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Efficient synthesis of substituted quinolines through intramolecular addition of aryl anion to carbonyl carbon

Yuichi Kobayashi *, Junji Igarashi, Chao Feng, Toshifumi, Tojo

Department of Biomolecular Engineering, Tokyo Institute of Technology, Box B52, Nagatsuta-cho 4259, Midori-ku, Yokohama 226-8501, Japan

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ABSTRACT

Substituted quinolines were synthesized in three steps from the Boc amides of substituted 2-iodoanilines and alkyl vinyl ketones. This method consists of (1) N-Michael addition of the Boc amide of 2-iodoaniline to alkyl vinyl ketone in the presence of Cs_2CO_3 in MeCN; (2) I–Mg exchange of the adduct with 3.5 equiv of *i*-PrMgCl·LiCl, and (3) acid-catalyzed reaction (excess AcCl in EtOH) of the resulting alcohol. Six examples are given with good yields.

Synthesis of substituted quinolines has been an important subject in organic synthesis because of the structural complexity and of the biological importance. Figure 1 shows typical examples of the substituted natural and artificial quinolines.[1,2] Doebner–Miller reaction, which is frequently referred as Scraup reaction, is a well-known method of this subject,[3,4] and consists of N-Michael addition of aniline to α,β-unsaturated ketone in the presence of ZnX_2 under acidic conditions and subsequent formation of the dihydroquinoline ring. Although being attractive due to the operational convenience, the method suffers from low reactivity with an electron-withdrawing substituent on the aniline ring and/or with an alkyl substituent on the β-position of α,β-unsaturated ketones.

To improve the reactivity, numerous efforts have been devoted to find other Lewis acid catalysts and/or other conditions,[5] whereas approaches using 2-substituted anilines and 2-haloanilines have been investigated as well by taking advantage of the reactions of the substituent[6] or the aryl-halogen moiety.[7,8] Despite these efforts, however, development of a new route to quinolines remains an active area of research.[9] Herein, we present a new access to substituted quinolines, which is illustrated in Scheme 1.

This method consists of the following reactions and thus irrelevant to the regioselectivity: (1) N-Michael addition of 2-iodoaniline derivative **1** to vinyl ketone **2**; (2) iodine–metal exchange to generate the anion for intramolecular addition to the carbonyl carbon to afford 4-hydroxytetrahydroquinoline **3**; (3) dehydration of **3** to dihydroquinoline **4**; (4) conversion of **4** to the targeted quinoline derivative **5** by base-assisted elimination[5d,10] of R^2–H or by deprotection of the R^2 group followed by dehydrogenation. Previously, a 2-iodoaniline derivative with the epoxide moiety on the side chain was converted into the corresponding anion by iodine–copper exchange with $Li_2Cu(CN)Me_3$, and the anion thus formed underwent intramolecular epoxide ring opening to afford a tetrahydroquinoline.[11] However, neither scope of the synthesis of tetrahydroquinolines nor further conversion to substituted quinoline was studied.

Our approach was initially examined with the Ts amide **1a** (R^2 = Ts), which was synthesized from 2-iodoaniline with TsCl in 96% yield. N-Michael addition to methyl vinyl ketone (**2a**) was achieved using Et_3N (0.1 equiv) in MeOH (rt, overnight) to give **6a** in 95% yield (Scheme 2). Iodine–lithium exchange of **6a** was examined with *t*-BuLi (2.2 equiv) in THF at −78 °C for 2 h to afford the desired alcohol **3a** in 82% yield. Subsequently, dehydration with a catalytic amount of *p*-TsOH·H_2O in toluene at 80 °C furnished dihydroquinoline **4a** quantitatively. Finally, base-assisted elimination of Ts-H to 4-methylquinoline (**5A**) was attempted with NaOH in refluxing MeOH and with KOH in DMSO at 140 °C according to the literature,[5d] but **4a** was recovered quantitatively.

Next, the *N*-Teoc amide **1b** (R^2 = Teoc = $CO_2CH_2CH_2TMS$) was sacrificed to this study with a prospect of deprotection of the derived dihydroquinoline **4b** with TBAF[12] followed by oxidation to **5A**. The amide **1b** was prepared from 2-iodoaniline and $TMS(CH_2)_2OH$ (3 equiv) in 54% yield with triphosgene (1 equiv) and K_2CO_3 (10 equiv). N-Michael addition of **1b** to methyl vinyl ketone (**2a**) (3 equiv) proceeded smoothly with Cs_2CO_3 (0.2 equiv) in MeCN (rt, 1 h) to produce **6b** in 90% yield.[13] Iodine–lithium

* Corresponding author. Tel./fax: +81 45 924 5789.
E-mail address: ykobayas@bio.titech.ac.jp (Y. Kobayashi).

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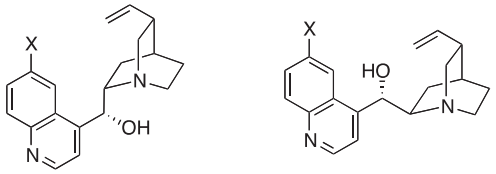
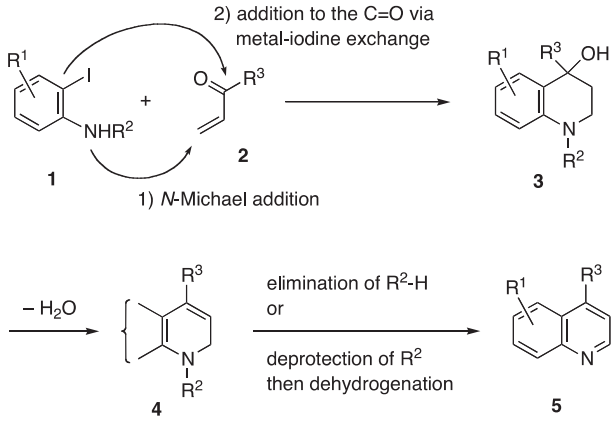


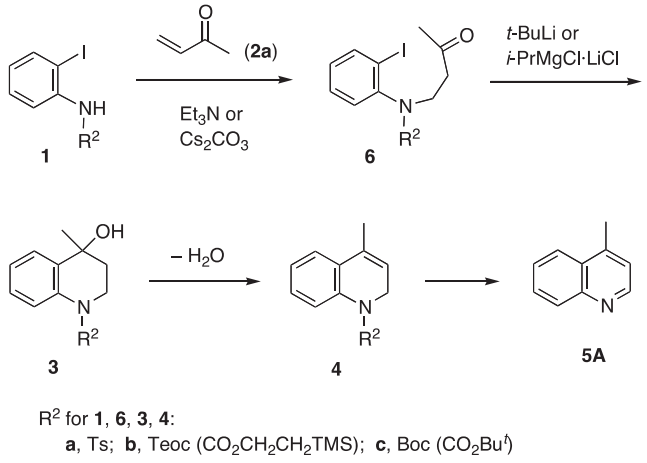
quinine: X = OMe
cinchonidine: X = H
F derivative: X = F

quinidine: X = OMe
cinchonine: X = H
F derivative: X = F

Figure 1. Typical examples of quinoline derivatives.



Scheme 1. Approach to 4-substituted quinolines.



R2 for **1**, **6**, **3**, **4**:
a, Ts; **b**, Teoc ($CO_2CH_2CH_2TMS$); **c**, Boc (CO_2Bu^t)

Scheme 2. Preliminary results.

exchange of **6b** with *t*-BuLi (2.2 equiv) unfortunately afforded a mixture of **3b** and other unidentified products, from which **3b** was isolated in 51% yield by chromatography.[14] Dehydration of **3b** under the conditions used for tosylate **3a** (*p*-TsOH·H_2O, toluene, 80 °C) produced **4b** in 37% yield. In contrast to these low yielding steps, subsequent TBAF-promoted deprotection of the Teoc group at 80 °C for 1 h proceeded cleanly to afford **5A** in 86% yield. The intermediate, 4-methyl-1,2-dihydroquinoline (i.e., **4** with R^2 = H), could not be detected by TLC and NMR analysis, indicating rapid dehydrogenation of the intermediate during the isolation.

The high-yielding conversion of **4b** to **5A** prompted the use of the Boc amide **4c** (R^2 = Boc), which was expected to be removed under acidic conditions being set for dehydration of **3c**. The Boc amide **1c** was synthesized from 2-iodoaniline in 81% yield with Boc_2O (1.1 equiv) and $NaN(TMS)_2$ (2 equiv) in THF,[15] and subjected to N-Michael addition to **2a** (3 equiv) in the presence of Cs_2CO_3 (0.2 equiv) in MeCN at room temperature for 3 h to afford amide **6c** in 87% yield. Due to the above unsatisfactory results of I–Li exchange of **6b** with *t*-BuLi, iodine–magnesium exchange with *i*-PrMgCl·LiCl was studied for **6c** according to the protocol developed by Knochel.[16] Initially, 1.5 equiv of *i*-PrMgCl·LiCl in THF was added to **6c** at −78 °C to afford a mixture of **3c** and the unreacted iodide **1c**. Formation of other unidentified byproducts was not detected by TLC. Next, optimization of the quantity of *i*-PrMgCl·LiCl was investigated. The reactions with 2.0, 2.5, and 3.0 equiv of the reagent were incomplete, whereas the use of 3.5 equiv of the reagent forwarded the reaction to be completed, furnishing **3c** in 91% yield after chromatography. The use of 4.0 and 5.0 equiv of *i*-PrMgCl·LiCl gave **3c** also cleanly judging from TLC analysis.

Exposure of **3c** with *p*-TsOH·H_2O (15 mol %) resulted in not only dehydration but also deprotection of the Boc group followed by dehydrogenation of the dihydroquinoline intermediate to afford **5A** in 74% yield. Since formation of a minor quantity of the unidentified byproducts was monitored by TLC analysis, other acidic conditions such as AcCl in EtOH, TMSCl in CH_2Cl_2, CF_3CO_2H in CH_2Cl_2 were examined. Among them, AcCl (10 equiv) in EtOH at 50 °C for 1 h cleanly afforded **5A** in 80% yield, whereas the other acidic conditions produced the dehydration product **4c** as a major product. The best result mentioned above is summarized in Eq. 1 of Scheme 3.

Next, electronic influence of a substituent on the 2-iodoaniline ring was examined briefly. As summarized in Scheme 3, Eqs. 2 and 3, amides **1d** and **1e** with a slightly or a strongly electron-donating substituent were found to be good starting compounds,[17] furnishing quinoline **5B** and **5C** in good yields.

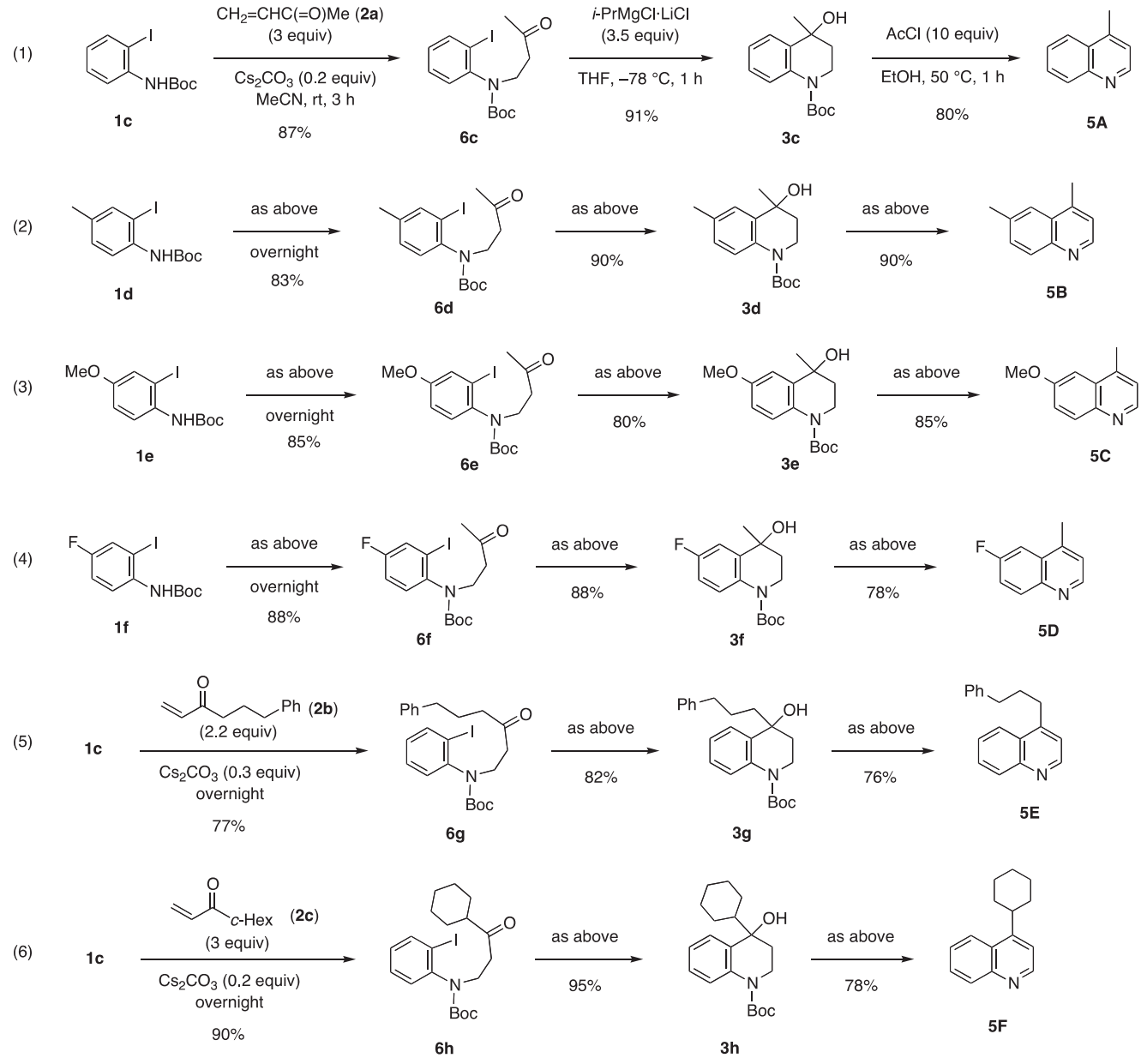
Amide **1f**[17] with electron-withdrawing fluorine atom was transformed to quinoline **5D** with similar efficiency to the entries mentioned above (Eq. 4). Synthesis of fluorine derivatives has been the subject in the field of organic synthesis. Up to date, the Scraup-type reaction of a F-substituted aniline,[18a] a synthesis using a 2-substituted aniline,[6s] direct fluorination of quinolines[18b] have been studied to find low to moderate yields and/or low regioselectivity. On the other hand, substitution of organotin compounds with F-TEDA-PF_6 produces F-quinolines in good yields.[2] As mentioned above, our method is efficient and would be complementary to the substitution.

Application of the present method to vinyl ketones **2b** and **2c** possessing a long alkyl chain or a sterically bulky group was examined next. Each step proceeded smoothly to produce **5E** and **5F** in good yields (Eqs. 5 and 6). These examples indicate that the present method is applicable to a wide variety of alkyl vinyl ketones.

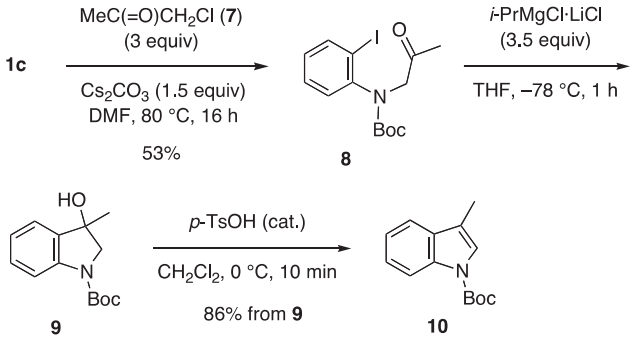
Furthermore, the present transformation was applied for construction of the indole ring as shown in Scheme 4.

In summary, we have presented a synthesis of quinolines consisting of the N-Michael addition of the Boc amide of the 2-iodoaniline to alkyl vinyl ketone,[19] the I–Mg exchange of the adduct, and the acid-catalyzed conversion of the resulting alcohol. The method is in principle regioselective due to the iodine atom at 2-position. Furthermore, the method is compatible with fluorine atom on the aromatic rings and suited to production of the 4-substituted quinolines as well.

Typical example of the procedure: To an ice-cold suspension of the Boc amide **1c** (441 mg, 1.38 mmol) and Cs_2CO_3 (89 mg, 0.273 mmol) in MeCN (2.8 mL) was added **2a** (286 mg, 4.08 mmol) dropwise. After 3 h of stirring at room temperature, the mixture was concentrated. The residue was diluted with EtOAc and the resulting mixture was filtered through a pad of Celite. The filtrate was concentrated and the resulting residue was purified by chromatography (hexane/EtOAc) to furnish **6c** (469 mg, 87%). To a suspension of **6c** (343 mg, 0.881 mmol) in THF (2.3 mL) was added *i*-



Scheme 3. Synthesis of quinoline derivatives.[a] [a]Conditions otherwise different from those of Eq. 1 are indicated.



Scheme 4. Construction of the indole ring.

PrMgCl·LiCl (2.10 mL, 1.47 M in THF, 3.09 mmol) dropwise at −78 °C. The solution was stirred at −78 °C for 1 h and poured into saturated NH_4Cl. The resulting mixture was extracted with EtOAc, and the crude product was purified by chromatography (hexane/EtOAc) to furnish **3c** (211 mg, 91%). To an ice-cold solution of **3c** (44 mg, 0.167 mmol) in EtOH (1.7 mL) was added AcCl (0.12 mL, 1.69 mmol) dropwise. The solution was stirred at room temperature for 10 min and then at 50 °C for 1 h, and diluted with saturated $NaHCO_3$. The mixture was extracted with EtOAc, and the crude product was purified by chromatography (hexane/EtOAc) to furnish **5A** (19 mg, 80%).[20]

Acknowledgments

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References and notes

1. (a) Cheng, C.-C.; Yan, S.-J. In *Organic Reactions*; Wiley: New York, 1982; Vol. 28, Chapter 2; (b) Seeman, J. I. *Angew. Chem., Int. Ed.* **2007**, *46*, 1378–1413.
2. (a) Tang, P.; Furuya, T.; Ritter, T. *J. Am. Chem. Soc.* **2010**, *132*, 12150–12154; (b) Furuya, T.; Strom, A. E.; Ritter, T. *J. Am. Chem. Soc.* **2009**, *131*, 1662–1663.

3. *Strategic Applications of Named Reactions in Organic Synthesis*; Kürti, L., Czkó, B., Eds.; Elsevier, 2005. pp 414–415.
4. (a) Campbell, K. N.; Schaffner, I. J. *J. Am. Chem. Soc.* **1945**, *67*, 86–89; (b) Wilson, S. R.; Grandi, M. J. D. *J. Org. Chem.* **1991**, *56*, 4766–4772; (c) Johns, D. M.; Mori, M.; Williams, R. M. *Org. Lett.* **2006**, *8*, 4051–4054.
5. Recent publications: (a) De, K.; Legros, J.; Crousse, B.; Bonnet-Delpon, D. *J. Org. Chem.* **2009**, *74*, 6260–6265; (b) Wu, Y.-C.; Liu, L.; Li, H.-J.; Wang, D.; Chen, Y.-J. *J. Org. Chem.* **2006**, *71*, 6592–6595; (c) Ranu, B. C.; Hajra, A.; Dey, S. S.; Jana, U. *Tetrahedron* **2003**, *59*, 813–819; (d) Tokuyama, H.; Sato, M.; Ueda, T.; Fukuyama, T. *Heterocycles* **2001**, *54*, 105–108; (e) Matsugi, M.; Tabusa, F.; Minamikawa, J. *Tetrahedron Lett.* **2000**, *41*, 8523–8525.
6. Selected publications: (a) Patil, N. T.; Raut, V. S. *J. Org. Chem.* **2010**, *75*, 6961–6964; (b) Isobe, A.; Takagi, J.; Katagiri, T.; Uneyama, K. *Org. Lett.* **2008**, *10*, 2657–2659; (c) Mierde, H. V.; Voort, P. V. D.; Vos, D. D.; Verpoort, F. *Eur. J. Org. Chem.* **2008**, 1625–1631; (d) Zhang, Z.; Tan, J.; Wang, Z. *Org. Lett.* **2008**, *10*, 173–175; (e) Sandelier, M. J.; DeShong, P. *Org. Lett.* **2007**, *9*, 3209–3212; (f) Gabriele, B.; Mancuso, R.; Salerno, G.; Ruffolo, G.; Plastina, P. *J. Org. Chem.* **2007**, *72*, 6873–6877; (g) Cho, C. S.; Ren, W. X.; Shim, S. C. *Tetrahedron Lett.* **2006**, *47*, 6781–6785; (h) Sivaprasad, G.; Rajesh, R.; Perumal, P. T. *Tetrahedron Lett.* **2006**, *47*, 1783–1785; (i) Bose, D. S.; Kumar, R. K. *Heterocycles* **2006**, *68*, 549–559; (j) Bennasar, M.-L.; Roca, T.; Monerris, M.; García-Díaz, D. *Tetrahedron Lett.* **2005**, *46*, 4035–4038; (k) Kobayashi, K.; Yoneda, K.; Miyamoto, K.; Morikawa, O.; Konishi, H. *Tetrahedron* **2004**, *60*, 11639–11645; (l) Theeraladanon, C.; Arisawa, M.; Nishida, A.; Nakagawa, M. *Tetrahedron* **2004**, *60*, 3017–3035; (m) McNaughton, B. R.; Miller, B. L. *Org. Lett.* **2003**, *5*, 4257–4259; (n) Palimkar, S. S.; Siddiqui, S. A.; Daniel, T.; Lahoti, R. J.; Srinivasan, K. V. *J. Org. Chem.* **2003**, *68*, 9371–9378; (o) Cho, C. S.; Kim, B. T.; Choi, H.-J.; Kim, T.-J.; Shim, S. C. *Tetrahedron* **2003**, *59*, 7997–8002; (p) Jiang, B.; Si, Y.-G. *J. Org. Chem.* **2002**, *67*, 9449–9451; (q) Swenson, R. E.; Sowin, T. J.; Zhang, H. Q. *J. Org. Chem.* **2002**, *67*, 9182–9185; (r) Cho, C. S.; Kim, B. T.; Kim, T.-J.; Shim, S. C. *Chem. Commun.* **2001**, 2576–2577; (s) Cho, I.-S.; Gong, L.; Muchowski, J. M. *J. Org. Chem.* **1991**, *56*, 7288–7291; (t) Qiang, L. G.; Baine, N. H. *J. Org. Chem.* **1988**, *53*, 4218–4222.
7. Selected publications: (a) Stone, M. T. *Org. Lett.* **2011**, *13*, 2326–2329; (b) Gowrisankar, S.; Lee, H. S.; Kim, J. M.; Kim, J. N. *Tetrahedron Lett.* **2008**, *49*, 1670–1673; (c) López-Alberca, M. P.; Mancheño, M. J.; Fernández, I.; Gómez-Gallego, M.; Sierra, M. A.; Torres, R. *Org. Lett.* **2007**, *9*, 1757–1759; (d) Cho, C. S.; Kim, J. U. *Tetrahedron Lett.* **2007**, *48*, 3775–3778; (e) Alacid, E.; Nájera, C. *Adv. Synth. Catal.* **2007**, *349*, 2572–2584; (f) Hogan, A.-M. L.; O'Shea, D. F. *Org. Lett.* **2006**, *8*, 3769–3772; (g) Korivi, R. P.; Cheng, C.-H. *J. Org. Chem.* **2006**, *71*, 7079–7082; (h) Parker, K. A.; Mindt, T. L. *Org. Lett.* **2002**, *4*, 4265–4268; (i) Larock, R. C.; Kuo, M.-Y. *Tetrahedron Lett.* **1991**, *32*, 569–572.
8. Selected publications: (a) Zhao, J.; Peng, C.; Liu, L.; Wang, Y.; Zhu, Q. *J. Org. Chem.* **2010**, *75*, 7502–7504; (b) Peng, C.; Wang, Y.; Liu, L.; Wang, H.; Zhao, J.; Zhu, Q. *Eur. J. Org. Chem.* **2010**, 818–822; (c) Liu, L.; Wang, Y.; Wang, H.; Peng, C.; Zhao, J.; Zhu, Q. *Tetrahedron Lett.* **2009**, *50*, 6715–6719; (d) Bernini, R.; Cacchi, S.; Fabrizi, G.; Filisti, E.; Sferrazza, A. *Synlett* **2009**, 1245–1250; (e) Sakai, N.; Annaka, K.; Fujita, A.; Sato, A.; Konakahara, T. *J. Org. Chem.* **2008**, *73*, 4160–4165; (f) Schramm, O. G.; Oeser, T.; Kaiser, M.; Brun, R.; Müller, T. J. J. *Synlett* **2008**, 359–362; (g) Sakai, N.; Annaka, K.; Konakahara, T. *J. Org. Chem.* **2006**, *71*, 3653–3655; (h) Cho, C. S. *J. Organometal. Chem.* **2005**, *690*, 4094–4097; (i) Abbiati, G.; Arcadi, A.; Canevari, V.; Capezzuto, L.; Rossi, E. *J. Org. Chem.* **2005**, *70*, 6454–6460; (j) Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Moreno-Mañas, M.; Vallriber, A. *Tetrahedron Lett.* **2002**, *43*, 5537–5540; (k) Suginome, M.; Fukuda, T.; Ito, Y. *Org. Lett.* **1999**, *1*, 1977–1979; (l) Arcadi, A.; Marinelli, F.; Rossi, E. *Tetrahedron* **1999**, *55*, 13233–13250.
9. Selected publications: (a) Lord, A.-M.; Mahon, M. F.; Lloyd, M. D.; Threadgill, M. D. *J. Med. Chem.* **2009**, *52*, 868–877; (b) Horn, J.; Marsden, S. P.; Nelson, A.; House, D.; Weingarten, G. G. *Org. Lett.* **2008**, *10*, 4117–4120; (c) Li, L.; Jones, W. D. *J. Am. Chem. Soc.* **2007**, *129*, 10707–10713; (d) Zhang, Q.; Zhang, Z.; Yan, Z.; Liu, Q.; Wang, T. *Org. Lett.* **2007**, *9*, 3651–3653; (e) Liu, X.-Y.; Ding, P.; Huang, J.-S.; Che, C.-M. *Org. Lett.* **2007**, *9*, 2645–2648; (f) Tanaka, S.; Yasuda, M.; Baba, A. *J. Org. Chem.* **2006**, *71*, 800–803; (g) Kharrat, S. E.; Skander, M.; Dahmani, A.; Laurent, P.; Blancou, H. *J. Org. Chem.* **2005**, *70*, 8327–8331; (h) Igarashi, T.; Inada, T.; Sekioka, T.; Nakajima, T.; Shimizu, I. *Chem. Lett.* **2005**, *34*, 106–107; (i) Zhang, X.; Campo, M. A.; Yao, T.; Larock, R. C. *Org. Lett.* **2005**, *7*, 763–766; (j) Ishikawa, T.; Manabe, S.; Aikawa, T.; Kudo, T.; Saito, S. *Org. Lett.* **2004**, *6*, 2361–2364; (k) Sangu, K.; Fuchibe, K.; Akiyama, T. *Org. Lett.* **2004**, *6*, 353–355; (l) Marull, M.; Lefebvre, O.; Schlosser, M. *Eur. J. Org. Chem.* **2004**, 54–63; (m) Du, W.; Curran, D. P. *Org. Lett.* **2003**, *5*, 1765–1768; (n) Epling, G. A.; Provatas, A. A. *Chem. Commun.* **2002**, 1036–1037; (o) Cho, C. S.; Kim, T. K.; Kim, B. T.; Kim, T.-J.; Shim, S. C. *J. Organometal. Chem.* **2002**, *650*, 65–68; (p) Amii, H.; Kishikawa, Y.; Uneyama, K. *Org. Lett.* **2001**, *3*, 1109–1112; (q) Cho, C. S.; Oh, B. H.; Kim, J. S.; Kim, T.-J.; Shim, S. C. *Chem. Commun.* **2000**, 1885–1886; (r) Wiebe, J. M.; Caillé, A. S.; Trimble, L.; Lau, C. K. *Tetrahedron* **1996**, *52*, 11705–11724; (s) Kimpe, N. D.; Keppens, M. *Tetrahedron* **1996**, *52*, 3705–3718; (t) Diamond, S. E.; Szalkiewicz, A.; Mares, F. *J. Am. Chem. Soc.* **1979**, *101*, 490–491.
10. Kim, J. N.; Lee, H. J.; Lee, K. Y.; Kim, H. S. *Tetrahedron Lett.* **2001**, *42*, 3737–3740.
11. Kondo, Y.; Matsudaira, T.; Sato, J.; Murata, N.; Sakamoto, T. *Angew. Chem., Int. Ed.* **1996**, *35*, 736–738.
12. Igarashi, J.; Kobayashi, Y. *Tetrahedron Lett.* **2005**, *46*, 6381–6384.
13. The use of Et_3N in MeOH as for **1a** marginally assisted addition of **1b** to **2A**, whereas other basis such as *t*-BuOK and NaH did not promote the reaction.
14. The I–Li exchange of the $COCF_3$ amide **6** with *t*-BuLi gave a mixture of unidentified products.
15. Guthrie, D. B.; Curran, D. P. *Org. Lett.* **2009**, *11*, 249–251.
16. Krasovskiy, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3333–3336.
17. The Boc amides **1d**–**f** were synthesized as follows. Compound **1d**, (a) 4-$MeC_6H_4NH_2$, I_2, $NaHCO_3$, 10–15 °C, H_2O; (b) Boc_2O, $NaN(TMS)_2$, THF, 92% over two steps. Compound **1e**, (a) 4-$MeOC_6H_4NH_2$, Boc_2O, Et_3N, CH_2Cl_2, 0 °C, 94%; (b) *t*-BuLi, Et_2O, 0 °C then $I(CH_2)_2I$, −78 °C to rt, 59%. Compound **1f**, (a) 4-$FC_6H_4NH_2$, I_2, $NaHCO_3$, H_2O; (b) Boc_2O, $NaN(TMS)_2$, THF, 85% over two steps.
18. (a) Krainer, Z. Y.; Gudz', P. F.; Yagupol'skii, L. M. *Chem. Heterocycl. Compd.* **1973**, *9*, 217–219; (b) Chambers, R. D.; Holling, D.; Sandford, G.; Batsanov, A. S.; Howard, J. A. K. *J. Fluorine Chem.* **2004**, *125*, 661–671.
19. Reaction of **1c** with phenyl vinyl ketone under the conditions for **2a** gave the product only in 10%.
20. The ^1H and/or ^{13}C NMR spectra of **5A**, **5B**, **5C**, and **5D** were identical with those reported. **5A**: Refs. 5a,c,6l **5B**: Refs. 5a,c,6i **5C**: Refs. 4c,5a,c,6i,l **5D**: Ref. 6s The NMR spectra of the intermediates are as follows: Compound **6c**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.34 (s, 9H), 2.14 (s, 3H), 2.80 (t, J = 7 Hz, 2H), 3.63 (dt, J = 14, 7 Hz, 1H), 3.99 (dt, J = 14, 7 Hz, 1H), 6.98 (t, J = 8 Hz, 1H), 7.15 (d, J = 8 Hz, 1H), 7.34 (t, J = 8 Hz, 1H), 7.85 (d, J = 8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.0, 29.8, 42.1, 44.5, 80.1, 100.2, 128.5, 128.8, 129.3, 139.2, 144.3, 153.5, 206.5. Compound **3c**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.53 (s, 9H), 1.58 (s, 3H), 1.82 (s, 1H), 2.02 (t, J = 6 Hz, 1H), 3.65 (dt, J = 13, 6 Hz, 1H), 3.94 (dt, J = 13, 6 Hz, 1H), 7.09 (t, J = 8 Hz, 1H), 7.22 (t, J = 8 Hz, 1H), 7.54 (d, J = 8 Hz, 1H), 7.70 (d, J = 8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.3, 29.3, 39.1, 41.6, 68.7, 81.0, 123.6, 123.8, 125.5, 127.2, 134.9, 136.9, 153.5. Compound **6d**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.35 (s, 9H), 2.15 (s, 3H), 2.31 (s, 3H), 2.79 (t, J = 7 Hz, 2H), 3.62 (dt, J = 14, 7 Hz, 1H), 3.97 (dt, J = 14, 7 Hz, 1H), 7.01 (d, J = 7 Hz, 1H), 7.13 (d, J = 7 Hz, 1H), 7.68 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.3, 28.0, 29.8, 42.1, 44.6, 80.0, 99.9, 128.8, 129.6, 138.6, 139.6, 141.7, 153.7, 206.7. Compound **3d**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.52 (s, 9H), 1.58 (s, 3H), 2.01 (t, J = 6 Hz, 2H), 2.32 (s, 3 H), 3.57–3.68 (m, 1H), 3.88–3.98 (m, 1H), 7.03 (d, J = 8 Hz, 1H), 7.34 (s, 1H), 7.57 (d, J = 8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 20.9, 28.4, 29.5, 39.3, 41.7, 68.9, 81.0, 123.8, 125.9, 128.1, 133.1, 134.4, 134.6, 153.6. Compound **6e**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.34 (s, 9H), 2.15 (s, 3H), 2.78 (t, J = 7 Hz, 1H), 3.58 (dt, J = 14, 7 Hz, 1H), 3.79 (s, 3H), 3.98 (dt, J = 14, 7 Hz, 1H), 6.86 (dd, J = 8, 3 Hz , 1H), 7.03 (d, J = 8 Hz, 1H), 7.35 (d, J = 3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.2, 30.1, 42.4, 44.9, 55.6, 80.3, 100.5, 114.6, 124.2, 129.5, 137.4, 154.2, 158.5, 207.2. Compound **3e**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.52 (s, 9H), 1.56 (s, 3H), 1.87 (s, 1H), 1.97–2.05 (m, 2H), 3.57–3.68 (m, 1H), 3.80 (s, 3H), 3.85–3.96 (m, 1H), 6.79 (dd, J = 9, 3 Hz, 1H), 7.06 (d, J = 3 Hz, 1H), 7.59 (d, J = 9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.4, 29.4, 39.4, 41.7, 55.5, 69.2, 80.9, 110.2, 113.4, 125.3, 130.3, 136.3, 153.8, 155.9. Compound **6f**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.35 (s, 9H), 2.16 (s, 3H), 2.80 (t, J = 7 Hz, 2H), 3.59 (dt, J = 14, 7 Hz, 1H), 3.98 (dt, J = 14, 7 Hz, 1H), 6.99–7.20 (m, 2H), 7.56 (dd, J = 8, 3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.3, 30.0, 42.2, 44.7, 80.5, 100.0 (d, J = 9 Hz), 115.9 (d, J = 22 Hz), 126.0 (d, J = 24 Hz), 130.0 (d, J = 9 Hz), 140.9 (d, J = 3 Hz), 153.7, 160.4 (d, J = 250 Hz), 206.8. Compound **3f**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.52 (s, 9H), 1.55 (s, 3H), 1.80 (s, 1H), 2.01 (ddd, J = 7, 5, 3.5 Hz, 2H), 3.64 (ddd, J = 13, 7, 5 Hz, 1H), 3.91 (ddd, J = 13, 7, 5 Hz, 1H), 6.92 (dd, J = 9, 8, 3 Hz, 1H), 7.23 (dd, J = 9, 3 Hz, 1H), 7.67 (dd, J = 9, 5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 28.3, 29.2, 39.0, 41.7, 68.9, 81.3, 111.9 (d, J = 23 Hz), 114.2 (d, J = 22 Hz), 125.6 (d, J = 8 Hz), 132.9 (d, J = 3 Hz), 137.1 (d, J = 7 Hz), 155.5 (d, J = 285 Hz), 160.7. Compound **6g**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.34 (s, 9 H), 2.41 (quint., J = 8 Hz, 1H), 2.59 (t, J = 8 Hz, 1H), 2.75 (t, J = 8 Hz, 1H), 3.63 (dt, J = 14, 7 Hz, 1H), 3.97 (dt, J = 14, 7 Hz, 1H), 6.98 (t, J = 8 Hz, 1H), 7.11–7.37 (m, 7H), 7.85 (d, J = 9 Hz, 1H). Compound **3g**: ^1H NMR (300 MHz, $CDCl_3$) δ 1.51 (s, 9H), 1.44–1.96 (m, 5H), 2.10 (ddd, J = 14, 8, 4 Hz, 1H), 2.48–2.69 (m, 2H), 3.46 (ddd, J = 13, 7, 5 Hz, 1H), 4.00 (ddd, J = 13, 7, 5 Hz, 1H), 7.03–7.31 (m, 7H), 7.44 (d, J = 8 Hz, 1H), 7.68 (d, J = 8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 25.7, 28.4, 36.0, 36.6, 40.5, 41.4, 70.9, 81.1, 123.7, 124.0, 125.3, 125.8, 127.2, 128.3, 128.4, 134.7, 137.3, 142.1, 153.6. Compound **5E**: ^1H NMR (300 MHz, $CDCl_3$) δ 2.11 (quint., J = 8 Hz, 2H), 2.77 (t, J = 8 Hz, 2H), 3.10 (t, J = 8 Hz, 2H), 7.18–7.35 (m, 6H), 7.53 (t, J = 7 Hz, 1H), 7.70 (t, J = 7 Hz, 1H), 7.95 (d, J = 9 Hz, 1H), 8.11 (d, J = 9 Hz, 1H), 8.81 (d, J = 4 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 31.5, 35.7, 120.8, 123.5, 126.0, 126.3, 127.5, 128.5, 129.0, 130.2, 141.5, 148.2, 148.3, 150.2. Compound **6h**: ^1H NMR (400 MHz, $CDCl_3$) δ 1.1–1.4 (m, 6H), 1.34 (s, 9H), 1.62–1.86 (m, 4H), 2.27–2.38 (m, 1H), 2.26–2.42 (m, 2H), 3.65 (ddd, J = 15, 9, 6 Hz, 1H), 3.93 (ddd, J = 15, 8, 6.5 Hz, 1H), 6.98 (t, J = 8 Hz, 1H), 7.11–7.23 (m, 1H), 7.33 (d, J = 8 Hz, 1H), 7.85 (d, J = 8 Hz, 1H). Compound **3h**: ^1H NMR (400 MHz, $CDCl_3$) δ 0.86–0.98 (m, 1H), 1.03–1.36 (m, 5H), 1.51 (s, 9H), 1.61–1.96 (m, 6H), 2.16 (ddd, J = 14, 10, 5 Hz, 1H), 3.25 (ddd, J = 13, 10, 4 Hz, 1H), 4.12 (dt, J = 5, 13 Hz, 1H), 7.09 (t, J = 8 Hz, 1H), 7.19 (t, J = 8 Hz, 1H), 7.45 (d, J = 8 Hz, 1H), 7.60 (d, J = 8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.5 (m), 27.7, 28.4, 33.7, 41.2, 46.8, 73.3, 80.9, 123.9, 124.4, 125.5, 127.0, 135.0, 138.0, 153.6. Compound **5F**: ^1H NMR (400 MHz, $CDCl_3$) δ 1.28–1.44 (m, 1H), 1.47–1.63 (m, 4H), 1.82–2.08 (m, 5H), 3.27–3.41 (m, 1H), 7.28 (d, J = 4.5 Hz, 1H), 7.56 (t, J = 8 Hz, 1H), 7.69 (t, J = 8 Hz, 1H), 8.10 (d, J = 8 Hz, 1H), 8.13 (d, J = 8 Hz, 1H), 8.84 (d, J = 4.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.3, 27.0, 33.6, 39.0, 117.5, 123.1, 126.3, 127.0, 128.9, 130.3, 148.2, 150.3, 153.7.