

N-Heterocyclic Carbene Catalyzed Enantioselective α -Fluorination of Aliphatic Aldehydes and α -Chloro Aldehydes: Synthesis of α -Fluoro Esters, Amides, and Thioesters**

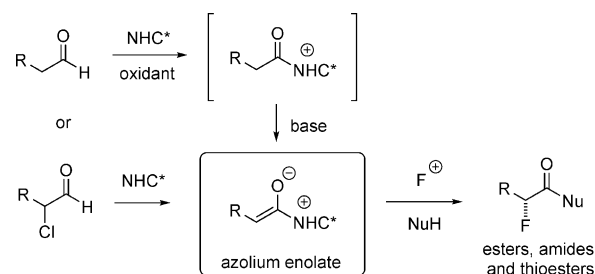
Xiuqin Dong, Wen Yang, Weimin Hu, and Jianwei Sun*

Abstract: The asymmetric fluorination of azolium enolates that are generated from readily available simple aliphatic aldehydes or α -chloro aldehydes and N-heterocyclic carbenes (NHCs) is described. The process significantly expands the synthetic utility of NHC-catalyzed fluorination and provides facile access to a wide range of α -fluoro esters, amides, and thioesters with excellent enantioselectivity. Pyrazole was identified as an excellent acyl transfer reagent for catalytic amide formation.

The development of efficient synthetic methods for chiral organofluorine molecules has recently attracted substantial interest, owing to the valuable applications of such compounds in medicinal chemistry, agrochemistry, and materials science.^[1,2] The catalytic asymmetric α -fluorination of carbonyl compounds is of particular interest. Over the past decade, significant progress has been made. Different metal and organocatalytic systems have been developed, particularly for easily enolizable carbonyl compounds, such as 1,3-dicarbonyl derivatives, aldehydes, and ketones. In contrast, efficient asymmetric methods for α -fluorine incorporation into less activated monocarbonyl compounds, such as esters, amides, and thioesters, remain to be developed.^[3,4]

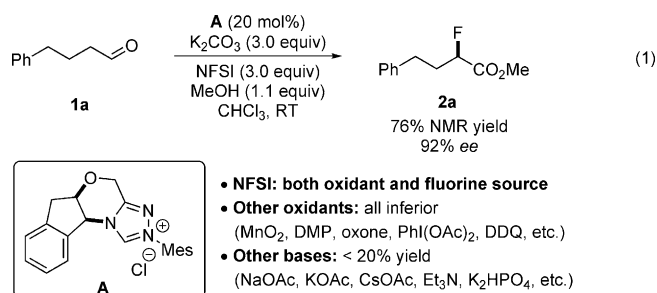
Catalytic systems that are based on N-heterocyclic carbenes (NHCs) have proven to be versatile in particular for establishing the α -stereogenic center of esters via key azolium enolate intermediates.^[5–8] Previously, we have reported the mono- and bisfluorination of vinylogous azolium enolates that were generated from α,β -unsaturated aldehydes bearing a leaving group in the γ position.^[9,10] However, this method not only suffered from a limited scope, but also required a multistep substrate synthesis. Recently, the Rovis and Chi groups have reported the successful generation of azolium enolates from simple aliphatic aldehydes under oxidative conditions.^[11] Inspired by their pioneering work, we envisioned the expansion of our asymmetric fluorination

method to readily available aliphatic aldehydes to enhance its synthetic utility. However, there are several compatibility issues to be addressed. For example, the oxidative conditions required for enolate generation should be compatible with the oxidizable NHC catalyst. The competition between substrate, oxidant, and electrophilic fluorination reagent to react with the NHC should also be balanced. Herein, we report the realization of the asymmetric synthesis of α -fluoro esters, amides, and thioesters from both simple aldehydes and α -chloro aldehydes (Scheme 1).



Scheme 1. Fluorination of azolium enolates generated from simple aliphatic aldehydes and α -chloro aldehydes.

We started the evaluation of our hypothesis with aldehyde **1a**. After considerable efforts comparing different reagents required for the reaction (e.g., precatalyst, base, fluorination reagent, oxidant), we were pleased to find that the desired α -fluoro ester **2a** could be formed with both good efficiency and enantioselectivity with Bode catalyst **A** [Eq. (1)].^[12] It is noteworthy that *N*-fluorobenzenesulfonimide (NFSI) served not only as the electrophilic fluorination reagent but also an excellent oxidant.^[13] Other oxidants, including MnO_2 , Dess–Martin periodinane (DMP), oxone, $\text{PhI}(\text{OAc})_2$, and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), proved to be inferior, presumably because of the excellent oxidation strength of NFSI. It probably outcompetes these oxidants, and



[*] Dr. X. Dong, Dr. W. Yang, Dr. W. Hu, Prof. Dr. J. Sun
Department of Chemistry
The Hong Kong University of Science and Technology
Clear Water Bay, Kowloon, Hong Kong SAR (China)
E-mail: sunjw@ust.hk

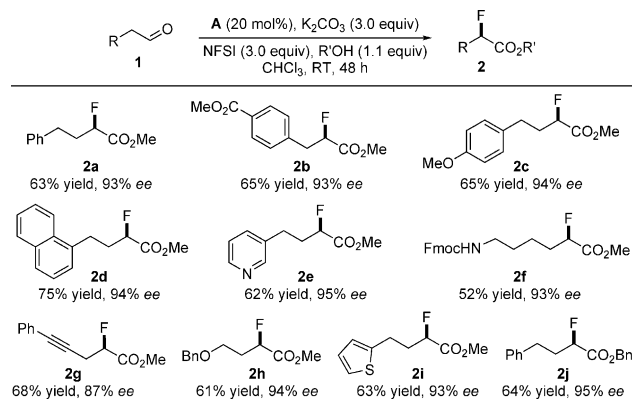
Dr. X. Dong
Department of Chemistry, Jinan University
Guangzhou 510632 (China)

[**] Financial support was provided by HKUST and Hong Kong RGC (ECS605812, M-HKUST607/12, and GRF604513).

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/ange.201409961>.

thus its subsequent function as a fluorine source is affected when one equivalent of NFSI is used in combination with another oxidant (1 equiv). Furthermore, K_2CO_3 was identified as the base of choice. Other bases, such as NaOAc, KOAc, and Et_3N , all resulted in significantly diminished yields. The suitable basicity not only ensures successful enolization of the acyl triazolium intermediate, but also suppresses the nonproductive aldol reaction and other side reactions.

With the standard conditions in hand, we next examined the substrate scope of the transformation (Scheme 2). Different aliphatic aldehydes all reacted smoothly to provide the corresponding α -fluoro esters in moderate to good yield and

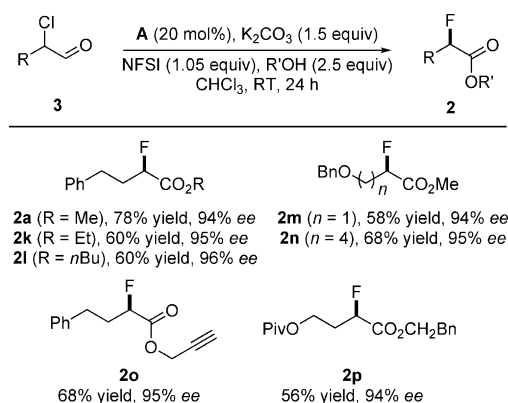


Scheme 2. Variation of the aliphatic aldehyde coupling partner. Reaction conditions: **1** (0.50 mmol), **A** (0.10 mmol), K_2CO_3 (1.5 mmol), $R'OH$ (0.56 mmol), $CHCl_3$ (2.5 mL). Yields of isolated products are given. Bn = benzyl, Fmoc = 9-fluorenylmethoxycarbonyl.

with excellent enantioselectivity. Various functional groups, such as Fmoc-protected amines, esters, ethers, and alkynes, were tolerated. Heterocycles, such as the easily oxidizable pyridine and thiophene, were also compatible with the strongly oxidative reaction conditions.

Aside from simple aliphatic aldehydes, we also examined the feasibility of using α -chloro aldehydes as the starting materials (Scheme 3). According to the proposed mechanism, an external oxidant is not required in this case. Indeed, with only one equivalent of NFSI under otherwise almost identical conditions, comparable results were obtained. The enantioselectivity remained excellent, which is consistent with the involvement of the same azolium enolate intermediates. Alcohols other than methanol were also suitable nucleophiles.

Considering the importance and challenges of catalytic amide formation, we were also interested in extending the fluorination process to the synthesis of α -fluoro amides. However, when the alcohol nucleophile was simply replaced with an amine, the desired product was not formed under the above-described standard conditions. The formation of amides by NHC catalysis is a known challenge that is presumably due to complications arising from competing non-productive imine formation reactions between the amines and aldehydes as well as the intrinsic reluctance of



Scheme 3. Reaction scope with α -chloro aldehydes. Reaction conditions: **3** (0.50 mmol), **A** (0.10 mmol), K_2CO_3 (0.75 mmol), NFSI (0.53 mmol), $R'OH$ (1.3 mmol), $CHCl_3$ (5.0 mL). Yields of isolated products are given.

the acyl transfer from acyl triazolium intermediates to amines (relative to that to alcohols).^[14,15] To overcome this challenge, the groups of Rovis and Bode pioneered the use of additives (e.g., 1-hydroxy-azobenzotriazole (HOAt), imidazole) as relay shuttles for acyl transfer to amines. Unfortunately, these known additives proved to be ineffective when used in combination with our asymmetric fluorination method (Table 1). However, additional screening identified pyrazole as a compatible and excellent additive. Thus, the one-pot synthesis of highly enantioenriched α -fluoro amides from both aniline and benzyl amine was achieved. It is noteworthy that phenyl hydrazine could also react to form the desired product **4c**. With the same method, α -fluoro thioesters could also be successfully synthesized in excellent enantiomeric excess.

Whereas simple aliphatic aldehydes are suitable substrates for our oxidative fluorination reaction, β,γ -unsaturated aldehydes might not be as practical owing to their

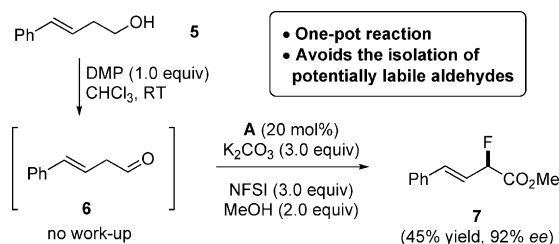
Table 1: One-pot synthesis of α -fluoro amides and thioesters.^[a]

 pyrazole Other inferior additives: imidazole, HOAt, $(CF_3)_2CHOH$, etc.				
Entry	NuH	Product	Yield ^[b] [%]	ee [%]
1	BnNH ₂	4a	72	97
2	PhNH ₂	4b	67	96
3	PhNHNH ₂	4c	62	96
4		4d	63	95
5		4e	52	95

[a] **3a** (0.50 mmol), **A** (0.10 mmol), K_2CO_3 (0.75 mmol), NFSI (0.53 mmol), pyrazole (1.0 mmol), $CHCl_3$ (5.0 mL). After stirring for approximately 12 hours, the nucleophile (1.0 mmol) was added.

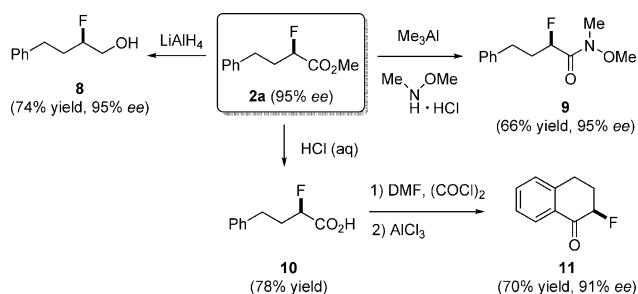
[b] Yields of isolated products.

relative instability. As the oxidative conditions for aldehyde synthesis from the corresponding alcohol should be compatible with our fluorination reaction, we envisaged the combination of the two steps into a one-pot process, thereby obviating the need for isolation of the potentially labile aldehyde. Therefore, alcohol **5** was initially treated with DMP. Without work-up, the reaction mixture was then directly subjected to the asymmetric fluorination conditions (Scheme 4). The desired β,γ -unsaturated α -fluoro ester **7** was obtained with reasonable overall efficiency and excellent enantioselectivity.



Scheme 4. One-pot synthesis of α -fluoro β,γ -unsaturated ester **7**.

The α -fluoro ester products can be transformed into other useful molecules, such as alcohol **8**, Weinreb amide **9**, and carboxylic acid **10** (Scheme 5). Fluoro acid **10** can also undergo an intramolecular Friedel–Crafts acylation to furnish fluorine-substituted tetralone **11**. Notably, all of these derivatives were obtained with excellent enantiopurity.



Scheme 5. Further transformations of an α -fluoro ester.

In summary, we have developed an efficient asymmetric α -fluorination of azolium enolates that were generated from simple aliphatic aldehydes and α -chloro aldehydes. With a suitable combination of precatalyst, oxidant, base, and fluorination reagent, the reaction proceeded smoothly to yield a wide range of α -fluoro esters, amides, and thioesters with excellent enantioselectivity. NFSI served as both the fluorine source and the oxidant in the reactions of simple aliphatic aldehydes. Pyrazole was employed as an effective acyl transfer reagent in the synthesis of α -fluoro amides and thioesters. The mild fluorination conditions can also be coupled with alcohol oxidation in a one-pot process to avoid the isolation of unstable aldehydes. The highly enan-

tioenriched fluorinated products were shown to be precursors to other useful fluorine-containing chiral building blocks.

Received: October 10, 2014

Revised: October 30, 2014

Published online: November 13, 2014

Keywords: asymmetric catalysis · enolates · fluorine · N-heterocyclic carbenes · organocatalysis

- [1] a) K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881; b) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320.
- [2] a) V. A. Brunet, D. O'Hagan, *Angew. Chem. Int. Ed.* **2008**, *47*, 1179; *Angew. Chem.* **2008**, *120*, 1198; b) J.-A. Ma, D. Cahard, *Chem. Rev.* **2008**, *108*, PR1; c) M. Ueda, T. Kano, K. Maruoka, *Org. Biomol. Chem.* **2009**, *7*, 2005; d) S. Lectard, Y. Hamashima, M. Sodeoka, *Adv. Synth. Catal.* **2010**, *352*, 2708; e) Y. Ku Kang, D. Y. Kim, *Curr. Org. Chem.* **2010**, *14*, 917; f) T. Furuya, A. S. Kamlet, T. Ritter, *Nature* **2011**, *473*, 470; g) G. Valero, X. Companyó, R. Rios, *Chem. Eur. J.* **2011**, *17*, 2018; h) U. Hennecke, *Angew. Chem. Int. Ed.* **2012**, *51*, 4532; *Angew. Chem.* **2012**, *124*, 4608.
- [3] For examples of metal-catalyzed asymmetric α -fluorination reactions of carbonyl compounds, see: a) L. Hintermann, A. Togni, *Angew. Chem. Int. Ed.* **2000**, *39*, 4359; *Angew. Chem.* **2000**, *112*, 4530; b) Y. Hamashima, K. Yagi, H. Takano, L. Tamás, M. Sodeoka, *J. Am. Chem. Soc.* **2002**, *124*, 14530; c) N. Shibata, J. Kohno, K. Takai, T. Ishimaru, S. Nakamura, T. Toru, S. Kanemasa, *Angew. Chem. Int. Ed.* **2005**, *44*, 4204; *Angew. Chem.* **2005**, *117*, 4276; d) D. S. Reddy, N. Shibata, J. Nagai, S. Nakamura, T. Toru, S. Kanemasa, *Angew. Chem. Int. Ed.* **2008**, *47*, 164; *Angew. Chem.* **2008**, *120*, 170; e) S. Suzuki, Y. Kitamura, S. Lectard, Y. Hamashima, M. Sodeoka, *Angew. Chem. Int. Ed.* **2012**, *51*, 4581; *Angew. Chem.* **2012**, *124*, 4659; f) Y. Hamashima, T. Suzuki, H. Takano, Y. Shimura, M. Sodeoka, *J. Am. Chem. Soc.* **2005**, *127*, 10164; g) T. Suzuki, Y. Hamashima, M. Sodeoka, *Angew. Chem. Int. Ed.* **2007**, *46*, 5435; *Angew. Chem.* **2007**, *119*, 5531; h) D. H. Paull, M. T. Scerba, E. Alden-Danforth, L. R. Widger, T. Lectka, *J. Am. Chem. Soc.* **2008**, *130*, 17260; i) J. Erb, D. H. Paull, T. Dudding, L. Belding, T. Lectka, *J. Am. Chem. Soc.* **2011**, *133*, 7536.
- [4] For examples of organocatalytic asymmetric α -fluorination reactions of carbonyl compounds, see: a) M. Marigo, D. Fielenbach, A. Branton, A. Kjærsgaard, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2005**, *44*, 3703; *Angew. Chem.* **2005**, *117*, 3769; b) D. D. Steiner, N. Mase, C. F. Barbás III, *Angew. Chem. Int. Ed.* **2005**, *44*, 3706; *Angew. Chem.* **2005**, *117*, 3772; c) T. D. Beeson, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2005**, *127*, 8826; d) J. Franzén, M. Marigo, D. Fielenbach, T. C. Wabnitz, A. Kjærsgaard, K. A. Jørgensen, *J. Am. Chem. Soc.* **2005**, *127*, 18296; e) T. Ishimaru, N. Shibata, T. Horikawa, N. Yasuda, S. Nakamura, T. Toru, M. Shiro, *Angew. Chem. Int. Ed.* **2008**, *47*, 4157; *Angew. Chem.* **2008**, *120*, 4225; f) K. Shibatomi, H. Yamamoto, *Angew. Chem. Int. Ed.* **2008**, *47*, 5796; *Angew. Chem.* **2008**, *120*, 5880; g) P. Kwiatkowski, T. D. Beeson, J. C. Conrad, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2011**, *133*, 1738; h) S. Y. Lee, S. Neufeind, G. C. Fu, *J. Am. Chem. Soc.* **2014**, *136*, 8899.
- [5] For recent reviews on NHC catalysis, see: a) H. U. Vora, P. Wheeler, T. Rovis, *Adv. Synth. Catal.* **2012**, *354*, 1617; b) X. Bugaut, F. Glorius, *Chem. Soc. Rev.* **2012**, *41*, 3511; c) J. Izquierdo, G. E. Hutson, D. T. Cohen, K. A. Scheidt, *Angew. Chem. Int. Ed.* **2012**, *51*, 11686; *Angew. Chem.* **2012**, *124*, 11854; d) D. T. Cohen, K. A. Scheidt, *Chem. Sci.* **2012**, *3*, 53; e) A.

- Grossmann, D. Enders, *Angew. Chem. Int. Ed.* **2012**, *51*, 314; *Angew. Chem.* **2012**, *124*, 320; f) J. W. Bode, *Nat. Chem.* **2013**, *5*, 813; g) S. De Sarkar, A. Biswas, R. C. Samanta, A. Studer, *Chem. Eur. J.* **2013**, *19*, 4664; h) S. J. Ryan, L. Candish, D. W. Lupton, *Chem. Soc. Rev.* **2013**, *42*, 4906; i) P. Chauhan, D. Enders, *Angew. Chem. Int. Ed.* **2014**, *53*, 1485; *Angew. Chem.* **2014**, *126*, 1509; j) J. Mahatthananchai, J. W. Bode, *Acc. Chem. Res.* **2014**, *47*, 696.
- [6] For reviews/articles describing the generation of azolium enolates and their reactivity, see: a) J. Douglas, G. Churchill, A. D. Smith, *Synthesis* **2012**, 2295; b) X.-Y. Chen, S. Ye, *Synlett* **2013**, 1614; c) B. Maji, H. Mayr, *Angew. Chem. Int. Ed.* **2013**, *52*, 11163; *Angew. Chem.* **2013**, *125*, 11370.
- [7] For pioneering work on the use of azolium enols/enolates, see: a) K. Y.-K. Chow, J. W. Bode, *J. Am. Chem. Soc.* **2004**, *126*, 8126; b) N. T. Reynolds, J. R. de Alaniz, T. Rovis, *J. Am. Chem. Soc.* **2004**, *126*, 9518; c) N. T. Reynolds, T. Rovis, *J. Am. Chem. Soc.* **2005**, *127*, 16406; d) M. He, G. J. Uc, J. W. Bode, *J. Am. Chem. Soc.* **2006**, *128*, 15088.
- [8] For pioneering work on the asymmetric halogenation of azolium enolates, see: J. Douglas, K. B. Ling, C. Concellón, G. Churchill, A. M. Z. Slawin, A. D. Smith, *Eur. J. Org. Chem.* **2010**, 5863.
- [9] a) Y.-M. Zhao, M. S. Cheung, Z. Lin, J. Sun, *Angew. Chem. Int. Ed.* **2012**, *51*, 10359; *Angew. Chem.* **2012**, *124*, 10505; b) X. Dong, Y.-M. Zhao, J. Sun, *Synlett* **2013**, 1221; c) Y.-M. Zhao, Y. Tam, Y.-J. Wang, Z. Li, J. Sun, *Org. Lett.* **2012**, *14*, 1398; d) X. Dong, J. Sun, *Org. Lett.* **2014**, *16*, 2450.
- [10] a) H. U. Vora, T. Rovis, *J. Am. Chem. Soc.* **2010**, *132*, 2860; b) P. Wheeler, H. U. Vora, T. Rovis, *Chem. Sci.* **2013**, *4*, 1674.
- [11] a) X. Zhao, K. E. Ruhl, T. Rovis, *Angew. Chem. Int. Ed.* **2012**, *51*, 12330; *Angew. Chem.* **2012**, *124*, 12496; b) J. Mo, X. Chen, B. Tiwari, Y. R. Chi, *Org. Lett.* **2013**, *15*, 50; c) J. Mo, L. Shen, Y. R. Chi, *Angew. Chem. Int. Ed.* **2013**, *52*, 8588; *Angew. Chem.* **2013**, *125*, 8750.
- [12] Precatalyst **A** was first disclosed by Bode and co-workers; see: a) M. He, J. R. Struble, J. W. Bode, *J. Am. Chem. Soc.* **2006**, *128*, 8418; b) J. R. Struble, J. W. Bode, *Org. Synth.* **2010**, *87*, 362.
- [13] For a review on the use of electrophilic fluorination agents as oxidants in organic synthesis, see: K. M. Engle, T.-S. Mei, X. Wang, J.-Q. Yu, *Angew. Chem. Int. Ed.* **2011**, *50*, 1478; *Angew. Chem.* **2011**, *123*, 1514.
- [14] a) H. U. Vora, T. Rovis, *J. Am. Chem. Soc.* **2007**, *129*, 13796; b) J. W. Bode, S. S. Sohn, *J. Am. Chem. Soc.* **2007**, *129*, 13798; c) K. B. Ling, A. D. Smith, *Chem. Commun.* **2011**, 47, 373; d) S. De Sarkar, A. Studer, *Org. Lett.* **2010**, *12*, 1992.
- [15] M. Movassaghi, M. A. Schmidt, *Org. Lett.* **2005**, *7*, 2453.