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Fluorinated (hetero)cycles via ring-closing metathesis of fluoride- and trifluoromethyl-functionalized olefins

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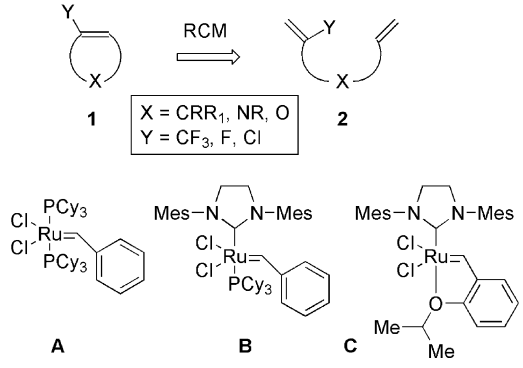
Abstract—Ring-closing metathesis (RCM) has been shown to be a viable tool to incorporate fluoride and trifluoromethyl substituents in (hetero)cyclic ring systems. 2-Fluoroacrylamides were cyclized to the corresponding lactams, and trifluoromethyl-substituted olefins were cyclized to yield trifluoromethylated cyclopentenes, pyrrolines and a dihydrofuran derivative.

Over the past few years, there has been a significantly growing interest from the pharmaceutical and agrochemical industry in fluorine- and trifluoromethyl-containing (hetero)cyclic building blocks.[1] This interest stems from the fact that fluorine substituents often display a positive effect on the pharmacokinetics and pharmacodynamic properties of potential drugs. The incorporation of both types of fluorine substituents in (hetero)cycles has so far, to a large extent, been limited to aromatic systems, since many fluorinated and trifluoromethylated aromatics are commercially available and there are various well-established synthetic methods to introduce these functional groups in (hetero)aromatic compounds.[2] This contrasts with the application of the same substituents in nonaromatic (hetero)cycles, which is considerably thwarted by the lack of general methodology to incorporate fluorine substituents.[3] Being aware of the general demand for such (hetero)cycles and in conjunction with previously developed methodology in our group concerning the determination of the scope of ring-closing metathesis (RCM) reactions,[4–6] we set out to study the use of RCM as a potentially powerful way to access both fluoro- and trifluoro-substituted (hetero)cyclic olefins (Scheme 1).



Scheme 1. RCM approach to fluorinated (hetero)cyclic systems.

Olefin RCM has gained widespread use in organic synthesis owing to the ease of handling and high functional group tolerance of the Ru-catalysts **A**–**C**.[7] In the past few years, it has been demonstrated that RCM is not only restricted to isolated or alkyl-substituted olefins, but is also applicable to olefins that bear heteroatoms such as oxygen[6,8] and nitrogen.[5,9]

Furthermore, it has been demonstrated that P-, Si- and B-substituted olefins can be readily cyclized under the influence of the same catalysts.[10,11] Very recent other RCM examples, that once more emphasize the versatility and importance of this particular transformation, include application to α-alkoxyethers by our own group,[6] to vinyl chlorides by the Weinreb group[12] and to

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vinyl fluorides by the group of Brown.[13] The latter two examples are especially important, since they show for the first time that vinyl halides can successfully participate in this reaction. The latter two publications also prompted us to disclose our own results in this area involving the use of fluoroacrylates and trifluoromethylalkenes as potential metathesis substrates, which may give rise to the corresponding fluoride- and trifluoromethyl-substituted carbo- and heterocyles. To the best of our knowledge, there have been no reports concerning RCM of fluoroacrylates, nor from trifluoromethylalkenes, except for a few articles about related metathesis examples of olefins with fluoride atoms at the allylic position.[14]

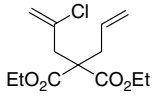
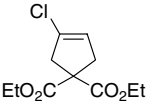
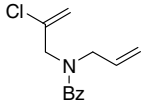
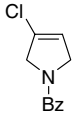
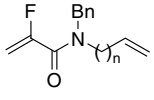
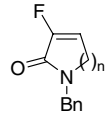
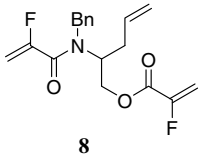
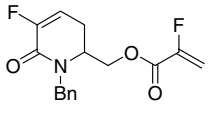
In order to probe the viability of the concept of vinyl fluoride metathesis, we initially conducted several experiments involving vinyl chloride precursors (Table 1). Despite some early reports of the Grubbs group describing unsuccessful attempts involving vinyl halides with the first generation catalyst **A**,[15] we anticipated that better results might be obtained with the second generation catalysts. Indeed, the vinyl chloride precursors **3** (previously cyclized by Weinreb)[12] and **4** readily ring closed to the corresponding cycloalkenes **9** and **10** in good yields using catalyst **B** in toluene at 100 °C for the indicated time.[16] Use of the Grubbs/Hoveyda catalyst **C** under the same conditions gave approximately the same result.

Encouraged by the vinyl chloride cyclizations, we commenced with the synthesis of the fluoroacrylates **5**–**8** as RCM precursors. This involved acylation of the amines with 2-fluoroacryloyl fluoride, which was readily prepared from 3,3,2,2-tetrafluoropropanol in three steps.[17] Optimal results were obtained by heating at 100 °C for the indicated time, during which the catalyst **B** was added in small portions to the reaction mixture. As can be seen in Table 1, RCM of precursors **5** and **6** proceeded readily under these conditions to form the corresponding unsaturated five- and six-membered lactams **11** and **12** in 68% and 80% yields, respectively (entries 3 and 4). It appeared that in these cases the benzyl protecting group on the nitrogen was essential for the cyclization to occur. Without a protecting group, subjection to the different catalysts **B** and **C** did not lead to cyclization, but eventually (upon prolonged reaction times) to decomposition of the amides.

The identity of the five-membered ring lactam **11** was unambiguously confirmed through an X-ray crystallographic determination of the crystal structure (Fig. 1).[18] Unfortunately, the eight-membered ring precursor **7** did not provide any cyclization product at all.

Furthermore, the allylglycinol-derived precursor **8** underwent selective ring closure to the six-membered lactam in an excellent yield. Thus, it has been shown that RCM of fluoroacrylates proceeds well and therefore

Table 1. RCM of vinyl halides

Entry	Precursor	Cat **B** (mol%)	Time (h)	Product (yield)
				
1	**3**	12	120	**9** (68%)
				
2	**4**	15	72	**10** (51%)
				
3	**5**: $n = 1$	7	4	**11**: $n = 1$ (68%)
4	**6**: $n = 2$	7	4	**12**: $n = 2$ (80%)
5	**7**: $n = 4$	7	72	**13**: $n = 4$ (0%)
				
6	**8**	4	4	**14** (99%)

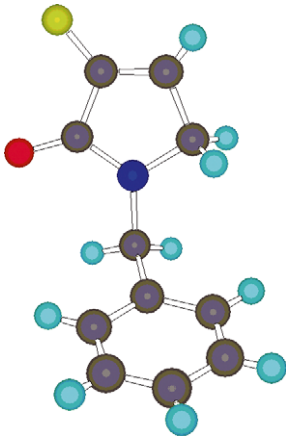
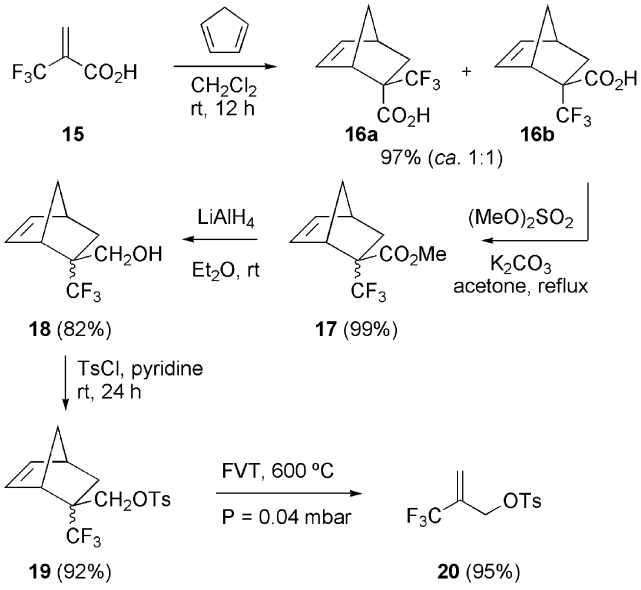


Figure 1. Crystal structure of lactam **11**.

represents a convenient way to synthesize fluorine-substituted heterocyclic building blocks.

We then focused on the incorporation of trifluoromethyl substituents in cyclic systems in a similar manner. This required the availability of 2-trifluoromethylacrylic acid (or derivatives thereof) and of 2-trifluoromethyl-2-propenol (or the corresponding halides). While the acid is commercially available, reproducible synthetic access to the corresponding alcohol does not exist. Because efficient procedures to prepare the alcohol (e.g., $LiAlH_4$ reduction of the acid,[19] or acid chloride formation,[20] followed by $LiAlH_4$ reduction)[21] appeared either unreliable or laborious, we decided to develop a novel pathway for its synthesis (Scheme 2). Since the majority of problems associated with the existing procedures arose from the reactivity of the α,β-unsaturated system, we envisaged that it would be advantageous to protect the olefin in some way. The protection strategy that was chosen proceeded via a Diels–Alder/retro Diels–Alder sequence; 2-trifluoromethylacrylic acid (**15**) was reacted with cyclopentadiene to give the corresponding Diels–Alder adduct **16** as a 2:1 mixture of *endo*/*exo*-diastereoisomers in excellent yield after recrystallization.[22] This mixture was then esterified ($(MeO)_2SO_2$), reduced ($LiAlH_4$) and reacted with TsCl to yield tosylate **19** in an excellent overall yield. Finally, subjection of **19** to flash vacuum thermolysis (FVT) afforded, after some optimization of the conditions (oven temperature 600 °C, 0.04 mbar), the required tosylate **20** in essentially pure form and excellent yield.[23] It was used without further purification for subsequent follow-up chemistry, but could also be further purified over a short silica gel column. Initial attempts to subject the alcohol **18** to the FVT conditions also provided the corresponding alcohol ($T = 550$ °C, 0.04 mbar), but due to the fact that additional manipulation and purification of the alcohol was necessary, we decided to choose the more practical procedure. Thus, this pathway represents an efficient synthesis of a potentially useful fluorinated alkylating agent.

Having reliable access to the acid **15** and the tosylate **20**, a set of RCM precursors **21**–**30** was prepared via well-established procedures (Table 2). The malonate and



Scheme 2. Synthesis of the alkylating agent **20**.

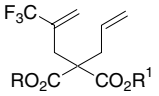
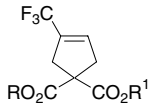
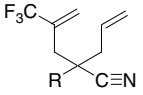
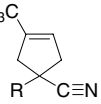
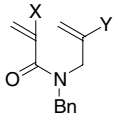
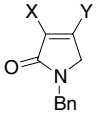
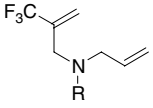
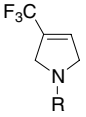
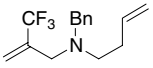
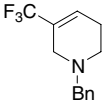
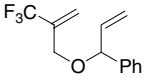
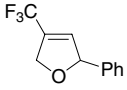
malononitriles **21**–**24** were prepared via consecutive alkylation with allyl bromide and the tosylate **20** under standard conditions. The other precursors were prepared via acylation of the amine (**25**, reaction with the acid chloride derived from 2-trifluoromethylacrylic acid),[20] or by alkylation of the corresponding amine or alcohol with tosylate **20** (precursors **26**–**30**).

The malonates **21** and **22** and malononitriles **23** and **24** (entries 1–4) gave facile cyclization to the corresponding cyclopentenes in moderate to good yields under the previously optimized conditions (catalyst **B**, added in portions during the reaction, toluene, 100 °C). The cyanides gave partial decomposition under these reaction conditions so that different temperatures were tried; precursor **24** gave the best result at 55 °C. Unfortunately, both acrylamides **25** and **26** did not give any cyclized product (entries 5 and 6). Probably, in these cases both olefins become too electron poor for the RCM reaction to take place. In contrast, the diolefins **27** and **28**—bearing an acyl group at the nitrogen—readily cyclized to the desired pyrrolidines **37** and **38** in good yields under the same conditions (entries 7 and 8). An attempt to cyclize **29** to the corresponding tetrahydropyridine **39** failed, which may well be due to the presence of the basic amine functionality (entry 9).

Gratifyingly, the ether precursor **30** underwent facile cyclization under identical conditions to give the trifluoromethyl-substituted dihydrofuran **40** in a good yield (entry 10). Thus, it has been shown that trifluoromethyl-substituted olefins in many cases readily cyclize to the corresponding cyclic olefins, which represent versatile building blocks for further synthetic transformations and potentially biologically active compounds.

In conclusion, we have identified RCM as a viable tool to incorporate fluoride and trifluoromethyl substituents in (hetero)cyclic ring systems. Several 2-fluoroacrylamides

Table 2. RCM of trifluoromethylated olefins

Entry	Precursor	Cat (mol%)	Time (h)	Product (yield)
				
1	**21**: R = R^1 = Et	4	4	**31**: R = R^1 = Et (88%)
2	**22**: R = ^{t}Bu, R^1 = Me	7	2	**32**: R = ^{t}Bu, R^1 = Me (45%)
				
3	**23**: R = CO_2Me	3	4	**33**: R = CO_2Me (52%)
4	**24**: R = CN	15	24	**34**: R = CN (42%)
				
5	**25**: X = CF_3, Y = H	3	72	**35**: X = CF_3, Y = H (0%)
6	**26**: X = H, Y = CF_3	7	4	**36**: X = H, Y = CF_3 (0%)
				
7	**27**: R = Bz	10	24	**37**: R = Bz (68%)
8	**28**: R = Boc	10	2	**38**: R = Boc (97%)
				
9	**29**	7	48	**39** (0%)
				
10	**30**	5	24	**40** (78%)

were readily cyclized to the corresponding unsaturated lactams, which are useful synthetic building blocks. In addition, a novel, reliable and efficient method has been developed for the synthesis of 2-trifluoromethyl-2-propenol and the corresponding tosylate, which is a strategic synthon for incorporating trifluoromethyl-substituted olefins into various systems. Finally, the viability of RCM on olefins bearing trifluoromethyl substituents has been demonstrated via the synthesis of a series of trifluoromethyl-substituted cyclopentenes, pyrrolines and a dihydrofuran derivative.

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References and notes

1. See, for example: (a) Ismail, F. M. D. *J. Fluorine Chem.* **2002**, *118*, 27; (b) *Biomedical Frontiers of Fluorine Chemistry*; Ojima, I., McCarthy, J. R., Welch, J. T., Eds.; ACS Symposium Series ACS, Washington, D.C. 1996; (c) Jeschke, P. *The Unique Role of Fluorine in the Design of Active Ingredients for Modern Crop Protection*, Book of abstracts, Fluorine in the life sciences symposium, Bürgenstock, 2003, pp 17–20.
2. For recent entries, see, for example: (a) Zhu, S. Z.; Wang, Y. L.; Peng, W. M.; Song, L. P.; Jin, G. F. *Curr. Org. Chem.* **2002**, *6*, 1057; (b) Saloutin, V. I.; Burgart, Y. V.; Chupakhin, O. N. *Russ. Chem. Rev.* **1999**, *68*, 203; (c) Sloop, J. C.; Bumgardner, C. L.; Loehle, W. D. *J. Fluorine Chem.* **2002**, *118*, 135.
3. For a review on trifluoromethyl-substituted saturated cycles, see: Lin, P.; Jiang, J. *Tetrahedron* **2000**, *56*, 3635.
4. (a) Rutjes, F. P. J. T.; Schoemaker, H. E. *Tetrahedron Lett.* **1997**, *38*, 677; (b) Rutjes, F. P. J. T.; Kooistra, T. M.; Hiemstra, H.; Schoemaker, H. E. *Synlett* **1998**, 192; (c) Tjen, K. C. M. F.; Kinderman, S. S.; Schoemaker, H. E.; Hiemstra, H.; Rutjes, F. P. J. T. *Chem. Commun.* **2000**,

699; (d) Doodeman, R.; Rutjes, F. P. J. T.; Hiemstra, H. *Tetrahedron Lett.* **2000**, *41*, 5979; (e) Kaptein, B.; Broxterman, Q. B.; Schoemaker, H. E.; Rutjes, F. P. J. T.; Veerman, J. J. N.; Kamphuis, J.; Peggion, C.; Formaggio, F.; Toniolo, C. *Tetrahedron* **2001**, *57*, 6567; (f) Kinderman, S. S.; Doodeman, R.; Van Beijma, J. W.; Russcher, J. C.; Tjen, K. C. M. F.; Kooistra, T. M.; Mohaselzadeh, H.; Van Maarseveen, J. H.; Hiemstra, H.; Schoemaker, H. E.; Rutjes, F. P. J. T. *Adv. Synth. Catal.* **2002**, *344*, 736.

5. Kinderman, S. S.; van Maarseveen, J. H.; Schoemaker, H. E.; Hiemstra, H.; Rutjes, F. P. J. T. *Org. Lett.* **2001**, *3*, 2045.
6. Hekking, K. F. W.; Van Delft, F. L.; Rutjes, F. P. J. T. *Tetrahedron* **2003**, *59*, 6751.
7. For review articles, see: (a) Fürstner, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 3012; (b) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18; (c) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4592.
8. For recent examples, see: (a) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783; (b) Postema, M. H. D.; Calimente, D.; Liu, L.; Behrmann, T. L. *J. Org. Chem.* **2000**, *65*, 6061; (c) Clark, J. S.; Kettle, J. G. *Tetrahedron Lett.* **1997**, *38*, 123, 127; (d) Sturino, C. F.; Wong, J. C. Y. *Tetrahedron Lett.* **1998**, *39*, 9623; (e) Rainier, J. D.; Cox, J. M.; Allwein, S. P. *Tetrahedron Lett.* **2001**, *42*, 179.
9. Arisawa, M.; Terada, Y.; Nakagawa, M.; Nishida, A. *Angew. Chem., Int. Ed.* **2002**, *41*, 4732.
10. Phosphorus-substituted olefins: (a) Hanson, P. R.; Stoianova, D. S. *Tetrahedron Lett.* **1999**, *40*, 3297; (b) Timmer, M. S. M.; Ovaa, H.; Filippov, D. V.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron Lett.* **2000**, *41*, 8635; (c) Stoianova, D. S.; Hanson, P. R. *Org. Lett.* **2000**, *2*, 1769; Silicon-substituted olefins: Denmark, S. E.; Yang, S.-M. *Org. Lett.* **2001**, *3*, 1749; Boron-substituted olefins: Ashe, A. J., III; Fang, X. *Org. Lett.* **2000**, *2*, 2089.
11. For cross-metathesis examples of P-, Si- and B-substituted olefins, see: Chatterjee, A. K.; Grubbs, R. H. *Angew. Chem., Int. Ed.* **2002**, *41*, 3172.
12. Chao, W.; Weinreb, S. M. *Org. Lett.* **2003**, *5*, 2505.
13. Salim, S. S.; Bellingham, R. K.; Satcharoen, V.; Brown, R. C. D. *Org. Lett.* **2003**, *5*, 3403.
14. (a) Imhof, S.; Randl, S.; Blechert, S. *Chem. Commun.* **2001**, 1692; (b) Percy, J. M.; Pintat, S. *Chem. Commun.* **2000**, 607; (c) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783.
15. Kirkland, T. A.; Grubbs, R. H. *J. Org. Chem.* **1997**, *62*, 7310.
16. All compounds were fully characterized using spectroscopic techniques. Data of selected compounds: **11**: ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 7.35$–7.20 (m, 5H, ArH), 6.24–6.21 (m, 1H, FC=C*H*), 4.63 (s, 2H, CH_2Ph), 3.74–3.72 (m, 2H, CHCH_2); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 162.7$ (d, $J = 31.2$ Hz, FC*C*=O), 152.7 (d, $J = 275.7$ Hz, *C*F), 136.2, 128.8, 128.1, 127.8, 112.7 (d, $J = 7.4$ Hz, H*C*=CF), 47.1, 45.5 (d, $J = 5.4$ Hz, *C*H_2CH=CF); IR (neat, cm^{-1}): 3058, 2920, 2854, 1697, 1664, 1452, 1232, 1219, 988, 926, 780, 720, 689; HRMS calcd for $C_{11}H_{10}NOF$ (M^+) 191.0764, found 191.0740. **20**: ^{1}H NMR (200 MHz, $CDCl_3$) $\delta = 7.77$ (d, $J = 8.5$ Hz, 2H, ArH), 7.34 (d, $J = 7.8$ Hz, 2H, ArH), 5.89 (br s, 1H, C*H*=CCF_3), 5.73 (d, $J = 1.2$ Hz, 1H, C*H*=CCF_3), 4.62 (s, 2H, CH_2O), 2.45 (s, 3H, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 145.3$, 132.4, 129.9, 127.9, 123.5 (q, $J = 5.1$ Hz, *C*H_2=CCF_3), 122.1 (q, $J = 270.8$ Hz, *C*F_3), 65.6, 21.9; IR (neat, cm^{-1}): 3118, 3068, 3041, 2962 1598, 1369, 1176, 1132, 1176, 972, 841, 777; HRMS calcd for $C_{11}H_{11}SO_3F_3$ (M^+) 280.0381, found 280.0375. **31**: ^{1}H NMR (300 MHz, $CDCl_3$) $\delta = 6.14$–6.12 (m, 1H, CF_3C=C*H*), 4.20 (q, $J = 7.2$ Hz, 4H, $2\times$C$H_2$$CH_3$), 3.18–3.14 (m, 4H, CF_3CH_2+HCCH_2), 1.26 (t, $J = 7.3$ Hz, 6H, $2\times$$CH_2CH_3$); ^{13}C NMR (75 MHz, $CDCl_3$) $\delta = 170.6$, 132.1, 130.7 (q, $J = 33.6$ Hz, *C*CF_3), 121.8 (q, $J = 266.8$ Hz, *C*H_3), 62.2, 59.1, 40.6, 38.2, 14.3; IR (neat, cm^{-1}): 2985, 2939, 1733, 1671, 1446, 1367, 1276, 1253, 1159, 1122, 1037; HRMS calcd for $C_{12}H_{15}F_3O_4$ (M^+) 280.0923, found 280.0918. **38**: ^{1}H NMR (300 MHz, $CDCl_3$, some signals appear as rotamers) $\delta = 6.32 + 6.27$ (br s, 1H, CF_3C=C*H*), 4.26 (br s, 4H, CF_3CCH_2+HCCH_2), 1.47 (s, 3H, $(CH_3)_3$); ^{13}C NMR (75 MHz, $CDCl_3$, some signals appear as rotamers) $\delta = 153.7$, 130.1–129.7 (m), 129.3 (q, $J = 35.1$ Hz, *C*CF_3), 122.8 (q, $J = 263.9$ Hz, *C*F_3), $80.5 + 80.4$, $53.4 + 53.2$, $50.8 + 50.6$, 28.6; IR (neat, cm^{-1}): 3058, 2919, 2867, 1713, 1632, 1385, 1303, 1269, 1165, 1122, 1043, 789, 694, 672; HRMS calcd for $C_{10}H_{14}NO_2F_3$ (M^+) 237.0977, found 237.0978.
17. Nguyen, T.; Wakselman, C. *J. Org. Chem.* **1989**, *54*, 5640.
18. Crystallographic data have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 223956.
19. For $LiAlH_4$ reduction of the corresponding fluoroacrylic acid, see: Laue, K. W.; Haufe, G. *Synthesis* **1998**, 1453.
20. Furuta, S.; Saito, Y.; Fuchigami, T. *J. Fluorine Chem.* **1998**, *87*, 209.
21. Solomon, M.; Hoekstra, W.; Zima, G.; Liotta, D. *J. Org. Chem.* **1988**, *53*, 5058.
22. (a) Hanzawa, Y.; Suzuki, M.; Kobayashi, Y. *Tetrahedron Lett.* **1989**, *30*, 571; (b) Hanzawa, Y.; Suzuki, M.; Kobayashi, Y.; Taguchi, T. *J. Org. Chem.* **1991**, *56*, 1718.
23. Carried out at scales ranging from 50 mg to 3 g.