

ChemComm

Accepted Manuscript



This is an *Accepted Manuscript*, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this *Accepted Manuscript* with the edited and formatted *Advance Article* as soon as it is available.

You can find more information about *Accepted Manuscripts* in the [Information for Authors](#).

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard [Terms & Conditions](#) and the [Ethical guidelines](#) still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this *Accepted Manuscript* or any consequences arising from the use of any information it contains.

Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/chemcomm

COMMUNICATION

Combination of Fluoroalkylation and Kornblum–DeLaMare Reaction: A New Strategy for the Construction of (*Z*)- β -Perfluoroalkyl Enaminones*

Chunmei Liu,^a Erbo Shi,^a Feng Xu,^b Qiang Luo,^a Hongxiang Wang,^a Jijun Chen,^a and Xiaobing Wan^{*a}

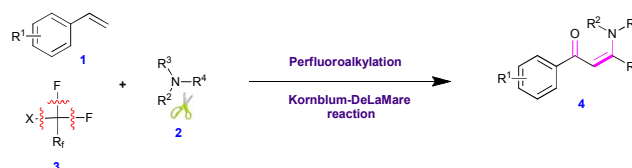
Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX
DOI: 10.1039/b000000x

A novel strategy has been developed for the highly *chemo*- and *stereo*-selective synthesis of (*Z*)- β -perfluoroalkyl enaminones from readily available starting materials via a multicomponent radical reaction involving sequential fluoroalkylation and Kornblum–DeLaMare reaction. Notably, this methodology involves the concurrent cleavage of at least three chemical bonds, including two C–F bonds and one C–X (X = Br or I) bond, as well as the formation of three new bonds, including one C=O bond, one C=C bond and one C–N bond, in one pot.

Perfluoroalkylation reactions have attracted considerable interest from academic research groups as well as researchers working in the pharmaceutical industry because perfluorinated compounds generally possess unique and highly desirable properties, including higher levels of metabolic stability, solubility, lipophilicity, bioavailability and biopotency.¹ In light of the enhanced properties associated with perfluorinated compounds, significant research efforts have been directed towards the development of synthetic methods providing access to these materials.^{1,2} The radical addition of perfluoroalkyl halides to olefins under non-oxidative conditions represents one of the most powerful methods for the construction of perfluorinated compounds, and the use of this reaction has been well documented in the literature.³ In contrast, there have been very few reports in the literature pertaining to the oxidative coupling of perfluoroalkyl halides and olefins.⁴ The Kornblum–DeLaMare reaction involves the base-promoted rearrangement of a peroxide into a ketone, and is a useful tool in organic synthesis as well as being a key step in the biosynthesis of prostaglandins.⁵ Considerable attention has recently been focused on the enantioselective version of the Kornblum–DeLaMare reaction^{5b} and its application to total synthesis,^{5c–g} which has led to noticeable progress in this field.

Although these two areas of research have developed independently of each other, we became interested in what would happen if the fluoroalkylation and Kornblum–DeLaMare reactions were combined into a single catalytic cycle. In this regard, it was envisaged that the combination of these two reactions would lead to the discovery of a novel chemical transformation, which would ultimately provide access to perfluoroalkyl-substituted ketones with unique structures and

functions that would be otherwise difficult to obtain using existing procedures. Inspired by this hypothesis, we herein developed the synthesis of (*Z*)- β -perfluoroalkyl enaminones (Scheme 1).



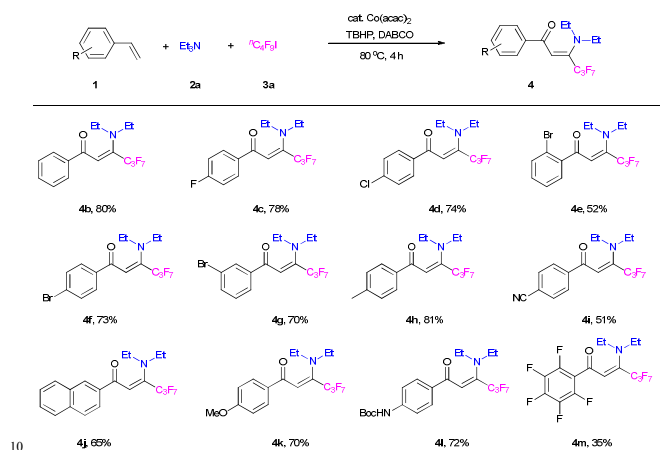
Scheme 1 Combination of fluoroalkylation and Kornblum–DeLaMare reaction to construct perfluoroalkyl-substituted ketones.

To begin with, we investigated the reaction of 1-(*tert*-butyl)-4-vinylbenzene **1a** with triethylamine **2a** and perfluorobutyl iodide **3a** in CCl_3CH_3 in the presence of TBAI and TBHP at 80 °C, which gave (*Z*)- β -perfluoroalkyl enaminones **4a** in 27% yield after 4 h (Table S1, entry 10, see Supporting Information).⁶ Judging from the structure of **4a**, it becomes apparent that its formation entails the *N*-dealkylation⁷ of the tertiary amine reactant **2a**. Subsequent optimization of the catalytic system revealed that the addition of 10 mol% $\text{Co}(\text{acac})_2$ and 5.8 equivalents of TBHP led to a significant increase in the yield of compound **4a** to 80% over the same reaction time (Table S1, entry 1).⁸ (*Z*)- β -Perfluoroalkyl enaminones are structural motifs that appear in biologically active compounds,⁹ and can also be used as synthetic intermediates.¹⁰ Existing methods¹¹ for the synthesis of these compounds, however, have been limited by some shortcomings, such as tedious procedures, low selectivity, narrow substrate scopes and the requirement for harsh conditions. In contrast, our multicomponent free radical synthesis¹² operate in open flask under air, and allow for the concurrent creation of a C–N single bond, C=C double bond and C=O double bond in one pot with high levels of *chemo*- and *stereo*-selectivity from readily available starting materials.

Based on this initial success, we proceeded to investigate the substrate scope and functional group compatibility of this transformation. As shown in Table 1, this transformation was successfully applied to a broad range of styrenes bearing various functional groups, including halide **4c–g** and **4m**, benzylic C–H **4h**, CN **4i**, ether **4k**, and BocNH **4l** groups. Minor steric effects were observed in the reaction. For example, the use of an *ortho*-

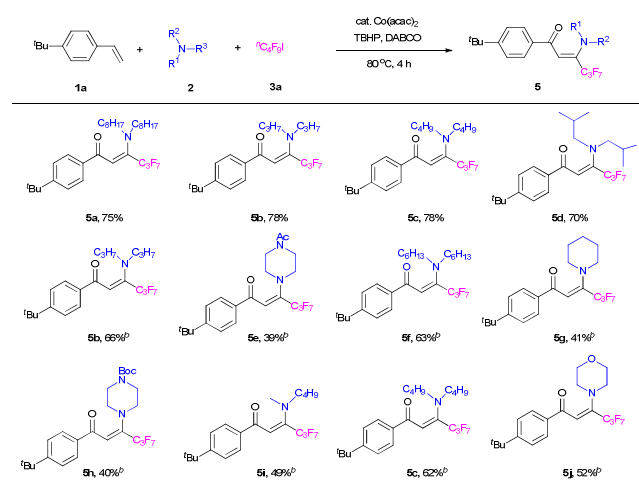
substituted styrene gave a lower yield **4e** than the corresponding *meta*- or *para*-substituted styrene. Remarkably, the use of pentafluorostyrene as the starting material furnished the corresponding product **4m** in 35% yield. The exact (*Z*)-⁵ configuration of product **4l** was determined by single-crystal X-ray crystallography (Scheme S1 in SI). Unfortunately, this procedure was not applicable to alkyl-substituted alkenes.

Table 1 Scope of styrenes^a



^a Reaction conditions: 0.5 mmol styrenes (**1**), 2.0 equiv triethylamine (**2a**), 2.0 equiv perfluorobutyl iodide (**3a**), 10 mol% Co(acac)₃, 5.8 equiv TBHP, 3.0 equiv DABCO, in 2.0 mL CCl₃CH₃ was stirred at 80 °C for 4 h.

Table 2 Scope of amines^a



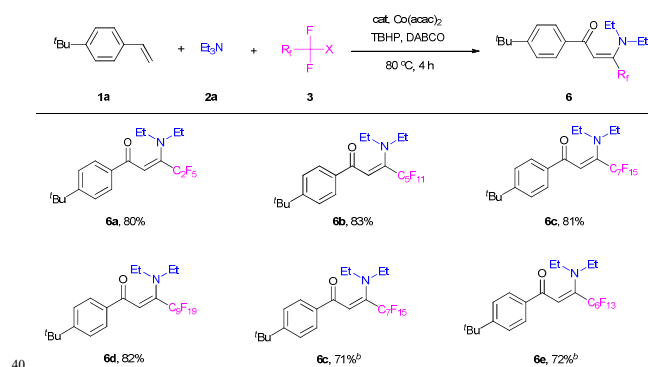
^a Reaction conditions: 0.5 mmol 1-(*tert*-butyl)-4-vinylbenzene (**1a**), 2.0 equiv amines (**2**), 2.0 equiv perfluorobutyl iodide (**3a**), 10 mol% Co(acac)₃, 5.8 equiv TBHP, 3.0 equiv DABCO, in 2.0 mL CCl₃CH₃ was stirred at 80 °C for 4 h. ^b Secondary amines were used.

The reaction of 1-(*tert*-butyl)-4-vinylbenzene **1a** with a variety of different amines revealed that both tertiary and secondary amines could serve as suitable coupling partners, with the corresponding products being obtained in moderate to good yields (Table 2). Increasing the size of the alkyl substituents on the nitrogen did not have a discernible impact on the oxidative coupling reaction **5a-d**. Cyclic **5e**, **5g**, **5h**, **5j** and functionalized amines bearing either an amide group **5e**, BocNH **5h** or ether unit

on their alkyl chain **5j** also proceeded smoothly under the optimized conditions to give the desired products in moderate yields.

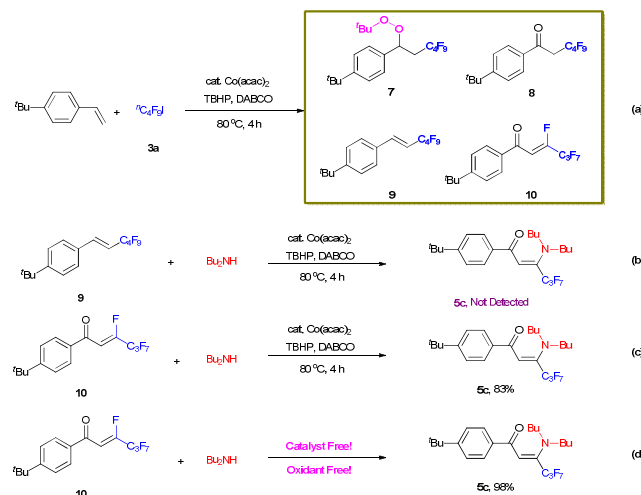
Next, we applied this process to a series of perfluoroalkyl iodides. As shown in Table 3, these reactions proceeded smoothly to afford the corresponding (*Z*)- β -perfluoroalkyl enaminones **6a-d** in high yields. Notably, perfluoroalkyl bromides also worked well for this reaction, and afforded the desired products **6c** and **6e** in good yields.

Table 3 Scope of perfluoroalkyl halides^a



^a Reaction conditions: 0.5 mmol 1-(*tert*-butyl)-4-vinylbenzene (**1a**), 2.0 equiv triethylamine (**2a**), 2.0 equiv perfluorobutyl halides (**3**), 10 mol% Co(acac)₃, 5.8 equiv TBHP, 3.0 equiv DABCO, in 2.0 mL CCl₃CH₃ was stirred at 80 °C for 4 h. ^b Perfluoroalkyl bromides were used.

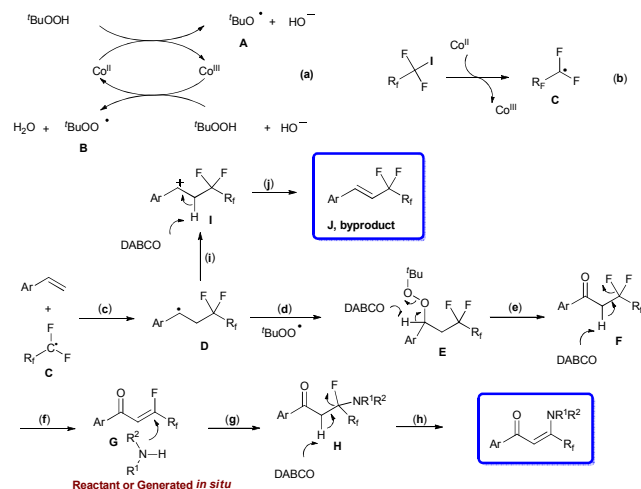
45



Scheme 2 Investigation on mechanism.

A mechanistic study of the transformation was conducted, which revealed that the addition of a radical inhibitor, such as 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO), effectively suppressed the reaction, suggesting that the transformation involved free radical intermediates (Figure S1 in SI). To identify the intermediates involved in the reaction, we intentionally excluded the amine reactant from the reaction system and carefully analyzed the resulting product profile, which revealed the presence of trace amounts of the styrene-derived compounds **7-10** (Scheme 2a). Notably, both the peroxide **7** and its Kornblum–DeLaMare rearrangement product **8** were detected in

this reaction mixture. Subsequent attempts to react compound **9** with Bu₂NH failed to afford the predicted product **5c** (Scheme 2b), which implied that this material was formed as a by-product of the reaction rather than being a reaction intermediate. In contrast, compound **10** readily reacted with the amine substrate to give **5c** in high yield with or without the inclusion of Co/TBHP (Scheme 2c-d). Based on this result, compound **10** was identified as actual critical intermediate in the catalytic cycle.



Scheme 3 Proposed mechanism for (*Z*)- β -perfluoroalkyl enaminones formation reaction.

Based on the results described above, we have proposed a plausible mechanism for the reaction (Scheme 3). The Co(II) catalyst would most likely be involved in two key radical processes, including the homolytic decomposition of TBHP to give ^tBuO• radical **A** and ^tBuOO• radical **B** (Scheme 3a),¹³ and the reductive cleavage of the C–I bond of the perfluoroalkyl iodide to give the electrophilic radical **C** (Scheme 3b). Radical **C** would be immediately trapped by styrene to form the more stable benzylic radical **D** (Scheme 3c), which could undergo a cross-coupling reaction with the electrophilic ^tBuOO• radical **B** to afford the peroxide intermediate **E** (Scheme 3d). The Kornblum–DeLaMare reaction of **E** would lead to the formation of the aryl ketone species **F** (Scheme 3e), which would readily undergo the DABCO-promoted elimination of hydrofluoric acid¹⁴ to give the α , β -unsaturated aryl ketone **G** (Scheme 3f). Ketone **G** would then undergo nucleophilic attack by a secondary amine (Scheme 3g), which was used as a reactant or generated *in situ* by oxidative dealkylation of the tertiary amine, and the resulting β -fluorinated aryl ketone **H** would eliminate a second molecule of hydrofluoric acid to afford the desired product (Scheme 3h). In addition, the sequential oxidation (Scheme 3i) and proton elimination reactions (Scheme 3j) of **D** would account for the observation of by-product **J**.

In summary, we have developed a novel procedure for the synthesis of (*Z*)- β -perfluoroalkyl enaminones from commercially available starting materials via a multicomponent radical process involving sequential fluoroalkylation and Kornblum–DeLaMare reaction. The high level of efficiency and selectivity of this oxidation reaction is highlighted by its concurrent cleavage of at least three chemical bonds, including two C–F bonds, and one C–X (X = Br or I) bond, and its creation of three new bonds,

including one C=O bond one C=C bond and one C–N bond. Further studies are currently underway in our laboratory focused on expanding the substrate scope of this reaction and elucidating the mechanism.

Acknowledgements

A Project Funded by the Priority Academic Program Development of Jiangsu Higher Education Institutions (PAPD) and NSFC (21272165).

Notes and references

^a Key Laboratory of Organic Synthesis of Jiangsu Province, College of Chemistry, Chemical Engineering and Materials Science, Soochow University, 199 Renai Road, 215123 Suzhou, China. Fax: (+86) 512-6588-0334; Tel: (+86) 512-6588-0334; E-mail: wanxb@suda.edu.cn

^b SABIC Technology Center, Riyadh 11551, Saudi Arabia;

† Electronic Supplementary Information (ESI) available: Experimental data and spectra of compounds. See DOI: 10.1039/b000000x/

- (a) P. Kirsch, *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*, Wiley-VCH, 2004; (b) R. D. Chambers, *Fluorine in Organic Chemistry*, Blackwell, 2004; (c) J. A. Gladysz, D. P. Curran and I. T. Horváth, *Handbook of Fluorous Chemistry*, Wiley-VCH, 2004; (d) K. Uneyama, *Organofluorine Chemistry*, Blackwell, 2006; (e) K. Müller, C. Faeh and F. Diederich, *Science*, 2007, **317**, 1881; (f) J.-P. Bégue and D. Bonnet-Delphon, *Bioorganic and Medicinal Chemistry of Fluorine*, Wiley, 2008; (g) S. Purser, P. R. Moore, S. Swallow and V. F. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320; (h) K. L. Kirk, *Org. Proc. Res. Dev.*, 2008, **12**, 305; (i) J. P. Begue and D. Bonnet-Delphon, *Bioorganic and Medical Chemistry of Fluorine*, Wiley, 2008; (j) I. Ojima, *Fluorine in Medicinal Chemistry and Chemical Biology*, Wiley, 2009; (k) D. O'Hagan, *J. Fluorine Chem.*, 2010, **131**, 1071; (l) O. A. Tomashenko and V. V. Grushin, *Chem. Rev.*, 2011, **111**, 4475; (m) C.-P. Zhang, Q.-Y. Chen, Y. Guo, J.-C. Xiao and Y.-C. Gu, *Chem. Soc. Rev.*, 2012, **41**, 4536.
- For recent examples, see: (a) I. Kietlsch, P. Eisenberger and A. Togni, *Angew. Chem. Int. Ed.*, 2007, **46**, 754; (b) K. Mikami, M. Murase and Y. Itoh, *J. Am. Chem. Soc.*, 2007, **129**, 11686; (c) M. Oishi, H. Kondo and H. Amii, *Chem. Commun.*, 2009, 1909; (d) G. G. Dubinina, H. Furutachi and D. A. Vacic, *J. Am. Chem. Soc.*, 2008, **130**, 8600; (e) N. D. Ball, J. W. Kampf and M. S. Sanford, *J. Am. Chem. Soc.*, 2010, **132**, 2878; (f) X. Wang, L. Truesdale and J. Q. Yu, *J. Am. Chem. Soc.*, 2010, **132**, 3648; (g) E. J. Cho, T. D. Senecal, T. Kinzel, Y. Zhang, D. A. Watson and S. L. Buchwald, *Science*, 2010, **328**, 1679; (h) A. Nagib and W. C. MacMillan, *Nature*, 2011, **480**, 224; (i) Y. Ji, T. Brueckl, R. D. Baxter, Y. Fujiwara, I. B. Seiple, S. Su, D. G. Blackmond and P. S. Baran, *Proc. Natl. Acad. Sci. USA* 2011, **108**, 14411; (j) C. P. Zhang, Z. L. Wang, Q. Y. Chen, C. T. Zhang, Y. C. Gu and J. C. Xiao, *Angew. Chem. Int. Ed.* 2011, **50**, 1896; (k) I. Popov, S. Lindeman and O. Daugulis, *J. Am. Chem. Soc.*, 2011, **133**, 9286; (l) A. Zanardi, M. A. Novikov, E. Martin, J. Benet-Buchholz and V. V. Grushin, *J. Am. Chem. Soc.*, 2011, **133**, 20901; (m) T. Knauber, F. Arikian, G.-V. Rösenthaller and L. J. Gooßen, *Chem. Eur. J.*, 2011, **17**, 2689; (n) X. Mu, T. Wu, H.-Y. Wang, Y.-L. Guo and G. Liu, *J. Am. Chem. Soc.*, 2012, **134**, 878; (o) G. K. S. Prakash, P. V. Jog, P. T. D. Batamack and G. A. Olah, *Science*, 2012, **338**, 1324; (p) L. L. Chu and F. L. Qing, *J. Am. Chem. Soc.*, 2012, **134**, 1298; (q) Q. Qi, Q. Shen and L. Lu, *J. Am. Chem. Soc.*, 2012, **134**, 6548; (r) N. D. Litvinas, P. S. Fier and J. F. Hartwig, *Angew. Chem. Int. Ed.*, 2012, **51**, 536; (s) T. Besset, C. Schneider and D. Cahard, *Angew. Chem. Int. Ed.*, 2012, **51**, 5048; (t) Y. Li and A. Studer, *Angew. Chem. Int. Ed.*, 2012, **51**, 8221; (u) Y. Yasu, T. Koike and M. Akita, *Angew. Chem. Int. Ed.*, 2012, **51**, 9567; (v) M. Hu, C. Ni and J. Hu, *J. Am. Chem. Soc.*, 2012, **134**, 15257; (w) C. Feng and T.-P. Loh, *Chem. Sci.*, 2012, **3**, 3458; (x) S. I. Kawaguchi, Y. Minamida, T. Ohe, A. Nomoto, M. Sonoda and A. Ogawa, *Angew. Chem. Int. Ed.*, 2013, **52**, 1748; (y) T. Liang, C. N. Neumann and T. Ritter, *Angew. Chem. Int. Ed.*, 2013, **52**, 8214; (z) M.

- Nappi, G. Bergonzini and P. Melchiorre, *Angew. Chem. Int. Ed.*, 2014, **53**, 4921.
- 3 (a) For reviews, see ref. 1a-d, 11-m; For representative examples, see: (b) W.-Y. Huang and L. Lu, *Chin. J. Chem.*, 1992, **10**, 268; (c) N. O. Brace, *J. Fluorine Chem.*, 1999, **93**, 1; (d) S. M. Igunnov, V. L. Don, V. A. Vyazkov and K. E. Narinyan, *Mendeleev Commun.*, 2006, **16**, 189; (e) T. Yajima and H. Nagano, *Org. Lett.*, 2007, **9**, 2513; (f) B. Eignerová, M. Dračinský and M. Kotorá, *Eur. J. Org. Chem.*, 2008, 4493; (g) S. Barata-Vallejo and A. Postigo, *J. Org. Chem.*, 2010, **75**, 6141; (h) P. M. Murphy, C. S. Baldwin and R. C. Buck, *J. Fluorine Chem.*, 2012, **138**, 3; (i) C.-J. Wallentin, J. D. Nguyen, P. Finkbeiner and C. R. J. Stephenson, *J. Am. Chem. Soc.*, 2012, **134**, 8875; (j) T. Yajima, I. Jahan, T. Tono, M. Shinmen, A. Nishikawa, K. Yamaguchi, I. Sekine and H. Nagano, *Tetrahedron*, 2012, **68**, 6856; (k) E. Yoshioka, S. Kohtani, K. Sawai, E. Tanaka and H. Miyabe, *J. Org. Chem.*, 2012, **77**, 8588; (l) T. Tamai, A. Nomoto, K. Tsuchii, Y. Minamida, T. Mitamura, M. Sonoda and A. Ogawa, *Tetrahedron*, 2012, **68**, 10516; (m) S. Barata-Vallejo and A. Postigo, *Coord. Chem. Rev.*, 2013, **257**, 3051; (n) Z.-W. Xiao, H.-W. Hu, J.-L. Ma, Q.-Y. Chen and Y. Guo, *Chin. J. Chem.*, 2013, **31**, 939; (o) T. Xu, C. W. Cheung and X. Hu, *Angew. Chem. Int. Ed.*, 2014, **53**, 4910.
- 4 (a) M. Yoshida, M. Ohkoshi, N. Aoki, Y. Ohnuma and M. Iyoda, *Tetrahedron Lett.*, 1999, **40**, 5731; (b) M. Yoshida, M. Ohkoshi, T. Muraoka, H. Matsuyama and M. Iyoda, *Bull. Chem. Soc. Jpn.*, 2002, **75**, 1833.
- 5 (a) N. Kornblum and H. E. DeLaMare, *J. Am. Chem. Soc.*, 1951, **73**, 880; (b) S. T. Staben, X. Linghu and F. D. Toste, *J. Am. Chem. Soc.*, 2006, **128**, 12658; (c) K. C. Nicolaou, S. Totokotsopoulos, D. Giguère, Y.-P. Sun and D. Sarlah, *J. Am. Chem. Soc.*, 2011, **133**, 8150; (d) M. J. Palframan, G. Kociok-Köhn and S. E. Lewis, *Chem. Eur. J.*, 2012, **18**, 4766; (e) H. Tan, X. Chen, Z. Liu and D. Z. Wang, *Tetrahedron*, 2012, **68**, 3952; (f) J. D. Parrish, M. A. Ischay, Z. Lu, S. Guo, N. R. Peters and T. P. Yoon, *Org. Lett.*, 2012, **14**, 1640; (g) M. Zhang, N. Liu and W. Tang, *J. Am. Chem. Soc.*, 2013, **135**, 12434; (h) X. Zheng, S. Lu and Z. Li, *Org. Lett.*, 2013, **15**, 5432.
- 6 Recently, we reported various oxidation reactions using TBAI/TBHP, see: (a) L. Chen, E. Shi, Z. Liu, S. Chen, W. Wei, H. Li, K. Xu and X. Wan, *Chem. Eur. J.*, 2011, **17**, 4085; (b) W. Wei, C. Zhang, Y. Xu and X. Wan, *Chem. Commun.*, 2011, **47**, 10827; (c) S. Chen, Y. Xu and X. Wan, *Org. Lett.*, 2011, **13**, 6152; (d) Z. Liu, J. Zhang, S. Chen, E. Shi, Y. Xu and X. Wan, *Angew. Chem. Int. Ed.*, 2012, **51**, 3231; (e) E. Shi, Y. Shao, S. Chen, H. Hu, Z. Liu, J. Zhang and X. Wan, *Org. Lett.*, 2012, **14**, 3384; (f) J. Zhang, J. Jiang, Y. Li, Y. Zhao and X. Wan, *Org. Lett.*, 2013, **15**, 3222; (g) J. Zhang, J. Jiang, Y. Li and X. Wan, *J. Org. Chem.*, 2013, 11366; (h) C. Zhang, C. Liu, Y. Shao, X. Bao and X. Wan, *Chem. Eur. J.*, 2013, **19**, 17917; (i) F. Zhang, P. Du, J. Chen, H. Wang, Q. Luo and X. Wan, *Org. Lett.*, 2014, **16**, 1932.
- 7 (a) S. Murahashi, T. Naota and K. Yonemura, *J. Am. Chem. Soc.*, 1988, **110**, 8256; (b) Y. Li, F. Jia and Z. Li, *Chem. Eur. J.*, 2013, **19**, 82.
- 8 Reviews on cobalt-catalyzed reactions: (a) G. Pattenden, *Chem. Soc. Rev.*, 1988, **17**, 361; (b) J. Iqbal, R. Sanghi and J. P. Nandy, *Use of Cobalt for Radical Initiation*. In *Radicals in Organic Synthesis*, P. Renaud and M. P. Sibi, Eds., Wiley-VCH, 2001; pp. 135-151; (c) H. Shinokubo and K. Oshima, *Eur. J. Org. Chem.*, 2004, 2081; (d) C. Gosmini, J.-M. Bégouin and A. Moncomble, *Chem. Commun.*, 2008, 3221; (e) A. Rudolph and M. Lautens, *Angew. Chem. Int. Ed.*, 2009, **48**, 2656; (f) M. Jeganmohan and C.-H. Cheng, *Chem. Eur. J.*, 2008, **14**, 10876; (g) C. Cahiez and A. Moyeux, *Chem. Rev.*, 2010, **110**, 1435.
- 9 G. Gellerman, N. Pariente, Z. Paz, A. Shnaiderman and O. Yarden, *J. Agric. Food Chem.*, 2009, **57**, 8303.
- 10 (a) H.-B. Yu and W.-Y. Huang, *J. Fluorine Chem.*, 1997, **84**, 65; (b) V. Ya. Sosnovskikh and V. A. Kutsenko, *Russ. Chem. Bull.*, 1999, **48**, 540; (c) V. Ya. Sosnovskikh, V. A. Kutsenko and Y. G. Yatluk, *Russ. Chem. Bull.*, 1999, **48**, 1395; (d) V. Ya. Sosnovskikh, V. A. Kutsenko, A. Ya. Aizikovitch and V. Yu. Korotnev, *Russ. Chem. Bull.*, 1999, **48**, 2112.
- 11 (a) T. Umemoto, Y. Kuriu, S.-I. Nakayama and O. Miyano, *Tetrahedron Lett.*, 1982, **23**, 1471; (b) P. Dousst and C. Portella, *J. Org. Chem.*, 1993, **58**, 6675; (c) M. A. Kurykin, I. M. Vol'pin and L. S. German, *J. Fluorine Chem.*, 1996, **80**, 9; (d) I. H. Jeong, S. L. Jeon, Y. K. Min and B. T. Kim, *Tetrahedron Lett.*, 2002, **43**, 7171.
- 12 For reviews on multicomponent free radical synthesis, see: (a) M. Tojino and I. Ryu, *Free-Radical-Mediated Multicomponent Coupling Reactions*. In *Multicomponent Reactions*, J. Zhu and H. Bienaymé, Eds., Wiley-VCH, 2005, pp. 169-198; (b) L. F. Tietze, G. Brasche and K. M. Gericke, *Domino Reactions in Organic Synthesis*, Wiley-VCH, 2005; For representative examples, see: (c) M. P. Sibi and J. Chen, *J. Am. Chem. Soc.*, 2001, **123**, 9472; (d) M. P. Sibi, M. Aasmul, H. Hasegawa and T. Subramanian, *Org. Lett.*, 2003, **5**, 2883; (e) A. Ogawa, I. Ogawa and N. Sonoda, *J. Org. Chem.*, 2000, **65**, 7682; (f) K. Tsuchii, M. Doi, T. Hirao and A. Ogawa, *Angew. Chem. Int. Ed.*, 2003, **42**, 3490; (g) K. Miura, H. Saito, N. Fujisawa, D. Wang, H. Nishikori and A. Hosomi, *Org. Lett.*, 2001, **3**, 4055; (h) S. Yamago, M. Miyoshi, H. Miyazoe and J. Yoshida, *Angew. Chem. Int. Ed.*, 2002, **41**, 1407; (i) S. Yamago, H. Miyazoe, T. Nakayama, M. Miyasgi and J. Yoshida, *Angew. Chem. Int. Ed.*, 2003, **42**, 117; (j) K. Mizutani, H. Shinokubo and K. Oshima, *Org. Lett.*, 2003, **5**, 3959; (k) R. Cannella, A. Clerici, W. Panzeri, N. Pastori, C. Punta and O. Porta, *J. Am. Chem. Soc.*, 2006, **128**, 5358; (l) S. H. Ueng, A. Solovveyev, X. Yuan, S. J. Geib, L. Fensterbank, E. Lacote, M. Malacria, M. Newcomb, J. C. Walton and D. P. Curran, *J. Am. Chem. Soc.*, 2009, **131**, 11256; (m) N. Pastori, C. Greco, A. Clerici, C. Punta and O. Porta, *Org. Lett.*, 2010, **12**, 3898; (n) V. Liautard, F. Robert and Y. Landais, *Org. Lett.*, 2011, **13**, 2658; (o) T. Kawamota, T. Fukuyama and I. Ryu, *J. Am. Chem. Soc.*, 2012, **134**, 857; (p) T. Kippo, K. Hamaoka and I. Ryu, *J. Am. Chem. Soc.*, 2013, **135**, 632; (q) T. Fukuyama, N. Nakashima, T. Okada and I. Ryu, *J. Am. Chem. Soc.*, 2013, **135**, 1006; (r) M. Rueping and C. Vila, *Org. Lett.*, 2013, **15**, 2092; (s) C. Poittevin, V. Liautard, R. Beniazza, F. Robert and Y. Landais, *Org. Lett.*, 2013, **15**, 2814.
- 13 (a) E. Spier, U. Neuenschwander and I. Hermans, *Angew. Chem. Int. Ed.*, 2013, **52**, 1581; (b) X. Han, Z. Zhou, C. Wan, Y. Xiao and Z. Qin, *Synthesis*, 2013, **45**, 615; (c) C. Jin, L. Zhang and W. Su, *Synlett*, 2011, 1435.
- 14 (a) X. Pigeon, M. Bergeron, F. Barabé, P. Dubé, H. N. Frost and J. F. Paquin, *Angew. Chem. Int. Ed.*, 2010, **49**, 1123; (b) ref. 11c.