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Spontaneous Resolution of Julia-Kocienski Intermediates Facilitates Phase Separation to Produce *Z*- and *E*-Monofluoroalkenes

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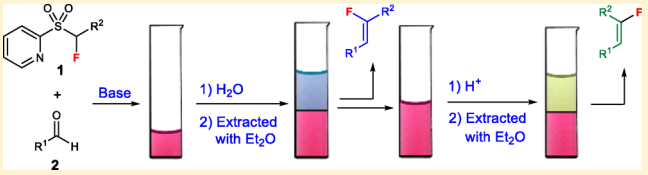
Supporting Information

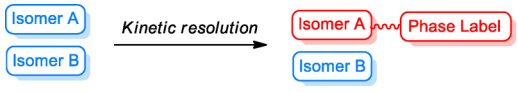
ABSTRACT: The monofluoroalkene motif is important in drug development as it serves as a peptide bond isostere and is found in a number of biologically active compounds with various pharmacological activities. Direct olefination of carbonyl compound is a straightforward way to prepare monofluoroalkenes; however, these methods often result in a mixture of *Z*- and *E*-isomers that cannot be easily separated. We discovered a unique spontaneous resolving reaction that simultaneously addresses the problems in the synthesis and separation of *Z*- and *E*-monofluoroalkenes. The reaction is accompanied by a highly efficient spontaneous kinetic resolution and phase labeling of monofluoroalkene precursors which allows the separation of *Z*- and *E*-monofluoroalkenes by liquid−liquid extraction. The application of the method is demonstrated by the synthesis and separation of potential anticancer agents, which are inseparable by HPLC.



INTRODUCTION

Stereoisomers usually possess different biological activity accompanied by relatively similar physical and chemical properties,[1] thus making their separation important but challenging. Chromatographic methods are typically required to allow the separation of the stereoisomers, but these technologies are expensive and laborious.[2] Liquid−liquid extraction is one of the most commonly used workup procedures in organic synthesis, which partitions a mixture into different liquid phases.[3] It represents as an ideal separation technology in terms of simplicity and low cost. Therefore, extractive separation of stereoisomers is highly desirable and attracts great interest.[4] The key elements that lead to a successful extractive separation of stereoisomers comprise a kinetic resolution of the isomers and a phase labeling of one isomer to allow its transfer from organic phase to aqueous or fluorous phase (Scheme 1).[5] As the kinetic resolution step must be efficient enough to enable a satisfactory separation of both isomers, most of the reported examples of extractive separation rely on enzymatic kinetic resolution.[5]

Scheme 1. Strategy for Extractive Separation of Stereoisomers



Monofluoroalkene is recognized as mimetic of the peptide bond and widely used as a structural or mechanistic probe in biological studies.[6] As a result of its enhanced stability toward proteases, the monofluoroalkene-bearing protein-based drug is expected to have a longer circulation time in the body. Moreover, as fluorine is an isostere of hydrogen, monofluoroalkenes are promising alternatives to their nonfluorinated analogues when pursuing novel bioactive compounds.[7] Olefination of carbonyl compounds is one of the most straightforward methods to prepare various alkenes.[8] Although both *Z* and *E* nonfluorinated alkenes are easily accessible through the Wittig, Horner−Wadsworth−Emmons or modified Julia reaction, tuning the *Z*/*E* selectivity of a monofluoroolefination reaction remains challenging.[9] Furthermore, as a result of the difficulty in separation, monofluoroalkene products are often obtained and characterized as an inseparable mixture of *Z* and *E* isomers.[9f−h] This is obvious from the fact that *Z*/*E* ratio of the monofluoroalkene products is often the same prior to and after purification. Extractive separation of *Z*- and *E*-monofluoroalkenes generated from carbonyl olefination reaction via the above-mentioned strategy is very appealing (Scheme 1); however, the realization of this idea is hampered by the lack of selective phase labeling reaction of the *E*- or *Z*-monofluoroalkene.[10] Herein, we report a spontaneous resolving reaction that simultaneously addresses the challenges in the synthesis and separation of *Z*- and *E*-monofluoroalkenes. The reaction is accompanied by a highly efficient spontaneous kinetic resolution and phase labeling of a pair of diastereomeric monofluoroalkene precursors which allows the separation of *Z*- and *E*-monofluoroalkenes by liquid−liquid extraction.

Despite being of a similar size to hydrogen atom, fluorine atom often carries a significant negative charge which makes it behave as a bigger substituent than hydrogen during a reaction. As a result, the control of the *Z*/*E* selectivity of a fluorinated

Received: February 26, 2015

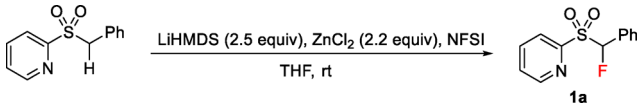
DOI: 10.1021/jacs.5b02112
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

alkene is different from their nonfluorinated analogues. We have recently revealed that difluoromethyl 2-pyridyl sulfone (2-$PySO_2CF_2H$) displayed a superior performance than other heteroaryl sulfones in Julia-Kocienski difluoroolefination reactions.[11] Improved reactivities were also observed in the reactions with alkyl halides, imines and lactones.[12] The striking effect of 2-pyridyl(sulfonyl) group in synthesizing diversified organofluorine compounds prompted us to examine its potential in preparing stereoisomerically pure monofluoroalkenes.

RESULTS AND DISCUSSION

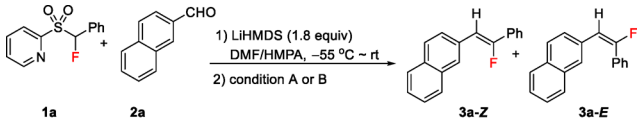
We began our investigation by preparing the monofluorinated 2-pyridyl benzyl sulfone (**1a**) by fluorination using *N*-fluorobenzenesulfonimide (NFSI) (Scheme 2).[13] Initial studies

Scheme 2. Preparation of the Monofluoroolefinating Reagent in This Study



using 2-naphthaldehyde (**2a**) as a model substrate revealed that **1a** displayed a good reactivity and gave the monofluoroalkene product **3a** in good yield, while the *Z*/*E* selectivity was not satisfactory even after screening a series of solvents and bases. Although this result seemed to support the fact that the control of the *Z*/*E* selectivity in monofluoroolefination of carbonyl compounds is a formidable task, we were intrigued by the observation that *Z*/*E* selectivity of our reaction varied if different workup procedures were employed (Scheme 3). The

Scheme 3. Distinct *Z*/*E* Selectivity Observed with Different Workup Procedure



A: HCl (3 M), yield: **3a-*Z*** (40%), **3a-*E*** (35%);
B: H_2O, yield: **3a-*Z*** (46%), **3a-*E*** (0%)

Z to *E* ratio in the reaction quenched with aqueous hydrochloric acid (HCl, 3 M) was 1.14:1, while it changed to >99:1 when water was used instead of HCl. Because in both cases, a similar yield of isomer **3a-*Z*** was obtained, we assumed that monofluoroalkene **3a-*E*** was generated only when the reaction system became acidic. Unfortunately, the attempt to isolate the compound correlated to the production of **3a-*E*** was not successful by column chromatography. To gain more insight into this interesting observation, we monitored the current monofluoroolefination reaction via ^{19}F NMR (Figure 1c). Two new species was observed when the reaction was warmed to ambient temperature. The doublet at −115 ppm was identified as the monofluoroalkene **3a-*Z*** (Figure 1a). Interestingly, instead of the anticipated product **3a-*E*** which should appear at −95 ppm (Figure 1b), an unknown species with a doublet signal at −181 ppm was observed. Direct isolation of this species is difficult as a result of its aqueous soluble nature. By treatment with CH_3I, a new species with a ^{19}F NMR of −173 ppm was produced, the structure of which was determined to be a methylated sulfone (**6a-*E***) by X-ray

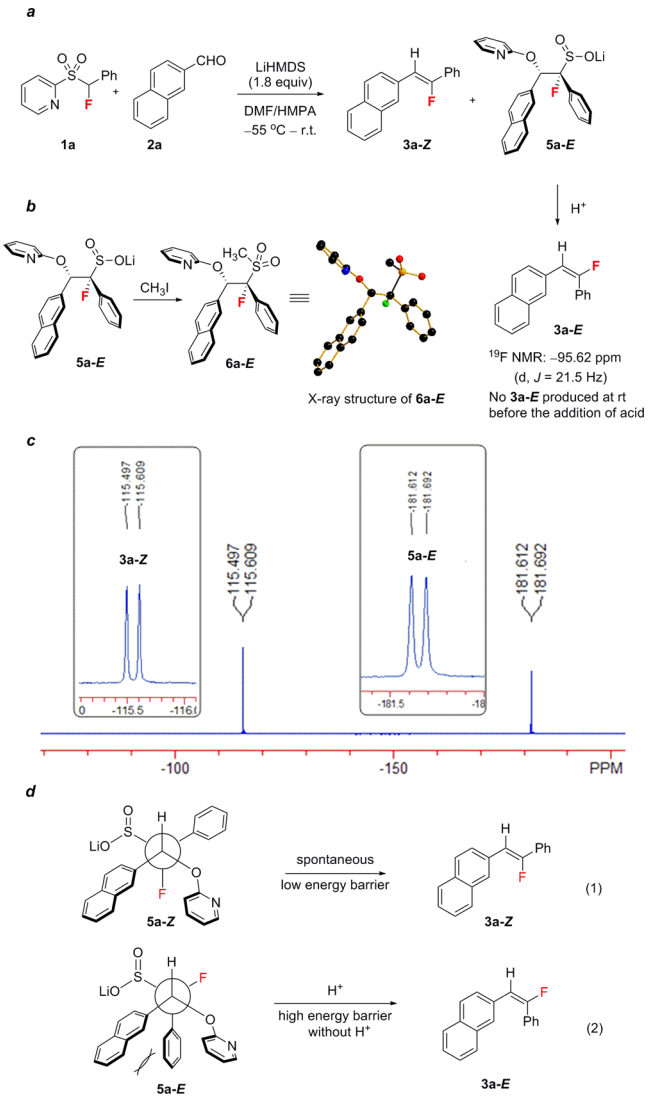


Figure 1. Proposed explanation of the kinetic resolution of sulfinate intermediate **5a**.

crystallography (as shown in Figure 1b). This result revealed that the aqueous soluble species with a ^{19}F NMR of −181 ppm is the corresponding sulfinate salt **5a-*E*** (Figure 1a). With the above information, the key elements of the mechanism of this reaction are described as following: (1) the sufinate salts **5a-*Z*** and **5a-*E*** produced from Smiles rearrangement[14] exhibit distinct stability. (2) Intermediate **5a-*Z*** spontaneously and rapidly decomposed to monofluoroalkene **3a-*Z*** at room temperature (Figure 1d, (1)), whereas its diastereomeric isomer **5a-*E*** only broke down upon addition of an acid (Figure 1d, (2)). In other words, a kinetic resolution of the sulfinate intermediates **5a** occurred as a result of distinct energy barriers for decomposition of intermediates **5a-*Z*** and **5a-*E***.

We realized that this reaction simultaneously possesses characters of spontaneous resolution and phase labeling/switching that are desirable for an extractive separation of stereoisomers (as shown in Scheme 1). With this mechanistic information, we speculated on the possibility of an extractive separation of *Z*- and *E*-monofluoroalkenes, the protocol of which is depicted in Figure 2. The key element that led to the success of this protocol is the aqueous soluble nature of sulfinate intermediate **5-*E*** that allows its separation from the

DOI: 10.1021/jacs.5b02112
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX

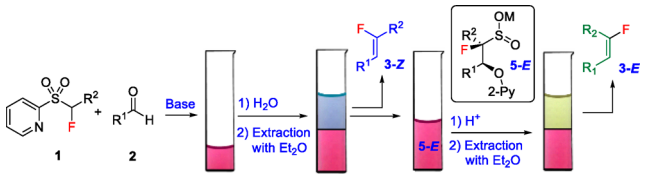


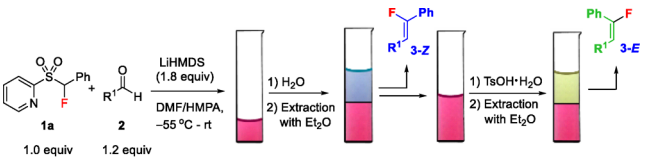
Figure 2. Schematic illustration of the protocol for the synthesis and separation of *Z*- and *E*-monofluoroalkenes.

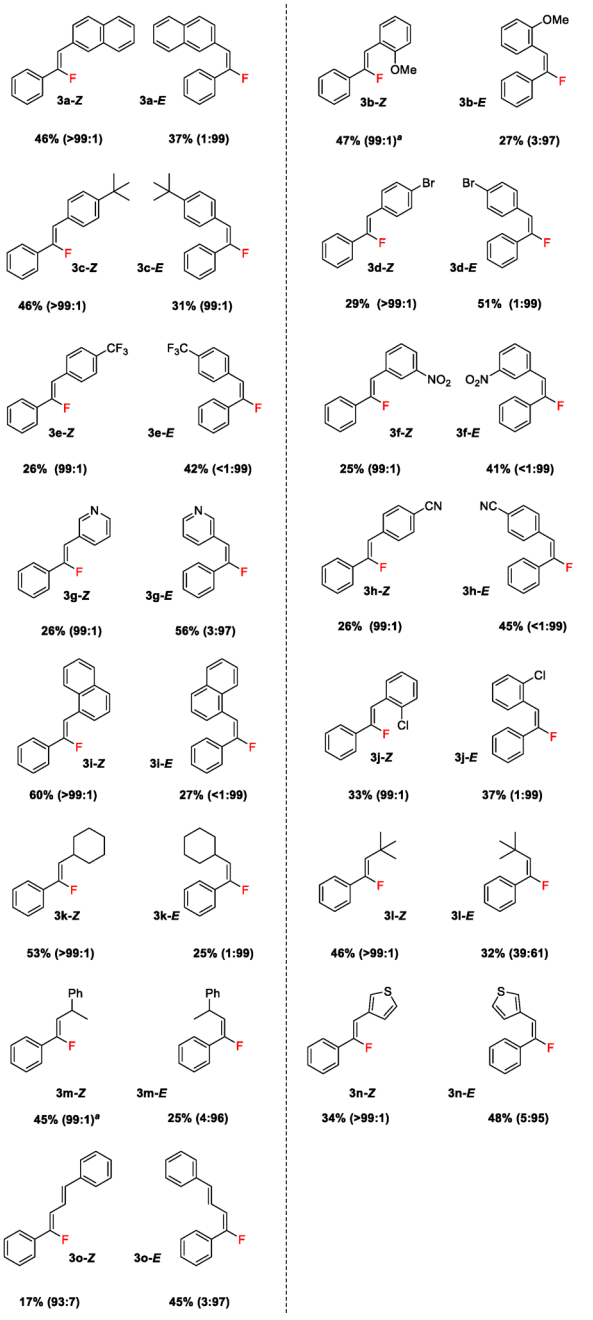
monofluoroalkene product **3-*Z*** by liquid–liquid extraction. After the separation of **3-*Z***, the other alkene **3-*E*** was generated by treatment of **5-*E*** with an acid. In addition to a highly efficient kinetic resolution of the sulfinate intermediates, we were also aware that the sulfinate **5-*E*** has to be sufficiently stable during the extraction that is generally performed at ambient temperature. As the Li–O bond is the strongest among M-O bonds (M = Li^+, Na^+, K^+), we surmised the use of a lithium as the counterion should impart the desired stability of sulfinate **5-*E***. Furthermore, to achieve a highly stereoselective transformation of sulfinate **5-*E*** to the alkene **3-*E***, a suitable acid was required. After a survey of reaction conditions, we found the use of lithium bis(trimethylsilyl)amide (LiHMDS) as the base and *p*-toluenesulfonic acid monohydrate ($TsOH·H_2O$) as the acid allows the realization of the above-mentioned protocol (Figure 2). Under the optimized conditions, monofluoroolefination of **2a** produced monofluoroalkene **3a-*Z*** in 46% yield (*Z*/*E* > 99:1) and its isomer **3a-*E*** in 37% yield (*Z*/*E* < 1:99). We next applied this protocol in accessing structurally diverse *Z*- and *E*-monofluoroalkenes. As shown in Table 1, both *Z*- and *E*-isomers of monofluoroalkenes could be obtained in highly geometrically enriched form using this spontaneous resolving reaction. The olefination reactions proceeded smoothly in the presence of either electron-donating or electron-withdrawing groups. The subsequent liquid–liquid extraction allowed the facile separation of the *Z* and *E* isomers. Pharmaceutically important heteroaromatics such as pyridine and thiophene are also compatible with the current protocol (Table 1, **3g** and **3n**). Satisfactory separation was also achieved with monofluoroalkenes derived from enolizable aliphatic (Table 1, **3m**) and *α*,*β*-unsaturated aldehydes (Table 1, **3o**), thus demonstrating the broad applicability of the current method. Notably, the *Z* to *E* ratio of most monofluoroalkene product **3-*E*** (**3a-*E***, **3c-*E***, **3d-*E***, etc.) is equal or lower than 1:99, while lower selectivity of product **3-*E*** was observed in the reactions with electron richer aldehydes (**2b**, **2l**–**2o**). In these cases, zwitterionic intermediates were likely to be involved in decomposition of sulfinate intermediate of **5-*E*** in addition to the regular antielimination pathway.[9b,15]

To evaluate the influence of the substituent on our approach, we prepared a variety of *α*-fluoro-2-pyridylsulfone reagents **1** (Table 2) and used 2-naphthaldehyde as a model substrate. Similar to the results obtained with reagent **1a**, both *Z* and *E* monofluoroalkenes **4-*Z*** and **4-*E*** were obtained in highly geometrically enriched form (Table 2).

Notably, the present methodology simultaneously meets the demanding expectations of simplicity and efficiency in the synthesis and the separation. No catalyst is required for kinetic resolution and no additional reagent or special solvent is necessary for the phase labeling/switching. All of the desired elements for extractive separation of ismoers are contained in the starting materials of the reaction. In this system, the starting materials are first phase labeled to produce two aqueous soluble precursors of the alkene products (sulfinate intermediates) and one of the precursors is spontaneously phase delabeled and goes into the organic phase.

Table 1. Synthesis and Separation of *Z*- and *E*-Monofluoroalkene with Reagent 1a[b]

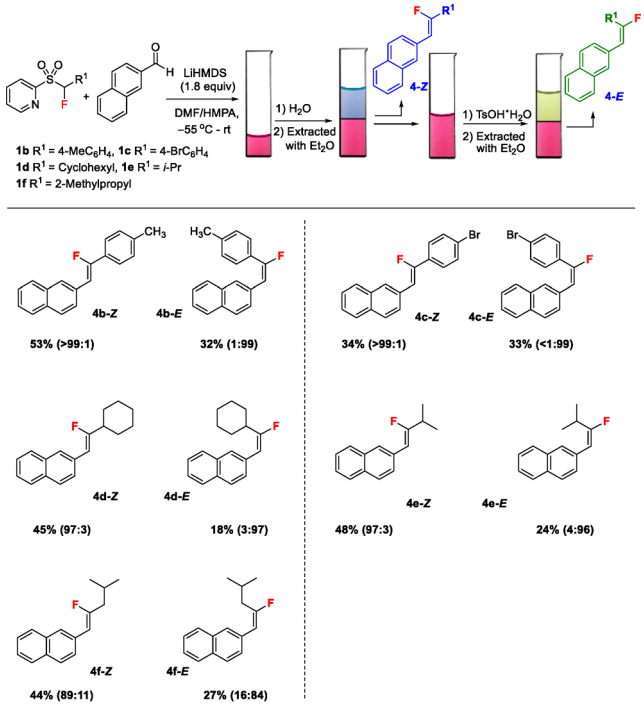




[a]An amount of 2.2 equiv of LiHMDS was used. [b]Experiments were performed with **1a** (1.0 mmol), aldehyde **2** (1.2 mmol) and LiHMDS (1.8 mL, 1.0 M in THF) in DMF/HMPA (3.3 mL, v/v = 10:1). Isolated yields were reported. *Z*/*E* ratio was determined by ^{19}F NMR analysis of the crude material and was given in parentheses.

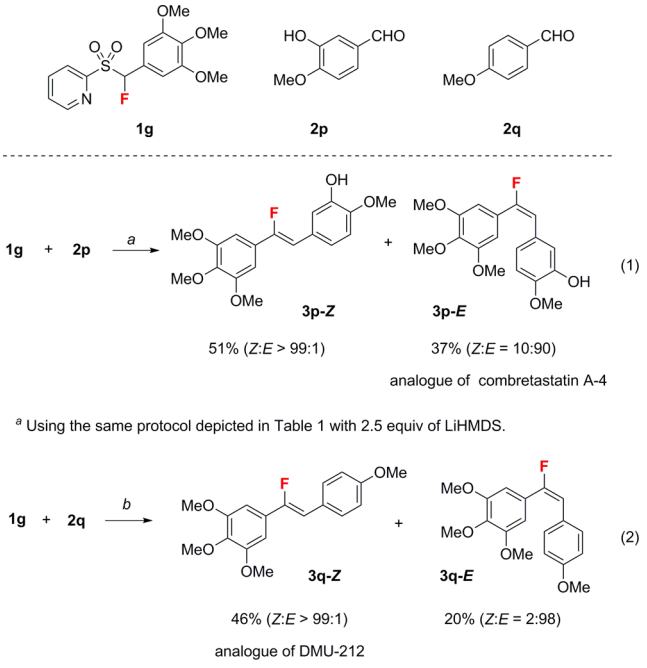
DOI: 10.1021/jacs.5b02112
J. Am. Chem. Soc. XXXX, XXX, XXX–XXX

Table 2. Synthesis and Separation of *Z*- and *E*-Monofluoroalkene with Structurally Diverse Reagents 1[a]



[a]Experiments were performed with **1** (1.0 mmol), aldehyde **2a** (1.2 mmol) and LiHMDS (1.8 mL, 1.0 M in THF) in DMF/HMPA (3.3 mL, v/v = 10:1). Isolated yields were reported. *Z*/*E* ratio was determined by ^{19}F NMR analysis of the crude material and was given in parentheses

Scheme 4. Synthetic Applications of the Current Spontaneous Resolving Reaction



[a] Using the same protocol depicted in Table 1 with 2.5 equiv of LiHMDS.

[b] Using the same protocol depicted in Table 1 with 1.8 equiv of LiHMDS.

To demonstrate the utilities of the current spontaneous resolving reaction in accessing both *Z*- and *E*-monofluoroalkenes via extractive separation, we applied it to the preparation of the fluorinated combretastatin analogues. Combretastatin A-4 is one of the most potent antimitotic agents which possess a strong cytotoxicity against various cancer cells.[16] Fluorinated combretastatin is thus interesting and had been synthesized through a multistep sequence.[17] It was found that the *Z* and *E* isomers could not be separated by preparative HPLC. In contrast, our protocol employing reagent **1g** smoothly afforded fluorinated analogues of combretastatin A-4 (**3p**-*E*) and its isomer (**3p**-*Z*), in highly geometrically enriched form (Scheme 4, reaction (1)). Notably, the reactive phenol group was tolerated in the current reaction, which mitigated the need of functional group protection. In a similar way, the fluorinated analogues of anticancer agents DMU-211 (**3q**-*Z*)[18] and its isomer (**3q**-*E*), could also be prepared (Scheme 4, reaction (2)). Given that both isomers are often required in the screening of pharmaceutical activity, fast access to both *Z* and *E* monofluoroalkenes is an additional benefit of the current protocol.

CONCLUSIONS

In conclusion, we have discovered a spontaneous resolving reaction that allows the synthesis and the separation of the *Z*- and *E*-monofluoroalkenes. No catalyst is required for kinetic resolution and no additional reagent or special solvent is necessary for the phase labeling/switching. The current methodology demonstrates the feasibility of spontaneous resolving reactions and represents a new strategy that meets the increasing expectations for economy and efficiency during synthesis and separation. We expect this strategy will find wide applications in life sciences and related fields, facilitate the drug screening process, and stimulate further exploration of novel spontaneous resolving systems.

ASSOCIATED CONTENT

Supporting Information

Crystallographic data in CIF format. Synthetic procedures and characterization of compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare the following competing financial interest(s): The authors have filed a patent on this technology.

ACKNOWLEDGMENTS

We thank J. A. Kalow and C. Ni for critical reading of the manuscript and Y. Yang for helpful discussion. This work was supported by the National Basic Research Program of China (2015CB931900, 2012CB215500), the National Natural Science Foundation of China (21372246, 21421002), Shanghai QMX program (13QH1402400) and the Chinese Academy of Sciences.

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DOI: 10.1021/jacs.5b02112
J. Am. Chem. Soc. XXXX, XXX, XXX−XXX