Chapter 4

Enantioselective Organocatalytic Direct α-Fluorination of Ketones

Introduction

In the previous chapter, the development of the enantioselective enamine-catalyzed α-fluorination of aldehydes was discussed. Due to the importance of fluorine stereocenters and the scarcity of direct methods for creating them, we subsequently sought to expand on this valuable methodology to include the α-fluorination of ketones. As mentioned in the previous chapter, the majority of direct asymmetric fluorination methods have focused (with the exception of the enamine-catalyzed aldehyde fluorination) on highly enolizable substrates such as β-ketoesters that are precluded from product epimerization.[1] Asymmetric construction of epimerizable α-fluoroketone stereocenters has only been accomplished with low yields and selectivities, or by multi-step syntheses. For example, a two-step procedure for preparing chiral α-fluoroketones introduced by Haufe and coworkers explored the possibility of desymmetrizing meso epoxides by catalytic asymmetric ring opening using a fluoride source, subsequent

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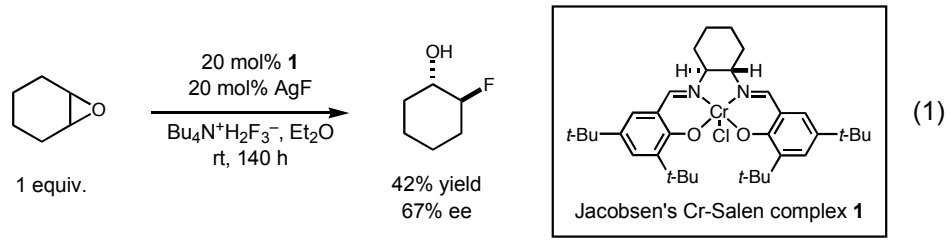
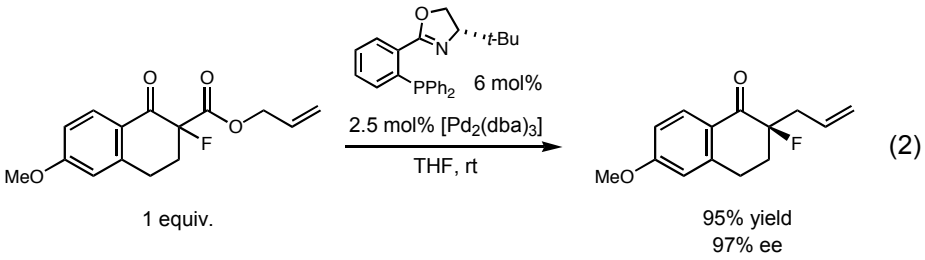
[1] (a) Hintermann, L.; Togni, A. *Angew. Chem. Int. Ed.* **2000**, *112*, 4530. (b) Frantz, R.; Hintermann, L.; Perseghini, M.; Broggini, D.; Togni, A. *Org. Lett.* **2003**, *5*, 1709. (c) Hamashima, Y.; Yagi, K.; Takano, H.; Tamás, L.; Sodeoka, M. *J. Am. Chem. Soc.* **2002**, *124*, 14530. (d) Kim, D. Y.; Park, E. J. *Org. Lett.* **2002**, *4*, 545. (e) Hamashima, Y.; Yagi, K.; Takao, H.; Hotta, D.; Sodeoka, M. *Org. Lett.* **2003**, *5*, 3225. (f) Ma, J.-A.; Cahard, D. *Tetrahedron: Asymmetry* **2004**, *15*, 1007. (g) Shibata, N.; Ishimaru, T.; Nagai, T.; Kohno, J.; Toru, T. *Synlett.* **2004**, 1703.

oxidation of which would yield the desired fluoroketones.[2] Using catalytic quantities of Jacobsen's chromium salen complex **1**, the fluorohydrin was obtained in 42% yield and 67% ee (equation 1). Higher conversions could be obtained but required stoichiometric amounts of the chromium complex.



(1)



(2)

Additionally, Nakamura et al. showed that racemic α-fluoro-β-ketoesters could undergo enantioselective decarboxylative allylation to generate α-allyl-α-fluoroketones in high yield and enantiomeric excess (equation 2).[3] However, as with most methodologies that produce α-fluoro stereocenters, this method also generates a product that is precluded from post-epimerization.

Recently, Szori, Szöllosi, and Bartók reported an asymmetric hydrogenation of racemic 2-fluorocyclohexanone over a cinchona alkaloid-modified platinum-aluminum oxide catalyst.[4] As the reaction progressed, a kinetic resolution was observed and one

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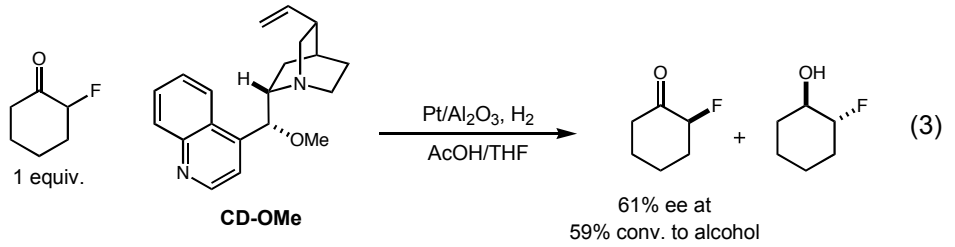
[2] (a) Haufe, G.; Bruns, S. *Adv. Synth. Catalysis* **2002**, *344*, 165. (b) Haufe, G.; Bruns, S.; Runge, M. *J. Fluorine Chem.* **2001**, *112*, 55.

[3] (a) Nakamura, M.; Hajra, A.; Endo, K.; Nakamura, E. *Angew. Chem. Int. Ed.* **2005**, *44*, 7248. (b) Burger, E. C.; Barron, B. R.; Tunge, J. A. *Synlett* **2006**, 2824.

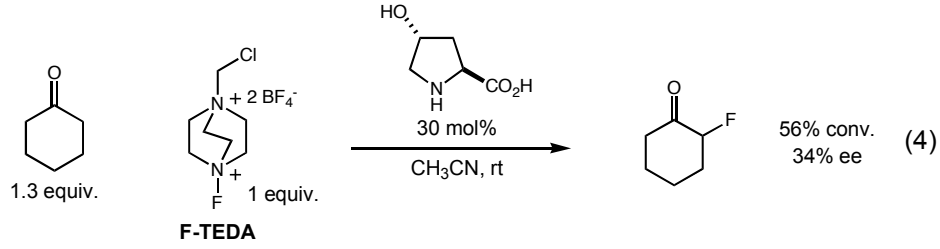
[4] Szori, K.; Szöllosi, G.; Bartók, M. *J. Catalysis* **2006**, *244*, 255.

enantiomer of the racemic starting material was accumulated in the reaction. Using methoxy-cinchonidine (CD-OMe), α-fluorocyclohexanone was observed at 61% ee when the reaction had reached 60% conversion (equation 3).



(3)

In an attempt to perform a direct α-fluorination of ketones using enamine activation, which had been successful with aldehydes, Enders and Hüttl studied α-fluorination of ketones using proline-based catalysts and F-TEDA as the fluorine source (equation 4).[5] Unfortunately, the best result obtained was 56% conversion and 34% ee for α-fluorocyclohexanone using 4-hydroxyproline as the catalyst. Enders has also demonstrated the asymmetric synthesis of fluoroketones using the SAMP/RAMP chiral auxiliaries to α-silate ketones enantioselectively, which can then be fluorinated diastereoselectively and desilated to generate the desired fluoroketones; however, this method requires a minimum of five synthetic steps.[6]



(4)

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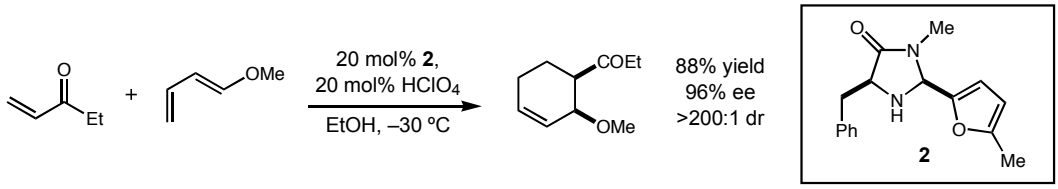
5 Enders, D.; Hüttl, M. R. M. *Synlett*, **2005**, 991.

6 Enders, D.; Faure, S.; Potthoff, M.; Runsink, J. *Synthesis* **2001**, 2307.

α-Fluorination using Imidazolidinone Catalysts

Like Enders, we also felt that the enamine activation mode could potentially provide direct access to fluorinated ketones, and in contrast to other established methods for creating stereogenic fluorine centers, enamine catalysis should enable the induction of epimerizable stereocenters. Since our lab's class of imidazolidinone catalysts had been shown to perform readily as enamine catalysts and had already achieved high levels of stereoselectivities for the α-chlorination and α-fluorination of aldehydes, we felt that this class of catalyst might be able to overcome the reactivity and selectivity issues that Enders had faced with proline-based catalysts. Although the typical imidazolidinone catalysts that yield high reactivities with aldehydes had been shown to react very poorly with ketones, former graduate student Alan Northrup successfully developed a furanyl-imidazolidinone **2** that facilitated the first enantioselective ketone Diels-Alder reaction with excellent yields and stereoselectivities (equation 5).[7,8]



(5)

Employing catalyst **2** with our previously determined aldehyde fluorination reaction conditions and two equivalents of *N*-fluorobenzenesulfonimide (NFSI) as the fluorine source, we were delighted to find that 2-fluorocyclohexanone could be obtained in 85% conversion and 34% enantiomeric excess (ee) (equation 6). While this result was

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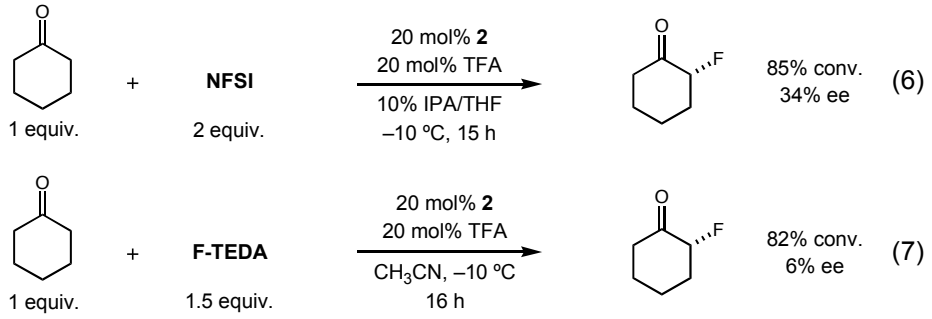
[7] Northrup, A. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2002**, *124*, 2458.

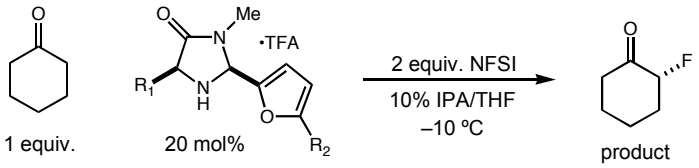
[8] Tuttle, J. B.; Ouellet, S. G.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2006**, *128*, 12662.

very promising, the stereoselectivity was far from optimal. Interestingly, when F-TEDA was used as the fluorine source, high levels of conversion were also obtained but with no stereoselectivity (equation 7). This result is possible evidence for the transition state proposed for the aldehyde fluorination with NFSI in which the sulfonimide of the fluorinating agent is hydrogen-bonded to the enamine through a proton.



During the development of the aldehyde α-fluorination (chapter 3), it was noted that the reaction medium had a large impact on the outcome of the reaction. We therefore investigated the ketone fluorination in a variety of solvents, both with and without the addition of 10% isopropanol (IPA). However, the initial reaction conditions were determined to be optimal and we next focused our efforts on evaluating the effect of catalyst architecture. With the goal of developing a more broadly useful catalyst for the enamine and iminium-catalyzed functionalization of ketones, graduate student Anthony Mastracchio had prepared a number of imidazolidinone catalysts with modified catalyst **2** architectures. As shown in Table 1, all catalysts achieved excellent reactivity; however, no significant improvement in enantioselectivity was obtained for any of the catalysts studied. A variety of pyrrolidine-based catalyst architectures were also studied but poor conversions and very low selectivities were obtained. Subsequently, we turned our attention to a class of mono-substituted imidazolidinone catalysts (Figure 1), which had been demonstrated to induce high levels of selectivity for the transfer hydrogenation of

Table 1. Effect of Modifications to Catalyst **2** Architecture



entry	R_1	R_2	time (h)	% conversion[a]	% ee[b]
1	Ph	Me	10	80	34
2	Ph	CF_3	11	97	29
3	*p*-NO_2-Ph	Me	10	90	8
4	*p*-NO_2-Ph	CF_3	10	89	14
5	*p*-O*t*-Bu-Ph	CF_3	3	87	36
6	2-naphthyl	CF_3	10	91	27
7	1-naphthyl	CF_3	10	86	13
8	Ph, Ph	CF_3	20	62[c]	13

(a) Conversion determined by GLC analysis relative to an internal standard (methyl cyclohexanecarboxylate). (b) Enantiomeric excess determined by GLC analysis (Macherey-Nagel Hydrodex-B-TBDAc). (c) Reaction performed at +4 ºC.

aldehydes[9] and shown promise as a catalyst for enamine-catalyzed reactions of ketones.[10] As shown in Table 2, reactions performed with catalyst **3** achieved very high levels of enantioselectivity; however, the bulky *tert*-butyl group severely hindered the reaction efficiency and a maximum of 23% conversion was obtained. Notably, the *cis*-diphenyl-diamino catalyst **6** developed by Jørgensen and successfully used for the α-chlorination

[9] Ouellet, S. G.; Tuttle, J. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 32.

[10] Kim, Y.-K.; MacMillan, D. W. C. unpublished results.

and α-bromination of ketones[11] yielded both low conversion and selectivity in the fluorination reaction.

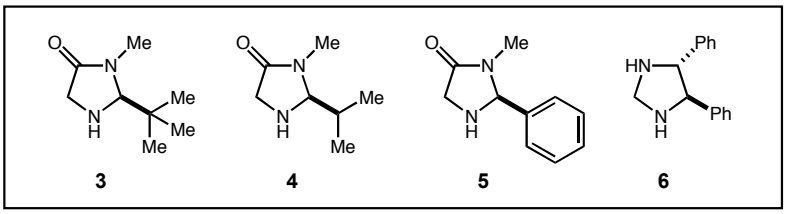
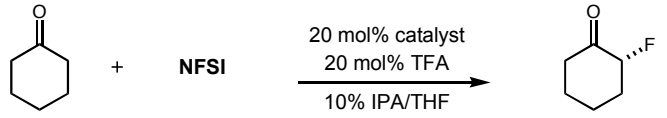


Figure 1. Structures of monosubstituted imidazolidinone catalysts and Jørgensen's *cis*-diphenyl-diamino catalyst.

Table 2. Mono-Substituted Imidazolidinone Catalysts



entry	catalyst	Temp (ºC)	time (h)	% conversion[a]	% ee[b]
1	**3**	+23	15	23[c]	73
2	**3**	+4	27	19[c,d]	87
3	**3**	–10	120	21[c,d]	87
4	**4**	+4	24	53	58
5	**4**	–10	24	35	64
6	**5**	–20	16	79	37
7	**5**	–40	16	45	45
8	**6**	+23	18	41[e]	25

(a) Conversion determined by GLC analysis relative to an internal standard (methyl cyclohexanecarboxylate). (b) Enantiomeric excess determined by GLC analysis (Macherey-Nagel Hydrodex-B-TBDAc). (c) Reactions using 20 mol% TCA instead of TFA. (d) Reactions performed without IPA. (e) Reactions using 20 mol% BzOH instead of TFA.

In an attempt to optimize the reaction efficiency using catalyst **3**, studies were conducted in which the solvent, alcohol additive, catalyst loading and concentration were varied. While increasing the reaction concentration from 0.125M to 1.0M did achieve

[11] (a) Marigo, M.; Bachmann, S.; Halland, N.; Braunton, A.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2004**, *43*, 5507. (b) Bertelsen, S.; Halland, N.; Bachmann, S.; Marigo, M.; Braunton, A.; Jørgensen, K. A. *Chem. Commun.* **2005**, 4821.

conversions as high as 38%, the enantioselectivity decreased with increasing concentration. Using 10% IPA as an additive, product epimerization with time was quite noticeable and switching to ethanol or methanol significantly slowed the loss of stereoselectivity; unfortunately the maximum conversions achieved were identical to those using IPA. Variations in solvent and catalyst loading were also found to have no beneficial effect.

Cinchona Alkaloid Catalysts

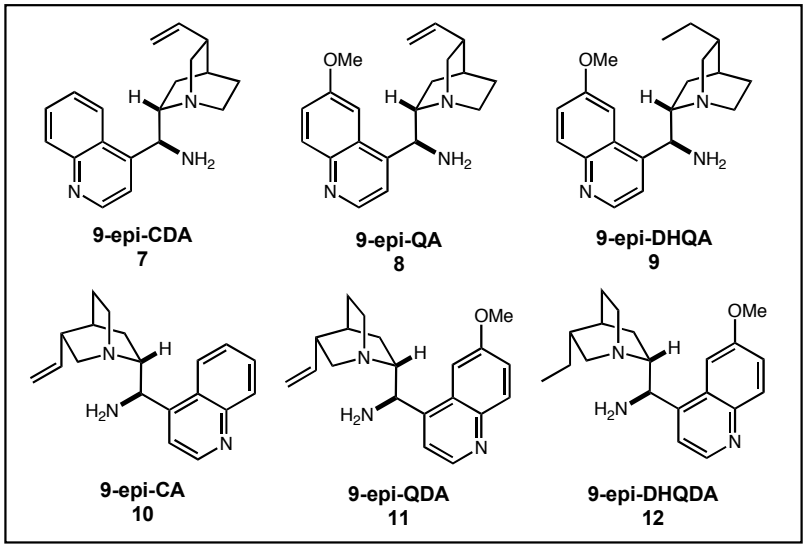
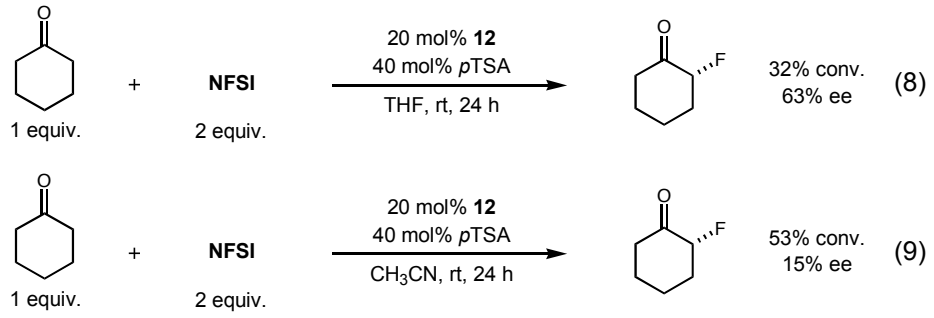


Figure 2. Structures of cinchona alkaloid-derived catalysts; CD=cinchonidine, Q=quinine, C=cinchonine, QD=quinidine DH=dihydro, A=amine.

Recently, McCooey and Connon introduced cinchona alkaloid-derived primary amine catalysts for the enamine-catalyzed addition of ketones to nitroolefins.[12] Since then a number of papers have been published demonstrating the broad usefulness of this

[12] McCooey, S. H.; Connon, S. J. *Org. Lett.* **2007**, *9*, 599.

class of catalysts for both enamine[13] and iminium catalysis.[14] We investigated this catalyst class in the α-fluorination of ketones and found that while the tris-HCl salt of 9-epi-DHQDA **12** resulted in no reaction, 20 mol% of the free-based catalyst with 40 mol% of *para*-toluenesulfonic acid (*p*TSA) as cocatalyst at ambient temperature achieved remarkably high enantioselectivity, albeit in low conversion (equation 8). Use of acetonitrile as solvent achieved much higher reaction efficiency; however, the stereoselectivity was very low (equation 9).



Interestingly, while reactions performed without cocatalyst yielded much lower conversions, the use of anywhere from 20 to 40 mol% of cocatalyst achieved identical results to those performed with 40 mol%. However, reactions performed with 60 mol% of cocatalyst resulted in precipitation of the catalyst and no reaction was observed. This led us to speculate that as the reaction progresses and an equivalent of acid is produced, the catalyst would eventually form a tris-salt and precipitate out of solution, leading to the reaction stalling at low conversion. To circumvent this problem, base additives were

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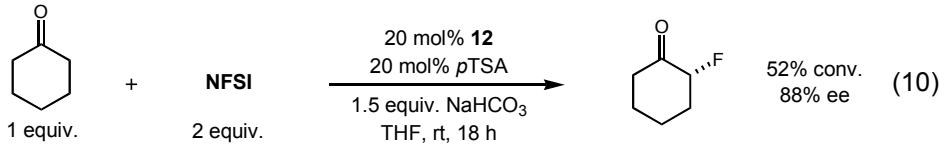
[13] Liu, T.-Y.; Cui, H.-L.; Zhang, Y.; Jiang, K.; Du, W.; He, Z.-Q.; Chen, Y.-C. *Org. Lett.* **2007**, *9*, 3671.

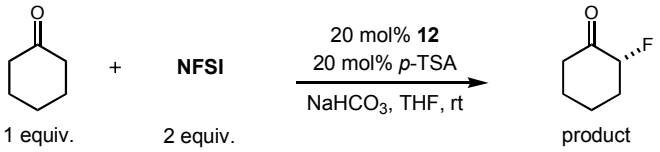
[14] (a) Xie, J.-W.; Chen, W.; Li, R.; Zeng, M.; Du, W.; Yue, L.; Chen, Y.-C.; Wu, Y.; Zhu, J.; Deng, J.-G. *Angew. Chem. Int. Ed.* **2007**, *46*, 389. (b) Bartoli, G.; Bosco, M.; Carlone, A.; Pesciaioli, F.; Sambri, L.; Melchiorre, P. *Org. Lett.* **2007**, *9*, 1403. (c) Ricci, P.; Carlone, A.; Bartoli, G.; Bosco, M.; Sambri, L.; Melchiorre, P. *Adv. Synth. Catal.* **2008**, *350*, 49. (d) Li, X.; Cun, L.; Lian, C.; Zhong, L.; Chen, Y.; Liao, J.; Zhu, J.; Deng, J. *Org. Biomol. Chem.* **2008**, *6*, 349.



(10)

investigated and to our delight, it was found that the addition of 1.5 equivalents of sodium bicarbonate ($NaHCO_3$) to the reaction mixture resulted in a significant increase in both conversion and enantioselectivity (equation 10). Other additives such as alcohols and molecular sieves, which had been used in literature procedures with cinchona-derived amine catalysts,[15] were not beneficial for the α-fluorination reaction.

Table 3. Effect of Concentration and Base



entry	conc. (M)	equiv. $NaHCO_3$	time (h)	% conversion[a]	% ee[b]
1	0.5	1.5	1	54	86
2	0.33	1	4	57	88
3	0.33	1.5	2	52	89
4	0.33	2	2	53	89
5	0.33	4	2	51	90
6	0.25	1.5	2	56	91
7	0.167	1.5	2	39	92
8	0.125	1.5	2	34	94

(a) Conversion determined by GLC analysis relative to an internal standard (methyl cyclohexanecarboxylate). (b) Enantiomeric excess determined by GLC analysis (Macherey-Nagel Hydrodex-B-TBDAc).

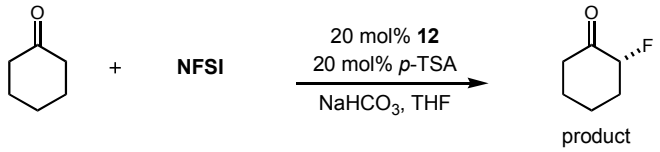
Subsequently, studies were performed to determine the effect of concentration and additional base additive (Table 3). Although increasing the amount of base used in the reaction resulted in slight increases in enantioselectivity (entry 5), conversions

[15] See reference 13.

remained unchanged. On the other hand, more dilute reaction conditions achieved significantly higher enantioselectivities (entry 8), but with lower reaction efficiency.

In all cases studied, it appeared that the reactions were stalling at about 50–60% maximum conversion, possibly due to tris-salt formation that was not being free-based by the excess $NaHCO_3$, or more likely, due to reaction of the catalyst with NFSI over time, generating either an unreactive or insoluble form of the catalyst. Notably, transfer fluorination from NFSI to cinchona alkaloids has been demonstrated in the literature and used for preparing cinchona-derived fluorinating agents.[16]

Table 4. Effect of Temperature and Stoichiometry



entry	equiv. ketone	Temp (ºC)	time (h)	% conversion[a]	% ee[b]
1	1	+23	2	53	85
2	1	+4	8	64	95
3	1	–10	24	71	94
4	1	–20	44	70	96
5	1.5	+4	8	72	96
6	1.5	–20	24	72	97
7	2	–20	24	88	97
8	3	+23	2	70	94

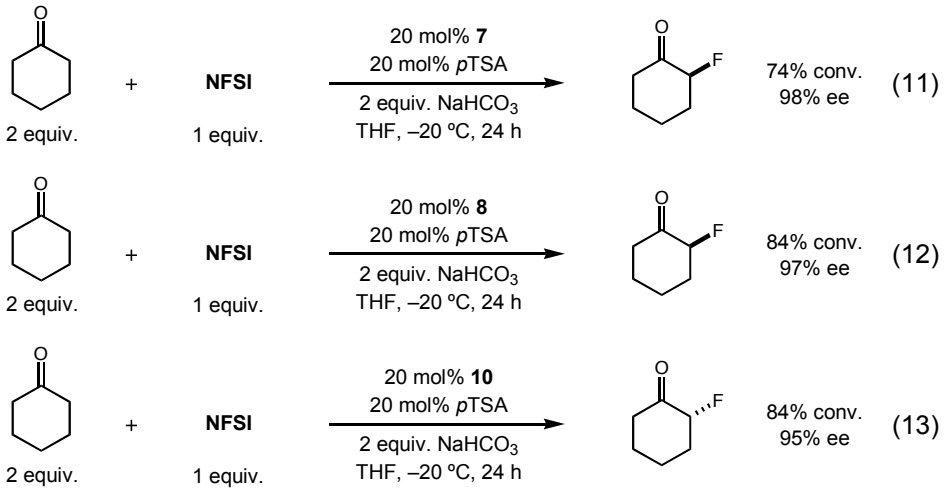
(a) Conversion determined by GLC analysis relative to an internal standard (methyl cyclohexanecarboxylate). (b) Enantiomeric excess determined by GLC analysis (Macherey-Nagel Hydrodex-B-TBDAc).

In order to circumvent unwanted fluorination of the catalyst and since the highly concentrated reactions were found to be complete in only 1 hour (Table 3, entry 1), the reaction temperature was lowered and the stoichiometry of the reaction was altered so

[16] Baudequin, C.; Loubassou, J.-F.; Plaquevent, J.-C.; Cahard, D. *J. Fluorine Chem.* **2003**, *122*, 189.

that NFSI was used as the limiting reagent. As shown in Table 4, reactions performed at –20 ºC with excess of ketone achieved excellent levels of conversion and enantioselectivity (entry 7; 88% conv., 97% ee). Reactions using these conditions performed in DME, EtOAc, CH_3CN, and DMF demonstrated that the choice of THF as the reaction medium was optimal.[17]

With these optimized reaction conditions in hand, we next investigated the use of other cinchona alkaloid-derived catalysts to determine if equal levels of enantioselectivity and reactivity could be achieved for the opposite enantiomer of the product. Gratifyingly, reactions performed with catalysts **7** and **8** resulted in equally high enantioselectivities and good conversions to the desired (*S*)-2-fluorocyclohexanone (equations 11 and 12). Catalyst **10** resulted in slightly lower selectivities than those obtained with catalyst **12**, but maintained excellent reaction efficiency (equation 13).



Lastly, these reaction conditions have now been applied to a variety of cyclic ketone substrates. Postdoctoral fellow Dr. Piotr Kwiatkowski has successfully

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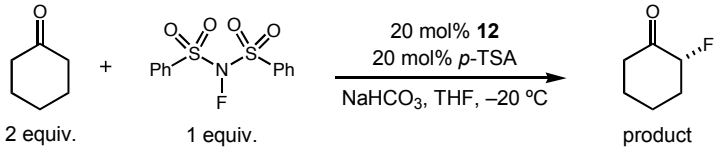
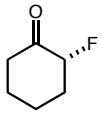
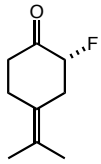
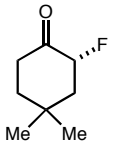
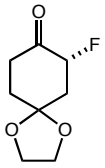
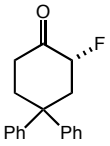
[17] Reactions performed using 1.5 equiv. ketone, 2 equiv. $NaHCO_3$ at –20 ºC for 24 h in DME: 68% conv., 96% ee; EtOAc: 63% conv., 90% ee; CH_3CN: 53% conv. 79% ee; DMF: 13% conv., 92% ee.

synthesized chiral 2-fluorocyclohexyl ketones in good yields and excellent enantioselectivities (Table 5). Further studies are being conducted by Dr. Kwiatkowski towards the fluorination of acyclic rings and heterocyclic ketones such as *N*-BOC-piperidone and 4-tetrahydropyranone, which react under the optimized reaction conditions with excellent enantioselectivities, but are currently difficult to isolate as they readily form hydrates and epimerize under standard chromatographic methods. Full details of the scope of this reaction will soon be reported.

Table 5. α-Fluorination of Ketone Substrates



entry	product	% yield[a]	% ee	entry	product	% yield	% ee
1		50[b] (88)	97	4		73 (79)	98
2		65[b] (95)	96	5		85 (90)	94
3		88	94				

(a) Isolated yields after silica gel chromatography. Yields in parentheses obtained by GLC analysis relative to an internal standard (methyl cyclohexanecarboxylate). (b) Volatile products.

Conclusion

In summary, the development of the first highly enantioselective direct α-fluorination of ketones has been accomplished using cinchona alkaloid-derived catalysts. While traditional catalysts for the amine-catalyzed functionalization of ketones failed to provide desired levels of conversion and stereoselectivity, high yields with excellent enantioselectivities were obtained using 20 mol% of 9-Epi-DHQDA catalyst and NFSI as the fluorine source. This method provides epimerizable fluorine stereocenters using an organocatalyst that is easily prepared and using reaction conditions that are insensitive to both air and moisture, making it a valuable tool for practitioners of pharmaceutical and synthetic chemistry.

Supporting Information

General Information. Commercial reagents were distilled prior to use following the guidelines of Perrin and Armarego.[18] Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator. Chromatographic purification of products was accomplished using forced-flow chromatography on EMD Silica Gel 60 230-400 mesh or Davisil® Silica Gel 200-425 mesh according to the method of Still.[19] Thin-layer chromatography (TLC) was performed on EM Reagents 0.25 mm silica gel 60-F plates. Visualization of the developed chromatogram was performed by fluorescence quenching using potassium permanganate stain. High performance liquid chromatography (HPLC) and gas liquid chromatography (GLC) assays to determine enantiomeric excess were developed using racemic samples.

^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on Bruker Ultrashield™ Plus 500 (500 MHz, 125 MHz) and ^{19}F NMR spectra were recorded on Varian Mercury 300 (282 MHz) as noted, and are internally referenced to residual protio solvent signals. Data for ^{1}H are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration, coupling constant (Hz), and assignment. Data for ^{13}C and ^{19}F NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), and coupling constant (Hz). IR spectra were recorded on a Perkin Elmer Spectrum BX FT-IR spectrometer and are reported in terms of frequency of absorption (cm^{-1}). Mass spectra were obtained from the

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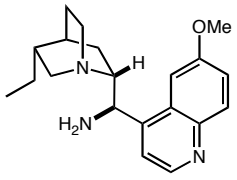
[18] Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals;* 3rd edition; Pergamon Press; Oxford, 1988.

[19] Still, W. C.; Kahn, M.; Mitra, A. J. *J. Org. Chem.* **1978**, *43*, 2923.

Princeton University Mass Spectral Facility. Gas liquid chromatography (GLC) was performed on a Hewlett-Packard 6850 Series gas chromatograph equipped with a split-mode capillary injection system and flame ionization detectors using a Macherey-Nagel Hydrodex-B-TBDAc (50 m x 0.25 mm) column. High performance liquid chromatography (HPLC) was performed on a Hewlett Packard 1100 Series chromatograph using a Chiralcel® OJ column (25 cm, 5 cm guard) as noted.

Starting Materials



9-epi-DHQDA
12

9-Epi-DHQDA: The triple HCl salt was prepared from hydroquinidine according to the procedure of McCooey and Connon.[20] Isolation of the pure salt was accomplished by dissolving the residue (15 mmol scale reaction) in approx. 250 mL of MeOH while heating to 55 ºC. EtOAc was dripped into the hot solution until the first signs of a fine powder begin to form. The solution was cooled to rt, then placed in a –20 ºC freezer overnight. Care must be taken not to crash out the powder by adding additional EtOAc, which results in impure catalyst. The triple salt was free-based by partitioning between 1N NaOH and DCM, extracting 3 x with DCM, and drying over Na_2SO_4. 1.9g obtained, 29% yield.

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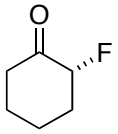
[20] McCooey, S. H.; Connon, S. J. *Org. Lett.* **2007**, *9*, 599.

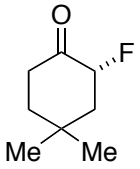
General Procedure for the α-Fluorination of Ketones: To a 10 mL round-bottom flask equipped with a magnetic stir bar and charged with 9-Epi-DHQDA (16 mg, 0.05 mmol), *p*-toluenesulfonic acid (9.5 mg, 0.05 mmol), *N*-fluorobenzenesulfonimide (79 mg, 0.25 mmol), and $NaHCO_3$ (42mg, 0.50 mmol) was added THF (1.0 mL) and the mixture was cooled to –20 °C. The mixture was stirred for 15 min to allow time for the catalyst to dissolve. Ketone (0.50 mmol) was added and the reaction mixture stirred at –20 ºC for 24 h. The reaction was filtered through a pad of silica gel, eluting with Et_2O and purified by silica gel chromatography. Purification of the resulting oil by forced flow chromatography afforded the title compounds. The enantioselectivity was determined either by chiral GLC analysis, chiral HPLC or SFC analysis. The GC yield was determined using methyl cyclohexane-carboxylate as an internal standard and calculated with a GC response factor.

α-Fluoro Ketones



(*R*)-2-Fluorocyclohexanone (Table 5, entry 1): Prepared according to the general procedure from cyclohexanone (259 μL, 2.50 mmol) to afford a colorless oil. Purification on silica gel (20–40% Et_2O/Pentanes) afforded (*S*)-2-fluorocyclohexanone as a colorless liquid (73 mg, 50% yield, 88% GC yield, 97% ee). IR (film) 2947, 2870, 1729, 1452, 1431, 1316, 1086, 1067, 951.5, 912.7, 879.7, 836.9, 743.2, 665.5 cm^{-1}; ^1H NMR (Varian 400 MHz, $CDCl_3$). δ 4.86 (dm, *J* = 49.0 Hz, 1H, FC**H**), δ 2.34–2.59 (m, 1H, O=CC$\mathbf{H}_2$), δ 2.28–2.46 (m, 2H, O=CC$\mathbf{H}_2$, FCHC$\mathbf{H}_2$), δ 1.92–2.06 (m, 2H,

FCHCH$_2$C**H$_2$**), δ 1.78–1.92 (m, 1H, FCHC**H$_2$**), δ 1.60–1.78 (m, 2H, O=CCH$_2$C**H$_2$**); ^{13}C NMR (125 MHz, $CDCl_3$) δ; 205.9 (d, *J* = 14.8 Hz), 92.9 (d, *J* = 190.3 Hz), 40.4, 34.4 (d, *J* = 18.6 Hz), 27.1 (d, *J* = 1.0 Hz), 22.9 (d, *J* = 10.0 Hz). ^{19}F NMR (282 MHz, $CDCl_3$) δ: –188.7 (dm, *J* = 48.4 Hz). HRMS (ES) exact mass calculated for $[M+H]^+$ (C_6H_9FO) requires *m/z* 116.0637, found *m/z* 116.0637. $[\alpha]_D$ = +44.0 (c = 0.68, C_6H_6).[21] Enantiopurity was determined by GLC using a Macherey-Nagel Hydrodex-B-TBDAc (50 m x 0.25 mm) column (120 °C, 15 min; 140 ºC, 30 min); (*S*) isomer t_r = 39.6 min and (*R*) isomer t_r = 41.2 min.



(*R*)-2-Fluoro-4,4-dimethylcyclohexanone (Table 5, entry 2): Prepared according to the general procedure from 4,4-dimethylcyclohexanone (66 mg, 0.50 mmol) to afford a colorless oil. Purification on silica gel (5–20% Et_2O/Pentanes) afforded (*S*)-2-Fluoro-4,4-dimethylcyclohexanone as colorless volatile crystals (24 mg, 65% yield, 95% GC yield, 96% ee). IR (film) 2595, 2933, 2866, 1727, 1474, 1424, 1366, 1316, 1179, 1129, 1115, 1083, 1048, 1016, 998, 911, 855, 732.1, 703.5 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$). δ 5.03 (dddd, *J* = 48.4, 12.5, 6.6, 0.8 Hz, 1H, FC**H**), δ 2.34–2.59 (m, 2H, O=CC**H$_2$**), δ 2.18 (dddd, *J* = 12.5, 6.8, 5.6, 3.2, 1H, FCHC**H$_2$**), δ 1.61–1.88 (m, 3H, FCHC**H$_2$**, O=CCH$_2$C**H$_2$**), 1.24 (s, 3H, C**H$_3$**), δ 1.10 (s, 3H, C**H$_3$**); ^{13}C NMR (125 MHz, $CDCl_3$) δ; 206.3 (d, *J* = 13.4 Hz), 90.6 (d, *J* = 189.4 Hz), 46.3 (d, *J* = 15.7 Hz), 39.5 (d,

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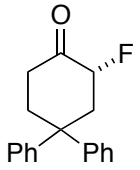
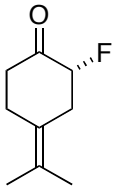
[21] (*R*)-2-Fluorocyclohexanone $[\alpha]_D$ = +54.8 (c = 0.68, C_6H_6): Enders, D.; Faure, S.; Potthoff, M.; Runsink, J. *Synthesis* **2001**, 2307.

J = 1.0 Hz), 36.8, 32.5 (d, *J* = 10.0 Hz), 31.4, 25.0. ^{19}F NMR (282 MHz, $CDCl_3$) δ: –193.9 (dm, *J* = 48.4 Hz). HRMS (ES) exact mass calculated for $[M+H]^+$ ($C_8H_{14}FO$) requires *m/z* 144.0950, found *m/z* 144.0950. $[\alpha]_D$ = +46.4 (c = 1.0, $CHCl_3$). Enantiopurity was determined by GLC using a Macherey-Nagel Hydrodex-B-TBDAc (50 m x 0.25 mm) column (120 °C, 15 min; 150 ºC, 30 min); (*S*) isomer t_r = 26.4 min and (*R*) isomer t_r = 28.3 min.

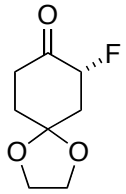


(*R*)-2-Fluoro-4,4-diphenylcyclohexanone (Table 5, entry 3): Prepared according to the general procedure from 4,4-diphenylcyclohexanone (252 mg, 1.04 mmol) to afford a colorless oil. Purification on silica gel (5–20% EtOAc/Petroleum ether) afforded (*S*)-2-Fluoro-4,4-diphenylcyclohexanone as a colorless solid (119 mg, 88% yield, 94% ee). IR (film) 3.59, 2960, 1738, 1599, 1496, 1447, 1072, 1033, 886.4, 841.1, 751.4, 700.5 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$). δ 7.56 (dd, *J* = 8.4, 1.2 Hz, 1H, **Ph**), δ 7.43–7.51 (m, 1H, **Ph**), δ 7.32–7.38 (m, 1H, **Ph**), δ 7.24–7.32 (m, 2H, **Ph**), δ 7.13–7.23 (m, 2H, **Ph**), δ 5.01 (ddd, *J* = 48.2, 12.8, 6.2 Hz, 1H, FC**H**), δ 3.28–3.54 (m, 1H, FCHC$\mathbf{H}_2$), δ 2.91–3.09 (m, 1H, FCHC$\mathbf{H}_2$), δ 2.51–2.66 (m, 2H, O=CCH_2C$\mathbf{H_2}$), δ 2.29–2.44 (m, 1H, O=CC$\mathbf{H_2}$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 205.0 (d, *J* = 13.5 Hz), 147.3, 142.2, 129.6, 128.8, 127.3, 127.0, 126.8, 126.0, 90.5 (d, *J* = 190.3 Hz), 47.4 (d, *J* = 10.4 Hz), 43.5 (d, *J* = 18.2 Hz), 37.5, 37.1. ^{19}F NMR (282 MHz, $CDCl_3$) δ: –192.5 (d, *J* = 49.0 Hz). HRMS (ES) exact mass calculated for $[M+H]^+$ ($C_{18}H_{18}FO$) requires *m/z* 268.1263,

found *m/z* 268.1262. $[\alpha]_D$ = +2.6 (c = 1.1, $CHCl_3$). Enantiopurity was determined by SFC analysis (Chiralcel®ADH 5-50% CH_3CN). t_R(minor) = 3.3 min. t_S(major) = 3.5 min.



(*R*)-2-Fluoro-4-(propan-2-ylidene)cyclohexanone (Table 5, entry 4): Prepared according to the general procedure from 4-(propan-2-ylidene)cyclohexanone (145 mg, 1.04 mmol) to afford a colorless oil. Purification on silica gel (10–20% Et_2O/Petroleum Ether) afforded (*S*)-2-Fluoro-4-(propan-2-ylidene)cyclohexanone as a colorless oil (57 mg, 73% yield, 79% GC yield, 98% ee). IR (film) 2987, 2915, 2859, 1734, 1450, 1429, 1376, 1105, 1070, 1026, 858.0 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$). δ 4.84 (ddd, *J* = 49.2, 11.8, 6.6 Hz, 1H, FC**H**), δ 3.14–3.37 (m, 1H, O=CC$\mathbf{H}_2$), δ 2.73–2.90 (m, 1H, O=CC$\mathbf{H}_2$), δ 2.45–2.64 (m, 1H, O=CC$\mathbf{H}_2$), δ 2.26–2.43 (m, 2H, FCHC$\mathbf{H}_2$, O=CCH_2C$\mathbf{H}_2$), δ 2.13–2.26 (m, 1H, O=CCH_2C$\mathbf{H}_2$), 1.79 (s, 3H, C$\mathbf{H_3}$), δ 1.77 (s, 3H, C$\mathbf{H_3}$); ^{13}C NMR (125 MHz, $CDCl_3$) δ; 205.8 (d, *J* = 14.0 Hz), 129.1, 123.1, 91.8 (d, *J* = 193.4 Hz), 39.4, 36.5 (d, *J* = 19.7 Hz), 28.6, 20.7. ^{19}F NMR (282 MHz, $CDCl_3$) δ: –188.2 (dm, *J* = 49.3 Hz). HRMS (ES) exact mass calculated for $[M+H]^+$ ($C_9H_{14}FO$) requires *m/z* 156.0950, found *m/z* 156.0949. $[\alpha]_D$ = +1.8 (c = 0.58, $CHCl_3$). Enantiopurity was determined by GLC using a Macherey-Nagel Hydrodex-B-TBDAc (50 m x 0.25 mm) column (120 °C, 15 min; 140 ºC, 40 min); (*R*) isomer t_r = 45.8 min and (*S*) isomer t_r = 48.1 min.



(*R*)-2-Fluoro-1,4-dioxaspiro[4.5]decan-8-one (Table 5, entry 5): Prepared according to the general procedure from 1,4-dioxaspiro[4.5]decan-8-one (158 mg, 1.00 mmol) to afford a colorless oil. Purification on silica gel (10–30% EtOAc/Petroleum Ether) afforded (*S*)-2-Fluoro-1,4-dioxaspiro[4.5]decan-8-one as a colorless crystalline solid (74 mg, 85% yield, 90% GC yield, 94% ee). IR (film) 2962, 2938, 2904, 1737, 1443, 1424, 1372, 1353, 1310, 1244, 1146, 1123, 1089, 1047, 984.5, 950.9, 930.5, 844.8, 706.8 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$). δ 5.11 (dm, *J* = 48.3 Hz, 1H, FC**H**), δ 3.94–4.15 (m, 4H, (OC$\mathbf{H_2}$)$_2$), δ 2.58–2.70 (m, 1H, O=CC$\mathbf{H}_2$), δ 2.37–2.58 (m, 2H, O=CC$\mathbf{H}_2$, FCHC$\mathbf{H}_2$), δ 2.08–2.26 (m, 1H, FCHC$\mathbf{H}_2$), δ 1.87–2.08 (m, 2H, O=CCH$_2$C$\mathbf{H_2}$); ^{13}C NMR (125 MHz, $CDCl_3$) δ; 204.6 (d, *J* = 14.3 Hz), 107.4 (d, *J* = 13.8 Hz), 90.2 (d, *J* = 191.2 Hz), 65.1 (d, *J* = 3.3 Hz), 41.7 (d, *J* = 17.6 Hz), 35.3, 34.5. ^{19}F NMR (282 MHz, $CDCl_3$) δ: –194.1 (dm, *J* = 48.1 Hz). HRMS (ES) exact mass calculated for $[M+H]^+$ ($C_8H_{12}FO_3$) requires *m/z* 174.0692, found *m/z* 174.0692. $[\alpha]_D$ = +40.5 (c = 1.1, $CHCl_3$). Enantiopurity was determined by GLC using a Macherey-Nagel Hydrodex-B-TBDAc (50 m x 0.25 mm) column (120 °C, 15 min; 140 ºC, 40 min); (*R*) isomer t_r = 50.9 min and (*S*) isomer t_r = 52.1 min.