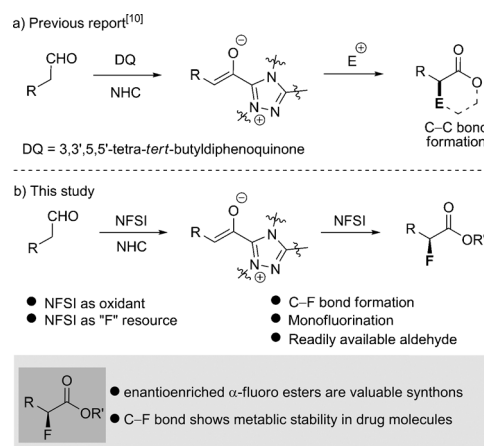


Oxidative Enantioselective α -Fluorination of Aliphatic Aldehydes Enabled by N-Heterocyclic Carbene Catalysis**

Fangyi Li, Zijun Wu, and Jian Wang*

Abstract: Described is the first study on oxidative enantioselective α -fluorination of simple aliphatic aldehydes enabled by N-heterocyclic carbene catalysis. N-fluorobis(phenyl)-sulfonimide serves as an oxidant and as an “F” source. The C–F bond formation occurs directly at the α position of simple aliphatic aldehydes, thus overcoming nontrivial challenges, such as competitive difluorination and nonfluorination, and proceeds with high to excellent enantioselectivities.

Organofluorine compounds display a wide range of distinct physical properties which often render them valuable to the pharmaceutical companies and agrochemical industries.^[1] In particular, fluorine atom incorporation has become an effective tool for medicinal chemists to alter the bioactivity of drug candidates.^[2] Despite the broad-spectrum utility of such C–F bond containing compounds, it is remarkable to consider that only a few catalytic methods exist for the asymmetric installation of fluorine onto carbogenic frameworks^[3] and that most of these methods have focused on the generation of non-enolizable products such as α -alkyl- β -ketoesters. Given that chiral α -fluoro carbonyl compounds have been identified as high-value synthons for chemical synthesis,^[4] great progress has been made by employing chiral metal complexes for electrophilic fluorination of activated ketones,^[3a,b,e] nucleophilic fluorination of ketenes, and using nucleophilic fluorine sources for enantioselective allylic fluorination.^[3k,l] Enamine catalysis has furnished a number of protocols for highly enantioselective α -fluorination of aldehydes^[5a–d] and ketones.^[5e] Cinchona alkaloids have been effective for fluorination of carbon nucleophiles^[6] and in a dual catalysis mechanism to enable the fluorination of acyl chlorides.^[7] Recently, a combination of chiral-anion phase-transfer catalysis and enamine catalysis has been reported to generate α -branched α -fluoroketones.^[8] Surprisingly, despite the availability of a variety of N-heterocyclic carbene (NHC) catalysts (e.g., catalysts **A–F** in Table 1),^[9] the utility of simple aldehydes in NHC-catalyzed α -fluorination reactions is still comprehensively elusive. In contrast to the NHC-catalyzed α -C–C bond formation reaction (Scheme 1a),^[10] the disclosure of enantioselective α -fluorination of simple aliphatic aldehydes catalyzed by chiral NHC catalysts has not yet been



Scheme 1. Oxidative NHC catalysis of aliphatic aldehydes.

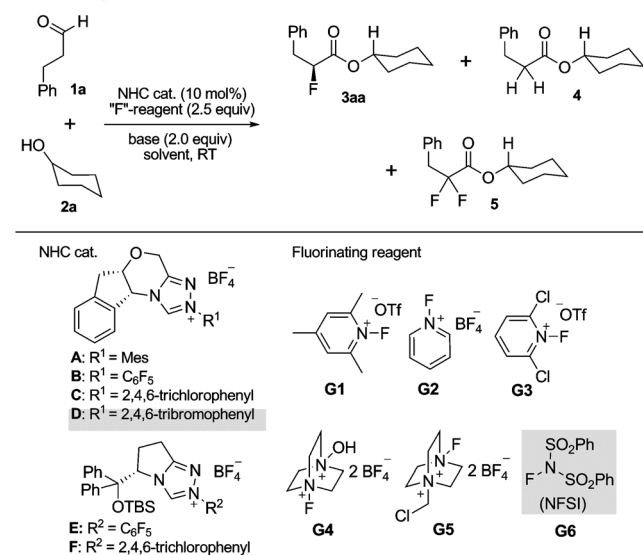
reported.^[11] Herein, we report the first example of oxidative enantioselective α -fluorination of simple aliphatic aldehydes catalyzed by an NHC catalyst. It is noteworthy that NFSI is disclosed not only as an electrophilic fluorinating resource^[12] but also as an oxidant^[13] in asymmetric organocatalysis (Scheme 1b).

Key results on optimization of the reaction conditions are summarized in Table 1. The reaction of the aliphatic aldehyde **1a** (0.2 mmol) with cyclohexanol (**2a**; 0.6 mmol) was chosen as a model reaction. Studies on chiral NHC catalysts revealed that when the indanol-derived catalysts **C** and **D**,^[14] with an *N*-2,4,6-trichloro- and *N*-2,4,6-tribromophenyl substituent, respectively, were used, the desired α -fluorinated product **3aa** was efficiently formed, albeit with a high enantioselectivity (entry 3 and 4). Notably, only a trace amount of the nonfluorinated ester **4** and difluorinated ester **5** was detected under these reaction conditions. To further improve the enantiocontrol, we turned our attention to screening solvents (entries 6–9). The results indicate that the use of 1,4-dioxane consistently afforded the desired product with a reliable chemical yield and a slightly enhanced *ee* value (entry 9). A switch of base from K_2CO_3 to NaOAc led to a slightly higher *ee* value and comparable yield (entry 13). At last we conducted experiments to test the effect of “F” resources. Surprisingly, all other commonly used fluorinating reagents (**G1–G5**) gave either no reaction (entries 14–16) or low conversion (entry 17 and 18). The high reactivity of NFSI (versus that of **G1–G5**) can probably be attributed to two factors: 1) NFSI has a higher oxidation potential (–0.78 V) and 2) NFSI has a better solubility in organic solvents.^[4a] Consequently, NFSI was selected as the most efficient

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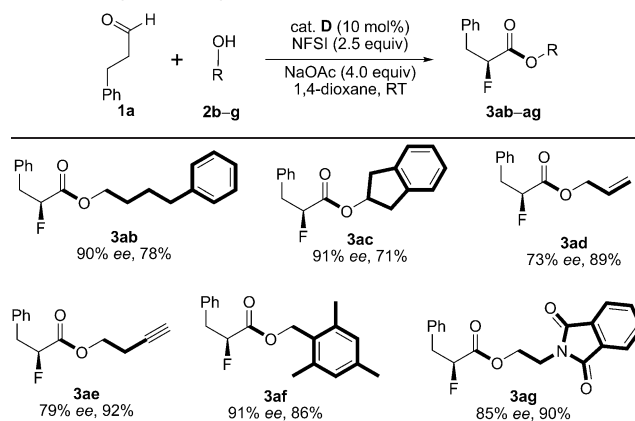
Table 1: Optimization of the reaction conditions.^[a]


Entry	NHC	Base	Solvent	"F" rea- gent	3 aa Yield [%] ^[a]	3 aa <i>ee</i> [%] ^[b]	4 Yield [%] ^[c]	5 ^[d]
1	A	K ₂ CO ₃	toluene	G6	n.r. ^[f]	— ^[g]	— ^[g]	trace
2	B	K ₂ CO ₃	toluene	G6	66	74	10	trace
3	C	K ₂ CO ₃	toluene	G6	84	92	< 5	trace
4	D	K ₂ CO ₃	toluene	G6	86	92	< 5	trace
5	E	K ₂ CO ₃	toluene	G6	< 5	— ^[g]	12	trace
6	F	K ₂ CO ₃	toluene	G6	— ^[g]	— ^[g]	20	trace
7	D	K ₂ CO ₃	CH ₂ Cl ₂	G6	56	93	< 10	trace
8	D	K ₂ CO ₃	THF	G6	46	86	< 10	trace
9	D	K ₂ CO ₃	1,4-dioxane	G6	72	94	< 5	trace
10	D	PhCO ₂ Na	1,4-dioxane	G6	50	92	< 5	trace
11	D	K ₃ PO ₄	1,4-dioxane	G6	77	94	< 5	trace
12	D	NaOAc	1,4-dioxane	G6	78	96	< 5	trace
13 ^[e]	D	NaOAc	1,4-dioxane	G6	84	96	< 5	trace
14	D	NaOAc	1,4-dioxane	G1	n.r. ^[f]	— ^[g]	— ^[g]	— ^[g]
15	D	NaOAc	1,4-dioxane	G2	n.r. ^[f]	— ^[g]	— ^[g]	— ^[g]
16	D	NaOAc	1,4-dioxane	G3	n.r. ^[f]	— ^[g]	— ^[g]	— ^[g]
17	D	NaOAc	1,4-dioxane	G4	< 5	— ^[g]	— ^[g]	— ^[g]
18	D	NaOAc	1,4-dioxane	G5	31	83	— ^[g]	— ^[g]

[a] Reactions were carried out with aldehyde **1a** (0.2 mmol), alcohol **2a** (0.6 mmol), cat. **A–F** (0.02 mmol), NFSI (0.5 mmol) and base (0.4 mmol) in 1,4-dioxane (2 mL) for 24 h at RT. [b] Enantiomeric excess (*ee*) was determined by chiral HPLC analysis. [c] Yields determined by ¹H NMR spectroscopy of the crude product. [d] Determined by GC-MS. [e] NaOAc (0.8 mmol, 4 equiv). [f] No reaction. [g] Not determined. TBS = *tert*-butyldimethylsilyl.

electrophilic fluorinating reagent and oxidant for next evaluation.

With the optimal reaction conditions in hand, we turned our attention to examining the scope of alcohols. As indicated in Table 2, the oxidative enantioselective α -fluorination reaction is not limited to the synthesis of cyclohexyl esters (**3aa**). It can also be applied to construct a diverse set of alkyl esters in the presence of various alcohols, such as 4-phenyl-1-butanol (**2b**), 2-indinol (**2c**), allylic alcohol (**2d**), propargyl alcohol (**2e**), mesitylmethanol (**2f**), as well as *N*-(2-hydroxyethyl)phthalimide (**2g**), in good yields and good to excellent enantioselectivities.

Table 2: Scope with respect to the alcohol.^[a–d]


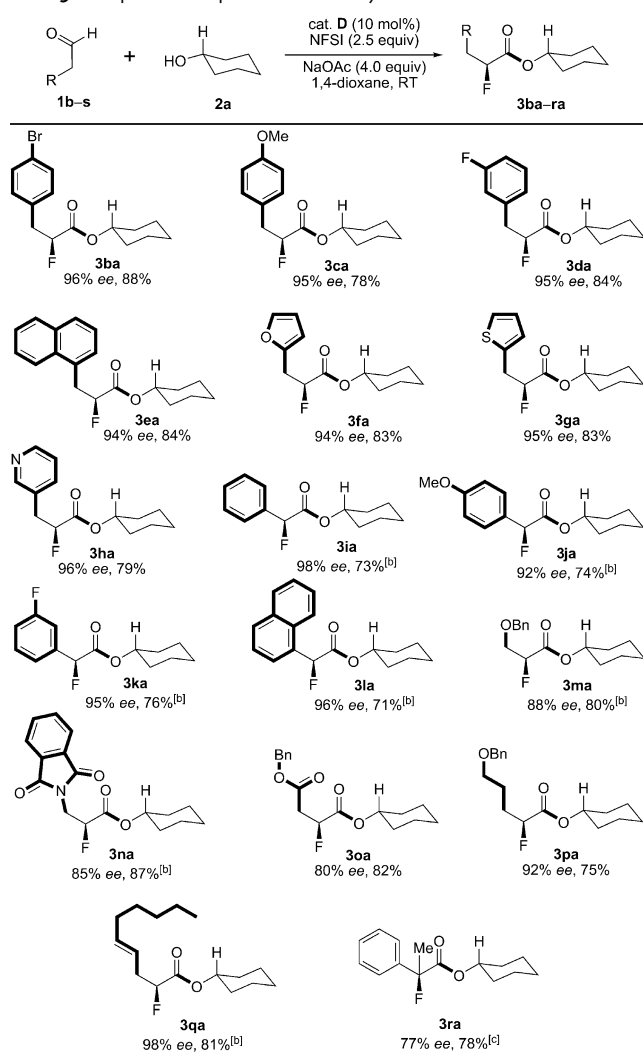
[a] Reactions were carried out with aldehyde **1a** (0.2 mmol), alcohol **2b–g** (0.4 mmol), cat. **D** (0.02 mmol), NFSI (0.5 mmol), and NaOAc (0.8 mmol) in 1,4-dioxane (2 mL) for 24 h at RT. [b] Yield is that of product isolated after column chromatography. [c] MeOH and EtOH gave a trace amount of α -fluoroester determined by GC-MS. [d] Unfortunately, *t*BuOH gave no desired α -fluoroester.

However, methanol and ethanol only gave trace amounts of the desired products. We speculated that less sterically hindered alcohols prefer to react with the intermediate **III** rather than intermediate **V** (Scheme 3) thus preventing the reaction and generating the nonfluorinated ester. However, *tert*-butanol is too sterically inaccessible for nucleophilic attack in this process and thus caused no reaction.

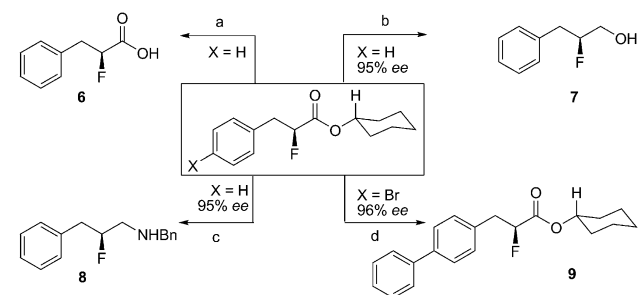
Next, we examined the scope of simple aliphatic aldehydes. Examples of aliphatic aldehydes and cyclohexanol which worked effectively under the optimal reaction conditions (Table 1, entry 13) are illustrated in Table 3. With **2a** as the model alcohol substrate, aliphatic aldehydes derived from α -(hetero)aryl aldehydes bearing various substituents all worked well, thus affording the corresponding α -fluorinated esters **3ba–ha** with good yields and excellent *ee* values (93–96% *ee*). Both electron-donating (**3ca**) and electron-withdrawing (**3ba** and **3da**) substituents on the β -phenyl unit were tolerated. Notably, aliphatic aldehydes containing different aryl (**3ia–la**) substituents at the α -position also reacted well, thus leading to the desired α -fluorinated products with good yields and excellent *ee* values (92–98% *ee*). Pleasingly, substrates (**1g** and **1h**) containing F-sensitive atoms (S and N) could be tolerated without any loss of yield and enantioselectivity (**3ga** and **3ha**). Furthermore, more bulky α -substituted aliphatic aldehydes required a longer reaction time than less sterically hindered α -substituted aliphatic aldehydes (72 h versus 24 h). With respect to the above aliphatic aldehydes, α -functionalized aldehydes (**1m** and **1n**) were also tolerated in this reaction (**3ma** and **3na**). When long alkyl chain based aldehydes were used, the enantioselectivity still maintained at high to excellent levels (**3oa–qa**). Pleasingly, the α,α -disubstituted aldehyde **1r** reacted well with **2a** and afforded the tertiary α -fluoroester **3ra** in the presence of 20 mol % cat. **D** (77% *ee* and 78% yield).

The enantioenriched α -fluoroesters can be transformed into a variety of other chiral secondary fluorinated derivatives

Table 3: Scope with respect to the aldehyde.^[a]

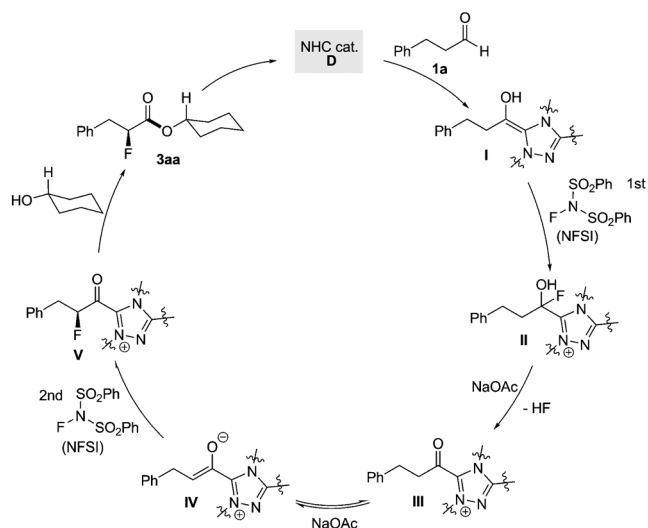


[a] Reaction conditions as in Table 2. [b] 72 h. [c] 20 mol % **D**, 72 h.



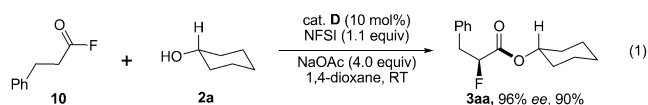
Scheme 2. Transformations of α -fluorinated esters. Reaction conditions: a) LiOH, aq. H_2O_2 , THF, $0^\circ\text{C} \rightarrow \text{RT}$, overnight, 86% yield; b) LiAlH_4 , THF, -20°C , 30 min, 91% yield; c) 1. DIBAL-H, CH_2Cl_2 , -78°C , 20 min; 2. BnNH_2 , $\text{NaBH}(\text{OAc})_3$, DCE, RT, overnight, 81% yield (2 steps); d) $\text{PhB}(\text{OH})_2$, $[\text{Pd}(\text{PPh}_3)_4]$, K_2CO_3 , toluene, 90°C , 2 h, 94% yield. DCE = 1,2-dichloroethane, DIBAL-H = diisobutylaluminum hydride, THF = tetrahydrofuran.

(Scheme 2). The absolute configuration of **7** was determined by optical rotation, which is comparable to the literature value,^[15] and the other products were assigned by its analogy.



Scheme 3. Postulated mechanism.

A postulated mechanism of this reaction process is depicted in Scheme 3. Reaction of **2a** with the NHC catalyst **D** in the presence of NaOAc forms the Breslow intermediate **I**. Nucleophilic addition of Breslow intermediate to NFSI converts **I** into the NHC-bound fluorinated intermediate **II**. Then conversion of **II** into **III** is accelerated by NaOAc through the elimination of HF. To prove the potential formation of **III**, we conducted an experiment using **10** as the starting material and catalyst **D** [Eq. (1)]. Pleasingly, this



in situ formed **III** could react with NFSI (only 1.1 equiv) to afford **3aa** as expected (90% yield and 96% ee). The subsequent deprotonation allows **III** and the enolate **IV** to reach a rapid equilibrium (Scheme 3). Finally, **IV** behaves as a nucleophile to interact with the second NFSI to eventually form the α -fluoroester product **3aa** along with the regeneration of NHC catalyst **D**.

In summary, the first study of an NHC-catalyzed oxidative enantioselective α -fluorination of simple aliphatic aldehydes using NFSI, which plays two roles, is presented. In the presence of an appropriate combination of a NHC precatalyst, a base, an oxidant (NFSI), and a "F" resource (NFSI), the C–F bond formation occurs directly at the α position of simple aliphatic aldehydes and proceeds with high to excellent enantioselectivities.

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- [1] a) *Fluorine in Pharmaceutical and Medicinal Chemistry* (Eds.: V. Gouverneur, K. Müller), Imperial College Press, London, **2012**; b) *Fluorine in Medicinal Chemistry and Chemical Biology* (Ed.: I. Ojima), Wiley, Chichester, **2009**.
- [2] a) K. Müller, C. Faeh, F. Diederich, *Science* **2007**, *317*, 1881; b) H.-J. Böhm, D. Banner, S. Bendels, M. Kansy, B. Kuhn, K. Müller, U. Obst-Sander, M. Stahl, *ChemBioChem* **2004**, *5*, 637; c) S. Purser, P. R. Moore, S. Swallow, V. Gouverneur, *Chem. Soc. Rev.* **2008**, *37*, 320.
- [3] For selected reviews and examples, 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) T. Suzuki, Y. Hamashima, M. Sodeoka, *Angew. Chem. Int. Ed.* **2007**, *46*, 5435; *Angew. Chem.* **2007**, *119*, 5531; d) D. H. Paull, M. T. Scerba, E. Alden-Danforth, L. R. Widger, T. Lectka, *J. Am. Chem. Soc.* **2008**, *130*, 17260; e) S. Lectard, Y. Hamashima, M. Sodeoka, *Adv. Synth. Catal.* **2010**, *352*, 2708; f) V. A. Brunet, D. O'Hagan, *Angew. Chem. Int. Ed.* **2008**, *47*, 1179; *Angew. Chem.* **2008**, *120*, 1198; g) J.-A. Ma, D. Cahard, *Chem. Rev.* **2008**, *108*, PR1; h) G. K. S. Prakash, P. Beirer, *Angew. Chem. Int. Ed.* **2006**, *45*, 2172; *Angew. Chem.* **2006**, *118*, 2228; i) P. M. Pihko, *Angew. Chem. Int. Ed.* **2006**, *45*, 544; *Angew. Chem.* **2006**, *118*, 558; j) N. E. J. Gooseman, D. O'Hagan, M. J. G. Peach, A. M. Z. Slawin, D. J. Tozer, R. J. Young, *Angew. Chem. Int. Ed.* **2007**, *46*, 5904; *Angew. Chem.* **2007**, *119*, 6008; k) J. A. Kalow, A. G. Doyle, *J. Am. Chem. Soc.* **2010**, *132*, 3268; l) M. H. Katcher, A. G. Doyle, *J. Am. Chem. Soc.* **2010**, *132*, 17402.
- [4] For reviews that include catalytic asymmetric fluorination, see: a) T. Liang, C. N. Neumann, T. Ritter, *Angew. Chem. Int. Ed.* **2013**, *52*, 8214; *Angew. Chem.* **2013**, *125*, 8372; b) V. Gouverneur, O. Lozano in *Science of Synthesis, Vol. 3* (Eds.: J. G. De Vries, G. A. Molander, P. A. Evans), Thieme, Stuttgart, **2011**, p. 851; c) G. Valero, X. Companyó, R. Rios, *Chem. Eur. J.* **2011**, *17*, 2018; d) D. Cahard, X. Xu, S. Couve-Bonnaire, X. Pannecoucke, *Chem. Soc. Rev.* **2010**, *39*, 558.
- [5] a) M. Marigo, D. Fielenbach, A. Braunton, 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. Barbas 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) D. Enders, M. R. M. Hüttl, *Synlett* **2005**, 0991; e) P. Kwiatkowski, T. D. Beeson, J. C. Conrad, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2011**, *133*, 1738.
- [6] a) 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; b) O. Lozano, G. Blessley, T. M. del Campo, A. L. Thompson, G. T. Giuffredi, M. Bettati, M. Walker, R. Borman, V. Gouverneur, *Angew. Chem. Int. Ed.* **2011**, *50*, 8105; *Angew. Chem.* **2011**, *123*, 8255; c) N. Shibata, E. Suzuki, Y. Takeuchi, *J. Am. Chem. Soc.* **2000**, *122*, 10728.
- [7] J. Erb, D. H. Paull, T. Dudding, L. Belding, T. Lectka, *J. Am. Chem. Soc.* **2011**, *133*, 7536; see also Ref. [3 d].
- [8] X. Yang, R. J. Phipps, F. D. Toste, *J. Am. Chem. Soc.* **2014**, *136*, 5225.
- [9] For selected recent reviews of NHC catalysis, see: a) D. Enders, T. Balensiefer, *Acc. Chem. Res.* **2004**, *37*, 534; b) K. Zeitler, *Angew. Chem. Int. Ed.* **2005**, *44*, 7506; *Angew. Chem.* **2005**, *117*, 7674; c) D. Enders, O. Niemeier, A. Henseler, *Chem. Rev.* **2007**, *107*, 5606; d) N. Marion, S. Diez-Gonzalez, S. P. Nolan, *Angew. Chem. Int. Ed.* **2007**, *46*, 2988; *Angew. Chem.* **2007**, *119*, 3046; e) V. Nair, S. Vellalath, B. P. Babu, *Chem. Soc. Rev.* **2008**, *37*, 2691; f) T. Rovis, *Chem. Lett.* **2008**, *37*, 2; g) A. J. Arduengo III, L. I. Iconaru, *Dalton Trans.* **2009**, 6903; h) E. M. Phillips, A. Chan, K. A. Scheidt, *Aldrichimica Acta* **2009**, *42*, 55; i) J. L. Moore, T. Rovis, *Top. Curr. Chem.* **2010**, *291*, 77; j) A. T. Biju, N. Kuhl, F. Glorius, *Acc. Chem. Res.* **2011**, *44*, 1182; k) K. Hirano, I. Piel, F. Glorius, *Chem. Lett.* **2011**, *40*, 786; l) P.-C. Chiang, J. W. Bode, *TCIMERU* **2011**, *149*, 2; m) V. Nair, R. S. Menon, A. T. Biju, C. R. Sinu, R. R. Paul, A. Jose, V. Sreekumar, *Chem. Soc. Rev.* **2011**, *40*, 5336; n) Z. Q. Rong, W. Zhang, G. Q. Yang, S.-L. You, *Curr. Org. Chem.* **2011**, *15*, 3077; o) H. U. Vora, T. Rovis, *Aldrichimica Acta* **2011**, *44*, 3; p) D. T. Cohen, K. A. Scheidt, *Chem. Sci.* **2012**, *3*, 53; q) A. Grossmann, D. Enders, *Angew. Chem. Int. Ed.* **2012**, *51*, 314; *Angew. Chem.* **2012**, *124*, 320.
- [10] a) B. E. Marki, K. A. Scheidt, *Org. Lett.* **2008**, *10*, 4331; b) X. Zhao, K. E. Ruhl, T. Rovis, *Angew. Chem. Int. Ed.* **2012**, *51*, 12330; *Angew. Chem.* **2012**, *124*, 12496; c) J. Mo, R. Yang, X. Chen, B. Tiwari, Y. R. Chi, *Org. Lett.* **2013**, *15*, 50; d) J. Mo, L. Shen, Y. R. Chi, *Angew. Chem. Int. Ed.* **2013**, *52*, 8588; *Angew. Chem.* **2013**, *125*, 8750.
- [11] 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; c) Y. M. Zhao, M. S. Cheung, Z. Lin, J. Sun, *Angew. Chem. Int. Ed.* **2012**, *51*, 10359; *Angew. Chem.* **2012**, *124*, 10505.
- [12] J. Baudoux, D. Cahard, *Org. React.*, Wiley, Hoboken, **2007**, p. 347; see also Ref. [3 g].
- [13] a) X. Wang, D. Leow, J.-Q. Yu, *J. Am. Chem. Soc.* **2011**, *133*, 13864; b) N. D. Ball, J. B. Gary, Y. Ye, M. S. Sanford, *J. Am. Chem. Soc.* **2011**, *133*, 7577; c) C. F. Rosewall, P. A. Sibbald, D. V. Liskin, F. E. Michael, *J. Am. Chem. Soc.* **2009**, *131*, 9488; d) P. A. Sibbald, C. F. Rosewall, R. D. Swartz, F. E. Michael, *J. Am. Chem. Soc.* **2009**, *131*, 15945.
- [14] For synthesis of the NHC precatalyst **D** (Rovis catalyst), see: D. A. DiRocco, K. M. Oberg, T. Rovis, *J. Am. Chem. Soc.* **2012**, *134*, 6143.
- [15] $[\alpha]_{\text{D}}^{25} = -16.8$ ($c = 1.0$, CHCl_3). For a related reference, see: F. A. Davis, W. Han, *Tetrahedron Lett.* **1992**, *33*, 1153.