Cascade Radical Reaction Induced by Polarity-Mismatched Perfluoroalkylation

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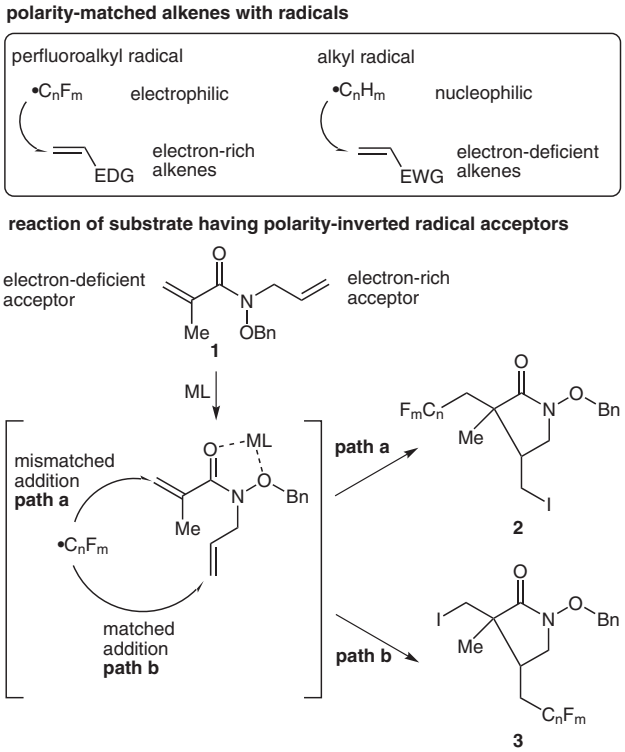
Abstract: Cascade radical addition–cyclization–trapping reaction proceeded via the unfavorable polarity-mismatched addition of electrophilic perfluoroalkyl radicals to electron-deficient acceptors.

Key word: radical, fluoro, cyclization, enantioselective, cascade

Over the last fifteen years, enantioselective radical reactions, particularly intermolecular radical reactions have made great advances.[1] However, enantiocontrol in radical cyclizations still remains a major challenge,[2] although significant progress has been made recently by several approaches.[3–10] Moreover, less is known about stereoselective reactions of perfluoroalkyl radicals.[11] Therefore, there have been no studies on perfluoroalkyl radical mediated enantioselective cyclizations.

In contrast to nucleophilic alkyl radicals which generally react with electron-deficient alkenes, perfluoroalkyl radicals are classified into electrophilic radicals (Scheme 1).[12] As expected from their electrophilic property, the reported studies have concentrated on the reaction with electron-rich alkenes including π-sufficient aromatic compounds.[13] The polarity-mismatched additions of perfluoroalkyl radicals to electron-deficient alkenes are rare,[14] which are frequently plagued by the formation of dimeric or polymeric by-products. Therefore, the development of the cascade transformations involving such process is a challenging task. In this communication, we report new cascade addition–cyclization–trapping reactions involving the unfavorable mismatched perfluoroalkylation, together with the control of enantioselectivities on the basis of our cyclization strategy.[10] With the objective to study the polarity-mismatched interaction of perfluoroalkyl radicals, the substrate **1**, having both electron-deficient and electron-rich acceptors, was employed, since the direct comparison of two competitive reaction pathways (path a and path b) could lead to informative suggestions regarding the dominant factors controlling perfluoroalkylation step in cascade process.

The reactions of **1** having two kinds of polarity-inverted radical acceptors were performed with triethylborane as a radical initiator in CH_2Cl_2 at 20 °C (Scheme 2). At first, *n*-C_3F_7I was employed as a primary perfluoroalkyl radical source and Lewis acids were evaluated (Table 1, entries 1–4). We were amazed to find the unfavorable mismatched path a giving **2a** as a major course. Particularly, $Zn(OTf)_2$ accelerated the present cascade sequence to form the products **2a** and **3a** in 71% combined yield and 73:27 ratio (entry 1).[15] Interestingly, square planar $Cu(OTf)_2$ led to an enhancement of ratio into 94:6, although the chemical yield diminished to 54% (entry 3).[16] Perfluoroalkyl radicals exhibit extraordinary reactivity, relative to their hydrocarbon counterparts.[17,18] Therefore, the enhanced reactivity of perfluoroalkyl radicals allowed for the polarity-mismatched perfluoroalkylation of an electron-deficient acceptor, though an electron-rich acceptor belongs to same molecule. In our previous investigation using substrate **1** and nucleophilic alkyl radicals, no cyclic product was obtained in the absence of Lewis acid.[10a] In marked contrast, the enhanced reactivity of perfluoroalkyl radical promoted the cyclization even without the geometry-control by Lewis acid (entry 4). Similar regioselectivity and chemical efficiency were observed when primary *n*-C_4F_9I was employed in the presence of $Zn(OTf)_2$ (entry 5). The branched secondary perfluoro-



Scheme 1 Cascade radical reaction of substrate **1** with perfluoroalkyl radical; ML = Lewis acid

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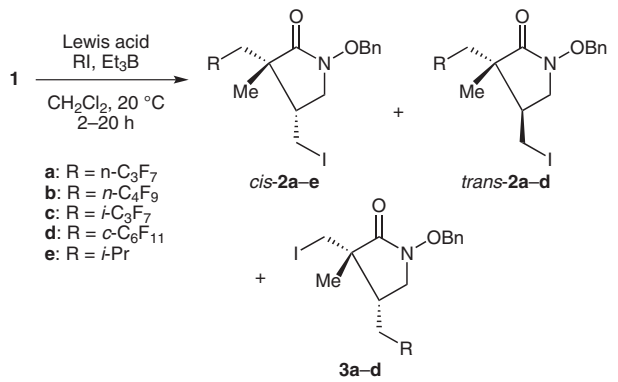
alkyl radicals are known to exhibit greater electrophilicities than primary perfluoroalkyl radicals.[19] The use of secondary *iso*-C_3F_7 and *cyclo*-C_6F_{11} radicals had a moderate impact on two competitive pathways and the formation of **3c** and **3d** increased via the matched path b (entries 6–8).



Scheme 2 Regiochemical courses in cascade radical reaction of **1**

The regiochemical courses are controlled by two factors: (1) the stability of intermediate radicals and (2) the polar effect by fluorine's potent σ inductive electron-withdrawing property (Figure 1).[20] With regard to factor 1, the stabilization of an intermediate radical **A** by resonance promotes the polarity-mismatched addition path a. With regard to factor 2,[20] the mismatched perfluoroalkyl radical addition path a leads to the matched polarization **C** in cyclization step, whereas matched path b gives the polarity-mismatched interaction **D**. For the comparison, the result using more nucleophilic isopropyl radical is shown in entry 9 (Table 1), which had selectively afforded the product **2e** with high *cis* selectivity.[10a] At this stage, erosion of *cis*/*trans* diastereoselectivities in perfluoroalkyl radical reactions is questioned. The stability of perfluoroalkyl radicals is lower than that of nucleophilic isopropyl radical;[12] thus, the final iodine atom-transfer process is relatively slow. Therefore, it can be assumed that the slow trapping step and the high stability of intermediate radical **A** would allow the reversibility between radical **A** and cyclized radical, leading to low *cis*/*trans* diastereoselectivity.

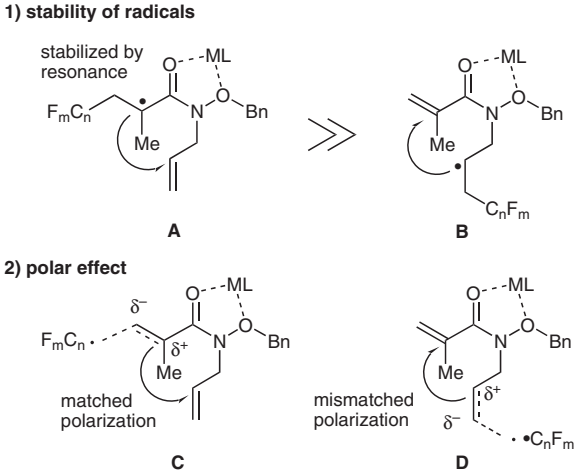


Figure 1 Two factors directing regiochemical courses

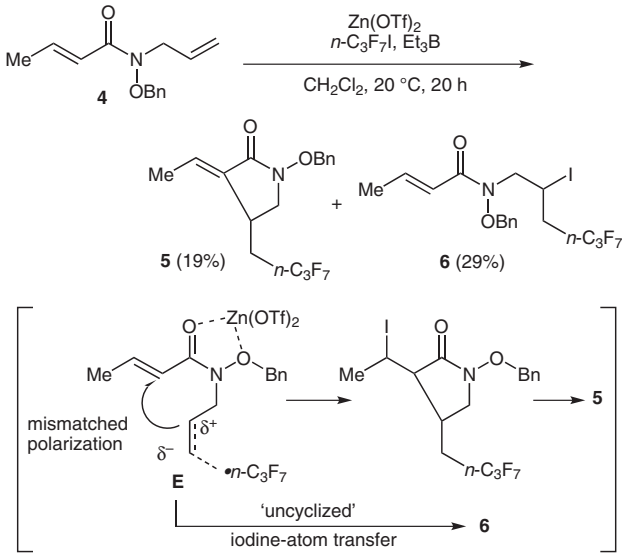
Introduction of a substituent at β-position of an electron-deficient acceptor apparently inhibits the mismatched addition due to steric effects (Scheme 3). The reaction of substrate **4** having a β-methyl group gave the cyclized but ethylidene product **5** and the simple adduct **6** predominantly through the matched addition. Notably, the formation of uncyclized adduct **6** supports our hypothesis of polar effect on cyclization step (see: **E**).

The circumstances in the presence of a chiral Lewis acid promoted the polarity-mismatched perfluoroalkylation of the electron-deficient acceptor in **1** (Scheme 4, Table 2). Reactions of **1** with perfluoroalkyl iodides were per-

Table 1 Cascade Reaction of **1** with Perfluoroalkyl Radicals

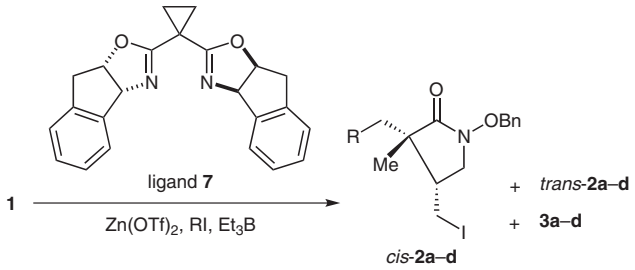
Entry	RI	Lewis acid	Product	Ratio[a] of **2**:**3**	Yield (%)[b]	*cis*/*trans*[a]
1[c]	*n*-C_3F_7I	$Zn(OTf)_2$	**2a** + **3a**	73:27	71	59:41
2[c]	*n*-C_3F_7I	$Yb(OTf)_3$	**2a** + **3a**	73:27	60	58:42
3[c]	*n*-C_3F_7I	$Cu(OTf)_2$	**2a** + **3a**	94:6	54	60:40
4[c]	*n*-C_3F_7I	none	**2a** + **3a**	72:28	49	54:46
5[c]	*n*-C_4F_9I	$Zn(OTf)_2$	**2b** + **3b**	72:28	74	63:37
6[c]	*i*-C_3F_7I	$Zn(OTf)_2$	**2c** + **3c**	62:38	77	79:21
7[c]	*i*-C_3F_7I	$Cu(OTf)_2$	**2c** + **3c**	78:22	36	81:19
8[c]	*c*-$C_6F_{11}I$	$Zn(OTf)_2$	**2d** + **3d**	61:39	66	77:23
9[d]	*i*-PrI	$Zn(OTf)_2$	**2e**		41	>98:2

[a] Determined by ^1H NMR spectroscopic analysis.
[b] Combined yield of the isolated products.
[c] Reactions were carried out with perfluoroalkyl iodides (5 equiv), Lewis acid (1 equiv), and Et_3B in hexane (1.0 M, 5 equiv).
[d] Reaction was carried out with isopropyl iodides (30 equiv), $Zn(OTf)_2$ (1 equiv), and Et_3B in hexane (1.0 M, 5 equiv); see ref. 10a.



Scheme 3 Reaction of substrate **4** having a β-methyl group

formed at –78 °C in the presence of chiral Lewis acid prepared from box ligand **7** and $Zn(OTf)_2$.[10] In general, the use of ligand **7** led not only to an enhancement in product ratio but also an improvement in *cis*/*trans* diastereoselectivity. The reaction of **1** with a *n*-C_3F_7 radical in CH_2Cl_2 proceeded effectively to form the products **2a** and **3a** in 95:5 ratio and 88% combined yield (entry 1). Although *cis*/*trans* diastereoselectivity was still low, the major product *cis*-**2a** was isolated in 76% ee along with *trans*-**2a** in 88% ee.[21] The addition of hexafluoro-2-propanol (HFIP) as an acidic solvent led to lower product ratio and enantioselectivity (entry 2). In contrast, higher enantioselectivities were obtained, when the reaction was carried out in CH_2Cl_2–toluene (1:1; entry 3). The enantioselectivities and *cis*/*trans* diastereoselectivities were increased by changing the perfluoroalkyl radicals from primary to secondary (entries 4–7). The reaction with secondary *iso*-C_3F_7 radical in CH_2Cl_2 gave the cyclic product *cis*-**2c** with 90% ee in 92:8 *cis*/*trans* selectivity, although product ratio diminished to 82:18 due to high electrophilicity of secondary perfluoroalkyl radicals (entry 4). Similar result was also obtained in CH_2Cl_2–toluene (entry 5). In the presence of activated 4 Å molecular sieves, *cis*-**2c** was formed with 92% ee (entry 6). Reaction with *cyclo*-C_6F_{11} radical was also facile to give *cis*-**2d** in 91% ee with good *cis*/*trans* diastereoselectivity (entry 7).



Scheme 4 Reaction in the presence of chiral Lewis acid

These results indicate that the three-dimensional arrangement of two radical acceptors was efficiently controlled by a ternary complex of ligand, Lewis acid and substrate at low temperature. Assuming that there is a tetrahedral or *cis*-octahedral geometry around the zinc center,[22] tentative model of octahedral complex is proposed for accounting the product stereochemistry (Figure 2). In this organization, two oxygen atoms of substrate **1** occupy two equatorial directions and the aryl group of ligand **7** shields the electron-rich allyl group of substrate **1**.

We finally explored the reaction of substrate **8** having a methyl group at a terminal of electron-rich acceptor (Scheme 5). As expected, the steric effect had an impact on regiochemical courses and promoted the polarity-mismatched perfluoroalkylation exclusively. The reaction with a *n*-C_3F_7 radical gave the four stereoisomeric cyclic

Table 2 Enantioselective Cascade Radical Reaction of **1**[a]

Entry	RI	Solvent	Time (d)	Ratio[b] of **2**:**3**	Yield (%)[c]	*cis*/*trans*[b]	ee (%)[d] *cis*-**2**	*trans*-**2**
1	*n*-C_3F_7I	CH_2Cl_2	2	95:5	88	62:38	76	88
2	*n*-C_3F_7I	CH_2Cl_2–HFIP (9:1)	3	78:22	78	86:14	6	13
3	*n*-C_3F_7I	CH_2Cl_2–toluene (1:1)	1	97:3	78	64:36	87	90
4	*i*-C_3F_7I	CH_2Cl_2	5	82:18	44	92:8	90	
5	*i*-C_3F_7I	CH_2Cl_2–toluene (1:1)	5	81:19	46	92:8	91	
6[e]	*i*-C_3F_7I	CH_2Cl_2	5	79:21	40	94:6	92	
7	*c*-$C_6F_{11}I$	CH_2Cl_2	3	74:26	73	92:8	91	

[a] Reactions were carried out with perfluoroalkyl iodides (5 equiv), $Zn(OTf)_2$ (1 equiv), ligand **7** (1 equiv), and Et_3B in hexane (1.0 M, 5 equiv) at –78 °C.
[b] Determined by ^1H NMR spectroscopic analysis.
[c] Combined yield.
[d] Determined by HPLC analysis.
[e] The reaction was carried out in the presence of activated 4 Å molecular sieves.

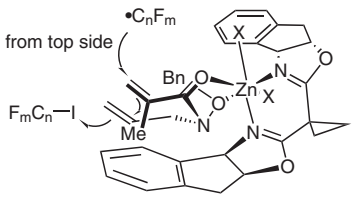
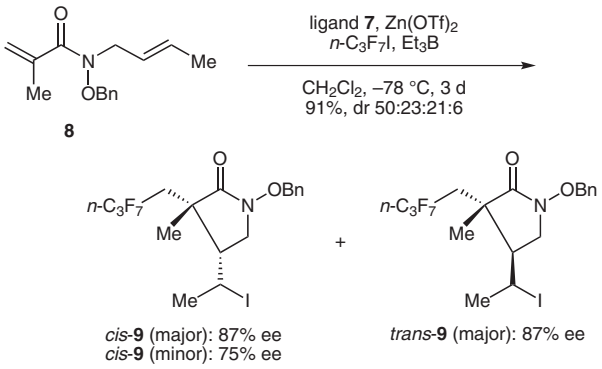


Figure 2 Tentative model

products **9** in 91% combined yield [*cis*-**9** (major)/*cis*-**9** (minor)/*trans*-**9** (major)/*trans*-**9** (minor) = 50:23:21:6].[23] The major isomer of *cis*-**9** was obtained with 87% ee, along with the minor isomer of *cis*-**9** (75% ee) and the major isomer of *trans*-**9** (87% ee).



Scheme 5 Enantioselective reaction of **8** with *n*-C_3F_7 radical

In conclusion, we have developed the cascade radical reactions[24] starting from the polarity-mismatched perfluoroalkylation of an electron-deficient acceptor, providing an enantioselective synthetic approach to chiral γ-lactams.

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(23) Both *cis*-**9** and *trans*-**9** were respectively obtained as two diastereomers concerning the newly generated stereocenter at iodinated carbon.
(24) **General Procedure for Enantioselective Radical Reaction**: A solution of substrate **1** or **8** (100 mg or 106 mg, 0.43 mmol), $Zn(OTf)_2$ (156 mg, 0.43 mmol) and ligand **7** (153 mg, 0.43 mmol) in CH_2Cl_2 (4.3 mL) was stirred for 1 h under Ar atmosphere at 20 °C. To the reaction mixture were added RI (2.15 mmol) and Et_3B (1.05 M in hexane, 2.05 mL, 2.15 mmol) at –78 °C. After being stirred at the same temperature for 1–5 d, the reaction mixture was diluted with sat. $NaHCO_3$ and then extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4 and concentrated at reduced pressure. The residue was roughly purified by preparative TLC (hexane–EtOAc, 3:1) to give the mixture of products. The ratio of products was determined by ^1H NMR analysis of the mixture. Second purification of the mixture by preparative TLC (benzene–EtOAc, 10:1 or hexane–EtOAc, 6:1, 2-fold development) afforded the isolated products.
Representative Products: ***cis*-2a**: colorless crystals; mp 99–99.5 °C (hexane). IR (KBr): 2948, 1717, 1458 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.38–7.50 (m, 5 H), 5.04 (d, *J* = 11.0 Hz, 1 H), 5.02 (d, *J* = 11.0 Hz, 1 H), 3.50 (dd, *J* = 9.2, 6.6 Hz, 1 H), 3.19–3.30 (m, 2 H), 2.73 (t, *J* = 11.4 Hz, 1 H), 2.39–2.58 (m, 2 H), 2.26 (br dd, *J* = 37.0, 16.0 Hz, 1 H), 1.32 (d, *J* = 1.6 Hz, 3 H). ^{13}C NMR ($CDCl_3$): δ = 170.8, 134.7, 129.6, 129.3, 128.7, 118.3 (tt, *J* = 257, 31 Hz), 117.5 (qt, *J* = 289, 34 Hz), 108.4 (tsext, *J* = 265, 36 Hz), 76.9, 51.1, 44.5, 44.2, 31.0 (t, *J* = 21 Hz), 22.2, 4.1. ^{19}F NMR ($CDCl_3$): δ = –80.6 (t, *J* = 19.5 Hz, 3 F), –106.2 (dm, *J* = 273 Hz, 1 F), –116.0 (dm, *J* = 273 Hz, 1 F), –128.3 (br s, 2 F). MS (EI^+): *m*/*z* = 528 (25) [M + H^+], 91 (100). HRMS (EI^+): *m*/*z* [M + H^+] calcd for $C_{17}H_{18}F_7INO_2$: 528.0270; found: 528.0260. Anal. Calcd for $C_{17}H_{17}F_7INO_2$: C, 38.73; H, 3.25; N, 2.66. Found: C, 38.74; H, 3.22; N, 2.60. HPLC (Chiralcel AD-H, hexane–2-propanol, 95:5; flow: 1.0 mL/min, l = 254 nm); t_R (major) = 6.7 min, t_R (minor) = 8.9 min. A sample of 87% ee by HPLC analysis gave $[\alpha]^{24}_D$ +28.3 (*c* = 0.40, $CHCl_3$). **3a**: colorless oil. IR (KBr): 2968, 2932, 1714, 1455 cm^{-1}. ^1H NMR ($CDCl_3$): δ = 7.34–7.47 (m, 5 H), 5.09 (d, *J* = 11.0 Hz, 1 H), 5.04 (d, *J* = 11.0 Hz, 1 H), 3.48 (t, *J* = 8.5 Hz, 1 H), 3.37 (dd, *J* = 8.5, 1.8 Hz, 1 H), 3.23 (d, *J* = 11.0 Hz, 1 H), 3.05 (d, *J* = 11.0 Hz, 1 H), 2.45 (m, 1 H), 2.26–2.42 (br m, 2 H), 1.30 (s, 3 H). ^{13}C NMR ($CDCl_3$): δ = 170.1, 134.7, 129.5, 129.1, 128.6, 117.6 (qt, *J* = 288, 34 Hz), 117.4 (tt, *J* = 256, 32 Hz), 108.4 (tsext, *J* = 265, 38 Hz), 77.2, 50.1 (d, *J* = 5 Hz), 44.0, 33.9, 28.1 (t, *J* = 21 Hz), 25.0, 6.4. ^{19}F NMR ($CDCl_3$): δ = –80.9 (t, *J* = 9 Hz, 3 F), –113.7 (dm, *J* = 273 Hz, 1 F), –116.0 (dm, *J* = 273 Hz, 1 F), –127.8 (dd, *J* = 290, 5 Hz, 1 F), –128.2 (dd, *J* = 290, 5 Hz, 1 F). HRMS (ESI): *m*/*z* [M + H^+] calcd for $C_{17}H_{18}F_7INO_2$: 528.0270; found: 528.0269.