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Stereoselective and catalyzed halogenation reactions

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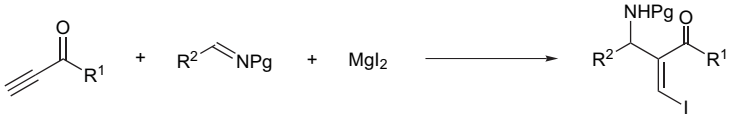
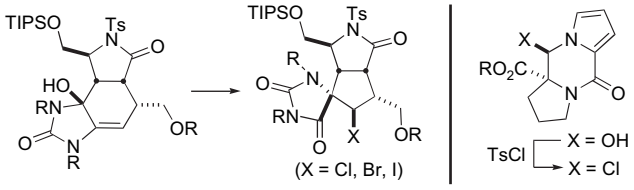
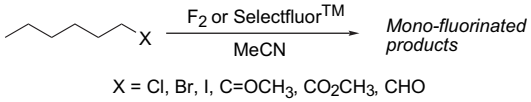
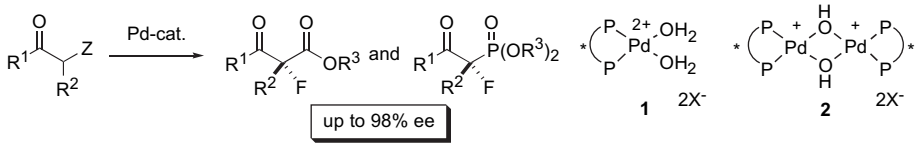


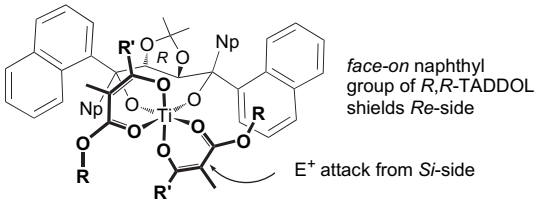
A multicomponent reaction between sulfonyl-protected imines, magnesium iodide, and acetylenic esters or ketones is described. The resulting β-iodo aza Morita–Baylis–Hillman adducts were obtained in good yields (68–84%) and excellent *Z*/*E* stereoselectivities (17:1–20:1) for 11 examples.

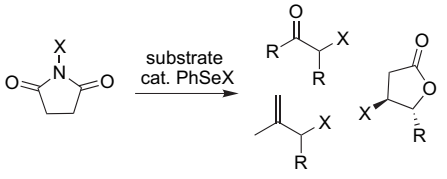


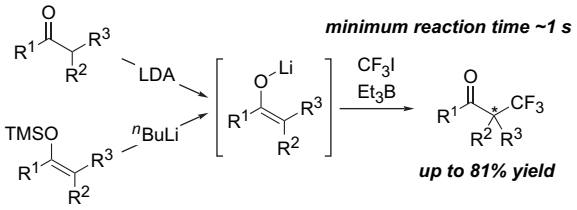


The effect of each functionality upon the conversion of unactivated carbon–hydrogen bonds to carbon–flourine bonds at sites within an alkyl chain is established.









Highly basic Li enolates are shown to be applicable to radical trifluoromethylation. The reaction is extremely fast and the minimum reaction time is ~1 s.

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COVER

The cover graphic depicts examples of selenium-promoted halogenations.

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Preface

Stereoselective and catalyzed halogenation reactions

Halogenation reactions are among the most practical and historically significant processes in organic chemistry—literally thousands of papers over the years have been published on this topic in virtually every chemistry journal. As well, the products of organic halogenations have long been valued as useful synthetic intermediates. Traditionally, the use of diatomic halides has predominated, although their harsh nature and high reactivity have often presented a problem, often resulting in mixtures of desired (and undesired) products. The development of milder, and more sophisticated halogenating reagents that offer significantly greater chemoselectivity and stereocontrol than diatomic halides has been critical to the realization of recent advances in halogenation methodology. This Symposium-in-Print presents a compact, but wide-ranging overview of new developments in the area of stereoselective and catalyzed halogenation reactions that highlight the use of new-generation halogenating agents.

For example, Li et al. report a highly stereoselective approach to iodinated aza Morita–Baylis–Hillman adducts; the Chambers and Sandford labs discuss electrophilic fluorination under the influence of electron-withdrawing groups; and Mikami and Itoh present a radical trifluoromethylation of ketones. Romo et al. have published a personalized account of selective halogenations leading to alkaloid natural products; Tunge's group discusses a new strategy for selenium-catalyzed oxidative halogenation; Togni et al. report new aspects of the enantioselective halogenation of 1,3-dicarbonyl compounds; and Sodeoka's group relates highly enantioselective fluorination reactions catalyzed by chiral palladium complexes.

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Highly *Z*/*E* stereoselective approach to β-iodo aza Morita–Baylis–Hillman adducts

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Abstract—A multicomponent reaction between sulfonyl-protected imines, magnesium iodide, and acetylenic esters or ketones is described. The resulting β-iodo aza Morita–Baylis–Hillman adducts were obtained in good yields and excellent *Z*/*E* stereoselectivities. The reaction showed good tolerance for sulfonyl protecting groups, as well as for acetylenic ketones and esters. This work presents the first synthetic approach to β-iodo aza Morita–Baylis–Hillman adducts.

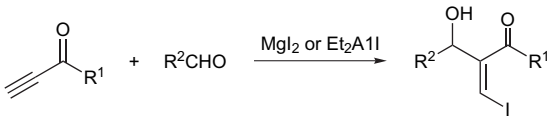
1. Introduction

Multicomponent reactions (MCRs) play a key role in organic chemistry due to the fact that highly complex structures can be formed in a simple one-pot process. Recent interest in MCRs has resulted in a number of elegant new reactions for the preparation of many new useful synthons.[1]

Recently, the Morita–Baylis–Hillman (MBH) reaction has received considerable interest from the synthetic community as a convenient reaction for the synthesis of allylic alcohols in an atom-economical fashion.[2] A number of useful Lewis base[3] and Lewis acid[4,5] catalyzed versions have been reported. Additionally, aza MBH reactions have been developed utilizing sulfonyl-protected imines, with useful asymmetric versions appearing only recently.[6,7]

An area of interest in our laboratory has been the synthesis of halo-aldol/halo-MBH adducts.[5,8] Such tandem C–C/C–X bond formation reactions lead to aldol or MBH products with an additional degree of functionalization not present in the classical versions of the respective reactions. The presence of a halogen in the product allows for a number of further transformations to be performed on the products, including eliminations, intermolecular and intramolecular displacements, and coupling reactions. Such transformations allow for the rapid synthesis of complex target molecules from simple starting materials.

One strategy we have recently employed involves the multicomponent coupling of α,β-acetylenic ketones or esters with aldehydes in the presence of a metal iodide (Et_2AlI or MgI_2) acting as Lewis acid promoter and halogen source (Scheme 1).[8,9] In particular, reactions utilizing MgI_2 have been found to be especially convenient since MgI_2 is a fairly air-stable solid that is easy to work with and is readily available.[9] Such reactions have led to the high stereoselective synthesis of β-iodo MBH adducts. In an effort to extend the scope of this reaction, we sought to utilize imines as electrophilic acceptors in order to obtain the corresponding aza MBH products. In this paper, we are pleased to report our initial results for the preparation of β-iodo aza MBH adducts.



Scheme 1.

2. Results and discussion

Initially, the tosyl imine of benzaldehyde was treated with 1.2 equiv 3-butyn-2-one and 1.1 equiv of MgI_2 in CH_2Cl_2 at 0 °C. The reaction was found to proceed to completion in 18 h to afford the product in 70% yield with exclusive *Z* stereoselectivity. The stereochemistry about the double bond was confirmed by 1D NOE spectroscopy in which an NOE enhancement was observed between the vinyl proton and the N–C*H*, and no enhancement was observed between the vinyl proton and the methyl group adjacent to the ketone.

Encouraged by these initial results, we sought to utilize esters to replace ketones since the resulting products would

Keywords: Morita–Baylis–Hillman adducts; Multicomponent reactions; Magnesium iodide; Imines.
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be the synthetically attractive di-protected β-amino acid derivatives. Fortunately, when methyl propiolate was used to replace 3-butyn-2-one, the yield was increased from 70 to 79%. It is noteworthy to mention that the crude reaction mixture was found to be cleaner for esters, possibly due to self-condensation of ketones. Further optimization experiments were thus conducted using methyl propiolate and the tosyl imine of benzaldehyde.

Initially, several solvents were screened and CH_2Cl_2 was found to be the best. Interestingly, the use of CH_3CN, THF, and toluene all resulted in the formation of no product at all. The NMR spectra (after aqueous workup) of crude reactions using these solvents were clean, containing only starting materials and β-iodo methyl acrylate, the result of quenching the iodo-allenolate intermediate. Increasing the reaction temperature from 0 °C to room temperature showed neither improvement in yield nor diminishment in stereoselectivity. The use of 1.5 equiv each of alkyne and MgI_2 did not result in a detectable increase in the rate of consumption of imine. With the above results in mind, all subsequent reactions were performed at 0 °C in CH_2Cl_2, utilizing 1.0 equiv imine, 1.2 equiv alkyne, and 1.1 equiv MgI_2.

Substrate scope was examined with regard to alkyne, protecting group, and aldehyde component of the imines. The results are summarized in Table 1. Interestingly, several *N*-sulfonyl protecting groups were found to be effective in this process. No obvious difference between tosyl (Ts) and benzenesulfonyl (Bs) protecting groups was noted. The methanesulfonyl (Ms) group also worked, however, the yield was somewhat diminished when compared to Ts and Bs substrates. Not surprisingly, *N*-benzyl and *N*-aryl imines failed to react in this system.

With regard to alkyne substrate scope, both the methyl ketone and the methyl esters worked well, however, as previously mentioned, the ester gave somewhat better yield and cleaner reaction mixtures than the ketone. Interestingly, the use of ethyl propiolate (entry 3, Table 1) resulted in the formation of the product in high yield but with somewhat diminished stereoselectivity.

It is worth noting that imines prepared from electron-rich and electron-deficient aldehydes both worked well. Furthermore, heteroaromatic imines (entries 10 and 11, Table 1) also provided satisfactory results. Unfortunately, aliphatic and α,β-unsaturated imines worked poorly, reacting only very sluggishly and affording low yields. Attempts to devise a process that is more amenable to these substrates are currently underway.

In summary, a convenient synthesis of β-iodo aza MBH products is reported. The reaction shows good substrate scope and high yields and stereoselectivities were obtained for a number of examples. These products give rise to numerous implications for the synthesis of novel β-amino acids for peptide and catalysis studies.

3. Experimental

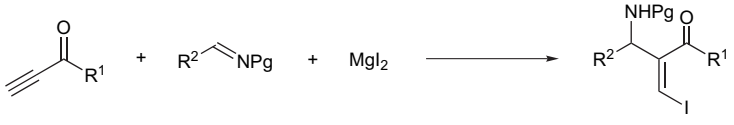
3.1. General

All reactions were performed in oven-dried glassware. Dichloromethane was dried by passing through an alumina column under an N_2 atmosphere. Imines were prepared according to standard procedures.[10] All other chemicals were commercially available and used without further purification. Stoichiometries were calculated based on the purities reported by the manufacturers. Flash chromatography was performed on silica gel (Merck 60, 230–400 mesh). Melting points were taken in open capillaries and are reported uncorrected. IR spectra were recorded as CH_2Cl_2 deposits on a NaCl disk. NMR spectra were recorded on a Varian Mercury NMR spectrometer operating at 300 MHz (^{1}H) and 75 MHz (^{13}C). Shift values are reported in parts per million and are referenced based on TMS or solvent for ^{1}H and ^{13}C, respectively. All spectra were recorded in $CDCl_3$.

3.2. Procedure for synthesis of β-iodo aza MBH products

Into an oven-dried vial was added imine (0.5 mmol) and MgI_2 (0.55 mmol). The vial was fitted with a septum and

Table 1. Results of the synthesis of β-iodo aza Morita–Baylis–Hillman adducts



Entry	R^1	R^2	Pg	*Z*/*E*[a]	Yield[b]
1	Me	Ph	Ts	>20:1	70
2	OMe	Ph	Ts	>20:1	79
3	OEt	Ph	Ts	17:1	84
4	OMe	Ph	Ms	>20:1	68
5	OMe	4-Me–C_6H_4	Bs	>20:1	72
6	OMe	4-MeO–C_6H_4	Ts	>20:1	77
7	OMe	3-BnO–C_6H_4	Ts	>20:1	73
8	OMe	4-F–C_6H_4	Ts	>20:1	82
9	OMe	4-Cl–C_6H_4	Bs	>20:1	84
10	OMe	2-Furyl	Ts	>20:1	83
11	OMe	2-Thienyl	Ts	>20:1	78

[a] Determined by ^{1}H NMR analysis of crude reaction mixture.
[b] Yield of analytically pure sample after purification via flash chromatography. >20:1 means that no minor isomer was observed.

flushed with nitrogen. Dichloromethane (3 mL) was then added and the reaction was allowed to stir at 0 °C for 20 min, at which time the alkyne (0.60 mmol) was added in one portion via a syringe. The reaction was allowed to stir at 0 °C for 18 h before being quenched with 5 mL 1 N HCl. The reaction mixture was extracted with dichloromethane (3×10 mL) and the combined organic layers were washed with brine and dried with Na_2SO_4. The mixture was concentrated under reduced pressure and purified via flash chromatography (EtOAc/hexane, 1:5) to afford the pure product.

3.2.1. Table 1, entry 1. Isolated as a white solid. Mp=145–147 °C. FTIR: 3275.7, 1700.5 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 7.68–7.64 (m, 2H), 7.28–7.23 (m, 5H), 7.14–7.10 (m, 2H), 6.58 (d, *J*=1.2 Hz, 1H), 5.73 (d, *J*=8.7 Hz, 1H), 5.21 (d, *J*=8.7 Hz, 1H), 2.41 (s, 3H), 2.17 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 203.6, 149.5, 143.7, 137.1, 136.9, 129.7, 128.9, 128.2, 127.2, 126.4, 81.9, 62.7, 30.5, 21.6. HRMS (MNa^+): expected: 477.9944, found: 477.9948.

3.2.2. Table 1, entry 2. Isolated as a white solid. Mp=95–97 °C. FTIR: 3286.5, 1728.5 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 7.69–7.66 (m, 2H), 7.29–7.22 (m, 5H), 7.17–7.12 (m, 2H), 7.07 (d, *J*=0.6 Hz, 1H), 5.85 (d, *J*=9.3 Hz, 1H), 5.32 (d, *J*=9.3 Hz, 1H), 3.59 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 165.2, 143.7, 140.6, 137.3, 137.2, 129.7, 128.7, 128.0, 127.1, 126.2, 89.1, 61.9, 51.9, 21.6. HRMS (MNa^+): expected: 493.9893, found: 493.9895.

3.2.3. Table 1, entry 3. Isolated as a white solid. Mp=97–98 °C. FTIR: 3286.7, 1719.5 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 7.69–7.66 (m, 2H), 7.29–7.22 (m, 5H), 7.18–7.14 (m, 2H), 7.02 (d, *J*=0.9 Hz, 1H), 5.80 (d, *J*=9.3 Hz, 1H), 5.31 (d, *J*=9.3 Hz, 1H), 4.11–4.01 (m, 2H), 2.42 (s, 3H), 1.09 (t, *J*=6.9 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 164.9, 143.7, 140.5, 137.4, 137.3, 129.7, 128.6, 128.0, 127.1, 126.2, 88.7, 62.0, 61.5, 21.6, 13.8. HRMS (MNa^+): expected: 508.0050, found: 508.0053.

3.2.4. Table 1, entry 4. Isolated as a colorless oil. FTIR: 3284.9, 1722.7 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 7.40–7.28 (m, 6H), 5.70 (d, *J*=9.3 Hz, 1H), 5.52 (d, *J*=9.3 Hz, 1H), 3.72 (s, 3H), 2.87 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 165.7, 142.6, 137.3, 129.0, 128.4, 126.5, 88.9, 61.9, 52.2, 41.9. HRMS (MNa^+): expected: 417.9580, found: 417.9586.

3.2.5. Table 1, entry 5. Isolated as a white solid. Mp=104–105 °C. FTIR: 3287.0, 1719.8 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 7.81–7.77 (m, 2H), 7.60–7.45 (m, 3H), 7.11 (d, *J*=0.9 Hz, 1H), 7.07–6.96 (m, 4H), 5.68 (d, *J*=9.0 Hz, 1H), 5.32 (d, *J*=9.0 Hz, 1H), 3.60 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 165.5, 140.8, 140.2, 138.0, 134.2, 132.8, 129.4, 129.1, 127.1, 126.1, 88.9, 61.8, 51.9, 21.0. HRMS (MNa^+): expected: 498.9893, found: 498.9899.

3.2.6. Table 1, entry 6. Isolated as a colorless oil. FTIR: 3283.5, 1719.6 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 7.69–7.65 (m, 2H), 7.30–7.26 (m, 2H), 7.07–7.02 (m, 3H), 6.80–6.75 (m, 2H), 5.63 (d, *J*=9.0 Hz, 1H), 5.26 (d, *J*=9.0 Hz, 1H), 3.76 (s, 3H), 3.61 (s, 3H), 2.43 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 165.5, 159.3, 143.7, 140.9, 137.2, 129.7, 129.3, 127.5, 127.2, 114.1, 88.4, 61.5, 55.2, 51.9, 21.6. HRMS (MNa^+): expected: 523.9999, found: 523.9983.

3.2.7. Table 1, entry 7. Isolated as a colorless oil. FTIR: 3286.0, 1729.4 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 7.68–7.65 (m, 2H), 7.39–7.31 (m, 5H), 7.26–7.23 (m, 2H), 7.18–7.12 (m, 1H), 7.06 (d, *J*=0.9 Hz, 1H), 6.85–6.81 (m, 1H), 6.77–6.70 (m, 2H), 5.87 (d, *J*=9.3 Hz, 1H), 5.29 (d, *J*=9.3 Hz, 1H), 4.94 (s, 2H), 3.58 (s, 3H), 2.39 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 165.3, 158.9, 143.7, 140.4, 138.9, 137.2, 136.6, 129.8, 129.7, 128.5, 128.0, 127.5, 127.1, 118.7, 114.5, 112.7, 89.3, 69.9, 61.8, 51.9, 21.5. HRMS (MNa^+): expected: 600.0312, found: 600.0316.

3.2.8. Table 1, entry 8. Isolated as a white solid. Mp=109–110 °C. FTIR: 3285.2, 1721.1 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 7.68–7.65 (m, 2H), 7.29–7.26 (m, 2H), 7.16–7.10 (m, 2H), 7.06 (d, *J*=0.9 Hz, 1H), 6.96–6.90 (m, 2H), 5.95 (d, *J*=9.3 Hz, 1H), 5.29 (d, *J*=9.3 Hz, 1H), 3.60 (s, 3H), 2.43 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 165.3, 163.9, 160.6, 143.9, 140.4, 137.0, 133.2, 129.8 (2C), 128.0, 127.1 (2C), 115.7, 115.4, 89.3, 61.4, 51.9, 21.6. ^{19}F NMR (282.3 MHz, $CDCl_3$): −114.3 (m). HRMS (MNa^+): expected: 511.9799, found: 511.9808.

3.2.9. Table 1, entry 9. Isolated as a white solid. Mp=105–106 °C. FTIR: 3282.7, 1728.8 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 7.80–7.76 (m, 2H), 7.61–7.54 (m, 1H), 7.52–7.45 (m, 2H), 7.23–7.19 (m, 2H), 7.14 (d, *J*=0.9 Hz, 1H), 7.12–7.07 (m, 2H), 6.03 (d, *J*=9.6 Hz, 1H), 5.33 (d, *J*=9.6 Hz, 1H), 3.60 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 165.2, 140.1, 140.0, 135.8, 134.0, 133.0, 129.2, 128.8, 127.6, 127.0, 89.9, 61.5, 52.0. HRMS (MNa^+): expected: 513.9347, found: 513.9348.

3.2.10. Table 1, entry 10. Isolated as a white solid. Mp=91–92 °C. FTIR: 3280.8, 1722.6 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 7.69–7.65 (m, 2H), 7.28–7.23 (m, 3H), 7.19 (d, *J*=0.9 Hz, 1H), 6.22 (dd, *J*=2.1 Hz, 3.3 Hz, 1H), 6.12–6.10 (m, 1H), 5.84 (d, *J*=9.3 Hz, 1H), 5.41 (d, *J*=9.3 Hz, 1H), 3.69 (s, 3H), 2.41 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 165.0, 149.7, 143.7, 142.7, 138.7, 137.1, 129.6, 127.1, 110.6, 107.9, 90.3, 56.4, 52.0, 21.5. HRMS (MNa^+): expected: 483.9686, found: 483.9688.

3.2.11. Table 1, entry 11. Isolated as a white solid. Mp=105–108 °C. FTIR: 3285.7, 1729.2 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): 7.69 (d, *J*=8.4 Hz, 2H), 7.29 (d, *J*=8.1 Hz, 2H), 7.21–7.18 (m, 2H), 6.88–6.85 (m, 1H), 6.77–6.76 (m, 1H), 5.95 (d, *J*=9.6 Hz, 1H), 5.49 (d, *J*=9.6 Hz, 1H), 3.66 (s, 3H), 2.43 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 165.1, 143.9, 141.6, 139.6, 137.1, 129.8 (2C), 127.2 (2C), 127.1, 125.8, 125.0, 90.5, 58.9, 52.0, 21.6. HRMS (MNa^+): expected: 499.9458, found: 499.9456.

Acknowledgements

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References and notes

1. For reviews, see: (a) Yus, M.; Ramon, D. J. *Angew. Chem., Int. Ed.* **2005**, *44*, 1602; (b) Domling, A.; Ugi, I. *Angew. Chem., Int. Ed.* **2000**, *39*, 3169; (c) Kobayashi, S. *Chem. Soc. Rev.* **1999**, *28*, 1; (d) Li, G.; Wei, H.-X.; Kim, S.-H.; Carducci, M. D. *Angew. Chem., Int. Ed.* **2001**, *40*, 4277.
2. For reviews, see: (a) Basavaiah, D.; Rao, A. J.; Satyanarayana, T. *Chem. Rev.* **2003**, *103*, 811; (b) Li, G.; Hook, J. D.; Wei, H.-X. *Recent Research Developments in Organic & Bioorganic Chemistry*; Transworld Research Network: Trivandrum, India, 2001; Vol. 4, p 49; (c) Ciganek, E. *Org. React.* **1997**, *51*, 201; (d) Basavaiah, D.; Rao, P. D.; Hyma, R. S. *Tetrahedron* **1996**, *52*, 8001.
3. (a) Yu, C.; Liu, B.; Hu, L. *J. Org. Chem.* **2001**, *66*, 5413; (b) Alcaid, B.; Almendros, P.; Aragoncillo, C. *J. Org. Chem.* **2001**, *66*, 1612; (c) Shi, M.; Li, C. Q.; Jiang, J. K. *Chem. Commun.* **2001**, 833; (d) Ramachandran, P. V.; Reddy, M. V. R.; Rudd, M. T. *Chem. Commun.* **2001**, 757; (e) Katoaka, T.; Kinoshita, S.; Kinoshita, H.; Fujita, M.; Iwamura, T.; Watanabe, S. *Chem. Commun.* **2001**, 1958; (f) Kataoka, T.; Iwama, T.; Iwamure, T.; Kinoshita, S.; Tsurukami, Y.; Tsujiyama, S.; Fujita, M.; Honda, E.; Iwamura, T.; Watanabe, S. *J. Organomet. Chem.* **2000**, *611*, 455; (g) Ramachandran, P.; Reddy, M. V. R.; Rudd, M. T. *Chem. Commun.* **1999**, 1979; (h) Aggarwal, V. K.; Mereu, A. *Chem. Commun.* **1999**, 2311.
4. (a) Yagi, K.; Turitani, T.; Shinokubo, H.; Oshima, K. *Org. Lett.* **2002**, *4*, 3111; (b) Shi, M.; Jiang, J. K.; Cui, S. C.; Feng, Y. S. *J. Chem. Soc., Perkin Trans. 1* **2001**, 390; (c) Basavaiah, D.; Screenivasulu, B.; Rao, J. S. *Tetrahedron Lett.* **2001**, *42*, 1147; (d) Uehira, S.; Han, Z.; Shinokubo, H.; Oshima, K. *Org. Lett.* **1999**, *1*, 1382.
5. (a) Chen, D.; Guo, L.; Kotti, S. R. S. S.; Li, G. *Tetrahedron: Asymmetry* **2005**, *16*, 1757; (b) Chen, D.; Timmons, C.; Liu, J.; Headley, A.; Li, G. *Eur. J. Org. Chem.* **2004**, 3330; (c) Pei, W.; Wei, H.-X.; Li, G. *Chem. Commun.* **2002**, 2412; (d) Pei, W.; Wei, H.-X.; Li, G. *Chem. Commun.* **2002**, 1856; (e) Li, G.; Gao, J.; Wei, H.-X.; Enright, M. *Org. Lett.* **2000**, *2*, 617; (f) Li, G.; Wei, H.-X.; Caputo, T. D. *Tetrahedron Lett.* **2000**, *41*, 1.
6. For recent imine chemistry see: (a) France, S.; Weatherwax, A.; Taggi, A. E.; Lectka, T. *Acc. Chem. Res.* **2004**, *37*, 592; (b) Wipf, P.; Pierce, J. G. *Org. Lett.* **2005**, *7*, 3537; (c) France, S.; Shah, M. H.; Weatherwax, A.; Wack, H.; Roth, J. P.; Lectka, T. *J. Am. Chem. Soc.* **2005**, *127*, 1206.
7. For recent aza MBH reaction see: (a) Shi, M.; Li, C. Q. *Tetrahedron: Asymmetry* **2005**, *16*, 1385; (b) Shi, M.; Chen, L. H.; Li, C. Q. *J. Am. Chem. Soc.* **2005**, *127*, 3790; (c) Shi, M.; Xu, Y. M.; Shi, Y. L. *Chem.—Eur. J.* **2005**, *11*, 1794; (d) Xu, Y. M.; Shi, M. J. *Org. Chem.* **2004**, *69*, 417; (e) Shi, M.; Chen, L. H. *Chem. Commun.* **2003**, 1310.
8. (a) Timmons, C.; Chen, D.; Cannon, J. F.; Headley, A. D.; Li, G. *Org. Lett.* **2004**, *6*, 2075–2078; (b) Li, G.; Xu, X.; Chen, D.; Timmons, C.; Carducci, M. D.; Headley, A. D. *Org. Lett.* **2003**, *5*, 329; (c) Li, G.; Wei, H.-X.; Phelps, B. S.; Purkiss, D. W.; Kim, S. H. *Org. Lett.* **2001**, *3*, 823.
9. (a) Wei, H.-X.; Jasoni, R. L.; Hu, J.; Li, G.; Paré, P. W. *Tetrahedron* **2004**, *60*, 10233; (b) Wei, H.-X.; Hu, J.; Jasoni, R. L.; Li, G.; Paré, P. W. *Helv. Chim. Acta* **2004**, *87*, 2359; (c) Wei, H.-X.; Timmons, C.; Farag, M. A.; Paré, P. W.; Li, G. *Org. Biomol. Chem.* **2004**, *2*, 2893.
10. Davis, F. A.; Zhang, Y.; Andemichael, Y.; Fang, T.; Fanelli, D. L.; Zhang, H. *J. Org. Chem.* **1999**, *64*, 1403.

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Planned and unplanned halogenations in route to selected oroidin alkaloids

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Abstract—Highly diastereoselective, substrate-controlled, halogenation/ring contraction sequences delivered the naturally occurring chlorinated and unnatural brominated and iodinated axinellamine core structure. An unexpected azide displacement of the chlorinated cyclopentane, which proceeded with retention of stereochemistry, suggested a modification of the Scheuer/Kinnel proposal that may account for the related natural product massadine. Two unsuccessful routes to access the stereochemistry proposed for palau'amine were S_N2 displacement of the bromo- and iodocyclopentane with excess chloride anion and an intramolecular directed chlorination pathway. Finally, an unexpected chlorination during our phakellstatin synthesis proceeded with retention of stereochemistry during tosylation possibly resulting from neighboring group participation.

1. Introduction

More than 3800 halogenated organic compounds, primarily bearing chlorine or bromine, have been isolated from natural sources including bacteria, fungi, plants, marine organisms, insects, and higher organisms including humans.[1] The structural diversity and large but still increasing number of halogenated organics found in nature is truly astounding. As a primary reservoir for chlorine on earth, oceans have an average chlorine concentration of 19.4 g L^{-1} and contain ~26 Zg (zettagram=10^{21} g) Cl in total.[2] More than 1000 halogen-containing natural products have been isolated from marine organisms and not unexpectedly, this accounts for a large portion of the naturally occurring halogenated natural products.[1] Among these, oroidin family of marine alkaloids was isolated from various species of marine sponges.[3] Our interest in this class of alkaloids has led to stereoselective approaches[4] to various members including the phakellins (e.g., **2**) and phakellstatins,[5] and palau'amines (**3**)[6] and the axinellamines (**4**) (Fig. 1).[7] This family of marine alkaloids has garnered much interest from a number of synthetic groups.[8] One of the most challenging aspects of these compounds is the highly substituted cyclopentane core structure, which includes a chlorine bearing stereocenter. This paper describes both planned and unplanned halogenations in our synthetic studies toward several members of the oroidin-derived marine alkaloids.

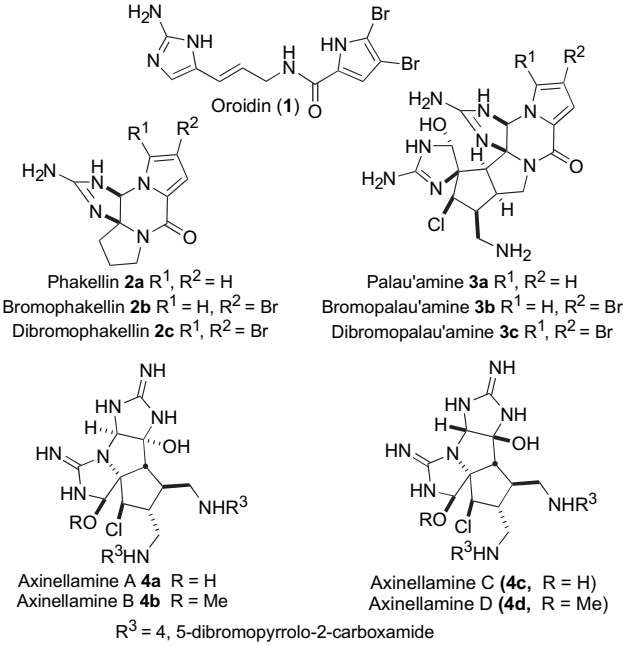

Figure 1. Oroidin-derived marine alkaloids.

1.1. Unified strategy toward axinellamine and palau'amine

Considering the structural similarities of the axinellamines and palau'amines, the two alkaloids were envisioned to arise from a common core structure, which differ in the relative stereochemistry of the chlorine and aminomethylene bearing stereocenters. Imidazolone annulation onto the common

Keywords: Oroidin alkaloids; Stereoselective chlorination; Bromination; Iodination.
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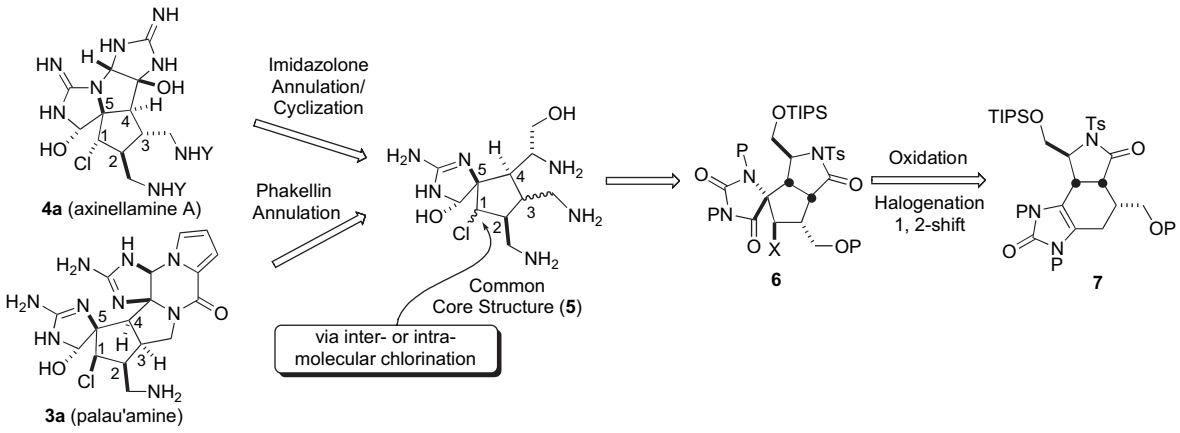


Scheme 1. Abbreviated retrosynthesis of axinellamine and palau'amine showing key oxidation/halogenation/ring contraction (1,2-shift) sequence.

core structure followed by cyclization would introduce the pyrrolidine ring required for axinellamine.

Alternatively, phakellin annulation[4c] onto the common core structure would allow access to palau'amine (Scheme 1). The core structure **5** could be derived from intermediate **7**, which was in turn synthesized by an enantioselective Diels–Alder reaction,[4d,e] followed by inter- or intramolecular chlorination.

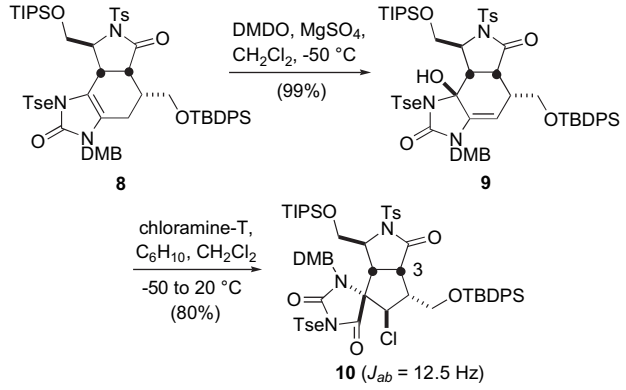
2. Results and discussion

2.1. Intermolecular chlorination/bromination/iodination

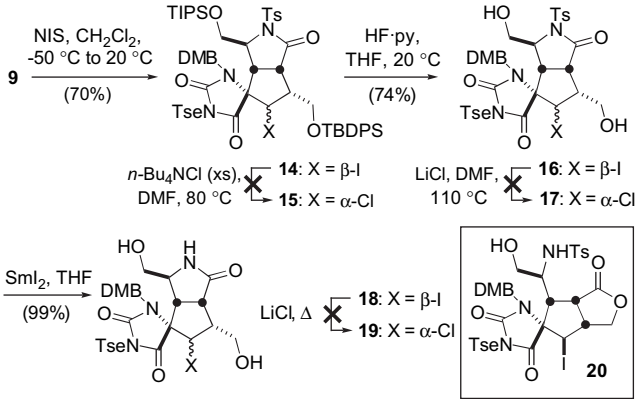
As reported previously, Diels–Alder adduct **8** was oxidized by dimethyldioxirane to give allylic alcohol **9**, which then underwent intermolecular stereoselective chlorination and a concomitant 1,2-shift/ring contraction to yield functionalized chlorocyclopentane **10** (Scheme 2).[4] This cyclopentane contains five stereocenters, identical to the proposed structure of axinellamine with the exception of C3.[9] The high stereoselectivity of oxidation and chlorination is due to the distinct cup-shaped topology of tricycle **8** and allylic alcohol **9**, respectively.

In order to install the stereochemistry at the chlorine bearing center as proposed for palau'amine, which is opposite to that of axinellamine, we considered S_N2 displacement of an appropriate leaving group. Bromination of allylic alcohol **11** with *N*-bromosuccinimide also led to the ring contraction process and delivered bromocyclopentane **12** (Scheme 3). However, attempts to displace the bromide with excess chloride anion under a variety of conditions led to no reaction.

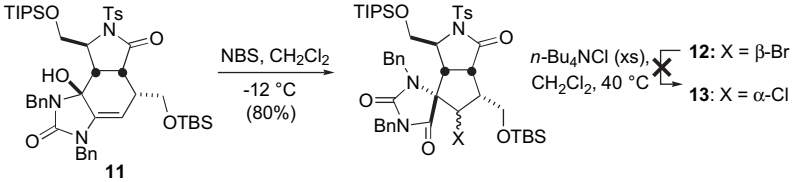
Allylic alcohol **9** could also be iodinated and following ring contraction provided iodocyclopentane **14** (Scheme 4). Iodide **14** was prepared with the expectation that this compound may undergo a more facile reverse Finkelstein



Scheme 2. Oxidation/chlorination/1,2-shift cascade of Diels–Alder adduct **8** leading to spirocycle **10**.



Scheme 4. Iodination/rearrangement sequence leading to iodocyclopentanes **14** and attempted S_N2 displacements.



Scheme 3. Bromination/rearrangement leading to bromocyclopentane **12** and attempted S_N2 displacement.

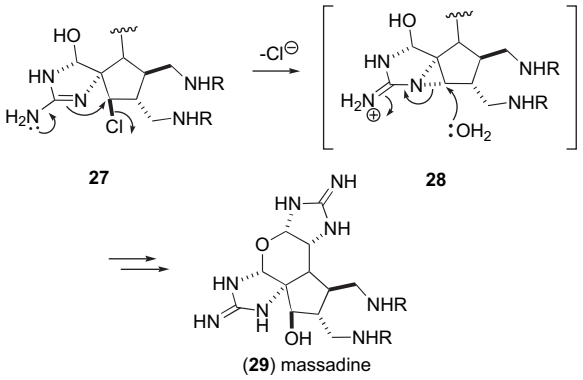
process under forcing conditions, however, no displacement was observed under several conditions to provide the desired α-chloro compound **15**. Silyl deprotection was attempted to remove any steric impedance, however, this did not facilitate the displacement. Instead, the only observed product in this case was lactam opening by the pendent alcohol to deliver lactone **20**. To prevent lactam cleavage, the *N*-tosyl group was removed;[10] however, further attempts at chlorination were also unsuccessful. The unreactivity of these spirocyclic systems toward S_N2 displacement is likely a result of the necessity of the nucleophile to enter the concave face and the adjacent spiro quaternary center. However, sterically less demanding nucleophiles were readily introduced (vide infra).

2.2. Halogen displacement with azide anion

Substitution of chloride was ultimately achieved unexpectedly during conversion of the pendant tosylate of spirocycle **21** to an azide during studies toward axinellamine. The chlorine atom was also displaced concomitantly and surprisingly with retention of stereochemistry as determined by coupling constant analysis to yield bisazide **23** (Scheme 5). As expected, displacement of iodide in spirocycle **22** was more facile and led to higher yields of the corresponding azide **24**.

Retention of stereochemistry may be rationalized by invoking neighboring group participation proceeding through an aziridinium ion **26** (Scheme 6). Following the facile tosylate displacement, intramolecular substitution by the proximal benzylated nitrogen atom, which appears well situated to displace the chloride of spirohydantoin **25**, leads to net retention of stereochemistry of the cyclopentyl azide **23**.

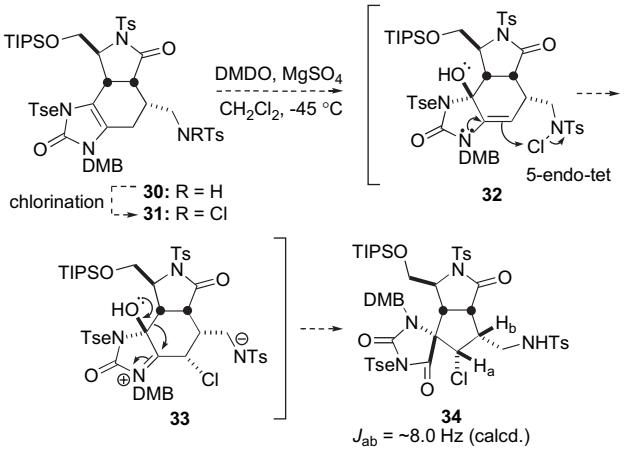
Considering the relative facility of this process with a spirohydantoin leads us to speculate that this may be a more facile process with the electron rich cyclic guanidine found in these natural products (e.g., **27**). Thus, a possible biosynthetic pathway leading to the recently isolated oroidin-derived alkaloid, massadine[11] may involve a related retentive displacement of a chloride proceeding through the aziridine **28** ultimately leading to massadine **29** (Scheme 7). A related process was recently proposed for the natural product, fasicularin.[12]



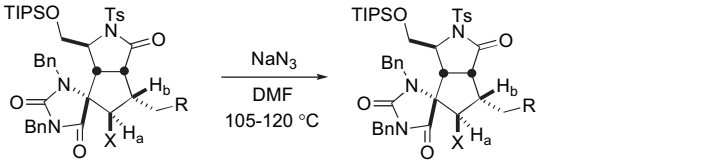
Scheme 7. Hypothesis for massadine biosynthesis involving retentive chloride displacement by water.

2.3. Intramolecular chlorination

In another approach toward introduction of the cyclopentane stereochemistry proposed for palau'amine, an intramolecular directed chlorination strategy was studied (Scheme 8). We envisioned that a pendant electrophilic chlorine source, such as a chloro-*p*-toluenesulfonamide, might deliver

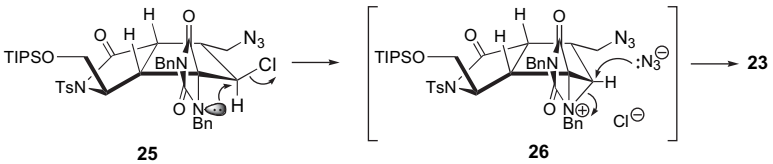


Scheme 8. Proposed oxidation/intramolecular chlorination/1,2-shift cascade.



21: X = Cl, R = OTs (J_{ab} = 12.5 Hz)
22: X = I, R = OTBDPS (J_{ab} = 13.5 Hz)
23: X = N_3, R = N_3 (41%, J_{ab} = 11.1 Hz)
24: X = N_3, R = OTBDPS (75%, J_{ab} = 11.0 Hz)

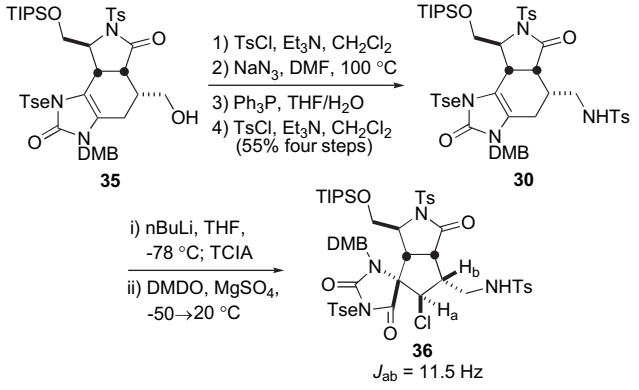
Scheme 5. Retentive displacement of cyclopentyl halides with azide anion.



Scheme 6. Proposed mechanism for retentive chloride displacement by azide ion.

chlorine in an intramolecular fashion to the concave face of tricycle **32** to deliver cyclopentane **34** following ring contraction. This strategy is reminiscent of an intramolecular directed chlorination reported by Breslow and Guo.[13] While the proposed trajectory would be an exception to Baldwin's rule (5-*endo*-tet),[14] there are numerous exceptions including attack at heteroatoms.[15]

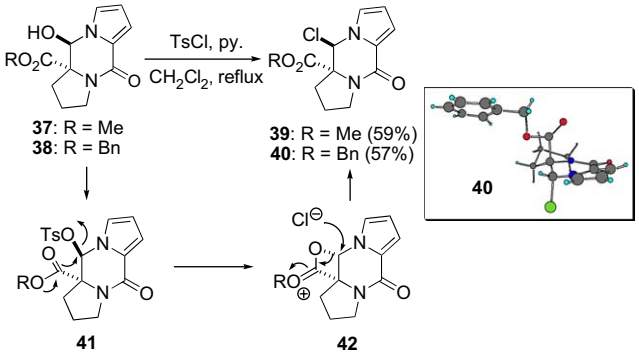
Preparation of the substrate for the proposed intramolecular chlorination began with Diels–Alder adduct **35**,[4] which was converted to sulfonamide **30** through an efficient four-step sequence (Scheme 9). In a model study with a simple *N*-sulfonamide (not shown), the intermediate chlorosulfonamide produced by deprotonation and chlorination could be isolated and purified. While the chlorinated adduct derived from *N*-sulfonamide **30** could not be purified, a one-pot, two-step protocol involving deprotonation and chlorination with trichloroisocyanuric acid (TCIA) [16] produced the presumed chlorinated adduct as evidenced by thin layer chromatographic analysis. The crude *N*-chlorosulfonamide was directly subjected to oxidation with DMDO; however, this process only delivered the β-chlorocyclopentane **36**. The stereochemistry was determined by coupling constant analysis and comparison to that obtained by deliberate intermolecular chlorination (see adduct **10**, Scheme 2). Chlorocyclopentane **36** presumably arises from more facile intermolecular chlorination. A modeling study suggested one possible explanation for this result. The cup-shaped conformation of the intermediate allylic alcohol **32** (see Scheme 8) and boat conformation of the cyclohexene, places the *N*-chlorosulfonamide in a pseudoequatorial position far removed from the nucleophilic carbon of the intermediate enamine (cf. **32**).



Scheme 9. Formation of sulfonamide **30** and attempted one-pot, two-step intramolecular chlorination.

2.4. An unexpected chlorination toward phakellstatin

In studies directed toward the related marine alkaloid phakellstatin, another retentive chlorination process was observed. The chlorides **39** and **40** were formed when carbinolamine **37** and **38**, respectively, were exposed to tosyl chloride under refluxing conditions (Scheme 10). Related chlorinations are known for benzylic and allylic alcohols.[17] The stereochemical outcome pointing toward a net retentive substitution process was confirmed by X-ray analysis of chloride **40** (inset, Scheme 10). Two possible rationalizations for this stereochemical outcome can be proposed including an S_N1 process followed by the attack of chloride from the most accessible face opposite to the ester substituent. Alternatively, neighboring group participation of the pendant ester could also leads to net retention proceeding through a transient β-lactone intermediate **42**.



Scheme 10. An unexpected retentive chlorination during tosylation of carbinolamines **37/38** (inset: X-ray crystal structure of chloride **40**).

3. Conclusion

The previously reported chlorination/ring contraction sequence leading to the highly functionalized chlorocyclopentane core structure of axinellamine and related oroidin alkaloids has been extended to provide brominated and iodinated cyclopentanes. In efforts to achieve the stereochemistry proposed for palau'amine attempted invertive displacement of these halogens by excess chloride was unsuccessful. An unexpected displacement of chloride by azide ion proceeding with retention of stereochemistry prompted us to propose a related process in the biogenesis of massadine. An attempted intramolecular directed chlorination was studied but led exclusively to an intermolecular chlorination process. An additional retentive displacement was observed in studies toward phakellstatin leading to a halogenated product during tosylation. The diversity of halogenated natural products, especially marine derived metabolites, will continue to drive studies of stereoselective halogenation reactions such as those described herein.

4. Experimental

4.1. General

All nonaqueous reactions were carried out under a nitrogen atmosphere in oven-dried glassware. Tetrahydrofuran, dichloromethane, and dimethylformamide (all from EM Science) were dried and purified by MBRAUN solvent purification system (water content ~10 ppm). Solutions of dimethyldioxirane (DMDO) in acetone were prepared according to literature procedures.[18] All other commercially available reagents were used as received unless specified otherwise.

Infrared spectra were recorded with a Nicolet Impact 410 FTIR spectrometer. ^1H and ^{13}C NMR spectra were obtained on a Varian Unity-500/Inova-500 spectrometer. Mass spectra were obtained on a MDS Sciex (Concord, Ontario,

Canada) API Qstar Pulsar (for ESI), or a ThermoFinnigan (San Jose, California) LCQ Deca Mass Spectrometer (for APCI) at the Mass Spectrometry Application and Collaboration Facility (Texas A&M University). Flash column chromatography was performed using 60 Å silica gel (EM Science, 230–400 mesh) as a stationary phase.

4.1.1. Bromospirohydantoin 12. To a cooled (−12 °C) solution of allylic alcohol **11** (9.9 mg, 0.011 mmol) in 50 μL CH_2Cl_2 was added *N*-bromosuccinimide (4.5 mg, 0.025 mmol) in 150 μL CH_2Cl_2. After 1.5 h the reaction mixture was diluted with water and CH_2Cl_2 and then the layers were separated. The aqueous layer was extracted with CH_2Cl_2 and the combined organic extracts were dried over $MgSO_4$, and concentrated in vacuo. Purification by flash chromatography (SiO_2, 20% EtOAc/hexane) gave bromospirocycle **12** as a light yellow foam (8.6 mg, 80%): R_f=0.58 (20% EtOAc/hexane); $[\alpha]_D^{25}$ −29.8 (*c* 1.28, CH_2Cl_2); IR (thin film) 1752, 1716 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 8.07 (d, *J*=8.5 Hz, 2H), 7.48 (d, *J*=8.5 Hz, 2H), 7.45 (d, *J*=6.0 Hz, 2H), 7.41 (d, *J*=7.5 Hz, 2H), 7.34–7.28 (m, 6H), 5.31 (d, *J*=16.0 Hz, 1H), 4.70 (d, *J*=15.0 Hz, 1H), 4.65 (d, *J*=15.0 Hz, 1H), 4.63 (br s, 1H), 4.33 (d, *J*=16.0 Hz, 1H), 4.12 (d, *J*=12.5 Hz, 1H), 4.07 (dd, *J*=3.5, 10.5 Hz, 1H), 4.03 (d, *J*=9.0 Hz, 1H), 3.89 (dd, *J*=2.0, 10.5 Hz, 1H), 3.84 (dd, *J*=3.0, 9.5 Hz, 1H), 3.46 (t, *J*=8.5 Hz, 1H), 3.30 (d, *J*=9.0 Hz, 1H), 3.15–3.08 (m, 1H), 2.45 (s, 3H), 0.95–0.92 (m, 21H), 0.88 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (75 MHz, acetone-d_6) δ 174.2, 171.9, 157.7, 146.7, 138.5, 137.2, 136.9, 130.8, 129.49, 129.47, 129.43, 129.3, 128.9, 128.7, 128.5, 76.8, 65.7, 61.3, 59.8, 50.7, 49.0, 47.9, 47.5, 46.3, 43.4, 26.4, 21.6, 18.4, 18.3, 12.7; HRMS (ESI) calcd for $C_{47}H_{66}BrN_3O_7SSi_2$ [M+H]: 952.3422; found: 952.3370.

4.1.2. Iodospirohydantoin 14. To a slurry of allylic alcohol **9** (55.0 mg, 0.048 mmol) and $MgSO_4$ (~100 mg) in CH_2Cl_2 at −50 °C was added *N*-iodosuccinimide (13.0 mg, 0.058 mmol). The reaction was allowed to warm to ambient temperature slowly and stirring was continued for 16 h. The reaction mixture was then filtered and the filtrate was concentrated in vacuo. Column purification (SiO_2 gel, 20→30% EtOAc/hexane) afforded the iodocyclopentane **14** as a colorless foam (32.0 mg, 52%): R_f=0.39 (40% EtOAc/hexane); IR (thin film) 2935, 2858, 1716, 1455 cm^{-1}; ^1H NMR (500 MHz, benzene-d_6) δ 8.26 (d, *J*=8.0 Hz, 2H), 7.97 (m, 2H), 7.87 (d, *J*=8.0 Hz, 2H), 7.83 (m, 2H), 7.48 (d, *J*=2.0 Hz, 1H), 7.35 (dd, *J*=2.0, 8.0 Hz, 1H), 7.20–7.29 (m, 6H), 6.84 (d, *J*=8.0 Hz, 2H), 6.77 (d, *J*=8.0 Hz, 2H), 6.38 (d, *J*=8.0 Hz, 1H), 5.85 (d, *J*=16.0 Hz, 1H), 4.89 (s, 1H), 4.63 (d, *J*=16.0 Hz, 1H), 4.60 (t, *J*=10.0 Hz, 1H), 4.39 (d, *J*=13.5 Hz, 1H), 4.25 (dd, *J*=2.0, 11.0 Hz, 1H), 4.19 (dd, *J*=4.0, 10.0 Hz, 1H), 4.14 (d, *J*=11.0 Hz, 1H), 3.89 (m, 1H), 3.81 (d, *J*=8.5 Hz, 1H), 3.63 (s, 3H), 3.56–3.61 (m, 2H), 3.43 (m, 1H), 3.31 (s, 3H), 3.24 (m, 1H), 2.94 (m, 1H), 1.88 (s, 3H), 1.85 (s, 3H), 1.21 (s, 9H), 0.91–0.99 (m, 21H); ^{13}C NMR (125 MHz, benzene-d_6) δ 174.48, 171.74, 156.60, 150.30, 150.01, 144.84, 144.68, 136.42, 136.18, 136.01, 135.70, 133.78, 133.62, 130.39, 129.81, 129.76, 129.55, 129.10, 129.06, 128.20, 128.01, 127.95, 127.82, 122.14, 113.79, 112.18, 77.86, 65.42, 61.42, 61.24, 55.68, 55.32, 50.56, 50.36, 48.59, 48.44, 45.84, 33.25, 30.08, 26.99, 25.96, 21.06, 21.02, 19.40, 18.11, 18.05, 12.11; HRMS (MALDI) calcd for $C_{61}H_{78}IN_3O_{11}S_2Si_2$ [M+Na]: 1298.3559; found: 1298.3560.

4.1.3. Iodocyclopentane 16. To a solution of iodocyclopentane **14** (11.0 mg, 0.0086 mmol) in THF (0.20 mL) was added HF·pyridine (70%, 50 μL, excess) at 20 °C. After 21 h, the reaction was quenched with satd $NaHCO_3$ (1 mL) and H_2O (3 mL) and then extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine and further dried over Na_2SO_4. After removal of solvent, the crude product was purified by flash column chromatography (SiO_2, 60→80% EtOAc/hexane) to give alcohol **16** as a colorless film (5.6 mg, 74%): R_f=0.22 (60% EtOAc/hexane); IR (thin film) 3493, 1711 cm^{-1}; ^1H NMR (500 MHz, benzene-d_6) δ 8.06 (d, *J*=8.0 Hz, 2H), 7.84 (d, *J*=8.0 Hz, 2H), 7.41 (dd, *J*=2.0, 8.0 Hz, 1H), 7.35 (d, *J*=2.0 Hz, 1H), 6.83 (d, *J*=8.0 Hz, 2H), 6.69 (d, *J*=8.0 Hz, 2H), 6.57 (d, *J*=8.0 Hz, 1H), 5.62 (d, *J*=16.0 Hz, 1H), 4.77 (s, 1H), 4.72 (d, *J*=13.0 Hz, 1H), 4.47 (d, *J*=16.0 Hz, 1H), 4.02 (m, 1H), 3.91 (m, 2H), 3.73 (s, 3H), 3.66–3.72 (m, 2H), 3.48–3.52 (m, 1H), 3.43 (d, *J*=9.0 Hz, 1H), 3.35 (s, 3H), 3.18–3.23 (m, 1H), 3.10 (dd, *J*=9.0, 6.0 Hz, 1H), 3.06 (t, *J*=9.0 Hz, 1H), 2.96 (m, 1H), 1.86 (s, 3H), 1.77 (s, 3H), 1.36 (s, 1H), 1.06 (s, 1H); ^{13}C NMR (125 MHz, benzene-d_6) δ 175.30, 174.26, 169.91, 156.60, 150.37, 150.09, 145.27, 144.82, 135.90, 135.27, 130.20, 129.90, 129.51, 129.28, 128.80, 128.20, 127.56, 122.29, 113.73, 112.38, 77.66, 63.70, 61.60, 59.93, 59.08, 55.71, 55.37, 50.78, 49.39, 49.35, 47.45, 45.93, 33.12, 31.82, 30.09, 26.33, 22.91, 21.06, 21.05, 20.41, 14.21, 14.08; HRMS (ESI) calcd for $C_{36}H_{40}IN_3O_{11}S_2$ [M+Li]: 888.1309; found: 888.1329.

4.1.4. Lactam 18. To a solution of iodocyclopentane **16** (3.7 mg, 0.0042 mmol) in THF (0.10 mL) was added SmI_2 (0.1 M solution in THF, 130 μL, 0.013 mmol) at 0 °C. After 30 min, a further portion of SmI_2 (0.10 mL) was added. The blue reaction mixture was stirred at ambient temperature for 10 min. The reaction was then quenched with satd $NaHCO_3$ (2 mL) and extracted with EtOAc (3×10 mL). The combined organic layers were washed sequentially with water and brine, and then dried over Na_2SO_4. Removal of solvent afforded lactam **18** as a colorless film and of sufficient purity for subsequent reactions (3.0 mg, 99%): R_f=0.14 (EtOAc); IR (thin film) 3345, 1711 cm^{-1}; ^1H NMR (500 MHz, benzene-d_6) δ 7.82 (d, *J*=8.0 Hz, 2H), 7.27 (d, *J*=2.0 Hz, 1H), 7.12 (dd, *J*=2.0, 8.0 Hz, 1H), 6.81 (d, *J*=8.0 Hz, 2H), 6.61 (d, *J*=8.0 Hz, 1H), 5.31 (s, 1H), 4.97 (d, *J*=16.0 Hz, 1H), 4.66 (d, *J*=12.5 Hz, 1H), 4.42 (br s, 1H), 4.16 (d, *J*=12.5 Hz, 1H), 4.06 (d, *J*=16.0 Hz, 1H), 3.95 (m, 1H), 3.74 (s, 3H), 3.60–3.65 (m, 1H), 3.51–3.56 (m, 1H), 3.38 (s, 3H), 3.33 (t, *J*=4.5 Hz, 1H), 3.18 (d, *J*=8.5 Hz, 1H), 3.10–3.15 (m, 3H), 2.98 (m, 1H), 2.90 (m, 1H), 2.68 (t, *J*=8.5 Hz, 1H), 1.85 (s, 3H), 1.32 (br s, 1H); ^{13}C NMR (125 MHz, benzene-d_6) δ 178.02, 174.52, 156.83, 150.45, 150.06, 144.83, 135.93, 130.05, 129.88, 128.73, 128.39, 127.37, 121.51, 113.31, 112.27, 77.35, 65.16, 59.93, 59.18, 55.46, 50.79, 48.46, 48.16, 47.40, 45.31, 33.04, 30.08, 26.91, 21.04, 14.21, 14.15, 14.08; HRMS (MALDI) calcd for $C_{29}H_{34}IN_3O_9S$ [M+H]: 728.1139; found: 728.1118.

4.1.5. Bisazide 23. To a solution of spirohydantoin **21** (68.5 mg, 0.072 mmol) in 500 μL DMF was added NaN_3

(77.3 mg, 1.189 mmol) and the reaction mixture was heated to 120 °C. After 16 h the reaction mixture was concentrated in vacuo and purified by flash chromatography (SiO_2, 0→60 EtOAc/hexane) to give bisazide **23** as a light yellow foam (24.3 mg, 41%): R_f=0.67 (30% EtOAc/hexane); $[\alpha]_D^{25}$ −22.3 (*c* 1.14, CH_2Cl_2); IR (thin film) 2116, 1716 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6) δ 8.08 (d, *J*=8.4 Hz, 2H), 7.51 (d, *J*=8.4 Hz, 2H), 7.44 (d, *J*=6.6 Hz, 2H), 7.43–7.29 (m, 8H), 5.35 (d, *J*=16.5 Hz, 1H), 4.71 (d, *J*=15.0 Hz, 1H), 4.65 (d, *J*=15.0 Hz, 1H), 4.65 (app t, *J*=1.8 Hz, 1H), 4.39 (d, *J*=16.5 Hz, 1H), 4.09–3.90 (m, 3H), 3.97 (d, *J*=11.1 Hz, 1H), 3.59 (dd, *J*=6.0, 12.9 Hz, 1H), 3.48 (t, *J*=8.4 Hz, 1H), 3.21 (d, *J*=8.7 Hz, 1H), 3.08–2.97 (m, 1H), 2.45 (s, 3H), 0.96–0.92 (m, 21H); ^{13}C NMR (125 MHz, acetone-d_6) δ 173.8, 172.5, 157.7, 146.8, 138.4, 137.2, 136.5, 130.7, 129.7, 129.4, 129.3, 128.8, 128.6, 128.43, 128.41, 128.3, 126.7, 75.2, 66.5, 65.4, 61.5, 49.5, 47.1, 46.6, 46.2, 44.0, 43.1, 21.5, 18.2, 18.1, 12.6; HRMS (ESI) calcd for $C_{41}H_{51}N_9O_6SSi$ [M+H]: 826.3531; found: 826.3458.

4.1.6. Azidocyclopentane 24. To a mixture of iodocyclopentane **22** (10 mg, 0.0078 mmol) and NaN_3 (34 mg, 0.52 mmol) in a dry vial was added anhydrous DMF (0.40 mL). The reaction vessel was purged with nitrogen and sealed and then heated to 105 °C. After 12 h, the reaction was cooled to ambient temperature, H_2O was added, and then the mixture was extracted with EtOAc. The organics were washed with brine and then dried over Na_2SO_4. Concentration in vacuo and column purification (SiO_2, 25% EtOAc/hexane) afforded the azidocyclopentane **24** as a colorless film (7.0 mg, 75%): R_f=0.38 (6:4 hexane/EtOAc); IR (thin film) 2926, 2113, 1716, 1113 cm^{-1}; ^1H NMR (500 MHz, benzene-d_6) δ 8.21 (d, *J*=8.0 Hz, 2H), 7.91 (m, 2H), 7.87 (d, *J*=8.0 Hz, 2H), 7.76 (m, 2H), 7.54 (d, *J*=2.0 Hz, 1H), 7.42 (dd, *J*=2.0, 8.0 Hz, 1H), 7.19–7.27 (m, 6H), 6.84 (d, *J*=8.0 Hz, 2H), 6.77 (d, *J*=8.0 Hz, 2H), 6.50 (d, *J*=8.0 Hz, 1H), 5.94 (d, *J*=16.0 Hz, 1H), 4.87 (s, 1H), 4.74 (d, *J*=16.0 Hz, 1H), 4.60 (dd, *J*=6.0, 11.0 Hz, 1H), 4.32 (d, *J*=11.0 Hz, 1H), 4.17–4.22 (m, 2H), 4.07 (d, *J*=9.5 Hz, 1H), 3.67 (s, 3H), 3.55–3.62 (m, 4H), 3.36 (m, 1H), 3.35 (s, 3H), 3.20 (m, 1H), 2.91 (m, 1H), 1.87 (s, 3H), 1.84 (s, 3H), 1.19 (s, 9H), 0.88–0.94 (m, 21H); ^{13}C NMR (125 MHz, benzene-d_6) δ 173.66, 172.29, 156.93, 150.72, 150.20, 144.88, 144.67, 136.31, 136.19, 135.84, 135.78, 133.64, 133.52, 130.19, 129.80, 129.53, 129.09, 129.01, 128.21, 128.02, 127.82, 127.63, 120.86, 112.72, 112.60, 75.24, 66.59, 65.29, 62.29, 61.31, 55.76, 55.44, 50.48, 47.78, 47.37, 47.20, 45.80, 33.35, 30.08, 26.95, 21.07, 21.01, 19.30, 18.06, 18.00, 12.04; HRMS (ESI) calcd for $C_{61}H_{78}N_6O_{11}S_2Si_2$ [M+Li]: 1197.4869; found: 1197.4800.

4.1.7. Sulfonamide 30. To a mixture of alcohol **35** (35 mg, 0.039 mmol) and TsCl (11 mg, 0.059 mmol) was added anhydrous CH_2Cl_2 (0.40 mL), followed by triethylamine (~80 μL, excess). The reaction mixture was stirred vigorously for 36 h at 23 °C and then extracted with CH_2Cl_2 (3×10 mL). The organic layer was washed with satd $NaHCO_3$ and brine, and then dried over Na_2SO_4. Purification by column chromatography (SiO_2, 50→80% EtOAc/hexane) afforded the tosylate as a colorless foam (35 mg, 85%), which was carried directly to the next step: R_f=0.61 (EtOAc); IR (thin film) 2940, 2863, 1742, 1690 cm^{-1}; ^1H NMR (500 MHz, benzene-d_6) δ 7.75 (d, *J*=8.0 Hz, 4H), 7.60 (d, *J*=8.0 Hz, 2H), 6.97 (d, *J*=2.0 Hz, 1H), 6.81 (dd, *J*=8.0, 2.0 Hz, 1H), 6.72 (d, *J*=8.0 Hz, 2H), 6.68 (d, *J*=8.0 Hz, 2H), 6.65 (d, *J*=8.0 Hz, 2H), 6.60 (d, *J*=8.0 Hz, 1H), 4.58 (d, *J*=15.5 Hz, 1H), 4.47 (dd, *J*=8.0, 10.0 Hz, 1H), 4.38 (dd, *J*=7.0, 10.0 Hz, 1H), 4.32 (m, 2H), 4.04–4.17 (m, 4H), 3.88 (m, 1H), 3.74 (d, *J*=6.5 Hz, 1H), 3.60 (s, 3H), 3.37 (s, 3H), 3.22 (dd, *J*=3.0, 7.0 Hz, 1H), 2.86 (dt, *J*=4.0, 14.0 Hz, 1H), 2.06 (dd, *J*=4.0, 15.0 Hz, 1H), 1.92 (s, 3H), 1.89 (m, 1H), 1.86 (s, 3H), 1.85 (s, 3H), 1.76 (m, 1H), 1.17–1.20 (m, 21H); ^{13}C NMR (125 MHz, benzene-d_6) δ 172.83, 153.76, 150.50, 149.74, 144.78, 144.38, 144.20, 137.76, 135.92, 133.94, 130.19, 129.86, 129.71, 129.43, 128.21, 128.03, 127.82, 127.54, 119.89, 119.05, 114.32, 112.32, 111.88, 70.85, 66.60, 65.39, 64.59, 63.95, 59.93, 55.75, 55.49, 52.77, 44.34, 41.77, 36.32, 34.82, 34.31, 30.86, 30.09, 21.16, 21.05, 21.01, 19.73, 18.20, 18.19, 12.15; HRMS (ESI) calcd for $C_{52}H_{67}N_3O_{12}S_3Si$ [M+Li]: 1056.3816; found: 1056.3789.

The crude tosylate (43.0 mg, 0.041 mmol) and NaN_3 (26 mg, 0.41 mmol) were dissolved in anhydrous DMF (1.0 mL) and the flask was purged with nitrogen and sealed. The reaction mixture was heated to 100 °C. After stirring for 16 h, water was added and the mixture was extracted with CH_2Cl_2 (3×10 mL). The combined organics were washed with brine and dried over Na_2SO_4. The azide was obtained in sufficient purity (38 mg, 100%) for the next step. To a mixture of the azide (38 mg, 0.041 mmol) and triphenylphosphine (54 mg, 0.20 mmol) in a dry flask was added THF (0.8 mL), followed by water (25 μL). The mixture was stirred vigorously at room temperature. After 12 h, the reaction mixture was concentrated in vacuo and azeotroped with benzene. The crude mixture was subjected to flash column purification (SiO_2, 2→5% MeOH/CH_2Cl_2) to yield an amine (27.3 mg, 75%).

To a mixture of the amine (27 mg, 0.030 mmol) and *p*-toluenesulfonyl chloride (21 mg, 0.11 mmol) were added CH_2Cl_2 (0.60 mL) and triethylamine (0.10 mL). The reaction mixture was stirred at 23 °C for 20 h and then partitioned between CH_2Cl_2/H_2O. The organic layer was washed with satd $NaHCO_3$, brine, and then dried over Na_2SO_4. Purification by flash column chromatography (50→75% EtOAc/hexane) afforded sulfonamide **30** as a colorless foam (26 mg, 83%): R_f=0.48 (80% EtOAc/hexane); IR (thin film) 2945, 2868, 2361, 1690 cm^{-1}; ^1H NMR (500 MHz, benzene-d_6) δ 7.79 (d, *J*=8.0 Hz, 2H), 7.77 (d, *J*=8.0 Hz, 2H), 7.64 (d, *J*=8.0 Hz, 2H), 7.03 (d, *J*=2.0 Hz, 1H), 6.87 (dd, *J*=2.0, 8.0 Hz, 1H), 6.82 (d, *J*=8.0 Hz, 2H), 6.75 (d, *J*=8.0 Hz, 2H), 6.73 (d, *J*=8.0 Hz, 2H), 6.64 (d, *J*=8.0 Hz, 1H), 4.94 (t, *J*=6.5 Hz, 1H), 4.69 (d, *J*=15.5 Hz, 1H), 4.35–4.39 (m, 2H), 4.10–4.24 (m, 4H), 3.91 (m, 1H), 3.84 (d, *J*=7.0 Hz, 1H), 3.65 (s, 3H), 3.39 (s, 3H), 3.28 (dd, *J*=3.0, 7.0 Hz, 1H), 3.18–3.24 (m, 2H), 2.86 (dt, *J*=4.0, 14.0 Hz, 1H), 2.11 (dd, *J*=4.0, 15.0 Hz, 1H), 1.97 (s, 3H), 1.95 (s, 3H), 1.91 (m, 1H), 1.88 (s, 3H), 1.72 (m, 1H), 1.19–1.21 (m, 21H); ^{13}C NMR (125 MHz, benzene-d_6) δ 173.64, 153.81, 150.44, 149.67, 144.94, 144.25, 142.79, 138.17, 137.79, 135.83, 130.30, 129.75, 129.67, 129.53, 127.59, 127.33, 119.94, 114.48, 112.31, 111.93, 65.29, 64.63, 55.83, 55.50, 52.74, 45.15, 44.35,

42.83, 36.32, 35.14, 34.78, 30.08, 21.20, 21.03, 20.50, 18.23, 18.22, 18.10, 12.17, 12.08; HRMS (ESI) calcd for $C_{52}H_{68}N_4O_{11}S_3Si$ [M+Li]: 1055.3976; found: 1055.3530.

4.1.8. 2-Chloro-3-carbomethoxy-pyrrole 39. A solution of 10.9 mg (0.04 mmol) of carbinolamine **38** and 16.6 mg (0.08 mmol) of *p*-toluenesulfonyl chloride (TsCl) in 1 mL CH_2Cl_2 was treated with 7 μL (0.08 mmol) pyridine. After 5 h at reflux, the solvent was removed in vacuo and the residue was purified by flash chromatography (SiO_2, 25% EtOAc/CH_2Cl_2) to afford 2-chloro-3-carbomethoxy-pyrrole **39** as a faint pink solid (6.9 mg, 59%): R_f=0.6 (50% CH_2Cl_2/EtOAc); IR (thin film) 2956, 1747, 1646, 1418 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 7.18 (dd, J=1.5, 2.6 Hz, 1H), 7.05 (s, 1H), 6.79 (ddd, J=0.8, 1.6, 3.7 Hz, 1H), 6.28 (dd, J=2.6, 3.7 Hz, 1H), 3.7–3.75 (m, 2H), 3.67 (s, 3H), 2.62 (ddd, J=8.0, 9.5, 13.5 Hz, 1H), 2.41 (ddd, J=4.1, 7.5, 11.5 Hz, 1H), 2.10–2.18 (m, 1H), 1.96–2.0 (m, 1H); ^{13}C NMR (125 MHz, acetone-d_6) δ 172.10, 156.60, 125.79, 124.49, 115.23, 112.81, 74.00, 72.68, 53.93, 45.48, 35.59, 22.53; HRMS (ESI) calcd for $C_{12}H_{13}ClN_2O_3$ [M+H]: 269.0693; found: 269.0626.

4.1.9. 2-Chloro-3-carbobenzyloxy-pyrrole 40. Chloride **40** was prepared in an identical manner to that described for chloride **39**: R_f=0.72 (50% CH_2Cl_2/EtOAc); IR (thin film) 2950, 1747, 1650, 1419 cm^{-1}; ^1H NMR (500 MHz, acetone-d_6) δ 7.30–7.32 (m, 3H), 7.18–7.21 (m, 2H), 7.14 (dd, J=1.7, 2.7 Hz, 1H), 7.06 (s, 1H), 6.79 (ddd, J=0.5, 1.5, 3.6 Hz, 1H), 6.27 (dd, J=3.0, 3.6 Hz, 1H), 5.15 (app d, J=0.5 Hz, 2H), 3.72 (dd, J=6.5, 8.0 Hz, 2H), 2.63 (ddd, J=8.0, 9.5, 13.5 Hz, 1H), 2.41 (ddd, J=4.2, 7.5, 13.0 Hz, 1H), 2.09–2.16 (m, 1H), 1.91–1.97 (m, 1H); ^{13}C NMR (125 MHz, acetone-d_6) δ 171.5, 156.7, 136.3, 129.3, 129.1, 128.5, 125.8, 124.5, 115.3, 112.8, 74.1, 72.6, 68.6, 45.5, 35.5, 22.5; HRMS (ESI) calcd for $C_{18}H_{17}ClN_2O_3$ [M+H]: 345.1006; found: 345.1034.

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References and notes

1. (a) Gribble, G. W. *Prog. Chem. Org. Nat. Prod.* **1996**, *68*, 1; (b) Gribble, G. W. *Acc. Chem. Res.* **1998**, *31*, 141; (c) Gribble, G. W. *Chem. Soc. Rev.* **1999**, *28*, 335; (d) Gribble, G. W. *Chemosphere* **2003**, *52*, 289.
2. Graedel, T. E.; Keene, W. C. *Pure Appl. Chem.* **1996**, *68*, 1689.
3. Mourabit, A. A.; Potier, P. *Eur. J. Org. Chem.* **2001**, 237.
4. (a) Dilley, A. S.; Romo, D. *Org. Lett.* **2001**, *3*, 1535; (b) Poullennec, K. G.; Kelly, A. T.; Romo, D. *Org. Lett.* **2002**, *4*, 2645; (c) Poullennec, K. G.; Romo, D. *J. Am. Chem. Soc.* **2003**, *125*, 6344; (d) Dransfield, P. J.; Wang, S.; Dilley, A.; Romo, D. *Org. Lett.* **2005**, *7*, 1679; (e) Dransfield, P. J.; Dilley, A.; Wang, S.; Romo, D. *Tetrahedron* **2006**, *62*, 5223.
5. (a) Burkholder, P. R.; Sharma, G. M. *Lloydia* **1969**, *32*, 466; (b) Sharma, G. M.; Burkholder, P. R. *J. Chem. Soc., Chem. Commun.* **1971**, 151; (c) Sharma, G. M.; Magdoff-Fairchild, B. *J. Org. Chem.* **1977**, *42*, 4118.
6. (a) Kinnel, R. B.; Gehrken, H.-P.; Scheuer, P. J. *J. Am. Chem. Soc.* **1993**, *115*, 3376; (b) Kato, T.; Shizuri, Y.; Izumida, H.; Yokoyama, A.; Endo, M. *Tetrahedron Lett.* **1995**, *36*, 2133; (c) Kinnel, R. B.; Gehrken, H.-P.; Swali, R.; Skoropowski, G.; Scheuer, P. J. *J. Org. Chem.* **1998**, *63*, 3281.
7. Urban, S.; Leone, P. D. A.; Carroll, A. R.; Fechner, G. A.; Smith, J.; Hooper, J. N. A.; Quinn, R. J. *J. Org. Chem.* **1999**, *64*, 731.
8. (a) Overman, L. E.; Rogers, B. N.; Tellow, J. E.; Trenkle, W. C. *J. Am. Chem. Soc.* **1997**, *119*, 7159; (b) Belanger, G.; Hong, F.-T.; Overman, L. E.; Rogers, B. N.; Tellow, J. E.; Trenkle, W. C. *J. Org. Chem.* **2002**, *67*, 7780; (c) Starr, J. T.; Koch, G.; Carreira, E. M. *J. Am. Chem. Soc.* **2000**, *122*, 8793; (d) Lovely, C. J.; Du, H.; Dias, H. V. R. *Org. Lett.* **2001**, *3*, 1319; (e) Lovely, C. J.; Du, H.; Dias, H. V. R. *Heterocycles* **2003**, *60*, 1; (f) He, Y.; Chen, Y.; Wu, H.; Lovely, C. J. *Org. Lett.* **2003**, *5*, 3623; (g) Koenig, S. G.; Miller, S. M.; Leonard, K. A.; Lowe, R. S.; Chen, B. C.; Austin, D. J. *Org. Lett.* **2003**, *5*, 2203; (h) Chung, R.; Yu, E.; Incarvito, C. D.; Austin, D. J. *Org. Lett.* **2004**, *6*, 3881; (i) Garrido-Hernandez, H.; Nakadai, M.; Vimolratana, M.; Li, O. Y.; Doundoulaskis, T.; Harran, P. G. *Angew. Chem., Int. Ed.* **2005**, *44*, 765; (j) Jacquot, D. E. N.; Zollinger, M.; Lindel, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 2295; (k) Jacquot, D. E. N.; Hoffmann, H.; Polborn, K.; Lindel, T. *Tetrahedron Lett.* **2002**, *43*, 3699; (l) Feldman, K. S.; Skoumbourdis, A. P. *Org. Lett.* **2005**, *7*, 929; (m) Du, H.; He, Y.; Sivappa, R.; Lovely, C. J. *Synlett* **2006**, 965.
9. The absolute stereochemistry of both axinellamine and palau'amine has not been determined conclusively.
10. (a) Knowles, H. S.; Parsons, A. F.; Pettifer, R. M.; Rickling, S. *Tetrahedron* **2000**, *56*, 979; (b) Knowles, H.; Parsons, A. F.; Pettifer, R. M. *Synlett* **1997**, 271.
11. Nishimura, S.; Matsunaga, S.; Shibazaki, M.; Suzuki, K.; Furihata, K.; van Soest, R. W. M.; Fusetani, N. *Org. Lett.* **2003**, *5*, 2255.
12. Dutta, S.; Abe, H.; Aoyagi, S.; Kibayashi, C.; Gates, K. S. *J. Am. Chem. Soc.* **2005**, *127*, 15004.
13. Breslow, R.; Guo, T. *Tetrahedron Lett.* **1987**, *28*, 3187.
14. (a) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734; (b) Baldwin, J. E.; Cutting, J.; Dupont, W.; Kruse, L.; Silberman, L.; Thomas, R. C. *J. Chem. Soc., Chem. Commun.* **1976**, 736.
15. For examples of exceptions to Baldwin's rule, see: (a) Prange, T.; Rodriguez, M. S.; Suarez, E. *J. Org. Chem.* **2003**, *68*, 4422; (b) Harris, J. M.; O'Doherty, G. A. *Tetrahedron* **2001**, *57*, 5161; (c) Coxon, J. M.; Morokuma, K.; Thorpe, A. J.; Whalen, D. *J. Org. Chem.* **1998**, *63*, 3875; (d) Johnson, C. D. *Acc. Chem. Res.* **1993**, *26*, 476; (e) Bilton, J. N.; Jones, P. S.; Ley, S. V.; Robinson, N. G.; Sheppard, R. N. *Tetrahedron Lett.* **1988**, *29*, 1849.
16. (a) De Luca, L.; Giacomelli, G.; Nieddu, G. *Synlett* **2005**, 223; (b) Back, T. G.; Chau, J. H.-L.; Dyck, B. P.; Gladstone, P. L. *Can. J. Chem.* **1991**, *69*, 1482.
17. For lead references, see: (a) Cushing, T. D.; Sanz-Cervera, J. F.; Williams, R. M. *J. Am. Chem. Soc.* **1996**, *118*, 557; (b) Lai, G.; Tan, P.-Z.; Ghoshal, P. *Synth. Commun.* **2003**, *33*, 1727.
18. (a) Murray, R. W.; Jeyaraman, R. *J. Org. Chem.* **1985**, *50*, 2847; (b) Ferrer, M.; Gibert, M.; Sanchez-Baeza, F.; Messeguer, A. *Tetrahedron Lett.* **1996**, *37*, 3585.

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Elemental fluorine. Part 19: Electrophilic fluorination of hexyl derivatives bearing electron withdrawing groups☆

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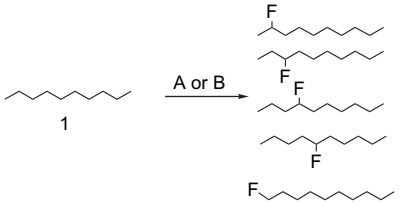
Abstract—Reaction of a series of model hexyl derivatives of the form C_6H_{13}–X (X=Cl, Br, I, CO_2Me, COMe, CHO) with both elemental fluorine and Selectfluor™ was studied in order to assess the impact of electron withdrawing functional groups upon fluorination of an alkyl chain. Fluorination generally occurs at secondary sites, with a slight preference for those that are furthest removed from the electron withdrawing group, consistent with an electrophilic substitution process, although mixtures of fluorinated products are obtained in most cases.

1. Introduction

Fluorination can confer unusual, and sometimes valuable, chemical and biological properties upon a molecular system and these effects have been exploited by the life science industries for the development of many fluorinated pharmaceuticals and agrochemicals.[2,3] Regio- and stereo-selective introduction of fluorine atoms at unactivated sites that are remote from a functional group in aliphatic systems by viable synthetic methodology that is also suitable for large scale synthesis, presents a formidable challenge to organofluorine chemistry.[4] Therefore, in this context, effective fluorination procedures that involve selective transformation of carbon–hydrogen to carbon–fluorine bonds at remote sites would be extremely valuable in order to expand the range of fluorinated systems that may be readily accessed from nonfluorinated precursors.

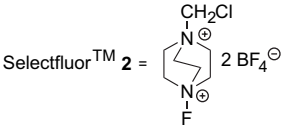
Electrophilic aliphatic substitution processes are not very common but Rozen[4] and, subsequently, the Durham group[5] have demonstrated that electrophilic fluorination of aliphatic sites by elemental fluorine and electrophilic fluorinating reagents of the N–F class[6] can be achieved. A broad parallel has been established between the products observed for reactions between open-chain hydrocarbons, such as *n*-decane **1** (Scheme 1) and with either elemental fluorine or Selectfluor™ **2**.[5] This is significant evidence for the role of fluorine as an electrophile, rather than a radical under the conditions used, because radical clock experiments conducted using Selectfluor™ showed no evidence of a radical process for fluorination of several unsaturated systems.[7,8] It is possible that acetonitrile performs a similar role of hydrogen bonding to the incipient fluoride ion in the transition state, similar to that suggested by Rozen for the role of chloroform (Scheme 2).



A (61% conv.) 63%, 2.4 : 1.3 : 1.1 : 1 : 0.5

B (84% conv.) 58%, 2.4 : 1.3 : 1 : 1.1

A, 10% F_2 in N_2 (*v/v*), CH_3CN, 0 °C; B, Selectfluor, CH_3CN, reflux 16 h.



Scheme 1.

☆ For Part 18 see Ref. 1.

Keywords: Fluorine; Selective fluorination; Fluorinating agents; Electrophilic aliphatic substitution.

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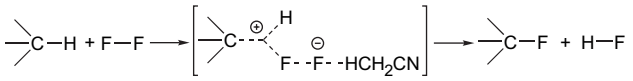
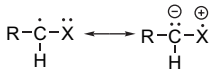


Scheme 2.

Selective electrophilic fluorination of aliphatic systems bearing functional groups could, in principle, offer methodology for the synthesis of a range of fluorinated systems where fluorine is attached to sites remote from the functional group itself, if the influence of individual functional groups on the approaching fluorinating agent can be established and eventually made sufficiently dominant.

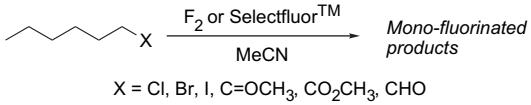
Chlorination and bromination of saturated aliphatic derivatives have been extensively studied[9–11] and the effect of a functional group upon the relative reactivities of the carbon–hydrogen bonds in an adjoining saturated aliphatic chain towards free radical chlorination has long been established. For example, it is well known that an inductively electron withdrawing substituent significantly deactivates the carbon–hydrogen bonds that are attached to the carbon atom bearing the functional group towards electrophilic chlorine atoms, although the effect rapidly falls off with distance.[9] Also, a competing mesomeric stabilising influence may render the 1-position active (Scheme 3).



Scheme 3.

To date, however, there is little related systematic assessment concerning reactions of fluorine with substituted alkanes.[12,13] Of the very few studies of this type, in research involving fluorination of various steroid derivatives, Rozen[4] demonstrated that electron withdrawing groups such as acetyl, chlorine and trifluoromethyl-acetyl favoured fluorination at the furthest removed tertiary carbon–hydrogen bonds, consistent with an electrophilic aliphatic substitution process.

In this series, we are developing the use of elemental fluorine as a viable reagent for organic synthesis[14] and, here, we describe the fluorination of a range of model hexyl systems, each bearing an electron withdrawing group (Scheme 4), in order to establish the effect of each functionality upon the conversion of unactivated carbon–hydrogen bonds to carbon–fluorine bonds, at sites within an alkyl chain.



Scheme 4.

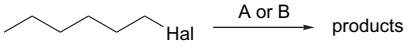
We set out to establish the relative selectivities at each carbon site in the aliphatic chain towards electrophilic fluorination. For comparison purposes, we also describe the fluorination of the same substrates by Selectfluor™. Fluorination of many unsaturated systems by Selectfluor™ have been reported,[6] but reactions at saturated sites remain largely limited to our previous work.

2. Results and discussion

Fluorination of 1-halohexanes with fluorine and Selectfluor™ were carried out using solutions in acetonitrile at 0 °C and reflux temperature, respectively, and the results are contained in Table 1.

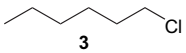
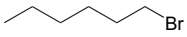
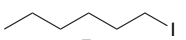
1-Chlorohexane **3** gave a mixture of three major products **4b–d** in the ratio 1:1.8:1.9, arising from substitution of hydrogen located at the 3-, 4- and 5-positions, respectively, and a large number of other components each in very small quantities. Fluorination by Selectfluor™ was slightly more selective with the 3-, 4- and 5-fluoro derivatives **4a–d** being formed in the ratio 1:2.7:5.2:10.1 in slightly higher overall yield. Preparative scale GC was used to isolate an analytically pure sample of an isomeric mixture of the two main products **4c** and **4d**. Identification of 1-chloro-5-fluorohexane **4d** could be made on the basis of the $^{2}J_{CF}$ coupling constant observed for the resonance attributed to the methyl group, readily identified by ^{13}C DEPT, whilst the methyl resonance for 1-chloro-4-fluorohexane **4c** showed only $^{3}J_{CF}$ coupling. In both cases, fluorination of the 1- and 2-positions was minor, indicating the deactivating effect of the chlorine atom at the adjacent sites. Moreover, these results demonstrate more selectivity than those observed for radical chlorination and, this is, of course, consistent with electrophilic fluorination at saturated carbon, where we would anticipate polar influences to be more important than for radical processes.

Table 1. Fluorination of haloalkanes



Hal = Cl, Br, I

A, 10% F_2 in N_2 (*v/v*), CH_3CN, 0 °C; B, Selectfluor, CH_3CN, reflux 16 h.

Substrate	Conditions A or B (conv. %)	Product(s) (yield %)
 **3**	A (72)	22%, **4a**:**4b**:**4c**:**4d**, trace:1:1.8:1.9+many unidentified products
	B (53)	56%, **4a**:**4b**:**4c**:**4d**, trace:1:2.7:5.2:10.1
 **5**	A (100)	Many unidentified products
	B (30)	75%, **6a**:**6b**:**6c**, 1:1.9:3.8
 **7**	A (100)	Many unidentified products
	B (100)	Many unidentified products

Direct fluorination of 1-bromohexane **5** by fluorine gave a very complex mixture from which no products could be identified. It is likely that the brominated substrate is oxidised by fluorine to either a BrF_2 or BrF_4 derivative followed by elimination, in processes analogous to those reported by Adcock et al. in perfluorination reactions of similar substrates.[15] In contrast, Selectfluor™ led to reasonable yields of products **6a–c** fluorinated at the 3-, 4- and 5-positions in a ratio 1:1.9:3.8, which is similar to those obtained upon fluorination of chlorohexane. The 5-fluoro-bromohexane **6c** and 4-fluoro-bromohexane **6b** products were isolated by preparative GC as a mixture of isomers and identified by the techniques described above.

1-Iodohexane **7** gave intractable tars upon reaction with either fluorine or Selectfluor™, probably arising from oxidation processes in both cases.

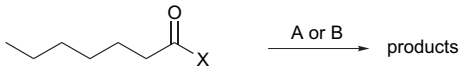
Results of fluorination reactions between model carbonyl containing hexyl systems and either fluorine or Selectfluor™ are collected in Table 2.

Fluorination of methyl enanthate **8** by fluorine gave four main products **9a–d** in the ratio 1:3.5:6.4:5.6 along with small quantities of numerous other products including trace quantities of other monofluorinated derivatives and some tar. The four major products were isolated as a mixture of isomers by preparative scale GC and this enabled their characterisation by NMR techniques indicated above. Similarly, Selectfluor™ gave the same four main products and traces of many other fluorinated systems.

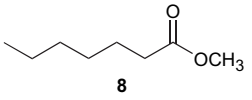
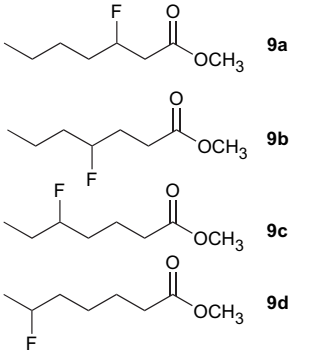
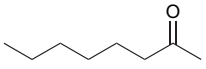
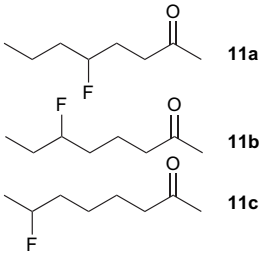
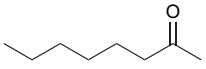
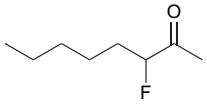
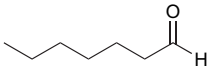
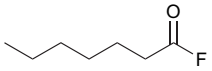
Fluorination of octan-2-one **10** with fluorine gave a mixture of three main monofluorinated products **11a–c** arising from substitution of carbon–hydrogen bonds at the 5-, 6- and 7-methylene sites in the ratio 1:1.7:1.3 along with other products and tar. In contrast, reaction of Selectfluor™ with octan-2-one was an efficient and selective process that gave 3-fluoro-heptan-2-one **11d** as the only product. Selectfluor™ makes the reaction medium more acidic in nature[5] and, therefore, promotes the formation of an enol form of the ketone, which allows selective fluorination of the enolic 3-position.

Fluorination of heptanal **12** with fluorine gave heptanoic acid fluoride **13** as a major product (Scheme 5), which could readily be identified by ^{19}F NMR (δ_F=+20 ppm) of the reaction mixture. Due to the instability of these systems towards hydrolysis, 2,4-dinitrobenzyl alcohol **14** was added to the reaction mixture and the corresponding ester **15** was isolated by column chromatography. A mechanism for the transformation of aldehydes to acid fluorides using fluorine is given

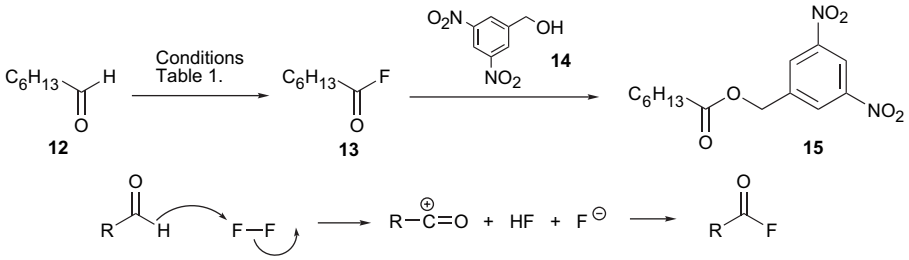
Table 2. Fluorination of carbonyl derivatives



A, 10% F_2 in N_2 (*v/v*), CH_3CN, 0 °C; B, Selectfluor, CH_3CN, reflux 16 h.

Substrate	Conditions A or B (conv. %)	Product(s) (yield %)
 **8**		 **9a**, **9b**, **9c**, **9d** + many other unidentified products in trace quantities
	A (64)	68%, **9a**:**9b**:**9c**:**9d**, 1:3.5:6.4:5.6
	B (57)	48%, **9a**:**9b**:**9c**:**9d**, 1:1.3:1.3:3.7
 **10**		 **11a**, **11b**, **11c**
	A (64%)	41%, **11a**:**11b**:**11c**, 1:1.7:1.3
 **10**		
	B (100)	**11d**, 65%
 **12**		
	A (100)	**13**, 66%[a]
	B (100)	Many unidentified products

[a] Isolated as an ester (see Scheme 5).



Scheme 5.

in Scheme 5. In contrast, Selectfluor™ gave a mixture of products, which could not be identified.

Fluorination reactions of benzaldehyde derivatives to acids, via acid fluorides, mediated by Selectfluor™ have been described by Banks et al.[16] and single electron transfer processes were suggested to account for this transformation.

3. Conclusions

In general, therefore, fluorination of model hexyl derivatives of the form C_6H_{13}–X (X=Cl, Br, I, CO_2Me, COMe, CHO) with either elemental fluorine or Selectfluor™ leads to a mixture of monofluorinated products that predominantly arise from fluorination of secondary, rather than primary, sites with slight selectivity for fluorination of methylene sites that are furthest removed from the electron withdrawing functionality. Fluorination does not, in general, occur at sites adjacent to the functional group with the exception being fluorination of ketones by Selectfluor™ and replacement of aldehydic hydrogens by fluorine using either reagent. Under the conditions used so far, the selectivity of the reactions, with the same exceptions, is not sufficient to be regarded as being synthetically useful, although the regioselectivity observed is generally consistent with an electrophilic aliphatic substitution process.

4. Experimental

4.1. General

All starting materials were obtained commercially (Aldrich) and all solvents were dried using literature procedures. NMR spectra were recorded in deuterochloroform, unless otherwise stated, on a Varian VXR 400S NMR spectrometer with tetramethylsilane and trichlorofluoromethane as internal standards. Spectral assignments were made with the aid of data collected by ^{1}H–^{1}H COSY and ^{1}H–^{13}C HETCOR experiments and coupling constants are given in hertz. In ^{19}F NMR spectra, upfield shifts are quoted as negative. Mass spectra were recorded on either a VG 7070E spectrometer or a Fisons VG Trio 1000 spectrometer coupled with a Hewlett Packard 5890 series II gas chromatograph. Accurate mass measurements were performed by the EPSRC National Mass Spectrometry service, Swansea, U.K. Elemental analyses were obtained on either a Perkin–Elmer 240 or a Carlo Erba Elemental Analyser. Melting points were recorded at atmospheric pressure and are uncorrected. Column chromatography was carried out on silica gel (Merck no. 1-09385, 230–400 mesh) and TLC analysis was performed on silica gel TLC plates using dichloromethane as an eluent.

4.2. Reactions with elemental fluorine

4.2.1. General procedure. Elemental fluorine, as a 10% (v/v) mixture with nitrogen, was passed at a rate of ca. 50 ml min^{-1} through a stirred, cooled (0 °C) mixture, which consisted of the substrate and acetonitrile. After addition of fluorine, the reaction mixture was poured into water (100 ml), neutralised ($NaHCO_3$) and extracted with dichloromethane (3×40 ml). The combined, dried ($MgSO_4$), organic extracts were evaporated to give a crude product. The composition of a weighed crude reaction mixture was determined by GC–MS analysis and the conversion of starting material was calculated from GC peak intensities. The amount of fluorinated product in the crude product was determined by adding a known amount of fluorobenzene to a weighed amount of the crude product mixture. Comparison of the relative intensities of the appropriate ^{19}F NMR resonances gave the yield of fluorinated derivative, based upon the conversion obtained above. Analytical samples of fluorinated products were obtained by either preparative scale GC or column chromatography. Yields of fluorinated products are based on the conversion of starting material.

4.2.1.1. 1-Chlorohexane 3. 1-Chlorohexane **3** (8.36 g, 69 mmol), elemental fluorine (208 mmol) and anhydrous acetonitrile (140 ml) gave a dark yellow crude mixture (9.02 g), which contained **4b**, **4c** and **4d** (1.51 g, 22%, 72% conv.) in the ratio 1.0:1.8:1.9, respectively, and a trace amount of 1-chloro-6-fluorohexane; δ_F −217.49 (m), a large number of other unidentified products (16%) and tar (10%). Purification of the crude product by preparative scale GC gave an analytically pure sample consisting of 1-chloro-4-fluorohexane **4c** and 1-chloro-5-fluorohexane **4d** as a mixture of isomers and as a colourless liquid; (Found: C, 51.8; H, 8.7. $C_6H_{12}ClF$ requires: C, 52.0; H, 8.7%); *1-chloro-4-fluorohexane* ***4c***: δ_H 0.98 (3H, t, $^3J_{HH}$ 7.6, CH_3), 1.4–2.0 (6H, m, CH_2), 3.60 (2H, m, CH_2Cl), 4.42 (1H, dm, $^2J_{HF}$ 49.5, CHF); δ_F −182.64 (m); δ_C 9.3 (d, $^3J_{CF}$ 6.4, C-6), 28.1 (d, $^2J_{CF}$ 21.0, C-5), 28.3 (d, $^3J_{CF}$ 3.8, C-2), 32.0 (d, $^2J_{CF}$ 21.3, C-3), 44.9 (s, CH_2Cl), 94.9 (d, $^1J_{CF}$ 168.3, CF); *m/z* (EI$^+$) 118 (M^+−HF, 5%), 91 (25), 82 (22), 73 (16), 55 (100); *1-chloro-5-fluorohexane* ***4d***: δ_H 1.35 (3H, dd, $^3J_{HF}$ 24.0, $^3J_{HH}$ 6.0, CH_3), 1.4–2.0 (6H, m, CH_2), 3.55 (2H, t, $^3J_{HH}$ 6.8, CH_2Cl), 4.68 (1H, dm, $^2J_{HF}$ 48.5, CHF); δ_F −173.29 (m); δ_C 21.0 (d, $^2J_{CF}$ 20.9, CH_3), 22.5 (d, $^3J_{CF}$ 5.0, C-3), 32.3 (s, C-2), 36.1 (d, $^2J_{CF}$ 21.0, C-4), 44.8 (s, CH_2Cl), 90.7 (d, $^1J_{CF}$ 164.4, CF).

4.2.1.2. 1-Bromohexane 5. 1-Bromohexane **5** (5.0 g, 30 mmol), elemental fluorine (60 mmol) and anhydrous acetonitrile (140 ml) gave an orange reaction mixture, which was decolourised using aqueous sodium metabisulfite and then worked up as above to give a yellow crude product mixture (6.2 g), which contained **5** (56%) and many unidentified products (>20). No further purification was attempted.

4.2.1.3. 1-Iodohexane 7. 1-Iodohexane **7** (8.0 g, 38 mmol), elemental fluorine (38 mmol) and anhydrous acetonitrile (ml) gave a red-purple reaction mixture, which was decolourised using aqueous sodium metabisulfite and then worked up as above to give a yellow crude product mixture (7.6 g), which contained many unidentified products (>20). No further purification was attempted.

4.2.1.4. Methyl enanthate 8. Methyl enanthate **8** (4.37 g, 30 mmol), elemental fluorine (91 mmol) and acetonitrile (140 ml) gave a brown crude product mixture (7.25 g), which contained **9a**, **9b**, **9c** and **9d** (2.14 g, 68%, 64% conv.) in the ratio 1.0:3.5:6.4:5.6, respectively, and a trace amount of methyl 7-fluoroenanthate; δ_F −217.23 (m) and several unidentified products (24%). Purification of the

crude product by preparative scale GC gave **9a–d** as a mixture of isomers and as a colourless liquid; (Found: C, 59.1; H, 9.3. $C_8H_{15}FO_2$ requires: C, 59.2; H, 9.3%); *methyl 3-fluoroenanthate* ***9a***: δ_F −183.62 (m); δ_C 92.4 (d, $^1J_{CF}$ 167.9, CHF), 173.9 (s, C═O); δ_H 0.80–1.00 (1H, m, CH_2 and/or CH_3), 1.27–1.65 (7H, m, CH_2 and/or CH_3), 2.30–2.38 (3H, m, CH_3), 3.67–6.68 (3H, m, OCH_3), 4.25–5.02 (1H, m, CHF); *methyl 4-fluoroenanthate* ***9b***: δ_F −180.08 (m); δ_C 90.6 (d, $^1J_{CF}$ 169.4, CHF), 174.6 (s, C═O); *methyl 5-fluoroenanthate* ***9c***: δ_F −182.8 (m); δ_C 95.4 (d, $^1J_{CF}$ 167.5, CHF), 174.1 (s, C═O); *methyl 6-fluoroenanthate* ***9d***: δ_F −173.14 (m); δ_C 21.2 (d, $^2J_{CF}$ 22.9, CH_3), 36.8 (d, $^2J_{CF}$ 20.6, CH_2CHF), 90.7 (d, $^1J_{CF}$ 164.5, CHF), 174.3 (s, C═O); other ^{13}C resonances that could not be assigned with certainty to each particular isomer, but are consistent with the structures of **9a–d** proposed, are as follows: δ_C 9.6 (d, J_{CF} 4.9, CH_3–B), 14.1 (s, CH_3–B), 14.2 (s, CH_3–B), 18.5 (s, CH_2), 18.6 (s, CH_2), 20.9 (d, J_{CF} 4.1, CH_2), 24.9 (d, J_{CF} 5.0, CH_2), 27.2 (d, J_{CF} 4.2, CH_2), 28.5 (d, $^2J_{CF}$ 22.6, CH_2CHF), 29.9 (d, J_{CF} 4.2, CH_2), 30.5 (d, $^2J_{CF}$ 21.4, CH_2CHF), 33.9 (s, CH_2), 34.2 (d, $^2J_{CF}$ 21.0, CH_2CHF), 34.8 (d, $^2J_{CF}$ 20.2, CH_2CHF), 37.4 (d, $^2J_{CF}$ 20.6, CH_2CHF), 40.5 (d, $^2J_{CF}$ 24.0, CH_2CHF), 51.7 (s, OCH_3), 51.8 (s, OCH_3), 51.8 (s, OCH_3), 51.9 (s, OCH_3); *m/z* (CI^+, NH_3) 180 (M^++18, 100%), all isomers gave similar results.

4.2.1.5. Octan-2-one 10. Elemental fluorine (120 mmol), octan-2-one (2.8 g, 24 mmol) and acetonitrile (140 ml) gave a brown oil (2.9 g, 64% conv.), which contained 7-fluoro-octan-2-one, 6-fluoro-octan-2-one and 5-fluoro-octan-2-one in the ratio 1.3:1.7:1. Purification of the crude product by column chromatography using hexane–ethyl acetate gave 7-fluoro-octan-2-one and 6-fluoro-octan-2-one as a yellow oil and as a mixture of isomers (1.0 g, 41%); *7-fluoro-octan-2-one*: δ_H 1.32 (dd, $^3J_{HF}$ 23.7, $^3J_{HH}$ 6.1, CH_3CFH), 1.35–1.6 (m), 2.10 (s, C═OCH_3), 4.25 (dm, $^2J_{HF}$ 45.4, C*H*F); δ_F 173.1 (dm, $^2J_{HF}$ 46.2); δ_C 21.1 (d, $^2J_{CF}$ 22.7, C-8), 23.7 (s, C-1), 24.8 (d, $^3J_{CF}$ 4.7, C-5), 30.0 (s, C-4), 36.8 (d, $^2J_{CF}$ 20.6, C-6), 43.7 (s, C-3), 90.6 (d, $^1J_{CF}$ 165.2, C-7), 208.8 (s, C-2); *m/z* (EI^+) 147.1 (M^++H, 3%), 146.0 (2), 126 (42), 41 (100); *6-fluoro-octan-2-one*: δ_H 0.9 (t, $^3J_{HH}$ 7.73, CH_3), 1.21–1.60 (m, CH_2), 2.11 (s, C═OCH_3), 2.43 (t, $^3J_{HH}$ 6.8, CH_2C═O), 4.44 (dm $^2J_{HF}$ 44.7, C*H*F); δ_F 182.3 (dtt, $^2J_{HF}$ 47.2, $^3J_{HF}$ 26.5, 20.5); δ_C 9.4 (d, $^3J_{CF}$ 5.8, C-8), 19.6 (d, $^3J_{CF}$ 4.0, C-4), 23.7 (s, C-1), 28.2 (d, $^2J_{CF}$ 21.8, C-7), 34.1 (d, $^2J_{HF}$ 21.0, C-5), 43.4 (s, C-3), 94.5 (d, $^1J_{HF}$ 165.5, C-6), 209.0 (s, C-1); *m/z* (EI^+) 146.1 (M^++H, 1%), 126.1 (12), 42 (100); *5-fluoro-octan-2-one*: δ_F 183.3 (dm, $^2J_{HF}$ 46.2); *m/z* (EI^+) 146.1 (M^++H, 1%), 126.1 (12), 42 (100).

4.2.1.6. Heptanal 12. Elemental fluorine (234 mmol) as a 10% (v/v) mixture with nitrogen was passed through a cooled (0 °C) and stirred mixture of heptanal (6.61 g, 58 mmol) and acetonitrile (140 ml). After all the fluorine has been added, 3,5-dinitrobenzyl alcohol **14** (5.0 g, 25 mmol) was added to the reaction mixture, which was then heated for 24 h at reflux temperature. After the usual work up and drying, a brown crude product was obtained and purification by column chromatography using dichloromethane as eluent gave *(3,5-dinitrophenyl)methyl heptanoate* **15** (2.57 g, 39%) as a pale yellow solid; mp 38–40 °C; (Found: C, 53.9; H, 5.8; N, 8.9. $C_{14}H_{18}N_2O_6$ requires C, 54.2; H, 5.9; N, 9.0%); δ_H 0.87 (3H, t, $^3J_{HH}$ 7.2, CH_3), 1.29 (6H, m, CH_2), 1.66 (2H, m, CH_2), 2.44 (2H, t, $^3J_{HH}$ 7.6, H-6), 5.29 (2H, s, H-8), 8.54 (2H, m, ArH), 8.99 (1H, m, ArH); δ_C 13.9 (s, CH_3), 22.4 (s, C-2), 24.7 (s, C-3), 28.7 (s, C-4), 31.3 (s, C-5), 33.9 (s, C-6), 63.5 (s, CH_2O), 118.4 (s, ArH), 127.7 (s, ArH), 140.8 (s, Ar), 148.6 (s, $ArNO_2$), 173.1 (s, C═O); *m/z* (EI^+) 223 (54), 181 (48), 129 (13), 43 (100).

4.3. Fluorinations using Selectfluor™ 2

4.3.1. General procedure. A solution consisting of **2**, substrate and acetonitrile (130 ml) was stirred and heated (65 °C). After 24 h, the reaction mixture was poured into water, neutralised ($NaHCO_3$) and extracted with dichloromethane (3×50 ml). The combined, dried ($MgSO_4$), organic extracts were evaporated to give a crude product, which was analysed by GC–MS and ^{19}F NMR as described above and purified by column chromatography.

4.3.1.1. 1-Chlorohexane 3. 1-Chlorohexane **3** (8.00 g, 67 mmol), **2** (25.96 g, 73 mmol) and acetonitrile (260 ml) gave a dark yellow product (8.24 g). Purification of the crude product by preparative scale GC gave an analytically pure sample of 1-chloro-2-fluorohexane, 1-chloro-3-fluorohexane, 1-chloro-4-fluorohexane and 1-chloro-5-fluorohexane (2.75 g, 56%, 53% conv.) as a mixture of isomers, in the ratio 1.0:2.7:5.2:10.1, respectively, as a yellow oil; spectral data as above.

4.3.1.2. 1-Bromohexane 5. 1-Bromohexane **5** (5.00 g, 30 mmol), **2** (11.80 g, 33 mmol) and acetonitrile (120 ml) gave a dark yellow product (7.93 g), which contained **6a**, **6b** and **6c** (1.10 g, 75%, 30% conv.) in the ratio 1.0:1.9:3.8, respectively, and a large number of other unidentified products (10%). Purification by preparative scale GC gave an analytically pure sample of 1-bromo-4-fluorohexane **6b** and 1-bromo-5-fluorohexane **6c** as a mixture of isomers and as a colourless oil; (Found: C, 39.6; H, 6.7. $C_6H_{12}BrF$ requires: C, 39.3; H, 6.6%); *1-bromo-4-fluorohexane* ***6b***: δ_H 0.98 (3H, t, $^3J_{HH}$ 7.6, CH_3), 1.2–2.0 (6H, m, CH_2), 3.40 (2H, m, CH_2Br), 4.43 (1H, dm, $^2J_{HF}$ 48.8, CHF); δ_F −181.18 (m); δ_C 9.3 (d, $^3J_{CF}$ 5.7, CH_3), 28.1 (d, $^2J_{CF}$ 21.0, C-5), 28.4 (d, $^3J_{CF}$ 3.8, C-2), 33.2 (d, $^2J_{CF}$ 20.9, C-3), 33.6 (s, C-1), 94.8 (d, $^1J_{CF}$ 168.3, CF); *m/z* (EI^+) 102 (M^+−HBr, 10%), 83 (31), 74 (52), 55 (100); *1-bromo-5-fluorohexane* ***6c***: δ_H 1.32 (3H, dd, $^3J_{HF}$ 23.0, $^3J_{HH}$ 6.0, CH_3), 1.2–2.0 (6H, m, CH_2), 3.40 (2H, m, CH_2Br), 4.66 (1H, dm, $^2J_{HF}$ 48.8, CHF); δ_F −171.83 (m); δ_C 21.0 (d, $^2J_{CF}$ 22.8, CH_3), 23.8 (d, $^3J_{CF}$ 4.6, C-3), 32.5 (s, C-2), 33.5 (s, CH_2Br), 35.9 (d, $^2J_{CF}$ 20.6, C-4), 90.7 (d, $^1J_{CF}$ 164.9, CHF).

4.3.1.3. 1-Iodohexane 7. 1-Iodohexane **7** (5.0 g, 24 mmol), **2** (9.2 g, 26 mmol) and acetonitrile (90 ml) gave, after 16 h of stirring, a red-purple reaction mixture, which was decolourised using aqueous sodium metabisulfite and then worked up as above to give a yellow crude product mixture (7.3 g), which contained >30 unidentified products by GC–MS. No further purification was attempted.

4.3.1.4. Methyl enanthate 8. Methyl enanthate **8** (4.00 g, 28 mmol), **2** (13.66 g, 31 mmol) and acetonitrile (140 ml)

gave a yellow product (4.68 g), which contained **9a**, **9b**, **9c** and **9d** (1.24 g, 48%, 57% conv.) as a mixture of isomers in the ratio 1.0:1.3:1.3:3.7, respectively, and as a colourless liquid; spectral data as above.

4.3.1.5. Octan-2-one 10. Octan-2-one **10** (5.00 g, 39 mmol), **2** (15.25 g, 43 mmol) and acetonitrile (150 ml) gave a yellow crude mixture (17.13 g), which contained **11e** (65%). Preparative GC gave an analytical sample of 3-fluoro-octan-2-one **11e** as a colourless liquid; (Found: C, 65.4; H, 10.4. $C_7H_{13}F$ requires C, 65.7; H, 10.3%); ν_{max}/cm^{-1} 1726 (C=O), 1081 (C–F); δ_H 0.89 (3H, m, CH_3), 1.31 (4H, m, H-6, H-7), 1.39 (2H, m, H-5), 1.8 (2H, m, H-4), 2.25 (3H, m, C=OCH_3), 4.65 (1H, m, CHF); δ_C 13.9 (s, C-8), 22.4 (s, C-7), 24.1 (d, $^3J_{CF}$ 3, C-5), 25.9 (s, C-1), 31.3 (s, C-6), 31.8 (d, $^2J_{CF}$ 21, C-4), 96.0 (d, $^1J_{CF}$ 185, C-3), 208.8 (d, $^2J_{CF}$ 25, C-2); δ_F −189.94 (m); *m*/*z* (EI$^+$) 146 (M$^+$, 4%), 111 (0.2), 99 (0.9), 76 (31), 55 (8).

4.3.1.6. Heptanal 12. Heptanal **12** (5.00 g, 44 mmol), **2** (17.04 g, 48 mmol) and acetonitrile (150 ml) gave a dark brown crude mixture (4.66 g), which contained many unidentified components by GC–MS and ^{19}F NMR analysis. No further purification was attempted.

Acknowledgements

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References and notes

1. For Part 18, see: Chambers, R. D.; Fox, M. A.; Sandford, G. *Lab Chip* **2005**, *5*, 1132.
2. Banks, R. E.; Smart, B. E.; Tatlow, J. C. *Organofluorine Chemistry: Principles and Commercial Applications*; Plenum: New York, NY, 1994.
3. Chambers, R. D. *Fluorine in Organic Chemistry*; Blackwell: Oxford, 2004.
4. Rozen, S. *Acc. Chem. Res.* **1988**, *21*, 307.
5. Chambers, R. D.; Parsons, M.; Sandford, G.; Moilliet, J. S. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2190.
6. Lal, G. S.; Pez, G. P.; Syvret, R. G. *Chem. Rev.* **1996**, *96*, 1737.
7. Differding, E.; Ruegg, G. M. *Tetrahedron Lett.* **1991**, *32*, 3815.
8. Vincent, S. P.; Burkhart, M. D.; Tsai, C.; Zhang, Z.; Wong, C. *J. Org. Chem.* **1999**, *64*, 5264.
9. Poutsma, M. L. *Free Radicals*; Kochi, J. K., Ed.; Wiley: New York, NY, 1973; Vol. 2, p 159.
10. Nonhebel, D. C.; Walton, J. C. *Free-radical Chemistry*; CUP: Cambridge, 1974.
11. Fossey, J.; Lefort, D.; Sorba, J. *Free Radicals in Organic Chemistry*; Wiley-Interscience: New York, NY, 1995.
12. Anson, P. C.; Tedder, J. M. *J. Chem. Soc.* **1957**, 4390.
13. Tedder, J. M. *Adv. Fluorine Chem.* **1961**, *2*, 104.
14. Hutchinson, J.; Sandford, G. *Topics in Current Chemistry*; Chambers, R. D., Ed.; Springer: Berlin, 1997; Vol. 193, p 1.
15. Adcock, J. L.; Evans, W. D.; Heller-Grossman, L. *J. Org. Chem.* **1983**, *48*, 4953.
16. Banks, R. E.; Lawrence, N. J.; Popplewell, A. L. *Synlett* **1994**, 831.

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Highly enantioselective fluorination reactions of β-ketoesters and β-ketophosphonates catalyzed by chiral palladium complexes

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Abstract—Using chiral palladium enolates as key intermediates, efficient catalytic enantioselective fluorination reactions of active methine compounds have been developed. These reactions can be conducted in alcoholic solvents without any precaution to exclude water and moisture, and various β-ketoesters and β-ketophosphonates were fluorinated in a highly enantioselective manner (up to 98% ee).

1. Introduction

Acquisition of novel activity distinct from that of the parent compound by replacing atom(s) in a biologically active compound with other atom(s) is a very important aspect of medicinal chemistry. In particular, introduction of fluorine, which rarely occurs in natural products, into bioactive compounds sometimes leads to significant improvement of their biological activity profiles,[1] probably due to the unique properties of the fluorine atom and/or the carbon–fluorine bond (Chart 1).

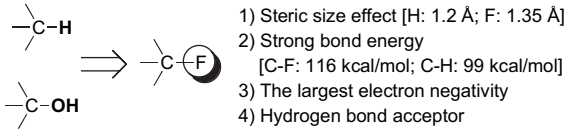

Chart 1. Properties of the fluorine atom and carbon–fluorine bonds.

For this reason, the effect of fluorine-substitution is often examined in the course of development of new drug candidates. Most such investigations have focused on replacement of hydrogen(s) on an aromatic ring with fluorine atom(s). The effect of substitution at sp^3 carbons has been less well investigated. For the synthesis of chiral fluorinated compounds, application of well-established asymmetric reactions, including hydrogenation of olefins, reduction of ketones, aldol reactions, and ene reactions, to fluorinated starting materials is an important strategy, and thus chiral compounds, which do not have a fluorine atom at a chiral carbon center can be utilized for the preparation of fluorinated drug candidates.[2,3] However, the use of optically active compounds bearing a fluorine atom at a chiral carbon center is restricted by the limited availability of effective methods for enantioselective construction of fluorinated stereogenic carbon centers. Thus, enantioselective synthesis of organofluorine compounds via direct introduction of fluorine atoms is still a highly desirable goal in synthetic organic chemistry.[4] In addition to diastereoselective fluorination reactions,[5] great efforts have been made to develop chiral fluorinating reagents.[6] Shibata et al. and Cahard et al. independently reported an ingenious procedure that allows in situ generation of a chiral fluorinating reagent from cinchona alkaloids and Selectfluor (see Chart 3).[7] Since the initial reports by Togni et al., catalytic enantioselective fluorination reactions have been attracting much attention.[8,9] In 2002, on the basis of our palladium enolate chemistry, we developed an efficient method for enantioselective fluorination reactions with high generality as regards β-ketoesters.[10] Subsequent studies from other laboratories revealed that late transition metal complexes consisting of Cu(II), Ni(II), and Zn(II) were also excellent catalysts for catalytic enantioselective fluorination reactions of active methine compounds.[11] Several groups have reported attempts at applying organocatalysis to asymmetric fluorination reactions, and catalytic enantioselective monofluorination of aldehydes having two hydrogens at the α-position has been achieved.[12,13] Although the scope of available substrates for asymmetric fluorination reactions is rapidly expanding, continuing exploitation of novel catalysts, including metal

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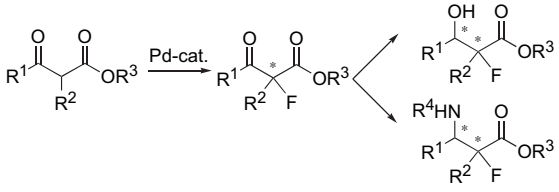
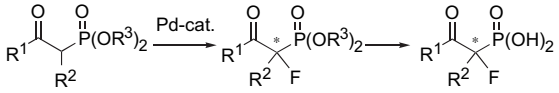
complexes and organic catalysts, is necessary to meet the need for various chiral fluorinated compounds, many of which are expected to find applications in the fields of medicinal chemistry, chemical biology, and material sciences. Herein, we present full details of our study on the catalytic enantioselective fluorination reactions of β-ketoesters and β-ketophosphonates (Eqs. 1 and 2).[10] Our palladium complexes were effective catalysts for such active methine compounds, affording the corresponding fluorinated products in a highly enantioselective manner (up to 98% ee). We confirmed the utility of our methods by stereoselective syntheses of fluorinated derivatives of fundamental units found in biologically active natural and unnatural compounds.



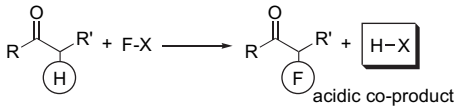
(1)



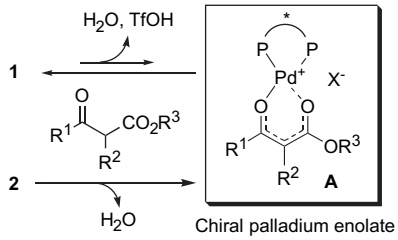
(2)

2. Results and discussion

In principle, electrophilic fluorination reactions of carbonyl compounds entail concomitant generation of an acidic coproduct during the reaction (Eq. 3). It seems difficult to carry out the reaction in the presence of strongly basic catalysts to remove a hydrogen atom at the α-position, because decomposition or neutralization of the catalysts might occur. Thus, activation of the nucleophiles under acidic or neutral conditions would be a promising alternative approach to carry out enantioselective electrophilic fluorination catalytically. We have already reported that the cationic palladium complexes **1** and **2** reacted with 1,3-dicarbonyl compounds, such as β-ketoesters, to form chiral palladium enolates **A** (Chart 2 and Scheme 1).[14] Because the palladium aqua and μ-hydroxo complexes are inherently acidic or neutral, this enolate formation is considered to occur under nonbasic conditions. We envisaged that this palladium enolate chemistry would be applicable to enantioselective electrophilic fluorination reactions. Development of the fluorination reactions of β-ketoesters is valuable, because optically active α-substituted α-fluoro-β-ketoesters are regarded as nonenolizable β-ketoesters. In addition, since ketone is easily converted to other functional groups, α-substituted α-fluoro-β-ketoesters would be versatile synthetic precursors of various α-fluorinated carboxylic acid derivatives. Therefore, we planned to examine the enantioselective fluorination reactions of β-ketoesters using the palladium complexes **1** and **2**.

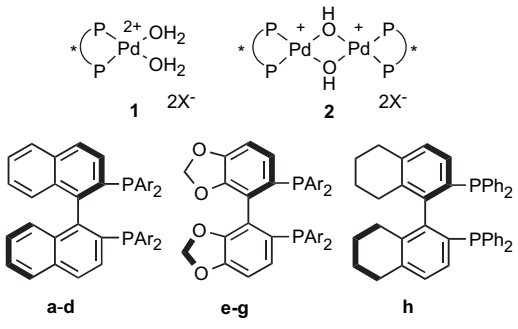


(3)



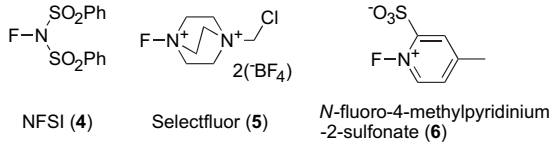
Scheme 1. Formation of chiral palladium enolates.

Since a bulky ester moiety was found to be essential for high asymmetric induction in our previous study on catalytic asymmetric Michael reactions,[14] we chose *tert*-butyl 2-oxo-cyclopentanecarboxylate **3a** as a model substrate. Among several electrophilic fluorinating reagents, *N*-fluorobenzenesulfonimide (NFSI) **4** was the most effective (Chart 3). While salt-type reagents, such as **5** and **6**, did not give the desired product **7a** in a detectable amount, the reaction of **3a** with **4** under the influence of **1a** (5 mol %) in THF proceeded smoothly to afford **7a** in 72% yield with 79% ee (Table 1, entry 1). It should be noted that the palladium complex retained its catalytic activity until the completion of the reaction. In contrast, a stoichiometric amount of a conventional base would be required for the reaction with NFSI, because sulfonimide [$(PhSO_2)_2NH$] with high acidity was formed during the reaction. Therefore, our reaction system was considered suitable for the development of fluorination reactions.



a: Ar = Ph: (*R*)-BINAP
b: Ar = 4-MeC_6H_4: (*R*)-Tol-BINAP
c: Ar = 4-$MeOC_6H_4$: (*R*)-MeO-BINAP
d: Ar = 3,5-$Me_2C_6H_3$: (*R*)-DM-BINAP
e: Ar = Ph: (*R*)-SEGPHOS
f: Ar = 3,5-$Me_2C_6H_3$: (*R*)-DM-SEGPHOS
g: Ar = 3,5-(*t*-Bu)$_2$-4-$MeOC_6H_2$: (*R*)-DTBM-SEGPHOS
h: (*R*)-H_8-BINAP

Chart 2. Chiral palladium complexes.

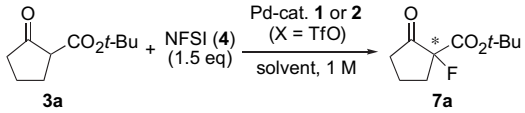


NFSI (**4**) Selectfluor (**5**) *N*-fluoro-4-methylpyridinium -2-sulfonate (**6**)

Chart 3. Electrophilic fluorinating reagents examined in this study.

To improve the enantioselectivity, we examined a series of chiral phosphine ligands. Among the diphosphines, bulkier ligands bearing substituents at the *meta* positions of aryl group on phosphine gave better enantioselectivity (entries

Table 1. Optimization of the reaction conditions



3a 7a

Entry	Catalyst[a] (mol %)[b]	Solvent	Temp (°C)	Time (h)	Yield[c] (%)	ee[d] (%)
1	**1a** (5)	THF	−20	12	72	79
2	**1b** (5)	THF	−20	12	87	83
3	**1c** (5)	THF	−20	7.5	92	80
4	**1d** (5)	THF	−20	39	99	88
5	**1e** (5)	THF	−20	39	82	71
6	**1g** (5)	THF	0	72	89	90
7	**1h** (5)	THF	−20	7.5	92	82
8	**2g** (2.5)	THF	10	48	83	92
9	**2g** (2.5)	Acetone	10	48	93	92
10	**2g** (2.5)	EtOH	20	18	73	92
11	**2g** (2.5)	*i*-PrOH	20	18	90	92
12	**2g** (2.5)	*t*-BuOH	20	18	68	93

[a] **1**–**2**: Catalyst structure; **a**–**h**: chiral ligand.
[b] Catalyst amount.
[c] Isolated yield.
[d] Determined by chiral HPLC analysis.

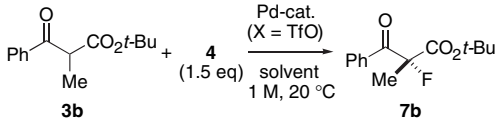
4 and 6), while substituents at the *para* position and semi-reduction of the binaphthyl scaffold did not significantly influence the reaction efficiency (entries 2, 3, and 7).[15] In contrast to the Michael reaction, the use of the Pd μ-hydroxo complex **2g** also promoted the reaction smoothly,[16] and the best selectivity of 92% ee was observed (entry 8). This difference in reactivity may be attributed to the higher electrophilicity of NFSI than that of the enone. Further optimization of the reaction conditions revealed that the reaction proceeded more rapidly in polar solvents (entries 9–12). Interestingly, an alcoholic solvent such as EtOH or *i*-PrOH was the best of those tested and the reaction time was reduced from 48 h to 18 h without any loss of enantioselectivity (entries 10 and 11). In the case of *t*-BuOH, however, the reaction was retarded and the starting material was not consumed completely after 18 h (entry 12).

A conspicuous solvent effect was observed when **3b** was tested as a substrate (Table 2). Probably because of steric repulsion derived from the phenyl ring of the substrate, the reaction did not proceed when **1g** was used (entry 1). The less bulky **1d** promoted the reaction, but the reaction in THF was sluggish, giving rise to **7b** in 63% yield with 82% ee after more than 250 h (entry 2). Fortunately, dramatic acceleration of the reaction was observed when EtOH was used as a solvent. The reaction reached completion after 48 h, affording the desired product in 96% yield with 91% ee (entries 3 and 4). Even when the concentration was reduced from 1 M to 0.1 M, **7b** was isolated in 54% yield, maintaining the same enantioselectivity (entry 5). ^{1}H NMR study revealed that stoichiometric reaction of **3a** with **2b** (0.5 equiv to **3a**) was completed within 10 min in CD_3OD, while the same reaction in THF-d_8 took 2 h for completion.[14a] Thus, we speculated that alcoholic solvents played a key role for rapid formation of the chiral palladium enolates, thereby significantly accelerating the reaction.

Because the palladium complexes are stable to water, the reaction could be performed in aqueous solvent systems (entries 6–9). Interestingly, the reaction in water without co-solvents proceeded at a synthetically useful level to give **7b** in 76% yield with 89% ee (entry 9).

With the optimized reaction conditions in hand, we next examined the generality of our fluorination reaction. As summarized in Table 3, other cyclic and acyclic β-ketoesters were converted to the desired products smoothly in the presence of 2.5 mol % of the palladium complexes. Except for **3g**, the desired fluorinated compounds were obtained in a highly enantioselective manner (up to 94% ee). As in the case of **3a**, the reaction of **3c** using **2d** gave the product with 94% ee, while a slight decrease of enantioselectivity was observed when **1d** was used (entries 1 and 7). In entry 3, the isolated chemical yield was lower due to the volatility of **7e**, but the excellent ee of 91% was observed. In contrast to **3f**, the reaction of **3g**, which has a different substitution

Table 2. Solvent effect on the reaction of **3b**

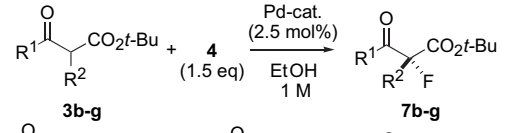


3b 7b

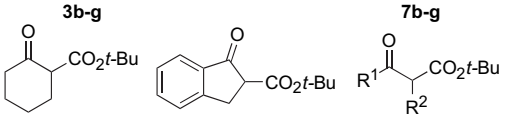
Entry	Catalyst (mol %)	Solvent	Time (h)	Yield (%)	ee (%)
1	**1g** (5)	THF	—	No reaction	
2	**1d** (5)	THF	255	63	82
3	**1d** (5)	EtOH	48	96	91
4[a]	**2d** (2.5)	EtOH	40	92	91
5[b]	**2d** (2.5)	EtOH	40	54	91
6	**2d** (2.5)	EtOH/H_2O (1/1)	66	57	78
7	**2d** (2.5)	EtOH/H_2O (4/1)	120	53	85
8	**2d** (2.5)	Acetone/H_2O (9/1)	96	73	88
9	**2d** (2.5)	H_2O	75	76	89

[a] X=BF_4.
[b] 0.1 M.

Table 3. Catalytic enantioselective fluorination reactions of β-ketoesters



3b-g 7b-g



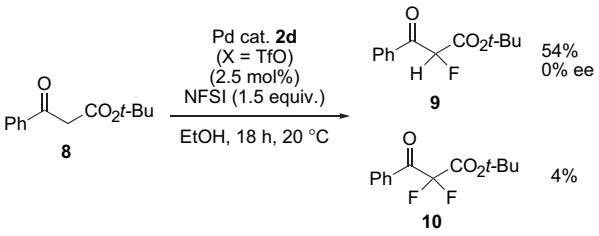
3c 3d

3e: R^1 = Me, R^2 = Me
3f: R^1 = Me, R^2 = Et
3g: R^1 = Et, R^2 = Me

Entry	**3**	Catalyst (X)	Temp (°C)	Time (h)	Yield (%)	ee (%)
1	**3c**	**2d** (BF_4)	−10	20	91	94
2	**3d**	**2d** (TfO)	−20	36	85	83[a]
3	**3e**	**2f** (TfO)	20	72	49[b]	91
4	**3f**	**2d** (TfO)	20	42	88	87
5	**3g**	**2d** (TfO)	20	72	47	69
6[c]	**3c**	**2d** (BF_4)	0	20	82	91
7	**3c**	**1d** (TfO)	−10	20	95	92
8[d]	**3b**	**1d** (TfO)	20	48	96	91[a]

[a] The absolute configuration was determined to be *R* after conversion to the known compound.
[b] Lower yield due to the volatility of **7e**.
[c] Compound **2d** (1 mol %).
[d] One gram scale.

pattern from **3f**, was slower and less enantioselective. Thus, **7g** was obtained in only 47% yield with 69% ee after 72 h. Even when the amount of catalyst was reduced to 1 mol %, comparable results were obtained (entry 6). It is also noteworthy that this reaction could be easily scaled up using reagent-grade non-distilled EtOH as a solvent (entry 8). In these reactions, we found that **2d** and **2g** were effective catalysts, and various substrates were selectively fluorinated by employing either of these two ligands according to the nature of the β-ketoesters. Notably, it is environmentally advantageous that this reaction proceeds well in alcoholic solvents and even in water. Unfortunately, the reaction of α-nonsubstituted β-ketoester **8** was unsuccessful (Scheme 2). Because the corresponding product **9** was more susceptible to enolization than **8**, no asymmetric induction was observed and a difluorinated compound **10** was obtained in 4% yield.

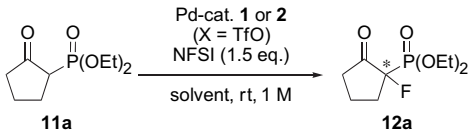


Scheme 2. Fluorination of α-nonsubstituted β-ketoester.

Encouraged by the success in the fluorination reactions of β-ketoesters, we next turned our attention to other active methine compounds. We envisaged that other bidentate carbonyl compounds would react with Pd complexes to form similar chiral palladium enolates. Among several candidates, we focused on β-ketophosphonates[17] because difluoro- and monofluorophosphonates have been utilized in drug design as mimics of phosphates.[18,19] Compared with non-fluorinated phosphonates and difluorophosphonates, α-monofluorophosphonates are expected to be a better surrogate of phosphates, because they show similar second pK_a values (~6.5) to those of biological phosphates (~6.5).[18] Although several non-enantioselective or diastereoselective syntheses of α-monofluorophosphonates have been reported,[20] there was no example of the catalytic enantioselective synthesis of chiral α-fluoro-β-ketophosphonates before we started our investigation. Independently, Jørgensen and Kim recently reported similar reactions using Zn(II)–Ph–DBFOX complexes and Pd–BINAP complexes, respectively.[11e,f]

Similar optimization of the reaction conditions using **11a** as a model substrate revealed that the combination of **1d** as a catalyst and EtOH as a solvent was the most appropriate for the fluorination of β-ketophosphonates (Table 4). Thus, when 5 mol % of **1d** was used in EtOH, the reaction of **11a** reached completion after only 2 h to give the desired fluorinated product **12a** in 91% yield (entry 3). Gratifyingly, the ee of the product was determined to be 95% by chiral HPLC analysis. When a bulkier ligand such as DTBM-SEGPHOS was used, a higher enantioselectivity of 98% was observed (entry 5), but the reaction rate was considerably decreased, probably due to severe steric repulsion. EtOH was found to be superior to other solvents in terms of chemical yield and enantioselectivity (entries 6–9). In this fluorination of

Table 4. Optimization of the reaction conditions



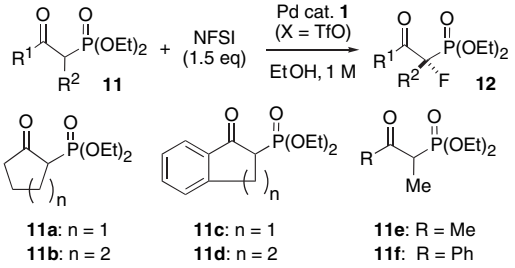
Entry	Catalyst (mol %)	Solvent	Time (h)	Yield[a] (%)	ee[b] (%)
1	**1a** (5)	EtOH	5	81	75
2	**1b** (5)	EtOH	5	82	79
3	**1d** (5)	EtOH	2	91	95
4	**1f** (5)	EtOH	2	87	95
5	**1g** (5)	EtOH	5	46	98
6	**1d** (5)	Acetone	3	70	93
7	**1d** (5)	THF	3	66	92
8	**1d** (5)	DMF	6	20	90
9	**1d** (5)	CH_2Cl_2	6	43	92
10	**2d** (2.5)	EtOH	2	91	95

[a] Isolated yield.
[b] Determined by HPLC analysis.

β-ketophosphonates, the Pdμ-hydroxo complex **2d** gave results comparable to those obtained using **1d** (entry 10).

This catalytic system was also applicable to various substrates including cyclic and acyclic β-ketophosphonates (Table 5). All the substrates examined were fluorinated in a highly enantioselective manner (up to 97% ee). As shown in entries 1 and 6, the reactions smoothly proceeded in the presence of as little as 1 mol % of the catalyst without deterioration of the reaction efficiency. When the reaction was carried out at 0 °C, the ee was improved to 97% ee (entry 5). In contrast to cyclic β-ketophosphonates, the reaction of acyclic substrates was found to be slow (entries 7 and 8). The starting materials **11e** and **11f** were not consumed at 40 °C even after 48 h. Although the chemical yield was modest to good, the ees of the products were found to be excellent (94 and 95% ee, respectively). For these reactions, **1f** gave

Table 5. Catalytic enantioselective fluorination of β-ketophosphonates

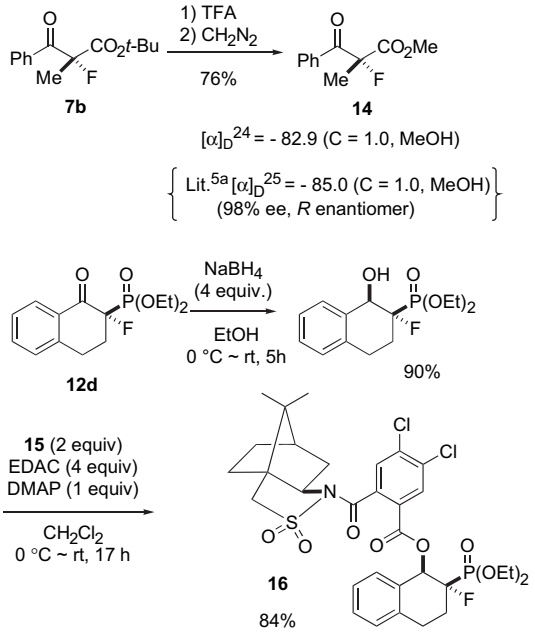


Entry	11	Catalyst (mol %)	Temp (°C)	Time (h)	Yield[a] (%)	ee[b] (%)
1	**11a**	**1d** (1)	rt	12	82	95
2	**11b**	**1d** (5)	rt	8	93	96
3	**11c**	**1d** (5)	rt	3	84	95
4	**11d**	**1d** (5)	rt	3	97	94[c]
5	**11d**	**1d** (5)	0	24	90	97
6	**11d**	**1d** (1)	rt	7	83	95
7	**11e**	**1f** (10)	40	48	57	94[d]
8	**11f**	**1f** (10)	40	48	38	95

[a] Isolated yield.
[b] Determined by HPLC analysis.
[c] The absolute configuration was determined by X-ray analysis.
[d] The ee was determined after conversion to the corresponding 2,4-dinitrophenylhydrazone **13**.

a slightly better selectivity than **1d**. Similarly decreased reaction rates in the case of acyclic substrates were noted in Kim's report.[11e] They examined various acyclic β-ketophosphonates employing Pd complexes similar to our Pd aqua complexes **1**, and longer reaction times (58–94 h) were required to obtain the products in yields ranging from 50–79%.

To establish the absolute configuration of these fluorinated products, the following conversion of **7b** and **12d** was carried out (Scheme 3). As described previously,[21] the absolute configuration of **7b** was determined to be *R* by comparison of optical rotation of **14** with the reported value.[5a] In addition, *R* configuration was observed in the case of **7d** after conversion to 2-fluoro-2-methyl indanone, whose optically active form was previously synthesized by Shibata and Takeuchi.[6c,7a,21] To determine the absolute stereochemistry of the fluorinated β-ketophosphonate **12d**, we planned to attach a chiral auxiliary in some way, because no appropriate reference compound could be found in the literature. Thus, stereoselective reduction with $NaBH_4$, followed by esterification with *N*-(2-carboxy-4,5-dichlorobenzoyl)-(−)-10, 2-camphorsultam (**15**) gave **16** in good yield.[22] Recrystallization of **16** from hexane/ethyl acetate (3/1) gave a single crystal suitable for X-ray structural analysis. As shown in Figure 1, on the basis of the known structure of (−)-camphorsultam, the absolute configuration of **12d** was unequivocally determined to be *S*.



Scheme 3. Determination of the absolute configuration of the products.

Because formation of the chiral palladium enolates was observed using ^1H NMR in the cases of both β-ketoesters and β-ketophosphonates,[10,14] we believe that these enolates are key intermediates in the fluorination reactions. If structurally similar enolates are generated in the reaction mixture, the absolute configuration observed in these reactions indicates that the fluorinating reagent reacts from the less hindered side of the enolates with the same sense of enantioselection (Fig. 2). In the case of β-ketoesters, a bulky *tert*-butyl group would be located at one enolate face to avoid steric repulsion

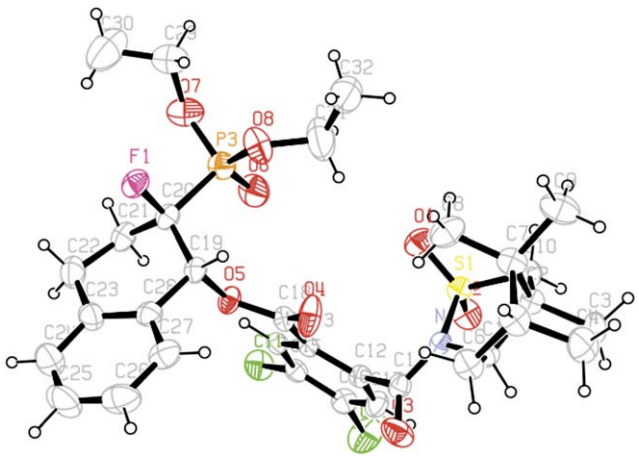


Figure 1. X-ray structure of **16**.

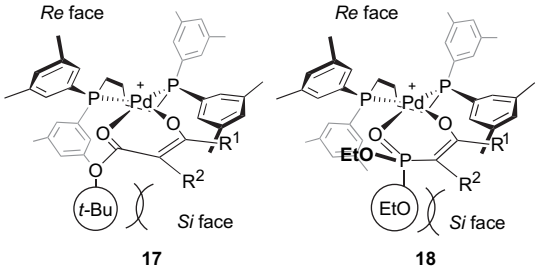
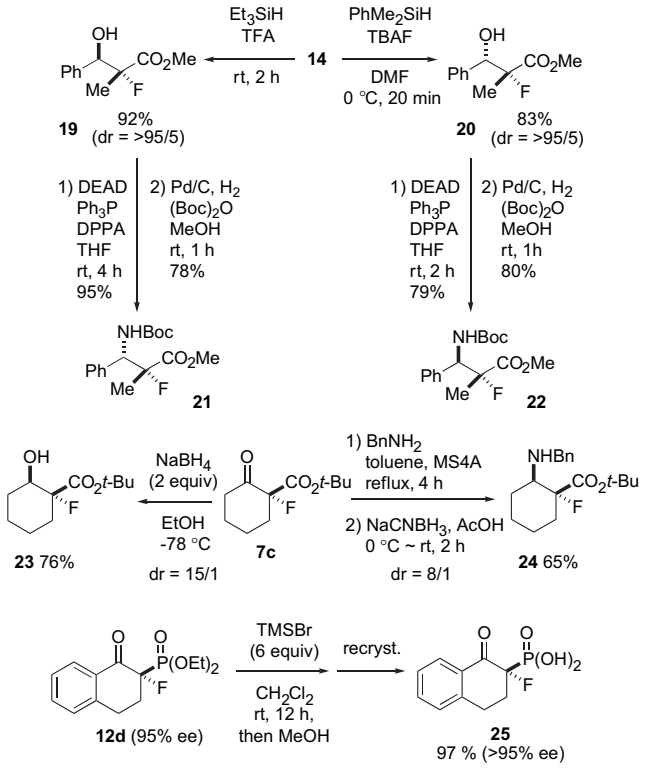


Figure 2. Plausible transition state models.

with the 3,5-dimethylphenyl group of the ligand. Thus, the *si*-face of the enolate **17** might be effectively shielded by the *tert*-butyl group and the aryl group on phosphine, forcing NFSI to approach from the *re*-face of the enolate. The face discrimination in the case of β-ketophosphonates can also be explained by postulating involvement of a similar intermediate. But, the structure of the corresponding enolate would be more complex because of the sp^3-hybridization of the phosphorus atom of the substrate. Likewise, the two ethoxy groups of the β-ketophosphonates **11** would be positioned to cause minimum steric repulsion with the aryl group on phosphine. Comparing **18** with **17**, the *si*-face of the enolate **18** seems more crowded than that of **17**, since one of the ethoxy groups should be oriented much closer to the reactive center. This speculation is in accord with the better enantioselectivity observed in the case of β-ketophosphonates than that of β-ketoesters.

Finally, to confirm the synthetic utility of our fluorination reactions, transformation of the fluorinated products was investigated (Scheme 4). Because β-hydroxy or β-amino acids are fundamental units in various natural or unnatural compounds, their α-fluorinated derivatives are of particular interest. First, conventional reduction with $NaBH_4$ in the presence of Lewis acids was examined, but it gave only a mixture of the reduced products **19** and **20** (~1/6). According to the reported procedure,[23] we next tried reduction with silanes. Although the use of $AlCl_3$ as an activator of the ketone was unsuccessful, the reaction in TFA afforded **19** in a highly diastereoselective manner. We previously reported that reduction with Ph_3SiH afforded **19** in 75% yield. When this silane was switched to Et_3SiH, the chemical yield

was improved to 92%. The relative configuration can be explained by assuming a chelation model. In addition, Lewis base activation of $PhMe_2SiH$ was found to be effective for stereoselective reduction (dr≥95/5).[23] This reaction is likely to proceed according to a Felkin–Anh model, and another diastereomer **20** was produced in 83% isolated yield. These compounds were subjected to azidation with inversion of configuration. Reduction of the azide group, followed by protection of the amino group, afforded the α-fluoro-β-amino esters **21** and **22** in good yields. Enantioenrichment of **21** by recrystallization from ethyl acetate was possible, and optically pure **21** was obtained (>99% ee). In addition, the cyclic fluorinated product **7c** was also converted to **23** as a major diastereomer in 76% yield. Relative stereochemistry of **23** was deduced from a comparison of the coupling constants of the methine proton adjacent to the hydroxyl group against the fluorine atom, which are larger than those between protons (**23**: J_{H-F}=10.0 Hz; minor isomer: J_{H-F}=24.0 Hz).[24] In the presence of benzylamine and $NaCNBH_3$, **7c** underwent reductive amination to give **24** as the major product in 65% yield (coupling constants of the methine protons; **24**: J_{H-F}=12.7 Hz; minor: J_{H-F}=27.6 Hz).[24] A further example is as follows. To evaluate the ability of the fluorinated phosphonates to act as phosphate mimics, dealkylation of **12d** is essential. When **12d** was treated with 6 equiv of TMSBr in CH_2Cl_2, removal of two ethyl groups occurred readily, affording the desired phosphonic acid **25** in excellent yield.[25]



Scheme 4. Conversion of the fluorinated products.

3. Conclusion

Using chiral palladium enolates as key intermediates, highly enantioselective fluorination reactions of β-ketoesters and β-ketophosphonates have been developed. Our reactions are operationally convenient because special precautions to exclude air and moisture are unnecessary, and reagent-grade non-distilled alcoholic solvents could be used as reaction media. In addition, transformation of the fluorinated products was successfully demonstrated, and the availability of these fluorinated fundamental units should be valuable in medicinal chemistry. Further studies to expand the scope of the fluorination reactions and their application for the development of enzyme inhibitors are under way in our laboratory.

4. Experimental

4.1. General

All asymmetric reactions were carried out without precautions to exclude air and moisture. Catalysts used in this paper were prepared according to the reported procedure.[10a,26] NMR spectra were recorded on a JEOL JNM-LA400 spectrometer, operating at 400 MHz for ^{1}H NMR and 100.4 MHz for ^{13}C NMR. Chemical shifts were reported downfield from TMS (=0) for ^{1}H NMR. For ^{13}C NMR, chemical shifts were reported relative to the solvent used as an internal reference. ^{19}F NMR was measured at 400 or 376 MHz, and CF_3COOH was used as an external standard. FAB–LRMS and FAB–HRMS were taken on JEOL JMS GCmate II using *m*-nitrobenzyl alcohol (*m*NBA) as a matrix. Optical rotations were measured on a JASCO DIP-370 polarimeter. Column chromatography was performed with silica gel 60 (40–100 μm) purchased from Kanto Chemical Co. The enantiomeric excesses (ees) were determined by HPLC or GC analysis. HPLC analysis was performed on Shimadzu HPLC systems consisting of the following components: pump, LC-10AD; detector, SPD-10A set at 254 or 280 nm; column, DAICEL CHIRALPAK AS, AD-H, and CHIRALCEL OJ-H; mobile phase, hexane/2-propanol (IPA). GC analysis was performed on Shimadzu GC-17A with Tokyo Kasei CHIRALDEX G-TA (0.25 mm i.d. ×30 m ×0.125 μm). Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl. EtOH was distilled from calcium hydride. Other reagents were purified by usual methods.

4.2. General procedure for the catalytic enantioselective fluorination of β-ketoesters

To a solution of the palladium complex **2** (0.005 mmol) in EtOH (0.2 mL) was added a β-ketoester (0.2 mmol) at room temperature. At the indicated temperature, NFSI (95 mg, 0.3 mmol) was added. The resulting mixture was stirred for the time given in Table 3. After the completion of the reaction (TLC, hexane/ether=10/1), saturated aqueous NH_4Cl was added for quenching. The aqueous layer was extracted with Et_2O (3×10 mL). The combined organic layers were washed with water and brine. After drying over Na_2SO_4, the solvent was removed under reduced pressure. Further purification was performed by flash column chromatography on SiO_2 (hexane/Et_2O=10/1) to give the pure product as a colorless oil. The ees of the products were determined by chiral HPLC or GC analysis. In this study, decoupled ^{19}F NMR spectra were obtained for all the products.

4.2.1. *tert*-Butyl 1-fluoro-2-oxocyclopentanecarboxylate (7a). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.49 (s, 9H), 2.07–2.15 (m, 2H), 2.21–2.34 (m, 1H), 2.44–2.57 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.0 (d, J=4.1 Hz), 27.9, 33.8 (d, J=20.6 Hz), 35.7, 84.0, 94.4 (d, J=199.1 Hz), 166.4 (d, J=27.9 Hz), 208.1 (d, J=16.4 Hz); ^{19}F NMR (400 MHz, $CDCl_3$) δ −163.2; FABMS (*m*NBA) *m/z* 202 $(M)^+$, 146 $(M-t\text{-Bu})^+$; $[\alpha]_D^{31}$ +72.7 (*c* 1.27, $CHCl_3$) (92% ee); HPLC (DAICEL CHIRALPAK AD-H, hexane/IPA=99/1, 0.40 mL/min, 280 nm) t_r (minor)=20.3 min, t_r (major)=24.7 min; FAB–HRMS (*m*NBA) Calcd for $C_{10}H_{15}O_3F$ $(M)^+$ 202.1005. Found 202.1002. Calcd for $C_{10}H_{16}O_3F$ $(M+1)^+$ 203.1084. Found 203.1082; IR (neat) ν 2978, 2927, 1764, 1746, 1458, 1395, 1370, 1145, 840 cm^{-1}.

4.2.2. (*R*)-*tert*-Butyl 2-fluoro-2-methyl-3-oxo-3-phenylpropionate (7b). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (s, 9H), 1.82 (d, J=22.4 Hz, 3H), 7.43–7.48 (m, 2H), 7.56–7.60 (m, 1H), 8.02–8.06 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.6 (d, J=23.9 Hz), 27.6, 84.0, 96.6 (d, J=193 Hz, 1H), 128.5, 129.5, 133.6, 167.5 (d, J=25.5 Hz), 191.7 (d, J=25.5 Hz); ^{19}F NMR (400 MHz, $CDCl_3$) δ −151.2; FABMS (*m*NBA) *m/z* 253 $(M+1)^+$, 197 $(M+2H-t\text{-Bu})^+$; $[\alpha]_D^{33}$ +74.0 (*c* 1.3, $CHCl_3$) (91% ee); HPLC (DAICEL CHIRALPAK AD-H, hexane/IPA=200/1, 0.40 mL/min, 254 nm) t_r (major)=17.7 min, t_r (minor)=19.1 min; FAB–HRMS (*m*NBA) Calcd for $C_{14}H_{18}O_3F$ $(M+1)^+$ 253.1240. Found 253.1240; IR (neat) ν 2981, 2935, 1754, 1700, 1449, 1395, 1370, 1288, 1247, 1145, 1123, 979, 696 cm^{-1}.

4.2.3. *tert*-Butyl 1-fluoro-2-oxocyclohexanecarboxylate (7c). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.53 (s, 9H), 1.82–2.12 (m, 5H), 2.40–2.74 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2 (d, J=6.6 Hz), 26.5, 27.8, 36.0 (d, J=21.4 Hz), 39.9, 83.8, 96.3 (d, J=195 Hz), 165.7 (d, J=23.9 Hz), 202.2 (d, J=19.0 Hz); ^{19}F NMR (400 MHz, $CDCl_3$) δ −159.6; FABMS (*m*NBA) *m/z* 217 $(M+1)^+$, 161 $(M+2-t\text{-Bu})^+$; $[\alpha]_D^{33}$ −88.6 (*c* 1.39, $CHCl_3$) (94% ee); HPLC (DAICEL CHIRALPAK AD-H, hexane/IPA=99/1, 1.0 mL/min, 280 nm) t_r (minor)=14.0 min, t_r (major)=16.6 min; FAB–HRMS (*m*NBA) Calcd for $C_{11}H_{18}O_3F$ $(M+1)^+$ 217.1240. Found 217.1243; IR (neat) ν 2937, 2865, 1736, 1726, 1452, 1395, 1370, 1291, 1252, 1144,1095, 838 cm^{-1}.

4.2.4. (*R*)-*tert*-Butyl 2-fluoro-1-oxoindane-2-carboxylate (7d). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (s, 9H), 3.40 (dd, J=17.6, 23.0 Hz, 1H), 3.73 (dd, J=10.7, 17.6 Hz, 1H), 7.43–7.50 (m, 2H), 7.67–7.71 (m, 1H), 7.83 (d, J=7.6 Hz 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.8, 38.3 (d, J=23.9 Hz), 84.1, 95.4 (d, J=201 Hz), 125.4, 126.4, 128.4, 133.6, 136.4, 150.9 (d, J=3.3 Hz), 166.2 (d, J=27.2 Hz), 195.8 (d, J=18.1 Hz); ^{19}F NMR (400 MHz, $CDCl_3$) δ −164.4; FABMS (*m*NBA) *m/z* 251 $(M+1)^+$, 195 $(M+2H-t\text{-Bu})^+$; $[\alpha]_D^{34}$ +3.8 (*c* 0.86, $CHCl_3$) (83% ee); HPLC (DAICEL CHIRALPAK AD-H, hexane/IPA=150/1, 0.75 mL/min, 254 nm) t_r (minor)=24.1 min, t_r (major)=33.7 min; FAB–HRMS (*m*NBA) Calcd for $C_{14}H_{16}O_3F$ $(M+1)^+$ 251.1084. Found 251.1083; IR (neat) ν 2980, 2927, 1758, 1725, 1466, 1395, 1370, 1214, 1151, 1073, 922, 834, 741 cm^{-1}.

4.2.5. *tert*-Butyl 2-fluoro-2-methyl-3-oxobutyrate (7e). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.48 (s, 9H), 1.63 (d, J=22.2 Hz, 3H), 2.30 (d, J=4.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.5 (d, J=23.1 Hz), 24.9, 27.5, 83.8, 97.7 (d, J=192 Hz), 165.9 (d, J=25.5 Hz), 202.5 (d, J=28.8 Hz); ^{19}F NMR (400 MHz, $CDCl_3$) δ −156.6; FABMS (*m*NBA) *m/z* 191 $(M+1)^+$; $[\alpha]_D^{34}$ −44.0 (*c* 0.91, $CHCl_3$) (89% ee); GC (Tokyo Kasei CHIRALDEX G-TA; 0.25 mm i.d. ×30 m ×0.125 μm; temp 70 °C, inj. temp 300 °C, det. temp 250 °C) t_r (minor)=21.0 min, t_r (major)=21.7 min; FAB–HRMS (*m*NBA) Calcd for $C_9H_{15}O_3F$ $(M)^+$ 190.1005. Found 190.1000; IR (neat) ν 2981, 2935, 1753, 1736, 1458, 1395, 1370, 1291, 1256, 1134, 1106, 840 cm^{-1}.

4.2.6. *tert*-Butyl 2-ethyl-2-fluoro-3-oxobutyrate (7f). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (t, J=7.4 Hz, 3H), 1.49 (s, 9H), 1.94–2.20 (m, 2H), 2.29 (d, J=4.64 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.00, 25.7, 26.9 (d, J=21.4 Hz), 27.8, 83.8, 100.6 (d, J=194 Hz), 165.3 (d, J=26.3 Hz), 202.4 (d, J=32.9 Hz); FABMS (*m*NBA) *m/z* 205 $(M+1)^+$, 147 $(M-t\text{-Bu})^+$, 148 $(M+2-t\text{-Bu})^+$; $[\alpha]_D^{31}$ −12.6 (*c* 1.45, $CHCl_3$) (87% ee); HPLC (DAICEL CHIRALPAK AD-H, hexane/IPA=150/1, 0.40 mL/min, 280 nm) t_r (minor)=11.6 min, t_r (major)=12.5 min; FAB–HRMS (*m*NBA) Calcd for $C_{10}H_{18}O_3F$ $(M+1)^+$ 205.1240. Found 205.1244; IR (neat) ν 2920, 2850, 1736, 1709, 1459, 1446, 1376, 1280, 1261, 1168, 1084, 797 cm^{-1}.

4.2.7. *tert*-Butyl 2-fluoro-2-methyl-3-oxopentanoate (7g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.09 (t, J=7.3 Hz, 3H), 1.47 (s, 9H), 1.63 (d, J=22.2 Hz, 3H), 2.65–2.70 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 7.2, 19.0 (d, J=23.0 Hz), 24.7, 27.5, 83.8, 97.7 (d, J=195 Hz), 164.9 (d, J=25.2 Hz), 201.5 (d, J=28.8 Hz); FABMS (*m*NBA) *m/z* 205 $(M+1)^+$, 147 $(M-t\text{-Bu})^+$, 148 $(M+2-t\text{-Bu})^+$; $[\alpha]_D^{31}$ −55.5 (*c* 2.28, CH_2Cl_2) (69% ee); HPLC (DAICEL CHIRALPAK AS, hexane/IPA=150/1, 0.20 mL/min, 280 nm) t_r (minor)=19.7 min, t_r (major)=22.3 min.

4.2.8. *tert*-Butyl 2-fluoro-3-oxo-3-phenylpropionate (9). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (s, 9H), 5.75 (d, J=49.2 Hz, 1H), 7.45 (t, J=7.6 Hz, 2H), 7.63 (t, J=8.7 Hz, 1H), 8.02 (d, J=8.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.7, 84.5, 90.1 (d, J=195.8 Hz), 1287.7, 129.4 (d, J=3.3 Hz), 133.6, 134.2, 163.6, 190.0; HPLC (DAICEL CHIRALPAK AD-H, hexane/IPA=200/1, 0.40 mL/min, 254 nm) t_r=18.9 min, t_r=20.3 min.

4.3. General procedure for the catalytic enantioselective fluorination of β-ketophosphonates

To a stirred solution of the Pd complex **1** (0.01 mmol) in EtOH (0.2 mL), **11** (0.2 mmol) and NFSI (94.8 mg, 0.3 mmol) were added successively at ambient temperature. The reaction was monitored by TLC (hexane/ethyl acetate=1/1). After completion of the reaction, saturated aqueous NH_4Cl was added for quenching. The aqueous layer was extracted with ethyl acetate (3×10 mL). The combined organic layers were washed with brine and dried over Na_2SO_4. After evaporation of the solvent, the obtained crude product was purified by flash column chromatography (hexane/ethyl acetate=1/1) to afford **12** as a colorless oil. The ees of the products were determined by chiral HPLC analysis. In this study, coupling constants against protons and phosphorus atoms were recorded in ^{19}F NMR.

4.3.1. Diethyl 1-fluoro-2-oxocyclopentylphosphonate (12a). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (t, J=7.1 Hz, 3H), 1.39 (t, J=7.1 Hz, 3H), 2.03–2.56 (m, 5H), 2.68–2.81 (m, 1H), 4.19–4.30 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.2 (d, J=5.7 Hz), 16.3 (d, J=5.7 Hz), 16.8 (dd, J=4.2, 5.8 Hz), 32.0 (dd, J=2.5, 18.1 Hz), 35.4 (d, J=2.5 Hz), 64.0 (d, J=6.2 Hz), 64.1 (d, J=6.2 Hz), 96.2 (dd, J=160.0, 200.8 Hz), 209.0 (dd, J=3.3, 13.2 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −98.1 (ddd, J=11.7, 25.2, 85.0 Hz); FAB–LRMS (*m*NBA) *m/z* 239 (M+1)$^+$; $[\alpha]_D^{28}$ +130.2 (*c* 0.75, $CHCl_3$) (96% ee); HPLC (DAICEL CHIRALPAK AD-H, *n*-hexane/IPA=95/5, 1.0 mL/min, 280 nm) t_r (major)=10.6 min, t_r (minor)=11.7 min; FAB–HRMS (*m*NBA) Calcd for $C_9H_{17}FO_4P$ (M+1)$^+$ 239.0849. Found 239.0855; IR (neat) ν 1756, 1259, 1047, 1022 cm^{-1}.

4.3.2. Diethyl 1-fluoro-2-oxocyclohexylphosphonate (12b). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.32 (t, J=7.1 Hz, 3H), 1.37 (t, J=7.1 Hz, 3H), 1.64–1.72 (m, 1H), 1.85–2.23 (m, 4H), 2.58–2.70 (m, 2H), 2.85–2.93 (m, 1H), 4.11–4.30 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.3 (d, J=6.6 Hz), 16.4 (d, J=5.7 Hz), 21.7 (d, J=8.2 Hz), 26.7, 36.1 (d, J=19.0 Hz), 40.8, 64.1 (d, J=6.5 Hz), 64.4 (d, J=6.6 Hz), 98.1 (dd, J=154.7, 196.6 Hz), 203.0 (dd, J=4.9, 14.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −91.0 (dd, J=18.4, 80.1 Hz); FAB–LRMS (*m*NBA) *m/z* 253 (M+1)$^+$; $[\alpha]_D^{28}$ +164.2 (*c* 1.0, $CHCl_3$) (96% ee); HPLC (DAICEL CHIRALPAK AD-H, *n*-hexane/IPA=99/1, 1.0 mL/min, 280 nm) t_r (major)=47.7 min, t_r (minor)=50.4 min; FAB–HRMS (*m*NBA) Calcd for $C_{10}H_{19}FO_4P$ (M+1)$^+$ 253.1005. Found 253.1009; IR (neat) ν 1726, 1257, 1013 cm^{-1}.

4.3.3. Diethyl 2-fluoro-2,3-dihydro-1-oxo-1*H*-inden-2-yl-2-phosphonate (12c). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.22 (t, J=7.1 Hz, 3H), 1.38 (t, J=7.1 Hz, 3H), 3.97 (ddd, J=9.3, 14.6, 17.9 Hz, 1H), 3.35–3.48 (m, 1H), 4.12–4.25 (m, 2H), 4.30 (quint, J=7.3 Hz, 2H), 7.42–7.48 (m, 2H), 7.67 (td, J=1.3, 7.7 Hz, 1H), 7.81 (d, J=7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.2 (d, J=5.8 Hz), 16.3 (d, J=5.7 Hz), 36.5 (dd, J=3.3, 21.4 Hz), 64.3 (d, J=6.6 Hz), 95.9 (dd, J=162.9, 199.9 Hz), 125.1, 126.4, 128.5, 134.1 (d, J=3.3 Hz), 136.4, 149.8 (t, J=4.6 Hz), 196.4 (dd, J=3.3, 14.8 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −101.1 (ddd, J=9.0, 26.4, 104.9 Hz); FAB–LRMS (*m*NBA) *m/z* 287 (M+1)$^+$; $[\alpha]_D^{28}$ +71.2 (*c* 0.85, $CHCl_3$) (95% ee); HPLC (DAICEL CHIRALPAK AD-H, *n*-hexane/IPA=95/5, 1.0 mL/min, 254 nm) t_r (major)=19.5 min, t_r (minor)=24.3 min; FAB–HRMS (*m*NBA) Calcd for $C_{13}H_{17}FO_4P$ (M+1)$^+$ 287.0848. Found 287.0852; IR (neat) ν 1725, 1260, 1018 cm^{-1}.

4.3.4. (*S*)-Diethyl 2-fluoro-1,2,3,4-tetrahydro-1-oxonaphthalen-2-yl-2-phosphonate (12d). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.12 (t, J=7.1 Hz, 3H), 1.37 (t, J=7.1 Hz, 3H), 2.44–2.64 (m, 1H), 2.81–2.91 (m, 1H), 3.06–3.11 (m, 1H), 3.44–3.53 (m, 1H), 4.00–4.16 (m, 2H), 4.25–4.34 (m, 2H), 7.26 (d, J=7.8 Hz, 1H), 7.34 (d, J=7.6 Hz, 1H), 7.53 (td, J=1.5, 7.6 Hz, 1H), 8.06 (dd, J=1.2, 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.0 (d, J=6.6 Hz), 16.3 (d, J=4.9 Hz), 26.0 (d, J=10.7 Hz), 31.6 (d, J=19.7 Hz), 63.8 (d, J=6.6 Hz), 64.6 (d, J=6.6 Hz), 95.5 (dd, J=156.3, 192.5 Hz), 126.9, 127.9, 128.6, 131.1, 134.2, 143.1, 190.6 (dd, J=3.3, 14.4 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −93.9 (ddd, J=6.8, 13.9, 83.1 Hz); FAB–LRMS (*m*NBA) *m/z* 301 (M+1)$^+$; $[\alpha]_D^{27}$ +49.1 (*c* 1.1, $CHCl_3$) (94% ee); HPLC (DAICEL CHIRALPAK AD-H, *n*-hexane/IPA=9/1, 1.0 mL/min, 254 nm) t_r (major)=10.2 min, t_r (minor)=13.6 min; FAB–HRMS (*m*NBA) Calcd for $C_{14}H_{19}FO_4P$ (M+1)$^+$ 301.1005. Found 301.1000; IR (neat) ν 1694, 1259, 1014, cm^{-1}.

4.3.5. Diethyl 2-fluoro-3-oxobutan-2-ylphosphonate (12e). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (dt, J=0.48, 7.1 Hz, 3H), 1.37 (t, J=0.48, 7.1 Hz, 3H), 1.71 (dd, J=15.4, 23.7 Hz, 3H), 2.38 (dd, J=0.72, 5.6 Hz, 3H), 4.18–4.28 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.3 (d, J=5.8 Hz), 16.3 (d, J=5.7 Hz), 19.3 (d, J=21.4 Hz), 26.2, 64.0 (d, J=7.4 Hz), 64.2 (d, J=7.5 Hz), 99.1 (dd, J=159.6, 190.0 Hz), 205.3 (dd, J=3.3, 25.5 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ 93.6 (qqd, J=4.5, 25.0, 84.5 Hz); FAB–LRMS (*m*NBA) *m/z* 227 [M+1]$^+$; $[\alpha]_D^{28}$ −80.8 (*c* 0.47, $CHCl_3$) (94% ee); IR (neat) ν 1724, 1261, 1012 cm^{-1}. The ee was determined after conversion to the corresponding 2,4-dinitrophenylhydrazone **13**.[27]

Compound **13**: yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33–1.38 (m, 1H), 1.90 (dd, J=13.9, 24.6 Hz, 3H), 2.24 (dd, J=1.2, 2.4 Hz, 3H), 4.16–4.28 (m, 4H), 7.95 (d, J=9.5 Hz, 1H), 8.34–8.37 (m, 1H), 9.15 (d, J=2.7 Hz, 1H), 11.14 (s, 1H); FAB–LRMS (*m*NBA) *m/z* 407 (M+1)$^+$; HPLC (DAICEL CHIRALPAK AD-H, *n*-hexane/IPA=9/1, 1.0 mL/min, 254 nm) t_r (major)=21.0 min, t_r (minor)=25.6 min; FAB–HRMS (*m*NBA) Calcd for $C_{14}H_{21}FN_4O_7P$ (M+1)$^+$ 407. 1132. Found 407.1131.

4.3.6. Diethyl 2-fluoro-1-oxo-1-phenylpropan-2-yl-phosphonate (12f). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, J=7.1 Hz, 3H), 1.29 (t, J=7.1 Hz, 3H), 1.85 (dd, J=15.2, 24.2 Hz, 3H), 4.10–4.26 (m, 4H), 7.38 (d, J=7.7 Hz, 2H), 7.48–7.52 (m, 1H), 7.99–8.02 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.4 (d, J=4.9 Hz), 16.4 (d, J=4.9 Hz), 21.5 (d, J=22.2 Hz), 64.1 (d, J=4.1 Hz), 64.2 (d, J=4.1 Hz), 100.5 (dd, J=161.7, 193.7 Hz), 128.2, 130.0 (d, J=7.4 Hz), 133.4, 134.7 (d, J=3.3 Hz), 197.6 (dd, J=4.1, 23.0 Hz); ^{19}F NMR (376 MHz, $CDCl_3$) δ −85.3 (ddd, J=24.1, 48.1, 83.8 Hz); FAB–LRMS (*m*NBA) *m/z* 289 (M+1)$^+$; $[\alpha]_D^{25}$ −36.3 (*c* 0.37, $CHCl_3$) (90% ee); HPLC (DAICEL CHIRALPAK AD-H, *n*-hexane/IPA=9/1, 1.0 mL/min, 254 nm) t_r (minor)=7.3 min, t_r (major)=7.9 min; FAB–HRMS (*m*NBA) Calcd for $C_{13}H_{19}FO_4P$ (M+1)$^+$ 289.1005. Found 289.1011; IR (neat) ν 1681, 1260, 1048, 1014 cm^{-1}.

4.4. Synthesis of 16

To a stirred solution of $NaBH_4$ (50 mg, 1.33 mmol) in EtOH (3 mL) was added a solution of the optically active **12d** (100 mg, 0.33 mmol, 95% ee) in EtOH (7 mL) under ice-bath cooling. The mixture was stirred at room temperature for 5 h, then saturated aqueous NH_4Cl was added to destroy the excess reagent. The aqueous layer was extracted with ether several times and the combined organic layers were washed with brine and dried over Na_2SO_4. Short column chromatography on silica gel (hexane/ethyl acetate=1/3–1/20) afforded the desired product in 90% yield (90 mg)

as a colorless oil. This reaction was stereoselective and no stereoisomer was detected in ^{1}H NMR of the crude products. Subsequently, the obtained alcohol (39 mg, 0.13 mmol) was mixed with the acid **15** (110 mg, 0.26 mmol) and DMAP (16 mg, 0.13 mmol) in CH_2Cl_2 (5 mL). After 5 min, EDAC (97.4 mg, 0.52 mmol) was added under ice-bath cooling, and the resulting mixture was stirred for 17 h at room temperature. After completion of the reaction, 1 N HCl was added and the aqueous layer was extracted with ethyl acetate. The combined organic layers were washed with saturated aqueous $NaHCO_3$, water, and brine, then dried over Na_2SO_4. Removal of the solvent, followed by flash column chromatography (hexane/ethyl acetate=1/1) afforded **16** as a white solid in 84% yield. Recrystallization from hexane/ethyl acetate (3/1) at ambient temperature gave colorless pillars in 76% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.98 (s, 3H), 1.21 (t, J=7.1 Hz, 3H), 1.25 (s, 3H), 1.26 (t, J=7.1 Hz, 3H), 1.33–1.48 (m, 2H), 1.87–1.97 (m, 3H), 1.98–2.15 (m, 1H), 2.35–2.7 (m, 3H), 2.97–3.14 (m, 2H), 3.34 (d, J=13.9 Hz, 1H), 3.43 (d, J=13.9 Hz, 1H), 3.88 (m, 1H), 4.05–4.25 (m, 4H), 6.47 (t, J=9.5 Hz, 1H), 7.16 (d, J=7.6 Hz, 1H), 7.19 (t, J=7.6 Hz, 1H), 7.27 (dt, J=1.5, 7.5 Hz, 1H), 7.44 (d, J=7.5 Hz, 1H), 7.53 (s, 1H), 8.15 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.2 (d, J=5.7 Hz), 1.63 (d, J=5.8 Hz), 20.0, 20.8, 24.3 (d, J=7.5 Hz), 26.1 (d, J=20.6 Hz), 26.5, 33.0, 37.5, 44.7, 47.7, 48.4, 53.0, 63.3 (d, J=6.6 Hz), 63.7 (d, J=5.7 Hz), 65.5, 71.0 (d, J=31.3 Hz), 77.2, 93.7 (d, J=175, 182 Hz), 126.6, 127.6, 128.2, 128.7, 130.0, 131.1 (d, J=7.4 Hz), 132.4, 134.5, 135.3, 135.6, 137.0, 162.0, 164.9; $[\alpha]_D^{27}$ −134.65 (c 0.73, $CHCl_3$).

4.5. Conversion of the fluorinated products

4.5.1. (2*R*,3*R*)-Methyl 2-fluoro-3-hydroxy-2-methyl-3-phenylpropanoate (19). To a stirred solution of **14** (125.8 mg, 0.598 mmol, 91% ee) in TFA (2 mL) was added Et_3SiH (0.3 mL, 1.79 mmol) at 0 °C. The reaction mixture was stirred at room temperature for 2 h. The mixture was diluted with ether (5 mL) and saturated aqueous $NaHCO_3$ was added under ice-bath cooling to neutralize the mixture. The separated aqueous layer was extracted with ether (2×10 mL). The combined organic layers were washed with water and brine. Concentration, followed by flash column chromatography (hexane/ethyl acetate=8/1) afforded the desired product **19** as a colorless oil in 92% yield (117.1 mg). ^{1}H NMR of the crude products indicated high diastereoselectivity (>95/5). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.60 (d, J=22.2 Hz, 3H), 3.70 (s, 3H), 4.98 (d, J=15.6 Hz, 1H), 7.30–7.44 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.3 (d, J=11.5 Hz), 52.6, 76.2 (d, J=23.0 Hz), 96.2 (d, J=190.1 Hz), 127.3, 127.4, 128.2, 128.6, 137.5, 171.3 (d, J=23.9 Hz); FABMS (*m*NBA) m/z 213 $(M+1)^+$, 212 $(M)^+$; $[\alpha]_D^{30}$ +2.68 (c 2.44, $CHCl_3$); FAB–HRMS (*m*NBA) Calcd for $C_{11}H_{14}O_3F$ $(M+1)^+$ 213.0927. Found 213.0922. Calcd for $C_{11}H_{13}O_3F$ $(M)^+$ 212.0849. Found 212.0844; IR (solid) ν 3465, 3001, 2953, 1737, 1452, 1375, 1291, 1182, 1109, 1051, 1027, 727, 700 cm^{-1}.

4.5.2. (2*R*,3*S*)-Methyl 2-fluoro-3-hydroxy-2-methyl-3-phenylpropanoate (20). To a stirred solution of **14** (40 mg, 0.19 mmol, 91% ee) in DMF (0.2 mL) were added $PhMe_2SiH$ (120 μL, 0.76 mmol) and TBAF (380 μL, 1 M in THF, 0.38 mmol) at 0 °C. Saturated aqueous NH_4Cl (3 mL) was added after 20 min. The aqueous layer was extracted with ether (5×10 mL). The combined organic layers were dried over Na_2SO_4. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (hexane/ethyl acetate=12/1). The desired product **20** was obtained in 83% yield as a colorless oil. The diastereoselectivity of this reaction was found to be more than 95% by ^{1}H NMR. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.39 (d, J=21.7 Hz, 3H), 3.83 (s, 3H), 4.94 (d, J=20.6 Hz, 1H), 7.32–7.39 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.4 (d, J=23.0 Hz), 52.8, 77.4 (d, J=19.7 Hz), 96.6 (d, J=192.5 Hz), 127.8, 127.8, 128.4, 128.7, 137.4, 171.6 (d, J=24.7 Hz); FABMS (*m*NBA) m/z 213 $(M+1)^+$, 212 $(M)^+$; $[\alpha]_D^{30}$ +22.9 (c 1.45, $CHCl_3$); FAB–HRMS (*m*NBA) Calcd for $C_{11}H_{13}O_3F$ $(M)^+$ 212.0849. Found 212.0844; IR (solid) ν 3483, 2992, 2957, 1741, 1453, 1375, 1295, 1188, 1135, 1113, 1053, 710 cm^{-1}.

4.5.3. *tert*-Butyl (1*S*,2*R*)-2-(methoxycarbonyl)-2-fluoro-1-phenylpropylcarbamate (21). The alcohol **19** (25 mg, 0.118 mmol) was dissolved in THF (0.3 mL). To this solution were added Ph_3P (49 mg, 0.19 mmol), DEAD (82 μL, 40% in toluene), and DPPA (33 μL, 0.15 mmol) successively in this order. After stirring for 2 h at room temperature, saturated aqueous NH_4Cl was added, and the resulting mixture was stirred for 5 min. The aqueous layer was extracted with ether (3×10 mL) and the combined organic layers were washed with water and brine, and dried over Na_2SO_4. Further purification was performed by flash column chromatography (hexane/ethyl acetate=15/1) to give the azide in 95% yield (26.7 mg). *Azide*: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (d, J=21.2 Hz, 3H), 3.88 (s, 3H), 4.85 (d, J=24.7 Hz, 1H), 7.37–7.48 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8 (d, J=23.0 Hz), 53.0, 69.4 (d, J=18.9 Hz), 95.7 (d, J=197.5 Hz), 128.8, 129.1, 129.1, 129.4, 132.9, 170.8 (d, J=25.5 Hz).

To a solution of this azide (160 mg, 0.598 mmol) in MeOH (8 mL) were added $(Boc)_2O$ (156.8 mg, 0.72 mmol) and 10% Pd–C (63 mg). The reaction mixture was stirred under a hydrogen atmosphere (balloon) for 1 h at room temperature, then passed through Celite to remove Pd–C, and the residue was washed with CH_2Cl_2. After the removal of solvent, the crude product was purified by flash column chromatography (hexane/ethyl acetate=12/1) to give the *N*-protected β-amino ester **21** in 78% yield (146 mg) as a white solid. Recrystallization from ethyl acetate enhanced the enantioselectivity to >99%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.38 (d, J=21.8 Hz, 3H), 1.39 (s, 9H), 3.80 (s, 3H), 5.07 (dd, J=9.6, 25.9 Hz, 1H), 5.55 (d, J=9.6 Hz, 1H), 7.29–7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5 (d, J=23.1 Hz), 28.2, 52.8, 59.3 (d, J=19.0 Hz), 80.0, 96.5 (d, J=190.1 Hz), 128.3, 128.3, 128.5, 136.4, 154.6, 171.1 (d, J=26.3 Hz); FABMS (*m*NBA) m/z 312 $(M+1)^+$; $[\alpha]_D^{30}$ +13.8 (c 0.73, $CHCl_3$); HPLC (DAICEL CHIRALCEl OJ-H, *n*-hexane/IPA=9/1, 1.0 mL/min, 254 nm) t_r (minor)=7.2 min, t_r (major)=13.5 min; FAB–HRMS (*m*NBA) Calcd for $C_{16}H_{23}NO_3F$ $(M+1)^+$ 312.1611. Found 312.1616; IR (solid) ν 3382, 2972, 2935, 1754, 1693, 1513, 1453, 1388, 1367, 1324, 1311, 1264, 1242, 1159, 1113, 1042, 1015, 980, 948, 910 cm^{-1}.

4.5.4. *tert*-Butyl (1*R*,2*R*)-2-(methoxycarbonyl)-2-fluoro-1-phenylpropylcarbamate (22). According to the same procedure described above, **20** was converted to **22**. *Azide*: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.76 (d, J=21.5 Hz, 3H), 3.63 (s, 3H), 4.80 (d, J=30.0 Hz, 1H), 7.32–7.43 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.7 (d, J=23.8 Hz), 52.6, 68.7 (d, J=20.6 Hz), 95.9 (d, J=195.0 Hz), 128.6, 128.6, 128.6, 129.2, 133.7, 169.9 (d, J=23.8 Hz). Compound **22**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.43 (s, 9H), 1.70 (d, J=21.7 Hz, 3H), 3.54 (s, 3H), 5.11 (dd, J=10.0, 27.1 Hz, 1H), 5.31 (d, J=10.0 Hz, 1H), 7.26–7.39 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.4 (d, J=23.9 Hz), 28.3, 52.3, 58.6 (d, J=17.3 Hz), 80.2, 97.2 (d, J=192.5 Hz), 127.8, 128.2, 128.5, 135.8, 137.4, 155.3, 170.3 (d, J=23.9 Hz); FABMS (*m*NBA) *m*/*z* 312 $(M+1)^+$, 311 $(M)^+$; $[\alpha]_D^{29}$ −30.5 (*c* 0.51, $CHCl_3$); FAB–HRMS (*m*NBA) Calcd for $C_{12}H_{15}NO_4F$ $(M+2H-t\text{-Bu})^+$ 256.0985. Found 256.0990. Calcd for $C_{12}H_{15}NO_4F$ $(M+2H-Boc)^+$ 212.1087. Found 212.1090; IR (solid) ν 3329, 2977, 2931, 1766, 1702, 1493, 1453, 1367, 1276, 1246, 1166, 1046, 1021, 982, 947, 882, 755, 703, 576 cm^{-1}.

4.5.5. *tert*-Butyl 1-fluoro-2-hydroxycyclohexanecarboxylate (23). To a stirred solution of **7c** (22 mg, 0.101 mmol, 94% ee) in EtOH (1 mL) was added $NaBH_4$ (9 mg, 0.24 mmol) at −78 °C. The reaction mixture was concentrated and the residue was diluted with ethyl acetate (10 mL). The organic layer was washed with water and brine. Further purification was performed by flash column chromatography (hexane/ethyl acetate=7/1) to give **23** in 81% yield (major: 76%, minor: 5%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.33–1.46 (m, 1H), 1.52 (s, 9H), 1.58–1.90 (m, 6H), 2.09 (dddd, J=5.6, 8.3, 13.9, 27.6 Hz, 1H), 3.08 (br s, 1H), 3.91–3.96 (ddd, J=3.9, 6.6, 10.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.1, 20.9 (J=4.1 Hz), 28.0, 28.8 (J=2.5 Hz), 29.7 (J=20.6 Hz), 70.1 (J=26.3 Hz), 28.8 (J=2.5 Hz), 83.2, 94.4 (J=185.9 Hz), 170.7 (J=23.8 Hz); $[\alpha]_D^{27}$ −18.7 (*c* 2.1, $CHCl_3$); FABMS (*m*NBA) *m*/*z* 219 $(M+1)^+$, 163 $(M+2-t\text{-Bu})^+$; FAB–HRMS (*m*NBA) Calcd for $C_{11}H_{18}FO_3$ $(M)^+$ 218.1318. Found 218.1318. *Minor isomer*: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30–1.94 (m, 16H), 2.01–2.09 (m, 1H), 3.87 (ddd, J=4.6, 9.5, 24.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.8, 23.7, 28.0, 30.2, 32.2 (J=22.3 Hz), 72.0 (J=20.6 Hz), 82.6, 96.0 (J=187.6 Hz), 169.9 (J=26.3 Hz); FABMS (*m*NBA) *m*/*z* 219 $(M+1)^+$, 163 $(M+2-t\text{-Bu})^+$; $[\alpha]_D^{27}$ 17.9 (*c* 0.25, CH_3CN).

4.5.6. *tert*-Butyl 2-benzylamino-1-fluorocyclohexanecarboxylate (24). To a solution of **7c** (26 mg, 0.12 mmol, 94% ee) in toluene (2 mL) was added $BnNH_2$ (14 μL, 0.132 mmol) at room temperature. The reaction mixture was stirred under reflux in the presence of a catalytic amount of TsOH (5 mg, 0.026 mmol) using MS4A as a dehydrating agent. After 4 h, the solvent was removed under reduced pressure. To this crude mixture were added AcOH (0.5 mL) and $NaCNBH_3$ (25 mg, 0.4 mmol) at room temperature. The mixture was stirred for an additional 2 h. After dilution with ether (10 mL), 1 N NaOH was added until the reaction mixture reached pH 9. The aqueous layer was extracted with ether (2×10 mL) and the combined organic layers were washed with water and brine. Evaporation of the solvent and flash column chromatography (hexane/ether=20/1) of the residue afforded the desired product **23** (major: 65%, minor: 8%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25–1.40 (m, 1H), 1.45–1.78 (m, 5H), 1.51 (s, 9H), 1.80–1.88 (m, 1H), 1.99–2.11 (m, 1H), 2.95 (ddd, J=4.6, 8.6, 12.7 Hz, 1H), 3.83 (d, J=13.2 Hz, 1H), 3.87 (d, J=13.2 Hz, 1H), 7.20–7.34 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.7 (d, J=7.4 Hz), 22.1, 27.6 (d, J=5.0 Hz), 28.1, 31.6 (d, J=21.4 Hz), 52.0, 59.8 (d, J=21.4 Hz), 82.0, 96.9 (d, J=183 Hz), 126.7, 128.0, 128.3, 140.7, 169.7 (d, J=26.3 Hz); FAB–LRMS (*m*NBA) *m*/*z* 308 $(M+1)^+$, 252 $(M+2H-t\text{-Bu})^+$; $[\alpha]_D^{26}$ −8.92 (*c* 1.44, $CHCl_3$). FAB–HRMS (*m*NBA) Calcd for $C_{18}H_{27}NO_2$ F $(M+1)^+$ 308.2026. Found 308.2016; *Minor*: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.51 (s, 9H), 1.55–2.10 (m, 8H), 2.90 (ddd, J=4.4, 11.4, 27.6 Hz, 1H), 3.72 (d, J=13.2 Hz, 1H), 3.91 (d, J=13.2 Hz, 1H), 7.19–7.34 (m, 5H).

4.5.7. (*S*)-2-Fluoro-1,2,3,4-tetrahydro-1-oxonaphthalen-2-yl-2-phosphonic acid (25). TMSBr (354 μL, 2.68 mmol) was added to a solution of **12d** (134 mg, 0.447 mmol, 95% ee) in CH_2Cl_2 (5 mL) under ice-bath cooling. The resulting mixture was stirred for 12 h at room temperature. After evaporation, MeOH (2 mL) was added and the mixture was stirred for an additional 2 h. Gradual removal of the solvent by leaving this solution still at ambient temperature gave a brownish solid. Washing this solid with $CHCl_3$ afforded pure **25** in 97% yield (106 mg). ^{1}H NMR (400 MHz, CD_3OD) δ 2.30–2.49 (m, 1H), 2.62–2.75 (m, 1H), 3.01 (dt, J=2.8, 17.3 Hz, 1H), 3.43 (ddd, J=4.9, 12.7, 21.0 Hz, 1H), 7.24 (d, J=7.5 Hz, 1H), 7.25 (t, J=7.8 Hz, 1H), 7.46 (dt, J=1.2, 7.5 Hz, 1H), 7.89 (dd, J=1.2, 8.1 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD) 27.2 (d, J=10.7 Hz), 32.9 (d, J=10.2 Hz), 96.8 (dd, J=153, 191 Hz), 127.8, 128.5 (d, J=1.7 Hz), 130.0, 132.9, 135.4, 145.3, 193.7 (dd, J=3.2, 13.1 Hz); $[\alpha]_D^{27}$ 58.9 (*c* 1.01, EtOH).

4.6. X-ray structural analysis of 16

Molecular formula: $C_{32}H_{37}Cl_2FNO_8PS$; molecular weight: 716.56; unit-cell dimensions: a=11.015(3) Å, α=90°, b=14.875(3) Å, β=98.092(1)°, c=21.073(5) Å, γ=90°; U=3452.6(15) Å^3, Z=4, d=1.379 g/cm^3; crystal system: orthorhombic; space group: P 21 21 21; type of diffractometer: Rigaku R-AXIS-CS, crystal size, 0.50×0.25×0.21 mm^3; temperature: 296 K; theta range: 3.01–24.69°; reflections collected: 29,415; independent reflections: 5830 [R(int)=0.0379]; absorption coefficient: 0.350 mm^{-1}; max and min transmission: 0.9301 and 0.7093; solution method: direct; refinement method: full-matrix least-squares on F^2; goodness of fit indicator: 1.206, $R1$=0.0511, $wR2$=0.1014. Crystallographic data for the structure reported in this paper have been deposited with Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 288122. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK [Fax: int. code +44 1223 336 033; E-mail: deposit@ccdc.cam.ac.uk].

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References and notes

1. (a) Kirsch, P. *Modern Fluoroorganic Chemistry: Synthesis, Reactivity, Applications*; Wiley-VCH: Weinheim, 2004; (b) Hiyama, T.; Kanie, K.; Kusumoto, T.; Morizawa, Y.; Shimizu, M. *Organofluorine Compounds: Chemistry and Applications*; Springer: Berlin, 2000; (c) *Biomedical Frontiers of Fluorine Chemistry*; Ojima, I., McCarthy, J. R., Welch, J. T., Eds.; ACS Symposium Series 639; American Chemical Society: Washington, DC, 1996; For reviews: (d) O'Hagan, D.; Rzepa, H. S. *Chem. Commun.* **1997**, 645–652; (e) Smart, B. E. *J. Fluorine Chem.* **2001**, *109*, 3–11; (f) Ismail, F. M. D. *J. Fluorine Chem.* **2002**, *118*, 27–33.
2. (a) *Asymmetric Fluoroorganic Chemistry: Synthesis, Application, and Future Directions*; Ramachandran, P. V., Ed.; ACS Symposium Series 746; American Chemical Society: Washington, DC, 2000; (b) *Enantiocontrolled Synthesis of Fluoro-Organic Compounds: Stereochemical Challenge and Biomedicinal Targets*; Soloshonok, V. A., Ed.; Wiley: New York, NY, 1999.
3. (a) Mikami, K.; Itoh, Y.; Yamanaka, M. *Chem. Rev.* **2004**, *104*, 1–16; (b) Iseki, K. *Tetrahedron* **1998**, *54*, 13887–13914.
4. Reviews of enantioselective fluorination reactions: (a) Ibrahim, H.; Togni, A. *Chem. Commun.* **2004**, 1147–1155; (b) Ma, J.-A.; Cahard, D. *Chem. Rev.* **2004**, *104*, 6119–6146; For a review of catalytic asymmetric α-halogenation reactions: (c) France, S.; Weatherwax, A.; Lectka, T. *Eur. J. Org. Chem.* **2005**, 475–479.
5. For representative examples: (a) Iwaoka, T.; Murohashi, T.; Sato, M.; Kaneko, C. *Tetrahedron: Asymmetry* **1992**, *3*, 1025–1028; (b) Davis, F. A.; Kasu, P. V. N. *Tetrahedron Lett.* **1998**, *39*, 6135–6138; (c) Enders, D.; Faure, S.; Potthoff, M.; Runsink, J. *Synthesis* **2001**, *15*, 2307–2319.
6. (a) Differding, E.; Lang, R. E. *Tetrahedron Lett.* **1988**, *29*, 6087–6090; (b) Davis, F. A.; Zhou, P.; Murphy, C. K.; Sundarababu, G.; Qi, H.; Han, W.; Przeslawski, R. M.; Chen, B.-C.; Carroll, P. *J. Org. Chem.* **1998**, *63*, 2273–2280; (c) Liu, Z.; Shibata, N.; Takeuchi, Y. *J. Org. Chem.* **2000**, *65*, 7583–7587.
7. (a) Shibata, N.; Suzuki, E.; Asahi, T.; Shiro, M. *J. Am. Chem. Soc.* **2001**, *123*, 7001–7009; (b) Mohar, B.; Baudoux, J.; Plaquevent, J.-C.; Cahard, D. *Angew. Chem., Int. Ed.* **2001**, *40*, 4214–4216; (c) Shibata, N.; Ishimaru, T.; Suzuki, E.; Kirk, K. L. *J. Org. Chem.* **2003**, *68*, 2494–2497; (d) Zoute, L.; Audouard, C.; Plaquevent, J.-C.; Cahard, D. *Org. Biomol. Chem.* **2003**, *1*, 1833–1834; (e) Greedy, B.; Paris, J.-M.; Vidal, T.; Gouverneur, V. *Angew. Chem., Int. Ed.* **2003**, *42*, 3291–3294; (f) Thierry, B.; Audouard, C.; Plaquevent, J.-C.; Cahard, D. *Synlett* **2004**, 856–860.
8. (a) Hintermann, L.; Togni, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 4359–4362; (b) Piana, S.; Devillers, I.; Togni, A.; Rothlisberger, U. *Angew. Chem., Int. Ed.* **2002**, *41*, 979–982; (c) Frantz, R.; Hintermann, L.; Perseghini, M.; Broggini, D.; Togni, A. *Org. Lett.* **2003**, *5*, 1709–1712.
9. Kim, D. Y.; Park, E. J. *Org. Lett.* **2002**, *4*, 545–547.
10. (a) Hamashima, Y.; Yagi, K.; Takano, H.; Tamás, L.; Sodeoka, M. *J. Am. Chem. Soc.* **2002**, *124*, 14530–14531; (b) Hamashima, Y.; Takano, H.; Hotta, D.; Sodeoka, M. *Org. Lett.* **2003**, *5*, 3225–3228; (c) Hamashima, Y.; Suzuki, T.; Shimura, Y.; Shimizu, T.; Umebayashi, N.; Tamura, T.; Sasamoto, N.; Sodeoka, M. *Tetrahedron Lett.* **2005**, *46*, 1447–1450.
11. For β-ketoesters: (a) Ma, J.-A.; Cahard, D. *Tetrahedron: Asymmetry* **2004**, *15*, 1007–1011; (b) Shibata, N.; Ishimaru, T.; Nagai, T.; Kohno, J.; Toru, T. *Synlett* **2004**, 1703–1706; (c) Shibata, N.; Kohno, J.; Takai, K.; Ishimaru, T.; Nakamura, S.; Toru, T.; Kanemasa, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 4204–4207; For cyanoesters: (d) Kim, H. R.; Kim, D. Y. *Tetrahedron Lett.* **2005**, *46*, 3115–3117; For β-ketophosphonates: (e) Bernardi, L.; Jørgensen, K. A. *Chem. Commun.* **2005**, 1324–1326; (f) Kim, S. M.; Kim, H. R.; Kim, D. Y. *Org. Lett.* **2005**, *7*, 2309–2311.
12. (a) Enders, D.; Hüttl, M. R. M. *Synlett* **2005**, 991–993; (b) Marigo, M.; Fielenbach, D.; Braunton, A.; Kjærsgaard, A.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2005**, *44*, 3703–3706; (c) Steiner, D. D.; Mase, N.; Barbas, C. F., III. *Angew. Chem., Int. Ed.* **2005**, *44*, 3706–3710; (d) Beeson, T. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 8826–8828; (e) Huang, Y.; Walji, A. M.; Larsen, C. H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 15051–15053.
13. For catalytic enantioselective monofluorination of oxindoles: Hamashima, Y.; Suzuki, T.; Takano, H.; Shimura, Y.; Sodeoka, M. *J. Am. Chem. Soc.* **2005**, *127*, 10164–10165.
14. (a) Hamashima, Y.; Hotta, D.; Sodeoka, M. *J. Am. Chem. Soc.* **2002**, *124*, 11240–11241; (b) Hamashima, Y.; Hotta, D.; Umebayashi, N.; Tsuchiya, Y.; Suzuki, T.; Sodeoka, M. *Adv. Synth. Catal.* **2005**, *347*, 1576–1586; (c) Sodeoka, M.; Hamashima, Y. *Bull. Chem. Soc. Jpn.* **2005**, *78*, 941–956.
15. Kumobayashi, H.; Miura, T.; Sayo, N.; Saito, T.; Zhang, X. *Synlett* **2001**, 1055–1064.
16. In the case of the Michael reaction, no reaction occurred with the Pd complexes **2**. The addition of a strong protic acid, such as TfOH, which promotes the reaction cooperatively with the Pd enolate as an activator of the enone, was necessary.
17. For the preparation of β-ketophosphonates: Calogeropoulou, T.; Hammond, G. B.; Wiemer, D. F. *J. Org. Chem.* **1987**, *52*, 4185–4190.
18. α-Fluorophosphonates have been used as mimics of a phosphate moiety. For a general review: Berkowitz, D. B.; Bose, M. *J. Fluorine Chem.* **2001**, *112*, 13–33.
19. For example: (a) Nieschalk, J.; O'Hagan, D. *J. Chem. Soc., Chem. Commun.* **1995**, 719–720; (b) Li, C.; Wu, L.; Otaka, A.; Smyth, M. S.; Roller, P. P.; Burke, T. R., Jr.; den Hertog, J.; Zhang, Z.-Y. *Biochem. Biophys. Res. Commun.* **1995**, *216*, 976–984; (c) Yokoyama, T.; Yamagishi, T.; Matsumoto, K.; Shibuya, S. *Tetrahedron* **1996**, *52*, 11725–11738; (d) Berkowitz, D. B.; Bose, M.; Pfannenstiel, T. J.; Doukov, T. *J. Org. Chem.* **2000**, *65*, 4498–4508.
20. (a) Kotoris, C. C.; Wen, W.; Lough, A.; Taylor, S. D. *J. Chem. Soc., Perkin Trans. 1* **2000**, 1271–1281; (b) Ruiz, M.; Ojea, V.; Quintela, J. M.; Guillín, J. J. *Chem. Commun.* **2002**, 1600–1601.
21. For details, see Supporting Information of Ref. 10a.
22. (a) Harada, N.; Koumura, N.; Feringa, B. L. *J. Am. Chem. Soc.* **1997**, *119*, 7256–7264; (b) Watanabe, M.; Kuwahara, S.; Harada, N.; Koizumi, M.; Ohkuma, T. *Tetrahedron: Asymmetry* **1999**, *10*, 2075–2078.

23. (a) Fujita, M.; Hiyama, T. *J. Am. Chem. Soc.* **1985**, *107*, 8294–8296; (b) Kitazume, T.; Kobayashi, T.; Yamamoto, T.; Yamazaki, T. *J. Org. Chem.* **1987**, *52*, 3218–3223.
24. The difference in coupling constants of the methine proton against the fluorine atom is derived from axial–equatorial and axial–axial relationships on the assumption that the ester group is at the equatorial position, as seen in the case of cyclohexane derivatives. The unambiguous stereochemistry observed in the reduction of **12d** under similar reaction conditions supports the predominant formation of **21**.
25. For phosphonate ester dealkylation: McKenna, C. E.; Schmidhauser, J. *J. Chem. Soc., Chem. Commun.* **1979**, 739.
26. Fujii, A.; Hagiwara, E.; Sodeoka, M. *J. Am. Chem. Soc.* **1999**, *121*, 5450–5458.
27. Gori, G.; Bartolucci, G. B.; Sturaro, A.; Pavoli, G.; Doretti, L.; Troiano, R.; Casetta, B. *J. Chromatogr., B* **1995**, 165–172.

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Structural and stereochemical aspects of the enantioselective halogenation of 1,3-dicarbonyl compounds catalyzed by Ti(TADDOLato) complexes

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Abstract—Complexes of the type [Ti(1-Np-TADDOLato)(carbonylenolato)$_2$] (**3a–d**), derived from β-keto esters, have been prepared and structurally characterized by NMR and X-ray crystallography. In solution, two main diastereoisomeric forms were identified. In the major C_2-symmetric isomer, the *face-on* naphthyl group of the (*S*,*S*)-TADDOL shields the *Si*-side of the coordinated enolate. Therefore, electrophilic attack of the halogenating agent can only occur at the *Re*-side of the substrate. α-Acyl-γ-lactams (**4**) were fluorinated with NFSI in the presence of the Ti(TADDOLato) catalyst in up to 87% ee. The absolute configuration of one of the products was determined by X-ray crystallography after derivatization. The observed absolute configuration at the fluorinated stereogenic center matches the one inferred from the structural analysis of the Ti(TADDOLato) complexes.

1. Introduction

We reported in 2000 the first catalytic enantioselective electrophilic fluorination of β-keto esters by Selectfluor® (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2,2,2]octane bis(tetrafluoroborate)) in the presence of catalytic amounts of $TiCl_2$(TADDOLato) complexes.[1] Meanwhile, the field of catalytic stereoselective halogenation chemistry has become a hot topic with fundamental and innovating contributions coming from several research groups. Thus, titanium is not the only metal able to catalyze electrophilic halogenation. Pd, Ni, and Cu have been added to the list of successful systems comprising also phase-transfer and most recently organocatalytic methods (recent examples of published work are given in the references).[2–8] This frontier of asymmetric catalysis already counts several review articles, thus demonstrating the great interest by the synthetic community.[9–12]

Our first report not only had the privilege to open this new area, but at the same time constituted an important addition to the already broad spectrum of transformations for which the TADDOL ligands (α,α,α′,α′-tetraaryl-2,2-dimethyl-1,3-dioxolan-4,5-dimethanol) play a crucial role.[13,14] Subsequently, we extended this type of electrophilic atom-transfer reaction to the related chlorination and bromination,[15] a geminal dihalogenation,[16] a direct hydroxylation,[17] and most recently the first transition-metal-catalyzed sulfenylation reactions (Scheme 1).[18] It is noteworthy that for all these transformations involving a 1,3-dicarbonyl compound, the most selective catalyst contains a TADDOL bearing 1-naphthyl groups, all other ligands tested gave much lower enantioselectivities. Moreover, for a given substrate, the level of enantioselectivity is comparable for different reactions, giving rise to the conjecture that these are mechanistically related and share common intermediates. The first and simple mechanistic view of these reactions involves the coordination of the substrate to titanium in a chelating fashion and its deprotonation, followed by the external attack by the electrophile. Starting from such a hypothesis, we performed QM/MM studies of the fluorination reaction whose results are represented in Scheme 2.[19] There are two key features derived from the calculations. The first one is that the C–F bond-forming step involves a single electron transfer (SET), a characteristic that is not too surprising in view of the oxidizing properties of N–F reagents such as Selectfluor, in general. However, we were so far not able to provide experimental corroboration for the SET feature. The second important aspect that was revealed by the calculations concerns the structure of the intermediates and the specific role of the 1-naphthyl substituents on the chiral ligand in determining the stereochemical course of the reaction. We therefore decided to prepare and study Ti(enolato)

Keywords: Catalytic fluorination; Ti(TADDOLato) complexes; α-Acyl-γ-lactams; Absolute configuration.
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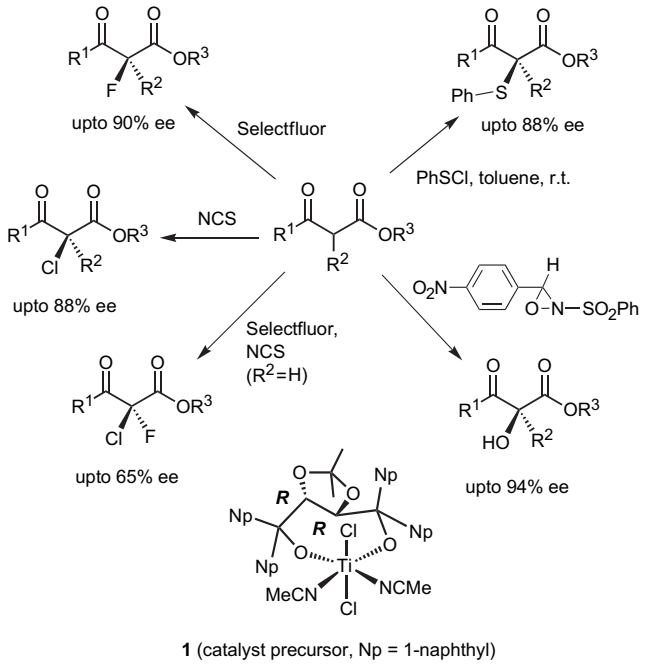
complexes derived from selected substrates used in the catalytic reactions. We also extended the applicability of the original fluorination reaction to 3-acyl lactams. The determination of the absolute configuration of one of the products, combined with the structural analysis of the complexes, concur in providing a clear picture as to the origin of enantioselectivity, not only for the fluorination, but also for all other related reactions.

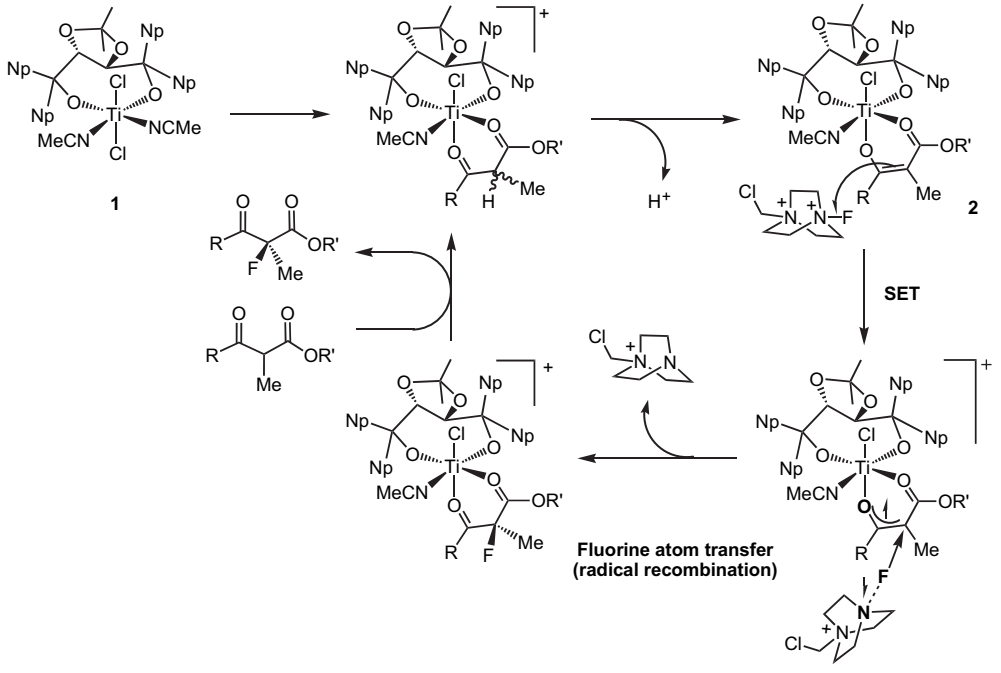


Scheme 1. Electrophilic atom-transfer reactions catalyzed by complex **1**.

2. Synthesis of Ti(enolato) complexes

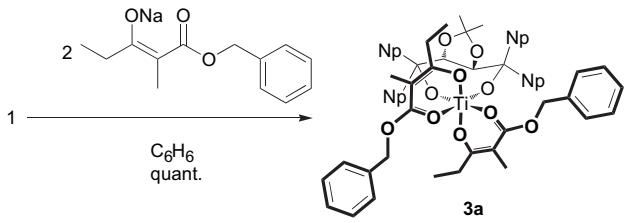
In contrast to the broad range of applications, only few examples of isolated and structurally characterized TADDOLato complexes are known.[20–30] This is possibly related to the fact that in most cases the catalysts are generated in situ. On the other hand, many crystal structures of free TADDOL ligands are known, providing insights into their common structural characteristics.[28]

The catalyst precursors used in our studies are air-stable complexes of the type [Ti(TADDOLato)Cl_2L_2], whose structures have been determined by X-ray crystallography.[31] Such complexes constitute ideal starting materials for the preparation of possible intermediates generated during the catalytic reaction. First attempts have been directed at the preparation of complexes such as those postulated in the mechanistic scheme used for the above-mentioned calculations, i.e., derivatives characterized by a 1:1 ratio of metal and enolized substrate. However, we found that by reacting equivalent amounts of the catalyst precursor **1** and a Na or Li enolate of selected β-keto esters did not afford the desired compounds of type **2** (Scheme 2), but the corresponding 1:2 adducts in low yield instead, along with several side-products, as verified by NMR spectroscopy. This does not necessarily imply that the former species cannot be formed during catalysis since the reaction conditions are different for the two processes, acidic for the catalysis and basic in the case of the complex preparation. Therefore, we decided to pursue the characterization of the 1:2 adducts, convinced that a structural study of such species would in any case provide useful information in view of judging stereochemical aspects important also for the 1:1 adducts. Thus, complexes of the type [Ti(1-Np-TADDOLato)(carbonylenolato)$_2$], **3**, were obtained by reacting the catalyst precursor **1** with



Scheme 2. Mechanistic scheme for the Ti-catalyzed fluorination of β-keto esters involving the formation of a Ti(carbonylenolato) intermediate undergoing SET with the fluorinating agent.

2 equiv of sodium enolate in benzene in up to quantitative yield (Scheme 3).



Scheme 3. The formation of complex **3a**.

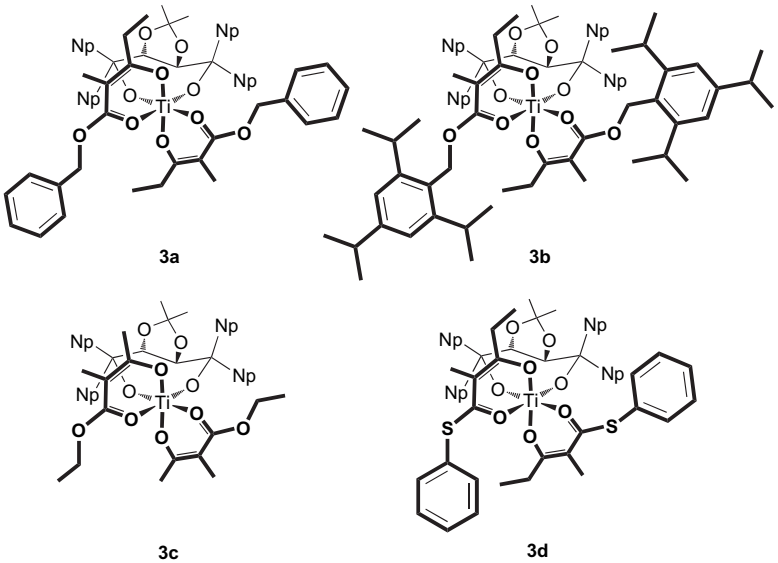
Complex **3a**, containing the enolate of 2-methyl-3-oxopentanoic acid benzyl ester, is a bright yellow powder slightly soluble in chlorinated solvents (deutero chloroform and methylene chloride), where a slow decomposition is observed, and in acetonitrile. Its solubility is higher in THF, benzene, and toluene. If a solution is left in contact with air, a slow decomposition is observed by NMR after 2 days. Its stability, though, is further demonstrated by the fact that in the presence of deoxygenated water only traces of decomposition can be observed after hours. Complex **3a** did not react with an ethereal solution of HCl nor with anionic ligands such as lithium *N*,*N*′-bis(trimethylsilyl)-benzamidinate,[32] thus confirming its stability. In view of comparing structural and reactivity features, we also prepared derivatives **3b–d** by a similar procedure, containing different carbonylenolato ligands as shown in Scheme 4. The four chosen β-keto esters afford in the catalytic fluorination reaction with Selectfluor enantioselectivities between 45% and 90% ee.

3. NMR characterization of complexes 3

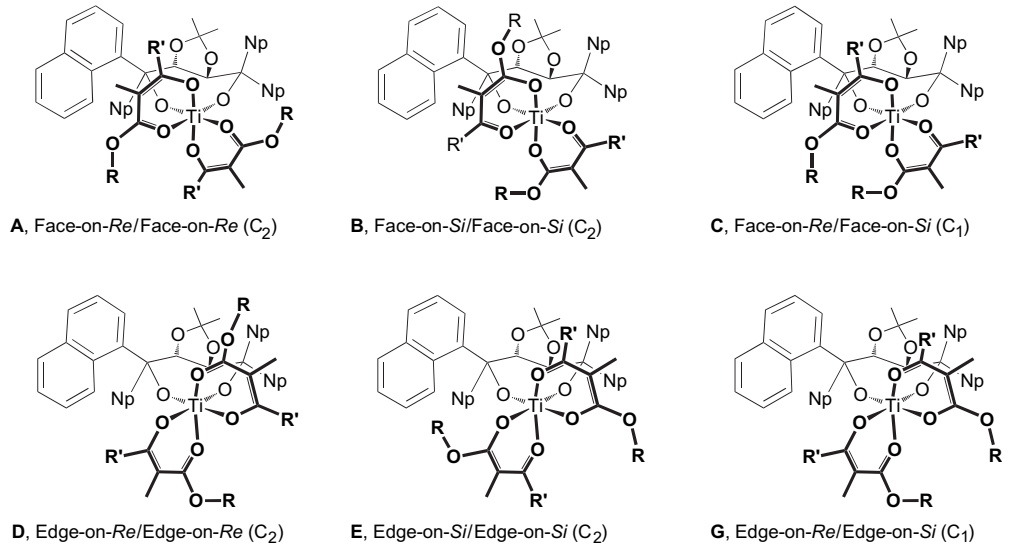
For complexes of type **3**, there are six possible configurational isomers, assuming a rigid conformation of the TADDOL ligand, as illustrated in Scheme 5. There are four C_2-symmetric configurations in which both carbonylenolato units show the same enantioface being shielded either by a *face-on* or an *edge-on* naphthyl group. On the other hand, in the two C_1-symmetric configurations opposite enantiofaces are shielded.

Examination of the 500 MHz ^{1}H NMR spectra of complex **3a** indicated the presence of several different species. As it will be explained below, the signal of the hydrogen atom in position 2 of a *face-on*-oriented naphthyl group appears as a doublet at relatively low field. Inspection of the spectral region between ca. 9.6 and 10 ppm allows to determine the number and relative concentration of the different isomers present in solution just by counting and integrating those signals (Fig. 1). Thus, two major isomers of **3a** in a ratio of ca. 70:30 can be identified, the major one of which is C_2-symmetric, whereas the second most abundant is not. Moreover, the ^{1}H NMR spectra reveal the presence of up to four further isomers, the concentration of which is however too low for an unambiguous identification. ^{13}C NMR measurements corroborate the observation made by ^{1}H NMR.

In order to determine the configuration and conformation of the two most abundant isomers, all corresponding proton and carbon signals for the first form, as well as relevant signals of the second form, respectively, were assigned by 2D NMR techniques. C,H-long-range correlation experiments have proven very useful for the assignment of the proton and carbon signals of the naphthyl groups. In fact, the signals of the protons in position 2 could be easily identified via their $^3J_{CH}$ correlations with the alcoholato carbon. One key point for the whole assignment is that only for the quaternary carbon atoms in position 8a of the naphthyl group there are four possible $^3J_{CH}$ interactions. Complementary H,H-COSY and TOCSY experiments confirmed the information obtained with the long-range experiment and allowed to complete the assignment. NOESY experiments delivered the necessary information to distinguish between the *face-on*- and the *edge-on*-oriented naphthyl substituents, thus determining the conformation of the TADDOLato ligand in the



Scheme 4. The four complexes of the type [Ti(1-Np-TADDOLato)(carbonylenolato)$_2$] prepared in this work.



Scheme 5. The six possible diastereoisomeric forms for complexes of the type [Ti(1-Np-TADDOLato)(carbonylenolato)$_2$], assuming a rigid conformation for the TADDOL ligand (the *R*,*R*-configuration of the ligand is represented).

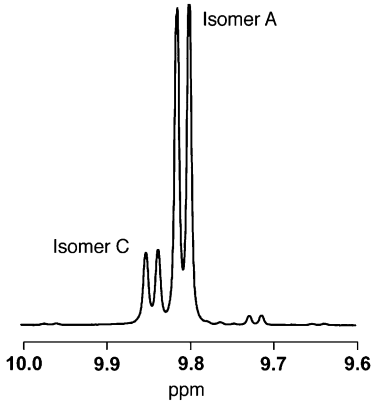


Figure 1. Section of the ^{1}H NMR spectrum (500 MHz, C_6D_6) of complex **3a** showing the signals of the hydrogen atoms in position 2 of an *edge-on* naphthyl group.

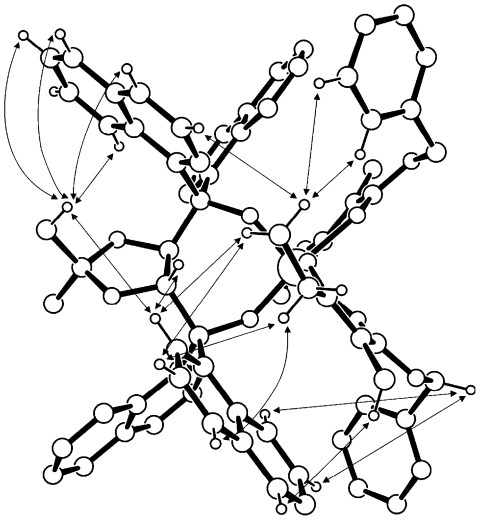


Figure 2. Selected NOEs observed for the major configuration of complex **3a**.

coordination sphere of the metal. In the next step, the NOE contacts between aromatic and aliphatic protons of the TADDOLato and carbonylenolato ligands were examined. Several NOE contacts between the protons of the *face-on* naphthyl groups and those of the carbonylenolato units allowed the determination of their relative position (Fig. 2). Furthermore, in the case of the C_2-symmetric structure **A**, contacts between aliphatic and aromatic protons of the two carbonylenolato units were observed ('head–tail' interactions).

In order to discern conformational aspects of the second most abundant form, several signals had to be assigned to the corresponding protons in the NMR spectrum. However, a complete assignment was not possible due to overlapping signals. Again, long-range interactions between protons in position 2 and the alcoholato carbons allowed the pairwise assignment of the four nonequivalent naphthyl groups to their corresponding alcoholato carbons. The *face-on* and *edge-on* substituents were then identified by NOE contacts between protons in position 2 and the H–(C) fragment of the dioxolane ring. NOE contacts between a terminal carbonylenolato H_3–(C) group and an *edge-on* naphthyl, combined with several contacts between naphthyl substituents and carbonylenolato units—as in the major form—led to the conclusion that the configuration of this form differs from that of the major form by a carbonylenolato ligand being turned by 180°, thus corresponding to isomer **C** in Scheme 5.

A first examination of the ^{1}H NMR spectra of derivatives **3b**,**c** indicated the presence of several forms, the most abundant being C_2-symmetric and accompanied by a second C_1-symmetric form, in a ratio of ca. 2:1 in both cases. The signal distribution was found to be very similar to that of complex **3a** and the subsequent 2D NMR studies confirmed configurations **A** and **C**, respectively. For complex **3d**, two isomers in a ratio of 70:30 could be identified, however, both displaying C_2-symmetry. For the major isomer, the configuration **A**

could be established again by 2D NMR methods. The determination of the configuration of the second most abundant form was complicated by overlapping signals of the thiophenyl group and some naphthyl protons which could not be assigned. However, the observation of NOE contacts between the protons of the alkanoyl group of the carbonylenolato ligand and those of both nonequivalent naphthyl groups suggests **E** as most probable configuration, i.e., both carbonylenolato ligands are shielded by *edge-on* naphthyl groups.

4. Crystal structure of complex 3a

Suitable crystals of complex **3a** (containing the *S*,*S*-configured TADDOL ligand) were grown from a mixture of THF and acetonitrile at −20 °C. Only configuration **A**—the major one observed in solution—is present in the solid state lying on a crystallographic C_2-symmetry axis, thus reducing the number of independent coordinates. The solid-state structure confirms the results obtained from the studies in solution, and clearly establishes the almost perfectly parallel orientation of the *face-on* naphthyl groups to their respective carbonylenolato units (Fig. 3).

The octahedral coordination geometry of **3a** is distorted, as shown, e.g., by the O–Ti–O angle for the apical oxygen donors derived from the keto functions of 163.46(9)°, whereas the corresponding angle for equatorially arranged ligands of 172.31(7)° is closer to the ideal value of 180° (the Ti atom and the two TADDOL oxygen atoms define the equatorial plane). Additional and probably related deviations from the usual values are found in the two O–C–C angles of the carbonylenolato chelate rings of 127.0(2)° and 123.3(2)° for the ester and keto function, respectively. The Ti–O bond length for the TADDOLato ligand atoms is 1.8006(13) Å, whereas for the carbonylenolato units the corresponding bond distances are 2.0874(15) and 1.9507(14) Å for the ester and keto function, respectively.

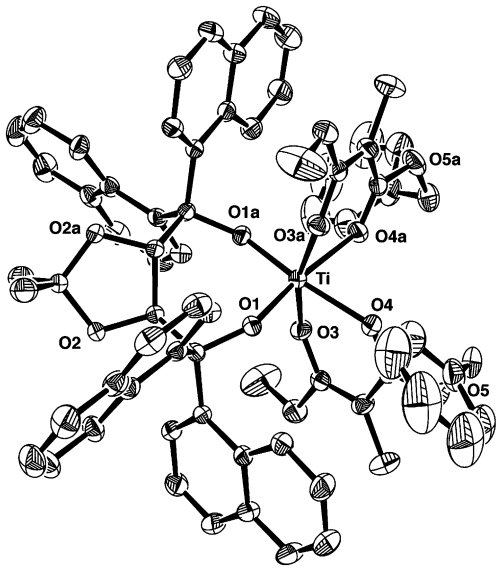


Figure 3. ORTEP drawing of the crystal structure of complex **3a**. Ellipsoids at the 30% probability level.

The least-square planes defined by the *face-on* naphthyl groups and their respective carbonylenolato chelate units are nearly parallel and form an angle of 5.68(6)°. The distances of the naphthyl carbon atoms from the carbonylenolato plane are found in the range 3.5134(22)–3.8768(26) Å, which corresponds to typical aromatic stacking distances (Fig. 4). Thus, the steric shielding of the *Si*-face of the carbonylenolato fragment by the *face-on* naphthyl substituent of the *S*,*S*-configured TADDOL ligand is virtually ideal and only the carbonylenolato *Re*-face is accessible.

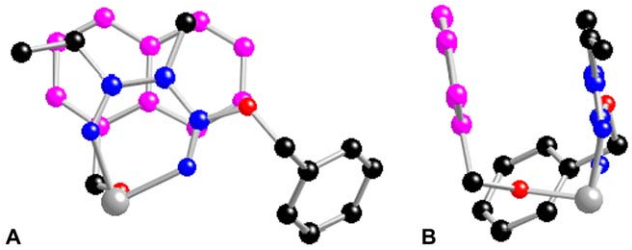


Figure 4. Partial representation of the crystal structure of complex (*S*,*S*)-**3a**, showing the shielding of the *Si*-enantioface of the carbonylenolato ligand (atoms forming the chelate ring in blue) by the *face-on* naphthyl substituent (in pink). (A) Projection on the plane of the naphthyl group; (B) side view.

5. Stoichiometric fluorination of complexes 3

In addition to the stability and reactivity experiments described above for derivative **3a**, we also performed stoichiometric fluorinations of the isomeric mixtures of the complexes. In all cases, the same preferred enantiomeric form of the products was formed as in the catalytic reaction. The fluorinated β-ketoester obtained from complex **3a** displayed an ee of 78%, slightly higher than the one obtained in the catalytic reaction using catalyst **1** (73% ee). For complexes **3b**,**c**, the enantiomeric excesses obtained were comparable to those of the catalytic reaction (90% and 77% vs 90% and 73%, respectively). For complex **3d**, a slightly lower value was observed (83% vs 90%). Furthermore, we also verified that complex **3a** can be used as a catalyst precursor and found that the corresponding enantioselectivities are close—but not identical—to those obtained with catalyst **1**. This was also the case when a mixture of two different β-keto esters (those contained in complexes **3c** and **3d**) was fluorinated using Selectfluor and catalyst **1**. These experiments do not prove the occurrence of intermediates of type **3** in the catalytic cycle, but they do not exclude it either.

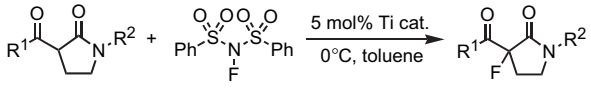
6. Fluorination and derivatization of α-acyl-γ-lactams

We addressed a class of dicarbonyl compounds that have not been fluorinated previously, the α-acyl-γ-lactams. Due to their structure and versatile functional groups, α-acyl-γ-lactams appear extremely interesting and may act as valuable building blocks for the synthesis of molecules with potentially useful biological activity. Thus, 3-acetyl-1-benzyl-2-pyrrolidinone (**4a**) was recently chosen as starting material for the preparation of novel β-lactam antibiotics.[33] The methyne hydrogen of the molecule remained unaffected throughout that synthesis, hence its initial replacement

with fluorine should lead to analogous bioactive target compounds.

We therefore started our investigation with compound **4a** and tested the previously reported fluorination protocol by using Selectfluor as the fluorinating agent and our standard catalyst **1**.[1,31] Substrate **4a** was rapidly fluorinated in α-position, albeit in very modest enantioselectivity of 5% ee as determined by chiral GC (Supelco β-dex column). The competing uncatalyzed process causes lowering of the level of enantioselectivity. Therefore, the use of milder and slow reacting fluorine sources,[34] such as 1-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate or *N*-fluorobenzenesulfonimide (NFSI), resulted in better values of enantiomeric excess (20% and 26% ee, respectively).

We subsequently focused on other α-acyl lactams, prepared by simple Claisen condensation reactions. The catalytic asymmetric fluorination was performed with NFSI in toluene at 0 °C, with 5 mol % of the Ti(TADDOLato) catalyst (Scheme 6). The results reported in Table 1 show that all substrates were successfully fluorinated in good yields. The enantioselectivities, ranging from scarce to good, were in all cases superior to those obtained with the fluorinating agents previously considered. This would indicate that the 'F$^+$'-donating species, in this case NFSI, plays an important role during the enantiodifferentiating step of the reaction. We took into account the influence of the R^1 and R^2 groups on the enantioselectivity. The couple of lactams **4c** (R^1=Ph, R^2=Me) and **4d** (R^1=Me, R^2=Ph) provided the lowest and the best ee values, respectively (6% and 87%). Unexpectedly, though, reciprocally exchanging the positions of the cyclohexyl and methyl group, as in the substrates **4e** and **4f** (entries 5 and 6), resulted in the same level of asymmetric induction (50% and 46% ee, respectively). These observations indicate that the enantioselectivity of the fluorination reaction is influenced not only by the steric bulk of the substituents R^1 and R^2, but also by their electronic nature. In the fluorination of the substrates **4d** and **4f**, in which the two relatively bulky R^2 groups (Ph and Cy, respectively) are clearly different electronically, we observed a marked difference in enantioselectivity.



4 5

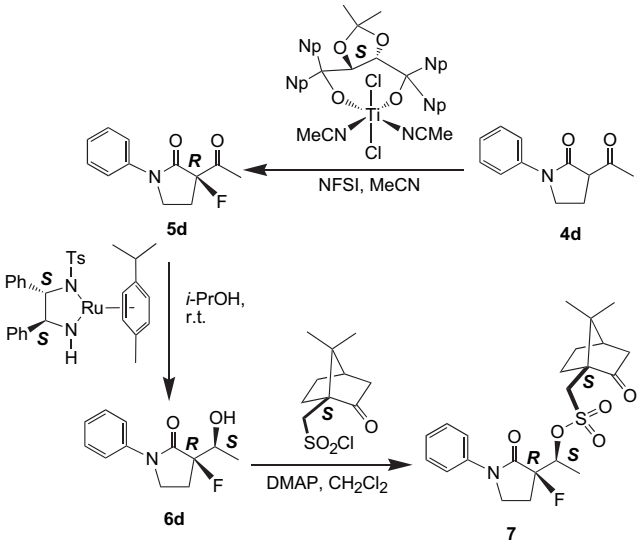
Scheme 6. Catalytic fluorination of α-acyl-γ-lactams.

Table 1. Fluorination of α-acyl-γ-lactams with NFSI catalyzed by (*S*,*S*)-**1**

Entry	Substrate	R^1	R^2	Yield[a] (%)	ee[b] (%)
1	**4a**	Me	CH_2Ph	75	26
2	**4b**	Ph	CH_2Ph	78	15
3	**4c**	Ph	Me	75	6
4	**4d**	Me	Ph	75	87
5	**4e**	Cy	Me	60	50
6	**4f**	Me	Cy	n/d	46
7	**4g**	*t*-Bu	Me	40	20

[a] Yields refer to isolated products.
[b] The absolute configuration *R* of the major enantiomer has been determined in the case of **5d** (vide infra).

Since the fluorinated products **5** are new compounds, it was important to determine the absolute configuration at least in one case, thus allowing to draw conclusions as to the sense of chiral induction. To this purpose, the enantiomerically enriched product **5d**, obtained upon fluorination with NFSI using (*S*,*S*)-**1** as a catalyst, was subjected to reduction by transfer hydrogenation using Noyori's Ru catalyst in isopropanol.[35] The α-(1-hydroxyalkyl)-γ-lactam **6d**, which is a mixture of two diastereoisomeric pairs of enantiomers, was subjected to column chromatographic purification. The major fraction was subsequently derivatized with *S*-camphorsulfonyl chloride affording **7** (Scheme 7). Derivative **7** turned out to be a crystalline material and crystals suited for an X-ray diffraction study were grown from a CD_2Cl_2 solution overlaid with hexane in an NMR tube. The solid-state structure of **7** allowed the determination of the absolute configuration of the two stereogenic centers generated in the two catalytic reactions, by internal comparison. The structure is illustrated in Figure 5 and clearly shows that the C–F stereogenic center has *R* absolute configuration and that, therefore, the fluorine atom has been delivered to the *Re*-enantioface of the corresponding enolate precursor while coordinated to Ti, as was to be expected for catalyst (*S*,*S*)-**1**, based on the consideration made above.



Scheme 7. Fluorination, reduction, and derivatization of α-acyl-γ-lactam **4d**.

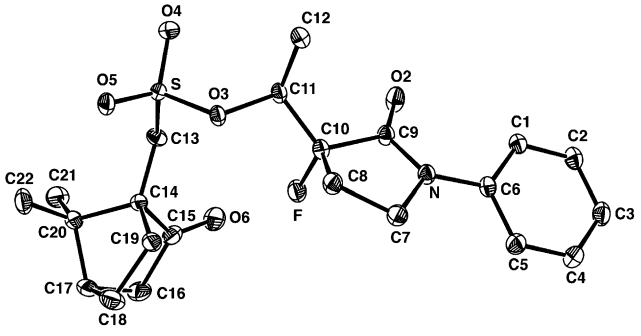


Figure 5. ORTEP drawing of the crystal structure of compound **7**. Ellipsoids at the 30% probability level.

7. Conclusion

The conformation and configuration of four Ti (TADDOLato) complexes bearing two carbonylenolato units (**3a**–**d**) have been determined in solution by 2D NMR methods. These materials consist of a mixture of up to six possible diastereoisomeric forms, two of which account for more than 90% of the mixture in all cases studied. The 1-naphthyl substituents of the TADDOL ligand are pairwise arranged in a *face-on* and *edge-on* orientation, respectively,[13] corresponding to a rigid conformation on the NMR timescale. The *face-on* naphthyl groups are responsible for an ideal steric shielding of one face of any bidentate chelating ligand occupying one equatorial and one apical position in a corresponding octahedral complex. This is clearly shown by the solid-state structure of derivative **3a**, the major species found in solution for this complex. Thus, in this steric shielding of one enantioface of the coordinated carbonylenolato ligand lies the origin of enantioselectivity of the Ti(TADDOLato) system in electrophilic atom-transfer reactions to 1,3-dicarbonyl compounds. However, the existence of isomeric forms of complexes containing both one or two carbonylenolato units, differing by the enantioface being shielded, explains why the enantioselectivities obtained with this system rarely go beyond ca. 90% ee. In other words, the observed enantioselectivity is the result of several factors, such as the isomeric composition of Ti(carbonylenolato) adducts, the relative rates by which they undergo atom-transfer reactions, their interconversion, and the degree of discrimination of the substrate enantiofaces when comparing *face-on* and *edge-on* shielding. Nevertheless, we can reduce the problem of enantioselectivity to a large extent to the problem of controlling the formation of the diastereoisomeric intermediates. Since the steric influence of the two ends of the substrate molecules does not let recognize clear trends, one should seek the solution to the problem in electronic factors, more specifically. How can the preference for the arrangement of the enolate and the carbonyl donor atoms in axial and equatorial position, respectively, be further enhanced? How should the TADDOL ligand be modified in order to achieve such an improved differentiation? We are currently working at these problems and shall deliver answers in due course.

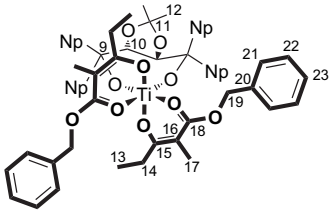
8. Experimental

8.1. General

Reactions were carried out under argon (Schlenk) or under nitrogen atmosphere (glovebox). Freshly distilled solvents were used throughout. Organic solvents were purified by standard procedures. ^{1}H, $^{13}C\{^{1}H\}$ NMR, and 2D NMR spectra were recorded with Bruker DPX-300 or DRX-500 spectrometers using standard pulse sequences. ^{1}H and ^{13}C chemical shifts are relative to tetramethylsilane and calibrated against solvent resonance. Coupling constants are given in Hz. In the assignment of naphthyl resonances for complexes **3**, A refers to *face-on* and B to *edge-on* groups, for C_2-symmetric forms. For C_1-symmetric forms, A and D are *face-on* and B and C are *edge-on* groups. Infrared spectra were recorded on Perkin–Elmer FT-IR Paragon 1000 spectrometers. Mass spectrometry was carried out by the Analytical Service of the Organic Chemistry Laboratory, ETH Zürich. Microanalysis was performed by the Microelemental Analysis Service of the Organic Chemistry Laboratory, ETH Zürich.

Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Center as supplementary publication numbers CCDC-208619 (**3a**) and CCDC-251473 (**7**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

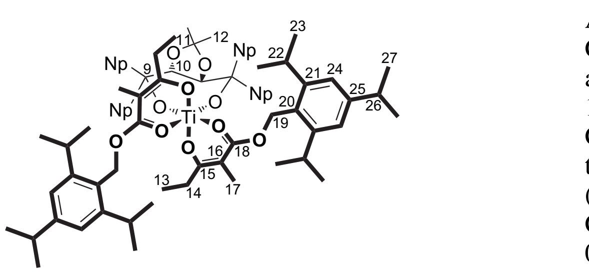
8.2. Titanium complex 3a



The precursor **1** was freshly prepared from 200 mg (300 μmol) 1-Np-TADDOL and 71.5 mg (302 μmol) $TiCl_2(O^iPr)_2$ in 4 ml MeCN. After stirring for 2 h, a white precipitate formed. The solvent was removed (HV), the light yellow residue dried (16 h, HV) and then dissolved in 10 ml benzene. To a suspension of 14.6 mg (608 μmol) sodium hydride in 6 ml benzene, 132.4 mg (601 μmol) benzyl 2-methyl-3-oxo-pentanoate was added. When gas evolution ceased (30 min), the suspension was added to the solution of complex **1**. After standing (2.5 h), the NaCl precipitate was removed by filtration and the obtained yellow solution was dried (HV). The yellow residue was dissolved in 2 ml benzene. Addition of 10 ml pentane caused the precipitation of a light yellow solid, which was separated, washed (3×4 ml pentane), and dried (HV) to give the product as light yellow powder (395 mg, quant.). Found: C, 76.16; H, 5.97. $C_{73}H_{66}O_{10}Ti$ (1151.20) requires: C, 76.16; H, 5.78. Major isomer: δ_H (500 MHz, C_6D_6): 0.13 (s, H–C(12)), 1.07 (s, H–C(17)), 1.40 (t, J=7.5, H–C(13)), 1.79 (dq, J=15.4, 7.5 H–C_{out}(14)), 2.09 (dq, J=15.4, 7.5, H–C_{in}(14)), 4.66 (d, J=12.0, H–C(19)), 4.86 (d, J=12.0, H–C(19)), 6.42 (dd, J=8.9, 7.2, H–C(7A)), 6.71 (s, H–C(10)), 6.73 (t, J=7.9, H–C(7B)), 6.85 (t, J=7.5, H–C(6B)), 6.88 (t, J=7.2, H–C(6A)), 6.94 (t, J=7.4, H–C(23)), 7.02 (t, J=7.4, H–C(22)), 7.13 (d, J=7.4, H–C(21)), 7.38 (dd, J=8.1, 7.5, H–C(3A)), 7.43 (d, J=8.1, H–C(5A)), 7.48 (d, J=8.1, H–C(5B)), 7.58 (d, J=8.1, H–C(4A)), 7.81 (d, J=8.0, H–C(4B)), 8.00 (dd, J=8.0, 7.5, H–C(3B)), 8.18 (d, J=9.1, H–C(8B)), 8.48 (d, J=8.9, H–C(8A)), 8.74 (d, J=7.5, H–C(2A)), 9.81 (dd, J=7.5, 1.2, H–C(2B)). δ_C (75.5 MHz, C_6D_6): 10.4 (C(13)), 11.2 (C(17)), 27.2 (C(12)), 29.1 (C(14)), 66.9 (C(19)), 83.1 (C(10)), 94.2 (C(16)), 97.1 (C(9)), 112.5 (C(11)), 124.3 (C(7B)), 124.8 (C(2A)), 124.8 (C(6B)), 124.9 (C(3A)), 124.9 (C(7A)), 125.0 (C(3B)), 125.1 (C(6A)), 127.7 (C(8A)), 128.2 (C(5A)), 128.2 (C(23)), 128.3 (C(5B)),

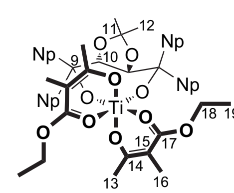
128.4 (C(2B)), 128.4 (C(22)), 128.7 (C(8B)), 128.9 (C(4A)), 129.3 (C(21)), 129.4 (C(4B)), 132.8 (C(8aA)), 134.1 (C(8aB)), 134.9 (C(4aB)), 135.0 (C(4aA)), 136.6 (C(20)), 142.5 (C(1B)), 144.5 (C(1A)), 171.5 (C(18)), 184.7 (C(15)). ν_{max} (cm^{-1}, KBr pellet): 3047m, 2981m, 2933m, 1625s, 1599s, 1494bs, 1452s, 1405s, 1347m, 1258bs, 1236s, 1185s, 1089s, 1047s, 970s, 889s, 801s, 779s, 699m, 644m, 518m, 467s, and 436s. *m/z* (FAB): 1152.1 (M^+). Second form (detected signals): δ_H (500 MHz, C_6D_6): 0.14 (s, H–C(12)), 0.29 (s, H–C(12)), 0.92 (t, J=7.7, H–C(13)), 1.14 (s, H–C(17)), 1.22 (s, H–C(17)), 1.47 (t, J=7.6, H–C(13)), 1.79 (H–C(14)), 1.89 (m, H–C(14)), 1.96 (m, H–C(14)), 2.15 (m, H–C(14)), 4.38 (d, J=12.4, H–C(19)), 4.85 (d, J=12.1, H–C(19)), 4.87 (d, J=12.1, H–C(19)), 4.97 (d, J=12.4, H–C(19)), 6.28 (t, J=7.7, H–C(7A)), 6.47 (t, J=7.8, H–C(7C)), 6.66 (d, J=6.1, H–C(10B)), 6.86, 6.86, 6.73, 6.92, 7.19 (H–C(10A)), 7.19, 7.25 (t, J=7.8, H–C(4A)), 7.30 (H–C(2C)), 7.30 (H–C(3D)), 7.40, 7.49, 7.57 (H–C(3A)), 7.57 (H–C(4D)), 7.88, 8.10 (d, J=9.1), 8.36 (d, J=8.8), 8.42 (d, J=7.3, C(2A)), 8.55 (d, J=7.5, H–C(2D)), 8.62 (d, J=7.2, H–C(8D)), 9.85 (d, J=7.3, H–C(2B)), 10.88 (d, J=8.8). δ_C (75.5 MHz, C_6D_6): 10.9, 11.3, 11.4, 11.5 (13, 13, 17, 17), 27.3 (C(12)), 28.2 (C(12)), 29.5 (C(14)), 29.5 (C(14)), 66.7 (C(19)), 66.7 (C(19)), 83.5 (C(10B)), 84.0 (C(10A)), 93.7 (C(16)), 94.7 (C(16)), 97.6 (C(9A)), 101.5 (C(9B)), 113.2 (C(11)), 123.5, 124.0, 124.6 (C(2D)), 125.2 (C(2A)), 127.9, 128.0 (C(2B)), 126.3, 128.7, 129.0 (C(21)), 129.3 (C(8D)), 129.7, 132.2 (C(2C)), 132.7 (C(8aA)), 134.3, 135.3, 135.6, 138.8 (C(1C)), 142.8 (C(1B)), 144.0 (C(1A)), 146.0 (C(1D)), 171.0 (C(18)), 172.0 (C(18)), 184.2 (C(15)), 184.9 (C(15)). Third form: δ_H (500 MHz, C_6D_6): 0.70 (d, J=7.6), 0.77 (t, J=7.5), 0.88 (t, J=7.5), 1.36 (t, J=7.5), 5.49 (d, J=12.2), 6.00 (d, J=12.2), 6.58 (*m*), 7.08 (d, J=7.7; this signal could also arise from two overlapping triplets), 7.96 (d, J=7.7), 8.14 (d, J=9.1), 8.29 (d, J=9.1), 8.88 (d, J=7.3), 9.03 (d, J=7.1), 9.72 (d, J=7.3).

8.3. Titanium complex 3b



A suspension of 149.6 mg (431.7 µmol) 2,4,6-triisopropyl 2-methyl-3-oxo-pentanoate and 10.5 mg (438 µmol) sodium hydride in 6 ml toluene was stirred for 1.5 h (after 10 min a colorless solution was observed). A solution of 178.0 mg (215.9 µmol) of complex **1** was added. After 4 h without stirring, no precipitate was observed, even after reduction of the solution volume to 3 ml and cooling at −100 °C. The solvent was removed completely (HV). The light brown residue was dried (HV, 5 h), then washed three times with 8 ml pentane and dried (HV, 6 h). The complex was analyzed without further purification. δ_H (500 MHz, C_6D_6): 0.13 (H–C(12)), 1.09 (s, H–C(17)), 1.13 (d, J=6.8, H–C(23)), 1.15 (d, J=6.9, H–C(27)), 1.24 (d, J=6.8, H–C(23′)), 1.38 (t, J=7.2, H–C(13)), 1.74–1.84 (m, H–C(14)), 2.06–2.16 (m, H–C(14)), 2.72 (sept, J=6.9, H–C(26)), 3.29 (sept, J=6.8, H–C(22)), 5.04 (d, J=12.2, H–C(19)), 5.59 (d, J=12.2, H–C(19)), 6.67 (H–C(7A)), 6.73 (H–C(10)), 6.74 (H–C(7B)), 6.88 (H–C(6B)), 6.91 (H–C(6A)), 7.06 (s, H–C(24)), 7.40 (t, J=8.2, H–C(3A)), 7.45 (d, J=8.4, H–C(5A)), 7.49 (d, J=8.4, H–C(5B)), 7.60 (d, J=8.2, H–C(4A)), 7.79 (d, J=7.8, H–C(4B)), 7.95 (t, J=7.7, H–C(3B)), 8.22 (d, J=8.6, H–C(8B)), 8.55 (d, J=8.3, H–C(8A)), 8.77 (d, J=7.3, H–C(2A)), 9.73 (d, J=7.3, H–C(2B)). δ_C (75.5 MHz, C_6D_6): 10.3 (C(13)), 11.4 (C(17)), 24.1 (C(27)), 24.5 (C(23)), 24.6 (C(23′)), 27.3 (C(12)), 29.2 (C(14)), 29.7 (C(22)), 34.8 (C(26)), 59.0 (C(19)), 83.3 (C(10)), 93.7 (C(16)), 96.8 (C(9)), 112.7 (C(11)), 121.3 (C(24)), 124.3 (C(7B)), 124.8 (C(6A)), 124.9 (C(3A)), 124.9 (C(7A)), 124.9 (C(6B)), 125.1 (C(2A)), 125.1 (C(3B)), 127.6 (C(20)), 127.8 (C(8A)), 128.3 (C(5A)), 128.3 (C(2B)), 128.4 (C(5B)), 128.8 (C(8B)), 128.9 (C(4A)), 129.4 (C(4B)), 132.9 (C(8aA)), 134.2 (C(8aB)), 134.9 (C(4aB)), 135.1 (C(4aA)), 142.4 (C(1B)), 144.5 (C(1A)), 149.2 (C(21)), 149.8 (C(25)), 171.0 (C(18)), 184.4 (C(15)). ν_{max} (cm^{-1}, KBr pellet): 3047m, 2961s, 2931s, 2869m, 1627s, 1603s, 1508bs, 1459s, 1404s, 1262bs, 1232bs, 1187s, 1090bs, 1045bs, 963s, 887s, 779s, 644m, 618m, 518m.

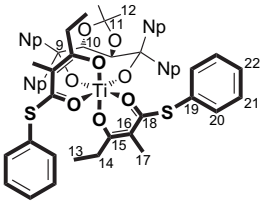
8.4. Titanium complex 3c



A solution of 5.0 mg (35 µmol) ethyl acetoacetate in 0.3 ml C_6D_6 was added to 1.4 mg (61 µmol) sodium hydride. After almost complete gas evolution, the suspension was added to 15.0 mg (17.3 µmol) of complex **1** and diluted to 1 ml with C_6D_6. To remove traces of uncoordinated ethyl acetoacetate, the solution was dried (HV, 1 h) and the residue washed (3×1 ml pentane), dried (HV, 3 h), and dissolved in 0.7 ml C_6D_6 for spectroscopic analyses. δ_H (500 MHz, C_6D_6): 0.12 (s, H–C(12)), 0.70 (t, J=7.2, H–C(19)), 0.98 (s, H–C(16)), 1.83 (s, H–C(13)), 3.53–3.61 (m, H_{out}–C(18)), 3.66–3.77 (m, H–C(18)), 6.66 (s, H–C(10)), 6.72 (H–C(7A)), 6.72 (H–C(7B)), 6.84 (H–C(6B)), 6.88 (H–C(6A)), 7.43 (H–C(5A)), 7.47 (H–C(5B)), 7.37 (t, J=7.8, H–C(3A)), 7.57 (H–C(4A)), 7.76 (t, J=8.0, H–C(4B)), 7.91 (t, J=8.0, H–C(3B)), 8.11 (d, J=8.8, H–C(8B)), 8.53 (d, J=9.0, H–C(8A)), 8.69 (d, J=7.4, H–C(2A)), 9.86 (d, J=7.6, H–C(2B)). δ_C (75.5 MHz, C_6D_6): 11.6 (C(16)), 13.5 (C(19)), 23.3 (C(13)), 27.1 (C(12)), 61.1 (C(18)), 95.5 (C(15)), 82.9 (C(10)), 97.1 (C(9)), 112.3 (C(11)), 124.2 (C(7B)), 124.3 (C(2A)), 124.7 (C(6B)), 124.8

(C(7A)), 124.9 (C(6A)), 125.1 (C(3A)), 125.1 (C(3B)), 127.5 (C(8A)), 128.4 (C(5A)), 128.4 (C(5B)), 128.7 (C(2B)), 128.7 (C(8B)), 128.9 (C(4A)), 129.4 (C(4B)), 132.8 (C(8aA)), 134.1 (C(8aB)), 134.8 (C(4aB)), 135.2 (C(4aA)), 143.1 (C(1B)), 144.9 (C(1A)), 172.1 (C(17)), 180.4 (C(14)). Second form (detected signals): δ_H (500 MHz, C_6D_6): 0.09 (s), 0.25 (s), 0.65 (t, J=7.2), 0.80 (7, J=7.2), 0.99 (s), 1.24 (s), 1.61 (s), 1.91 (s), 3.45–3.56 (m), 3.82–3.88 (m), 8.04 (d, J=9.0), 8.39 (d, J=7.2), 8.42 (d, J=9.0), 9.82 (d, J=7.4), 10.93 (d, J=8.4).

8.5. Titanium complex 3d



A solution of 41.5 mg (187 μmol) thiophenyl 2-methyl-3-oxo-pentanoate in 3 ml toluene was added to 4.5 mg (0.19 mmol) sodium hydride. After the gas evolution ceased, the solution was added to 80.4 mg (92.9 μmol) of complex **1** in 12 ml toluene. After standing (15 h), the yellow solution was separated from the white precipitate and dried (HV). The light yellow oil was washed (3×1 ml pentane). The resulting yellow powder was dried (HV, 4 h), affording 55 mg (53%) product. Major isomer: δ_H (500 MHz, C_6D_6): 0.06 (s, H–C(12)), 1.11 (s, H–C(17)), 1.16 (t, J=7.2, H–C(13)), 1.42–1.51 (m, H_{out}–C(14)), 1.69–1.78 (m, H_{in}–C(14)), 6.50 (s, H–C(10)), 6.72 (H–C(7B)), 6.84 (H–C(6B)), 6.99 (H–C(7A)), 7.03 (H–C(6A)), 7.34 (t, J=7.0, H–C(3A)), 7.46 (H–C(5A)), 7.46 (H–C(5B)), 7.56 (d, J=8.1, H–C(4A)), 7.71 (H–C(4B)), 7.79 (t, J=7.4, H–C(3B)), 8.19 (d, J=9.0, H–C(8B)), 8.39 (d, J=8.3, H–C(8A)), 8.64 (d, J=7.2, H–C(2A)), 9.32 (d, J=7.2, H–C(2B)). Not detected: H–C(20) to H–C(22). δ_C (126 MHz, C_6D_6): 9.2 (C(13)), 12.4 (C(17)), 27.2 (C(12)), 29.3 (C(14)), 83.2 (C(10)), 96.9 (C(9)), 104.1 (C(16)), 112.7 (C(11)), 124.8 (C(3A)), 124.8 (C(6A)), 124.3 (C(7A)), 124.7 (C(2B)), 124.8 (C(3B)), 125.4 (C(6B)), 125.8 (C(7B)), 127.8 (C(8B)), 128.0 (C(5B)), 128.1 (C(2A)), 128.3 (C(5A)), 128.7 (C(8A)), 128.8 (C(4B)), 129.4 (C(4A)), 132.7 (C(8aB)), 134.0 (C(8aA)), 134.8 (C(4aA)), 134.8 (C(4aB)), 141.9 (C(1A)), 144.3 (C(1B)), 183.5 (C(15)), 187.3 (C(18)). Not detected: C(19) to C(22). Second form (detected signals): δ_H (500 MHz, C_6D_6): 0.73 (t, J=7.4, H–C(13)), 1.17 (m, H–C(14)), 1.58 (s, H–C(17)), 1.87–1.96 (m, H–C(14)), 6.68 (H–C(7B)), 6.77 (s, H–C(10)), 6.79 (H–C(7A)), 7.74 (H–C(4)), 7.50 (H–C(3A)), 7.77 (H–C(3B)), 8.99 (d, J=7.2, H–C(2B)), 8.02 (d, J=9.0, H–C(8B)), 8.43 (d, J=8.8, H–C(8A)), 8.77 (d, J=7.3, H–C(2A)). δ_C (126 MHz, C_6D_6): 9.4 (C(13)), 13.1 (C(17)), 29.7 (C(14)), 82.3 (C(10)), 97.0 (C(9)), 105.0 (C(16)), 124.8 (C(2A)), 127.6 (C(2B)), 128.0 (C(8A)), 128.6 (C(8B)), 132.9 (C(8aA)), 134.2 (C(8aB), 134.9 (C(4aB)), 135.2 (C(4aA)), 143.0 (C(1B)), 143.7 (C(1A)), 184.5 (C(15)), 188.1 (C(18)).

8.6. Typical experimental procedure for the catalytic fluorination of α-acyl-γ-lactams

Complex **1** (0.05 mmol) was added to a solution of α-acyl-γ-lactam **4** (1 mmol) in dry toluene at room temperature. After 15 min, the mixture was cooled to 0 °C, then NFSI (1.2 mmol) was added. The reaction was monitored by TLC and GC–MS, and after completion water was added. The organic layer was extracted with TBME, dried over $MgSO_4$, and the crude product was purified by column chromatography. Spectroscopic and analytical data for selected examples follow.

8.6.1. 3-Acetyl-1-benzyl-3-fluoro-2-pyrrolidinone (5a). δ_H (200 MHz, $CDCl_3$): 2.05–2.35 (m, 1H, CH_2), 2.49 (d, 3H, CH_3, $^4J_{HF}$=5.0), 2.55–2.75 (m, 1H, CH_2), 3.25–3.45 (m, 2H, CH_2), 4.51 (s, 2H, CH_2), 7.20–7.45 (m, 5H, Ph); δ_C NMR (75 MHz, $CDCl_3$): 26.4 (CH_3), 28.6 (d, CH_2, $^2J_{CF}$=21.4), 43.0 (d, CH_2, $^3J_{CF}$=3.1), 47.2 (CH_2), 99.5 (d, C, J_{CF}=199.0), 127.9 (CH), 128.0 (CH), 128.8 (CH), 134.9 (C), 166.8 (d, C, $^2J_{CF}$=23.7), 205.7 (d, C, $^2J_{CF}$=32.3); δ_F (188 MHz, $CDCl_3$): −158.5/−158.8 (m); m/z (EI): 235 (M^+), 215, 192, 118, 91 (100), 65, 43. Found: C, 66.25; H, 6.21; N, 5.95. $C_{13}H_{14}NO_2F$ (235.26) requires: C, 66.37; H, 6.00; N, 5.95.

8.6.2. 3-Benzoyl-1-methyl-3-fluoro-2-pyrrolidinone (5c). δ_H (250 MHz, $CDCl_3$): 2.25–2.55 (m, 1H, CH_2), 2.85–3.00 (m, 1H, CH_2), 2.95 (s, 3H, CH_3), 3.47 (dt, 1H, CH_2, J_{HH}=9.0, J_{HH}=2.5), 3.55–3.60 (m, 1H, CH_2), 7.45–7.65 (m, 3H, Ph), 8.20–8.25 (m, 2H, Ph); δ_C (75 MHz, $CDCl_3$): 30.3 (CH_3), 30.7 (d, CH_2, $^2J_{CF}$=21.8), 45.8 (d, CH_2, $^3J_{CF}$=3.8), 100.5 (d, C, J_{CF}=202.3), 128.2 (d, CH, $^5J_{CF}$=1.1), 130.2 (d, CH, $^4J_{CF}$=6.6), 133.6 (CH), 134.0 (d, C, $^3J_{CF}$=4.3), 167.9 (d, C, $^2J_{CF}$=23.7), 196.4 (d, C, $^2J_{CF}$=29.3); δ_F (188 MHz, $CDCl_3$): −152.4 (d, C, $^3J_{HF}$=25.8); m/z (EI): 221 (M^+), 201, 116, 105 (100), 77, 51. Found: C, 65.13; H, 5.61; N, 6.30. $C_{12}H_{12}NO_2F$ (221.23) requires: C, 65.15; H, 5.47; N, 6.33.

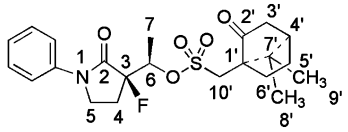
8.6.3. 3-Acetyl-3-fluoro-1-phenyl-2-pyrrolidinone (5d). δ_H (200 MHz, $CDCl_3$): 2.30–2.60 (m, 1H, CH_2), 2.52 (d, 3H, CH_3, $^4J_{HF}$=4.8), 2.75–3.00 (m, 1H, CH_2), 3.85–4.10 (m, 2H, CH_2), 7.20–7.25 (m, 1H, Ph), 7.40–7.55 (m, 2H, Ph), 7.60–7.70 (m, 2H, Ph); δ_C (75 MHz, $CDCl_3$): 26.2 (CH_3), 28.2 (d, CH_2, $^2J_{CF}$=21.0), 44.8 (d, CH_2, $^3J_{CF}$=3.4), 99.6 (d, C, J_{CF}=199.7), 119.9 (CH), 125.7 (CH), 128.9 (CH), 138.1 (C), 165.6 (d, C, $^2J_{CF}$=23.7), 205.0 (d, C, $^2J_{CF}$=32.5); δ_F (188 MHz, $CDCl_3$): −157.0/−157.5 (m); m/z (EI): 221 (M^+), 201, 179 (100), 159, 119, 104, 77, 43. Found: C, 65.22; H, 5.71; N, 6.34. $C_{12}H_{12}NO_2F$ (221.23) requires: C, 65.15; H, 5.47; N, 6.33.

8.7. 3-Fluoro-3-(1-hydroxyethyl)-1-phenyl-2-pyrrolidinone (6d)

A sample of 3-acetyl-3-fluoro-1-phenyl-2-pyrrolidinone (**5d**, 100 mg, 0.45 mmol, 53% ee, as obtained from the fluorination of **4d** using *S*,*S*-**1** as catalyst and Selectfluor) and [Ru((1*S*,2*S*)-*p*-TsNCH(C_6H_5)CH(C_6H_5)NH)(η^6-*p*-cymene)] (2.5 mg, 0.0045 mmol, 1 mol%) in 3 ml of isopropanol was stirred under argon at room temperature for 10 h. The reaction mixture was concentrated under reduced pressure.

The residue was purified by flash chromatography on silica gel using a 1:1 hexane/TBME mixture as an eluent to afford the products (44 mg, 43.6%) and recovered starting material (43 mg). Less polar isomer of the product (14 mg, 90% ee): R_f (hexane/TBME 1:2)=0.34 (UV, $KMnO_4$). δ_H (200 MHz, $CDCl_3$): 1.31 (d, J=6.4, 3H, CH_3), 2.13–2.31 (m, 1H), 2.47–2.74 (m, 2H), 3.75–4.00 (m, 2H), 4.31 (dq, J=10, 7, 1H), 7.21 (t, J=7.4, 1H), 7.40 (t, J=8.2, 2H), 7.65 (d, J=8.0); δ_F (188.3 MHz, $CDCl_3$): δ −158.1 (dt, J=26, 6.5); HPLC conditions: Agilent 1100, Daicel Chiracel Column (250×4.6 mm) OD–H, hexane/*i*-PrOH (96:4), 1.0 ml/min, detector 210 nm, retention times 20.5 (major) and 23.0 min. More polar isomer (30 mg, 96% ee): R_f (hexane/TBME 1:2)=0.40 (UV, $KMnO_4$). δ_H (200 MHz, $CDCl_3$): 1.25 (d, J=6.4, 3H, CH_3), 2.12–2.52 (m, 2H), 3.69–3.81 (m, 2H), 3.87–3.99 (m, 2H), 4.22(dq, J=16, 7, 1H), 7.21 (t, J=7.2, 1H), 7.39 (t, J=8.0, 2H), 7.63 (d, J=8.2); δ_F (188.3 MHz, $CDCl_3$): −164.0–164.3 (m); HPLC conditions: Agilent 1100, Daicel Chiracel Column (250×4.6 mm) OD–H, hexane/*i*-PrOH (96:4), 1.0 ml/min, detector 210 nm, retention times 41.9, 43.2 (major).

8.8. Compound 7



A solution of 3-fluoro-3-(1-hydroxyethyl)-1-phenyl-2-pyrrolidinone (**6d**, 30 mg, 0.13 mmol, 96% ee) and DMAP (22.6 mg, 0.2 mmol, 1.5 equiv) in 2 ml of dichloromethane was cooled to 0 °C and *S*-camphorsulfonyl chloride (40 mg, 0.16 mmol, 1.2 equiv) was added. Stirring was continued for 2 h at 0 °C, and then 3 days at room temperature before water (10 ml) was added. The reaction mixture was diluted with CH_2Cl_2 (20 ml). The organic phase was washed with brine, dried over $MgSO_4$, and concentrated under vacuo. The product was purified by flash chromatography on silica gel (hexane/EA=2:1) to afford 9.5 mg of a white solid, along with recovered starting material (20 mg). R_f (hexane/EA 1:2)=0.24 (UV, Mostaine). δ_H (300 MHz, $CDCl_3$): 0.98 (s, CH_3–camphor, 3H), 1.21 (s, CH_3–camphor, 3H), 1.37–1.46 (s, CH_2-6′, 1H), 1.65–1.74 (m, CH_2-6′, 1H), 1.53 (d, J=6.6, CH_3-6, 3H), 1.91 (s, CH_2-3′, 1H), 1.97 (s, CH_2-3′, 1H), 2.01–2.17 (m, CH-4′, 1H), 2.35–2.51 (m, CH_2-5′, 2H), 2.53–2.77 (m, CH_2-3, 2H), 3.15 (d, J=15.0, CH_3-10′, 1H), 3.67 (d, J=15.0, CH_3-10′, 1H), 3.81–3.90 (m, CH_2-4, 1H), 3.94–4.02 (m, CH_2-4, 1H), 5.23–5.33 (m, CH-5, 1H), 7.24 (t, J=7.8, 1H, Ph), 7.42 (t, J=8.0, 2H, Ph), 7.65 (d, J=7.8, 2H, Ph); δ_C (75.5 MHz, $CDCl_3$): 16.7 (CH_3–camphor), 16.8 (CH_3–camphor), 19.9 (d, J=14.6, CH_3-7), 25.3 (CH_2-5′), 26.1 (d, J=23.5, CH_3-3), 27.0 (CH_2-6′), 42.6 (CH_2-3′), 43.0 (CH-4′), 44.9 (CH_2-4), 48.1 (C-7′), 48.7 (CH_2-10′), 58.2 (C-1′), 79.3 (d, J=27.6, CHOH-5), 97.7 (d, J=187.0, C-2), 120.3 (CH), 126.1 (CH), 129.3 (CH), 138.4 (C), 166.8 (d, J=22.2, CON-1), 214.1 (CO-2′); δ_F (188.3 MHz, $CDCl_3$): −149.8 (td, J=23.0, 10.8); ν_{max} (cm^{-1}, KBr pellet): 2960.9, 1749.4, 1704.1, 1497.3, 1358.2, 1168.1, 967.5, 920.8, 772.3, 506.5. Found: C, 60.55; H, 6.67; N, 2.98. $C_{22}H_{28}FNO_5S$ requires: C, 60.39; H, 6.45; N, 3.20.

Acknowledgements

We thank Dr. Diego Broggini and Dr. Sebastian Gischig for determining the crystal structures of compounds **3a** and **7**, Dr. Heinz Rüegger for assistance with the 2D NMR characterization of complexes **3**, and ETH for financial support (Ph.D. theses of M.P. and Y.L.).

References and notes

1. Hintermann, L.; Togni, A. *Angew. Chem., Int. Ed.* **2000**, *39*, 4359–4362.
2. Enders, D.; Hüttl, M. R. M. *Synlett* **2005**, 991–993.
3. Bernardi, L.; Jørgensen, K. A. *Chem. Commun.* **2005**, 1324–1326.
4. Hamashima, Y.; Suzuki, T.; Shimura, Y.; Shimizu, T.; Umebayashi, N.; Tamura, T.; Sasamoto, N.; Sodeoka, M. *Tetrahedron Lett.* **2005**, *46*, 1447–1450.
5. Shibata, N.; Kohno, J.; Takai, K.; Ishimaru, T.; Nakamura, S.; Toru, T.; Kanemasa, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 4204–4207.
6. Steiner, D. D.; Mase, N.; Barbas, C. F., III. *Angew. Chem., Int. Ed.* **2005**, *44*, 3706–3710.
7. Ran Kim, H.; Young Kim, D. *Tetrahedron Lett.* **2005**, *46*, 3115–3117.
8. Beeson, T. D.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 8826–8828.
9. France, S.; Wheatherwax, A.; Lectka, T. *Eur. J. Org. Chem.* **2005**, 475–479.
10. Oestreich, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 2324–2327.
11. Ibrahim, H.; Togni, A. *Chem. Commun.* **2004**, 1147–1155.
12. Ma, J.-A.; Cahard, D. *Chem. Rev.* **2004**, *104*, 6119–6146.
13. Seebach, D.; Beck, A. K.; Heckel, A. *Angew. Chem., Int. Ed.* **2001**, *40*, 92–138.
14. Mikami, K.; Terada, M. *Lewis Acids in Organic Synthesis*; Yamamoto, H., Ed.; Wiley-VCH: Weinheim, 2000; Vol. 2, pp 799–848.
15. (a) Hintermann, L.; Togni, A. *Helv. Chim. Acta* **2000**, *83*, 2425–2435; (b) Ibrahim, H.; Kleinbeck, F.; Togni, A. *Helv. Chim. Acta* **2004**, *87*, 605–610.
16. Frantz, R.; Hintermann, L.; Perseghini, M.; Broggini, D.; Togni, A. *Org. Lett.* **2003**, *5*, 1709–1712.
17. Toullec, P. Y.; Bonaccorsi, C.; Mezzetti, A.; Togni, A. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5810–5814.
18. Jereb, M.; Togni, A. *Org. Lett.* **2005**, *7*, 4041–4043.
19. Piana, S.; Devillers, I.; Togni, A.; Röthlisberger, U. *Angew. Chem., Int. Ed.* **2002**, *41*, 979–982.
20. Shao, M.-Y.; Gau, H.-M. *Organometallics* **1998**, *17*, 4822–4827.
21. Shao, M.-Y.; Sheen, W.-S.; Gau, H.-M. *Inorg. Chim. Acta* **2001**, *314*, 105–110.
22. Haase, C.; Sarko, C. R.; DiMare, M. *J. Org. Chem.* **1995**, *60*, 1777–1787.
23. Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. *J. Am. Chem. Soc.* **1995**, *117*, 4435–4436.
24. Gothelf, K. V.; Jørgensen, K. A. *J. Chem. Soc., Perkin Trans. 2* **1997**, 111–115.

25. Jensen, K. B.; Gothelf, K. V.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **1997**, *62*, 2471–2477.
26. Pichota, A.; Pregosin, P. S.; Valentini, M.; Wörle, M.; Seebach, D. *Angew. Chem., Int. Ed.* **2000**, *39*, 153–156.
27. Inoue, T.; Kitagawa, O.; Ochiai, O.; Shiro, M.; Taguchi, T. *Tetrahedron Lett.* **1995**, *36*, 9333–9336.
28. Seebach, D.; Plattner, D. A.; Beck, A. K.; Wang, Y. M. *Helv. Chim. Acta* **1992**, *75*, 2171–2209.
29. Hafner, A.; Duthaler, R. O.; Marti, R.; Rihs, G.; Rothe-Streit, P.; Schwarzenbach, F. *J. Am. Chem. Soc.* **1992**, *114*, 2321–2336.
30. Duthaler, R. O.; Hafner, A.; Alsters, P. L.; Bold, G.; Rihs, G.; Rothe-Streit, P.; Wyss, B. *Inorg. Chim. Acta* **1994**, *222*, 95–113.
31. Hintermann, L.; Broggini, D.; Togni, A. *Helv. Chim. Acta* **2002**, *85*, 1597–1612.
32. Sanger, A. R. *Inorg. Nucl. Chem. Lett.* **1973**, *9*, 351–354.
33. Hattori, K.; Yamada, A.; Kuroda, S.; Chiba, T.; Murata, M.; Sakane, K. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 383–386.
34. Toullec, P. Y.; Devillers, I.; Frantz, R.; Togni, A. *Helv. Chim. Acta* **2004**, *87*, 2706–2711.
35. Ohkuma, T.; Noyori, R. *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 2004; Supplement 1, pp 1–41, and references cited therein.

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Selenium-catalyzed oxidative halogenation

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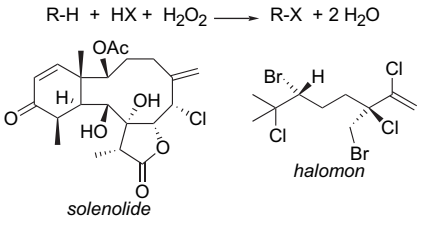
Abstract—Organoselenides catalyze the oxidation of halides by H_2O_2. Furthermore, these selenides catalyze the transfer of oxidized halogens from *N*-halosuccinimides to olefins and ketones. Thus, organoselenides catalyze oxidative halogenation reactions including halolactonization, α-halogenation of ketones, and allylic halogenation. The ability of selenium to undergo reversible $2e^-$ oxidation–reduction chemistry facilitates halogenation through selenium-bound halogen intermediates.

1. Introduction

Biological systems use haloperoxidase enzymes to catalyze the halogenation of organic substrates with H_2O_2/X^- (X= Cl, Br, and I; Scheme 1), resulting in a wealth of halogenated natural products.[1–4] While their biological function is often unknown, several halometabolites have been shown to be involved in chemical defense.[5] The properties that make these compounds feed deterrents also lead to antibacterial, antifungal, antiviral, and antitumor activity.[6] Common structural motifs include substituted tetrahydrofurans and tetrahydropyrans, which are apparently derived from halocyclization reactions.[3] Also, products such as the antiviral solenolide[7] and the antitumor agent halomon[8] are seemingly derived from simple additions such as dihalogenation, allylic halogenation, and halohydration of terpenes. The efficient synthesis of such compounds necessitates the selective introduction of carbon–halogen bonds, unfortunately most attempts to selectively halogenate substrates in vitro using haloperoxidase enzymes have failed.[9,10] This failure has been ascribed to the propensity of the enzymes to release freely-diffusing sources of oxidized halogen (HOX and X_2).[1] Thus, the development of a synthetic haloperoxidase that halogenates substrates through reagent-bound intermediates remains a significant challenge.



Scheme 1.

Selenium compounds are of interest for haloperoxidase mimicry due to the biological role of selenium in peroxide activation. In response to oxidative stress, the enzyme glutathione peroxidase utilizes catalytic selenocysteine residues to remove peroxides by oxidation of the sulfide glutathione.[11] Since oxidative stress has been correlated with aging and disease,[12] various synthetic selenium antioxidants have been produced as potential pharmaceuticals.[13] Many of these have been shown to be effective at catalytic reduction of peroxide.[14] In fact, some selenium-containing peroxidase catalysts have been used to catalyze oxidative halogenations,[15] however, these catalysts appear to function only as halide oxidants that produce freely-diffusing electrophilic halogen sources such as Br_2. Thus, in pursuit of reagent-controlled selectivity, our goal is to catalyze oxidative halogenation *through catalyst-bound halogen sources*.

Initially, potential catalysts were screened for their ability to catalyze haloperoxidase-like chemistry. The conversion of phenol red to bromophenol blue was used as a qualitative measure of the haloperoxidase activity. Electrophilic halogenation of phenol red produces bromphenol blue, so electrophilic halogenation through oxidized halogen species can be easily probed by color change (Scheme 2).[16] Treatment of a 0.08 M aqueous NaBr solution containing phenol red (0.1 mmol) and PhSeCl (0.02 mmol) with H_2O_2 resulted in a steady change in color from red to deep blue over a period of 24 h. The cyclic selenamide Ebselen behaved similarly, although its solubility was significantly lower. The control, which contained no selenium, remained unchanged.

Having identified several potential selenium catalysts for oxidative halogenation, attention was turned to the development of synthetic methods for the introduction of halogen functionality. While the oxidation of phenol red was a useful initial screen, it was unclear from these experiments whether the oxidative halogenation was occurring through

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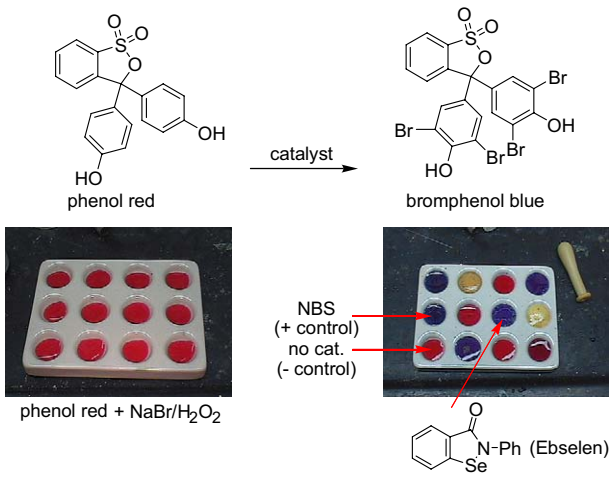


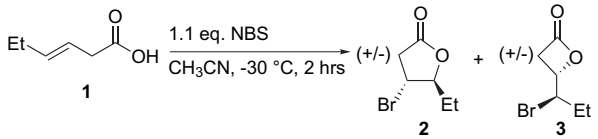
Scheme 2. Screening for haloperoxidase-like activity.

freely-diffusing oxidized halogens (i.e., Br_2 and HOBr) or through reagent-bound oxidized halogens. With the eventual goal of exploiting catalyst-control of regio- or stereoselectivity, we felt it was crucial that the catalysts halogenate organic substrates through reagent-bound halogen species. Thus, a reagent that can catalytically oxidize Br^- to 'Br^+' must also be capable of catalyzing Br^+ addition to the substrates. Since we know that various selenium catalysts are capable of catalyzing the oxidation of halides, we shifted our focus to catalyzing X^+ transfer from 'preoxidized' halogen sources such as *N*-halosuccinimides.

Since haloperoxidase enzymes seemingly control a wide variety of halogenation reactions, we chose to investigate the ability of organoselenium compounds to catalyze a diverse array of oxidative halogenation reactions. These include halolactonization, α-halogenation of ketones, and allylic halogenation.[17]

2. Halolactonization

To begin, a variety of selenium catalysts were screened for their ability to control the regioselectivity of bromolactonization with *N*-bromosuccinimide (NBS).[17a] Although it was not tested in our model study using phenol red, diphenyl diselenide turned out to be the most active and selective catalyst for bromolactonization (Scheme 3). While cyclization of *trans*-3-hexenoic acid using NBS in the absence of catalyst exhibited a 2:1 selectivity for the formation of the γ-lactone, performing the same reaction in the presence of 5 mol % diphenyl diselenide led to a useful regioselectivity of

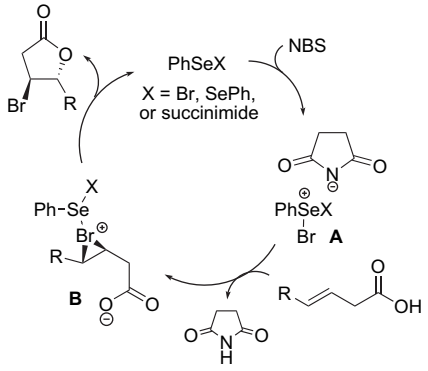


	2	3
no catalyst	2	1
5 mol % PhSeSePh	17	1
5 mol % PhSeBr	4	1
5 mol % PhSe(pthalimide)	2	1

Scheme 3. Selenium-catalyzed halolactonization.

17:1 in favor of the γ-lactone (**2**). Furthermore, the β-lactone (**3**) was not converted to the γ-lactone under the conditions of catalysis, so the observed regioselectivity is the result of kinetic control rather than thermodynamic control.

Careful investigation of this transformation substantiated the catalytic effect of PhSeSePh. Specifically, time-dependent ^1H NMR spectroscopic investigation of the reaction mixtures with and without catalyst were performed at −30 °C in CD_3CN. At this temperature, hexenoic acid failed to react with NBS in the absence of catalyst, however, NBS rapidly reacted in the presence of 5 mol % PhSeSePh. Furthermore, the fact that free NBS is not observed in solution suggested that the overall rate of the catalytic reaction was dictated by the rate of dissolution of NBS in CH_3CN. While conclusive mechanistic studies remain to be done, we propose that the electrophilic NBS is activated via nucleophilic attack by PhSeSePh (Scheme 4). The oxidized selenium halide is then capable of cyclizing the olefin in a manner similar to bromopyridinium reagents, where the pyridine (or selenium) derivative remains coordinated to bromine during lactone ring formation.[18]



Scheme 4.

Encouraged by the reactivity of the selenium catalyst, we were able to show multiple examples of halocyclizations of other unsaturated acids, as well as an example of chlorolactonization utilizing NCS and PhSeCl (Fig. 1).

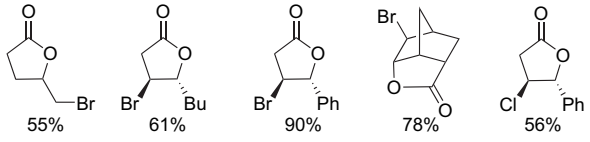


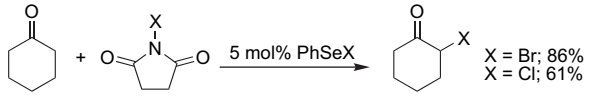
Figure 1. Products of selenium-catalyzed halolactonization.

3. α-Halogenation

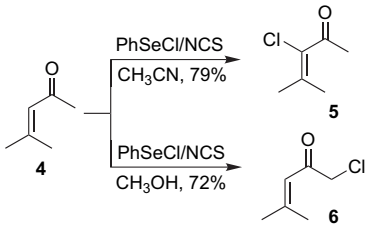
Having demonstrated that organoselenium reagents can activate electrophilic halogen sources toward oxidative halogenation, we turned our attention to α-halogenation of ketones.[17b] In this case, a catalyst screen revealed phenylselenium halides to be more active than other selenium catalysts such as diphenyl diselenide.

Cyclohexanone underwent α-monohalogenation with either NCS or NBS and 5 mol % of the corresponding phenylselenium halide (Scheme 5). No reaction was observed for either

case in the absence of the selenium catalyst. Mesityl oxide (**4**) also underwent clean α-chlorination with a curious solvent-dependent regioselectivity (Scheme 6). In acetonitrile, only the product of vinyl halogenation (**5**) was formed,[19] while in methanol only the product of methyl halogenation (**6**) was observed. This difference in regiochemistry is likely caused by different catalyst speciation in CH_3OH versus CH_3CN.

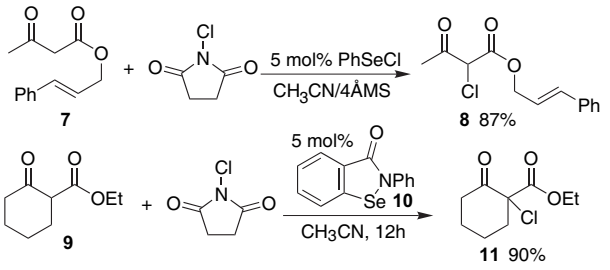


Scheme 5.



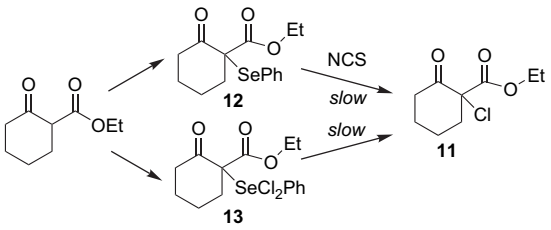
Scheme 6.

Halogenation of β-ketoesters was also investigated. Bromination of β-ketoesters was difficult to control, producing mixtures of mono- and α,α-dibrominated products. However, chlorination proceeded smoothly to provide mono-chloro-β-ketoesters in good yield. While a variety of β-ketoesters undergo monochlorination, the ability to monochlorinate the β-ketoester fragment of **7** in the presence of a reactive olefin is particularly noteworthy (Scheme 7). In addition, the pharmaceutical peroxidase Ebselen (**10**) was a competent catalyst, however, the rate of catalysis was slow due to the poor solubility properties of the cyclic selenimide.

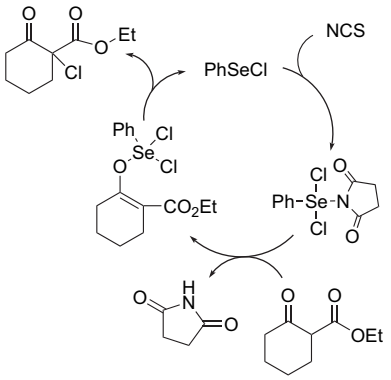


Scheme 7.

The mechanism of oxidative chlorination was probed by preparation of several potential intermediates (**12** and **13**, Scheme 8). The fact that formation of chlorinated product from α-selenylated intermediates is not kinetically competent with the observed catalysis strongly suggests that the reaction proceeds by an electrophilic chlorination mechanism rather than electrophilic selenylation. This is important because it indicates that selenium catalysts function by enhancing the electrophilicity of oxidized halogen sources. We speculate that the activation of NCS proceeds by oxidative addition to PhSeCl to form an Se(IV) intermediate (Scheme 9).[20] Deprotonation and halogen transfer would complete the catalytic cycle.



Scheme 8.

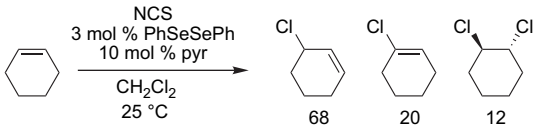


Scheme 9.

4. Allylic halogenation

While the halolactonization and α-halogenation reactions do not proceed by formation of C–Se bonds, the reaction of Se(II)- and Se(IV)-halogen reagents with alkenes is a well-known method for the stereospecific *anti*-addition of Se–X bonds to olefins.[21] Often times, this stoichiometric addition is followed by oxidative *syn*-elimination of selenium to regenerate an alkene.[22] Thus the selenium addition–elimination sequence is a potentially powerful synthetic tool for creating carbon–halogen bonds without loss of any substrate functionality (i.e., olefins are regenerated).

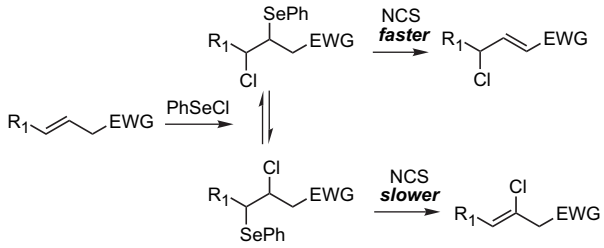
Sharpless initially reported that the addition and elimination steps can be combined in one pot, resulting in allylic halogenation,[20] however, the reaction was complicated by competing formation of regioisomers as well as vinyl halides and dihalides (Scheme 10).



Scheme 10.

We felt that a synthetically useful procedure would result if competing formation of vinyl halide was circumvented by providing either an electronic or steric bias for the elimination reaction (Scheme 11). Toward this end, β,γ-unsaturated carboxylic acids, nitriles, and esters were subjected to our modified conditions for selenium-catalyzed allylic halogenation.[17c] In each of these cases, the allylic chlorides are isolated as single regioisomers, and <5% of vinyl chlorides and dichlorides are formed (Fig. 2). Clearly the presence of an

electron-withdrawing group leads to preferred formation of the conjugated products.



Scheme 11. Electronic control of the elimination regiochemistry.

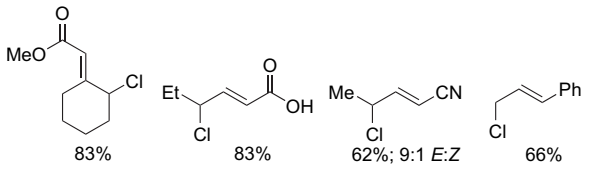
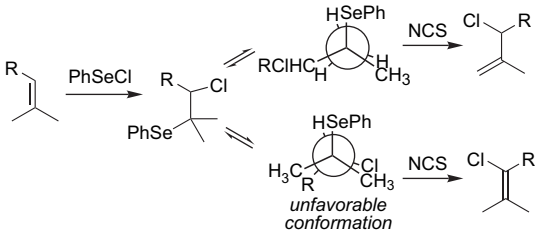


Figure 2.

In addition to the electronic bias present in the above substrates, the selectivity of halogenation can also be controlled by sterics. This is most evident in the high selectivity for allylic halogenation exhibited by prenyl olefins (Scheme 12). If we assume that the elimination proceeds by *syn*-elimination of H and Se, as is common for selenium eliminations, then the elimination to form vinyl chloride requires adoption of a high-energy eclipsed conformation. Consistent with this picture, treatment of a variety of prenyl olefins under the conditions for selenocatalytic allylic chlorination produced the terminal olefinic regioisomers with high selectivity (>85%, Fig. 3).



Scheme 12.

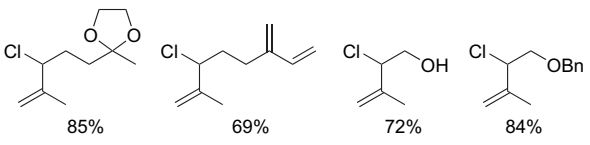
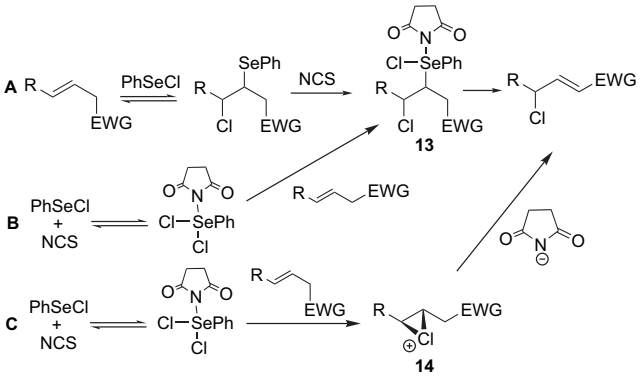


Figure 3.

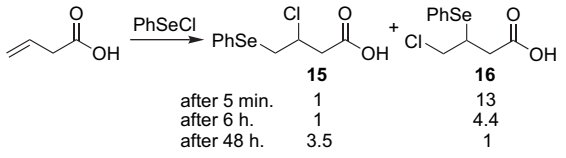
5. Mechanism of allylic chlorination

We envisioned that allylic chlorination might occur in one of three ways,[23] designated paths A, B, and C (Scheme 13). Path A is characterized by 1,2-addition of phenylselenium chloride across the olefin. Oxidation of the addition product by NCS would lead to **13**. Finally, elimination of succinimide would produce the allyl halide and regenerate the catalyst. Path B involves oxidative addition of NCS to phenylselenium chloride,[20] forming phenyl(succinimidyl)-selenium dichloride. The selenium(IV) chloride could then add across the olefin, producing **13**, which will follow the same course as in path A. Finally, in mechanism C, an oxidized selenium compound could act as a source of chloronium ions, leading to allyl halide through a pathway similar to that observed for Walling chlorination with ROCl.[24] Ultimately, pathways A and B are distinguished by the oxidation states of selenium in the addition and C is distinguished by the lack of formation of a C–Se bond.



Scheme 13.

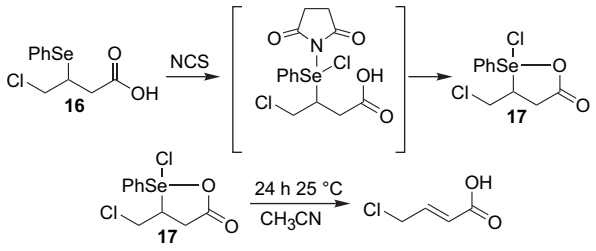
To distinguish between these pathways, experiments were conducted with stoichiometric quantities of PhSeCl in hopes of observing the elementary steps of catalysis. We chose to initiate studies by investigating the elementary steps in the order proposed for mechanism A: addition of PhSeCl to the olefin, oxidation of Se(II) to Se(IV), and subsequent elimination. Thus, we first treated 3-butenoic acid [0.23 M] with 1 equiv PhSeCl in dry CD_2Cl_2. After 5 min at ambient temperature, a 1:13 ratio of **15**:**16** exists (Scheme 14).[25] Upon prolonged standing, this mixture equilibrates to a 3.5:1 ratio of **15**:**16**. Thus, **16** is the kinetic product and **15** is the thermodynamic product.



Scheme 14.

Next, in order to look at the oxidation step necessary for mechanism A, a solution of kinetic addition products was generated followed by the addition of NCS after 5 min. The oxidation occurred rapidly (<5 min), forming succinimide and a new compound in >90% yield as judged by integration of the ^{1}H NMR spectrum. Although the oxidized product was not stable to isolation, it has been tentatively assigned as the selenurane **17** based on NMR spectroscopic characterization and the observed liberation of succinimide (Scheme 15). The formation of this compound can be explained by oxidation of addition product **16** by NCS, followed by elimination of succinimide.[26] Importantly, allowing **17** to stand at room temperature resulted in the clean liberation of allylic halide. Furthermore, the elimination occurred with a concomitant change in the color of the solution

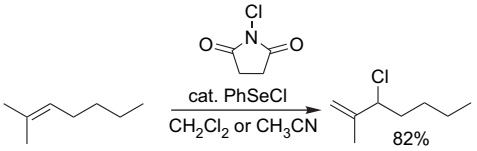
to orange, the color expected if PhSeCl was regenerated. The formation of a relatively stable selenurane is also consistent with the faster reaction of esters (which cannot form selenurane) as compared to carboxylic acids. In fact, no intermediates were observed when the NCS oxidation was performed on the analogous substrate where the carboxylic acid was protected as the methyl ester.



Scheme 15.

While we have not ruled out potential mechanism B, the combination of each of the steps observed with stoichiometric selenium represents a closed catalytic cycle for selenocatalytic allylic halogenation through mechanism A.

At this point, one major issue remained unexplained. Qualitatively, these reactions appeared to be inhibited by NCS, with the most dramatic inhibition occurring with β,γ-unsaturated carboxylic acids. Because the halogenation of acids was inhibited by even a small excess of NCS relative to PhSeCl, we chose to conduct kinetic experiments on a more easily studied substrate, 2-methyl-2-heptene (Scheme 16).



Scheme 16.

The reaction of 2-methyl-2-heptene with pseudo-first order concentrations of NCS was studied by ^{1}H NMR spectroscopy in CD_2Cl_2. The control reaction of 2-methyl-2-heptene with NCS in the absence of PhSeCl was slow, providing 5% conversion upon standing for 24 h in CH_2Cl_2 at ambient temperature. In contrast, the initial rates of 2-methyl-2-heptene conversion in the presence of 2.5 and 5 mol % PhSeCl and 0.24 M NCS were $3.6(5)\times10^{-4}$ s^{-1} and $6.7(3)\times10^{-4}$ s^{-1} ($t_{1/2}$~17 min), respectively.[27]

Examining the effect of higher NCS concentrations on the rate proved more interesting. The overall rates of product formation decrease with increasing [NCS], confirming that NCS is inhibiting the reaction (Fig. 4). However, close analysis of the data shows that the initial rates of reaction are the same throughout the range of 0.24–0.54 M [NCS] (Fig. 5). In other words, the initial catalysis is zero-order in NCS, but the overall rates and conversions are inhibited by NCS.

Given the observed kinetics, the rate law for selenium-catalyzed allylic halogenation follows the rate law $-$d[2-methyl-heptene]/dt=k[PhSeCl][olefin] at an early reaction

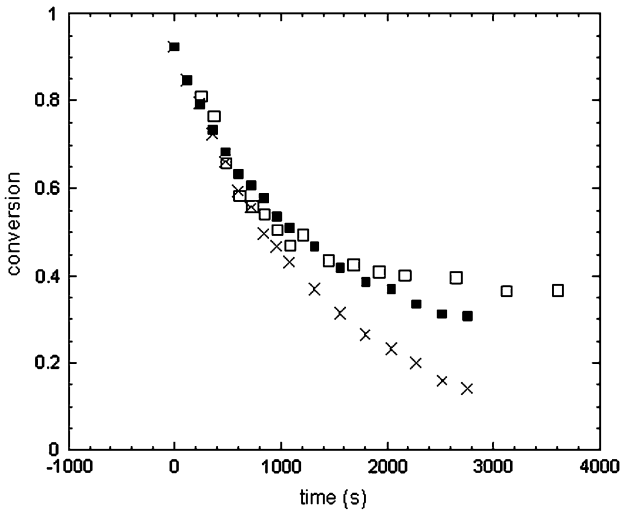


Figure 4. Decay of 0.016 M 2-methyl-2-heptene at × 0.24 M, ■ 0.37, and □ 0.55 M NCS in CD_2Cl_2.

time. We have conclusively shown that the rate-limiting step for allylic halogenation of β,γ-unsaturated acids is the elimination step. Since the addition of PhSeCl to alkenes and the oxidation of Se(II) to Se(IV) are processes that are known to be rapid,[20] we propose that elimination is rate-limiting for other substrates as well. The zero-order dependence of the initial rate on [NCS] is most easily explained if one assumes that the resting state of the catalyst is PhSe(succinimide)Cl_2 (Scheme 17). Under these conditions the compositions of both the resting state and rate-limiting transition state (elimination) include one NCS molecule, thus a zero-order dependence on [NCS] would be expected. Consistent with the hypothesis of PhSe(succinimide)Cl_2 as the resting state, the ^{77}Se resonance for PhSeCl in CD_2Cl_2 (δ 1042 ppm) is immediately replaced by a new species with a resonance at δ 701 ppm upon addition of 1 equiv of NCS. Furthermore, the inhibition of both rate and conversion at high [NCS] and long reaction times indicates the presence of a process that irreversibly destroys the catalyst. Importantly, over the timescale of typical catalysis (1–3 h), the ^{77}Se resonance at 701 ppm slowly decays with the appearance of a new species at δ 905 ppm. While we cannot

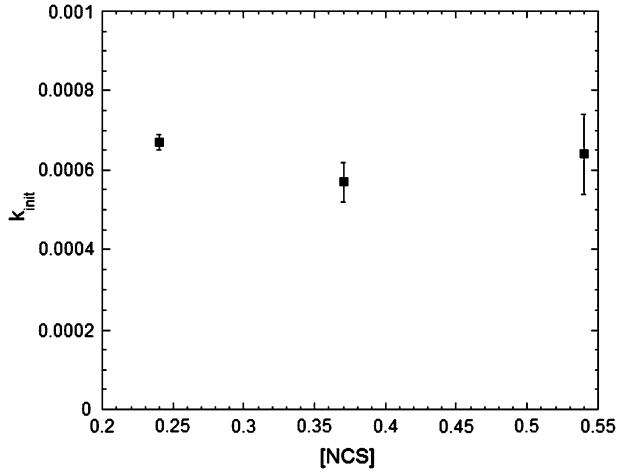
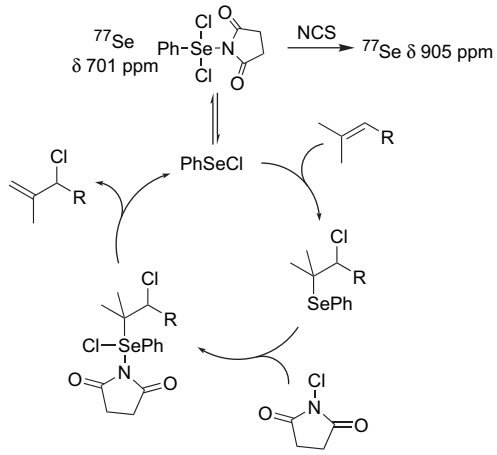


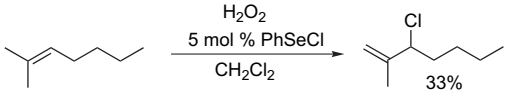
Figure 5. Initial rate of 2-methyl-2-heptene decay as a function of [NCS].

comment further on the identity of this selenium complex, it seems likely that it is the product of over-oxidation to a Se(VI) complex.



Scheme 17.

Finally, since arylselenides have been established as peroxidase catalysts as well as catalysts for oxidative halogenation, we were interested in the possibility of using simple arylselenides as selective haloperoxidase analogous. Indeed, when phenylselenium chloride (5 mol %) is allowed to react with 2-methyl-2-heptene and sodium chloride in a biphasic CH_2Cl_2/30% H_2O_2 mixture, allyl halide **8a** is produced in 33% yield after 1 h (Scheme 18). While the conversion is not high, this experiment demonstrates the potential utility of selenium reagents as selective, synthetic haloperoxidases.



Scheme 18.

6. Conclusions

In conclusion, allylic oxidation of alkenes takes advantage of the facile 1,2-addition and 1,2-elimination reactions afforded by Se(II) and Se(IV), respectively. Ultimately, catalysis of halolactonization, α-halogenation, and allylic chlorination is made possible through the accessibility of selenium-centered $2e^-$ oxidation–reduction cycles. In this way, selenium is analogous to many transition metal catalysts, which operate by similar Tolman cycles.

7. Experimental

7.1. General

^1H NMR spectra were obtained on a Bruker Avance 400 spectrometer and referenced to residual protio solvent signals. ^{13}C and ^{77}Se NMR spectra were obtained on a Bruker Avance 500 DRX spectrometer. Structural assignments are based on ^1H, ^{13}C, DEPT-135, COSY, and HMQC spectroscopies. Column chromatography was performed with silica gel, (0.06–0.2 mm). Reactions were monitored by thin-layer chromatography on Merck Kieselgel $60F_{254}$.

7.2. General procedure for bromolactonization

Diphenyl diselenide (0.05 mmol) was dissolved in 5 mL of CH_3CN (stored over 4 Å MS), which produced a yellow solution. The unsaturated acid (1.00 mmol) was added, and the resulting mixture was cooled to −30 °C. Next, *N*-bromosuccinimide (1.1 mmol) was added with stirring, and the resulting reaction mixture was stirred until reaction went to completion as determined by TLC analysis (1–5 h). The resulting solution was concentrated to <1 mL, and diethyl ether (10 mL) was added. The ether was decanted from the solid and washed with H_2O (2×3 mL). The resulting ether layer was dried over $MgSO_4$, concentrated, and the residue was purified by flash chromatography (100% methylene chloride).

7.3. General procedure for α-halogenation

The ketone (1 mmol) and PhSeCl (0.05 mmol) were dissolved in dry CH_3CN (stored over 4 Å MS). *N*-Chlorosuccinimide (1.1 mmol) was added and the solution was stirred at room temperature. Upon completion as determined by TLC analysis, the reaction was poured into H_2O (5 mL) and extracted with Et_2O (3×10 mL). The resulting ether layer was dried over $MgSO_4$, concentrated, and the residue was purified by flash chromatography.

7.4. General procedure for allylic halogenation of unsaturated acids

Phenylselenium chloride (10 mol %, 0.052 mmol) was dissolved in 3 mL CH_3CN (stored over 4 Å MS), producing an orange solution. To this solution 4 Å MS (four beads, ~0.15 g) was added followed by addition of the β,γ-unsaturated acid (0.52 mmol). The addition of the olefin resulted in an immediate color change from orange to pale yellow. A solution of *N*-chlorosuccinimide (0.57 mmol, in 3 mL CH_3CN) was prepared and drawn into a 5 mL GASTIGHT syringe equipped with a Teflon needle. The solution of NCS was added via syringe pump at the rate of 0.191 mL/h. After 16 h, completion of the reaction was confirmed by ^1H NMR. This solution was concentrated to <1 mL, and 10 mL diethyl ether was added. The ether was decanted from the solid and washed with H_2O (2×3 mL). The resulting ether layer was dried over $MgSO_4$, concentrated and the residue was purified by flash chromatography (95:5 hexane/ethyl acetate).

7.5. General procedure for allylic halogenation of prenyl olefins

Phenylselenium chloride (10 mol %, 0.052 mmol) was dissolved in 3 mL CH_3CN (stored over 4 Å MS), producing an orange solution. To this solution, olefin (0.52 mmol) was added. The addition of the olefin resulted in an immediate color change from orange to pale yellow. *N*-chlorosuccinimide (77 mg, 0.57 mmol) was then added to reaction. After 1 h, completion of the reaction was confirmed by ^1H NMR. This solution was concentrated to <1 mL, and

10 mL diethyl ether was added. The ether was decanted from the solid and washed with H_2O (2×3 mL). The resulting ether was dried over $MgSO_4$, concentrated, and the residue was purified by flash chromatography.

7.6. In situ generation of 4-chloro-3-(phenylselanyl)-butanoic acid (16)

PhSeCl (20 mg, 0.1 mmol) was dissolved in 600 μL CD_2Cl_2 in an NMR tube to produce an orange solution. To this solution, 3-butenoic acid (1 equiv) was added with shaking. The completion of the reaction was noted by a rapid color change to pale yellow. ^1H NMR characterization is consistent with the assigned structure:[25] ^1H NMR (400 MHz, CD_2Cl_2) δ 2.70 (dd, J=8.6, 16.7 Hz, 1H, CH*H*CHSePh), 3.19 (dd, J=4.3, 16.9 Hz, 1H, C*H*HCHSePh), 3.61 (m, 1H, CHSePh), 3.67 (app. t, J=10.39 Hz, 1H, CH*H*Cl), 3.96 (dd, J=3.8, 10.6 Hz, 1H, C*H*HCl), 7.34 (m, 3H, Ar–H), 7.62 (d, J=6.8 Hz, 2H, Ar–H), 10.70 (br s, 1H, CO_2H). Allowing the solution of **16** to stand at room temperature for 2 d led to complete equilibration to a 1:3.5 mixture of **16** and **3**-chloro-**4**-(phenylselanyl)butanoic acid (**15**): ^1H NMR (400 MHz, CD_2Cl_2) δ 2.79 (dd, J=9.1, 16.4 Hz, 1H, CH*H*CHCl), 3.22 (m, 1H, CH*H*CHCl), 3.30 (dd, J=3.5, 16.3 Hz, 1H, C*H*HSePh), 3.45 (dd, J=4.8, 13.1 Hz, 1H, CH*H*SePh), 4.38 (dt, J=4.4, 4.4, 9.1, 9.1 Hz, 1H, CHCl), 7.33 (d, J=2.5 Hz, 3H, Ar–H), 7.57 (dd, J=2.3, 5.8 Hz, 2H, Ar–H), 11.00 (br s, 1H, CO_2H).

7.7. In situ generation of selenurane (17)

A solution of **16** was generated as described above. After 5 min, NCS (14 mg, 0.1 mmol) was added. Shaking this mixture resulted in the formation of a colorless solution that contains a 1:1 mixture of succinimide and **17**. ^1H NMR (400 MHz, CD_2Cl_2) δ 2.87 (dd, J=9.1, 17.4 Hz, 1H, CH*H*CHSePh), 3.17 (d, J=17.4 Hz, 1H, CH*H*CHSePh), 4.22 (dd, J=12.4 Hz, 1H, C*H*HCl), 4.62 (dd, J=4.5, 12.4 Hz, 1H, CH*H*Cl), 4.72 (br s, 1H, CHSePhClO), 7.58 (m, 3H, Ar–H), 7.83 (d, J=8.0 Hz, 2H, Ar–H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 34.8 (*C*H_2CO_2), 43.8 (CH_2Cl), 69.6 (CHSe), 129.3 (Ar C–H), 130.5 (Ar C–H), 132.6 (Ar C–H), 134.5 (q Ar–C).

7.8. Kinetics

N-Chlorosuccinimide (19–43 mg) was dissolved in dry CD_2Cl_2 (580 μL). Upon complete dissolution of the NCS, 2-methyl-2-heptene (10 μL of a 0.97 M standard solution in CD_2Cl_2) was added. The NMR tube was sealed with a septum and immediately taken to the NMR spectrometer. Next, PhSeCl (10 μL of a 0.05 M standard solution in CD_2Cl_2) was injected and the sample was mixed by shaking. The resulting solutions were quickly inserted into the spectrometer for analysis.

References and notes

1. *Biohalogenation*; Neidleman, S. L., Geigert, J., Eds.; Wiley: New York, NY, 1986.
2. Butler, A.; Walker, J. V. *Chem. Rev.* **1993**, *93*, 1937–1944.
3. (a) Faulkner, D. J. *Nat. Prod. Rep.* **2002**, *19*, 1–48; (b) Faulkner, D. J. *Nat. Prod. Rep.* **2000**, *17*, 1–6.
4. Winterton, N. *Green Chem.* **2000**, *2*, 173–225.
5. (a) Paul, V. J.; Hay, M. E.; Duffy, J. E.; Fenical, W.; Gustafson, K. *J. Exp. Mar. Bio. Ecol.* **1988**, *114*, 249–260; (b) Cowart, J. D.; Fielman, K. T.; Woodin, S. A.; Lincoln, D. E. *Mar. Biol.* **2000**, *136*, 993–1002.
6. Faulkner, D. J. *Oceanus* **1992**, 29–35.
7. Groweiss, A.; Look, S. A.; Fenical, W. *J. Org. Chem.* **1988**, *53*, 2401–2406.
8. (a) Egorin, M. J.; Rosen, D. M.; Benjamin, S. E.; Callery, P. S.; Sentz, D. L.; Eiseman, J. L. *Cancer Chemother. Pharmacol.* **1997**, *41*, 9–14; (b) Jung, M. E.; Parker, M. H. *J. Org. Chem.* **1997**, *62*, 7094–7095.
9. Asymmetric oxidation of sulfides to sulfoxides has been successful with a haloperoxidase enzyme. Andersson, M.; Willets, A.; Allenmark, S. *J. Org. Chem.* **1997**, *62*, 8455–8458.
10. (a) Martinez, J. S.; Carroll, G. L.; Tschirret-Guth, R. A.; Altenhoff, G.; Little, R. D.; Butler, A. *J. Am. Chem. Soc.* **2001**, *123*, 3289–3294; (b) Itoh, N.; Hasan, A. K. M. Q.; Izumi, Y.; Yoshikazu, Y.; Yamada, H. *Eur. J. Biochem.* **1988**, *172*, 477–484.
11. (a) Kohrle, J.; Brigelius-Flohe, R.; Bock, A.; Gartner, R.; Meyer, O.; Flohe, L. *Biol. Chem.* **2000**, *381*, 849–864; (b) Gamble, S. C.; Wiseman, A.; Goldfarb, P. S. *J. Chem. Technol. Biotechnol.* **1997**, *68*, 123–134.
12. *Free Radicals in Molecular Biology, Aging and Disease*; Armstrong, D., Sohal, R. S., Cutler, R. G., Slater, T. F., Eds.; Raven: New York, NY, 1984.
13. Mugesh, G.; du Mont, W.-W.; Sies, H. *Chem. Rev.* **2001**, *101*, 2125–2179.
14. (a) Back, T. G.; Moussa, Z. *J. Am. Chem. Soc.* **2002**, *124*, 12104–12105; (b) Iwaoka, M.; Tomoda, S. *J. Am. Chem. Soc.* **1994**, *116*, 2557–2561; (c) Mugesh, G.; Panda, A.; Singh, H. B.; Punekar, N. S.; Butcher, R. J. *J. Am. Chem. Soc.* **2001**, *123*, 839–850.
15. (a) Drake, M. D.; Bateman, M. A.; Detty, M. R. *Organometallics* **2003**, *22*, 4158–4162; (b) Higgs, D. E.; Nelen, M. I.; Detty, M. R. *Org. Lett.* **2001**, *3*, 349–352.
16. (a) Stenger, V. A.; Kolthoff, I. M. *J. Am. Chem. Soc.* **1935**, *57*, 831–833; (b) Martinez, J. S.; Carroll, G. L.; Tschirret-Guth, R. A.; Altenhoff, G.; Little, R. D.; Butler, A. *J. Am. Chem. Soc.* **2001**, *123*, 3289–3294.
17. (a) Mellegaard, S. R.; Tunge, J. A. *J. Org. Chem.* **2004**, *69*, 8979–8981; (b) Wang, C.; Tunge, J. A. *Chem. Commun.* **2004**, 2694–2695; (c) Tunge, J. A.; Mellegaard, S. R. *Org. Lett.* **2004**, *6*, 1205–1207.
18. (a) Neverov, A. A.; Brown, R. S. *J. Org. Chem.* **1998**, *63*, 5977–5982; (b) Neverov, A. A.; Feng, H. X.; Hamilton, K.; Brown, R. S. *J. Org. Chem.* **2003**, *68*, 3802–3810.
19. Ley, S. V.; Whittle, A. J. *Tetrahedron Lett.* **1981**, *34*, 3301–3304.
20. (a) Hori, T.; Sharpless, K. B. *J. Org. Chem.* **1979**, *44*, 4204–4208; (b) Hori, T.; Sharpless, K. B. *J. Org. Chem.* **1979**, *44*, 4208–4210.
21. (a) *The Chemistry of Double-bonded Functional Groups*; Patai, S., Ed.; Wiley: New York, NY, 1977; (b) Engman, L. *J. Org. Chem.* **1987**, *52*, 4086–4094.
22. (a) Jones, D. N.; Mundy, D.; Whitehouse, R. D. *J. Chem. Soc., Chem. Commun.* **1970**, 86–87; (b) Sharpless, K. B.; Young, M. W.; Lauer, R. F. *Tetrahedron Lett.* **1973**, 1979–1982; (c) Reich, H. J. *Acc. Chem. Res.* **1979**, *12*, 22–30.
23. Radical inhibitors do not inhibit this reaction.

24. Walling, C.; Thaler, W. *J. Am. Chem. Soc.* **1961**, *83*, 3877–3884.
25. Selenolactonization of butenoic acid only occurs after passage through silica gel: Goldsmith, D.; Liotta, D.; Lee, C.; Zima, G. *Tetrahedron Lett.* **1979**, *50*, 4801–4804.
26. For a similar transformation see: Kataoka, T.; Iwamura, T.; Tsutsui, H.; Kato, Y.; Banno, Y.; Aoyama, Y.; Shimizu, H. *Heteroat. Chem.* **2001**, *12*, 317–326.
27. Clean first-order decay of the 2-methyl-2-heptene was observed over >3 half-lives only when [NCS]<0.3 M.

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Radical trifluoromethylation of ketone Li enolates

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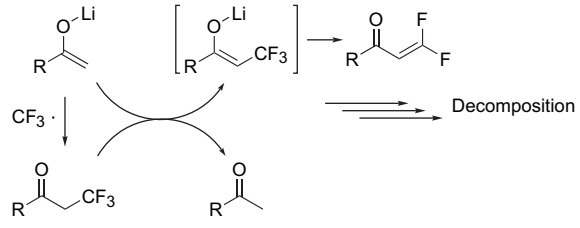
Abstract—It has generally been believed that highly basic Li enolates cannot be applied as substrates for radical trifluoromethylation due to defluorination of the α-CF_3 product. However, Li enolates can be in fact employed for radical trifluoromethylation. Moreover, the reaction is extremely fast and the minimum reaction time is only ∼1 s.

1. Introduction

CF_3 units could make a significant functional modification of an organic molecule as a new material and medicine.[1] In recent years, we have been engaged in exploring the synthetic potential of α-CF_3 carbonyl compounds as a new building block for CF_3 containing organic compounds.[2] The α-CF_3 carbonyl compounds are sensitive to basic conditions and facile defluorination is always a problem in the synthesis (Scheme 1). Only several synthetic methodologies for introducing CF_3 unit to α-position of carbonyl group have been developed.[2d,e,3–7] We have already reported the radical trifluoromethylation of Li[2e] enolates. Further exploration of this reaction is herein reported.

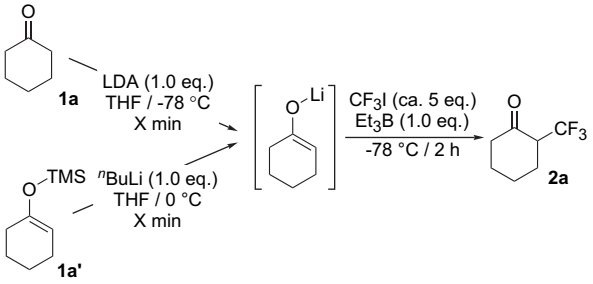


Scheme 1.

2. Results and discussion

There are two methods for the preparation of the Li enolate. One is the reaction of ketone with LDA at −78 °C and the other is the reaction of silyl enol ether with ^{n}BuLi at 0 °C (silyl-to-lithium method).[8] The former method could generate kinetic Li enolate and the latter could afford both kinetic and thermodynamic enolates depending on the parent silyl enol ether. The effect of the preparation time of the Li enolate was first investigated (Table 1). In the case of LDA method, 60 min of preparation time was necessary to give sufficient yield of the α-CF_3 product (entry 3). However, longer preparation time (120 min) was not necessary (entry 4). Without radical initiator Et_3B (entry 2), no product was detected and a large amount of cyclohexanone was recovered, indicating the radical reaction mechanism. On the other hand, in the case of silyl-to-lithium transmetallation method,

Table 1. Preparation time of the Li enolate



Entry	Substrate	*X* (min)	Yield (%)[a]
1	**1a**	30	63
2[b]		30	0
3		60	73
4		120	72
5	**1a′**	15	77
6		30	77
7		60	74
8		120	74

[a] Determined by ^{19}F NMR using BTF as an internal standard.
[b] The reaction was carried out without Et_3B.

Keywords: Trifluoromethylation; Li enolate; Radical addition.
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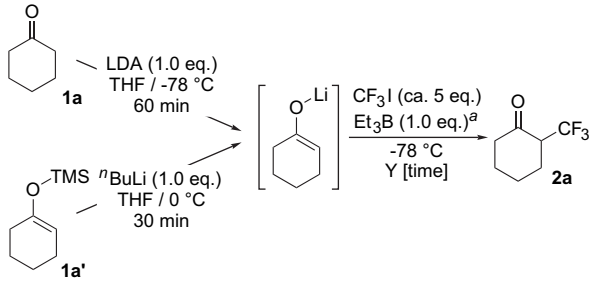
the yields of the α-CF_3 product did not change over the preparation time investigated (entries 5–8, 15–120 min). This indicates that silyl-to-lithium transmetallation is completed within 15 min. However, 30 min was adopted to ensure that the transmetallation was completed.

Next, radical reaction time was investigated (Table 2). In the case of Li enolate prepared by the LDA method, 1 h of reaction time gave the product in 80% yield (entry 3). The yield decreased when the reaction was carried out for 13 h (entry 1, 62% yield), probably due to the decomposition of the α-CF_3 product when the product was exposed to basic condition for prolonged time. However, shorter reaction time did not affect the yield; found to be 'long' ~1 s is enough to give the α-CF_3 product in 81% yield (entry 5).[9] On the other hand, with Li enolate prepared by silyl-to-lithium transmetallation method, the maximum yield was given at 2 h reaction time (entry 7, 77%). Shorter reaction time decreases the yield and ~1 s reaction time gave only 34% of the α-CF_3 product (entry 9). In order to make the reaction condition almost the same as that for LDA method, the reaction was carried out in the presence of LDA (entry 10). However, LDA did not affect the reaction. The difference between these two methods is not clear. However, it can be said that 2 h of reaction time is required for silyl-to-lithium method.

A variety of ketonic substrates were investigated using LDA to generate Li enolate (Table 3). In the case of cyclohexanone (entry 1) and 4-^{t}Bu- (entry 2), 2-Me- (entry 3), and 2-Ph- (entry 4) cyclohexanones, the reactions proceeded with extremely fast reaction rates and provided the α-CF_3 products in fair to good yields. The reaction rates of cyclopentanone (entry 5) and cycloheptanone (entry 6) were relatively slow (5 min). For acyclic substrates (entries 7–9), the yields were poor. Ester and amide were also investigated but did not give the α-CF_3 product at all. From the results described above, cyclohexanone derivatives are the most suitable substrate for this reaction system.

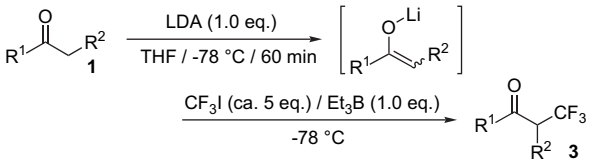
Table 2. Investigation of the trifluoromethylation time



Entry	Substrate	Reaction time Y	Yield (%)[b]
1	**1a**	13 h	62
2		2 h	73
3		1 h	80
4		1 min	83
5		~1 s	81
6	**1a′**	13 h	52
7		2 h	77
8		30 min	67
9		~1 s	34
10[c]		~1 s	36

[a] Et_3B was added in flat 15 s.
[b] Determined by ^{19}F NMR using BTF as an internal standard.
[c] In the presence of LDA.

Table 3. Radical trifluoromethylation of Li enolates prepared by LDA method



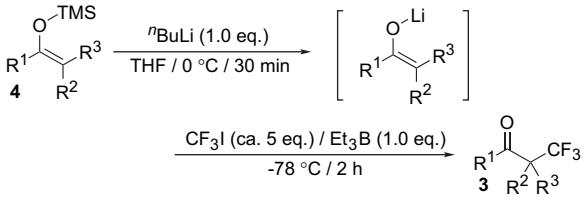
Entry[a]	Substrate	Product	Reaction time	Yield (%)[b]
1	**1a**	**2a**	~1 s	81
2	**1b**	**2b**	~1 s	71 (67) [73:27]
3	**1c**	**2c**	~1 s	74 [57:43]
4	**1d**	**2d**	~1 s	43 (40) [57:43]
5	**1e**	**2e**	5 min	40
6	**1f**	**2f**	5 min	48
7	**1g**	**2g**	5 min	25
8	**1h**	**2h**	5 min	17
9	**1i**	**2i**	1 min	35

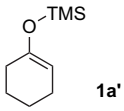
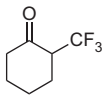
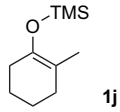
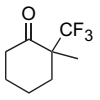
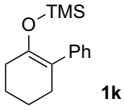
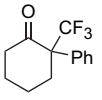
[a] Et_3B was added in flat 15 s.
[b] Determined by ^{19}F NMR using BTF as an internal standard. The values in ( ) refer to the yields of isolated products. The values in [ ] are the diastereomeric ratio.

Li enolates prepared by silyl-to-lithium transmetallation method were also investigated for the most suitable cyclohexanone derivatives (Table 4). α-Me- and α-Ph-cyclohexanones provided the products, which bear quaternary carbon centers attached with CF_3, in fair yields (entries 2 and 3).

In view of asymmetric radical trifluoromethylation, several solvents and additives were examined (Table 5). α-Ph-cyclohexanone was adopted as the substrate in order to prevent the racemization of the product. The parent Li enolate was generated by silyl-to-lithium method in the presence of DME or TMEDA. In THF, addition of DME (entry 2) and TMEDA

Table 4. Radical trifluoromethylation of Li enolates prepared by silyl-to-lithium method

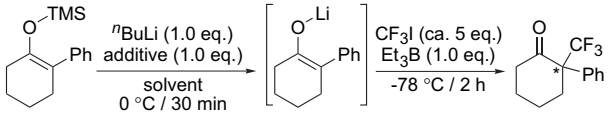


Entry[a]	Substrate	Product	Yield (%)[b]
1	 **1a'**	 **2a**	77
2[c]	 **1j**	 **2j**	58
3[d]	 **1k**	 **2k**	44 (45)

[a] Et$_3$B was added in flat 15 s.
[b] Determined by ^{19}F NMR using BTF as an internal standard. The values in ( ) refer to the yields of isolated products.
[c] Silyl enol ether of α-Me-cyclohexanone consists of thermodynamic and kinetic enol ethers (87:13).
[d] Silyl enol ether of α-Ph-cyclohexanone consists only thermodynamic enol ether.

(entry 3) made no significant effect. When the reaction was carried out in Et_2O solution, the α-CF_3 product was obtained only in 11% (entry 4). The reaction was accelerated by DME (entry 5, 34% yield) or TMEDA (entry 6, 26% yield) in Et_2O solution. The product was obtained only when the TMEDA was added though in only 9% (entry 9) in $^iPr_2O$ solution. The reaction was also accelerated in ^{t}BuOMe solution. The yield was 5% without additive. Addition of DME (entry 11) and TMEDA (entry 12) increased the yield to 15 and 18%, respectively. When the reaction was carried out with 1.0 equiv of (*S*,*S*)-hydrobenzoin dimethyl ether in Et_2O, the product was obtained in 39% yield with 27% ee. In ^{t}BuOMe solution, the reaction with (−)-sparteine gave the product in 13% yield with −44% ee. These results show the possibility of catalytic asymmetric radical trifluoromethylation of enolates.

Table 5. Effect of the bidentate additive



Entry	Solvent	Additive	Yield (%)
1	THF	—	45[a]
2		DME	38[a]
3		TMEDA	34[a]
4	Et_2O	—	11[b]
5		DME	34[a]
6		TMEDA	26[a]
7	$^iPr_2O$	—	—
8		DME	—
9		TMEDA	9[b]
10	^{t}BuMeO	—	5[b]
11		DME	15[b]
12		TMEDA	18[b]

[a] Yield of the isolated products.
[b] Determined by ^{19}F NMR using BTF as an internal standard.

In summary, we have discovered that highly basic Li enolates can be employed for radical trifluoromethylation. The reaction rate is extremely fast compared to the previous radical trifluoromethylation. The direct use of Li enolates is simpler and faster than that of Ti ate enolates or any other previous enolate equivalents.

3. Experimental

3.1. General

^{1}H NMR and ^{13}C NMR were measured on Varian Gemini 2000 (300 MHz) spectrometer and ^{19}F NMR was measured on Varian UNITY INOVA (400 MHz) spectrometer. Chemical shifts of ^{1}H NMR were expressed in parts per million downfield from tetramethylsilane as an internal standard (δ=0) in $CDCl_3$. Chemical shifts of ^{13}C NMR were expressed in parts per million downfield from $CDCl_3$ as an internal standard (δ=77.0) in $CDCl_3$. Chemical shifts of ^{19}F NMR were expressed in parts per million downfield from BTF as an internal standard (δ=−63.24) in $CDCl_3$. IR spectra were measured on JASCO FT/IR-5000 spectrometer. EI mass spectra were measured on Shimadzu QP-5000 spectrometer. Analytical thin layer chromatography (TLC) was performed on glass plates and/or aluminum sheets pre-coated with silica gel (Merck Kieselgal 60 F254, layer thickness 0.25 and 0.2 mm). Visualization was accomplished by UV light (254 nm), anisaldehyde, $KMnO_4$, and phosphomolybdic acid. Column chromatography was performed on Merck Kieselgel 60 and KANTO Silica Gel 60N (spherical, neutral), employing hexane ethyl acetate mixture as an eluent unless otherwise noted. THF was distilled from benzophenone-ketyl under Ar prior to use. All experiments were carried out under argon atmosphere unless otherwise noted.

3.2. General procedure: starting from ketone

To a solution of $^iPr_2NH$ (28.0 μl, 0.20 mmol) in THF (2.0 ml) was added ^{n}BuLi (126.3 μl of 1.58 M solution in hexane, 0.20 mmol) at −78 °C. The reaction mixture was stirred at 0 °C for 30 min and then cooled to −78 °C. To the solution was added cyclohexanone (20.7 μl, 0.2 mmol) and the solution was stirred for 60 min at the temperature. Then, gaseous CF_3I (ca. 200 mg, ca. 1.0 mmol) was added with a cannula. Next, a syringe, which was filled with 0.12 ml of 5 M solution of acetic acid in THF, was set to the reaction vessel and kept untouched till quenching the reaction. Then Et_3B (0.2 ml of 1.0 M solution in hexane, 0.2 mmol) was added in flat 15 s to start the radical addition reaction. The reaction mixture was immediately quenched (in ∼1 s) by acetic acid solution, which was set beforehand, at −78 °C. After warming to room temperature, BTF (10 μl, 0.082 mmol) was added as an internal standard. The yield was determined by ^{19}F NMR of the crude mixture (81%).

3.3. General procedure: starting from silyl enol ether

To a solution of 1-(trimethylsilyloxy)cyclohexene (38.9 μl, 0.2 mmol) in THF was added ^{n}BuLi (128.2 μl of 1.56 M solution in hexane, 0.20 mmol) at 0 °C and stirred for 30 min at the temperature. Then, the reaction mixture was cooled to −78 °C. To the mixture was added gaseous CF_3I (ca. 200 mg, ca. 1.0 mmol) with a cannula followed by Et_3B (0.2 ml of 1.0 M solution in hexane, 0.2 mmol). The reaction mixture was stirred for 2 h at −78 °C and then quenched by acetic acid (0.12 ml of 5 M solution in THF) at −78 °C. After warming to room temperature, BTF (10 μl, 0.082 mmol) was added as an internal standard. The yield was determined by ^{19}F NMR of the crude mixture (77%).

3.4. 2-Trifluoromethyl-cyclohexanone (2a)

^{1}H NMR ($CDCl_3$): δ 1.62–1.88 (m, 3H), 1.92–2.14 (m, 2H), 2.24–2.39 (m, 2H), 2.42–2.53 (m, 1H), 2.98–3.13 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 23.7, 27.1, 27.5 (q, *J*=2.4 Hz), 42.2, 53.6 (q, *J*=25.7 Hz), 124.6 (q, *J*=279.5 Hz), 203.0. ^{19}F NMR ($CDCl_3$): δ −69.3 (d, 7.9 Hz). IR (neat): 2954, 2876, 2364, 1729, 1272, 1170, 1125, 1060 cm^{-1}. EI-MS *m*/*z*: 166 [M$^{+\bullet}$].

3.5. 4-Tertiarybutyl-2-trifluoromethyl-cyclohexanone (2b)

Major isomer: ^{1}H NMR ($CDCl_3$): δ 0.94 (s, 9H), 1.42–1.68 (m, 3H), 2.18–2.20 (m, 1H), 2.26–2.42 (m, 2H), 2.44–2.56 (m, 1H), 3.00–3.16 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 27.5, 28.1, 28.6, 32.5, 41.7, 46.1, 53.0 (q, *J*=25.7 Hz), 124.6 (q, *J*=279.6 Hz), 203.2. ^{19}F NMR ($CDCl_3$): δ −69.7 (d, *J*=7.9 Hz). IR (KBr): 2970, 2878, 1734, 1392, 1369, 1274, 1170, 1120, 1067 cm^{-1}. EI-MS *m*/*z*: 222 [M$^{+\bullet}$]. Minor isomer (isomerization was observed during isolation. Therefore, only ^{19}F NMR data could be shown): ^{19}F NMR ($CDCl_3$): δ −66.1 (d, *J*=10.5 Hz).

3.6. 2-Methyl-6-trifluoromethyl-cyclohexanone (2c)

Major isomer: ^{1}H NMR ($CDCl_3$): δ 1.03 (d, *J*=6.3 Hz, 3H), 1.34–1.49 (m, 1H), 1.63–1.87 (m, 2H), 1.88–2.03 (m, 1H), 2.08–2.19 (m, 1H), 2.30–2.49 (m, 2H), 2.98–3.16 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 13.8, 24.0, 28.3, 36.3, 45.9, 53.7 (q, *J*=25.7 Hz), 124.8 (q, *J*=279.5 Hz), 204.6. ^{19}F NMR ($CDCl_3$): δ −69.8 (d, *J*=8.3 Hz). IR (neat): 2942, 2874, 2366, 1731, 1456, 1392, 1332, 1272, 1170, 1137, 1123, 1038, 832, 688 cm^{-1}. EI-MS *m*/*z*: 180 [M$^{+\bullet}$]. Minor isomer: ^{1}H NMR ($CDCl_3$): δ 1.11 (d, *J*=6.6 Hz, 3H), 1.46–2.21 (m, 6H), 2.57–2.71 (m, 1H), 3.07–3.22 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 15.0, 20.2, 26.9, 29.6, 34.2, 44.5, 52.3 (q, *J*=25.7 Hz), 125.2 (q, *J*=280.7 Hz), 206.3. ^{19}F NMR ($CDCl_3$): δ −66.7 (d, *J*=10.2 Hz). IR (neat): 2928, 2858, 2364, 2344, 1725, 1458, 1265, 1143, 801 cm^{-1}. EI-MS *m*/*z*: 180 [M$^{+\bullet}$].

3.7. 2-Phenyl-6-trifluoromethyl-cyclohexanone (2d)

Major isomer: ^{1}H NMR ($CDCl_3$): δ 1.83–2.21 (m, 4H), 2.28–2.40 (m, 1H), 2.40–2.56 (m, 1H), 3.16–3.35 (m, 1H), 3.56–3.68 (dd, *J*=5.4, 12.6 Hz, 1H), 7.11–7.17 (m, 2H), 7.25–7.40 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 24.2, 28.3, 35.6, 54.1 (q, *J*=25.6 Hz), 57.8, 124.6 (q, *J*=280.8 Hz), 127.4, 128.4, 128.8, 137.0, 201.6. ^{19}F NMR ($CDCl_3$): δ −69.6 (d, *J*=7.9 Hz). IR (KBr): 3036, 2946, 2872, 1722, 1605, 1452, 1385, 1270, 1168, 1133, 1045, 761, 704, 592 cm^{-1}. EI-MS *m*/*z*: 242 [M$^{+\bullet}$]. Minor isomer: ^{1}H NMR ($CDCl_3$): δ 1.86–2.28 (m, 5H), 2.37–2.52 (m, 1H), 3.12–3.30 (dq, *J*=6.0, 9.3 Hz, 1H), 3.82–3.92 (distorted t, *J*=6.3 Hz, 1H), 7.17–7.43 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 20.4, 27.4, 31.3, 52.0 (q, *J*=26.9 Hz), 55.1, 125.1 (q, *J*=280.8 Hz), 127.4, 127.6, 129.0, 136.7, 203.5. ^{19}F NMR ($CDCl_3$): δ −67.9 (d, *J*=9.0 Hz). IR (neat): 3066, 3032, 2954, 2878, 2364, 1725, 1603, 1584, 1499, 1454, 1390, 1332, 1274, 1183, 1141, 698 cm^{-1}. EI-MS *m*/*z*: 242 [M$^{+\bullet}$].

3.8. 2-Trifluoromethyl-cyclopentanone (2e)

^{1}H NMR ($CDCl_3$): δ 1.77–2.00 (m, 1H), 2.01–2.21 (m, 2H), 2.22–2.48 (m, 3H), 2.78–2.97 (qm, *J*=9.6 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 20.0, 24.4, 38.5, 51.1 (q, *J*=26.9 Hz), 124.6 (q, *J*=278.3 Hz), 209.4. ^{19}F NMR ($CDCl_3$): δ −67.9 (d, *J*=10.5 Hz). IR (neat): 2986, 2896, 2366, 2344, 1758, 1638, 1367, 1313, 1257, 1187, 1151, 1096, 1046 cm^{-1}. EI-MS *m*/*z*: 152 [M$^{+\bullet}$].

3.9. 2-Trifluoromethyl-cycloheptanone (2f)

^{1}H NMR ($CDCl_3$): δ 1.22–1.48 (m, 2H), 1.48–1.75 (m, 2H), 1.86–2.05 (m, 3H), 2.09–2.20 (m, 1H), 2.54–2.61 (m, 2H), 3.16–3.31 (qdd, *J*=4.1, 8.9, 11.1 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 24.4, 24.7 (q, *J*=2.4 Hz), 27.5, 29.1, 43.1, 55.5 (q, *J*=24.5 Hz), 124.9 (q, *J*=280.8 Hz), 205.9. ^{19}F NMR ($CDCl_3$): δ −69.0 (d, 9.0 Hz). IR (neat): 2940, 2866, 1721, 1178, 1151, 1096 cm^{-1}. EI-MS *m*/*z*: 180 [M$^{+\bullet}$].

3.10. 1,1,1-Trifluoro-5-phenyl-3-pentanone (2g)

^{1}H NMR ($CDCl_3$): δ 2.80–3.00 (m, 4H), 3.19 (q, *J*=10.2 Hz, 2H), 7.14–7.35 (m, 5H). ^{13}C NMR ($CDCl_3$): δ 29.2, 44.9, 46.5 (q, *J*=28.1 Hz), 123.5 (q, *J*=277.1 Hz), 126.4, 128.3, 128.6, 140.1, 199.1. ^{19}F NMR ($CDCl_3$): δ −62.9 (t, *J*=10.2 Hz). IR (neat): 3068, 3032, 2922, 1734, 1605, 1497, 1456, 1419, 1377, 1261, 1154, 1096, 750, 700 cm^{-1}. EI-MS *m*/*z*: 216 [M$^{+\bullet}$].

3.11. 1,1,1-Trifluoro-4,4-dimethyl-5-phenyl-3-pentanone (2h)

^{1}H NMR ($CDCl_3$): δ 1.16 (s, 6H), 2.81 (s, 2H), 3.17 (q, *J*=9.9 Hz, 2H), 7.07 (ddd, *J*=1.7, 2.1, 6.3 Hz, 2H), 7.19–7.32 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 23.8, 41.4 (q, *J*=28.1 Hz), 45.3, 48.9, 123.9 (q, *J*=277.1 Hz), 126.8, 128.2, 130.2, 136.8, 205.2. ^{19}F NMR ($CDCl_3$): δ −63.0 (t, *J*=9.8 Hz). IR (neat): 3034, 2976, 1721, 1369, 1282, 1133, 1100 cm^{-1}. EI-MS *m*/*z*: 244 [M$^{+\bullet}$].

3.12. 7-Trifluoromethyl-6-undecanone (2i)

^{1}H NMR ($CDCl_3$): δ 0.90 (t, *J*=3.9 Hz, 6H), 1.18–1.41 (m, 8H), 1.53–1.65 (m, 2H), 1.65–1.79 (m, 1H), 1.81–1.97 (m, 1H), 2.47 (dt, *J*=18.0, 7.2 Hz, 1H), 2.61 (dt, *J*=7.4, 18.0 Hz, 1H), 3.11–3.26 (m, 1H). ^{13}C NMR ($CDCl_3$): δ 13.6, 13.8, 22.4, 22.7, 25.59, 25.62, 29.0, 31.1, 43.6, 55.6 (q, *J*=24.4 Hz), 124.9 (q, *J*=280.7 Hz), 204.5. ^{19}F NMR ($CDCl_3$): δ 67.4 (d, *J*=9.0 Hz). IR (neat): 2966, 2938, 2870, 1731, 1263, 1164 cm^{-1}. EI-MS *m*/*z*: 238 [M$^{+\bullet}$].

3.13. 2-Methyl-2-trifluoromethyl-cyclohexanone (2j)

^{1}H NMR ($CDCl_3$): δ 1.36 (s, 3H), 1.70–2.00 (m, 5H), 2.06–2.20 (m, 1H), 2.35–2.58 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 17.7 (q, J=2.4 Hz), 20.5, 26.4, 33.5, 39.4, 53.7 (q, J=23.2 Hz), 126.5 (q, J=283.2 Hz), 206.2. ^{19}F NMR ($CDCl_3$): δ −73.6 (s). IR (neat): 2936, 2874, 1725, 1274, 1170, 1137 cm^{-1}. EI-MS m/z: 180 [M$^{+\bullet}$].

3.14. 2-Phenyl-2-trifluoromethyl-cyclohexanone (2k)

^{1}H NMR ($CDCl_3$): δ 1.63–1.86 (m, 3H), 1.89–2.00 (m, 1H), 2.12–2.25 (m, 1H), 2.31–2.40 (m, 2H), 2.91 (qd, J=3.0, 14.4 Hz, 1H), 7.29–7.35 (m, 2H), 7.35–7.47 (m, 3H). ^{13}C NMR ($CDCl_3$): δ 20.2, 27.4, 29.9 (q, J=2.4 Hz), 39.8, 62.2 (q, J=22.0 Hz), 125.1 (q, J=283.2 Hz), 128.7, 128.8, 129.0, 131.8, 204.7. ^{19}F NMR ($CDCl_3$): δ −72.9 (s). IR (neat): 3066, 2954, 2874, 1725, 1282, 1255, 1176, 1152 cm^{-1}. EI-MS m/z: 242 [M$^{+\bullet}$].

References and notes

1. (a) Ma, J.-A.; Cahard, D. *Chem. Rev.* **2004**, *104*, 6119–6146; (b) Mikami, K.; Itoh, Y.; Yamanaka, M. *Chem. Rev.* **2004**, *104*, 1–16; (c) Hiyama, T.; Kanie, K.; Kusumoto, T.; Morizawa, Y.; Shimizu, M. *Organofluorine Compounds*; Springer: Berlin, Heidelberg, 2000; (d) *Enantiocontrolled Synthesis of Fluoro-Organic Compounds*; Soloshonok, V. A., Ed.; Wiley: Chichester, UK, 1999; (e) *Asymmetric Fluoroorganic Chemistry, Synthesis, Applications, and Future Directions*; Ramachandran, P. V., Ed.; American Chemical Society: Washington, DC, 2000; (f) *Organofluorine Chemistry*; Chambers, R. D., Ed.; Springer: Berlin, 1997; (g) Iseki, K. *Tetrahedron* **1998**, *54*, 13887–13914; (h) *Biomedical Frontiers of Fluorine Chemistry*; Ojima, I., McCarthy, J. R., Welch, J. T., Eds.; American Chemical Society: Washington, DC, 1996; (i) Smart, B. E., Ed.; *Chem. Rev.* **1996**, *96*, 1555–1824 (Thematic issue of Fluorine Chemistry); (j) *Organofluorine Chemistry: Principles and Commercial Applications*; Banks, R. E., Smart, B. E., Tatlow, J. C., Eds.; Plenum: New York, NY, 1994; (k) McClinton, M. A.; McClinton, D. A. *Tetrahedron* **1992**, *48*, 6555–6666; (l) Hudlicky, M. *Chemistry of Organic Fluorine Compounds*, 2nd ed. Ellis Horwood: Chichester, UK, 1976.
2. (a) Itoh, Y.; Yamanaka, M.; Mikami, K. *Org. Lett.* **2003**, *5*, 4803–4806; (b) Itoh, Y.; Yamanaka, M.; Mikami, K. *Org. Lett.* **2003**, *5*, 4807–4809; (c) Itoh, Y.; Yamanaka, M.; Mikami, K. *J. Am. Chem. Soc.* **2004**, *126*, 13174–13175; (d) Itoh, Y.; Mikami, K. *Org. Lett.* **2005**, *7*, 649–651; (e) Our preliminary report on the radical trifluoromethylation of Li enolates: Itoh, Y.; Mikami, K. *Org. Lett.* **2005**, *7*, 4883–4885.
3. Trifluoromethylation of Li enolate of hindered imides (only exception for the use of Li enolate): (a) Iseki, K.; Nagai, T.; Kobayashi, Y. *Tetrahedron Lett.* **1993**, *34*, 2169–2170; (b) Iseki, K.; Nagai, T.; Kobayashi, Y. *Tetrahedron: Asymmetry* **1994**, *5*, 961–974. They have succeeded in trifluoromethylation by adopting Evans oxazolidinones with bulky substituent at α-position to suppress defluorination.
4. Perfluoroalkylation of silyl and germyl enol ethers of esters and ketones: (a) Miura, K.; Taniguchi, M.; Nozaki, K.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1990**, *31*, 6391–6394; (b) Miura, K.; Takeyama, Y.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 1542–1553. Perfluoroalkylation of silyl enol ethers provided the products in good yields except for trifluoromethylation. Trifluoromethylation of ketone germyl enol ethers proceeds in good yield.
5. Trifluoromethylation of enamines: (a) Cantacuzène, D.; Wakselman, C.; Dorme, R. *J. Chem. Soc., Perkin Trans. 1* **1977**, 1365–1371; (b) Kitazume, T.; Ishikawa, N. *J. Am. Chem. Soc.* **1985**, *107*, 5186–5191.
6. Trifluoromethylation of enol acetates: Langlois, B. R.; Laurent, E.; Roidot, N. *Tetrahedron Lett.* **1992**, *33*, 1291–1294.
7. There are some reports of trifluoromethylation using CF_3^+: (a) Yagupol'skii, L. M.; Kondratenko, N. V.; Timofeeva, G. N. *J. Org. Chem. USSR* **1984**, *20*, 115–118; (b) Umemoto, T.; Ishihara, S. *J. Am. Chem. Soc.* **1993**, *115*, 2156–2164; (c) Umemoto, T.; Adachi, K. *J. Org. Chem.* **1994**, *59*, 5692–5699.
8. (a) Stork, G.; Hudrlik, P. F. *J. Am. Chem. Soc.* **1968**, *90*, 4462–4464; (b) Stork, G.; Hudrlik, P. F. *J. Am. Chem. Soc.* **1968**, *90*, 4464–4465.
9. For accuracy, Et_3B was added in flat 15 s and the reaction time was counted from the time when the addition of Et_3B was completed.