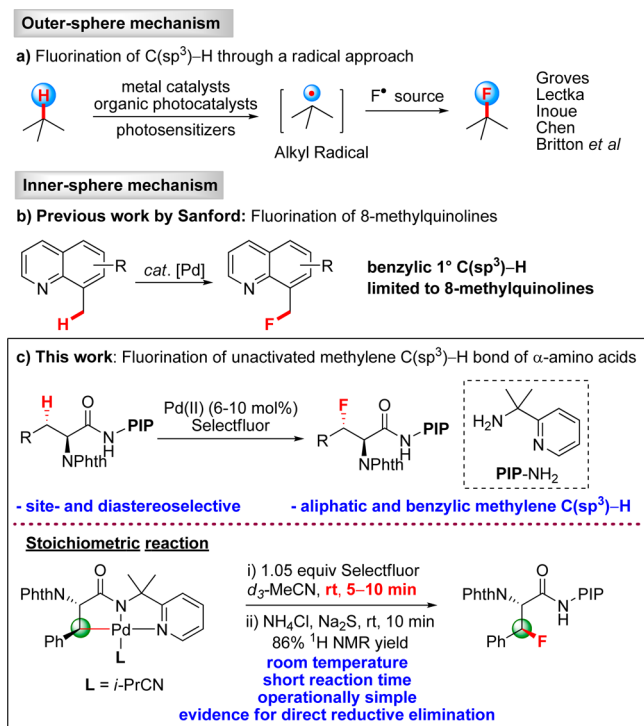


Figure 1. Strategies for fluorination of unactivated C(sp³)-H bonds. (a) Radical C(sp³)-H fluorination (outer-sphere mechanism). (b) Benzylic 1° C(sp³)-H fluorination (inner-sphere mechanism). (c) Unactivated methylene C(sp³)-H fluorination (inner-sphere mechanism).

tion of unactivated C(sp³)-H bond would thus be highly desirable.

Herein, we describe the synthesis of chiral β F-AAs via Pd(II)-catalyzed methylene C(sp³)-H fluorination of α -amino acid derivatives. Notably, this represents the first example of fluorination of β -methylene C(sp³)-H bonds through an inner-sphere mechanism.¹⁶ Stoichiometric fluorination of an isolated palladacycle intermediate takes place rapidly under very mild reaction conditions (room temperature, 5–10 min). Data from preliminary mechanistic studies are consistent with direct C–F reductive elimination from a high-valent intermediate (Figure 1c).^{12d}

2. RESULTS AND DISCUSSION

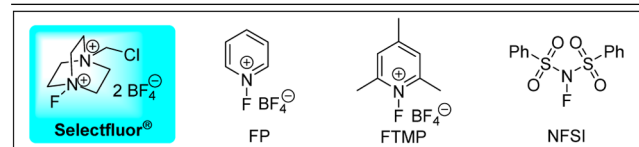
2.1. Fluorination of Benzylic Methylene C(sp³)-H of α -Amino Acids. Direct fluorination of unactivated methylene C(sp³)-H bonds remains a tremendous challenge because of the inherently low reactivity of methylene C(sp³)-H bonds and because C–F reductive elimination is typically kinetically disfavored.^{6,17} Inspired by the seminal work of Daugulis on the Pd-catalyzed functionalization of methylene C(sp³)-H bonds with *N,N*-bidentate directing groups,^{18,19} we recently developed a bidentate auxiliary derived from 2-(pyridine-2-yl)-isopropylamine (PIP-amine), which is easily attachable and removable and has been found to exhibit superior reactivity in the activation of methylene C(sp³)-H bonds.^{20,21} We thus hypothesized that the PIP directing group would prove beneficial in the proposed methylene C–H fluorination. Our rationale was as follows: (1) Previous DFT calculations and experimental studies revealed that the presence of a *gem*-dimethyl group in the PIP auxiliary can facilitate otherwise

difficult cyclopalladations.^{20a,22} (2) Gagne reported that steric congestion around a high-valent Pt(IV) center dramatically accelerated C–F reductive elimination over competing β -hydride elimination.²³ We reasoned that the sterically bulky PIP directing group could facilitate an otherwise kinetically disfavored C–F reductive elimination.

To test this hypothesis, we began our investigation using *N*-phthaloyl phenylalanine derivative **1a** as a model substrate.²⁴ We were delighted to find that desired product **2a** could be obtained in 8% yield in the presence of 10 mol % Pd(OAc)₂ when acetonitrile was used as the solvent and Selectfluor was used as the F⁺ reagent (Table 1, entry 1).²⁵ Subsequent

Table 1. Evaluation of Reaction Conditions for Benzylic C(sp³)-H Fluorination

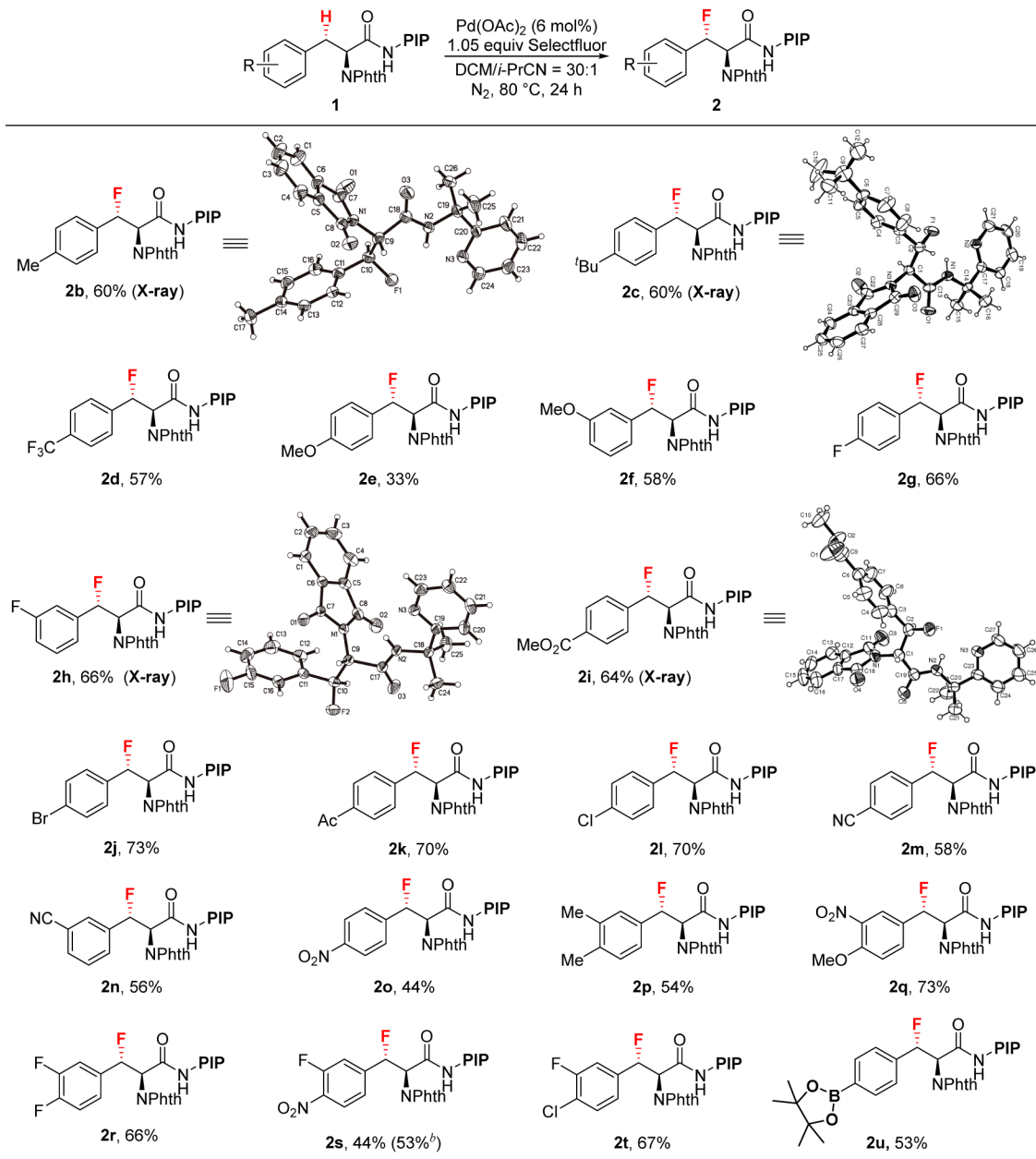
Entry	Pd(OAc) ₂	"F ⁺ " reagent	Solvent	Yield (%) ^a	RSM (%) ^b
1	10 mol %	Selectfluor	MeCN	8	15
2	10 mol %	Selectfluor	Toluene	22	51
3	10 mol %	Selectfluor	DCM	28	40
4	10 mol %	Selectfluor	DCM/MeCN = 30:1	51	12
5	10 mol %	Selectfluor	DCM/ <i>i</i> -PrCN = 30:1	64	15
6	6 mol %	Selectfluor	DCM/ <i>i</i> -PrCN = 30:1	73 (65) ^c	21
7	2 mol %	Selectfluor	DCM/ <i>i</i> -PrCN = 30:1	53	35
8	6 mol %	FP	DCM/ <i>i</i> -PrCN = 30:1	10	9
9	6 mol %	FTMP	DCM/ <i>i</i> -PrCN = 30:1	70	21
10	6 mol %	NFSI	DCM/ <i>i</i> -PrCN = 30:1	10	61



^aYield was determined by ¹H NMR of the crude reaction mixture using dimethyl malonate as an internal standard. ^bRSM = recovered starting materials. ^cIsolated yield in parentheses. DCM = dichloromethane.

investigations revealed that the use of a mixture of DCM and *i*-PrCN (v/v = 30:1) led to an improvement in yield (64%, entry 6). The yield further increased to 73% when the loading of Pd(OAc)₂ was reduced to 6 mol %, presumably because of suppression of catalyst-mediated substrate and product decomposition (entry 7, 65% isolated yield). After screening various commercially available electrophilic fluorinating reagents, such as FP, FTMP, and NFSI, Selectfluor was found to be superior (entries 8–10). Consistent with precedents, *N*-phthaloyl was determined to be the optimal protecting group for the fluorination reaction.²⁴

As illustrated in Table 2, this novel fluorination protocol allows for the direct incorporation of fluorine into a broad range of substituted phenylalanine derivatives. Both electron-donating and -withdrawing substituents at different positions on the aryl ring are well-tolerated, providing the corresponding fluorinated products in satisfactory yields. A variety of functional groups, such as acetyl (**2k**), methoxycarbonyl (**2i**), cyano (**2m** and **2n**), nitro (**2o**), and pinacolborane (**2u**) moieties, were compatible with the optimized conditions. Moreover, halides, such as fluoride, chloride, and bromide, remained intact during the reaction, affording the desired

Table 2. Pd(II)-Catalyzed Fluorination of Benzylic Methylene C(sp³)-H Bonds^a

^aReaction conditions: **1** (0.3 mmol), Pd(OAc)₂ (6 mol %), Selectfluor (1.05 equiv), *i*-PrCN (100 μL), and DCM (3 mL), 80 °C, 24 h. Isolated yield. The absolute and relative stereochemistry of **2i** was determined by single-crystal X-ray diffraction; other products were assigned by analogy. The *syn*-diastereoisomer could not be detected. ^b10 mol % Pd(OAc)₂.

products in moderate to good yields (**2g**, **2h**, **2j**, **2l**, and **2r–2t**). Importantly, all of the reactions described in this manuscript were set up on the benchtop, without the need for an inert-atmosphere glovebox or rigorously moisture-free conditions. The reaction was found to be highly diastereoselective, affording a single diastereoisomer as the product. The relative and absolute stereochemistry of the fluorinated products was unambiguously determined by single-crystal X-ray diffraction of **2b**, **2c**, **2h**, and **2i**. CCDC 1404395 (**2b**), CCDC 1404394 (**2c**), CCDC 1404396 (**2h**), CCDC 1040924 (**2i**), and CCDC 1049486 (**14**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif. It was found that the *N*-

phthaloyl group and the newly incorporated fluorine atom are oriented anti to one another, consistent with previous reports.^{18b,24}

2.2. Fluorination of Aliphatic Methylene C(sp³)-H of α-Amino Acids. The successful fluorination of benzylic C(sp³)-H bonds led us to test whether the fluorination protocol could also be applied to aliphatic secondary C(sp³)-H bonds. Gratifyingly, we found that the desired product **4a** was obtained in 35% yield under the established conditions (Table 3, entry 1). Considering the significant effects of acid or acid anhydride additives on C–H functionalization reactions,²⁶ we then surveyed the fluorination with a broad range of these additives (entries 2–18). Acid additives did not improve the efficiency (entries 2–5). When 0.2 equiv of Ac₂O was used, the

Table 3. Additive Screening in the Fluorination of Aliphatic Methylene C(sp³)-H Bonds

entry	additive	yield (%) ^a	entry	additive	yield (%) ^a
1	none	35	10	BAH	40
2	AcOH	25	11	2-Cl BAH	33
3	PivOH	30	12	4-AcNH-BAH	36
4	4-MeO-PhCO ₂ H	33	13	4-NO ₂ -BAH	30
5	TFA	13	14	2-MeO-BAH	32
6	Ac ₂ O	39	15	2-Me-BAH	50
7	succinic anhydride	27	16 ^b	2-Me-BAH	54 (46) ^c
8	isobutyric anhydride	43	17	2,4,6-tri-Me-BAH	29
9	Boc ₂ O	33	18	2-Ph-BAH	30

^aYield was determined by ¹H NMR of the crude reaction mixture using dimethyl malonate as internal as standard. ^bPd(OPiv)₂ instead of Pd(OAc)₂, 24 h. ^cIsolated yield in parentheses. BAH = benzoic anhydride

Table 4. Pd(II)-Catalyzed Fluorination of Aliphatic Methylene C(sp³)-H Bonds^a

 4a , 46%, 99% ee (23%)	 4b , 33% (37%)	 4c , 32% (42%)	 4d , 45% (15%)
 4e , 39% (14%)	 4f , 32% (34%)	 4g , 42% (26%)	 4h , 46% (25%)
 4i , 41% (25%)	 4j , 44% (24%)	 4k , 37% (31%)	

^aThe *syn*-diastereoisomer could not be detected. Yields of recovered starting materials were presented in parentheses.

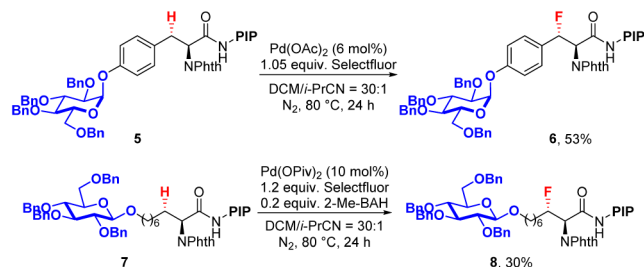
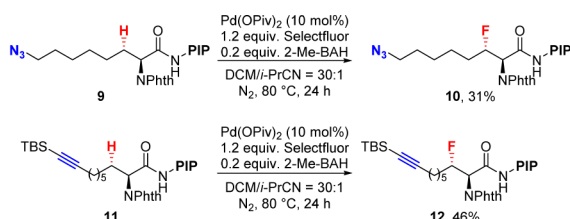
yield was improved slightly (entry 6, 39% yield). Among the various acid anhydride additives, 2-methylbenzoic anhydride (2-Me-BAH) was optimal (entry 7–15). Pd(OPiv)₂ proved to be a superior catalyst, giving the desired product in 54% yield (entry 16). Other more sterically hindered acid anhydrides, such as 2,4,6-tri-Me-BAH and 2-Ph-BAH, resulted in reduced yields (entries 17 and 18). (See Table S1–S5 in the Supporting Information for detailed optimization.) The exact role of this additive remains unclear at this stage. Importantly, the desired product **4a** was obtained without any observable epimerization (99% ee). (See the Supporting Information for details.)

A large number of protected natural and unnatural amino acid derivatives containing the PIP directing group were compatible with the fluorination protocol, providing the desired products in moderate yields (Table 4). Sterically hindered substrates containing adjacent secondary alkyl groups were reactive, but the yields were slightly diminished (**4c**). We were also pleased to observe that several synthetically useful functional groups, such as silyl-protected alcohols (**4h** and **4j**), a cyclic acetal (**4i**), and an alkene (**4k**), were also tolerated under the standard conditions.

2.3. Synthetic Applications. Because the palladium-catalyzed C–H fluorination protocol was found to tolerate a diverse collection of functional groups, we further assessed the potential of this reaction for fluorination of secondary C(sp³)-H bonds in more complex molecules. We first conducted the palladium-catalyzed fluorination of a pair of glyco-amino acids, which are fundamental components of biologically important glycopeptides and glycoproteins. Glycopeptides play a critical role in the nucleocytoplasmic transport and are widely used as antibiotics and therapeutics to treat Alzheimer's disease.²⁷ Because most glycoproteins are heterogeneous, their isolation from natural sources is frequently very difficult and time-consuming. The chemical synthesis of various homogeneous glycopeptides and glycoproteins therefore is the most reliable and preferred method for corresponding biological studies. As shown in Scheme 1a, two representative glyco-amino acid derivatives bearing Bn-protected *O*-glucose (**5** and **7**) were subjected to C–H fluorination, affording the desired fluorinated glyco-amino acids **6** and **8** (53 and 30% yield, respectively). On the basis of these results, we anticipate that this C–H fluorination protocol should be suitable for the

Scheme 1. Application of Direct C(sp³)-H Fluorination to Complex Molecules

a) Direct fluorination of glyco-amino acids

b) Direct fluorination of α -amino acids bearing "clickable" functional groups.

synthesis of diverse fluorinated glyco-amino acids, which are valuable building blocks for the synthesis of biologically important glycopeptides. The late-stage introduction of a fluorine atom into glycopeptides or glycoproteins opens the opportunity for noninvasively imaging relevant metabolic changes in vivo by PET.^{2c}

Furthermore, the ability to incorporate "clickable" functional groups, such as an azide (**10**) and a terminal alkyne (**12**), is especially useful, because these functional groups could be used to attach biologically important fluorescent tags for visualization and identification of cellular targets of bioactive peptides and proteins (Scheme 1b).

The operationally convenient nature of this transformation makes it amenable to scale up. Thus, a gram-scale reaction was performed, and the fluorinated product **2a** was obtained in 69% yield (0.89 g, Scheme 2).

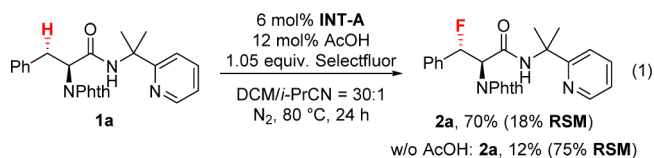
The ability to easily remove the PIP auxiliary from the final products is crucial for synthesis applications of this reaction. Thus, with the scope of the C(sp³)-H fluorination firmly established, we next sought to demonstrate that the PIP auxiliary could serve as a versatile masked carboxylic acid. Previously, we reported that the PIP directing group could be easily removed through a mild nitrosylation/hydrolysis sequence.^{18b} In the present manuscript, an additional, complementary protocol was developed to remove the PIP auxiliary without affecting the newly introduced fluorine atom. This two-step, one-pot protocol involves in situ esterification of a highly electrophilic pyridinium triflate intermediate.²⁸ Application of this procedure allowed secondary amide **2a** to be directly converted to corresponding *anti*- β -fluoro- α -amino acid methyl ester **13**, in 52% yield with 98.8% ee (Scheme 2). This result also suggests the potential of attacking the

intervening PIP-pyridinium triflate intermediate with other nucleophilic reagents, and research on this topic is ongoing.

2.4. Mechanistic Studies. To elucidate the mechanism of this reaction, several experiments were performed (Figure 2). First, we allowed **1a** to react with 1 equiv. Pd(OAc)₂ in DCM at room temperature and were able to isolate the corresponding palladacycle intermediate (INT-A). The structure of INT-A was characterized by NMR spectroscopy. INT-A is stable at ambient temperature without notable decomposition; however, attempts to obtain X-ray quality crystal were unsuccessful. The analogous complex **14** was synthesized from INT-A via ligand exchange with pyridine, and its structure was unambiguously confirmed by single-crystal X-ray diffraction (Figure 2a). The structure of complex **14** showed a trans orientation of *N*-Phth and the phenyl group.

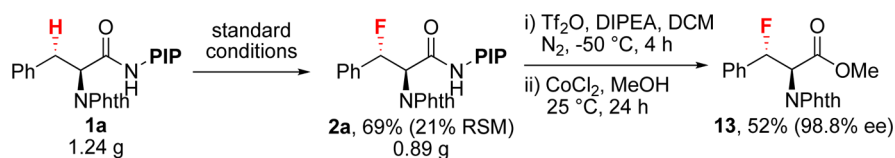
Second, we attempted a stoichiometric reaction of INT-A with 1.05 equiv of Selectfluor in *d*₃-MeCN. We observed that the reaction proceeded rapidly to give INT-C in 78% yield within 5–10 min. The ¹⁹F NMR spectrum of INT-C revealed a singlet at –170.59 ppm, and the ¹H NMR spectrum showed two characteristic hydrogen resonances for the β -H (6.52 ppm, dd, *J*_{H-F} = 46.8 Hz, *J*_{H-H} = 8.8 Hz) and the α -H (5.50 ppm, dd, *J*_{H-F} = 15.6 Hz, *J*_{H-H} = 8.4 Hz; Figures 2b and S4 in the Supporting Information). Treatment of INT-C with an aqueous solution of NH₄Cl and Na₂S provided the fluorinated product **2a** in 86% yield within 10 min. It is worth noting that in the conversion of INT-A to **2a**, the product was generated with retention of configuration, consistent with direct C–F reductive elimination from the palladium center.^{12d,23} The stoichiometric fluorination of palladacycle INT-A is of particular interest, given its potential for use in ¹⁸F-labeling of α -amino acids using [¹⁸F]Selectfluor.²⁹ The present reaction is rapid, highly diastereoselective, and operationally convenient (room temperature, short reaction time, and simple setup). Thus, the stoichiometric version of this reaction could potentially be used to prepare ¹⁸F-labeled amino acids that are difficult to access with conventional methods.³⁰ However, the relatively long time to remove the PIP group (>24 h) might limit its application to the preparation of ¹⁸F-labeled amino acids. Further studies to establish a quick removal of the protecting group and PIP group are ongoing.

Finally, we found that INT-A was a viable precatalyst for C–H fluorination of **1a** (eq 1). In the presence of added catalytic AcOH, **2a** was formed in 70% yield, comparable with the result under the standard conditions.



On the basis of our experimental results and earlier precedents, a catalytic cycle for this directed methylene C(sp³)-H fluorination reaction is proposed in Figure 3. We

Scheme 2. Large-Scale Synthesis and Removal of the PIP Directing Group



a) Synthesis and stoichiometric reaction of INT-A

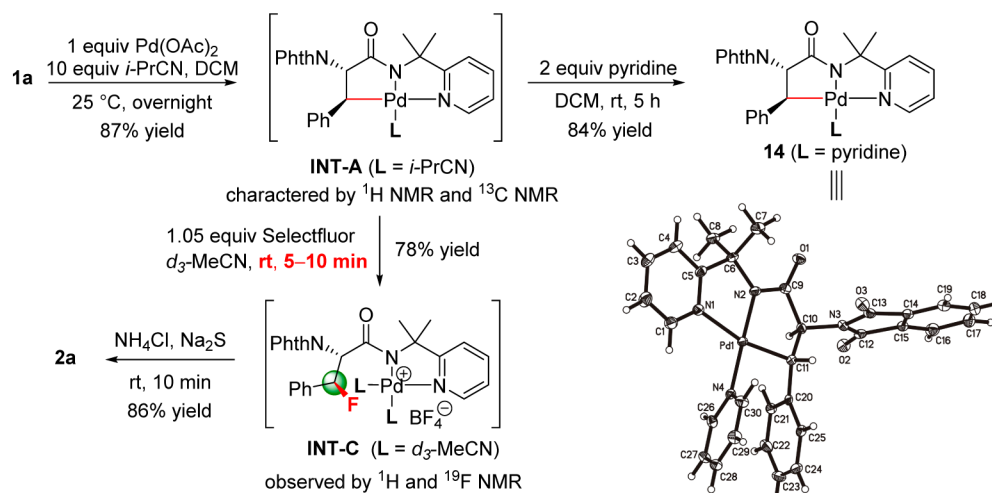
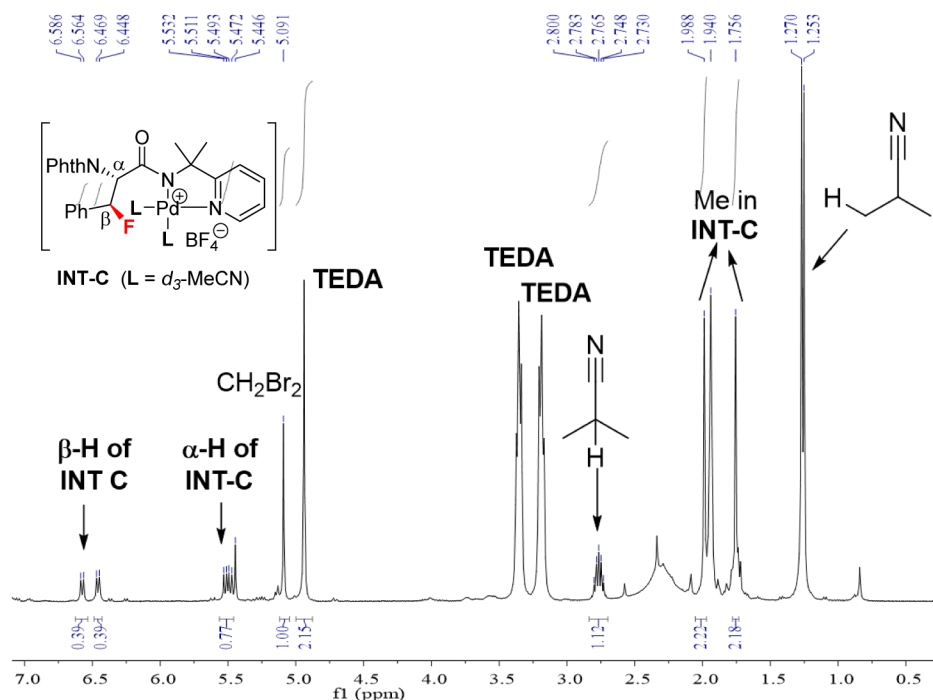
b) Crude ^1H NMR of stoichiometric reaction of INT-A in $d_3\text{-MeCN}$ to generate INT-C

Figure 2. Synthesis and stoichiometric reaction of INT-A.

propose that *i*-PrCN promotes $\text{C}(\text{sp}^3)\text{-F}$ bond formation in several ways. First, it facilitates the formation of the $\text{Pd}(\text{II})$ -palladacycle intermediate (INT-A) by providing a neutral ligand. Second, interaction with the PIP auxiliary destabilizes the cationic, pentacoordinate $\text{Pd}(\text{IV})$ -fluoride complex INT-B through steric crowding, thereby promoting C-F reductive elimination.

3. CONCLUSIONS

In conclusion, we have reported the first example of $\text{Pd}(\text{II})$ -catalyzed fluorination of β -methylene $\text{C}(\text{sp}^3)\text{-H}$ bonds by an inner-sphere mechanism.³¹ A range of substrates containing both aliphatic and benzylic $\text{C}(\text{sp}^3)\text{-H}$ bonds were found to be compatible with this protocol, leading to an array of β -fluorinated α -amino acids. Stoichiometric fluorination of an isolated palladacycle proceeded at room temperature and was

complete in 5–10 min, offering the potential for translation to a radiochemistry setting for preparing ^{18}F -labeled amino acids. Preliminary mechanistic studies are consistent with direct C-F reductive elimination. We anticipate that this $\text{C}(\text{sp}^3)\text{-H}$ fluorination method may enable the synthesis of novel peptide-based drugs and probes for application in medicine and biology.

4. EXPERIMENTAL SECTION

4.1. General Procedure for Fluorination of Benzylic $\text{C}(\text{sp}^3)\text{-H}$ Bonds (GP 2). To a 50 mL Schlenk tube were added 1 (0.3 mmol), $\text{Pd}(\text{OAc})_2$ (4.0 mg, 0.018 mmol), Selectfluor (111.6 mg, 0.315 mmol), *i*-PrCN (100 μL), and DCM (3.0 mL). The tube was evacuated under high vacuum, charged with N_2 , and sealed. The mixture was then heated at 80°C for 24 h. After cooling to room temperature, the reaction

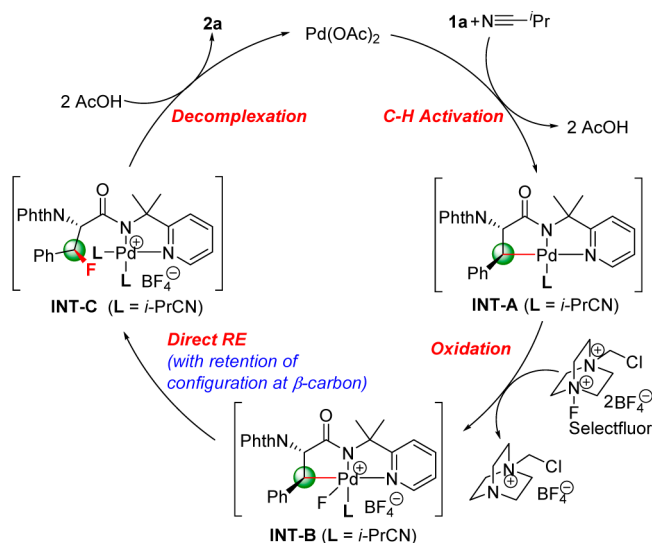


Figure 3. Proposed mechanism.

mixture was diluted with DCM (10 mL) and filtered through a short pad of MgSO₄. After concentration in vacuo, the crude reaction mixture was purified by silica-gel flash chromatography.

4.2. General Procedure for Fluorination of Aliphatic Methylene C(sp³)-H Bonds (GP 3). To a 50 mL Schlenk tube were added 3 (0.15 mmol), Pd(OPiv)₂ (4.6 mg, 0.015 mmol), Selectfluor (63.8 mg, 0.18 mmol), 2-methylbenzoic anhydride (7.6 mg, 0.03 mmol), i-PrCN (50 μL), and DCM (1.5 mL). The tube was evacuated under high vacuum, charged with N₂, and sealed. The mixture was then heated at 80 °C for 24 h. After cooling to room temperature, the reaction mixture was diluted with DCM (10 mL) and filtered through a short pad of MgSO₄. After concentration in vacuo, the crude reaction mixture was purified by silica-gel flash chromatography.

■ ASSOCIATED CONTENT

● Supporting Information

Experimental procedures, spectra data for all new compounds and X-ray for compound 2b, 2c, 2h, 2i, and 14. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b03989.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Kirsch, P. *Modern fluoroorganic chemistry: synthesis, reactivity, applications*, 2nd ed.; Wiley-VCH: Weinheim, Germany, 2013.

- (b) Grushin, V. V. *Acc. Chem. Res.* **2010**, *43*, 160. (c) O'Hagan, D. *Chem. Soc. Rev.* **2008**, *37*, 308. (d) Purser, S.; Moore, P. R.; Swallow, S.; Gouverneur, V. *Chem. Soc. Rev.* **2008**, *37*, 320. (e) Furuya, T.; Kuttruff, C. A.; Ritter, T. *Curr. Opin. Drug Discovery Dev.* **2008**, *11*, 803. (f) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881.
- (2) (a) Salwiczek, M.; Nyakatura, E. K.; Gerling, U. I. M.; Ye, S.; Koks, B. *Chem. Soc. Rev.* **2012**, *41*, 2135. (b) Kukhar, V. P., Soloshonok, V. A., Eds. *Fluorine-Containing Amino Acids: Synthesis and Properties*; John Wiley & Sons: New York, 1995. (c) Huang, C.; McConathy, J. *Curr. Top. Med. Chem.* **2013**, *13*, 871.
- (3) (a) Qiu, X.-L.; Qing, F.-L. *Eur. J. Org. Chem.* **2011**, *18*, 3261. (b) Sutherland, A.; Willis, C. L. *Nat. Prod. Rep.* **2000**, *17*, 621. (c) Qiu, X.-L.; Meng, W.-D.; Qing, F.-L. *Tetrahedron* **2004**, *60*, 6711.
- (4) (a) Noisier, A. F. M.; Brimble, M. A. *Chem. Rev.* **2014**, *114*, 8775. (b) Lu, X.; Yi, J.; Zhang, Z.-Q.; Dai, J.-J.; Liu, J.-H.; Xiao, B.; Fu, Y.; Liu, L. *Chem.—Eur. J.* **2014**, *20*, 15339.
- (5) (a) Watson, D. A.; Su, M.; Teverovskiy, G.; Zhang, Y.; Garcia-Fortanet, J.; Kinzel, T.; Buchwald, S. L. *Science* **2009**, *325*, 1661. (b) Grushin, V. V. *Acc. Chem. Res.* **2010**, *43*, 160. (c) Furuya, T.; Kamlet, A. S.; Ritter, T. *Nature* **2011**, *473*, 470. (d) Hollingworth, C.; Gouverneur, V. *Chem. Commun.* **2012**, *48*, 2929.
- (6) (a) Ma, J.-A.; Li, S. *Org. Chem. Front.* **2014**, *1*, 712. (b) Lin, A.; Huehls, C. B.; Yang, J. *Org. Chem. Front.* **2014**, *1*, 434. (c) Li, Y.; Wu, Y.; Li, G.-S.; Wang, X.-S. *Adv. Synth. Catal.* **2014**, *356*, 1412.
- (7) (a) Rozen, S.; Gal, C.; Faust, Y. *J. Am. Chem. Soc.* **1980**, *102*, 6860. (b) Rozen, S. *Acc. Chem. Res.* **1988**, *21*, 307. (c) Chambers, R. D.; Parsons, M.; Sandford, G.; Bowden, R. *Chem. Commun.* **2000**, 959. (d) Standford, G. J. *Fluor. Chem.* **2007**, *128*, 90.
- (8) For representative examples of fluorination of C(sp³)-H bonds using a free radical strategy, see (a) Liu, W.; Huang, X.; Cheng, M.-J.; Nielsen, R. J.; Goddard, W. A., III; Groves, J. T. *Science* **2012**, *337*, 1322. (b) Bloom, S.; Pitts, C. R.; Miller, D. C.; Haselton, N.; Holl, M. G.; Urheim, E.; Lectka, T. *Angew. Chem., Int. Ed.* **2012**, *51*, 10580. (c) Amaoka, Y.; Nagatomo, M.; Inoue, M. *Org. Lett.* **2013**, *15*, 2160. (d) Xia, J.-B.; Zhu, C.; Chen, C. J. *Am. Chem. Soc.* **2013**, *135*, 17494. (e) Halperin, S. D.; Fan, H.; Chang, S.; Martin, R. E.; Britton, R. *Angew. Chem., Int. Ed.* **2014**, *53*, 4690. (f) Bloom, S.; Knippel, J. L.; Lectka, T. *Chem. Sci.* **2014**, *5*, 1175. (g) Xu, P.; Guo, S.; Wang, L.; Tang, P. *Angew. Chem., Int. Ed.* **2014**, *53*, 5955. (h) Xia, J.-B.; Ma, Y.; Chen, C. *Org. Chem. Front.* **2014**, *1*, 468.
- (9) (a) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439. (b) Crabtree, R. H. *J. Chem. Soc., Dalton Trans.* **2001**, 2437.
- (10) Isolated examples of radical C(sp³)-H fluorination of phenylalanine derivatives with limited efficiency and low diastereoselectivity have been reported via the free radical strategy.
- (11) (a) Hull, K. L.; Anani, W. Q.; Sanford, M. S. *J. Am. Chem. Soc.* **2006**, *128*, 7134. (b) McMurtrey, K. B.; Racowski, J. M.; Sanford, M. S. *Org. Lett.* **2012**, *14*, 4094.
- (12) (a) Furuya, T.; Ritter, T. *J. Am. Chem. Soc.* **2008**, *130*, 10060. (b) Ball, N. D.; Sanford, M. S. *J. Am. Chem. Soc.* **2009**, *131*, 3796. (c) Furuya, T.; Ritter, T. *J. Am. Chem. Soc.* **2010**, *132*, 3793. (d) Racowski, J. M.; Gary, J. B.; Sanford, M. S. *Angew. Chem., Int. Ed.* **2012**, *51*, 3414.
- (13) (a) Wang, X.; Mei, T.-S.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 7520. (b) Chan, K. S. L.; Wasa, M.; Wang, X.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2011**, *50*, 9081.
- (14) Lou, S.-J.; Xu, D.-Q.; Xu, Z.-Y. *Angew. Chem., Int. Ed.* **2014**, *53*, 10330.
- (15) Truong, T.; Klimovica, K.; Daugulis, O. *J. Am. Chem. Soc.* **2013**, *135*, 9342.
- (16) For an example of Pd-catalyzed allylic C-H fluorination, see Braun, M.-G.; Doyle, A. G. *J. Am. Chem. Soc.* **2013**, *135*, 12990.
- (17) For recent reviews on C(sp³)-H activation, see (a) Gutekunst, W. R.; Baran, P. S. *Chem. Soc. Rev.* **2011**, *40*, 1976. (b) Baudoin, O. *Chem. Soc. Rev.* **2011**, *40*, 4902. (c) Wasa, M.; Engle, K. M.; Yu, J.-Q. *Isr. J. Chem.* **2010**, *50*, 605. (d) Li, H.; Li, B.-J.; Shi, Z.-J. *Catal. Sci. Technol.* **2011**, *1*, 191. (e) Jazzar, R.; Hitce, J.; Renaudat, A.; Sofack-Kreutzer, J.; Baudoin, O. *Chem.—Eur. J.* **2010**, *16*, 2654. (f) Mo, F.; Tabor, J. R.; Dong, G. *Chem. Lett.* **2014**, *43*, 264.

(18) For pioneering work on the use of bidentate auxiliaries, see (a) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154. (b) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965.

(19) For representative reviews, see (a) Rouquet, G.; Chatani, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 11726. (b) Corbet, M.; De Campo, F. *Angew. Chem., Int. Ed.* **2013**, *52*, 9896. (c) Daugulis, O.; Roane, J.; Tran, L. D. *Acc. Chem. Res.* **2015**, *48*, 1053.

(20) For the development and application of PIP directing group in methylene C(sp³)-H functionalization, see (a) Chen, F.-J.; Zhao, S.; Hu, F.; Chen, K.; Zhang, Q.; Zhang, S.-Q.; Shi, B.-F. *Chem. Sci.* **2013**, *4*, 4187. (b) Zhang, Q.; Chen, K.; Rao, W.-H.; Zhang, Y.-J.; Chen, F.-J.; Shi, B.-F. *Angew. Chem., Int. Ed.* **2013**, *52*, 13588. (c) Zhang, Q.; Yin, X.-S.; Zhao, S.; Fang, S.-L.; Shi, B.-F. *Chem. Commun.* **2014**, *50*, 8353. (d) Chen, F.-J.; Liao, G.; Li, X.; Wu, J.; Shi, B.-F. *Org. Lett.* **2014**, *16*, 5644. (e) Yan, S.-Y.; Liu, Y.-J.; Liu, B.; Liu, Y.-H.; Shi, B.-F. *Chem. Commun.* **2015**, *51*, 4069.

(21) The application of PIP directing group in total synthesis: Dailer, D.; Danoun, G.; Baudoin, O. *Angew. Chem., Int. Ed.* **2015**, *54*, 4919.

(22) Shaw, B. L. *J. Am. Chem. Soc.* **1975**, *97*, 3856.

(23) Zhao, S. B.; Becker, J. J.; Gagne, M. R. *Organometallics* **2011**, *30*, 3926.

(24) N-phthaloyl has been determined to be the optimal protecting group for Pd-catalyzed C-H functionalization of α -amino acids; see (a) Reddy, B. V. S.; Reddy, L. R.; Corey, E. J. *Org. Lett.* **2006**, *8*, 3391. (b) Tran, L. D.; Daugulis, O. *Angew. Chem., Int. Ed.* **2012**, *51*, 5188. (c) Chen, K.; Hu, F.; Zhang, S.-Q.; Shi, B.-F. *Chem. Sci.* **2013**, *4*, 3906. (d) Zhang, S.-Y.; Li, Q.; He, G.; Nack, W. A.; Chen, G. *J. Am. Chem. Soc.* **2013**, *135*, 12135. (e) He, J.; Li, S.; Deng, Y.; Fu, H.; Laforteza, B. N.; Spangler, J. E.; Homs, A.; Yu, J.-Q. *Science* **2014**, *343*, 1216. (f) Chen, K.; Zhang, S.-Q.; Jiang, H.-Z.; Xu, J.-W.; Shi, B.-F. *Chem.—Eur. J.* **2015**, *21*, 3264.

(25) For selected reviews and examples of the use of Selectfluor, see (a) Nyffeler, P. T.; Duron, S. G.; Burkart, M. D.; Vincent, S. P.; Wong, C.-H. *Angew. Chem., Int. Ed.* **2005**, *44*, 192. (b) Yin, F.; Wang, Z.; Li, Z.; Li, C. *J. Am. Chem. Soc.* **2012**, *134*, 10401. (c) Li, Z.; Song, L.; Li, C. *J. Am. Chem. Soc.* **2013**, *135*, 440.

(26) For reviews, see (a) Engle, K. M.; Yu, J.-Q. *J. Org. Chem.* **2014**, *79*, 8927. (b) Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315.

(27) Specker, D.; Wittmann, V. *Top. Curr. Chem.* **2007**, *267*, 65.

(28) (a) Charette, A. B.; Chua, P. *Synlett* **1998**, 163. (b) Bechara, W. S.; Pelletier, G.; Charette, A. B. *Nat. Chem.* **2012**, *4*, 228.

(29) Teare, H.; Robins, E. G.; Kirjavainen, A.; Forsback, S.; Sandford, G.; Solin, O.; Luthra, S. K.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2010**, *49*, 6821.

(30) Lee, E.; Kamlet, A. S.; Powers, D. C.; Neumann, C. N.; Boursalian, G. B.; Furuya, T.; Choi, D. C.; Hooker, J. M.; Ritter, T. *Science* **2011**, *334*, 639.

(31) Zhu, R.-Y.; Tanaka, K.; Li, G.-C.; He, J.; Fu, H.-Y.; Li, S.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2015**, *137*, 7067.