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Palladium(II)-Catalyzed Highly Enantioselective C−H Arylation of Cyclopropylmethylamines

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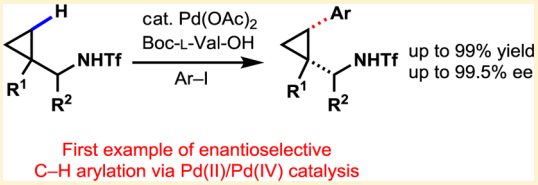
Supporting Information

ABSTRACT: C−H arylation via a Pd(II)/Pd(IV) catalytic cycle has been one of the most extensively studied C−H activation reactions since the 1990s. Despite the rapid development of this reaction in the past two decades, an enantioselective version has not been reported to date. Herein, we report a Pd(II)-catalyzed highly enantioselective (up to 99.5% ee) arylation of cyclopropyl C−H bonds with aryl iodides using mono-*N*-protected amino acid (MPAA) ligands, providing a new route for the preparation of chiral *cis*-aryl-cyclopropylmethylamines. The enantiocontrol is also shown to override the diastereoselectivity of chiral substrates.



1. INTRODUCTION

Although Pd-catalyzed enantioselective activation of prochiral C−H bonds has been demonstrated with both Pd(0)[1,2] and Pd(II)[3−9] catalysts, achieving high levels of reactivity and enantioselectivity using different classes of substrates in these reactions remain a significant challenge. Previously, we demonstrated that Pd(II) complexes coordinated to a chiral mono-*N*-protected amino acid (MPAA) ligand catalyze both C(sp^2)−H[4a−7] and C(sp^3)−H[4a,8−10] activation, leading to a range of enantioselective carbon−carbon, carbon−oxygen, and carbon−halogen bond forming reactions. However, despite Pd(II)/Pd(IV) arylation being one of the most studied C−H activation reactions since the 1990s,[11] an enantioselective version has not been demonstrated to date.

The use of MPAA ligands to accelerate or enable Pd(II)-catalyzed C−H functionalization reactions is crucial for controlling and achieving high enantioselectivities. In 2011, our lab reported a MPAA ligand-catalyzed enantioselective cross-coupling cyclopropyl C−H activation reaction via Pd(II)/Pd(0) catalysis.[8] This report provided early examples of enantioselective coupling reactions, but the scope was limited to carboxylic acid-derived substrates and not compatible with α-hydrogens. The yields and enantioselectivity (up to 93%) remain to be substantially improved. More recently, we also reported enantioselective C(sp^2)−H iodination of benzylamine substrates,[7] but no examples of enantioselective cyclopropyl or other C(sp^3)−H bonds in amines have yet been reported. Compared to the extensive development of β-C−H functionalizations of aliphatic acids using weakly coordinating directing groups,[8−10] C−H functionalization of alkyl amines via weak coordination has been demonstrated with only a single example,[7] highlighting the challenge of developing enantioselective C−H activation reactions of alkyl amines.

In addition to the aforementioned fundamental challenges, the widespread presence of cyclopropyl moieties in drug and agrochemical molecules provided further motivation for us to develop enantioselective arylation of cyclopropyl C−H bonds in cyclopropylmethylamines (Figure 1).[12] Notably, synthesis of chiral *cis*-aryl-cyclopropylmethylamines remains a significant challenge.[13]

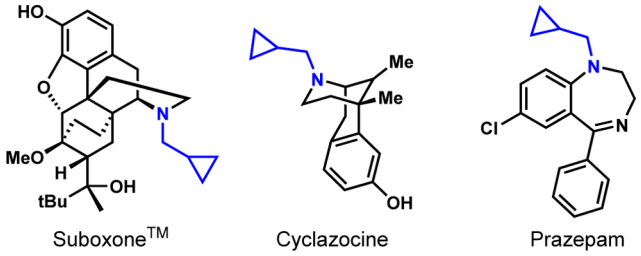


Figure 1. Drugs containing cyclopropylmethylamine moieties.

Herein, we report a Pd(II)-catalyzed enantioselective arylation of cyclopropyl C−H bonds of triflyl-protected cyclopropylmethylamines using a chiral MPAA ligand, demonstrating the first example of C−H arylation via Pd(II)/Pd(IV) catalysis. Both yields (up to 99%) and enantiomeric excesses (up to 99.5%) are superior to prior reports of enantioselective C−H activation reactions involving various modes of catalysis. The observed exclusive monoselectivity is also a highly desirable feature in C−H arylation reactions. This reaction allows for the rapid generation of two chiral centers in a single step, yielding a single *cis*-functionalized enantiomer from a prochiral substrate, and provides a new route for the synthesis of enantiopure *cis*-aryl-cyclopropylmethylamines. Remarkably, the chiral MPAA ligand can also override the innate diastereoselectivity of chiral substrates, thus providing a method to construct four different diastereomers, each with three chiral centers.

Received: December 9, 2014
Published: January 12, 2015

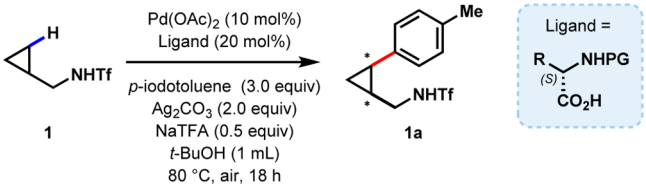
DOI: 10.1021/ja512529e
J. Am. Chem. Soc. 2015, 137, 2042−2046

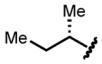
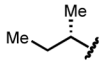
2. RESULTS AND DISCUSSION

Following our recent success in using triflyl-protected amines as a weak coordinating directing group for C(sp^3)−H activation,[10] we first focused on the reaction of **1** with *p*-iodotoluene in the presence of acetyl-*N*-protected amino acids (Table 1, entries 1−5). We found that bulky substituents on the amino acid side chain improved the ees without affecting the yields (entries 1−5). Linear substituents (*n*-alkyl) did not perform as well as branched chains. We then explored the protecting groups on the amino group. Formyl protection performed poorly (entry 6). Increasing bulk did not improve either reactivity or selectivity (entries 7 and 8). The electron-withdrawing trifluoroacetyl group substantially improved the ee to 94.2% (entry 9). Carbamates are most effective for this reaction, affording both high yields and excellent ees (entries 11−15), with Boc-protected valine reaching the highest ee of 98.8% (entry 12). Notably, the high enantioselectivities are obtained in spite of the relatively high reaction temperature (80 °C).

With the optimized reaction conditions in hand, we explored the enantioselective arylation reaction of various substrates with *p*-iodotoluene in the presence of Boc-L-Val-OH (Table 2). The unsubstituted cyclopropylmethylamine **1** gave a single mono-arylated product **1a** in good yield and an excellent ee of 98.8%.

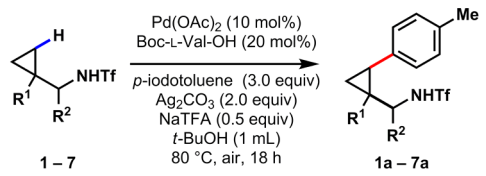
Table 1. Screening of Ligands[a,b]

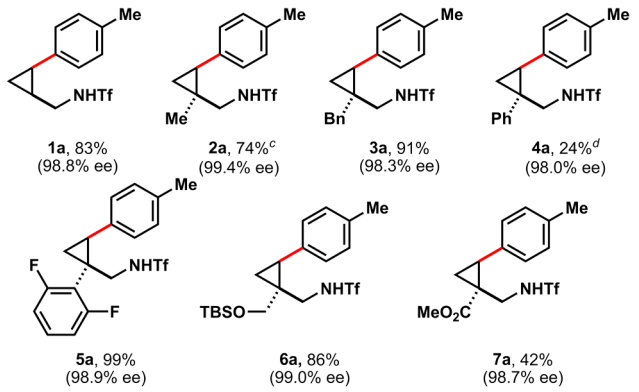


Entry	Ligand R	Ligand PG	Yield (%)[a]	ee (%)
1	Me	Ac	84	76.3
2	*n*-Pr	Ac	89	93.6
3	*i*-Bu	Ac	87	96.0
4		Ac	94	96.0
5	*i*-Pr	Ac	94	87.8
6	*i*-Pr	Formyl	40	55.8
7	*i*-Pr		64	89.9
8	*i*-Pr		37	56.3
9	*i*-Pr		70	94.2
10	*i*-Pr		70	98.1
11		Boc	94	98.5
12	***i*-Pr**	**Boc**	**91**	**98.8**
13	*i*-Pr	Fmoc	93	98.2
14	*i*-Pr	Cbz	85	98.5
15	*i*-Pr	Troc	76	95.3

[a]Experiments were performed with **1** (0.2 mmol), *p*-iodotoluene (0.6 mmol), $Pd(OAc)_2$ (0.02 mmol), Ag_2CO_3 (0.4 mmol), sodium trifluoroacetate (0.1 mmol), and ligand (0.04 mmol) in *t*-BuOH (1 mL) for 18 h at 80 °C under air. [b]Yields were determined by ^1H NMR spectroscopy using CH_2Br_2 as an internal standard.

Table 2. Substrate Scope for the Enantioselective Arylation of Cyclopropylmethylamines[a,b]





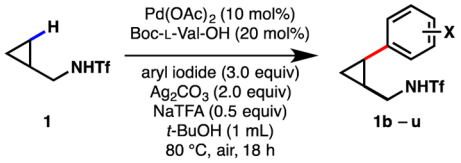
[a]Experiments were performed with substrate (0.2 mmol), *p*-iodotoluene (0.6 mmol), $Pd(OAc)_2$ (0.02 mmol), Ag_2CO_3 (0.4 mmol), sodium trifluoroacetate (0.1 mmol), and Boc-L-Val-OH (0.04 mmol) in *t*-BuOH (1 mL) for 18 h at 80 °C under air. [b]Isolated yields. [c]Substrate **2** was run at 0.179 mmol scale. [d]Substrate **4** was run at 0.25 mmol scale.

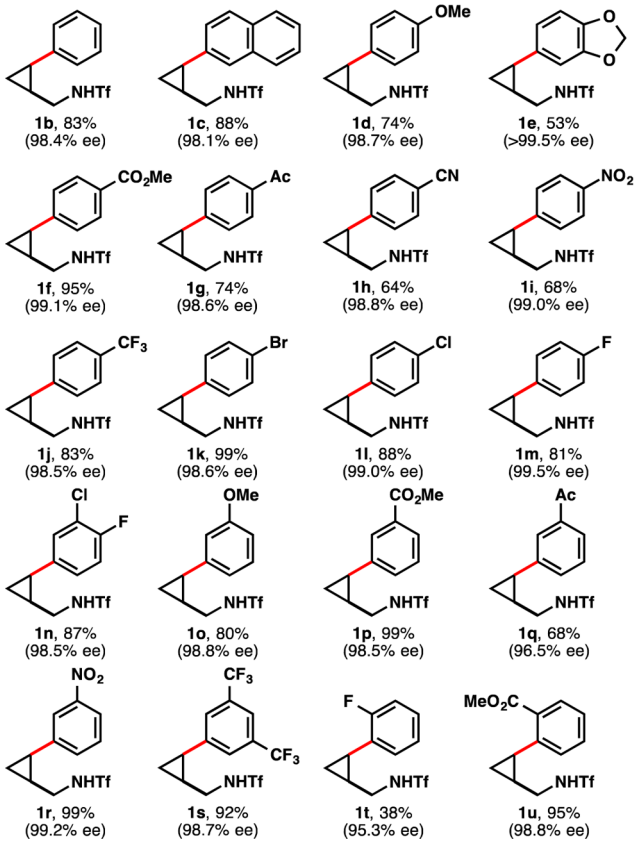
The observed exclusive monoselectivity is rare with C−H arylation reactions using aryl iodides. Excellent mass balance was retained with unreacted starting material fully recovered. In the presence of competing terminal methyl C(sp^3)−H bonds, benzylic C(sp^3)−H bonds, and aryl C(sp^2)−H bonds (substrates **2**−**4**), the regioselectivity for the cyclopropyl C(sp^3)−H bonds remained exclusive. Although the yield was significantly lower for **4a**, mass balance remained excellent and unreacted starting material was fully recovered. To explore this anomaly further, we subjected substrate **5**, an electron-deficient analog of substrate **4**, to the same reaction conditions. To our delight, a nearly quantitative yield of the desired product in 98.9% ee was obtained. We hypothesized that the electron-rich π ring in **4** or **4a** could interfere with the active catalyst, but the electronegative F atoms in the rings in **5** or **5a** reduced the electron density in the rings so that the reaction could proceed. The TBS-protected 1,3-amino alcohol derivative **6** reacted in excellent yield and correspondingly high ee. The *β*-amino acid **7** was compatible with the reaction conditions, and in spite of lower yields, the excellent ee of 98.7% was obtained. The lowered yield of **7a** could be due to possible competing coordination modes of the ester moiety, which may prevent the Pd center from approaching the C−H bond.

In order to derive diversified chiral cyclopropanes from simple cyclopropylmethylamine **1**, it is crucial that a wide range of aryl iodides can be used as coupling partners. We were delighted to find that a wide range of electron-donating and electron-withdrawing substituents in para, meta, and ortho positions on the aryl iodides are compatible affording good to excellent yields (Table 3). In all but one example the enantioselectivity is higher than 98% ee. Electron-donating substituents at the para position of the aryl iodide appeared to lower the yield slightly (products **1d**−**1e**) but did not

DOI: 10.1021/ja512529e
J. Am. Chem. Soc. 2015, 137, 2042−2046

Table 3. Scope of Aryl Iodide Reagents for Enantioselective Arylation of Cyclopropylmethylamines[a,b]



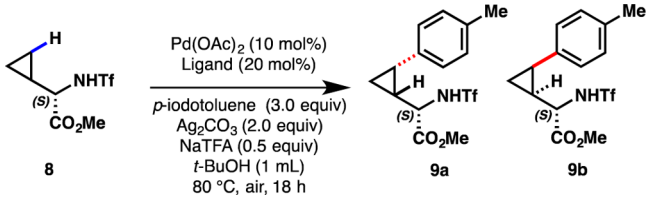


[a]Experiments were performed with **1** (0.2 mmol), aryl iodide (0.6 mmol), $Pd(OAc)_2$ (0.02 mmol), Ag_2CO_3 (0.4 mmol), sodium trifluoroacetate (0.1 mmol), and Boc-L-Val-OH (0.04 mmol) in *t*-BuOH (1 mL) for 18 h at 80 °C under air. [b]Isolated yields.

compromise the ee of the reaction. The highest ee of >99.5% was obtained in the reaction with 1-iodo-3,4-methylenedioxybenzene affording **1e**. Electron-withdrawing substituents such as ester, acetyl, cyano, nitro, and trifluoromethyl groups at the para position gave good yields and excellent ees (**1f–j**). Aryl iodides containing halogens at the para positions performed well (**1k–n**), with yields ranging from 81% to quantitative yields. Both electron-donating (**1o**) and electron-withdrawing substituents such as ester, acetyl, nitro, and 3,5-di-(trifluoromethyl) (**1p–s**) at the meta position afforded good to excellent yields and ees. Although the *o*-fluoro substituent afforded the lowest yield of 38% and lowest ee of 95.3%, we were particularly delighted to find that aryl iodide containing an *o*-ester substituent is an excellent coupling partner (95% yield, 98.8% ee). At this stage of development, heterocyclic iodides are incompatible with the reaction (see Supporting Information).

The excellent enantiocontrol of this ligand prompted us to test whether we can override substrate-controlled diastereoselectivity in substrates containing a chiral center, thereby providing access to all four possible diastereomers. When we subjected the cyclopropylglycine (*S*)-**8** to the optimized conditions with Boc-L-Val-OH (Table 4 entry 1), a >20:1

Table 4. Overriding the Diastereoselectivity[a,b]



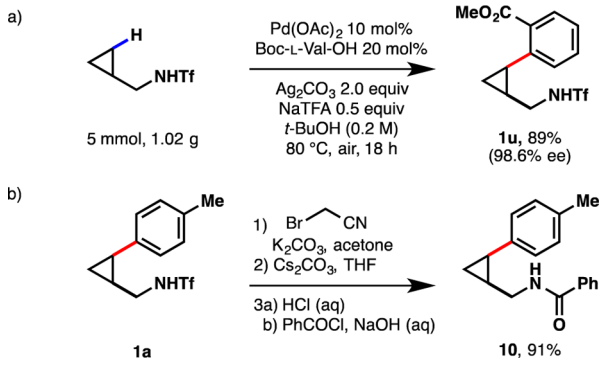
entry	ligand	major diastereomer	yield	dr (major:minor)
1	Boc-L-Val-OH	**9a**	35%	>20:1
2	Boc-Gly-OH	**9a**	11%	2:1
3	Boc-D-Val-OH	**9b**	28%	>20:1

[a]Experiments were performed with **8** (0.2 mmol), *p*-iodotoluene (0.6 mmol), $Pd(OAc)_2$ (0.02 mmol), Ag_2CO_3 (0.4 mmol), sodium trifluoroacetate (0.1 mmol), and ligand (0.04 mmol) in *t*-BuOH (1 mL) for 18 h at 80 °C under air. [b]Isolated yields reported are combined yields of diastereomers. Relative stereoconfiguration is reported.

diastereomeric ratio (dr) favoring product **9a** was obtained. To discern whether the observed stereoselectivity was controlled by the substrate or ligand, we performed a series of control experiments. The use of achiral Boc-Gly-OH (entry 2) resulted in a drastic decrease of stereoselectivity, suggesting that substrate control is not responsible for the observed high selectivity. The use of Boc-D-Val-OH afforded a >20:1 dr favoring the other diastereomer **9b** (entry 3), suggesting that the external chiral ligand is overriding substrate control of stereoselectivity. These results indicate that the careful choice of ligands allows access to all four diastereomers in high dr >20:1. It is therefore possible to enantioselectively arylate racemic **8** to give two diastereomers which can be separated by chromatography or recrystallization. The diminished yield is probably caused by the α-ester group coordinating to the Pd-center and hindering the reaction turnover.

To test the scalability of the reaction, we proceeded to run a gram-scale reaction of the simple cyclopropylmethylamine **1** with methyl-2-iodobenzoate (Scheme 1a). Scaled by 25 times to 5 mmol, the reaction proceeded as expected, affording 89% isolated yield and excellent ee (98.6% ee). The triflamide could also be removed in a two-step procedure to yield the free amine in excellent yields (Scheme 1b). For simplicity in product isolation, we decided to trap the free amine with benzoyl

Scheme 1. Scale up and Deprotection of Triflamide



DOI: 10.1021/ja512529e
J. Am. Chem. Soc. 2015, 137, 2042–2046

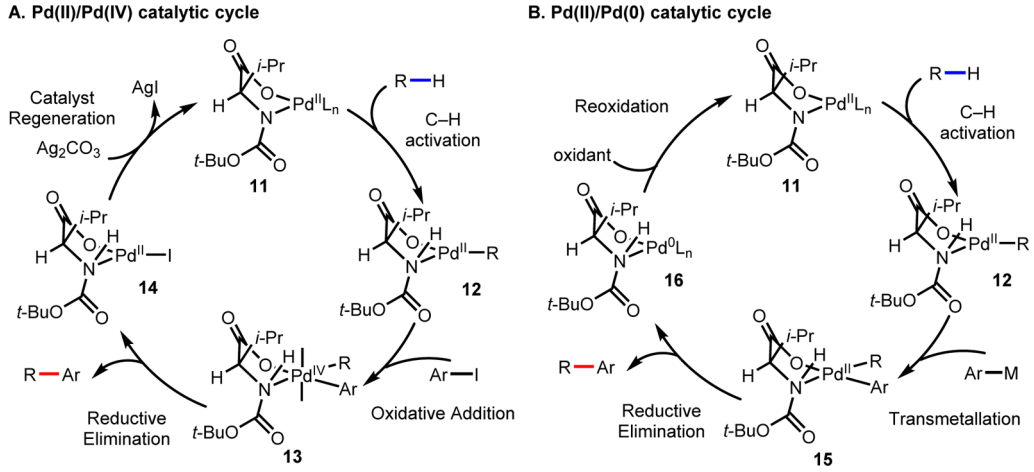


Figure 2. Catalytic cycles possible with the Pd(II)/MPAA system.

chloride and the reaction yielded 91% over three steps with unchanged ee.

On the basis of the extensive studies of Pd(II)-catalyzed C–H arylation with aryl iodides via Pd(II)/Pd(IV) redox chemistry,[11] a catalytic cycle is proposed for the enantioselective C–H arylation of cyclopropylmethylamines (Figure 2a). Cleavage of the C–H bond generates palladacycle **12**. Oxidative addition of Ar–I onto the palladacycle affords Pd(IV) complex **13**. Subsequently, reductive elimination occurs from the high-energy intermediate to give product R–Ar and Pd(II) complex **14**. Silver salt scavenges the iodide anion from **14** to regenerate the active catalyst **11**, thus closing the catalytic cycle. The silver salt is also known to promote the oxidative addition of Ar–I as well as the reductive elimination by interacting with the iodide. Although the Pd(IV) intermediate in this type of arylation has not been isolated, the reaction of the Pd(II) palladacycle with Ar–I to give the arylated product has been rigorously demonstrated by Daugulis, which is consistent with a Pd(II)/Pd(IV) instead of a Pd(0)/Pd(II) catalytic cycle.[14] A closely related Pd(II)/Pd(III) catalytic cycle[15] is also unlikely in this case because the bisdentate coordination of the MPAA to Pd(II) does not permit the dimerization via the bridging carboxylate.

In comparison to our previous Pd(II)/MPAA-catalyzed C–H arylation via a Pd(II)/Pd(0) catalytic cycle (Figure 2b),[8] each step in this reaction except for the C–H cleavage is fundamentally different. The lack of trace reaction in the absence of a silver salt rules out the possibility of involving a Pd(II)/Pd(0) catalytic cycle (see Supporting Information), because one catalytic turnover would be observed otherwise.[8] In addition, a Pd(II)/Pd(0) catalytic cycle for C–H arylation with aryl iodides has never been conceived or experimentally supported in the literature. On the other hand, a Pd(0)/Pd(II) catalytic cycle for an intermolecular C(sp^3)–H arylation[16] is conceivable. However, this redox chemistry is known to be incompatible with silver salts.[16,17] In addition, the commonly used Pd(0) catalysts such as allylpalladium(II) chloride dimer, bis(dibenzylideneacetone)palladium(0), and tris(dibenzylidene acetone)dipalladium(0) are not reactive under the standard conditions in our exploratory studies. While we do not have concrete evidence in support of a Pd(II)/Pd(IV) catalytic cycle at this stage, the reaction pathway depicted in Figure 2a provides the best explanation for the experimental data.

3. CONCLUSION

In summary, Pd(II)-catalyzed highly enantioselective arylation of cyclopropylmethylamines with aryl iodides has been achieved using Pd(II)–MPAA catalysts in excellent yields and ees. This reaction represents the first example of enantioselective C–H arylation through a Pd(II)/Pd(IV) catalytic manifold. In light of the lack of efficient methods for the preparation of chiral *cis*-aryl-cyclopropylmethylamines, this transformation is a valuable addition to the tool box for making chiral cyclopropanes.

4. EXPERIMENTAL SECTION

General Procedure for the Enantioselective C(sp^3)–H Activation of Cyclopropylmethylamines (Table 2). A 50 mL sealed tube was charged with the starting material (0.2 mmol), aryl iodide (0.6 mmol), $Pd(OAc)_2$ (4.5 mg, 0.02 mmol), Boc-L-Val-OH (8.7 mg, 0.04 mmol), sodium trifluoroacetate (13.6 mg, 0.1 mmol), Ag_2CO_3 (110.3 mg, 0.4 mmol), and *t*-BuOH (1 mL, 0.2 M). The reaction mixture was then stirred at 80 °C for 18 h. After being allowed to cool to room temperature, the mixture was diluted with a 1:1 mixture of hexanes:ethyl acetate and filtered through a pad of Celite. The filtrate was concentrated in vacuo, and the resulting mixture was purified by column chromatography using an eluent of hexanes:ethyl acetate.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures; characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We gratefully acknowledge The Scripps Research Institute and the National Institutes of Health (NIGMS, 2R01GM084019) for financial support. K.S.L.C. thanks the Agency for Science, Technology and Research (A*STAR), Singapore, for a predoctoral fellowship. H.Y.F. is a visiting scholar sponsored by Sichuan University, People's Republic of China.

DOI: 10.1021/ja512529e
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DOI: 10.1021/ja512529e
J. Am. Chem. Soc. 2015, 137, 2042−2046