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Enantioselective Synthesis of Functionalized Fluorinated Cyclohexenones via Robinson Annulation Catalyzed by Primary−Secondary Diamines

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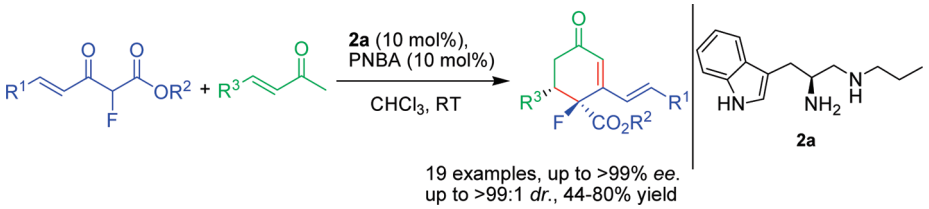

Primary−secondary diamine catalysts were used to catalyze the asymmetric Robinson annulation to synthesize multiply substituted fluorinated chiral cyclohexenones with two contiguous stereogenic centers, one of which is a fluorinated quaternary chiral center, with excellent enantioselectivities and diastereoselectivities in moderate to good yields.

Introduction

Fluorine-containing organic compounds play an important role in materials, medicinal, pharmaceutical, and agrochemical science due to the unique properties of the fluorine atom.[1] Recently, the organocatalytic asymmetric synthesis of fluorinated molecules has received considerable attention among organic chemists.[2] However, the enantioselective catalytic construction of chiral fluorinated quaternary carbon centers, which are a class of versatile and important monofluorinated synthons utilized in organic synthesis,[2−4] is still a very challenging subject in organic chemistry.[2,3] On the other hand, being both atom- and step-economic and environmentally friendly, asymmetric organocatalytic tandem reactions have recently received much attention and have become powerful and efficient tools in organic chemistry.[5,6] However, applications of organocatalytic domino transformations in the asymmetric construction of fluorine-containing molecules are very limited.[7]

Chiral cyclohexenones have been a long-standing targets of asymmetric synthesis due to their presence as a common structural motif of many biologically active molecules and very important building blocks in organic synthesis.[8]

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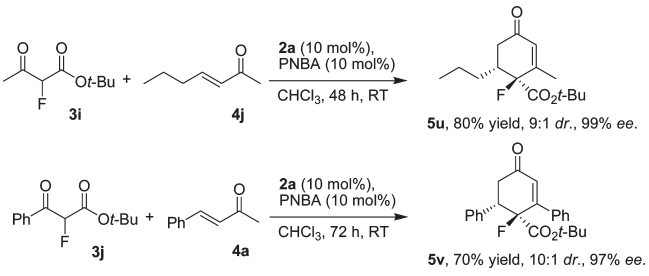
SCHEME 1. Reactions of Other Substrates



The well-known Robinson annulation, which combines three reactions, Michael addition, intramolecular aldol reaction, and dehydration, is one of the most important ways to access various substituted cyclohexenones.[9] Using a phenylalanine-derived imidazolidine catalyst, Jørgensen and coworkers were the first to realize a highly enantio- and diastereoselective Michael-adol reaction of ketoesters and enones to provide functionalized chiral cyclohexanes, which after dehydration in the presence of an acid could be converted to chiral cyclohexenones. However, a long reaction time was generally required (95−240 h).[10] Recently, we have developed some primary−secondary diamine catalysts, which were readily available from primary amino acids in three steps, for the Michael additions of malonates to α,β-unsaturated ketones with outstanding results (Scheme 1).[11,12] Being interested in the application of organocatalysis to the synthesis of chiral fluorinated molecules, we report herein an asymmetric organocatalytic Robinson annulation catalyzed by primary−secondary diamine catalysts, which provided enantioenriched fluorinated cyclohexenones with multiple stereocenters, one of which is a fluorinated quaternary center.

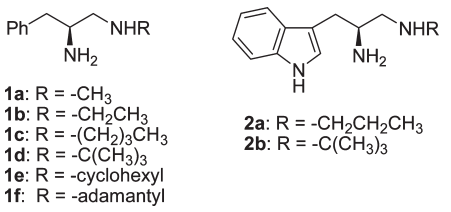


FIGURE 1. Structures of catalysts studied.

Results and discussion

In our previous work, we found that the acid additives played an important role in the Michael additions of malonates to α,β-unsaturated ketones catalyzed by primary−secondary diamines; therefore, different acid additives were first tested. Catalyzed by **1a** (Figure 1) and different acids, the reaction between α-fluoro-β-keto ester **3a**, which was selected for investigation mainly due to the easy modifiability of the vinyl group for further useful conversion of the corresponding product, and benzylideneacetone **4a** gave the Robinson annulation product **5a** and Michael−aldol reaction product **6a** (Table 1, entries 2−6). Among the acids screened, PNBA (4-nitrobenzoic acid) gave the highest yield (82%) and > 99% ee value (Table 1, entry 2) and thus was chosen for further studies.

After the screening of acids, a series of primary−secondary diamines were evaluated in $CHCl_3$ at room temperature in the presence of 20 mol % of *p*-nitrobenzoic acid as the additive (Table 2, entries 1−8). Generally, the reaction gave two products: the desired cyclohexenone product **5a** as the major one and the undehydrated product **6a** as the minor one. The absolute configurations of **5a** and **6a** were determined by X-ray crystallographic analysis.[13] As shown in Table 2, the catalysts examined produced only slight differences in the ratios of the two products, the yields and ee values of **5a**, while a remarkable difference in the diastereoselectivity was observed. Taking into account all of these factors, catalyst **2a** was selected as the optimal catalyst for further optimization (Table 2, entry 8). Notably, reducing the catalyst loading of **2a** to 10 mol % still gave the same excellent yield, albeit with a longer reaction time (Table 2, entry 9). Replacing the solvent $CHCl_3$ with CH_2Cl_2 led to a slight drop in the product ratio and the enantioselectivity of **5a** (Table 2, entry 10). Inferior results were observed when THF or Et_2O was used (Table 2, entries 11 and 12). While the use of toluene also provided excellent results besides a reduced product ratio, the protic solvent ethanol was completely unsuitable for this reaction (Table 2, entries 13 and 14). Therefore, the reaction was best performed with 10 mol % of catalyst **2a** and PNBA in $CHCl_3$ at room temperature (Table 2, entry 9).

With the optimized reaction conditions in hand, a selected spectrum of different substrates were examined to test the scope of this reaction and a series of useful chiral 3-alkenyl

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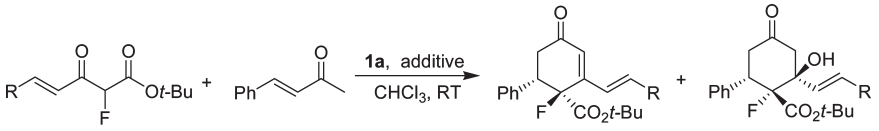
TABLE 1. Screening of Acids

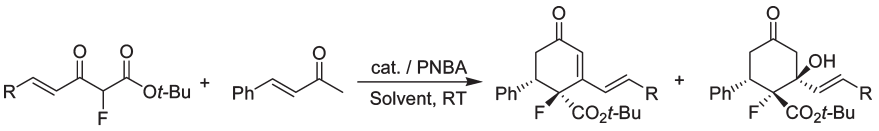


3a: R = -C_6H_4Br-*p* **4a** **5a** **6a**

entry	acid	time/h	yield of **5a**/%[b]	**5a**:**6a**[c]	ee of **5a**/%[d]
1	none	36	30	ND	ND
2	*p*-$NO_2C_6H_4CO_2H$	12	82	5.4:1	>99
3	$PhCO_2H$	17	79	5.3:1	>99
4	*p*-TsOH	17	60	2.3:1	98
5	CH_3CO_2H	17	81	5:1	>99
6	CF_3CO_2H	17	43	5:1	98

[a]Reaction conditions: **3a** (1.0 equiv), **4a** (1.0 equiv), **1a** (20 mol %), acid (20 mol %), $CHCl_3$ (0.5 mL). [b]Yield of the isolated product after column chromatography. [c]Determined by ^{19}F NMR. [d]Determined by HPLC.

TABLE 2. Screening of Catalysts and Solvents [a]



3a: R = -C_6H_4Br-*p* **4a** **5a** **6a**

					5a		
entry	solvent	cat.	*t* [h]	**5a**: **6a**[c]	yield [%][d]	dr[c]	ee [%][e]
1	$CHCl_3$	**1a**	12	5.4:1	82	16:1	>99
2	$CHCl_3$	**1b**	12	4:1	80	18:1	98
3	$CHCl_3$	**1c**	12	3.6:1	77	8:1	96
4	$CHCl_3$	**1d**	12	5.4:1	85	14:1	98
5	$CHCl_3$	**1e**	12	4.5:1	80	>99:1	97
6	$CHCl_3$	**1f**	12	5:1	80	30:1	99
7	$CHCl_3$	**2a**	12	5:1	77	30:1	>99
8	$CHCl_3$	**2b**	12	5:1	80	24:1	98
9[b]	$CHCl_3$	**2a**	20	5:1	80	30:1	>99
10	CH_2Cl_2	**2a**	12	4:1	76	>99:1	97
11	THF	**2a**	24	2.6:1	66	6:1	97
12	Et_2O	**2a**	24	2.4:1	60	10:1	98
13	Toluene	**2a**	24	3.6:1	74	>99:1	>99
14	EtOH	**2a**	36	ND	trace	ND	ND

[a]Unless otherwise noted, the reaction was carried out with **3a** (0.1 mmol), **4a** (0.1 mmol), catalyst (20 mol %), PNBA (20 mol %), and solvent (0.5 mL) at room temperature. [b]**2a** (10 mol %) and PNBA (10 mol %) were used. [c]Determined by ^{19}F NMR. [d]Isolated yield after column chromatography on silica gel. [e]Determined by chiral HPLC analysis.

cyclohexen-2-ones were obtained (Table 3).[14] For substrates **3a**−**f** with different substituents on the phenyl ring of R^1, generally excellent ee and dr values were obtained irrespective of the electronic nature or positions of the substituents, though slightly lower yields were observed for substrates bearing electron-donating substituents (Table 3, entries 1−6). Changing the bulky *tert*-butyl group (R^2) of **3a** to a less sterically demanding ethyl group (**3g**) led to diminished dr value and yield of the desired product **5**, but still with excellent ee values (Table 3, entry 7). When R^1 was a methyl group, the product **5h** was obtained in moderate yield and excellent enantioselectivity although requiring a long reaction time (Table 3, entry 8). Subsequently, the scope of the other reaction component **4** was also examined. When R^3 was an aryl group, substrates with electron-donating or -withdrawing substituents at the para or ortho position of the benzene ring all provided the desired products in moderate yields, with excellent dr and ee values (Table 3, entries 8−11 and 13−18). However, substrate **4f** with an *o*-Cl substituent gave both significantly lower yield and dr value, but still with an excellent ee value (Table 3, entry 12). Notably, alkyl-substituted enone **4i** also proved to be applicable to the reaction system, giving the desired product **5t** in excellent dr and ee values and with moderate yield. Moreover, when both reaction components were aliphatic substrates **3i** and **4j**, the reaction still proceeded efficiently to give the desired product **5u** in 80% yield, 9:1 dr, and 99% ee (Scheme 1), which provides an easy access to this kind of important synthetic targets.[15] When substrates were **3j** and **4a**, the

(14) Selected examples: (a) Hénon, H.; Manduit, M.; Alexakis, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 9122–9124. (b) Schachtschabel, D.; Boland, W. *J. Org. Chem.* **2007**, *72*, 1366–1372. (c) Luo, J. D.; Huang, S.; Cheng, Y. J.; Kim, T. D.; Shi, Z. W.; Zhou, X. H.; Jen, A. K. Y. *Org. Lett.* **2007**, *9*, 4471–4474. (d) Luo, J. D.; Cheng, Y. J.; Kim, T. D.; Hau, S.; Jang, S. H.; Shi, Z. W.; Zhou, X. H.; Jen, A. K. Y. *Org. Lett.* **2006**, *8*, 1387–1390. (e) Akai, S.; Tanimoto, K.; Kita, Y. *Angew. Chem., Int. Ed.* **2004**, *43*, 1407–1410.

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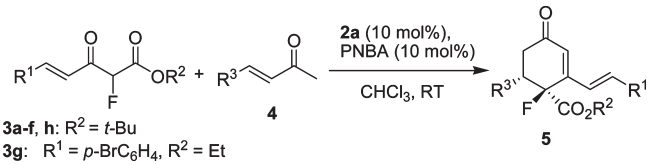
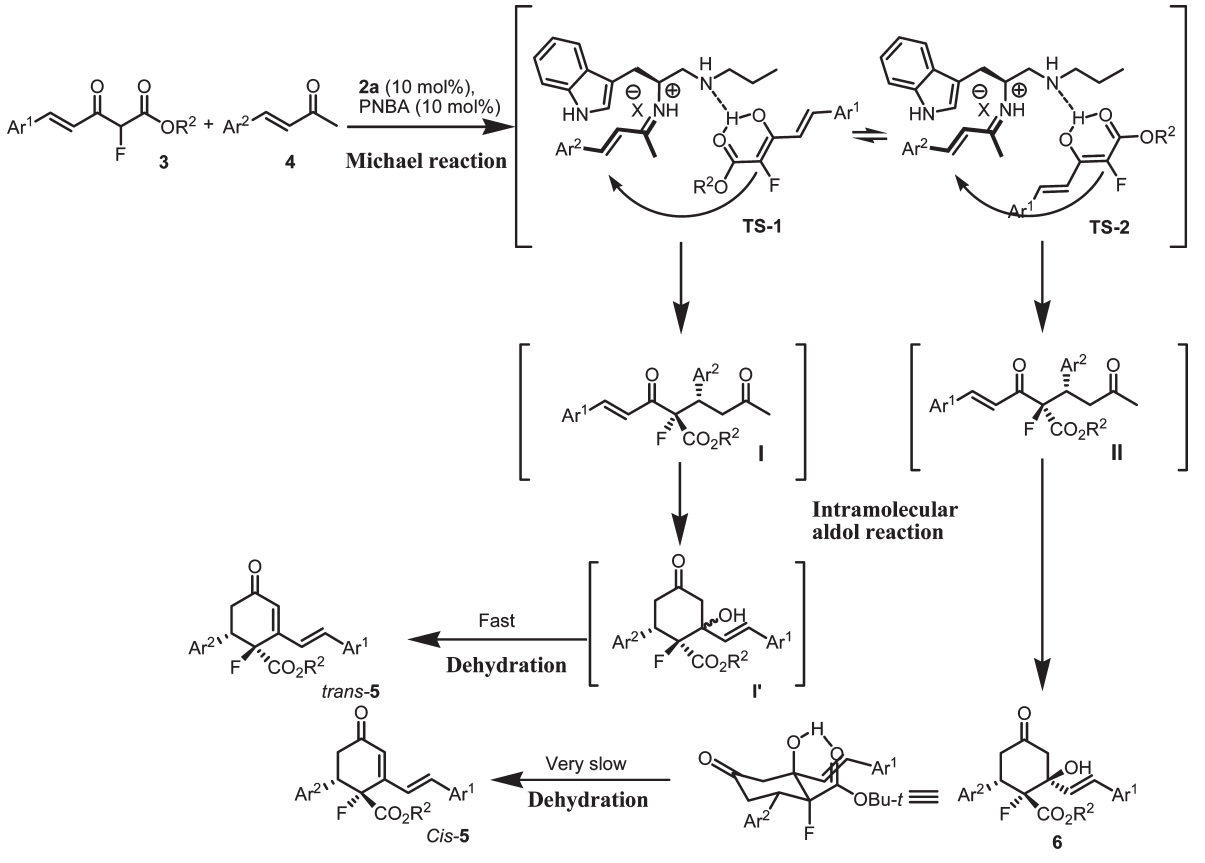
TABLE 3. Investigation of Reaction Scope[a]

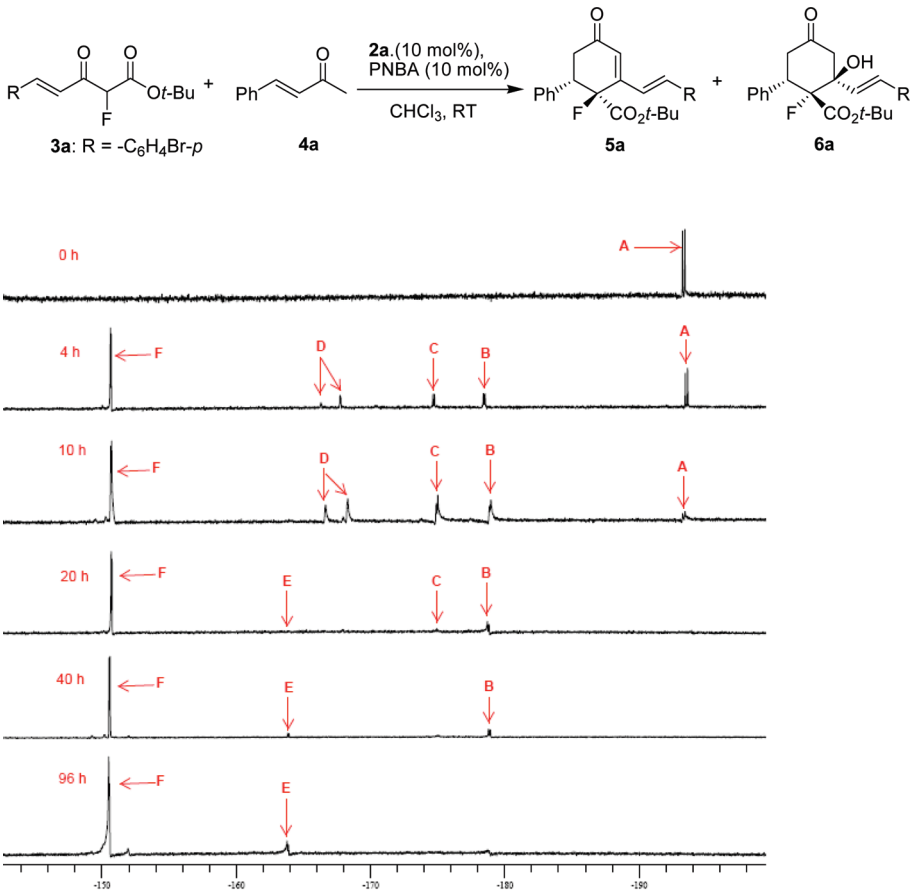


					5		
entry	R^1	R^3	*t* [h]	**5**:**6**[c]	yield [%][b]	dr[c]	ee [%][d]
1	*p*-BrC_6H_4 (**3a**)	Ph (**4a**)	20	5:1	80 (**5a**)	30:1	> 99
2	*m*-BrC_6H_4 (**3b**)	Ph (**4a**)	19	5:1	78 (**5b**)	25:1	> 99
3	*o*-BrC_6H_4 (**3c**)	Ph (**4a**)	26	6:1	80 (**5c**)	> 99:1	> 99
4	*p*-$NO_2C_6H_4$ (**3d**)	Ph (**4a**)	24	5:1	80 (**5d**)	> 99:1	> 99
5	*p*-$MeOC_6H_4$ (**3e**)	Ph (**4a**)	24	5:1	68 (**5e**)	30:1	> 99
6	Ph (**3f**)	Ph (**4a**)	27	4:1	67 (**5f**)	> 99:1	> 99
7	**3g**	Ph (**4a**)	20	3:1	61 (**5g**)	10:1	99
8	Me (**3h**)	Ph (**4a**)	48	ND	60 (**5h**)	10:1	> 99
9	Ph (**3f**)	*p*-FC_6H_4 (**4b**)	20	4:1	60 (**5i**)	35:1	99
10	Ph (**3f**)	*p*-ClC_6H_4 (**4c**)	29	5:1	74 (**5j**)	46:1	99
11	Ph (**3f**)	*p*-BrC_6H_4 (**4d**)	20	4:1	67 (**5k**)	20:1	> 99
12	Ph (**3f**)	*m*-ClC_6H_4 (**4e**)	19	4:1	63 (**5l**)	20:1	99
13	Ph (**3f**)	*o*-ClC_6H_4 (**4f**)	48	1:1	44 (**5m**)	6:1	98
14	Ph (**3f**)	*p*-$MeOC_6H_4$ (**4g**)	24	5:1	70 (**5n**)	47:1	99
15	Ph (**3f**)	*p*-$NO_2C_6H_4$ (**4h**)	40	4:1	68 (**5o**)	36:1	> 99
16	Ph (**3f**)	*p*-MeC_6H_4 (**4b**)	23	5:1	77 (**5p**)	44:1	> 99
17	*p*-$MeOC_6H_4$ (**3e**)	*p*-$MeOC_6H_4$ (**4g**)	29	6:1	60 (**5q**)	24:1	> 99
18	*p*-$MeOC_6H_4$ (**3e**)	*p*-$NO_2C_6H_4$ (**4h**)	29	5:1	65 (**5r**)	34:1	> 99
19	*p*-BrC_6H_4 (**3a**)	*p*-BrC_6H_4 (**4d**)	19	5:1	70 (**5s**)	50:1	> 99
20	Ph (**3f**)	*n*-C_4H_9 (**4i**)	24	5:1	62 (**5t**)	> 99:1	99

[a]Reaction conditions: **3** (1.0 equiv), **4** (1.0 equiv), **2a** (10 mol %), PNBA (10 mol %), $CHCl_3$ (0.5 mL). [b]Isolated yield after column chromatography on silica gel. [c]Determined by ^{19}F NMR. [d]Determined by chiral HPLC analysis.

SCHEME 2. Possible Mechanism for the Robinson Annulation





A: **3a**; **B**: **6a**; **C**: **I'**; **D**: unassignable peaks; **E**: **5a**; **F**: *cis*-**5a**

FIGURE 2. Monitoring the reaction of **3a** with **4a** by ^{19}F NMR

reaction performed slow and product **5v** was gained in 70% yield, 9:1 dr, and 99% ee (Scheme 1).

In accord with the above experimental results and previous related studies, a probable mechanism for the current transformation was proposed (Scheme 2). First, the Michael reaction between **3** and **4** provided intermediates **I** (trans) and **II** (cis) as a mixture, which then underwent intramolecular aldol reactions to form **I′** and **6**, respectively. The intermediate **I′** underwent the dehydration step quickly to deliver the desired product **5**. However, the dehydration of **6** was so sluggish that it could be detected after the reaction time, which may be attributed to the stabilization of this compound structure resulting from the intramolecular hydrogen bond interaction between the hydroxyl group and the ester carbonyl group as revealed by the X-ray structure of **6a**.

In an effort to gain an insight into the mechanism of the reaction, the reaction between **3a** and **4a** was monitored by ^{19}F NMR (Figure 2). As expected, the dehydration of the intermediate **I′** was almost complete after the reaction time indicated in Table 3, entry 1 (20 h), while the dehydration of **6a** was very slow. In addition, no signals assignable to the assumed diastereoisomers of the intermediate **I′** and **6a** was observed, which might imply that the intramolecular aldol reaction also proceeded in a highly diastereoselective way. The ^{19}F NMR also showed that the diastereomeric ratio of **5a** was dependent on the dehydration rates of **6a**: when the reaction time was prolonged to 96 h, the ratio of **5a** decreased as the signal of **6a** almost disappeared.

Conclusion

In summary, we have developed an asymmetric Robinson annulation system to synthesize multiply substituted fluorinated chiral cyclohexenones with two contiguous stereogenic centers, one of which is a fluorinated quaternary chiral center. With use of readily available primary−secondary diamines as the catalysts, the desired products were obtained with excellent enantioselectivities and diastereoselectivities in moderate to good yields.

Experimental Section

General Procedure for the Preparation of α-Fluoro-*β*-keto Esters: (*E*)-*tert*-Butyl 5-(4-Bromophenyl)-2-fluoro-3-oxopent-4-enoate, 3a. To a solution of **7a** (972 mg, 3.0 mmol) in acetonitrile (4 mL) was added Selectfluor (1.6 g, 4.5 mmol) at room temperature and the mixture was stirred for 10 h. Upon completion of the reaction (monitored by TLC), the solvent was removed in vacuum, the residue was mixed with 20 mL of ethyl ether, and the mixture was then filtered through a pad of Celite. The filtrate was then concentrated under vacuum to provide a white solid. After recrystallization from petroleum ether and ethyl acetate at −10 °C, **3a** (875 mg, 85% yield) was obtained as white solid: mp 67−68 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, J = 15.9 Hz, 1H), 7.51 (AB, J = 28.1 Hz, 4H), 7.07

(dd, J = 2.2, 15.9 Hz, 1H), 5.31 (d, J = 49.2 Hz, 1H), 1.51 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −194.13 (d, J = 49.5 Hz, 1F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 189.3 (d, J = 21.8 Hz), 163.3 (d, J = 24.1 Hz), 144.8 (d, J = 3.2 Hz), 132.8, 132.3, 130.1, 125.8, 120.0, 91.3 (d, J = 197.6 Hz), 84.5, 27.9; IR (KBr) ν 1758, 1703, 1611 cm^{-1}; EI−MS (m/z) 342 (M^+, 3.2%), 57 (100), 209 (75), 211 (73), 102 (54), 41 (20), 133 (13), 75 (12), 286 (12); HRMS (EI) m/z calcd for $C_{15}H_{16}BrFO_3$ 342.0267, found 342.0266 $[M]^+$.

General Procedure for the Enantioselective Robinson Annulation: (1*S*,6*S*,*E*)-*tert*-Butyl 2-(4-Bromostyryl)-1-fluoro-4-oxo-6-phenylcyclohex-2-enecarboxylate, 5a. To a solution of **3a** (34 mg, 0.1 mmol) and **4a** (15 mg, 0.1 mmol) in 0.5 mL of chloroform were added **2a** (2 mg, 0.01 mmol, 10 mol %) and 4-nitrobenzoic acid (2 mg, 0.01 mmol, 10 mol %). The mixture was stirred at room temperature and monitored by TLC. After completion (20 h), the mixture was concentrated by rotary evaporation and the residue was purified by flash chromatography (ethyl acetate/petroleum ether: 1/10) to provide pure **5a** (38 mg, 80% yield) as a white solid: mp 101−102 °C; $[\alpha]^{25}_D$ −205.8 (c 0.400 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.40 (AB, J = 41.9 Hz, 4H), 7.39−7.33 (m, 5H), 7.26 (d, J = 16.5 Hz, 1H), 6.76 (d, J = 16.5 Hz, 1H), 6.35 (s, 1H), 3.96−3.84 (m, 1H), 3.54−3.43 (m, 1H), 2.80−2.72 (m, 1H), 1.29 (s, 9H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −150.78 (d, J = 15.9 Hz, 1F); ^{13}C NMR (75 MHz, $CDCl_3$) δ 197.4 (d, J = 2.1 Hz), 166.0 (d, J = 14.5 Hz), 151.8 (d, J = 21.1 Hz), 137.2 (d, J = 6.1 Hz), 135.4 (d, J = 0.8 Hz), 134.8 (d, J = 0.9 Hz), 132.1, 128.8 (d, J = 1.1 Hz), 128.7, 128.5 (d, J = 4.4 Hz), 128.4, 128.2, 123.9 (d, J = 1.8 Hz), 123.6, 94.4 (d, J = 193.5 Hz), 84.4, 47.8 (d, J = 21.9 Hz), 39.2 (d, J = 8.8 Hz), 27.7; IR (KBr) ν 1721, 1676, 1664, 1596, 1584 cm^{-1}; ESI-MS (m/z) 493 (M + 23), 471 (M + 1); HRMS (EI) m/z calcd for $C_{25}H_{24}Br(81)FO_3$ 472.0872, found 472.0869 $[M]^+$. HPLC separation conditions: Chiralcel AD, 20 °C, 254 nm, 9:1 hexane: *i*-PrOH, 0.8 mL/min; t_R = 19.2 min (minor enantiomer), 25.4 min (major enantiomer).

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Supporting Information Available: Experimental procedures, ^{1}H and ^{13}C NMR and HRMS data for substrates **3** and product **5** and **6a**, and X-ray crystal data in CIF format for **5a** and **6a**. This material is available free of charge via the Internet at http://pubs.acs.org.