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Fluorinated Aromatic Ketones as Nucleophiles in the Asymmetric Organocatalytic Formation of C–C and C–N Bonds: A Facile Route to the Construction of Fluorinated Quaternary Stereogenic Centers

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The development of a broadly useful platform for the organocatalytic nucleophilic addition of carbonyl compounds represents a major research field in asymmetric catalysis.[1] Recent research efforts have mainly focused on dicarbonyl compounds such as β-ketoesters and β-ketosulfones, which are easily activated and widely used in many conjugated addition reactions.[1,2] Most of the aliphatic ketones and acetophenone nucleophiles used in organocatalytic asymmetric transformations rely on the formation of highly reactive enamine intermediates.[3–5] On the other hand, Brønsted bases[6] are seldom used as catalysts in reactions of simple carbonyls because of to the rather low basicity of most organobases, and thus their inability to activate the carbonyl group through enolization. Successful strategies are those that try to increase the acidity of the α-proton.[7] For example, activated esters, such as trifluoroethyl thioesters,[7a–c] α-cyanothioacetates,[7d] α-substituted cyanoacetates,[7e–k] and α-nitroacetates,[7l–o] are valuable nucleophiles for organic base-catalyzed reactions because of their enhanced acidity. In contrast, fused cyclic aromatic ketones are still challenging substrates to activate as a result of the difficulty in forming the enamine intermediate and their poor reactivity.[8] To our knowledge, the use of activated aromatic ketones as nucleophiles for Brønsted base-catalyzed reactions is restricted to several reports which focused on α-cyano ketones.[9]

Organofluorine compounds are important in medicinal and bioorganic chemistry.[10] Enantiopure compounds containing a fluorine atom directly connected to a quaternary carbon center[11] are nontrivial to prepare. The most common approach thus far is to generate such compounds through an enantioselective fluorination of tertiary carbon nucleophiles using chiral transition-metal complexes or organocatalysts.[12] The less explored route is the asymmetric formation of C–C bonds by using fluorocarbon nucleophiles.[13] Recently, α-fluoro-β-ketoesters have been employed as fluorocarbon nucleophiles in organocatalytic processes, asymmetric Michael, amination, and Mannich reactions.[13a–d,m] The asymmetric alkylation of α-fluoro-β-ketoesters under phase-transfer conditions,[13e] and asymmetric Robinson annulations[13f] have been carried out using fluorocarbon nucleophiles. Other fluorocarbon nucleophiles such as 1-fluoro-bis(phenylsulfonyl)methane (FBSM)[13g–i] and 1-fluoro-1-nitro(phenylsulfonyl)methane (FNSM)[13j] were also developed. We have also shown that the α-fluoro-β-ketoester and the α-fluoro-β-ketoacyloxazolidinone underwent guanidine-catalyzed[14] enantioselective Michael and Mannich reactions, which resulted in high enantioselectivities.[15] The use of simple α-fluorinated aromatic ketones as nucleophiles has been less studied. However, there were two independent reports on the use of phase-transfer catalysts for asymmetric alkylation reactions of α-fluorotetralone that resulted in unsatisfactory enantioselectivities and yields.[13k,l]

Herein, we present the highly enantioselective formation of C–N and C–C bonds using α-fluorinated aromatic ketones as nucleophiles. Our initial efforts focused on the α-amination reaction[16] of α-fluorinated aromatic ketones catalyzed by a bicyclic chiral guanidine. To the best of our knowledge, there are no reports on enantioselective synthesis of nitrogen-substituted fluorinated stereogenic carbons from α-fluorinated ketones using organocatalytic processes. However, successful examples using α-fluoro-β-ketoesters and catalyzed with copper and nickel complexes of Cinchona alkaloid derivatives have been reported.[13m,17]

Direct α-amination of α-fluorinated aromatic cyclic ketones **1d** catalyzed by chiral guanidine **2** with azodicarboxylates **3** led to optically active α-hydrozino-α-fluorinated aromatic cyclic ketones **4** and **5d**. When di-*tert*-butyl azodicarboxylate **3a** was used as the nitrogen source (Table 1, entries 1–7), the best result obtained was 84% *ee* in THF (Table 1, entry 7). A bulkier version of azodicarboxylate, di-3-ethylpentan-3-yl azodicarboxylate **3b** (EocN=NEoc), was designed as we are aware that bicyclic guanidine catalyst responds positively to an increase in the steric demand of the

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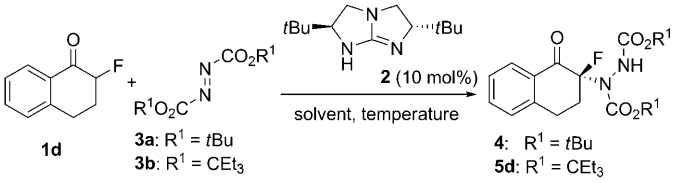
Table 1. Reaction optimization for the α-amination of **1d**.



Entry	Solvent	3	T [°C]	t [h]	Product	Yield [%][a]	ee [%][b]
1	CH_2Cl_2	**3a**	RT	24	**4**	80	45
2	hexane	**3a**	RT	20	**4**	81	72
3	toluene	**3a**	RT	20	**4**	88	64
4	acetone	**3a**	RT	5	**4**	92	72
5	Et_2O	**3a**	RT	2	**4**	90	75
6	THF	**3a**	RT	2	**4**	95	76
7	THF	**3a**	−20	15	**4**	92	84
8	THF	**3b**	0	30	**5d**	86	94

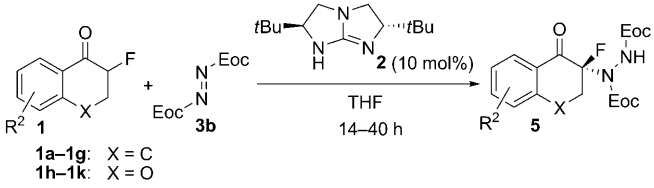
[a] Yield of isolated product. [b] Determined by HPLC analysis on a chiral stationary phase.

substrate. Azodicarboxylate **3b** was easily synthesized from 1,1′-carbonyldiimidazole (CDI) and 3-ethylpentan-3-ol using a five-step procedure modified from a protocol that is used to prepare azodicarboxylate **3a** (See the Supporting Information for details).[18] Azodicarboxylate **3b** was obtained as stable yellow crystals in a good yield. α-Hydrozino-α-fluorinated aromatic cyclic ketone **5d** was obtained in 94% *ee* with 86% yield when this novel azodicarboxylate **3b** was used as the nitrogen source (Table 1, entry 8).

With the optimal reaction conditions in hand, the scope of the α-amination reaction between α-fluorinated aromatic cyclic ketones **1a–k** and azodicarboxylate **3b** was investigated. A variety of cyclic ketones **1a–g** with varying substituents on the aromatic ring was prepared from α-tetralone derivatives. Excellent yields and high *ee* values were achieved irrespective of the electronic nature or positions of the substituents on the aromatic ring (Table 2, entries 1–7). Substrate **1e**, which contains an electron-donating group, underwent α-amination reaction in 94% yield and 95% *ee* (Table 2, entry 5). With substrate **1f**, which contains a strong electron-withdrawing nitro group at the 7-position of the aromatic ring, the reaction was complete even at −40 °C (Table 2, entry 6). Similarly, the α-fluorinated 4-chromanones derivatives also reacted efficiently with azodicarboxylate **3b**, thus giving the chiral α-hydrozino-α-fluorinated 4-chromanones derivatives **5h–k** in good yields and enantioselectivities (Table 2, entries 8–11). The chromanone moiety can be found in flavanones and in many natural products and compounds that are important in medicinal and biological chemistry, because of the antitumor and anti-inflammatory properties attributed to the chromanone unit.[19]

Excited by the results obtained in the asymmetric α-amination reaction, we next turned out attention to asymmetric Mannich reactions[20] with these fluorocarbon nucleophiles. In preliminary studies, we first examined the Mannich reaction of fluorinated aromatic ketone **1d** with *N*-mesyl (Ms) imine **6a**. The adduct **7d** obtained was shown to consist

Table 2. Asymmetric direct α-amination of α-fluorinated aromatic ketones **1** with azodicarboxylates **3b** catalyzed by chiral guanidine **2**.



Entry	1 (α-Fluorinated ketones)	5	T [°C]	Yield [%][a]	ee [%][b]
1	**1a**	**5a**	−20	88	90
2	**1b**	**5b**	−20	98	96
3	**1c**	**5c**	−20	90	91
4	**1d**	**5d**	0	86	94
5	**1e**	**5e**	0	94	95
6	**1f**	**5f**	−40	96	90
7	**1g**	**5g**	−20	86	93
8	**1h**	**5h**	−40	83	92
9[c]	**1i**	**5i**	−40	93	90
10	**1j**	**5j**	−40	87	84
11	**1k**	**5k**	−40	88	86

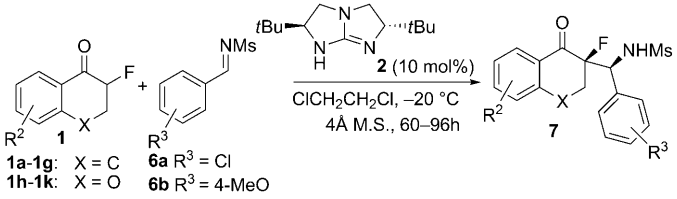
[a] Yield of isolated product. [b] Determined by HPLC analysis on a chiral stationary phase. [c] Reaction performed with bicyclic chiral guanidine (**2**; 20 mol%).

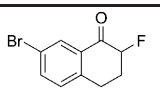
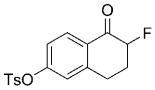
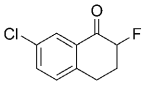
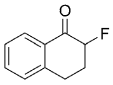
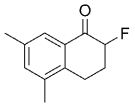
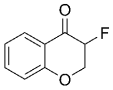
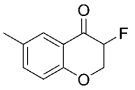
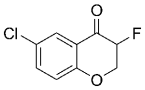
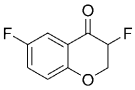
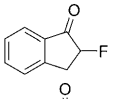
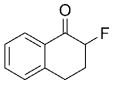
mainly of *syn*-isomers. We also noticed a significant amount of aldehyde arising from the decomposition of imine **6a**; 4 Å molecular sieves (M.S.) were therefore added to reduce this side product. The *syn*-**7d** isomer was formed with high enantioselectivity and excellent yield; while the observed diastereoselectivity was moderate. With imine **6a** as electrophile, a simple study of the substrate scope revealed that excellent enantioselectivities and high yields can be obtained regardless of the electronic properties and steric hindrance of the aromatic ring (Table 3, entries 1–10). The reaction with fluoronucleophile 2-fluoro-2,3-dihydro-1H-inden-1-one

(**1l**), which is reported for the first time, gave the enantiopure adduct **7j** with good yield (Table 3, entry 10). Ketones **1h–k**, which were derived from 4-chromanones, were also found to be suitable for this Mannich reaction, thereby providing enantioselectivities of up to 98% *ee*. The imine **6b**, bearing electron-donating group on its aromatic ring, exhibited relatively lower reactivity. The reaction was thus carried out at −5°C with 20% the chiral guanidine **2**. The enantioselectivity observed is still high and a reaction yield of 79% was obtained (Table 3, entry 11). The enantioselectivitie values for the minor *anti*-isomers were typically lower than 33%; however, the two diastereoisomers were easily separated by flash chromotography.

In summary, a series of α-fluorinated aromatic ketones have been employed as fluorocarbon nucleophiles for asymmetric catalysis. It has been found that these α-fluorinated aromatic ketones are excellent fluorocarbon nucleophiles. These fluorocarbon nucleophiles have been successfully employed for the organocatalytic formation of C–N and C–C bonds. Highly enantioselective amination and Mannich addition reactions were carried out. This synthetic method is a simple and efficient approach to the construction of nitrogen-containing fluorinated quaternary stereogenic centers.

Table 3. Asymmetric Mannich reaction of α-fluorinated aromatic ketones 1 catalyzed by bicyclic chiral guanidine **2**.



Entry	**1** (α-Fluorinated ketones)	**7**	d.r.[a]	Yield [%][b]	*ee* [%][c]
1	 **1a**	**7a**	5.2:1	87	96 (8)
2	 **1b**	**7b**	3.4:1	92	95 (6)
3	 **1c**	**7c**	3.0:1	90	95 (9)
4	 **1d**	**7d**	3.0:1	78	96 (5)
5	 **1e**	**7e**	3.3:1	70	96 (14)
6	 **1h**	**7f**	3.0:1	88	98 (14)
7	 **1i**	**7g**	4.6:1	94	97 (8)
8	 **1j**	**7h**	3.0:1	88	97 (8)
9	 **1k**	**7i**	2.4:1	90	95 (8)
10	 **1l**	**7j**	3.4:1	87	>99 (25)
11[d]	 **1d**	**7k**	1.8:1	79	96 (33)

[a] d.r. = diastereomeric ratio, determined by ^{1}H NMR analysis. [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase; the *ee* values of the *anti*-isomers are in parentheses. [d] Reaction performed with bicyclic chiral guanidine (20 mol%) at −5°C; imine **6b** was used.

Experimental Section

Representative procedure for the synthesis of 5d: 2-Fluoro-3,4-dihydronaphthalen-1(2H)-one **1d** (33.0 mg, 0.2 mmol, 4.0 equiv) and **2** (1.12 mg, 0.005 mmol, 0.1 equiv) were dissolved in THF (0.4 mL) and stirred at 0°C for 20 min. Di-3-ethylpentan-3-yl azodicarboxylate **3b** (17.0 mg, 0.05 mmol, 1.0 equiv) was subsequently added. The reaction mixture was stirred at 0°C and monitored by TLC. After 45 h, upon complete consumption of **3b**, the reaction solvent was removed under reduced pressure and the crude product was directly loaded onto a short silica-gel column. Flash chromatography was performed using gradient elution with *n*-hexane/CH_2Cl_2 mixtures (100:1–10:1). After removing the solvent, product **5d** (21.5 mg) was obtained as a liquid in 86% yield.

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Keywords: amination · fluorine · Mannich reaction · organocatalysis · quaternary stereogenic center

[1] a) *Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), Wiley-Blackwell, New York, **2010**; b) A. Berkessel, H. Groger, *Asymmetric Organocatalysis: From Biomimetic Concepts to Applications in Asymmetric Synthesis*, Wiley-VCH, Weinheim, **2005**.

[2] For reviews, see: a) A. Ting, J. M. Goss, N. T. McDougal, S. E. Schaus, *Top. Curr. Chem.* **2009**, *291*, 145–200; b) M. Nielsen, C. B. Jacobsen, N. Holub, M. W. Paixão, K. A. Jørgensen, *Angew. Chem.* **2010**, *122*, 2726–2738; *Angew. Chem. Int. Ed.* **2010**, *49*, 2668–2679.

[3] For reviews on the activation of ketones in organocatalysis, see: a) S. B. Tsogoeva, *Eur. J. Org. Chem.* **2007**, 1701–1716; b) B. List, *Tetrahedron* **2002**, *58*, 5573–5590; c) W. Notz, F. Tanaka, C. F. Barbas III, *Acc. Chem. Res.* **2004**, *37*, 580–591; d) B. List, *Chem. Commun.* **2006**, 819–824.

[4] For examples of fluoroacetone in organocatalysis, see: a) G. Zhong, J. Fan, C. F. Barbas III, *Tetrahedron Lett.* **2004**, *45*, 5681–5684; b) X.-Y. Xu, Y.-J. Wang, L.-F. Cun, L.-Z. Gong, *Tetrahedron: Asymmetry* **2007**, *18*, 237–242; c) X.-Y. Xu, Y.-Z. Wang, L.-Z. Gong, *Org. Lett.* **2007**, *9*, 4247–4249; d) T. Hoffmann, G. Zhong, B. List, D. Shabat, J. Anderson, S. Gramatikova, R. A. Lerner, C. F. III. Barbas, *J. Am. Chem. Soc.* **1998**, *120*, 2768–2779.

[5] For examples of acetophenone and acetone in organocatalysis, see: a) L. Yue, W. Du, Y.-K. Liu, Y.-C. Chen, *Tetrahedron Lett.* **2008**, *49*, 3881–3884; b) X. Jiang, Y. Zhang, A. S. C. Chan, R. Wang, *Org.*

Lett. **2009**, *11*, 153–156; c) C. G. Kokotos, G. Kokotos, *Adv. Synth. Catal.* **2009**, *351*, 1355–1362; d) K. Liu, H.-F. Cur, J. Nie; K.-Y. Dong, X.-J. Li, J.-A. Ma, *Org. Lett.* **2007**, *9*, 923–925; K.-Y. Dong, X.-J. Li, J.-A. Ma, *Org. Lett.* **2007**, *9*, 923–925; e) Q. Guo, M. Bhanushali, C.-G. Zhao, *Angew. Chem.* **2010**, *122*, 9650–9654; *Angew. Chem. Int. Ed.* **2010**, *49*, 9460–9464.

[6] For selected reviews, see: a) D. Leow, C.-H. Tan, *Chem. Asian J.* **2009**, *4*, 488–507; b) D. Leow, C.-H. Tan, *Synlett* **2010**, 1589–1605; c) C. Palomo, M. Oiarbide, R. López, *Chem. Soc. Rev.* **2009**, *38*, 632–653; d) J. Seayad, B. List, *Org. Biomol. Chem.* **2005**, *3*, 719–724.

[7] For selected examples using organocatalysts, see: a) D. A. Alonso, S. Kitagaki, N. Utsumi, C. F. Barbas III, *Angew. Chem.* **2008**, *120*, 4664–4667; *Angew. Chem. Int. Ed.* **2008**, *47*, 4588–4591; b) N. Utsumi, S. Kitagaki, C. F. Barbas III, *Org. Lett.* **2008**, *10*, 3405–3408; c) M. C. Kohler, J. M. Yost, M. R. Garnsey, D. M. Coltart, *Org. Lett.* **2010**, *12*, 3376–3379; d) M. Terada, D. Tsushima, M. Nakano, *Adv. Synth. Catal.* **2009**, *351*, 2817–2821; e) C. Guo, M.-X. Xue, M.-K. Zhu, L.-Z. Gong, *Angew. Chem.* **2008**, *120*, 3462–3465; *Angew. Chem. Int. Ed.* **2008**, *47*, 3414–3417; f) F. Marini, S. Sternativo, F. D. Verme, L. Testaferri, M. Tiecco, *Adv. Synth. Catal.* **2009**, *351*, 103–106; g) T.-Y. Liu, R. Li, Q. Chai, J. Long, B.-J. Li, Y. Wu, L.-S. Ding, Y.-C. Chen, *Chem. Eur. J.* **2007**, *13*, 319–327; h) S. Saaby, M. Bella, K. A. Jørgensen, *J. Am. Chem. Soc.* **2004**, *126*, 8120–8121; i) X. Liu, H. Li, L. Deng, *Org. Lett.* **2005**, *7*, 167–169; j) X. Wang, M. Kitamura, K. Maruoka, *J. Am. Chem. Soc.* **2007**, *129*, 1038–1039; k) H. Li, J. Song, X. Liu, L. Deng, *J. Am. Chem. Soc.* **2005**, *127*, 8948–8949; l) J. Wang, L. Zu, W. Jiang, W. Duan, W. Wang, *J. Am. Chem. Soc.* **2006**, *128*, 12652–12653; m) H. W. Moon, D. Y. Kim, *Tetrahedron Lett.* **2010**, *51*, 2906–2908; n) A. Prieto, N. Halland, K. A. Jørgensen, *Org. Lett.* **2005**, *7*, 3897–3900; o) D. Uraguchi, K. Koshimoto, T. Ooi, *J. Am. Chem. Soc.* **2008**, *130*, 10878–10879.

[8] T.-Y. Liu, H.-L. Cui, Y. Zhang, K. Jiang, W. Du, Z.-Q. He, Y.-C. Chen, *Org. Lett.* **2007**, *9*, 3671–3674.

[9] For selected examples, see: a) B. Wang, F. Wu, X. Liu, L. Deng, *J. Am. Chem. Soc.* **2007**, *129*, 768–769; b) Y. Wang, X. Liu, L. Deng, *J. Am. Chem. Soc.* **2006**, *128*, 3928–3930; c) J.-H. Lee, D. Y. Kim, *Adv. Synth. Catal.* **2009**, *351*, 1779–1782; d) S. M. Kim, J. H. Lee, D. Y. Kim, *Synlett* **2008**, 2659–2662; e) S.-L. Zhao, C.-W. Zheng, H.-F. Wang, G. Zhao, *Adv. Synth. Catal.* **2009**, *351*, 2811–2816.

[10] *Fluorine in Medicinal Chemistry and Chemical Biology* (Ed.: I. Ojima), Wiley-Blackwell, New York, **2009**.

[11] For a recent review of the organocatalytic formation of quaternary stereocenters, see: M. Bella, T. Gasperi, *Synthesis* **2009**, 1583–1614.

[12] For highlight articles and recent reviews, see: a) P. M. Pihko, *Angew. Chem.* **2006**, *118*, 558–561; *Angew. Chem. Int. Ed.* **2006**, *45*, 544–547; b) G. K. S. Prakash, P. Beier, *Angew. Chem.* **2006**, *118*, 2228–2230; *Angew. Chem. Int. Ed.* **2006**, *45*, 2172–2174; c) V. A. Brunet, D. O'Hagan, *Angew. Chem.* **2008**, *120*, 1198–1201; *Angew. Chem. Int. Ed.* **2008**, *47*, 1179–1182; d) J.-A. Ma, D. Cahard, *Chem. Rev.* **2004**, *104*, 6119–6146; e) N. Shibaba, T. Ishimaru, S. Nakamura, T. Toru, *J. Fluorine Chem.* **2007**, 128, 469–483; f) H. Ibrahim, A. Togni, *Chem. Commun.* **2004**, 1147–1155; g) S. Lectard, Y. Hamashima, M. Sodeoka, *Adv. Synth. Catal.* **2010**, *352*, 2708–2732; h) C. Bobbio, V. Gouverneur, *Org. Biomol. Chem.* **2006**, *4*, 2065–2075; i) S. Brandes, B. Niess, M. Bella, A. Prieto, J. Overgaard, K. A. Jørgensen, *Chem. Eur. J.* **2006**, *12*, 6039–6052.

[13] a) H. Li, S. Zhang, C. Yu, X. Song, W. Wang, *Chem. Commun.* **2009**, 2136–2138; b) X. Han, J. Luo, C. Liu, Y. Lu, *Chem. Commun.* **2009**, 2044–2046; c) X. Han, J. Kwiatkowski, F. Xue, K-W. Huang, Y. Lu, *Angew. Chem.* **2009**, *121*, 7740–7743; *Angew. Chem. Int. Ed.* **2009**, *48*, 7604–7607; d) Y. Oh, S. M. Kim, D. Y. Kim, *Tetrahedron Lett.* **2009**, *50*, 4674–4676; e) C. Ding, K. Maruoka, *Synlett* **2009**, 664–666; f) H.-F. Cui, Y.-Q. Yang, Z. Chai, P. Li, C.-W. Zheng, S.-Z. Zhu, G. Zhao, *J. Org. Chem.* **2010**, *75*, 117–122; g) F. Ullah, G-L. Zhao, Deiana, L. M. Zhu, P. Dziedzic, I. Ibrahem, P. Hammar, J. Sun, A. Córdova, *Chem. Eur. J.* **2009**, *15*, 10013–10017; h) T. Furukawa, N. Shibata, S. Mizuta, S. Nakamura, T. Toru, M. Shiro, *Angew. Chem.* **2008**, *120*, 8171–8174; *Angew. Chem. Int. Ed.* **2008**, *47*, 8051–8054; i) S. Mizuta, N. Shibata, Y. Goto, T. Furukawa, S. Nakamura, T. Toru, *J. Am. Chem. Soc.* **2007**, *129*, 6394–6395; j) G. K. S. Prakash, F. Wang, T. Stewart, T. Mathew, G. A. Olah, *Proc. Natl. Acad. Sci. USA* **2009**, *106*, 4090–4094; k) S. Arai, M. Oku, T. Ishida, T. Shioiri, *Tetrahedron Lett.* **1999**, *40*, 6785–6789; l) B. Thierry, T. Perrard, C. Audouard, J.-C. Plaquevent, D. Cahard, *Synthesis* **2001**, 1742–1746; m) X. Han, F. Zhong, Y. Lu, *Adv. Synth. Catal.* **2010**, *352*, 2778–2782.

[14] For recent contributions from other research groups on guanidine-catalyzed reactions, see: a) Z. Yu, X. Liu, L. Zhou, L. Lin, X. Feng, *Angew. Chem.* **2009**, *121*, 5297–5300; *Angew. Chem. Int. Ed.* **2009**, *48*, 5195–5198; b) H. Ube, M. Shimada, M. Terada, *Angew. Chem.* **2010**, *122*, 1902–1905; *Angew. Chem. Int. Ed.* **2010**, *49*, 1858–1861; c) T. Misaki, G. Takimoto, T. Sugimura, *J. Am. Chem. Soc.* **2010**, *132*, 6286–6287; d) S. Dong, X. Liu, X. Chen, F. Mei, Y. Zhang, B. Gao, L. Lin, X. Feng, *J. Am. Chem. Soc.* **2010**, *132*, 10650–10651.

[15] a) Z. Jiang, Y. Pan, Y. Zhao, T. Ma, R. Lee, Y. Yang, K.-W. Huang, M. W. Wang, C.-H. Tan, *Angew. Chem.* **2009**, *121*, 3681–3685; *Angew. Chem. Int. Ed.* **2009**, *48*, 3627–3631; b) Y. Pan, Y. Zhao, T. Ma, Y. Yang, H. Liu, Z. Jiang, C.-H. Tan, *Chem. Eur. J.* **2009**, *15*, 779–782.

[16] The reaction between nonfluorinated tetralone and **3a** was very slow under the same reaction conditions.

[17] a) J. Y. Mang, D. G. Kwon, D. Y. Kim, *J. Fluorine Chem.* **2009**, *130*, 259–262; b) D. P. Huber, K. Stanek, A. Togni, *Tetrahedron: Asymmetry* **2006**, *17*, 658–664.

[18] a) R. D. Little, R. G. Venegas, *Org. Syn.* **1983**, *61*, 17–20; b) L. A. Carpino, B. A. Carpino, C. A. Giza, P. H. Terry, *Org. Syn.* **1964**, *44*, 15–17; c) L. A. Carpino, P. J. Crowley, *Org. Syn.* **1964**, *44*, 18–20.

[19] a) *The Flavonoids: Advances in Research Since 1980* (Ed.: J. B. Harborne), Chapman and Hall, New York, **1994**; b) *Flavonoid in Biology and Medicine III: Proceedings of 3rd International Symposium on Flavonoids in Biology Medicine* (Ed.: N. P. Das), National University of Singapore, Singapore, **1989**.

[20] For reviews of asymmetric organocatalytic Mannich reactions, see: a) A. Ting, S. E. Schaus, *Eur. J. Org. Chem.* **2007**, 5797–5815; b) J. M. M. Verkade, L. J. C. Hemert, P. J. L. M. Quaedflieg, F. P. J. T. Ruties, *Chem. Soc. Rev.* **2008**, *37*, 29–41.

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