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Target-Directed Organocatalysis: A Direct Asymmetric Catalytic Approach to Chiral Propargylic and Allylic Fluorides

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Abstract: A simple, direct one-pot organocatalytic approach to the formation of optically active propargylic fluorides is presented. The approach is based on organocatalytic α-fluorination of aldehydes and trapping and homologation of the intermediate providing optically active propargylic fluorides in good yields and enantioselectivities up to 99% ee. The procedure takes place by addition of NFSI, in the presence of 2-[bis(3,5-bis-trifluoromethylphenyl)trimethylsilyloxymethyl]pyrrolidine (as low as 0.25 mol %) as the catalyst, to aldehydes in combination with dimethyl 2-oxopropylphosphonate and 4-acetamidobenzenesulfonyl azide. The scope of the reaction is demonstrated by the formation of a number of optically active propargylic fluorides. It is also shown that optically active fluoro-containing triazoles can be obtained in one-pot procedures from aldehydes using click-chemistry. Furthermore, important coupling and multicomponent reactions of the optically active propargylic fluorides can be performed without affecting the enantiomeric excess. The direct one-pot formation of optically active allylic fluorides from aldehydes is also demonstrated. Finally, the mechanisms for both the formation of the propargylic and allylic fluorides are outlined.

Introduction

Due to its unique chemical and biological properties, fluorine has obtained a privileged status in organic chemistry. Replacement of C—H or C—OH with C—F has significant pharmacological effects, such as increased in vivo stability and bioavailability, and as a result, fluorinated molecules are regularly explored as isosters of biologically active compounds today.[1] To meet the growing academic and industrial interests in and demands of organic fluorine compounds, various electrophilic and nucleophilic fluorination procedures have been reported.[2]

Among organic fluorine compounds, propargylic and allylic fluorides constitute an indispensable class of chiral organofluorine building blocks essential for organic synthesis.[3] Due to the transformational diversity of the alkynyl and alkenyl groups,[4] a wide library of chiral fluorinated compounds can be accessed by propargylic or allylic precursors by simple functional group manipulations. Moreover, propargylic and allylic fluorides are prevalent motifs in life science, such as crop-protection products, fluorinated analogues of vitamin D, leukotrienes, and prostanoids (Scheme 1).[3,5]

Optically active terminal propargylic fluorides are of particular interest due to their ability to participate in important reactions such as the Sonogashira coupling, hydrozirconation, hydroamidation, click reactions, cycloadditions, and cycloisomerizations. Interestingly, despite the wide utility of optically active propargylic fluorides only limited reports on their synthesis are present in the literature. The traditional route to this motif proceeds by substitution of activated or unactivated chiral

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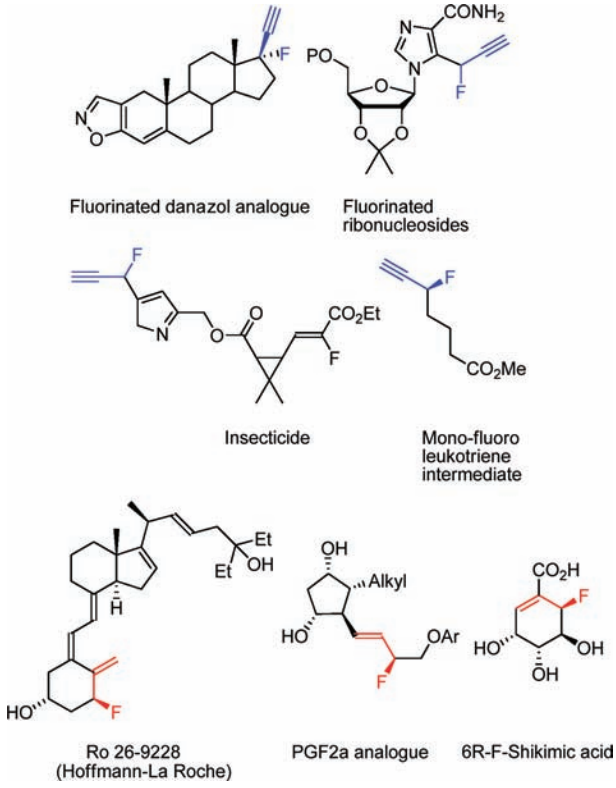
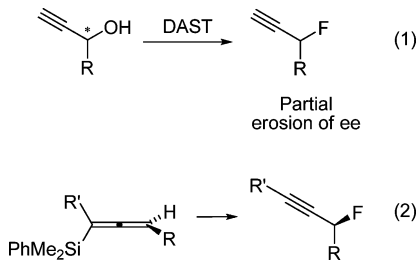
Scheme 1. Examples of Optically Active Propargylic and Allylic Fluorides in Life Science



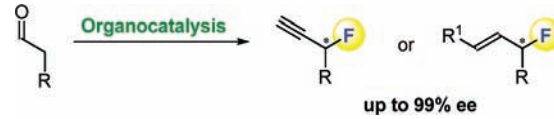
Scheme 2. Synthesis of Optically Active Propargylic Fluorides



propargylic alcohols using nucleophilic fluorine sources such as DAST or Yarovenko's reagent (Scheme 2, eq 1).[6] However, considerable loss of optical activity is observed using these methods due to competitive S_N1 and S_N2 pathways and, moreover, the use of alkyne protecting groups is often required. Recently, Gouverneur et al. reported the first enantioselective synthesis of propargylic fluorides (internal) using an electrophilic fluorine source.[7] Starting from highly enantioenriched allenylsilanes, complete chirality transfer was achieved; however, a drawback of this approach is the extended and time-costly synthesis of starting materials, limiting its application on larger scales (Scheme 2, eq 2).

Recently, the amino-catalyzed enantioselective α-fluorination of aldehydes was independently reported by the groups of

Scheme 3. Organocatalytic Synthesis of Optically Active Propargylic and Allylic Fluorides from Aldehydes



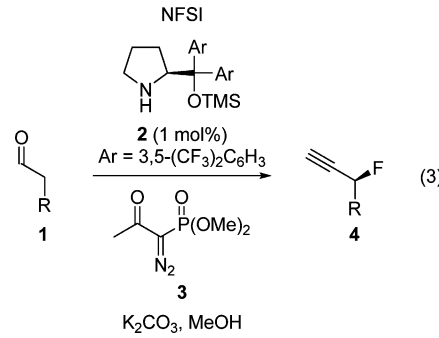
MacMillan, Barbas, Enders, and us.[8] On the basis of the organocatalyzed α-fluorination of aldehydes, we envisioned that a general and straightforward one-pot procedure to optically active propargylic fluorides, leading to a significant reduction in time costs, manual operations, and waste-product formation, should be possible.

Herein, we disclose a direct one-pot, fully scalable, and protecting-group free synthesis of optically active terminal propargylic fluorides with catalyst loading as low as 0.25 mol % (Scheme 3). The concept was also revealed to be readily adopted to the synthesis of optically active allylic fluorides. These new procedures afford rapid and efficient routes to two privileged classes of optically active fluorine compounds.

Results and Discussion

Propargylic Fluorides. Our concept for the formation of enantioenriched propargylic fluorides is based on the observed lability of optically active α-fluoro aldehydes, which need to be reduced to the corresponding fluoro-alcohols for isolation.[8d] These observations led us to envision that a one-pot procedure involving the organocatalytic α-fluorination of aldehydes, followed by in situ trapping and homologation might provide optically active propargylic fluorides in one operation. Furthermore, as it will be shown (vide infra) the concept can be extended to include the formation of optically active allylic fluorides.

Table 1. Scope of the Formation of Optically Active Propargylic Fluorides **4** from Aldehydes[a]



entry	R	time (h)	product[g]	yield (%)[b]	ee (%)[c]
1	−Bn	5	**4a**	56	95
2	$-(CH_2)_7CH_3$	4	**4b**	67	93
3	$-(CH_2)_{13}CH_3$	5	**4c**	65	99
4	$-(CH_2)_7CH{=}CH_2$	5	**4d**	55	92[d]
5	*p*-OMe-$C_6H_4CH_2-$	8	**4e**	65	91[d]
6	*p*-Br-$C_6H_4CH_2-$	8	**4f**	69	92[d]
7[e]	*o*-OMe-$C_6H_4CH_2-$	8	**4g**	58[f]	99
8[e]	*o*-Br-$C_6H_4CH_2-$	8	**4h**	47	94
9[e]	$-(CH_2)_3CO_2Me$	6	**4i**	45	93[d]

[a] All reactions, unless otherwise stated, were performed with 0.2 mmol NFSI, 0.22 mmol aldehyde, 1 mol % catalyst and 0.4 mL MTBE at rt. [b] Isolated yield. [c] Determined by chiral stationary phase GC (see the Supporting Information). [d] Determined on the corresponding click product **5** (see the Supporting Information). [e] 0.2 mmol aldehyde and 0.26 mmol NFSI were employed. [f] Isolated together with 5% difluorinated product. [g] The absolute configuration was determined by chemical correlation or analogy.

(7) (a) Carroll, L.; McCullough, S.; Rees, T.; Claridge, T. D. W.; Gouverneur, V. *Org. Biomol. Chem.* **2008**, *6*, 1731. (b) Carroll, L.; Pacheco, M. C.; Garcia, L.; Gouverneur, V. *Chem. Commun.* **2006**, 4113.

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Scheme 4. One-Pot Synthesis of Optically Active Propargylic Fluorides by in Situ Generation of the Ohira-Bestmann Reagent

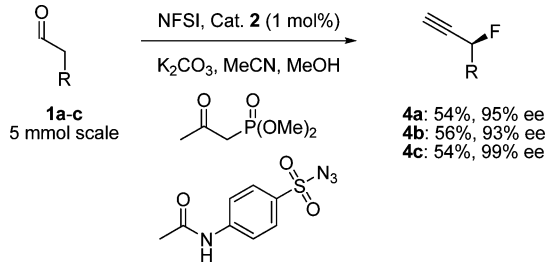
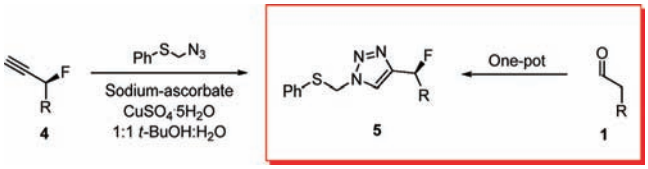


Table 2. "Clicking" the Optically Active Propargylic Fluorides[a]



entry	R	product	yield (%)[b]	ee (%)[c]
1	−Bn	**5a**	82	95
2	$-(CH_2)_7CH_3$	**5b**	87	93
3	$-(CH_2)_7CH{=}CH_2$	**5c**	68	92
4	*p*-OMe-$C_6H_4CH_2-$	**5d**	77	91
5	*p*-Br-$C_6H_4CH_2-$	**5e**	84	92
6	$-(CH_2)_3CO_2Me$	**5f**	73	93
7	−Bn	**5a**	50[d]	95

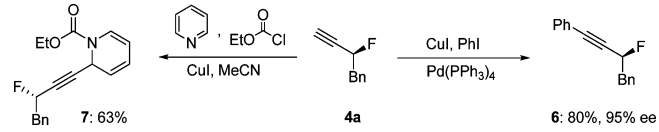
[a] All reactions were performed on 0.1 mmol scale. [b] Isolated yield. [c] Determined by chiral stationary phase HPLC (see the Supporting Information). [d] Overall yield over 3 steps from **1a** without intermediate purification.

We have evaluated several methods for the purpose of in situ homologation to form the optically active propargylic fluorides. The chiral α-fluoro aldehyde adducts are prone to rapid enolization due to the acidity of the α-carbonyl proton; consequently, adoption of a mild process was required to avoid racemisation. To our delight, we discovered that the Ohira-Bestmann modification of the Seyferth-Gilbert method[9] provided full compatibility with the organocatalyzed α-fluorination.

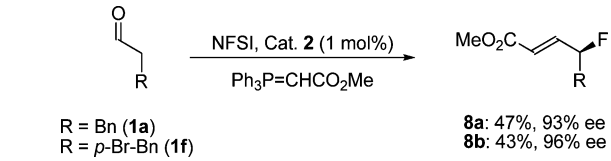
The direct and one-pot formation of optically active propargylic fluorides thus takes place by reacting aldehydes **1** with *N*-fluoro-dibenzene-sulfonimide (NFSI) in the presence of (*S*)-2-[bis(3,5-bis-trifluoromethylphenyl)trimethylsilyloxymethyl]-pyrrolidine **2** as the catalyst[10] and the Ohira-Bestmann reagent **3** in combination with MeOH and K_2CO_3 (see the Supporting Information). Despite the presence of base, no racemisation is observed, affording the desired propargylic fluorides **4** in good yields and excellent enantioselectivities (eq 3). The results for the reaction of various aldehydes **1** are presented in Table 1.

As shown in Table 1, various substrates were examined; linear saturated and unsaturated aldehydes of different length all furnished the desired optically active propargylic fluorides in good yield and excellent enantioselectivity. For the benzyl and alkyl substituted aldehydes, the corresponding propargylic fluorides **4a**−**d** were isolated in good yields and excellent enantioselectivities, up to 99% ee (entries 1−4). It is also demonstrated that aldehydes, in which the aromatic group has different substitution patterns, are well-tolerated, affording the corresponding terminal propargylic fluorides **4e**−**h** in 47−69% yield and 91−99% ee (entries 5−8). Moreover, aldehydes carrying functionalities, such as an ester group, also undergoes the desired transformation as shown for the formation of the

Scheme 5. Some Transformations of the Optically Active Propargylic Fluorides



Scheme 6. Scope of the Formation of Optically Active Allylic Fluorides **9** from Aldehydes



propargylic fluoride **4i**, a key intermediate for the synthesis of monofluorinated leukotrienes (Scheme 1, Table 1, entry 9). This compound has previously been synthesized in a seven step sequence,[5f] while the same product was obtained by our approach in one-step in 45% yield and 93% ee.

The reported new method for the preparation of optically active propargylic fluorides **4** (eq 3), proved to be robust and fully scalable, even at lower catalyst loading, for example, using catalyst **2** in 0.25 mol % provided **4a** in 43% yield and 94% ee. Furthermore, to encounter the emerging demands for time-costs reduction in chemical synthesis, preparation of the Ohira-Bestmann reagent **3** can be avoided, minimizing the number of manual operations. Alternatively, in situ generation of **3** afforded an one-pot synthesis of **4** using only commercially available sources demonstrating the simplicity in this procedure. Scheme 4 illustrates the direct formation of **4a-c** afforded by addition of dimethyl 2-oxopropylphosphonate and 4-acetamidobenzenesulfonyl azide to the reaction mixture. Results, obtained using this in situ generation method, are comparable to those in Table 1.

The optically active propargylic fluorides **4** are set up for a range of important transformations, some of which are presented in Table 2 and Scheme 5. Click reaction between organic azides and alkynes provides a powerful and reliable method for the synthesis of versatile heterocycles.[11] Due to the great importance of both the heterocyclic and chiral fluorine motif in life science (Scheme 1), we envisioned that by "clicking" the propargylic fluorides with azides, various chiral fluorinated heterocyclic structures could be furnished in a simple manner. As a proof of

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(10) For catalyst synthesis, see: (a) Franzén, J.; Marigo, M.; Fielenbach, D.; Wabnitz, T. C.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 18296. For selected review and applications of catalyst **2**, see: (b) Mielgo, A.; Palomo, C. *Chem. Asian J.* **2008**, *3*, 922, and references herein. Recent papers: (c) Franke, P. T.; Johansen, R.-L.; Bertelsen, S.; Jørgensen, K. A. *Chem. Asian J.* **2008**, *3*, 216. (d) Liu, K.; Chougnet, A.; Woggon, W.-D. *Angew. Chem., Int. Ed.* **2008**, *47*, 5827. (e) Gianelli, C.; Sambri, L.; Carlone, A. F.; Bartoli, G.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 8700. (f) Cabrera, S.; Reyes, E.; Alemán, J.; Milelli, A.; Kobbelgaard, S.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2008**, *130*, 12031 For other proline or prolinol-based organocatalysts, see. (g) Ishikawa, H.; Suzuki, T.; Hayashi, Y. *Angew. Chem., Int. Ed.* **2009**, *48*, 1304. (h) Enders, D.; Wang, C.; Bats, J. W. *Angew. Chem., Int. Ed.* **2008**, *47*, 7539. (i) Kano, T.; Mii, H.; Maruoka, K. *J. Am. Chem. Soc.* **2009**, *131*, 3450. (j) Chandler, C.; Galzerano, P.; Michrowska, A.; List, B. *Angew. Chem., Int. Ed.* **2009**, *48*, 1978.

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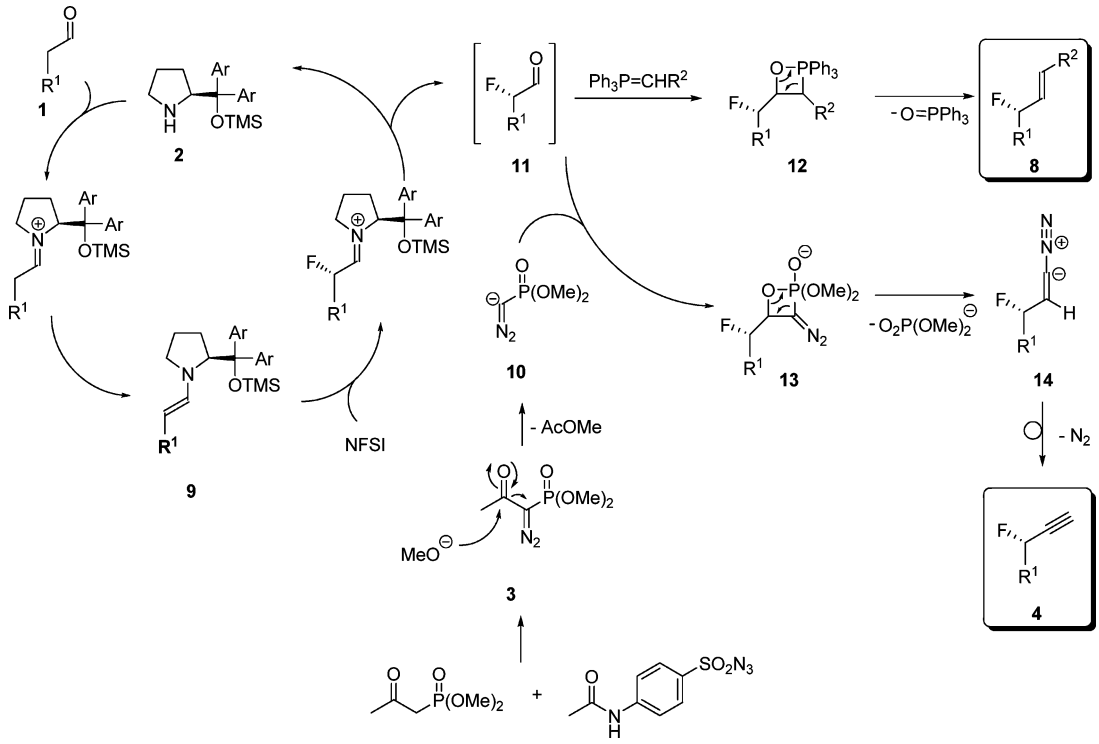
Scheme 7. Mechanism of the Formation of the Optically Active Propargylic and Allylic Fluorides



concept, a series of copper-catalyzed click reactions between **4** and azidomethyl phenyl sulfide was performed, giving the click products in 68−87% yield with full conservation of the optical integrity (Table 2, entries 1−6). Furthermore, the click adducts could also be obtained without intermediate purification of the propargylic fluorides, allowing the direct and clean conversion of the crude product **4** to the desired click adduct **5** directly from the aldehyde (entry 7) in 50% yield over 3 steps (see the Supporting Information).

Peptides and peptide-mimics are important classes of bioisosters;[12] additionally, rapid conversion of simple building blocks into libraries of compounds, used for bioactivity screenings, represents an essential factor in the efficiency of drug-development process.[13] Herein, multicomponent reactions,[14] for example, the Ugi reaction,[15] play a crucial role. Recently, various metal-catalyzed multicomponent reactions have been reported,[16] of which, the copper-iodide catalyzed three component reaction between an pyridine, an acid chloride/chloroformate and a terminal alkyne is of particular interest as it involves the formation of a peptide bond adjacent to an alkyne.[17] Extending the use of the propargylic fluorides, obtained by the reported organocatalytic method, for this multicomponent reaction gives rise to a simple entry to the formation of chiral fluorinated peptides and peptide-mimics, with many possibilities for substrate variation and product elaboration. As illustrated in Scheme 5, under nonoptimized conditions, the propargylic fluoride **4a** reacts with pyridine and ethyl chloroformate to give the product **7** in 63% yield based on recovered starting material. We have also demonstrated the application of **4a** in other robust C—C or C—X coupling reactions, such as the Sonogashira coupling, frequently applied in complex organic synthesis as shown for the formation of the propargylic fluoride **6**, which was obtained from **4a** in 80% yield and maintaining the enantiomeric excess of 95% ee.

Allylic Fluorides. Next, we examined the possibility of adopting the concept of α-fluorination/elongation for the synthesis of chiral allylic fluorides. Gratifyingly, the Wittig reaction is fully compatible with the organocatalytic asymmetric fluorination reaction. As shown in Scheme 6, the one-pot reaction, organocatalytic formation of α-fluoro aldehydes in combination with the commercially available methyl (triphenylphosphoranylidene) acetate, furnished the corresponding allylic fluorides **8a**,**b** in 43−47% yield and 93−96% ee.

Mechanism. The proposed mechanisms for the formation of propargylic and allylic fluorides are outlined in Scheme 7. The reaction is initiated with the organocatalytic fluorination cycle with condensation of the catalyst **2** and aldehyde **1** leading to the formation of a reactive enamine species **9**, which favors electrophilic attack from the Si-face due to steric shielding of the Re-face by the catalyst. Previous kinetic experiments[8d] have revealed that the prolinol-derived catalyst **2** preferably difluorinates the minor enantiomer, thereby, increasing the enantiomeric excess of the α-fluoro aldehyde in a resolution manner. The intermediate product **11** can be trapped following two pathways: (i) upon reaction with a Wittig reagent and the formation of the oxaphosphatane intermediate **12**, the allylic fluorides **8** are obtained via a Wittig mechanism by elimination of Ph_3PO (Scheme 7, top); (ii) via the Ohira-Bestmann reagent **3**, either preformed or formed in situ, in combination with base and MeOH, forming the carbene species **10** by methanolysis. The reactive species **10** traps the α-fluoro aldehyde intermediate

(12) *Advances in Amino Acid Mimetics and Peptidomimetics*; Abell, A., Eds.; JAI Press: Oxford, U.K., 1999; Vol 2.
(13) Rang, H. P. *Drug Discovery and Development: Technology in Transition*; Churchill Livingstone/Elsevier: New York, 2005.
(14) *Multicomponent Reactions*; Zhu, J., Bienaymé, H., Eds.; Wiley-VCH: Germany, 2005.
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11 to give **13**, by which the propargylic fluoride **4** is formed by a 1,2-proton shift and elimination of N_2 from intermediate **14**. Remarkably, despite the complexity of the reaction mixtures, no racemization is observed in either pathway.

Conclusion

In conclusion, we have reported a simple, direct asymmetric catalytic one-pot approach to optically active propargylic and allylic fluorides in good yields and with excellent enantioselectivities. The described method differentiates from conventional approaches as it effectively utilizes the organocatalytic electrophilic α-fluorination reaction of aldehydes, thus, avoiding the use of nucleophilic fluorination reagents and the synthesis of complex starting materials. The optically active propargylic fluorides are all obtained from commercially available compounds, and can successfully participate in a number of important transformations, for example, click reactions, Sonogashira coupling and multicomponent reactions. This new chemistry reveals easy and straightforward procedures for the formation of chiral fluorinated compounds of great importance to life-science.

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Supporting Information Available: Complete experimental procedures and characterization (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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