JOC The Journal of Organic Chemistry

Article

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Polarity-Mismatched Addition of Electrophilic Carbon Radicals to an Electron-Deficient Acceptor: Cascade Radical Addition−Cyclization−Trapping Reaction

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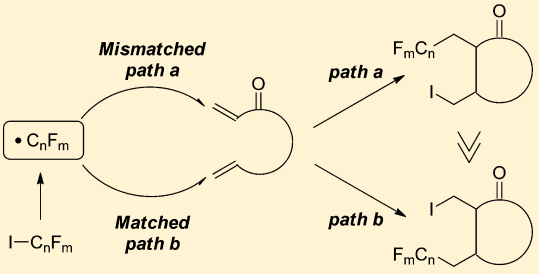
Supporting Information

ABSTRACT: The polarity-mismatched perfluoroalkyl radical addition to electron-deficient alkenes was studied. For this study, several substrates having two polarity-different radical acceptors were employed to investigate the regiochemical courses of cascade reaction. In the case of substrate **1** having a methacryloyl moiety, we found polarity-mismatched perfluoroalkylation giving **15a−e** as a major course over the polarity-matched perfluoroalkylation giving **16a−e**. Moreover, in the case of substrates **2−7**, perfluoroalkyl radicals selectively added to an electron-deficient alkene moiety of **2−7**, to give polarity-mismatched perfluoroalkylation products without the formation of regioisomers. Next, the control of enantioselectivity was studied. In the case of substrates **1** and **3**, the reaction proceeded with good enantioselectivities by employing a chiral Lewis acid, prepared from chiral box ligand **24** and $Zn(OTf)_2$. For direct comparison, we also studied the reaction with other carbon radicals, derived from ICH_2CO_2Et, ICH_2CN, $BrC(CO_2Et)_2Me$, and CCl_3Br, which have electrophilic character.



INTRODUCTION

Perfluoroalkyl radicals, which are classified into electrophilic radicals, have played a significant role in free radical chemistry.[1] Although the use of perfluoroalkyl radicals in organic synthesis has continued to increase, the reported studies have concentrated on the polarity-matched reaction with electron-rich alkenes including π-sufficient aromatic compounds (Figure 1).[2] In contrast, the polarity-mismatched additions of perfluoroalkyl radicals to electron-deficient alkenes are rare,[3] which are frequently plagued by the formation of dimeric or polymeric byproducts. In 1991, the reductive addition of perfluoroalkyl radicals to electron-deficient alkenes was discovered by Hu's group.[3a,b] Burton's group also reported that polarity-mismatched perfluoroalkyl radical addition proceeded effectively under photochemical conditions using low intensity 254 nm light.[3f] Recently, Yajima reported photoinduced diastereoselective addition to electron-deficient alkenes in the presence of an aqueous solution of $Na_2S_2O_3$.[3h] However, to the best of our knowledge, there have been no reports on the cascade carbon−carbon bond-forming reactions involving the polarity-mismatched perfluoroalkyl radical addition process and on their stereocontrol. In this context, we have been interested in achieving the electronically unfavorable cascade transformation.

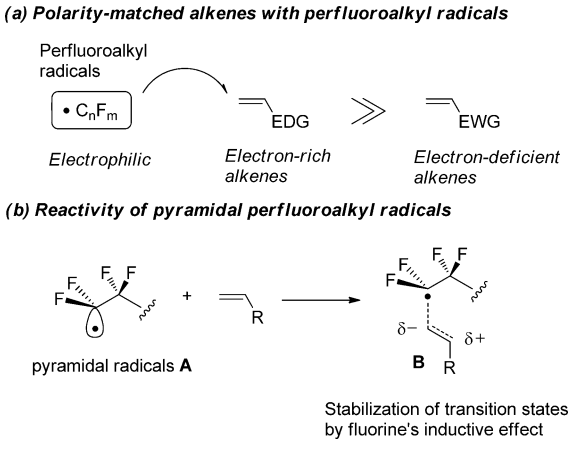


Figure 1. Properties of perfluoroalkyl radicals.

Electrophilic perfluoroalkyl radicals exhibit extraordinary reactivity, relative to their hydrocarbon counterparts.[4,5] The effect of fluorine atoms on the reactivity of radicals is usually considered to derive from fluorine's electronic nature, because of the small size of fluorine atom. The main influence of fluorine substituents is the fluorine's potent σ-inductive electron-withdrawing effect, which gives rise to stabilizing polarization of the transition state **B** (b in Figure 1).[6] Additionally, the pyramidal perfluoroalkyl σ-radicals **A** have an energetic advantage over the planar nucleophilic alkyl π-radicals, because further bending is not required in the transition state for radical addition. Therefore, it is expected that the unique reactivity of perfluoroalkyl radicals would allow for a wide variety of cascade reactions.

Received: July 24, 2012
Published: September 10, 2012

dx.doi.org/10.1021/jo3015227 | J. Org. Chem. 2012, 77, 8588−8604

As presumed from the electrophilic property of perfluoroalkyl radicals, the polarity-matched addition−cyclization reactions of the substrates **C** having two electron-rich radical acceptors were studied (a in Figure 2).[7] However, the cascade

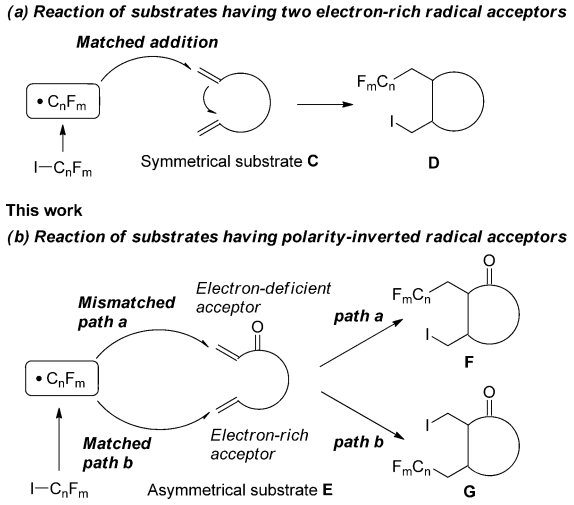


Figure 2. Cascade reaction using perfluoroalkyl radicals.

reaction of substrates **E** having two polarity-inverted radical acceptors has remained unstudied (b in Figure 2). In this reaction, two competitive reaction pathways, path a and path b, are presumed. Particularly, the selective synthesis of the product **F** via polarity-mismatched perfluoroalkylation (path a) is a challenging task. We recently reported the cascade addition−cyclization−trapping reaction involving the polarity-mismatched interaction of perfluoroalkyl radicals.[8] In this paper, we report in details of the addition of electrophilic carbon radicals to electron-deficient radical acceptors, together with the control of enantioselectivities on the basis of our cyclization strategy.[9]

RESULTS AND DISCUSSION

Reaction of Substrates Having Polarity-Inverted Radical Acceptors. To compare the effect of radical acceptors on the reactivity and regiochemical courses, our experiments began with the investigation of cascade addition−cyclization−trapping reaction of several substrates **1**−**7** (Figure 3).

Different types of substrates, **1**−**7**, were synthesized from *N*-(*tert*-butoxycarbonyl)-*O*-benzylhydroxylamine **8**,[10] which was prepared from *O*-benzylhydroxylamine hydrochloride (Scheme 1). In the presence of Cs_2CO_3 as a base, the reaction of **8** with allyl bromide derivatives in DMF gave the synthetic intermediates **9**−**11**. Treatment of **9**−**11** with trifluoroacetic

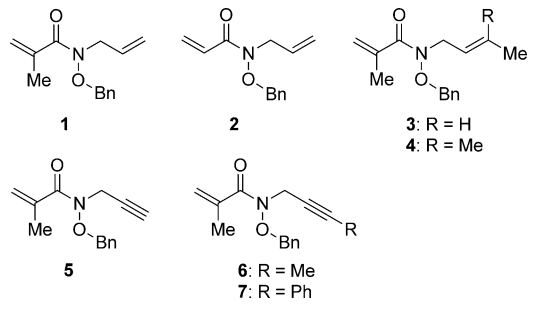
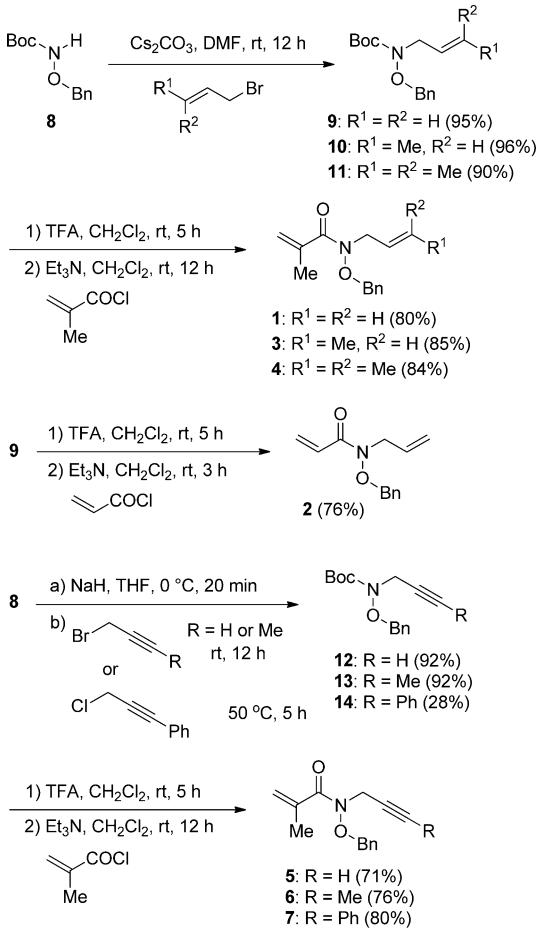


Figure 3. Substrates for this study.

Scheme 1. Preparation of Substrates



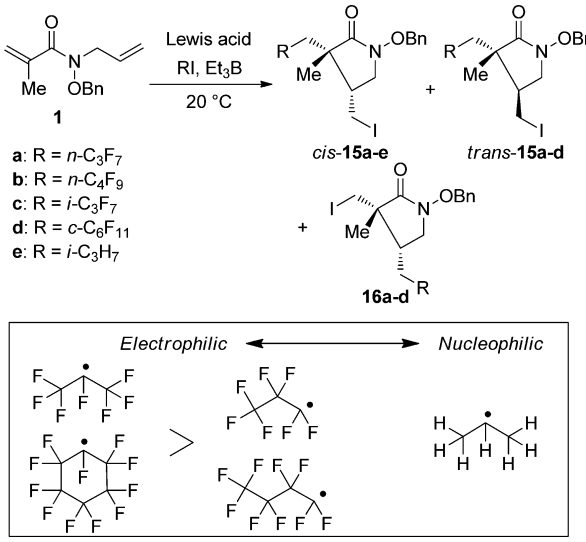
acid in CH_2Cl_2 gave the deprotected amines, which were then subjected to reaction with methacryloyl chloride or acryloyl chloride to afford substrates **1**−**4**. N-Propargylation of **8** in the presence of NaH gave **12**−**14**, which were converted into substrates **5**−**7**.

At first, we investigated the regiochemical course of the cascade reaction by employing the substrate **1** having a methacryloyl moiety (Scheme 2). All reactions were performed with readily available perfluoroalkyl iodides and Et_3B as a radical initiator at 20 °C under tin-free iodine atom-transfer conditions.[11] The reaction was evaluated by checking the competitive formation of three cyclic products *cis*-**15a**−**d**, *trans*-**15a**−**d**, and **16a**−**d**.

We studied the reaction using *n*-heptafluoropropyl iodide (*n*-C_3F_7I) as a primary perfluoroalkyl radical source (Table 1). In the presence of a stoichiometric amount of $Zn(OTf)_2$, *n*-C_3F_7I (5 equiv) and Et_3B (5 equiv) were added to a solution of **1** in CH_2Cl_2 and then the solution was stirred for 2 h (entry 1). The cyclic products *cis*-**15a**, *trans*-**15a**, and **16a** were obtained in 71% combined yield.[12] These products could be separated. The ratio of **15a** and **16a** was 73:27; thus, we were gratified to find polarity-mismatched perfluoroalkylation giving **15a** was a preferred course over the polarity-matched perfluoroalkylation giving **16a**. Among several Lewis acids tested, $Cu(OTf)_2$ led to an enhancement of the **15a**:**16a** ratio to 94:6, although the chemical yield diminished to 54% (entries 2−4).[13] In our previous study,[9a] we reported that the reaction of substrate **1** with nucleophilic alkyl radicals did not proceed effectively in the absence of a Lewis acid. In marked contrast, the cyclic

dx.doi.org/10.1021/jo3015227 | J. Org. Chem. 2012, 77, 8588−8604

Scheme 2. Regiochemical Course of Cascade Reaction



products *cis*-**15a**, *trans*-**15a**, and **16a** were formed in the reaction with electrophilic *n*-C_3F_7 radical even without geometry control by the Lewis acid (entry 5). Next, the amount of Et_3B was checked (entries 6 and 7). Decreasing the amount of Et_3B to 1.0 or 0.5 equiv resulted in an acceptable chemical efficiency. The desired products were obtained in 56% combined yield, accompanied by 14% yield of the recovered starting material **1** (entry 7). In regard to the solvent effect, the replacement of CH_2Cl_2 with DMF or CH_3OH led to an increase in the chemical yields, although solvents did not influence the regiochemical courses and cis/trans selectivities of **15a** so much (entries 8−13). The use of DMF improved the chemical yield to 89% (entry 12). In these reactions, cis/trans diastereoselectivities of **15a** were low, although the polarity-matched product **16a** was obtained as a single cis-isomer.

We next studied the reaction using other perfluoroalkyl radicals. Several trends in Table 2 are noteworthy. The cyclic products **15b** and **16b** were obtained in 74% combined yield and 72:28 ratio when primary *n*-C_4F_9I was employed in the presence of $Zn(OTf)_2$ (entry 1). This ratio is analogous to that of *n*-C_3F_7I (entry 1 in Table 1). As shown in Scheme 2, the branched secondary perfluoroalkyl radicals are known to exhibit electrophilicities greater than those of primary perfluoroalkyl radicals.[14] The use of secondary perfluoroalkyl iodide iso-C_3F_7I had a moderate impact on the two competitive reaction pathways. As expected, the formation of **16c** slightly increased via polarity-matched perfluoroalkylation. In contrast to *n*-C_3F_7I, the cyclic products **15c** and **16c** were obtained in 78:22 ratio even in the presence of $Cu(OTf)_2$ (entry 4 in Table 2 vs entry 4 in Table 1). Similar regioselectivity and chemical efficiency were observed when secondary cyclo-$C_6F_{11}I$ was employed (entry 5). For direct comparison, the previously reported result using nucleophilic isopropyl radical has shown high selectivity, affording the product **15e** with high cis selectivity (entry 6).[9a] Additionally, a large excess of the isopropyl iodide (30 equiv) was required for the successful reaction (entry 6). Therefore, it is important to note that the reaction with perfluoroalkyl radicals proceeded effectively by employing only 5 equiv of perfluoroalkyl iodides (entries 1−5). This is probably due to the extraordinary reactivity of perfluoroalkyl radicals, relative to their hydrocarbon counterparts.[4,5]

Two competitive reaction pathways are shown in Figures 4 and 5. The cyclic products **15a−d** were formed through mismatched addition (path a), whereas the cyclic product **16a−d** were formed through matched addition (path b). As shown in Tables 1 and 2, polarity-mismatched perfluoroalkylation (path a) giving the cyclic products **15a−d** was observed as a major course. Here, two factors directing regiochemical courses are discussed. First of all, the regiochemical courses are controlled by the stability of intermediate radicals (Figure 4). The stabilization of an intermediate radical by resonance promotes polarity-mismatched addition to electron-deficient acceptor (path a) giving the resonance-stabilized radical **H** over the polarity-matched addition (path b) to electron-rich acceptor giving the unstable radical **I**.

We next consider the polar effect by fluorine's potent σ-inductive electron-withdrawing property on transition states (Figure 5). As the possible transition states, we also have presumed the polar transition states **J** and **K** in which weak radical character has been transferred to radical acceptors.[1,2b] In particular, these polarizations are assumed to play an important role in the cyclization step. In other words, the matched addition (path b) leads to the polarity-mismatched interaction in the cyclization step as shown in the transition state **K** (the mismatched cyclization path d), whereas the facile cyclization

Table 1. Cascade Radical Reaction of 1 with *n*-C_3F_7 Radical[a]

entry	Lewis acid	solvent	Et_3B (equiv)	time (h)	ratio[b] of **15a**:**16a**	yield (%)[c]	cis:trans[b] of **15a**	cis:trans[b] of **16a**
1	$Zn(OTf)_2$	CH_2Cl_2	5.0	2	73:27	71	59:41	>98:2
2	$Mg(OTf)_2$	CH_2Cl_2	5.0	2.5	79:21	41	48:52	>98:2
3	$Yb(OTf)_3$	CH_2Cl_2	5.0	2	73:27	60 (8)	58:42	>98:2
4	$Cu(OTf)_2$	CH_2Cl_2	5.0	7	94:6	54 (3)	60:40	>98:2
5	none	CH_2Cl_2	5.0	3	72:28	49	54:46	>98:2
6	$Zn(OTf)_2$	CH_2Cl_2	1.0	2	71:29	65 (3)	61:39	>98:2
7	$Zn(OTf)_2$	CH_2Cl_2	0.5	2.5	71:29	56 (14)	61:39	>98:2
8	$Zn(OTf)_2$	toluene	5.0	2	74:26	70 (7)	57:43	>98:2
9	$Zn(OTf)_2$	Et_2O	5.0	2	78:22	62	58:42	>98:2
10	$Zn(OTf)_2$	THF	5.0	2	76:24	72 (4)	55:45	>98:2
11	$Zn(OTf)_2$	CH_3CN	5.0	2	76:24	67	65:35	>98:2
12	$Zn(OTf)_2$	DMF	5.0	2	76:24	89	59:41	>98:2
13	$Zn(OTf)_2$	CH_3OH	5.0	2	73:27	81	62:38	>98:2

[a]Reactions were carried out with *n*-C_3F_7I (5 equiv), Lewis acid (1 equiv), and Et_3B in hexane (1.0 M) at 20 °C. [b]Determined by ^1H NMR spectroscopic analysis. [c]Combined yield of the isolated products; the yield in parentheses is for the recovered starting material **1**.

dx.doi.org/10.1021/jo3015227 | J. Org. Chem. 2012, 77, 8588−8604

Table 2. Reaction of 1 with Perfluoroalkyl Radicals

entry	RI	Lewis acid	time (h)	product (ratio)[a]	yield (%)[b]	cis:trans[a] of **15b−e**	cis:trans[a] of **16b−e**
1[c]	*n*-C_4F_9I (5 equiv)	$Zn(OTf)_2$	2	**15b** + **16b** (72:28)	74	63:37	>98:2
2[c]	*i*-C_3F_7I (5 equiv)	$Zn(OTf)_2$	2.5	**15c** + **16c** (62:38)	77	79:21	>98:2
3[c]	*i*-C_3F_7I (5 equiv)	$Yb(OTf)_3$	3	**15c** + **16c** (60:40)	42 (5)	75:25	>98:2
4[c]	*i*-C_3F_7I (5 equiv)	$Cu(OTf)_2$	8	**15c** + **16c** (78:22)	74	81:19	>98:2
5[c]	*c*-$C_6F_{11}I$ (5 equiv)	$Zn(OTf)_2$	2.5	**15d** + **16d** (61:39)	66 (6)	77:23	>98:2
6[d]	*i*-C_3H_7I (30 equiv)	$Zn(OTf)_2$	4	**15e**	41 (42)	>98:2	>98:2

[a]Determined by ^1H NMR spectroscopic analysis. [b]Combined yield of the isolated products; the yield in parentheses is for the recovered starting material **1**. [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 9a.

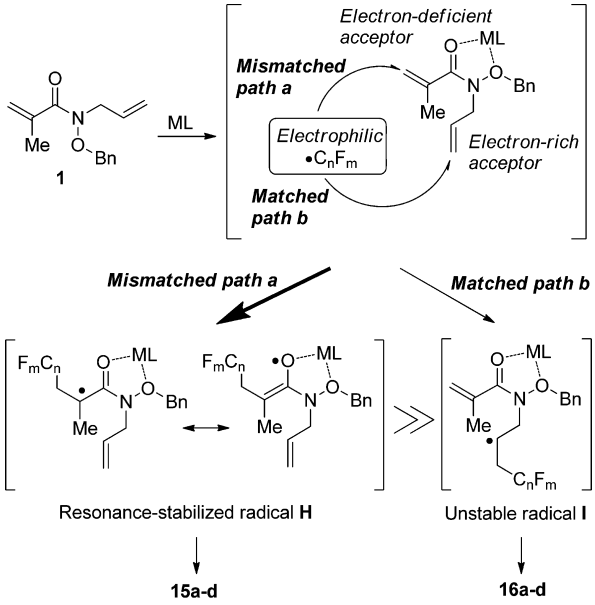


Figure 4. Stability of intermediate radicals in the addition step.

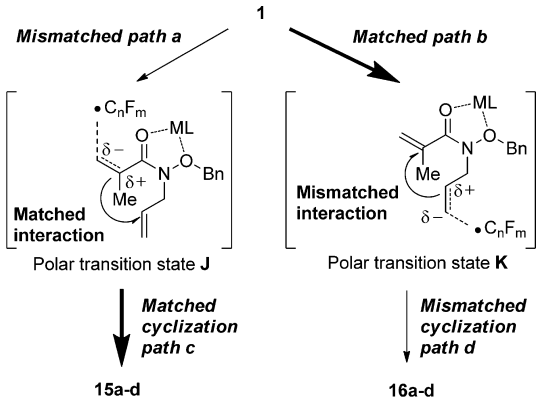


Figure 5. Polar effect on the cyclization process.

proceeds through mismatched addition (path a) as shown in the matched interaction in the transition state **J** (the matched cyclization path c). Therefore, these electronically disparate interactions between addition step and cyclization step direct regiochemical courses, although the net impact on regiochemical courses is derived from a complex interplay involving the activation by Lewis acid.

Moreover, the stability of the intermediate radical and the polar effect on transition states affect the reversibility in the cyclization step as well as the rate-determining step (Figure 6). In comparison with high cis selectivity in the reaction using a

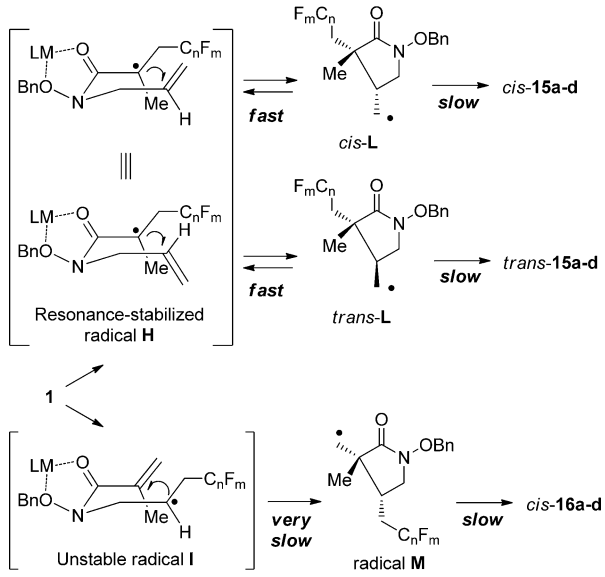


Figure 6. Reversibility and reaction rate.

nucleophilic isopropyl radical (entry 6 in Table 2), we observed erosion of cis/trans diastereoselectivities of **15a−d** in perfluoroalkyl radical reactions. Although the change in stability of alkyl radicals by fluorination does not show a clear trend, the difference in stability between the fully fluorinated alkyl radicals and alkyl radicals show a clear trend.[1,15] We simulated the stability of the fully fluorinated alkyl radicals and alkyl radicals by calculating the bond dissociation energies for F_3C-H, H_3C-H, $(F_3C)_2FC-H$, $(H_3C)_2HC-H$, $F_3CF_2CF_2C-H$, and $H_3CH_2CH_2C-H$, which are reported in Supporting Information.[16] In our calculation studies, the most striking observation is that in which the H_mC_n-H bonds are evidently made 6−4.5 kcal mol^{-1} stronger by the full substitution with fluorine atoms. Therefore, the final iodine atom-transfer process giving *cis*-**15a−d** or *trans*-**15a−d** is relatively slow (Figure 6).[17] Additionally, the matched interaction in the polar transition state **J** could enhance the rate for the cyclization step (Figure 5). Consequently, the slow iodine atom-transfer step, the fast cyclization step, and the high stability of the intermediate radical **H** allow the reversibility between the two cyclized radicals *cis*-**L** and *trans*-**L**, leading to low cis/trans diastereoselectivity. Therefore, it assumes that the final iodine atom-transfer process would be a rate-determining step in this pathway. In contrast, another pathway gave the cyclic products **16a−d** as a single cis-isomer. In this pathway, the rate for the cyclization step is smaller than that for iodine atom-transfer step, probably due to the lower stability of intermediate radical **I** and the polarity-mismatched interaction in the cyclization

dx.doi.org/10.1021/jo3015227 | J. Org. Chem. 2012, 77, 8588−8604

step as indicated by **K** (Figure 5). Thus, the unstable radical **I** gave the cyclic intermediate radical **M** without equilibration, leading to high diastereoselectivity. Probably, in this pathway, the cyclization step is a rate-determining step, which suppressed the initial polarity-mismatched perfluoroalkyl radical addition step.

To learn about the effect of an electron-deficient acceptor on regiochemical courses, the cascade reaction was next studied by employing the substrate **2** having an acryloyl moiety (Scheme 3

Scheme 3. Cascade Radical Reaction of 2

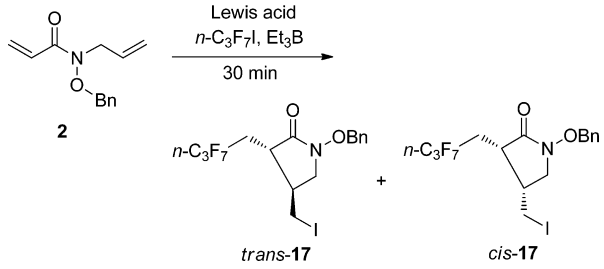


Table 3. Reaction of 2 with *n*-C_3F_7 Radical[a]

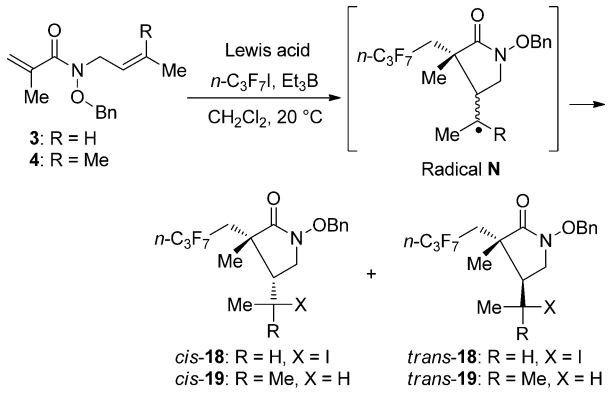
entry	Lewis acid	solvent	T (°C)	yield (%)[b]	trans:cis[c] of **17**
1	$Zn(OTf)_2$	CH_2Cl_2	20	53	62:38
2	$Zn(OTf)_2$	toluene	20	28 (21)	66:34
3	$Zn(OTf)_2$	THF	20	30 (6)	67:33
4	$Mg(OTf)_2$	CH_2Cl_2	20	40	64:36
5	$Yb(OTf)_3$	CH_2Cl_2/THF (4:1, v/v)	20	ND[d] (57)	–
6	$Cu(OTf)_2$	CH_2Cl_2	20	28 (12)	64:36
7	$Zn(OTf)_2$	CH_2Cl_2	−20	46	62:38

[a]Reactions were carried out with *n*-C_3F_7I (5 equiv), Lewis acid (1 equiv), and Et_3B in hexane (1.0 M, 5 equiv). [b]Combined yield of *trans*-**17** and *cis*-**17**; the yield in parentheses is for the recovered starting material **2**. [c]Determined by ^1H NMR spectroscopic analysis. [d]Not detected.

and Table 3). In contrast to the substrate **1** having a methacryloyl moiety, the cyclization proceeded under the conditions of geometry control by a Lewis acid. The addition of $Zn(OTf)_2$ remarkably promoted the desired cascade reaction in CH_2Cl_2 at 20 °C due to the Lewis acid-induced geometry control (entry 1). Interestingly, the regiochemical course of the cascade reaction of **2** was controlled well. The 5-exo cyclization products *trans*-**17** and *cis*-**17** was obtained in 53% combined yield and 62:38 ratio via the polarity-mismatched radical addition to the acryloyl moiety. In this reaction, the formation of products starting from the polarity-matched perfluoroalkylation was not observed. Chemical yields decreased by changing the solvent from CH_2Cl_2 to toluene or THF; instead, the starting material **2** was recovered (entries 2 and 3). In regard to the effect of the Lewis acid, the use of $Mg(OTf)_2$, $Yb(OTf)_3$, or $Cu(OTf)_2$ led to a decrease in the chemical yields (entries 4−6). Next, the reaction was conducted at −20 °C in the presence of $Zn(OTf)_2$ (entry 7). As expected, a 41% combined yield of *trans*-**17** and *cis*-**17** was formed. As compared with the substrate **1** having the methacryloyl moiety, the reaction of **2** showed the lower chemical efficiency. The moderate chemical yields of *trans*-**17** and *cis*-**17** were attributed to the side reactions such as competitive polymerization of **2** having a labile acrylamide moiety.

We next studied the substituent effect of an electron-rich acceptor on regiochemical courses by employing substrates **3** and **4** (Scheme 4 and Table 4). As expected, the introduction of

Scheme 4. Regioselective Reaction of 3 and 4



a methyl substituent at the allyl moiety had an impact on the perfluoroalkyl radical addition step. At first, the cascade reaction of substrate **3** (R = H) was studied (entries 1−3). The regiochemical course was controlled well because of the steric effect of the substituent. The four stereoisomeric cyclic products were formed via polarity-mismatched perfluoroalkylation. In other words, the products *cis*-**18** and *trans*-**18** were respectively obtained as two diastereomeric mixtures regarding the newly generated stereocenter at the iodinated carbon. In the presence of $Zn(OTf)_2$, *cis*-**18** (major), *cis*-**18** (minor), *trans*-**18** (major), and *trans*-**18** were obtained in 74% combined yield in a 38:31:22:9 ratio (entry 1). Next, the cascade reaction of the substrate **4** (R = Me) was studied. However, the formation of cyclic products was not observed under similar conditions. This result indicates that the iodine atom-transfer from perfluoroalkyl iodide (*n*-C_3F_7I) to stable tertiary radical **N** (R = Me), generated from **4**, was a less effective process, although the iodine atom-transfer to secondary radical **N** (R = H) proceeded effectively. Thus, Bu_3SnH was used as an additive for trapping stable tertiary radical **N** (R = Me) (entries 4 and 5). As expected, the desired cyclic products *cis*-**19** and *trans*-**19** were formed in low chemical yield.

To understand the generality and practicality of the cascade reaction induced by the polarity-mismatched addition of perfluoroalkyl radicals, the next substrate of choice was **5** having a carbon−carbon triple bond (Scheme 5 and Table 5). The reaction of alkyne **5** with *n*-C_3F_7I proceeded with high regioselectivity to give the polarity-mismatched perfluoroalkylation products *Z*-**20a** and *E*-**20a** without the formation of cyclic product via matched perfluoroalkylation (entries 1−7). In the presence of $Zn(OTf)_2$, *Z*-**20a** and *E*-**20a** were obtained in 79% combined yield and 82:18 ratio (entry 1). Other Lewis acids $Mg(OTf)_2$, $Yb(OTf)_3$, and $Cu(OTf)_2$ promoted the reaction of **5** with similar *Z*/*E* selectivities (entries 2−4). The replacement of CH_2Cl_2 with toluene, THF, or CH_3CN did not influence the chemical efficiency and *Z*/*E* selectivity (entries 5−7). We tested the isomerization of the *Z*-isomer to the *E*-isomer by treating pure *Z*-**20a** under radical conditions using *n*-C_3F_7I and Et_3B. However, the formation of *E*-**20a** was not observed, and the starting substrate *Z*-**20a** was recovered. The secondary perfluoroalkyl iodide iso-C_3F_7I also worked well

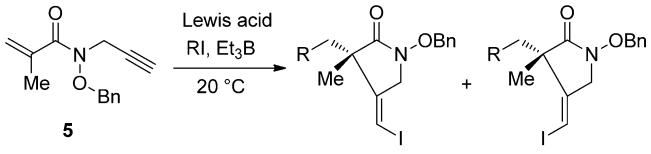
dx.doi.org/10.1021/jo3015227 | J. Org. Chem. 2012, 77, 8588−8604

Table 4. Reaction of 3 and 4 with n-C_3F_7 Radical[a]

entry	substrate	additive	Lewis acid	time (h)	product	yield (%)[b]	ratio
1	**3**	none	$Zn(OTf)_2$	2.5	**18**	74	38:31:22:9[d]
2	**3**	none	$Yb(OTf)_3$	3.5	**18**	59	37:32:22:9[d]
3	**3**	none	$Cu(OTf)_2$	4.5	**18**	52 (16)	38:31:21:10[d]
4[c]	**4**	Bu_3SnH	$Zn(OTf)_2$	12	**19**	23 (12)	36:64[e]
5[c]	**4**	Bu_3SnH	$Yb(OTf)_3$	12	**19**	19 (18)	–

[a]Reactions were carried out with perfluoroalkyl iodides (5 equiv), Lewis acid (1 equiv), and Et_3B in hexane (1.0 M, 5 equiv). [b]Combined yield of the isolated products; the yield in parentheses is for the recovered starting material **3** or **4**. [c]Bu_3SnH (1.5 equiv) was employed. [d]Determined by ^1H NMR spectroscopic analysis. The ratio for *cis*-**18** (major):*cis*-**18** (minor):*trans*-**18** (major):*trans*-**18** (minor). [e]Determined by isolated yields. The ratio for *cis*-**19**:*trans*-**19**.

Scheme 5. Cascade Radical Reaction of 5



5

a: R = n-C_3F_7
b: R = i-C_3F_7
c: R = i-C_3H_7

Z-**20a-c** *E*-**20a-b**

Table 5. Reaction of 5 with Perfluoroalkyl Radicals

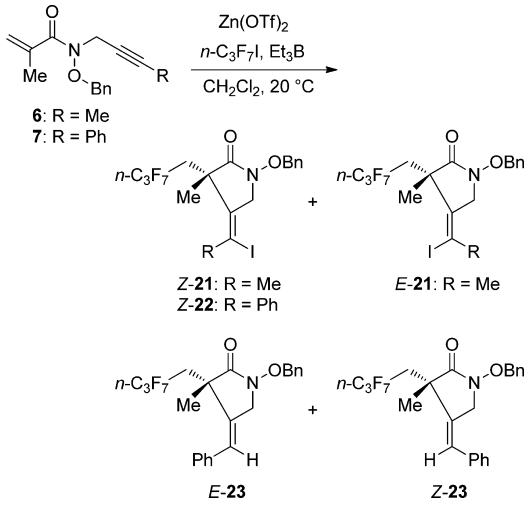
entry	RI	Lewis acid	solvent	time (h)	product (% yield)[a]	Z:E[b]
1[c]	n-C_3F_7I (5 equiv)	$Zn(OTf)_2$	CH_2Cl_2	5	**20a** (79)	82:18
2[c]	n-C_3F_7I (5 equiv)	$Mg(OTf)_2$	CH_2Cl_2	5	**20a** (79)	83:17
3[c]	n-C_3F_7I (5 equiv)	$Yb(OTf)_3$	CH_2Cl_2	5	**20a** (88)	85:15
4[c]	n-C_3F_7I (5 equiv)	$Cu(OTf)_2$	CH_2Cl_2	5	**20a** (75)	84:16
5[c]	n-C_3F_7I (5 equiv)	$Zn(OTf)_2$	toluene	5	**20a** (73)	82:18
6[c]	n-C_3F_7I (5 equiv)	$Zn(OTf)_2$	THF	5	**20a** (61)	85:15
7[c]	n-C_3F_7I (5 equiv)	$Zn(OTf)_2$	CH_3CN	5	**20a** (75)	85:15
8[c]	i-C_3F_7I (5 equiv)	$Zn(OTf)_2$	CH_2Cl_2	2	**20b** (59)	84:16
9[d]	i-C_3H_7I (30 equiv)	$Zn(OTf)_2$	CH_2Cl_2	5	**20c** (80)	>98:2

[a]Combined yield of the isolated products. [b]Determined by ^1H NMR spectroscopic analysis. [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).

(entry 8). The products *Z*-**20b** and *E*-**20b** were obtained in 59% combined yield and 84:16 ratio. In contrast, high Z/E selectivity was observed to give the product *Z*-**20c** in >98:2 ratio when iso-C_3H_7I was employed as an alkyl radical source (entry 9).

To gain further insight into the effect of a carbon−carbon triple bond as a radical acceptor, we next explored the reaction of substrates **6** and **7** having substituents at the terminal position of the triple bond (Scheme 6 and Table 6). As expected, the polarity-mismatched perfluoroalkylation proceeded exclusively. In the presence of $Zn(OTf)_2$, the reaction of **6** (R = Me) with n-C_3F_7I gave the products *Z*-**21** and *E*-**21** in 81% combined yield and 76:24 ratio (entry 1). Next, the reaction of **7** (R = Ph) was carried out for 1 h (entry 2). In

Scheme 6. Reaction of 6 and 7



6: R = Me
7: R = Ph

Z-**21**: R = Me
Z-**22**: R = Ph

E-**21**: R = Me

E-**23** *Z*-**23**

Table 6. Reaction of 6 and 7 with n-C_3F_7 Radical[a]

entry	substrate	Et_3B	time (h)	product (% yield)[b]	ratio
1	**6**	5 equiv	5	**21** (81)	*Z*-**21**:*E*-**21** = 76:24[d]
2	7	5 equiv	1	**22** (45)	*Z*-**22**:*E*-**22** = >98:2[d]
3	7	5 equiv	5	**22** (63) + **23** (8)	*Z*-**22**:*E*-**22** = >98:2[d]
4[c]	7	5 equiv × 2	12	**22** (8) + **23** (45)	*E*-**23**:*Z*-**23** = 73:27[e]

[a]Reactions were carried out with n-C_3F_7I (5 equiv), $Zn(OTf)_2$ (1 equiv), and Et_3B in hexane (1.0 M). [b]Combined yield of the isolated products. [c]Et_3B (5 equiv) was employed twice. [d]Determined by ^1H NMR spectroscopic analysis. [e]Determined by isolated yields.

contrast to substrate **6**, the reaction of **7** gave the product *Z*-**22** in >98:2 ratio (entry 2). Interestingly, the formation of the reduction products *E*-**23** and *Z*-**23** was newly observed after being stirred for 5 h, although a hydrogen atom donor is still unclear (entry 3). The high Z selectivity of **22** was maintained. The products *E*-**23** and *Z*-**23** are assumed to be generated by the hydrogen atom transfer from substrate, products, reagents, or solvent into intermediate π-radicals. Actually, when an excess amount of Et_3B (5 equiv × 2) was employed, the reduction products *E*-**23** and *Z*-**23** were obtained in a 73:27 ratio as major products (entry 4).

The E,Z selectivities are determined when vinyl radicals are captured by atom-transfer reagents. Particularly, the E,Z selectivities of **20a**-**23** would be influenced by the steric hindrance between the substituents on α-carbon atom of

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intermediated radicals **O**-**Q** and perfluoroalkyl iodides (Figure 7). The vinyl radicals generated from **5** are σ-radicals, which are

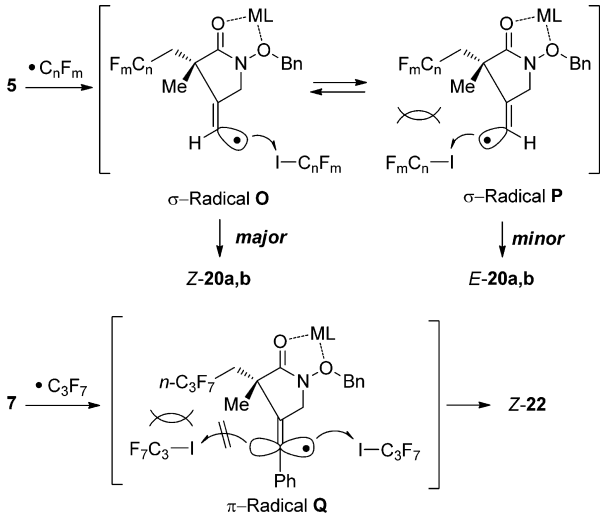


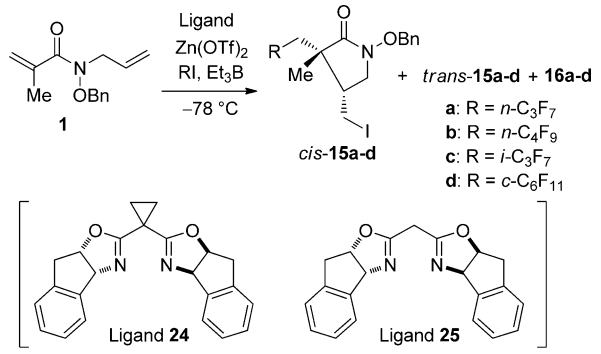
Figure 7. *Z* and *E* selectivity.

in very fast equilibrium between *E*- and *Z*-isomers **O** and **P**. Thus, it assumes that the small steric effect around σ-radicals on an sp^2-carbon atom would lead to low *Z*/*E* selectivity. In contrast, the reaction of **7** gave a stable intermediate π-radical **Q** conjugated with the aromatic ring; thus, π-radical **Q** on an sp-carbon atom was strongly influenced by the steric hindrance and directed the *Z* selectivity.

Enantioselective Cascade Reaction Using a Chiral Lewis acid. The control of stereochemistry in free radical-mediated reactions has been of great importance to organic synthesis.[18] Hence, in recent years, significant progress has been observed in enantioselective radical addition reactions, allylation, H-atom transfer reactions, and so on.[19−21] However, the enantiocontrol in radical cyclizations still remains a major challenge,[22] although significant progress has been made recently by several approaches.[23−29] Only a handful of reports describes chiral Lewis acid-mediated enantioselective radical cyclizations.[23,24] Moreover, less is known about enantioselective reactions of perfluoroalkyl radicals,[30] and there have been no studies on perfluoroalkyl radical-mediated enantioselective cyclizations. Thus, we have studied the chiral Lewis acid-mediated enantioselective reaction with perfluoroalkyl radicals based on our approaches to control stereochemistry of the cascade radical addition−cyclization reaction by taking advantage of the hydroxamate ester.[9]

At first, we investigated the chiral Lewis acid-mediated reactions of **1** with perfluoroalkyl iodides at −78 °C (Scheme 7). The enantiomeric purities of products were checked by chiral HPLC analysis. The combinations of chiral box ligands **24** or **25** and Lewis acids $Zn(OTf)_2$ promoted the polarity-mismatched perfluoroalkylation of the electron-deficient acceptor in **1** (Table 7).[31] Because the enantioselective radical reaction at −78 °C was slow, elongation of the reaction time improved the chemical yields. The use of chiral Lewis acid, prepared from ligand **24** and $Zn(OTf)_2$, led to not only an enhancement in product ratio but also an improvement in cis/trans diastereoselectivity. In the presence of ligand **24**, the reaction with a *n*-C_3F_7 radical in CH_2Cl_2 proceeded effectively to form the products **15a** and **16a** in 95:5 ratio and 88% combined yield (entry 1). Although cis/trans diastereoselectivity was still low, the major product *cis*-**15a** was isolated in 76% ee along with *trans*-**16a** in 88% ee. 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. In regard to the solvent effect, the addition of hexafluoro-2-propanol (HFIP) as an acidic solvent led to lower product ratio and enantioselectivity (entry 2). In contrast, the replacement of CH_2Cl_2 with CH_2Cl_2−toluene (1:1, v/v) led to an increase in enantioselectivities (entry 4), although the nearly racemic products were obtained when reaction was carried out in toluene (entry 3). The use of CH_2Cl_2−toluene (1:1, v/v) improved the enantioselectivity of *cis*-**15a** into 87% and the enantioselectivity of *trans*-**16a** into 90% (entry 4). When primary *n*-C_4F_9I was employed, similar improvement of the product ratio was also observed to give the products **15b** and **16b** in 95:5 ratio (entry 5). The enantioselectivity and cis/trans diastereoselectivity were increased by changing the primary perfluoroalkyl radicals to secondary iso-C_3F_7 radical (entry 6). The reaction with secondary iso-C_3F_7 radical in CH_2Cl_2 gave the cyclic product *cis*-**15c** with 90% ee in 92:8 cis/trans selectivity. However, the product ratio of **15c** and **16c** diminished to 82:18 due to higher electrophilicity of secondary iso-C_3F_7 radical. When the ligand **25** was employed instead of ligand **24**, the product ratio, cis/trans diastereoselectivity, and enantioselectivity were all lowered (entry 7). Decreasing the amount of chiral Lewis acid to 0.5 equiv resulted in a low enantioselectivity (entry 8). Again, the improvement in enantioselectivity was observed, when reaction was carried out in CH_2Cl_2−toluene (1:1, v/v) (entry 9). Additionally, the enantioselectivity of *cis*-**15c** increased to 92% by using the activated 4 Å molecular sieves (entry 10). Under analogous reaction conditions, outstanding levels of enantio- and diastereoselectivities were also obtained by employing cyclo-C_6F_{11} iodide as a radical precursor (entry 11).

Scheme 7. Cascade Reaction of 1 Using a Chiral Lewis Acid



We next explored the enantioselective reaction of substrate **3** having a methyl group at a terminal position of the electron-rich acceptor (Scheme 8). In this case, polarity-mismatched perfluoroalkylation proceeded exclusively to give four isomers. As expected, the circumstances in the presence of a chiral Lewis acid led to an enhancement in diastereoselectivity (dr *cis*-**18** (major)/*cis*-**18** (minor)/*trans*-**18** (major)/*trans*-**18** (minor) = 50:23:21:6), as compared with the reaction in the absence of ligand (entry 1 in Table 4). The reaction with a *n*-C_3F_7 radical gave the cyclic products in 91% combined yield. The major isomer of *cis*-**18** was obtained with 87% ee, along with the minor isomer of *cis*-**18** (75% ee) and the major isomer of *trans*-**18** (87% ee). In the case of secondary iso-C_3F_7 radical, the

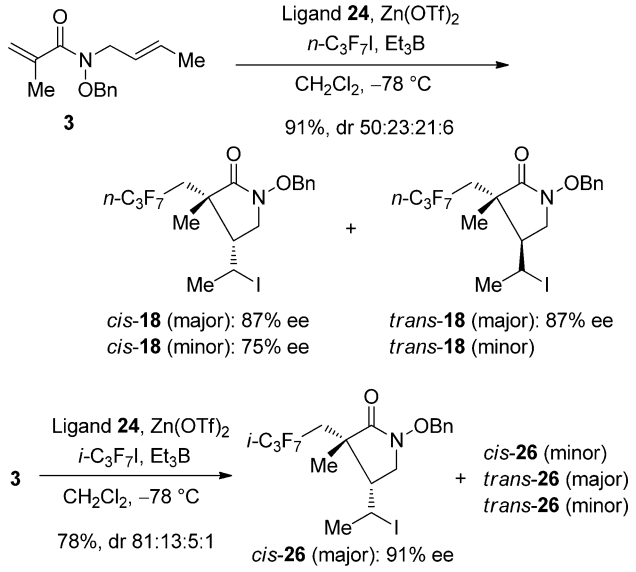
dx.doi.org/10.1021/jo3015227 | *J. Org. Chem.* 2012, 77, 8588−8604

Table 7. Enantioselective Reaction of 1 with Perfluoroalkyl Radicals[a]

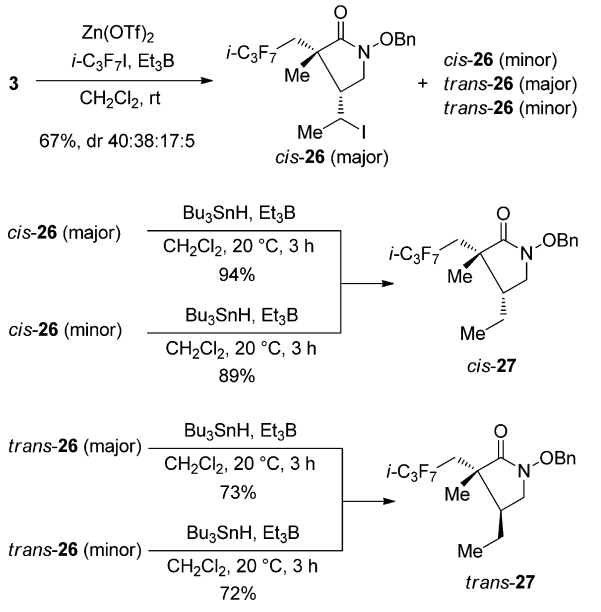
entry	RI	solvent	time (d)	ratio[b] of **15**:**16**	yield (%)[c]	cis:trans[b] of **15**	ee(%)[d] *cis*-**15**	ee(%)[d] *trans*-**15**
1	*n*-C_3F_7I	CH_2Cl_2	2	95:5	88	62:38	76	88
2	*n*-C_3F_7I	CH_2Cl_2/HFIP (9:1, v/v)	3	78:22	78	86:14	6	13
3	*n*-C_3F_7I	toluene	3	91:9	84	81:19	1	0
4	*n*-C_3F_7I	CH_2Cl_2/toluene (1:1, v/v)	1	97:3	78	64:36	87	90
5	*n*-C_4F_9I	CH_2Cl_2	2	95:5	72	66:34	77	85
6	*i*-C_3F_7I	CH_2Cl_2	5	82:18	44	92:8	90	
7[e]	*i*-C_3F_7I	CH_2Cl_2	2	72:28	45	88:12	51	
8[f]	*i*-C_3F_7I	CH_2Cl_2	5	79:21	46	94:6	65	
9	*i*-C_3F_7I	CH_2Cl_2/toluene (1:1, v/v)	5	81:19	46	92:8	91	
10[g]	*i*-C_3F_7I	CH_2Cl_2	5	79:21	40	94:6	92	
11	*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 **24** (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 of the isolated products. [d]Determined by HPLC analysis. [e]The ligand **25** was employed instead of ligand **24**. [f]Reaction was carried out with $Zn(OTf)_2$ (0.5 equiv) and ligand **24** (0.5 equiv). [g]In the presence of activated 4 Å molecular sieves.

Scheme 8. Enantioselective Cascade Reaction of 3



Scheme 9. Reductive Deiodination of Four Stereoisomers



reaction proceeded with better diastereoselectivity (dr *cis*-**26** (major)/*cis*-**26** (minor)/*trans*-**26** (major)/*trans*-**26** (minor) = 81:13:5:1) to give the major isomer of *cis*-**26** with 91% ee.

The configuration of cis- and trans-isomers was confirmed by the reduction of four stereoisomers (Scheme 9). Four isomers *cis*-**26** (major), *cis*-**26** (minor), *trans*-**26** (major), and *trans*-**26** (minor) were prepared in 40:38:17:5 ratio under the racemic reaction conditions. The cis-configuration was confirmed by converting *cis*-**26** (major) and *cis*-**26** (minor) into the same product *cis*-**27**. The reduction of *trans*-**26** (major) and *trans*-**26** (minor) gave *trans*-**27**.

Next, the enantioselective reaction of substrates having a triple bond was tested (Scheme 10). Although the reaction of **6** with a *n*-C_3F_7 radical proceeded effectively at −78 °C, moderate enantioselectivity and low *Z*/*E* selectivity were observed. The major product *E*-**21** was formed in 33% ee along with *Z*-**21** in 48% ee. In the case of substrate **7**, high *Z* selectivity was obtained. However, enantioselectivity of *Z*-**22** was low. In contrast to the reaction in the absence of ligand (entry 3 in Table 6), the formation of the reduction products *E*-**23** and *Z*-**23** was not observed under enantioselective reaction conditions.

Reaction with Other Electrophilic Carbon Radicals. Carbon radicals having electron-withdrawing groups possess electrophilic character.[32] We next studied the reaction of **1** with the moderately electron-deficient radicals derived from ICH_2CO_2Et, ICH_2CN, and $BrC(CO_2Et)_2Me$ (Scheme 11). In the presence of $Zn(OTf)_2$, the reaction proceeded effectively by employing only 5 equiv of alkyl iodides as well as perfluoroalkyl iodides (Table 8). These radicals selectively added to an electron-deficient alkene moiety of **1**, to give *cis*-**28a**−**c** and *trans*-**28a**−**c** without the formation of regioisomers. This regiochemical course is similar to that using a nucleophilic isopropyl radical (Table 2, entry 6). The difference between these electron-deficient radicals and an isopropyl radical is the cis/trans diastereoselectivity. The cis/trans selectivities of **28a**−**c** were low (Table 8, entries 1−3), whereas high cis selectivity was observed in the reaction with an isopropyl radical (Table 2, entry 6). Thus, the cis/trans selectivities of **28a**−**c** are similar to those using perfluoroalkyl radicals (Tables 1 and 2). These

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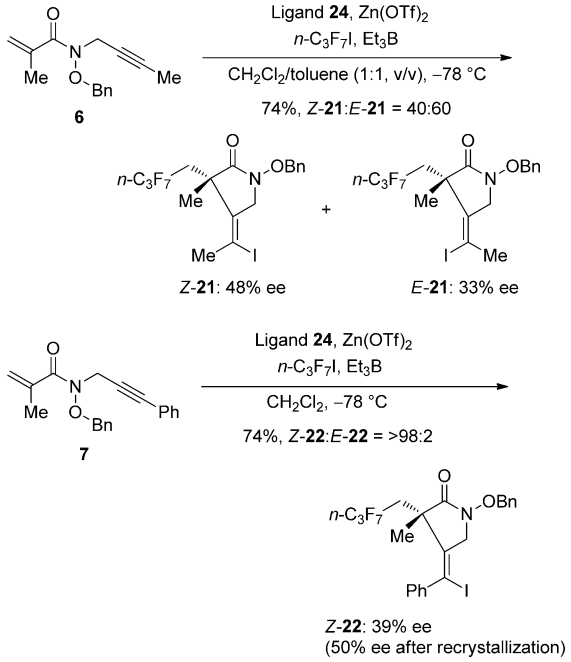
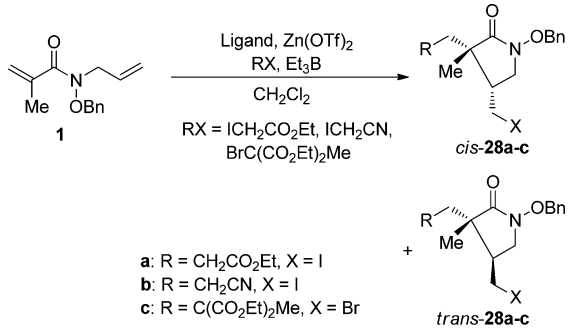
Scheme 10. Enantioselective Cascade Reaction of 6 and 7



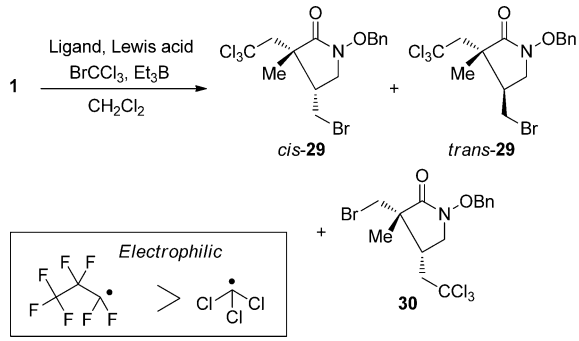
Scheme 11. Regiochemical Course of Reaction with Other Radicals



observations indicate reversibility in the cyclization step. It is important to note that the reaction with $BrC(CO_2Et)_2Me$ proceeded effectively via the bromine-atom transfer process due to the high stability of $C(CO_2Et)_2Me$ radical (Table 8, entry 3). As expected, the brominated products *cis*-**28c** and *trans*-**28c** were obtained in 84% yield and 81:19 ratio. We also investigated the enantioselective reaction (entries 4 and 5) and found moderate enantioselectivities and cis/trans selectivities of the reaction. The erosion of these selectivities of **28a** and **28c** also supports reversibility in the cyclization step as a rate-determining step.

Finally, we investigated the reaction of **1** with a trichloromethyl radical, which has electrophilicity lower than that of perfluoroalkyl radicals (Scheme 12 and Table 9).[33] As

Scheme 12. Regiochemical Course of Reaction with $BrCCl_3$



expected, polarity-mismatched radical addition was observed as a major pathway. Compared with $n\text{-}C_3F_7$ radical (Table 1, entry 1), the low electrophilicity of trichloromethyl radical led to a slight enhancement of ratio of **29**:**30** to 79:21 (Table 9, entry 1). However, the chemical yield was low probably because of a less effective bromine-atom transfer process as a final step. The use of $Cu(OTf)_2$ led to the selective formation of **29** (**29**:**30** = 96:4 ratio), although the chemical yield diminished to 24% (entry 2). We next explored the enantioselective reaction with CCl_3Br (entries 3 and 4). However, the reaction did not proceed effectively at −78 °C to give *cis*-**29** in 8% yield and 77% ee (entry 3). Chiral Lewis acid accelerated the reaction at **20** °C to improve the chemical yield to 60%, although the enantioselectivity of *cis*-**29** was 49% ee (entry 4).

CONCLUSION

We have demonstrated that cascade radical reactions, starting from polarity-mismatched perfluoroalkylation of an electron-deficient acceptor, proceeded effectively. These cascade radical reactions involve a cyclization process, which proceed with good chemical efficiency by using a hydroxamate ester as a coordination site with a Lewis acid, providing the synthetic approach to chiral γ-lactams. In certain cases, they proceed with good enantio- and diastereoselectivities by employing a chiral Lewis acid, prepared from a chiral box ligand and $Zn(OTf)_2$.

EXPERIMENTAL SECTION

General. Melting points are uncorrected. ^{1}H NMR spectra were measured at 400 or 600 MHz. ^{13}C NMR spectra were measured at 101

Table 8. Reaction of 1 with Other Radicals

entry	RX	ligand	*T* (°C)	time (h)	yield (%)[a]	cis:trans[b] of **28**	ee (%)[c] *cis*-**28**	ee (%)[c] *trans*-**28**
1[d]	ICH_2CO_2Et	none	20	1.5	89	47:53		
2[d]	ICH_2CN	none	20	2	90	47:53		
3[d]	$BrC(CO_2Et)_2Me$	none	20	1.5	84	81:19		
4[e]	ICH_2CO_2Et	**24**	−78	70	83	66:34	55	54
5[e]	$BrC(CO_2Et)_2Me$	**24**	−78	40	88	79:21	51	27

[a]Combined yield of the isolated products. [b]Determined by ^{1}H NMR spectroscopic analysis. [c]Determined by HPLC analysis. [d]Reactions were carried out with RX (5 equiv), $Zn(OTf)_2$ (1 equiv), and Et_3B in hexane (1.0 M) in CH_2Cl_2 at 20 °C. [e]Reactions were carried out with RX (5 equiv), $Zn(OTf)_2$ (1 equiv), ligand **24** (1 equiv), and Et_3B in hexane (1.0 M, 5 equiv) in CH_2Cl_2 at −78 °C.

dx.doi.org/10.1021/jo3015227 | J. Org. Chem. 2012, 77, 8588−8604

Table 9. Reaction of 1 with Other Radicals

entry	Lewis acid	ligand	T (°C)	time	ratio[a] of **29**:**30**	yield (%)[b]	cis:trans[a] of **29**	ee (%)[c]
1[d]	$Zn(OTf)_2$	none	20	4.5 h	79:21	38	85:15	
2[d]	$Cu(OTf)_2$	none	20	20 h	96:4	24 (8)	91:9	
3[e]	$Zn(OTf)_2$	**24**	−78	1.5 d	−	8 (46)	−	77
4[e]	$Zn(OTf)_2$	**24**	20	70 d	86:14	60	86:14	49

[a]Determined by ^{1}H NMR spectroscopic analysis. [b]Combined yield of the isolated products; the yield in parentheses is for the recovered starting material **1**. [c]Determined by HPLC analysis. [d]Reactions were carried out with $BrCCl_3$ (5 equiv), $Zn(OTf)_2$ (1 equiv), and Et_3B in hexane (1.0 M) in CH_2Cl_2. [e]Reactions were carried out with $BrCCl_3$ (5 equiv), $Zn(OTf)_2$ (1 equiv), ligand **24** (1 equiv), and Et_3B in hexane (1.0 M, 5 equiv) in CH_2Cl_2.

or 126 MHz. ^{19}F NMR spectra were measured at 376 MHz with C_6F_6 as an internal standard (−162.2 ppm). The commercial reagents were used without further purification. HRMS measurements using electrospray ionization (ESI) were performed with a time-of-flight (TOF) mass analyzer. HRMS measurements using electron ionization (EI) were performed with a magnetic sector mass analyzer.

General Procedure for the Preparation of Allylamines 9 and 10. To a stirred suspension of **8** (1.00 g, 4.48 mmol) and Cs_2CO_3 (2.04 g, 6.27 mmol) in DMF (15 mL) was added allyl bromide derivative (5.38 mmol) at room temperature. After being stirred at same temperature for 12 h, the reaction mixture was diluted with water and then extracted with AcOEt. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by flash silica gel column chromatography (AcOEt:hexane = 1:15) afforded the products **9** (1.121 g, 95%), **10** (1.193 g, 96%), and **11** (1.174 g, 90%).

*N-(Phenylmethoxy)-N-2-propenylcarbamic Acid 1,1-Dimethylethyl Ester (**9**).* A colorless oil. IR ($CHCl_3$) 1699 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.41−7.30 (5H, m), 5.87 (1H, m), 5.22 (1H, dd, J = 17.1, 1.6 Hz), 5.17 (1H, dd, J = 10.4, 1.6 Hz), 4.83 (2H, s), 4.00 (2H, br d, J = 6.1 Hz), 1.49 (9H, s). ^{13}C NMR ($CDCl_3$) δ 156.6, 135.6, 132.7, 129.3, 128.4, 128.3, 118.0, 81.3, 77.1, 52.7, 28.1. MS (EI$^+$): m/z 263 (M$^+$, 0.2), 91 (100). HRMS (EI$^+$): calcd for $C_{15}H_{21}NO_3$ (M$^+$): 263.1516, Found: 263.1519.

*N-(Phenylmethoxy)-N-2-butenylcarbamic Acid 1,1-Dimethylethyl Ester (**10**).* A colorless oil. IR (KBr) 2976, 1704, 1454 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.43−7.24 (5H, m), 5.70−5.61 (1H, m), 5.56−5.47 (1H, m), 4.82 (2H, s), 3.92 (2H, d, J = 6.4 Hz), 1.69 (3H, dd, J = 6.4, 1.4 Hz), 1.50 (9H, s). ^{13}C NMR ($CDCl_3$) δ 156.7, 135.7, 129.7, 129.4, 128.4 (2C), 125.3, 81.3, 77.2, 52.1, 28.3, 17.8. HRMS (ESI$^+$): calcd for $C_{16}H_{23}NO_3Na$ (M + Na$^+$): 300.1570, Found: 300.1566.

*N-(Phenylmethoxy)-N-(3-methyl-2-butenyl)carbamic Acid 1,1-Dimethylethyl Ester (**11**).* A colorless oil. IR (KBr) 2976, 1704, 1453 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.40−7.29 (5H, m), 5.29 (1H, m), 4.81 (2H, s), 3.98 (2H, d, J = 6.9 Hz), 1.72 (3H, br s), 1.65 (3H, br s), 1.50 (9H, s). ^{13}C NMR ($CDCl_3$) δ 156.8, 136.3, 135.7, 129.4, 128.4, 128.3, 118.8, 81.2, 77.2, 47.7, 28.3, 25.8, 17.9. MS (EI$^+$): m/z 291 (M$^+$, 0.4), 91 (100). HRMS (EI$^+$): calcd for $C_{17}H_{25}NO_3$ (M$^+$): 291.1829, Found: 291.1849.

General Procedure for the Preparation of Propargylamines 12−14. After NaH (60% oil suspension, 470 mg 11.7 mmol) was washed with hexanes three times under argon atmosphere, THF (10 mL) was added. To this stirred suspension was added a solution of **8** (2.50 g, 11.2 mmol) in THF (10 mL) at 0 °C. After being stirred at same temperature for 20 min, propargyl bromide derivative (13.4 mmol) or 3-chloro-1-phenyl-1-propyne (1.4 mL, 10.2 mmol) was added to the reaction mixture. In the case of propargyl bromide derivatives, the reaction mixture was stirred at the room temperature for 12 h. In the case of 3-chloro-1-phenyl-1-propyne, the reaction mixture was stirred at 50 °C for 5 h. The reaction mixture was diluted with water and then extracted with AcOEt. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. Purification of the residue by flash silica gel column chromatography (AcOEt:hexane = 1:20) afforded the products **12** (2.693 g, 92%), **13** (2.837 g, 92%), and **14** (1.058 g, 28%).

*N-(Phenylmethoxy)-N-2-propyn-1-ylcarbamic Acid 1,1-Dimethylethyl Ester (**12**).* A colorless oil. IR ($CHCl_3$) 1702 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.45−7.40 (2H, m), 7.38−7.30 (3H, m), 4.93 (2H, s), 4.11 (2H, d, J = 2.4 Hz), 2.23 (1H, t, J = 2.4 Hz), 1.49 (9H, s). ^{13}C NMR ($CDCl_3$) δ 156.6, 135.6, 129.5, 128.6, 128.4, 82.3, 78.5, 77.8, 71.8, 40.2, 28.1. MS (EI$^+$): m/z 261 (M$^+$, 0.1), 91 (100). HRMS (EI$^+$): calcd for $C_{15}H_{19}NO_3$ (M$^+$): 261.1359, Found: 261.1366.

*N-2-Butyn-1-yl-N-(phenylmethoxy)carbamic Acid 1,1-Dimethylethyl Ester (**13**).* A colorless oil. IR ($CHCl_3$) 1707 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.46−7.41 (2H, m), 7.38−7.31 (3H, m), 4.93 (2H, s), 4.09 (2H, q, J = 2.1 Hz), 1.82 (3H, t, J = 2.1 Hz), 1.50 (9H, s). ^{13}C NMR ($CDCl_3$) δ 156.7, 135.7, 129.5, 128.5, 128.3, 81.9, 79.3, 77.6, 73.6, 40.4, 28.1, 3.4. MS (FAB$^+$): m/z 276 (M + H$^+$, 12), 91 (100). HRMS (FAB$^+$): calcd for $C_{16}H_{22}NO_3$ (M + H$^+$): 276.1594, Found: 276.1607.

*N-(Phenylmethoxy)-N-(3-phenyl-2-propyn-1-yl)carbamic Acid 1,1-Dimethylethyl Ester (**14**).* A colorless oil. IR ($CHCl_3$) 1705 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.48−7.40 (4H, m), 7.37−7.31 (3H, m), 7.30−7.25 (3H, m), 5.00 (2H, s), 4.38 (2H, s), 1.52 (9H, s). ^{13}C NMR ($CDCl_3$) δ 156.5, 135.6, 131.7, 129.5, 128.5, 128.4, 128.3, 128.2, 122.8, 84.0, 83.4, 82.1, 77.9, 41.0, 28.1. MS (EI$^+$): m/z 337 (M$^+$, 0.1), 57 (100). HRMS (EI$^+$): calcd for $C_{21}H_{23}NO_3$ (M$^+$): 337.1672, Found: 337.1651.

General Procedure for the Preparation of Substrates 1−7. To a solution of **9**−**14** (3.0 mmol) in CH_2Cl_2 (15 mL) was added TFA (2.3 mL, 30 mmol) under argon atmosphere at 0 °C. After being stirred at room temperature for 5 h, the reaction mixture was neutralized with saturated aqueous $NaHCO_3$ and then extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure to give crude amine. To a solution of crude amine and Et_3N (1.25 mL, 9.0 mmol) in CH_2Cl_2 (15 mL) was added acid chloride (3.3 mmol) under argon atmosphere at room temperature. After being stirred at the same temperature for 3 h, the reaction mixture was diluted with water and then extracted with AcOEt. Purification of the residue by flash silica gel column chromatography (AcOEt:hexane = 1:6−1:3) afforded the products **1** (555 mg, 80%), **2** (495 mg, 76%), **3** (626 mg, 85%), **4** (653 mg, 84%), **5** (488 mg, 71%), **6** (555 mg, 76%), and **7** (733 mg, 80%).

*2-Methyl-N-(phenylmethoxy)-N-2-propen-1-yl-2-propenamide (**1**).* A colorless oil. IR ($CHCl_3$) 1655, 1631 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.45−7.30 (5H, m), 5.88 (1H, m), 5.34 (1H, s), 5.29 (1H, dd, J = 17.1, 1.3 Hz), 5.28 (1H, s), 5.23 (1H, br d, J = 10.1 Hz), 4.84 (2H, s), 4.23 (2H, d, J = 6.1 Hz), 1.98 (3H, s). ^{13}C NMR ($CDCl_3$) δ 171.9, 140.6, 134.8, 132.3, 129.4, 128.9, 128.6, 118.5, 117.5, 77.4, 50.7, 19.9. MS (EI$^+$): m/z 231 (M$^+$, 45), 159 (100). HRMS (EI$^+$): calcd for $C_{14}H_{17}NO_2$ (M$^+$): 231.1254, Found: 231.1252.

*N-(Phenylmethoxy)-N-2-propen-1-yl-2-propenamide (**2**).* A colorless oil. IR ($CHCl_3$) 1653, 1618 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.42−7.32 (5H, m), 6.74 (1H, dd, J = 17.1, 10.4 Hz), 6.42 (1H, dd, J = 17.1, 1.8 Hz), 5.90 (1H, m), 5.73 (1H, dd, J = 10.4, 1.8 Hz), 5.28 (1H, dd, J = 17.1, 1.2 Hz), 5.23 (1H, dd, J = 10.4, 1.2 Hz), 4.86 (2H, s), 4.31 (2H, d, J = 6.1 Hz). ^{13}C NMR ($CDCl_3$) δ 166.9, 134.3, 132.1, 129.4, 129.2, 129.0, 128.7, 126.3, 118.6, 77.5, 49.4. MS (EI$^+$): m/z 217 (M$^+$, 4), 91 (100). HRMS (EI$^+$): calcd for $C_{13}H_{15}NO_2$ (M$^+$): 217.1097, Found: 217.1098.

*N-2-Buten-1-yl-2-methyl-N-(phenylmethoxy)-2-propenamide (**3**).* A colorless oil. IR (KBr) 2984, 1738, 1461 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.40−7.30 (5H, m), 5.75−5.65 (1H, m), 5.56−5.47 (1H, m), 5.32 (1H, br s), 5.26 (1H, br s), 4.83 (2H, s), 4.15 (2H, d, J = 5.0 Hz), 1.97 (3H, t, J = 1.4 Hz), 1.71 (3H, br dd, J = 6.4, 1.4 Hz). ^{13}C NMR

dx.doi.org/10.1021/jo3015227 | J. Org. Chem. 2012, 77, 8588−8604

($CDCl_3$) δ 171.6, 140.6, 134.7, 130.1, 129.3, 128.7, 128.5, 124.9, 117.2, 77.2, 50.1, 19.9, 17.8. MS (EI^+): m/z 245 (M^+, 0.6), 91 (100). HRMS (EI^+): calcd for $C_{15}H_{19}NO_2$ (M^+): 245.1410, Found: 245.1438.

*2-Methyl-**N**-(3-methyl-2-buten-1-yl)-**N**-(phenylmethoxy)-2-propenamide (**4**).* A colorless oil. IR (KBr) 2921, 1658, 1452 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.40−7.30 (5H, m), 5.31 (1H, br s), 5.28 (1H, m), 5.26 (1H, br s), 4.83 (2H, s), 4.22 (2H, d, J = 7.4 Hz), 1.97 (3H, t, J = 1.4 Hz), 1.74 (3H, s), 1.68 (3H, s). ^{13}C NMR ($CDCl_3$) δ 171.5, 140.6, 136.8, 134.7, 129.3, 128.7, 128.5, 118.4, 117.1, 46.0, 25.8, 19.9, 17.9. One peak of ^{13}C NMR was missing due to overlap with carbon peaks of $CDCl_3$. MS (EI^+): m/z 259 (M^+, 7.6), 91 (100). HRMS (EI^+): calcd for $C_{16}H_{21}NO_2$ (M^+): 259.1567, Found: 259.1574.

*2-Methyl-**N**-(phenylmethoxy)-**N**-2-propyn-1-yl-2-propenamide (**5**).* A colorless oil. IR ($CHCl_3$) 1659, 1639 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.43−7.30 (5H, m), 5.41 (1H, s), 5.33 (1H, s), 4.98 (2H, s), 4.38 (2H, d, J = 2.4 Hz), 2.30 (1H, t, J = 2.4 Hz), 1.98 (3H, s). ^{13}C NMR ($CDCl_3$) δ 172.1, 139.8, 134.5, 129.4, 128.9, 128.6, 118.3, 77.9, 77.7, 72.3, 38.3, 19.5. MS (EI^+): m/z 229 (M^+, 10), 92 (100). HRMS (EI^+): calcd for $C_{14}H_{15}NO_2$ (M^+): 229.1097, Found: 229.1109.

***N*-2-Butyn-1-yl-2-methyl-*N*-(phenylmethoxy)-2-propenamide (*6*).** A colorless oil. IR ($CHCl_3$) 1657, 1639 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.45−7.32 (5H, m), 5.38 (1H, s), 5.30 (1H, s), 4.98 (2H, s), 4.33 (2H, q, J = 2.4 Hz), 1.97 (3H, s), 1.83 (3H, t, J = 2.4 Hz). ^{13}C NMR ($CDCl_3$) δ 171.9, 140.0, 134.7, 129.4, 128.8, 128.5, 118.0, 80.0, 77.6, 73.2, 38.8, 19.6, 3.4. MS (FAB^+): m/z 244 (M + H^+, 100). HRMS (FAB^+): calcd for $C_{15}H_{18}NO_2$ (M + H^+): 244.1332, Found: 244.1333.

*2-Methyl-**N**-(phenylmethoxy)-**N**-(3-phenyl-2-propyn-1-yl)-2-propenamide (**7**).* A colorless oil. IR ($CHCl_3$) 1659, 1631 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.45−7.29 (10H, m), 5.43 (1H, t, J = 1.2 Hz), 5.34 (1H, t, J = 1.4 Hz), 5.06 (2H, s), 4.63 (2H, s), 2.00 (3H, t, J = 1.4 Hz). ^{13}C NMR ($CDCl_3$) δ 171.9, 139.9, 134.6, 131.8, 129.4, 128.8, 128.6, 128.5, 128.3, 122.5, 118.2, 84.0, 83.4, 77.9, 39.3, 19.7. HRMS (ESI^+): calcd for $C_{20}H_{20}NO_2$ (M + H^+): 306.1489, Found: 306.1489.

General Procedure for Radical Reaction in the Absence of Ligand. A solution of substrate (0.43 mmol) and $Zn(OTf)_2$ (156 mg, 0.43 mmol) in CH_2Cl_2 (4.3 mL) was stirred for 30 min under Ar atmosphere at 20 °C. In the case of **8**, Bu_3SnH (0.65 mmol) was added. To a reaction mixture were added RX (2.15 mmol) and Et_3B (1.05 M in hexane, 2.05 mL, 2.15 mmol) at 20 °C. After being stirred at the same temperature for 2−20 h, the reaction mixture was diluted with saturated $NaHCO_3$ 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:AcOEt = 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:AcOEt = 10:1 or hexane:AcOEt = 6:1, 2-fold development) afforded the isolated products, *trans*-**17** (72.5 mg, 33%) and *cis*-**17** (44.4 mg, 20%) [entry 1 in Table 3], *cis*-**19** (15.3 mg, 8%) and *trans*-**19** (27.2 mg, 15%) [entry 4 in Table 4], *Z*-**20a** (146 mg, 65%) and *E*-**20a** (32.1 mg, 14%) [entry 1 in Table 5], *Z*-**20b** (112 mg, 50%) and *E*-**20b** (21.3 mg, 9%) [entry 8 in Table 5], *Z*-**20c** (138 mg, 80%) [entry 9 in Table 5], *Z*-**22** (20.7 mg, 8%), *E*-**23** (67.1 mg, 33%) and *Z*-**23** (24.8 mg, 12%) [entry 4 in Table 6], and *cis*-**28b** (72.4 mg, 42%) and *trans*-**28b** (81.7 mg, 48%) [entry 2 in Table 8]. As regards the ratio of products, slight differences between ^1H NMR analysis of the mixture (the first purification) and the isolated yields (the second purification) were observed.

General Procedure for Enantioselective Radical Reaction. A solution of substrate (0.43 mmol), $Zn(OTf)_2$ (156 mg, 0.43 mmol), and ligand (153 mg, 0.43 mmol) in CH_2Cl_2 (4.3 mL) was stirred for 1 h under Ar atmosphere at 20 °C. To a reaction mixture were added RX (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 days, the reaction mixture was diluted with saturated $NaHCO_3$ 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:AcOEt = 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:AcOEt = 10:1 or hexane:AcOEt = 6:1, 2-fold development) afforded the isolated products, *cis*-**15a** (110 mg, 48%), *trans*-**15a** (61 0.7 mg, 27%) and **16a** (5.3 mg, 2%) [entry 4 in Table 7], *cis*-**15b** (112 mg, 45%), *trans*-**15b** (57.7 mg, 23%), and **16b** (8.9 mg, 4%) [entry 5 in Table 7], *cis*-**15c** (67.3 mg, 30%), *trans*-**15c** (4.3 mg, 2%), and **16c** (19.0 mg, 8%) [entry 10 in Table 7], *cis*-**15d** (137 mg, 50%), *trans*-**15d** (11.9 mg, 4%), and **16d** (52.2 mg, 19%) [entry 11 in Table 7], *cis*-**18** (major, 106 mg, 46%), *cis*-**18** (minor, 48.7 mg, 21%), *trans*-**18** (major, 44.5 mg, 19%), and *trans*-**18** (minor, 12.7 mg, 5%) [Scheme 8], *Z*-**21** (68.6 mg, 30%) and *E*-**21** (103 mg, 44%) [Scheme 10], *Z*-**22** (191 mg, 74%) [Scheme 10], *cis*-**26** (major, 147 mg, 63%), *cis*-**26** (minor, 23.6 mg, 10%), *trans*-**26** (major, 9.1 mg, 4%), and *trans*-**26** (minor, 1.8 mg, 1%) [Scheme 8], *cis*-**28a** (105 mg, 55%) and *trans*-**28a** (54.0 mg, 28%) [entry 4 in Table 8], *cis*-**28c** (145 mg, 70%) and *trans*-**28c** (38.5 mg, 18%) [entry 5 in Table 8], and *cis*-**29** (82.2 mg, 44%), *trans*-**29** (13.4 mg, 7%), and **30** (15.6 mg, 8%) [entry 4 in Table 9]. As regards the ratio of products, slight differences between ^1H NMR analysis of the mixture (the first purification) and the isolated yields (the second purification) were observed.

*(3*S*,4*R*)-3-(2,2,3,3,4,4,4-Heptafluorobutyl)-4-(iodomethyl)-3-methyl-1-(phenylmethoxy)-2-pyrrolidinone (cis-**15a**).* Colorless crystals. mp 99−99.5 °C (hexane). IR (KBr) 2948, 1717, 1458 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.50−7.38 (5H, m), 5.04 (1H, d, J = 11.0 Hz), 5.02 (1H, d, J = 11.0 Hz), 3.50 (1H, dd, J = 9.2, 6.6 Hz), 3.30−3.19 (2H, m), 2.73 (1H, t, J = 11.4 Hz), 2.58−2.39 (2H, m), 2.26 (1H, br dd, J = 37.0, 16.0 Hz), 1.32 (3H, d, J = 1.6 Hz). ^{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 (tsex, 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 (3F, t, J = 19.5 Hz), −106.2 (1F, dm, J = 273 Hz), −116.0 (1F, dm, J = 273 Hz), −128.3 (2F, br s). MS (EI^+): m/z 528 (M + H^+, 25), 91 (100). HRMS (EI^+): calcd for $C_{17}H_{18}F_7INO_2$ (M + H^+): 528.0265, Found: 528.0260. Elemental analysis (%) 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, 1.0 mL/min, 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, $CHCl_3$).

*(3*S*,4*S*)-3-(2,2,3,3,4,4,4-Heptafluorobutyl)-4-(iodomethyl)-3-methyl-1-(phenylmethoxy)-2-pyrrolidinone (trans-**15a**).* A colorless oil. IR (KBr) 2973, 1717, 1457 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.47−7.37 (5H, m), 5.03 (1H, d, J = 10.5 Hz), 4.96 (1H, d, J = 10.5 Hz), 3.51 (1H, t, J = 8.3 Hz), 3.29 (1H, dd, J = 9.6, 4.1 Hz), 2.95 (2H, t, J = 10.5 Hz), 2.76 (1H, m), 2.59−2.27 (2H, br m), 1.07 (3H, s). ^{13}C NMR ($CDCl_3$) δ 172.0, 134.6, 129.6, 129.2, 128.6, 118.0 (tt, J = 258, 32 Hz), 117.7 (qt, J = 289, 34 Hz), 108.4 (tsex, J = 265, 36 Hz), 77.2, 51.4, 43.6, 40.5 (d, J = 3 Hz), 35.0 (t, J = 20 Hz), 17.5, 0.6. ^{19}F NMR ($CDCl_3$) δ −80.6 (3F, t, J = 10 Hz), −108.9 (1F, dm, J = 269 Hz), −115.2 (1F, dm, J = 269 Hz), −128.0 (1F, dd, J = 289, 8 Hz), −128.5 (1F, dd, J = 289, 6 Hz). HRMS (ESI^+): calcd for $C_{17}H_{18}F_7INO_2$ (M + H^+): 528.0265, Found: 528.0271. HPLC (Chiralcel AD-H, hexane/2-propanol = 95/5, 1.0 mL/min, 254 nm) t_r (major) = 13.6 min, t_r (minor) = 8.2 min. A sample of 90% ee by HPLC analysis gave $[\alpha]^{24}_D$ +28.8 (c 0.23, $CHCl_3$).

*cis-4-(2,2,3,3,4,4,4-Heptafluorobutyl)-3-(iodomethyl)-3-methyl-1-(phenylmethoxy)-2-pyrrolidinone (**16a**).* A colorless oil. IR (KBr) 2968, 2932, 1714, 1455 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.47−7.34 (5H, m), 5.09 (1H, d, J = 11.0 Hz), 5.04 (1H, d, J = 11.0 Hz), 3.48 (1H, t, J = 8.5 Hz), 3.37 (1H, dd, J = 8.5, 1.8 Hz), 3.23 (1H, d, J = 11.0 Hz), 3.05 (1H, d, J = 11.0 Hz), 2.45 (1H, m), 2.42−2.26 (2H, br m), 1.30 (3H, s). ^{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 (tsex, 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 (3F, t, J = 9 Hz), −113.7 (1F, dm, J = 273 Hz), −116.0 (1F, dm, J = 273 Hz), −127.8 (1F, dd, J = 290, 5 Hz), −128.2 (1F, dd, J = 290, 5 Hz). HRMS (ESI^+): calcd for $C_{17}H_{18}F_7INO_2$ (M + H^+): 528.0265, Found: 528.0269.

*(3*S*,4*R*)-4-(Iodomethyl)-3-methyl-3-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)-1-(phenylmethoxy)-2-pyrrolidinone (cis-**15b**).* Colorless crystals. mp 95−96 °C (hexane). IR (KBr) 2975, 2949, 1717, 1458 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.45−7.37 (5H, m), 5.02 (1H, d, J = 11.4 Hz), 4.99 (1H, d, J = 11.4 Hz), 3.48 (1H, dd, J = 9.6, 6.8 Hz), 3.24−3.18

dx.doi.org/10.1021/jo3015227 | J. Org. Chem. 2012, 77, 8588−8604

(2H, m), 2.71 (1H, t, J = 9.6 Hz), 2.57−2.37 (2H, br m), 2.26 (1H, br dd, J = 37.1, 16.0 Hz), 1.29 (3H, d, J = 2.8 Hz). ^{13}C NMR ($CDCl_3$) δ 170.8, 134.7, 129.5, 129.2, 128.7, 118.8 (tt, J = 256, 31 Hz), 117.2 (qt, J = 287, 33 Hz), 110.0 (tquin, J = 264, 33 Hz), 108.6 (tsex, J = 267, 37 Hz), 76.8, 51.1, 44.5, 44.2, 31.2 (t, J = 21 Hz), 22.2, 4.0. ^{19}F NMR ($CDCl_3$) δ −81.5 (3F, br s), −105.4 (1F, dm, J = 272 Hz), −115.0 (1F, dm, J = 272 Hz), −124.8 (1F, dm, J = 298 Hz), −125.0 (1F, dm, J = 298 Hz), −125.9 (1F, dm, J = 295 Hz), −126.6 (1F, dm, J = 295 Hz). MS (EI$^+$): m/z 578 (M + H$^+$, 0.6), 91 (100). HRMS (EI$^+$): calcd for $C_{18}H_{18}F_9INO_2$ (M + H$^+$): 578.0233, Found: 578.0239. Elemental analysis (%) calcd for $C_{18}H_{17}F_9INO_2$: C, 37.45; H, 2.97; N, 2.43, found: C, 37.45, H, 2.94, N, 2.42. HPLC (Chiralcel AD-H, hexane/2-propanol = 95/5, 1.0 mL/min, 254 nm) t_r (major) = 6.8 min, t_r (minor) = 7.7 min. A sample of 77% ee by HPLC analysis gave $[\alpha]^{19}_D$ +20.0 (c 0.49, $CHCl_3$).

*(3S,4S)-4-(Iodomethyl)-3-methyl-3-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)-1-(phenylmethoxy)-2-pyrrolidinone (trans-**15b**).* A colorless oil. IR (KBr) 2973, 2944, 1717, 1458 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.45−7.36 (5H, m), 5.02 (1H, d, J = 11.0 Hz), 4.95 (1H, d, J = 11.0 Hz), 3.50 (1H, t, J = 8.2 Hz), 3.23 (1H, dd, J = 9.6, 4.1 Hz), 2.94 (2H, t, J = 10.1 Hz), 2.75 (1H, m), 2.51 (1H, br dd, J = 38.5, 15.1 Hz), 2.42−2.26 (1H, br m), 1.07 (3H, s). ^{13}C NMR ($CDCl_3$) δ 172.0, 134.6, 129.6, 129.2, 128.6, 118.6 (tt, J = 259, 32 Hz), 117.3 (qt, J = 290, 33 Hz), 109.8 (tquin, J = 267, 36 Hz), 108.6 (tsex, J = 271, 34 Hz), 77.2, 51.4, 43.6, 40.5 (d, J = 3 Hz), 35.2 (t, J = 20 Hz), 17.5, 0.6. ^{19}F NMR ($CDCl_3$) δ −81.5 (3F, t, J = 10 Hz), −108.1 (1F, dm, J = 269 Hz), −114.3 (1F, dm, J = 269 Hz), −124.9 (2F, br s), −126.0 (1F, ddd, J = 295, 16, 9 Hz), −126.5 (1F, dt, J = 295, 15 Hz). MS (EI$^+$): m/z 578 (M + H$^+$, 0.7), 91 (100). HRMS (EI$^+$): calcd for $C_{18}H_{18}F_9INO_2$ (M + H$^+$): 578.0233, Found: 578.0224. HPLC (Chiralcel AD-H, hexane/2-propanol = 95/5, 1.0 mL/min, 254 nm) t_r (major) = 11.2 min, t_r (minor) = 8.0 min. A sample of 85% ee by HPLC analysis gave $[\alpha]^{22}_D$ +33.6 (c 0.56, $CHCl_3$).

*cis-3-(Iodomethyl)-3-methyl-4-(2,2,3,3,4,4,5,5,5-nonafluoropentyl)-1-(phenylmethoxy)-2-pyrrolidinone (**16b**).* A colorless oil. IR (KBr) 2969, 2933, 1715, 1456 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.48−7.34 (5H, m), 5.08 (1H, d, J = 10.5 Hz), 5.03 (1H, d, J = 10.5 Hz), 3.48 (1H, t, J = 8.7 Hz), 3.37 (1H, m), 3.22 (1H, d, J = 11.0 Hz), 3.04 (1H, d, J = 11.0 Hz), 2.49−2.25 (3H, br m), 1.30 (3H, s). ^{13}C NMR ($CDCl_3$) δ 170.1, 134.7, 129.6, 129.1, 128.6, 118.0 (tt, J = 257, 32 Hz), 117.2 (qt, J = 290, 34 Hz), 110.1 (tquin, J = 267, 36 Hz), 108.6 (tsex, J = 271, 39 Hz), 77.2, 50.1 (d, J = 5 Hz), 44.0, 33.9, 28.3 (t, J = 22 Hz), 25.0, 6.4. ^{19}F NMR ($CDCl_3$) δ −81.5 (3F, t, J = 9 Hz), −112.9 (1F, dm, J = 257 Hz), −115.1 (1F, dm, J = 257 Hz), −124.7 (2F, br s), −126.5 (2F, m). HRMS (ESI$^+$): calcd for $C_{18}H_{18}F_9INO_2$ (M + H$^+$): 578.0233, Found: 578.0224.

*(3S,4R)-4-(Iodomethyl)-3-methyl-1-(phenylmethoxy)-3-[2,3,3,3-tetrafluoro-2-(trifluoromethyl)propyl]-2-pyrrolidinone (cis-**15c**).* Colorless crystals. mp 95.5−96.5 °C (hexane). IR (KBr) 2946, 1719, 1496, 1458 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.49−7.36 (5H, m), 5.04 (1H, d, J = 11.0 Hz), 5.00 (1H, d, J = 11.0 Hz), 3.48 (1H, dd, J = 9.6, 4.0 Hz), 3.31 (1H, dd, J = 10.1, 3.2 Hz), 3.23 (1H, dd, J = 9.6, 2.8 Hz), 2.73 (1H, dd, J = 11.9, 10.1 Hz), 2.64 (1H, br t, J = 17.5 Hz), 2.39 (1H, m), 2.15 (1H, br t, J = 17.5 Hz), 1.27 (3H, br s). ^{13}C NMR ($CDCl_3$) δ 171.0, 134.7, 129.5, 129.3, 128.7, 121.0 (qd, J = 287, 29 Hz), 120.6 (qd, J = 291, 29 Hz), 92.1 (dseq, J = 210, 33 Hz), 76.9, 51.1, 46.1, 44.8, 28.5 (d, J = 19 Hz), 22.0, 3.5. ^{19}F NMR ($CDCl_3$) δ −76.7 (3F, dq, J = 10, 7 Hz), −77.0 (3F, br quin, J = 9 Hz), −185.2 (1F, m). HRMS (ESI$^+$): calcd for $C_{17}H_{18}F_7INO_2$ (M + H$^+$): 528.0265, Found: 528.0259. Elemental analysis (%) calcd for $C_{17}H_{17}F_7INO_2$: C, 38.73; H, 3.25; N, 2.66, found: C, 38.73, H, 3.22, N, 2.65. HPLC (Chiralcel AD-H, hexane/2-propanol = 95/5, 1.0 mL/min, 254 nm) t_r (major) = 6.2 min, t_r (minor) = 8.8 min. A sample of 92% ee by HPLC analysis gave $[\alpha]^{24}_D$ +33.0 (c 0.40, $CHCl_3$).

*trans-4-(Iodomethyl)-3-methyl-1-(phenylmethoxy)-3-[2,3,3,3-tetrafluoro-2-(trifluoromethyl)propyl]-2-pyrrolidinone (trans-**15c**).* A colorless oil. IR (KBr) 2929, 1721, 1458 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.46−7.36 (5H, m), 5.04 (1H, d, J = 11.0 Hz), 4.94 (1H, d, J = 11.0 Hz), 3.55 (1H, t, J = 8.2 Hz), 3.22 (1H, dd, J = 9.2, 3.7 Hz), 2.94 (1H, br t, J = 10.1 Hz), 2.91 (1H, dd, J = 12.4, 10.1 Hz), 2.75 (1H, m), 2.54 (1H, br t, J = 15.1 Hz), 2.26 (1H, br t, J = 15.1 Hz), 1.04 (3H, br s). ^{13}C NMR ($CDCl_3$) δ 171.6, 134.6, 129.5, 129.1, 128.6, 120.8 (qd, J = 288, 28 Hz), 120.6 (qd, J = 288, 29 Hz), 91.4 (dseq, J = 241, 33 Hz), 77.2, 51.3, 45.0, 40.2 (d, J = 5 Hz), 32.1 (d, J = 18 Hz), 18.6, 0.6. ^{19}F NMR ($CDCl_3$) δ −77.5 (3F, br quin, J = 9 Hz), −78.3 (3F, dq, J = 9, 7 Hz), −186.9 (1F, m). HRMS (ESI$^+$): calcd for $C_{17}H_{18}F_7INO_2$ (M + H$^+$): 528.0265, Found: 528.0269.

*cis-3-(Iodomethyl)-3-methyl-1-(phenylmethoxy)-4-[2,3,3,3-tetrafluoro-2-(trifluoromethyl)propyl]-2-pyrrolidinone (**16c**).* A colorless oil. IR (KBr) 2966, 2930, 1715, 1456 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.46−7.36 (5H, m), 5.08 (1H, d, J = 11.0 Hz), 5.02 (1H, d, J = 11.0 Hz), 3.46 (1H, dd, J = 9.2, 6.9 Hz), 3.32 (1H, m), 3.23 (1H, d, J = 11.0 Hz), 3.06 (1H, d, J = 11.0 Hz), 2.44−2.24 (3H, br m), 1.29 (3H, s). ^{13}C NMR ($CDCl_3$) δ 169.8, 134.6, 129.5, 129.1, 128.6, 120.8 (qd, J = 288, 29 Hz), 120.6 (qd, J = 288, 28 Hz), 91.7 (dseq, J = 206, 32 Hz), 76.9, 50.1 (d, J = 6 Hz), 44.4, 35.3, 26.1 (d, J = 19 Hz), 25.0, 6.1. ^{19}F NMR ($CDCl_3$) δ −76.0 (3F, br quin, J = 9 Hz), −78.2 (3F, dq, J = 9, 7 Hz), −185.3 (1F, m). HRMS (ESI$^+$): calcd for $C_{17}H_{18}F_7INO_2$ (M + H$^+$): 528.0265, Found: 528.0266.

*(3S,4R)-4-(Iodomethyl)-3-methyl-1-(phenylmethoxy)-3-[(1,2,2,3,3,4,4,5,5,6,6-undecafluorocyclohexyl)methyl]-2-pyrrolidinone (cis-**15d**).* Colorless crystals. mp 154−155 °C (hexane). IR (KBr) 2979, 2939, 1713, 1461 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.46−7.38 (5H, m), 5.04 (1H, d, J = 11.2 Hz), 5.01 (1H, d, J = 11.2 Hz), 3.48 (1H, dd, J = 9.7, 6.4 Hz), 3.35 (1H, dd, J = 9.7, 3.2 Hz), 3.24 (1H, dd, J = 9.7, 2.6 Hz), 2.77 (1H, dd, J = 11.5, 9.7 Hz), 2.64 (1H, br t, J = 17.6 Hz), 2.39 (1H, br m), 2.15 (1H, br t, J = 17.6 Hz), 1.29 (3H, t, J = 2.9 Hz). ^{13}C NMR ($CDCl_3$) δ 171.0, 134.8, 129.5, 129.3, 128.7, 111−106 (5C, m), 92.5 (dquit, J = 205, 26 Hz), 76.9, 51.3, 45.8, 44.9, 26.4 (d, J = 20 Hz), 22.8, 3.1. ^{19}F NMR ($CDCl_3$) δ −117.2 (1F, br d, J = 295 Hz), −118.3 (1F, br d, J = 295 Hz), −122.8 (2F, br d, J = 279 Hz), −124.4 (1F, br d, J = 284 Hz), −131.7 (1F, br d, J = 295 Hz), −132.3 (1F, br d, J = 295 Hz), −139.0 (2F, br d, J = 279 Hz), −142.5 (1F, br d, J = 284 Hz), −184.9 (1F, br s). HRMS (ESI$^+$): calcd for $C_{20}H_{18}F_{11}INO_2$ (M + H$^+$): 640.0201, Found: 640.0215. HPLC (Chiralcel AD-H, hexane/2-propanol = 95/5, 1.0 mL/min, 254 nm) t_r (major) = 6.0 min, t_r (minor) = 8.3 min. A sample of 91% ee by HPLC analysis gave $[\alpha]^{22}_D$ +27.9 (c 0.52, $CHCl_3$).

*trans-4-(Iodomethyl)-3-methyl-1-(phenylmethoxy)-3-[(1,2,2,3,3,4,4,5,5,6,6-undecafluorocyclohexyl)methyl]-2-pyrrolidinone (trans-**15d**).* A colorless oil. IR (KBr) 2972, 2878, 1720, 1458 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.45−7.36 (5H, m), 5.04 (1H, d, J = 11.0 Hz), 4.95 (1H, d, J = 11.0 Hz), 3.55 (1H, t, J = 7.8 Hz), 3.21 (1H, dd, J = 9.6, 4.2 Hz), 2.94 (1H, br t, J = 7.8 Hz), 2.92 (1H, br t, J = 9.6 Hz), 2.75 (1H, m), 2.62 (1H, br dd, J = 19.7, 15.0 Hz), 2.36 (1H, br t, J = 15.0 Hz), 1.06 (3H, s). ^{13}C NMR ($CDCl_3$) δ 171.6, 134.6, 129.5, 129.1, 128.6, 113−103 (5C, m), 91.8 (dquit, J = 233, 28 Hz), 76.9, 51.3, 44.9, 40.1, 29.6 (d, J = 19 Hz), 18.7, 0.3 (d, J = 2 Hz). ^{19}F NMR ($CDCl_3$) δ −118.1 (2F, br t, J = 265 Hz), −122.7 (2F, br d, J = 288 Hz), −124.1 (1F, br d, J = 288 Hz), −132.7 (1F, br d, J = 295 Hz), −134.2 (1F, br d, J = 295 Hz), −139.1 (2F, br d, J = 270 Hz), −142.5 (1F, br m), −185.5 (1F, br s). HRMS (ESI$^+$): calcd for $C_{20}H_{18}F_{11}INO_2$ (M + H$^+$): 640.0201, Found: 640.0211.

*cis-3-(Iodomethyl)-3-methyl-1-(phenylmethoxy)-4-[(1,2,2,3,3,4,4,5,5,6,6-undecafluorocyclohexyl)methyl]-2-pyrrolidinone (**16d**).* Colorless crystals. mp 97−98 °C (hexane). IR (KBr) 2970, 2885, 1715, 1456 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.46−7.35 (5H, m), 5.08 (1H, d, J = 11.0 Hz), 5.03 (1H, d, J = 11.0 Hz), 3.45 (1H, m), 3.35 (1H, m), 3.23 (1H, d, J = 11.0 Hz), 3.10 (1H, d, J = 11.0 Hz), 2.52−2.42 (3H, m), 1.29 (3H, s). ^{13}C NMR ($CDCl_3$) δ 169.7, 134.6, 129.4, 129.0, 128.5, 113−105 (5C, m), 91.7 (dquit, J = 203, 24 Hz), 76.9, 50.1 (d, J = 6 Hz), 44.5, 35.4, 25.0, 23.2 (d, J = 20 Hz), 6.1. ^{19}F NMR ($CDCl_3$) δ −118.0 (1F, br d, J = 295 Hz), −118.3 (1F, br d, J = 295 Hz), −122.7 (1F, br d, J = 280 Hz), −123.1 (1F, br d, J = 280 Hz), −124.5 (1F, br d, J = 280 Hz), −132.3 (1F, br d, J = 295 Hz), −134.2 (1F, br d, J = 295 Hz), −139.5 (2F, br d, J = 280 Hz), −142.4 (1F, br d, J = 285 Hz), −185.1 (1F, br s). HRMS (ESI$^+$): calcd for $C_{20}H_{18}F_{11}INO_2$ (M + H$^+$): 640.0201, Found: 640.0211.

*trans-3-(2,2,3,3,4,4,4-Heptafluorobutyl)-4-(iodomethyl)-1-(phenylmethoxy)-2-pyrrolidinone (trans-**17**).* A colorless oil. IR (KBr)

dx.doi.org/10.1021/jo3015227 | J. Org. Chem. 2012, 77, 8588−8604

2949, 2884, 1716, 1434, 1353 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.45−7.35 (5H, m), 5.00 (2H, dd, J = 10.8, 9.6 Hz), 3.42 (1H, t, J = 8.7 Hz), 3.35 (1H, dd, J = 10.1, 3.7 Hz), 3.13−3.07 (2H, m), 2.89−2.74 (1H, m), 2.54 (1H, ddd, J = 10.1, 7.3, 2.8 Hz), 2.29−2.00 (2H, m). ^{13}C NMR ($CDCl_3$) δ 169.0, 134.6, 129.5, 129.1, 128.6, 117.6 (qt, J = 289, 34 Hz), 117.6 (tt, J = 256, 31 Hz), 108.4 (tsex, J = 266, 35 Hz), 76.9, 52.3, 39.8 (d, J = 1.9 Hz), 37.7, 31.4 (t, J = 21 Hz), 7.9 (d, J = 4.8 Hz). ^{19}F NMR ($CDCl_3$) δ −80.8 (3F, t, J = 9.6 Hz), −112.2 (1F, dm, J = 268 Hz), −114.6 (1F, dm, J = 268 Hz), −128.1 (2F, dd, J = 290, 6.0 Hz). HRMS (ESI$^+$): calcd for $C_{16}H_{16}F_7INO_2$ (M + H$^+$): 514.0108, Found: 514.0104.

*cis-3-(2,2,3,3,4,4,4-Heptafluorobutyl)-4-(iodomethyl)-1-(phenylmethoxy)-2-pyrrolidinone (cis-**17**).* A colorless oil. IR (KBr) 2942, 2913, 1711, 1444, 1354 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.45−7.40 (5H, m), 5.27 (2H, dd, J = 11.2, 3.6 Hz), 3.47 (1H, dd, J = 9.6, 5.3 Hz), 3.31 (1H, d, J = 9.6 Hz), 3.23 (1H, dd, J = 9.2 1.4 Hz), 2.85−2.63 (4H, m), 2.25−2.10 (1H, m). ^{13}C NMR ($CDCl_3$) δ 167.9, 134.7, 129.5, 129.3, 128.8, 117.6 (qt, J = 289, 34 Hz), 117.6 (tt, J = 255, 31 Hz), 108.4 (tsex, J = 265, 35 Hz), 77.0, 52.2, 37.7, 36.4, 25.8 (t, J = 22 Hz), 3.8 (d, J = 2.9 Hz). ^{19}F NMR ($CDCl_3$) δ −80.8 (3F, t, J = 9.6 Hz), −114.2 (1F, dm, J = 270 Hz), −116.0 (1F, dm, J = 270 Hz), −128.1 (2F, dd, J = 290, 6.2 Hz). HRMS (ESI$^+$): calcd for $C_{16}H_{16}F_7INO_2$ (M + H$^+$): 514.0108, Found: 514.0102.

*(3S,4R)-3-(2,2,3,3,4,4,4-Heptafluorobutyl)-4-(1-iodoethyl)-3-methyl-1-(phenylmethoxy)-2-pyrrolidinone (cis-**18**).* **A major isomer:** A colorless oil. IR (KBr) 2948, 1715, 1458 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.49−7.34 (5H, m), 5.10 (1H, d, J = 11.0 Hz), 5.02 (1H, d, J = 11.0 Hz), 4.06 (1H, m), 3.43 (1H, br t, J = 9.6 Hz), 3.30 (1H, dd, J = 9.6, 2.3 Hz), 2.75−2.44 (2H, br m), 1.92 (3H, d, J = 6.8 Hz), 1.78 (1H, br m), 1.30 (3H, s). ^{13}C NMR ($CDCl_3$) δ 170.3, 134.9, 129.4, 129.0, 128.5, 118.6 (tt, J = 256, 31 Hz), 117.6 (qt, J = 289, 35 Hz), 108.4 (tsex, J = 266, 36 Hz), 76.7, 49.4, 47.8, 43.6, 30.9 (t, J = 20 Hz), 28.0, 25.8, 24.5. ^{19}F NMR ($CDCl_3$) δ −80.5 (3F, br m), −105.7 (1F, dm, J = 273 Hz), −115.3 (1F, dm, J = 273 Hz), −128.2 (2F, br m). MS (EI$^+$): m/z 542 (M + H$^+$, 0.6), 91 (100). HRMS (EI$^+$): calcd for $C_{18}H_{20}F_7INO_2$ (M + H$^+$): 542.0421, Found: 542.0430. HPLC (Chiralcel AD-H, hexane/2-propanol = 95/5, 1.0 mL/min, 254 nm) t_r (major) = 8.2 min, t_r (minor) = 9.4 min. A sample of 87% ee by HPLC analysis gave $[\alpha]^{24}_D$ +59.2 (c 0.86, $CHCl_3$). **A minor isomer:** A colorless oil. IR (KBr) 2950, 1719, 1457 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.47−7.33 (5H, m), 5.06 (1H, d, J = 11.0 Hz), 4.99 (1H, d, J = 11.0 Hz), 4.34 (1H, br qt, J = 6.8, 5.5 Hz), 3.45 (1H, dd, J = 10.1, 6.9 Hz), 3.40 (1H, dd, J = 10.1, 3.6 Hz), 2.72 (1H, m), 2.61 (1H, ddd, J = 32.5, 16.0, 9.6 Hz), 2.22 (1H, br dd, J = 37.5, 16.0 Hz), 1.64 (3H, d, J = 6.8 Hz), 1.35 (3H, d, J = 2.3 Hz). ^{13}C NMR ($CDCl_3$) δ 171.3, 134.9, 129.3, 129.1, 128.6, 118.1 (tt, J = 257, 31 Hz), 117.6 (qt, J = 289, 34 Hz), 108.4 (tsex, J = 266, 36 Hz), 76.7, 50.0, 48.0, 43.7, 30.9 (t, J = 21 Hz), 24.0, 23.8, 23.6. ^{19}F NMR ($CDCl_3$) δ −80.5 (3F, t, J = 9.7 Hz), −106.3 (1F, dm, J = 271 Hz), −114.9 (1F, dm, J = 271 Hz), −128.2 (2F, br s). MS (EI$^+$): m/z 542 (M + H$^+$, 0.3), 91 (100). HRMS (EI$^+$): calcd for $C_{18}H_{20}F_7INO_2$ (M + H$^+$): 542.0421, Found: 542.0411. HPLC (Chiralcel AD-H, hexane/2-propanol = 95/5, 1.0 mL/min, 254 nm) t_r (major) = 5.8 min, t_r (minor) = 6.9 min. A sample of 75% ee by HPLC analysis gave $[\alpha]^{24}_D$ +22.1 (c 0.42, $CHCl_3$).

*(3S,4S)-3-(2,2,3,3,4,4,4-Heptafluorobutyl)-4-(1-iodoethyl)-3-methyl-1-(phenylmethoxy)-2-pyrrolidinone (trans-**18**).* **A major isomer:** A white solid. IR (KBr) 2974, 2878, 1722, 1455 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.44−7.35 (5H, m), 5.02 (1H, d, J = 11.0 Hz), 4.94 (1H, d, J = 11.0 Hz), 4.14 (1H, m), 3.48 (1H, t, J = 8.2 Hz), 2.97 (1H, t, J = 8.2 Hz), 2.90 (1H, dd, J = 39.4, 15.6 Hz), 2.78 (1H, q, J = 10.1 Hz), 2.10 (1H, m), 2.03 (3H, d, J = 6.4 Hz), 1.06 (3H, s). ^{13}C NMR ($CDCl_3$) δ 172.1, 134.6, 129.6, 129.1, 128.5, 117.7 (tt, J = 258, 32 Hz), 117.6 (qt, J = 289, 35 Hz), 108.1 (tsex, J = 266, 37 Hz), 77.0, 53.6, 44.8, 42.9, 35.7 (t, J = 20 Hz), 28.0, 25.3, 17.6. ^{19}F NMR ($CDCl_3$) δ −80.5 (3F, br m), −104.4 (1F, dm, J = 270 Hz), −115.7 (1F, dm, J = 270 Hz), −127.8 (1F, dm, J = 289 Hz), −128.6 (1F, dm, J = 289 Hz). HRMS (ESI$^+$): calcd for $C_{18}H_{20}F_7INO_2$ (M + H$^+$): 542.0421, Found: 542.0419. HPLC (Chiralcel AD-H, hexane/2-propanol = 95/5, 1.0 mL/min, 254 nm) t_r (major) = 11.0 min, t_r (minor) = 7.0 min. A sample of 87% ee by HPLC analysis gave $[\alpha]^{24}_D$ +32.6 (c 0.50, $CHCl_3$). **A minor isomer:** A white solid. IR (KBr) 2973, 2878, 1722, 1457 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.45−7.34 (5H, m), 5.03 (1H, d, J = 11.0 Hz), 4.92 (1H, d, J = 11.0 Hz), 3.93 (1H, m), 3.33 (1H, t, J = 7.8 Hz), 3.00−2.82 (3H, m), 2.62 (1H, dd, J = 38.0, 15.6 Hz), 1.84 (3H, d, J = 6.8 Hz), 1.18 (3H, s). ^{13}C NMR ($CDCl_3$) δ 172.5, 134.9, 129.6, 129.0, 128.6, 118.0 (tt, J = 259, 31 Hz), 117.8 (qt, J = 289, 35 Hz), 108.3 (tsex, J = 266, 34 Hz), 77.1, 48.6, 43.9, 43.2, 34.1 (t, J = 19 Hz), 27.1, 20.5, 17.6. ^{19}F NMR ($CDCl_3$) δ −80.5 (3F, br m), −105.5 (1F, dm, J = 270 Hz), −114.3 (1F, dm, J = 270 Hz), −128.1 (1F, dm, J = 288 Hz), −128.6 (1F, dm, J = 288 Hz). HRMS (ESI$^+$): calcd for $C_{18}H_{20}F_7INO_2$ (M + H$^+$): 542.0421, Found: 542.0420.

*cis-3-(2,2,3,3,4,4,4-Heptafluorobutyl)-3-methyl-4-(1-methylethyl)-1-(phenylmethoxy)-2-pyrrolidinone (cis-**19**).* A white solid. IR (KBr) 2966, 2881, 1716, 1458 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.46−7.33 (5H, m), 5.03 (1H, d, J = 11.0 Hz), 4.95 (1H, d, J = 11.0 Hz), 3.30 (1H, t, J = 9.2 Hz), 3.13 (1H, dd, J = 9.2, 4.6 Hz), 2.52−2.23 (2H, m), 1.85 (1H, m), 1.78 (1H, m), 1.33 (3H, s), 0.93 (3H, d, J = 6.9 Hz), 0.74 (3H, d, J = 6.9 Hz). ^{13}C NMR ($CDCl_3$) δ 171.8, 135.2, 129.3, 128.9, 128.5, 118.2 (tt, J = 258, 32 Hz), 117.8 (qt, J = 289, 34 Hz), 108.5 (tsex, J = 266, 37 Hz), 76.5, 47.9, 46.6, 42.7, 31.3 (t, J = 20 Hz), 27.1, 24.5, 22.0, 18.1. ^{19}F NMR ($CDCl_3$) δ −80.6 (3F, t, J = 10 Hz), −106.6 (1F, dm, J = 272 Hz), −114.8 (1F, dm, J = 272 Hz), −128.2 (2F, br s). HRMS (ESI$^+$): calcd for $C_{19}H_{23}F_7NO_2$ (M + H$^+$): 430.1612, Found: 430.1606.

*trans-3-(2,2,3,3,4,4,4-Heptafluorobutyl)-3-methyl-4-(1-methylethyl)-1-(phenylmethoxy)-2-pyrrolidinone (trans-**19**).* A white solid. IR (KBr) 2970, 2879, 1722, 1458 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.45−7.34 (5H, m), 5.01 (1H, d, J = 11.0 Hz), 4.92 (1H, d, J = 11.0 Hz), 3.25 (1H, t, J = 8.2 Hz), 2.92 (1H, t, J = 8.2 Hz), 2.85 (1H, dd, J = 39.9, 16.0 Hz), 2.21−2.00 (2H, m), 1.72−1.62 (1H, m), 1.08 (3H, s), 0.98 (3H, d, J = 6.4 Hz), 0.82 (3H, d, J = 6.9 Hz). ^{13}C NMR ($CDCl_3$) δ 173.1, 135.0, 129.6, 128.9, 128.5, 117.9 (tt, J = 258, 32 Hz), 117.8 (qt, J = 289, 34 Hz), 108.2 (tsex, J = 267, 36 Hz), 76.8, 49.2, 42.2 (2C), 35.7 (t, J = 20 Hz), 28.2, 21.5 (t, J = 2 Hz), 21.0, 18.4. ^{19}F NMR ($CDCl_3$) δ −80.6 (3F, t, J = 10 Hz), −104.3 (1F, dm, J = 270 Hz), −115.8 (1F, dm, J = 270 Hz), −127.9 (1F, ddd, J = 289, 10, 5 Hz), −128.7 (1F, dd, J = 289, 9 Hz). HRMS (ESI$^+$): calcd for $C_{19}H_{23}F_7NO_2$ (M + H$^+$): 430.1612, Found: 430.1608.

*(3S,4Z)-3-(2,2,3,3,4,4,4-Heptafluorobutyl)-4-(iodomethylene)-3-methyl-1-(phenylmethoxy)-2-pyrrolidinone (Z-**20a**).* A colorless oil. IR (KBr) 2934, 2878, 1722, 1453, 1353 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.45−7.37 (5H, m), 6.37 (1H, t, J = 2.5 Hz), 5.06 (1H, d, J = 11.0 Hz), 4.98 (1H, d, J = 11.0 Hz), 3.86 (2H, ddd, J = 15.5, 14.2, 2.8 Hz), 2.73 (1H, ddd, J = 31.6, 15.5, 4.0 Hz), 2.29 (1H, ddd, J = 31.6, 15.5, 7.5 Hz), 1.33 (3H, s). ^{13}C NMR ($CDCl_3$) δ 170.5, 144.6, 134.5, 129.5, 129.1, 128.5, 117.6 (qt, J = 289, 34 Hz), 116.9 (tt, J = 258, 31 Hz), 108.1 (tsex, J = 265, 37 Hz), 76.8, 73.0 (d, J = 2.9 Hz), 54.9, 45.5, 37.6 (t, J = 20 Hz), 26.7. ^{19}F NMR ($CDCl_3$) δ −80.6 (3F, t, J = 9.8 Hz), −110.8 (1F, dm, J = 271 Hz), −113.8 (1F, dm, J = 271 Hz), −128.3 (2F, dd, J = 30, 6.7 Hz). HRMS (ESI$^+$): calcd for $C_{17}H_{16}F_7INO_2$ (M + H$^+$): 526.0108, Found: 526.0101.

*(3S,4E)-3-(2,2,3,3,4,4,4-Heptafluorobutyl)-4-(iodomethylene)-3-methyl-1-(phenylmethoxy)-2-pyrrolidinone (E-**20a**).* A colorless oil. IR (KBr) 2976, 2936, 1721, 1454, 1352 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.43−7.35 (5H, m), 6.24 (1H, t, J = 1.8 Hz), 5.04 (1H, d, J = 11.0 Hz), 4.96 (1H, d, J = 11.0 Hz), 3.95 (1H, dd, J = 12.8, 1.8 Hz), 3.87 (1H, dd, J = 12.8, 1.8 Hz), 3.19 (1H, ddd, J = 29.7, 15.5, 9.2 Hz), 2.61 (1H, ddd, J = 31.3, 15.5, 6.5 Hz), 1.54 (3H, s). ^{13}C NMR ($CDCl_3$) δ 171.2, 140.4, 134.8, 129.5, 129.1, 128.6, 117.7 (qt, J = 289, 34 Hz), 117.2 (tt, J = 258, 32 Hz), 108.3 (tsex, J = 266, 36 Hz), 76.9, 73.0 (d, J = 2.9 Hz), 52.9, 44.8, 33.6 (t, J = 20 Hz), 22.6. ^{19}F NMR ($CDCl_3$) δ −80.7 (3F, t, J = 9.8 Hz), −113.5 (2F, dm, J = 193 Hz), −128.5 (2F, br s). HRMS (ESI$^+$): calcd for $C_{17}H_{16}F_7INO_2$ (M + H$^+$): 526.0108, Found: 526.0103.

*(3S,4Z)-4-(Iodomethylene)-3-methyl-1-(phenylmethoxy)-3-[2,3,3,3-tetrafluoro-2-(trifluoromethyl)propyl]-2-pyrrolidinone (Z-**20b**).* A colorless oil. IR (KBr) 2976, 2935, 1731, 1456 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.45−7.35 (5H, m), 6.33 (1H, t, J = 2.3 Hz), 5.05 (1H, d, J = 10.8 Hz), 4.96 (1H, d, J = 10.8 Hz), 3.80 (2H, ddd, J = 15.8, 14.2, 2.4 Hz), 2.72 (1H, br t, J = 15.1 Hz), 2.34 (1H, br t, J =

dx.doi.org/10.1021/jo3015227 | J. Org. Chem. 2012, 77, 8588−8604

15.3 Hz), 1.33 (3H, s). ^{13}C NMR ($CDCl_3$) δ 171.1, 144.2, 134.5, 129.4, 129.0, 128.5, 120.5 (br qd, J = 289, 26 Hz), 90.6 (dsep, J = 209, 33 Hz), 76.7, 76.5, 54.8 (d, J = 2.9 Hz), 46.7 (d, J = 4.8 Hz), 34.8 (d, J = 18 Hz), 28.2; One carbon peak was missing due to overlapping. ^{19}F NMR ($CDCl_3$) δ −77.7 (6F, dq, J = 36, 8.4 Hz), −187.7 (1F, sep, J = 7.1 Hz). HRMS (ESI^+): calcd for $C_{17}H_{16}F_7INO_2$ ($M + H^+$): 526.0108, Found: 526.0104.

*(3S,4E)-4-(Iodomethylene)-3-methyl-1-(phenylmethoxy)-3-[2,3,3,3-tetrafluoro-2-(trifluoromethyl)propyl]-2-pyrrolidinone (E-**20b**).* A colorless oil. IR (KBr) 2978, 2937, 1725, 1455 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.42−7.36 (5H, m), 6.23 (1H, t, J = 1.8 Hz), 5.02 (1H, d, J = 11.0 Hz), 4.94 (1H, d, J = 11.0 Hz), 3.93 (1H, dd, J = 12.8, 2.3 Hz), 3.78 (1H, dd, J = 12.8, 1.0 Hz), 3.17 (1H, br t, J = 15.4 Hz), 2.58 (1H, br t, J = 16.5 Hz), 1.57 (3H, s). ^{13}C NMR ($CDCl_3$) δ 171.0, 140.1, 134.9, 129.4, 129.0, 128.6, 120.7 (qd, J = 291, 28 Hz), 120.5 (qd, J = 287, 28 Hz), 91.0 (dsep, J = 208, 33 Hz), 76.9, 73.3, 53.1 (d, J = 3.8 Hz), 45.8 (d, J = 3.8 Hz), 31.2 (d, J = 18 Hz), 24.4. ^{19}F NMR ($CDCl_3$) δ −77.2 (6F, dm, J = 138 Hz), −187.7 (1F, m). HRMS (ESI^+): calcd for $C_{17}H_{16}F_7INO_2$ ($M + H^+$): 526.0108, Found: 526.0109.

*(3S,4Z)-4-(Iodomethylene)-3-methyl-3-(2-methylpropyl)-1-(phenylmethoxy)-2-pyrrolidinone (Z-**20c**).* A colorless oil. IR ($CHCl_3$) 3019, 1711, 1418, 1363 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.48−7.33 (5H, m), 6.11 (1H, t, J = 2.8 Hz), 5.05 (1H, d, J = 10.7 Hz), 5.01 (1H, d, J = 10.7 Hz), 3.77 (2H, m), 1.75 (1H, dd, J = 13.4, 6.4 Hz), 1.50−1.35 (2H, m), 1.20 (3H, s), 0.79 (3H, d, J = 6.7 Hz), 0.76 (3H, d, J = 6.4 Hz). ^{13}C NMR ($CDCl_3$) δ 173.5, 148.0, 134.9, 129.5, 129.1, 128.6, 76.9, 74.3, 55.5, 49.9, 47.6, 27.0, 25.3, 24.2, 23.2. MS (CI^+): m/z 400 ($M + H^+$, 4), 91 (100). HRMS (CI^+): calcd for $C_{17}H_{23}INO_2$ ($M + H^+$): 400.0774, Found: 400.0775.

*(3S,4Z)-3-(2,2,3,3,4,4,4-Heptafluorobutyl)-4-(1-iodoethylidene)-3-methyl-1-(phenylmethoxy)-2-pyrrolidinone (Z-**21**).* A colorless oil. IR (KBr) 2980, 2937, 1727, 1454, 1352 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.46−7.36 (5H, m), 5.06 (1H, d, J = 10.6 Hz), 4.97 (1H, d, J = 10.6 Hz), 3.86 (2H, ddd, J = 20.5, 13.5, 1.9 Hz), 2.90 (1H, br dd, J = 34.8, 15.6 Hz), 2.61 (3H, br t, J = 1.8 Hz), 2.48 (1H, br ddd, J = 29.8, 15.6, 8.7 Hz), 1.42 (3H, s). ^{13}C NMR ($CDCl_3$) δ 171.3, 134.9, 134.4, 129.4, 128.9, 128.4, 117.5 (qt, J = 289, 34 Hz), 116.8 (tt, J = 257, 31 Hz), 108.1 (tsex, J = 229, 37 Hz), 97.6 (d, J = 1.9 Hz), 76.5, 57.8, 44.5 (d, J = 1.9 Hz), 35.7 (t, J = 20 Hz), 30.0 (d, J = 1.9 Hz), 24.6. ^{19}F NMR ($CDCl_3$) δ −80.7 (3F, t, J = 9.7 Hz), −113.1 (1F, ddq, J = 273, 35, 9.3 Hz), −116.3 (1F, ddt, J = 275, 29, 8.3 Hz), −128.4 (2F, ddd, J = 289, 113, 7.3 Hz). HRMS (ESI^+): calcd for $C_{18}H_{18}F_7INO_2$ ($M + H^+$): 540.0265, Found: 540.0265. HPLC (Chiralcel AD-H, hexane/2-propanol = 95/5, 1.0 mL/min, 254 nm) t_r (major) = 7.2 min, t_r (minor) = 11.6 min. A sample of 48% ee by HPLC analysis gave $[\alpha]^{24}_D$ −10.4 (c 0.42, $CHCl_3$).

*(3S,4E)-3-(2,2,3,3,4,4,4-Heptafluorobutyl)-4-(1-iodoethylidene)-3-methyl-1-(phenylmethoxy)-2-pyrrolidinone (E-**21**).* A colorless oil. IR (KBr) 2930, 2873, 1726, 1453, 1354 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.44−7.35 (5H, m), 5.07 (1H, d, J = 11.0 Hz), 4.96 (1H, d, J = 11.0 Hz), 3.96 (2H, ddd, J = 21.1, 12.8, 1.4 Hz), 3.34−3.21 (1H, m), 2.53 (1H, br ddd, J = 29.5, 15.3, 8.1 Hz), 2.39 (3H, br t, J = 1.1 Hz), 1.52 (3H, s). ^{13}C NMR ($CDCl_3$) δ 171.9, 134.7, 133.1, 129.4, 129.0, 128.5, 117.7 (qt, J = 289, 34 Hz), 117.3 (tt, J = 258, 31 Hz), 108.3 (tsex, J = 266, 36 Hz), 90.9 (d, J = 1.9 Hz), 76.7, 50.6, 45.1, 33.2 (t, J = 20 Hz), 31.3, 22.8. ^{19}F NMR ($CDCl_3$) δ −80.7 (3F, t, J = 9.7 Hz), −113.9 (2F, dm, J = 101 Hz), −128.5 (2F, br s). HRMS (ESI^+): calcd for $C_{18}H_{18}F_7INO_2$ ($M + H^+$): 540.0265, Found: 540.0263. HPLC (Chiralcel AD-H, hexane/2-propanol = 95/5, 1.0 mL/min, 254 nm) t_r (major) = 5.7 min, t_r (minor) = 6.2 min. A sample of 33% ee by HPLC analysis gave $[\alpha]^{24}_D$ −4.7 (c 0.21, $CHCl_3$).

*(3S,4Z)-3-(2,2,3,3,4,4,4-Heptafluorobutyl)-4-(1-iodo-1-phenylmethylene)-3-methyl-1-(phenylmethoxy)-2-pyrrolidinone (Z-**22**).* Colorless crystals. mp 98−101 °C (hexane). IR (KBr) 3033, 2940, 2878, 1728, 1455, 1353 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.50−7.21 (10H, m), 5.11 (1H, d, J = 10.5 Hz), 5.01 (1H, d, J = 10.5 Hz), 3.86 (2H, dd, J = 13.7, 12.4 Hz), 2.41 (1H, ddd, J = 26.8, 15.4, 10.4 Hz), 2.02 (1H, ddd, J = 28.4, 15.4, 9.8 Hz), 1.14 (3H, s). ^{13}C NMR ($CDCl_3$) δ 171.0, 142.0, 138.7, 134.6, 129.5, 129.1, 128.9, 128.6, 128.4, 128.0, 117.6 (qt, J = 289, 34 Hz), 117.2 (tt, J = 258, 31 Hz), 108.1 (tsex, J = 266, 36 Hz), 97.8, 76.8, 58.4, 45.0, 36.6 (t, J = 19 Hz), 25.9. ^{19}F NMR ($CDCl_3$) δ −80.6 (3F, t, J = 9.7 Hz), −113.3 (2F, dm, J = 77 Hz), −128.3 (2F, br s). HRMS (ESI^+): calcd for $C_{23}H_{20}F_7INO_2$ ($M + H^+$): 602.0421, Found: 602.0427. Elemental analysis (%) calcd for $C_{23}H_{19}F_7INO_2$: C, 45.94; H, 3.18; N, 2.33, found: C, 45.88; H, 3.28; N, 2.20. HPLC (Chiralcel AD-H, hexane/2-propanol = 95/5, 1.0 mL/min, 254 nm) t_r (major) = 6.8 min, t_r (minor) = 8.1 min. A sample of 39% ee by HPLC analysis gave $[\alpha]^{24}_D$ −16.0 (c 0.55, $CHCl_3$).

*(3S,4Z)-3-(2,2,3,3,4,4,4-Heptafluorobutyl)-3-methyl-1-(phenylmethoxy)-4-(1-phenylmethylene)-2-pyrrolidinone (Z-**23**).* A colorless oil. IR (KBr) 2973, 2932, 2876, 1723, 1452, 1353 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.46−7.28 (8H, m), 7.13 (2H, br d, J = 7.3 Hz), 6.47 (1H, br s), 5.07 (1H, d, J = 10.8 Hz), 5.00 (1H, d, J = 10.8 Hz), 4.39 (1H, dd, J = 13.3, 2.5 Hz), 4.26 (1H, dd, J = 13.3, 2.3 Hz), 2.83 (1H, ddd, J = 33.2, 15.4, 4.0 Hz), 2.35 (1H, ddd, J = 30.9, 15.4, 7.6 Hz), 1.44 (3H, s). ^{13}C NMR ($CDCl_3$) δ 170.7, 135.4, 134.7, 133.2, 129.5, 129.0, 128.7, 128.5, 128.1, 127.7, 125.9, 117.7 (qt, J = 293, 33 Hz), 117.2 (tt, J = 258, 31 Hz), 108.3 (tsex, J = 251, 36 Hz), 76.7, 50.2, 43.7, 38.1 (t, J = 20 Hz), 27.1. ^{19}F NMR ($CDCl_3$) δ −80.7 (3F, t, J = 9.8 Hz), −110.6 (1F, dm, J = 271 Hz), −113.9 (1F, dm, J = 271 Hz), −128.4 (2F, ddd, J = 289, 83, 6.5 Hz). HRMS (ESI^+): calcd for $C_{23}H_{21}F_7NO_2$ ($M + H^+$): 476.1455, Found: 476.1454.

*(3S,4E)-3-(2,2,3,3,4,4,4-Heptafluorobutyl)-3-methyl-1-(phenylmethoxy)-4-(1-phenylmethylene)-2-pyrrolidinone (E-**23**).* A colorless oil. IR (KBr) 2973, 2937, 2877, 1726, 1454, 1352 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.48−7.29 (8H, m), 7.15 (2H, d, J = 7.3 Hz), 6.64 (1H, br s), 5.08 (1H, d, J = 11.0 Hz), 5.00 (1H, d, J = 11.0 Hz), 4.15 (1H, dd, J = 12.4, 2.3 Hz), 4.02 (1H, dd, J = 12.4, 1.8 Hz), 2.57 (1H, ddd, J = 29.3, 15.1, 8.2 Hz), 2.01 (1H, ddd, J = 28.7, 15.1, 9.8 Hz), 1.19 (3H, s). ^{13}C NMR ($CDCl_3$) δ 171.9, 136.0, 135.0, 133.8, 129.5, 128.9, 128.5, 128.3, 127.6, 117.7 (qt, J = 289, 34 Hz), 117.4 (tt, J = 257, 31 Hz), 108.3 (tsex, J = 266, 37 Hz), 76.8, 51.9, 42.8, 37.3 (t, J = 20 Hz), 25.9; two carbon peaks were missing because of overlapping. ^{19}F NMR ($CDCl_3$) δ −80.7 (3F, t, J = 9.7 Hz), −113.3 (2F, dm, J = 107 Hz), −128.4 (2F, br s). HRMS (ESI^+): calcd for $C_{23}H_{21}F_7NO_2$ ($M + H^+$): 476.1455, Found: 476.1455.

*(3S,4R)-4-(1-Iodoethyl)-3-methyl-1-(phenylmethoxy)-3-[2,3,3,3-tetrafluoro-2-(trifluoromethyl)propyl]-2-pyrrolidinone (cis-**26**).* **A major isomer:** Colorless crystals. mp 58−59 °C (hexane). IR (KBr) 2979, 2945, 1717, 1457 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.47−7.34 (5H, m), 5.12 (1H, d, J = 10.9 Hz), 5.02 (1H, d, J = 10.9 Hz), 4.15 (1H, m), 3.40 (1H, dd, J = 10.0, 7.6 Hz), 3.29 (1H, dd, J = 10.0, 3.2 Hz), 2.67 (1H, t, J = 17.6 Hz), 2.54 (1H, t, J = 17.6 Hz), 1.94 (3H, d, J = 7.0 Hz), 1.77 (1H, m), 1.27 (3H, s). ^{13}C NMR ($CDCl_3$) δ 170.5, 135.0, 129.4, 129.0, 128.6, 121.1 (qd, J = 287, 29 Hz), 120.7 (qd, J = 293, 28 Hz), 92.4 (tseq, J = 209, 33 Hz), 76.8, 49.6, 48.7, 45.2, 28.2 (d, J = 19 Hz), 28.0, 25.4, 24.6. ^{19}F NMR ($CDCl_3$) δ −76.6 (3F, dq, J = 11, 7 Hz), −77.1 (3F, br quin, J = 11 Hz), −185.0 (1F, m). HRMS (ESI^+): calcd for $C_{18}H_{20}F_7INO_2$ ($M + H^+$): 542.0421, Found: 542.0419. HPLC (Chiralcel AD-H, hexane/2-propanol = 95/5, 1.0 mL/min, 254 nm) t_r (major) = 7.3 min, t_r (minor) = 8.8 min. A sample of 91% ee by HPLC analysis gave $[\alpha]^{24}_D$ +57.4 (c 0.55, $CHCl_3$). **A minor isomer:** A colorless oil. IR (KBr) 2947, 1718, 1496, 1457 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.47−7.35 (5H, m), 5.05 (1H, d, J = 10.9 Hz), 4.98 (1H, d, J = 10.9 Hz), 4.47 (1H, m), 3.42 (2H, d, J = 4.7 Hz), 2.72 (1H, t, J = 16.8 Hz), 2.69 (1H, m), 2.14 (1H, br t, J = 16.8 Hz), 1.61 (3H, d, J = 7.0 Hz), 1.29 (3H, s). ^{13}C NMR ($CDCl_3$) δ 171.5, 134.9, 129.3, 129.1, 128.6, 121.0 (qd, J = 288, 28 Hz), 120.7 (qd, J = 291, 31 Hz), 92.2 (tseq, J = 210, 33 Hz), 76.7, 50.5, 48.0, 45.3, 28.2 (d, J = 19 Hz), 23.7 (2C), 23.6. ^{19}F NMR ($CDCl_3$) δ −76.7 (3F, m), −76.9 (3F, br quin, J = 9.3 Hz), −184.9 (1F, m). HRMS (ESI^+): calcd for $C_{18}H_{20}F_7INO_2$ ($M + H^+$): 542.0421, Found: 542.0418.

*trans-4-(1-Iodoethyl)-3-methyl-1-(phenylmethoxy)-3-[2,3,3,3-tetrafluoro-2-(trifluoromethyl)propyl]-2-pyrrolidinone (trans-**26**).* **A major isomer:** Colorless crystals. mp 87−89 °C (hexane). IR (KBr) 2973, 2933, 1726, 1455 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.46−7.35 (5H, m), 5.04 (1H, d, J = 10.8 Hz), 4.92 (1H, dd, J = 10.8 Hz), 4.14 (1H, m), 3.57 (1H, t, J = 8.2 Hz), 2.99 (1H, td, J = 8.9, 1.2 Hz), 2.77 (1H, t,

dx.doi.org/10.1021/jo3015227 | J. Org. Chem. 2012, 77, 8588−8604

J = 8.9 Hz), 2.75 (1H, dd, J = 32.8, 15.8 Hz), 2.23 (1H, dd, J = 16.5, 9.2 Hz), 2.02 (3H, dd, J = 6.9, 1.4 Hz), 1.10 (3H, s). ^{13}C NMR ($CDCl_3$) δ 171.7, 134.7, 129.4, 129.0, 128.6, 120.7 (qd, J = 288, 28 Hz), 120.5 (qd, J = 288, 28 Hz), 91.9 (dsep, J = 208, 33 Hz), 76.9, 53.3, 44.4, 44.0 (d, J = 5.8 Hz), 33.5 (d, J = 18 Hz), 28.0 (d, J = 2.9 Hz), 25.9, 19.4. ^{19}F NMR ($CDCl_3$) δ −75.4 (3F, br quin, J = 9.8 Hz), −78.0 (3F, m), −183.5 (1F, m). HRMS (ESI$^+$): calcd for $C_{18}H_{20}F_7INO_2$ (M + H$^+$): 542.0421, Found: 542.0416. **A minor isomer**: A colorless oil. IR (KBr) 2970, 2929, 1724, 1458 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.44−7.36 (5H, m), 5.05 (1H, d, J = 11.0 Hz), 4.91 (1H, d, J = 11.0 Hz), 3.96 (1H, quin, J = 7.1 Hz), 3.49−3.41 (1H, m), 2.99−2.87 (3H, m), 2.46 (1H, dd, J = 27.5, 16.0 Hz), 1.84 (3H, d, J = 6.4 Hz), 1.21 (3H, s). ^{13}C NMR ($CDCl_3$) δ 172.0, 134.9, 129.4, 129.0, 128.6, 120.8 (qd, J = 289, 28 Hz), 120.7 (qd, J = 288, 28 Hz), 91.9 (dsep, J = 208, 32 Hz), 77.2, 48.4, 44.6, 43.5 (d, J = 4.8 Hz), 31.8 (d, J = 19 Hz), 26.9, 20.9, 19.0. ^{19}F NMR ($CDCl_3$) δ −76.0 (3F, br quin, J = 9.8 Hz), −77.3 (3F, m), −184.9 (1F, m). HRMS (ESI$^+$): calcd for $C_{18}H_{20}F_7INO_2$ (M + H$^+$): 542.0421, Found: 542.0414.

*(3S,4R)-4-(1-Iodoethyl)-3-methyl-2-oxo-1-(phenylmethoxy)-3-pyrrolidinepropanoic Acid Ethyl Ester (cis-**28a**).* A colorless oil. IR (KBr) 2977, 1729, 1711, 1456 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.45−7.35 (5H, m), 5.01 (1H, d, J = 11.0 Hz), 4.96 (1H, d, J = 11.0 Hz), 4.11 (2H, q, J = 7.3 Hz), 3.45 (1H, dd, J = 8.9, 7.3 Hz), 3.22 (1H, dd, J = 10.1, 4.6 Hz), 2.99 (2H, br t, J = 10.1 Hz), 2.46 (1H, m), 2.41−2.31 (2H, m), 1.73−1.64 (1H, m), 1.59−1.51 (1H, m), 1.25 (3H, t, J = 7.3 Hz), 1.17 (3H, s). ^{13}C NMR ($CDCl_3$) δ 173.1, 172.3, 134.7, 129.5, 129.0, 128.5, 76.6, 60.4, 51.2, 46.2, 44.6, 28.7, 26.5, 20.9, 14.1, 1.5. MS (EI$^+$): m/z 445 (M$^+$, 0.2), 91 (100). HRMS (EI): calcd for $C_{18}H_{24}INO_4$ (M$^+$): 445.0745, Found: 445.0761. HPLC (Chiralcel AD-H, hexane/2-propanol = 95/5, 1.0 mL/min, 254 nm) t_r (major) = 44.0 min, t_r (minor) = 48.3 min. A sample of 55% ee by HPLC analysis gave $[\alpha]^{24}_D$ +19.2 (c 0.21, $CHCl_3$).

*(3S,4S)-4-(1-Iodoethyl)-3-methyl-2-oxo-1-(phenylmethoxy)-3-pyrrolidinepropanoic Acid Ethyl Ester (trans-**28a**).* A colorless oil. IR (KBr) 2975, 1727, 1714, 1456 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.45−7.36 (5H, m), 5.01 (1H, d, J = 11.0 Hz), 4.96 (1H, d, J = 11.0 Hz), 4.14 (2H, q, J = 7.3 Hz), 3.46 (1H, br t, J = 8.7 Hz), 3.19 (1H, dd, J = 9.6, 4.1 Hz), 2.92 (1H, t, J = 8.7 Hz), 2.89 (1H, dd, J = 11.4, 9.6 Hz), 2.39−2.25 (3H, m), 1.94−1.78 (2H, m), 1.27 (3H, t, J = 7.3 Hz), 0.96 (3H, s). ^{13}C NMR ($CDCl_3$) δ 173.3, 173.0, 134.8, 129.6, 129.1, 128.6, 76.8, 60.7, 51.4, 45.6, 41.2, 31.0, 29.3, 16.9, 14.2, 2.3. MS (EI$^+$): m/z 445 (M$^+$, 0.2), 91 (100). HRMS (EI): calcd for $C_{18}H_{24}INO_4$ (M$^+$): 445.0745, Found: 445.0761. HPLC (Chiralcel AD-H, hexane/2-propanol = 95/5, 1.0 mL/min, 254 nm) t_r (major) = 50.5 min, t_r (minor) = 36.4 min. A sample of 54% ee by HPLC analysis gave $[\alpha]^{24}_D$ +17.7 (c 0.28, $CHCl_3$).

*cis-4-(1-Iodoethyl)-3-methyl-2-oxo-1-(phenylmethoxy)-3-pyrrolidinepropanenitrile (cis-**28b**).* A colorless oil. IR (KBr) 2966, 2935, 2247, 1707, 1455 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.48−7.38 (5H, m), 5.04 (1H, d, J = 11.0 Hz), 4.96 (1H, d, J = 11.0 Hz), 3.49 (1H, dd, J = 9.2, 7.8 Hz), 3.17 (1H, dd, J = 9.8, 4.6 Hz), 2.98 (1H, t, J = 9.2 Hz), 2.91 (1H, dd, J = 11.5, 9.8 Hz), 2.53−2.30 (3H, m), 1.65−1.58 (2H, m), 1.20 (3H, s). ^{13}C NMR ($CDCl_3$) δ 171.4, 134.5, 129.6, 129.4, 128.7, 119.5, 77.2, 51.1, 46.0, 44.4, 28.0, 20.4, 12.2, 0.2. MS (EI$^+$): m/z 398 (M$^+$, 2.1), 91 (100). HRMS (EI): calcd for $C_{16}H_{19}IN_2O_2$ (M$^+$): 398.0486, Found: 398.0509.

*trans-4-(1-Iodoethyl)-3-methyl-2-oxo-1-(phenylmethoxy)-3-pyrrolidinepropanenitrile (trans-**28b**).* A colorless oil. IR (KBr) 2967, 2936, 2247, 1708, 1456 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.45−7.38 (5H, m), 5.00 (1H, d, J = 11.0 Hz), 4.97 (1H, d, J = 11.0 Hz), 3.50 (1H, dd, J = 9.2, 7.8 Hz), 3.14 (1H, dd, J = 10.1, 5.0 Hz), 2.93 (1H, t, J = 9.2 Hz), 2.92 (1H, t, J = 10.1 Hz), 2.50−2.31 (3H, m), 2.01−1.93 (1H, m), 1.89−1.80 (1H, m), 1.00 (3H, s). ^{13}C NMR ($CDCl_3$) δ 172.3, 134.5, 129.5, 129.2, 128.6, 119.3, 76.7, 51.0, 45.0, 41.1, 32.0, 16.4, 12.3, 0.7. HRMS (ESI$^+$): calcd for $C_{16}H_{20}IN_2O_2$ (M + H$^+$): 399.0564, Found: 399.0562.

*2-[(3S,4R)-4-(1-Iodoethyl)-3-methyl-2-oxo-1-(phenylmethoxy)-3-pyrrolidinyl]-2-methylpropanedioic Acid 1,3-Diethyl Ester (cis-**28c**).* A colorless oil. IR (KBr) 2980, 2937, 1728, 1454 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.48−7.33 (5H, m), 4.98 (1H, d, J = 10.9 Hz), 4.96 (1H, d, J = 10.9 Hz), 4.21 (1H, m), 4.18−4.11 (3H, m), 3.48 (1H, dd, J = 10.3, 4.4 Hz), 3.36 (1H, dd, J = 8.8, 7.0 Hz), 3.28−3.20 (2H, m), 2.45 (1H, d, J = 14.4 Hz), 2.27 (1H, m), 1.75 (1H, d, J = 14.4 Hz), 1.64 (3H, s), 1.28 (3H, s), 1.25 (3H, t, J = 7.3 Hz), 1.23 (3H, t, J = 7.1 Hz). ^{13}C NMR ($CDCl_3$) δ 172.7, 172.3, 171.4, 135.2, 129.4, 128.9, 128.5, 76.8, 61.7 (2C), 53.2, 49.1, 47.9, 44.6, 35.2, 30.0, 23.1, 20.6, 13.9, 13.8. HRMS (ESI$^+$): calcd for $C_{22}H_{31}{}^{79}BrNO_6$ (M + H$^+$): 484.1329, Found: 484.1322. HRMS (ESI$^+$): calcd for $C_{22}H_{31}{}^{81}BrNO_6$ (M + H$^+$): 486.1309, Found: 486.1300. HPLC (Chiralcel AD-H, hexane/2-propanol = 95/5, 1.0 mL/min, 254 nm) t_r (major) = 28.9 min, t_r (minor) = 71.0 min. A sample of 51% ee by HPLC analysis gave $[\alpha]^{24}_D$ +13.7 (c 0.18, $CHCl_3$).

*2-[(3S,4S)-4-(1-Iodoethyl)-3-methyl-2-oxo-1-(phenylmethoxy)-3-pyrrolidinyl]-2-methylpropanedioic Acid 1,3-Diethyl Ester (trans-**28c**).* A colorless oil. IR (KBr) 2965, 2933, 1727, 1456 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.45 (2H, m), 7.44−7.33 (3H, m), 5.01 (1H, d, J = 10.9 Hz), 4.93 (1H, d, J = 10.9 Hz), 4.27 (1H, m), 4.22−4.11 (3H, m), 3.61 (1H, t, J = 8.8 Hz), 3.57 (1H, dd, J = 9.7, 3.5 Hz), 3.12 (1H, dd, J = 11.8, 9.7 Hz), 2.98 (1H, t, J = 8.8 Hz), 2.47 (1H, m), 2.37 (1H, d, J = 15.3 Hz), 2.24 (1H, d, J = 15.3 Hz), 1.37 (3H, s), 1.29 (3H, t, J = 7.0 Hz), 1.25 (3H, t, J = 7.0 Hz), 0.93 (3H, s). ^{13}C NMR ($CDCl_3$) δ 173.4, 172.2, 171.8, 135.0, 129.4, 129.0, 128.5, 76.6, 61.9 (2C), 52.7, 49.5, 44.6, 39.0, 38.8, 30.6, 20.1, 20.0, 14.0, 13.9. HRMS (ESI$^+$): calcd for $C_{22}H_{31}{}^{79}BrNO_6$ (M + H$^+$): 484.1329, Found: 484.1326. HRMS (ESI$^+$): calcd for $C_{22}H_{31}{}^{81}BrNO_6$ (M + H$^+$): 486.1309, Found: 486.1304. HPLC (Chiralcel AD-H, hexane/2-propanol = 95/5, 1.0 mL/min, 254 nm) t_r (major) = 22.4 min, t_r (minor) = 46.5 min. A sample of 27% ee by HPLC analysis gave $[\alpha]^{24}_D$ −4.6 (c 0.05, $CHCl_3$).

*(3S,4R)-4-(1-Bromoethyl)-3-methyl-1-(phenylmethoxy)-3-(2,2,2-trichloroethyl)-2-pyrrolidinone (cis-**29**).* Colorless crystals. mp 129−131 °C (hexane). IR (KBr) 2970, 2883, 1716, 1456 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.46−7.36 (5H, m), 5.04 (1H, d, J = 11.4 Hz), 5.01 (1H, d, J = 11.4 Hz), 3.73 (1H, ddd, J = 10.1, 3.2, 0.9 Hz), 3.48 (1H, ddd, J = 9.6, 5.9, 0.9 Hz), 3.46 (1H, d, J = 16.5 Hz), 3.36 (1H, dd, J = 9.6, 0.9 Hz), 2.96 (1H, dd, J = 11.0, 10.1 Hz), 2.92 (1H, d, J = 16.5 Hz), 2.61−2.55 (1H, m), 1.44 (3H, s). ^{13}C NMR ($CDCl_3$) δ 170.7, 134.7, 129.6, 129.3, 128.7, 97.0, 76.9, 53.6, 48.8, 47.4, 43.9, 33.0, 20.1. HRMS (ESI$^+$): calcd for $C_{15}H_{18}BrCl_3NO_2$ (M + H$^+$): 427.9581, Found: 427.9590. HPLC (Chiralcel AD-H, hexane/2-propanol = 95/5, 1.0 mL/min, 254 nm) t_r (major) = 14.0 min, t_r (minor) = 35.8 min. A sample of 77% ee by HPLC analysis gave $[\alpha]^{24}_D$ +10.8 (c 0.17, $CHCl_3$).

*trans-4-(1-Bromoethyl)-3-methyl-1-(phenylmethoxy)-3-(2,2,2-trichloroethyl)-2-pyrrolidinone (trans-**29**).* A white solid. IR (KBr) 2928, 2877, 1714, 1650, 1457 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.45−7.32 (5H, m), 5.01 (1H, d, J = 11.0 Hz), 4.95 (1H, d, J = 11.0 Hz), 3.70 (1H, t, J = 8.3 Hz), 3.62 (1H, dd, J = 9.2, 2.8 Hz), 3.52 (1H, d, J = 15.6 Hz), 3.35−3.27 (1H, m), 3.23 (1H, dd, J = 11.4, 9.2 Hz), 3.09 (1H, t, J = 8.3 Hz), 2.79 (1H, d, J = 15.6 Hz), 1.00 (3H, s). ^{13}C NMR ($CDCl_3$) δ 172.3, 134.8, 129.4, 129.0, 128.5, 96.1, 76.7, 56.7, 49.2, 46.0, 36.9, 29.7, 18.7. HRMS (ESI$^+$): calcd for $C_{15}H_{18}BrCl_3NO_2$ (M + H$^+$): 427.9581, Found: 427.9583.

*cis-3-(1-Bromoethyl)-3-methyl-1-(phenylmethoxy)-4-(2,2,2-trichloroethyl)-2-pyrrolidinone (**30**).* A colorless oil. IR (KBr) 2965, 2929, 1713, 1648, 1457 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 7.48−7.43 (2H, m), 7.41−7.36 (3H, m), 5.10 (1H, d, J = 10.6 Hz), 5.03 (1H, d, J = 10.6 Hz), 3.67 (1H, t, J = 8.7 Hz), 3.60 (1H, t, J = 8.7 Hz), 3.58 (1H, d, J = 11.0 Hz), 3.23 (1H, d, J = 11.0 Hz), 3.18 (1H, dd, J = 14.7, 10.1 Hz), 2.92 (1H, dd, J = 14.7, 1,8 Hz), 2.65−2.57 (1H, br m), 1.31 (3H, s). ^{13}C NMR ($CDCl_3$) δ 169.8, 134.8, 129.4, 129.0, 128.6, 98.2, 76.9, 52.8, 51.6, 46.0, 38.8, 34.5, 23.6. HRMS (ESI$^+$): calcd for $C_{15}H_{18}BrCl_3NO_2$ (M + H$^+$): 427.9581, Found: 427.9582.

Typical Procedure for Reductive Deiodination. To a stirred solution of major isomer of *cis*-**26** (130 mg 0.241 mmol) and Bu_3SnH (126 μL, 0.482 mmol) in CH_2Cl_2 (4.8 mL) was added Et_3B (1.05 M in hexane, 1.15 mL, 1.21 mmol) at room temperature. After being stirred at the same temperature for 3 h, the reaction mixture was diluted with saturated $NaHCO_3$ 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 short column chromatography

dx.doi.org/10.1021/jo3015227 | J. Org. Chem. 2012, 77, 8588−8604

(hexane) to give a mixture of products. Further purification of the mixture by preparative TLC (hexane:AcOEt = 6:1, 2-fold development) afforded the isolated products *cis*-**27** (94.7 mg, 94%). Under similar reaction conditions, the product *cis*-**27** (41.6 mg, 89%) was obtained from a minor isomer of *cis*-**26** (60.7 mg 0.111 mmol), the product *trans*-**27** (16.9 mg, 72%) was obtained from a major isomer of *trans*-**26** (30.0 mg 0.0550 mmol), and the product *trans*-**27** (10.7 mg, 73%) was obtained from a minor isomer of *trans*-**26** (19.3 mg 0.0357 mmol).

*cis-4-Ethyl-3-methyl-1-(phenylmethoxy)-3-[2,3,3,3-tetrafluoro-2-(trifluoromethyl)propyl]-2-pyrrolidinone (cis-**27**).* A colorless oil. IR (KBr) 2969, 2942, 1716, 1460 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.44−7.35 (5H, m), 4.98 (2H, dd, J = 28.4, 11.0 Hz), 3.33 (1H, dd, J = 9.3, 6.9 Hz), 2.95 (1H, dd, J = 9.3, 3.9 Hz), 2.55 (1H, br t, J = 16.5 Hz), 2.12 (1H, dd, J = 21.1, 16.5 Hz), 1.87−1.83 (1H, m), 1.51−1.42 (1H, m), 1.24 (3H, d, J = 1.8 Hz), 1.01 (1H, m), 0.77 (3H, t, J = 7.3 Hz). ^{13}C NMR ($CDCl_3$) δ 172.1, 135.2, 129.5, 129.0, 128.5, 121.1 (qd, J = 290, 28 Hz), 120.9 (qd, J = 287, 28 Hz), 92.2 (dsep, J = 210, 32 Hz), 76.8, 48.7, 44.7, 44.4, 28.9 (d, J = 19 Hz), 21.7, 21.0, 11.9. ^{19}F NMR ($CDCl_3$) δ −76.8 (3F, br quin, J = 9.8 Hz), −77.2 (3F, m), −184.8 (1F, m). HRMS (ESI^+): calcd for $C_{18}H_{21}F_7NO_2$ ($M + H^+$): 416.1455, Found: 416.1439.

*trans-4-Ethyl-3-methyl-1-(phenylmethoxy)-3-[2,3,3,3-tetrafluoro-2-(trifluoromethyl)propyl]-2-pyrrolidinone (trans-**27**).* A colorless oil. IR (KBr) 2971, 2939, 1721, 1460 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.44−7.36 (5H, m), 5.02 (1H, d, J = 11.0 Hz), 4.91 (1H, d, J = 11.0 Hz), 3.37 (1H, br t, J = 8.0 Hz), 2.87 (1H, td, J = 8.8, 1.6 Hz), 2.57 (1H, br dd, J = 21.1, 16.0 Hz), 2.32−2.25 (1H, m), 2.15 (1H, br t, J = 14.9 Hz), 1.55−1.45 (1H, m), 1.25−1.14 (1H, m), 1.01 (3H, s), 0.85 (3H, t, J = 7.6 Hz). ^{13}C NMR ($CDCl_3$) δ 172.6, 135.1, 129.5, 128.9, 128.5, 120.9 (qd, J = 287, 28 Hz), 120.7 (qd, J = 288, 28 Hz), 91.6 (dsep, J = 208, 33 Hz), 76.7, 49.7, 43.8, 38.2 (d, J = 3.9 Hz), 32.0 (d, J = 19 Hz), 20.7, 19.5, 11.8. ^{19}F NMR ($CDCl_3$) δ −77.0 (3F, br quin, J = 9.6 Hz), −78.2 (3F, m), −186.6 (1F, m). HRMS (ESI^+): calcd for $C_{18}H_{21}F_7NO_2$ ($M + H^+$): 416.1455, Found: 416.1446.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

HMQC, HMBC, and NOESY experiments for *cis*-**15a**, *trans*-**15a**, **16a**, *cis*-**15c**, *trans*-**15c**, **16c**, *trans*-**17**, and *cis*-**17**, ^1H, ^{13}C, and ^{19}F NMR spectra for all new compounds, and HPLC chromatograms for chiral products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported in part by Grant-in-Aid for Scientific Research (C) (H.M.) from Japan Society for the Promotion of Science.

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