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Diastereoselective Silver-Catalyzed 1,3-Dipolar Cycloaddition of Azomethine Ylides with Fluorinated Imine

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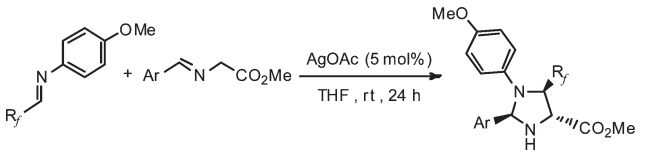

We described hereby an instance of diastereoselective silver-catalyzed 1,3-dipolar cycloaddition of azomethine ylides with imine compounds. This new method provided synthetically useful, highly substituted tetrahydroimidazole derivatives with efficiency and high diastereoselectivity. We can conveniently obtain fluorinated dihydroimidazole, imidazole, and diamino esters through simple modification.

The performance of organofluorine compounds in all aspects of the chemical industry such as materials, pharmaceuticals, agrochemicals, and fine chemicals is phenomenal. Organofluorine compounds are rare in natural products, but 20−25% of drugs in the pharmaceutical pipeline contain at least one fluorine atom.[1] As the incorporation of fluorine and/or fluorine-containing groups into an organic molecule often drastically alters the chemical, physical, and biological properties of the parent compound, it is only logical to conclude that the above modification necessitates the invention of novel reagents and materials endowed with fluorine imparting properties. As a matter of fact, extensive studies have been carried out in seeking new synthetic fluorination methodologies during the last 30 years.[2]

The catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides to electron-deficient alkenes has become one of the most convenient and diversity-oriented syntheses for the construction of highly substituted pyrrolidines with up to four stereogenic centers.[3] Although various methods have been developed for this transformation, most of the electron-deficient alkenes applied in the 1,3-dipolar cycloadditions of azomethine ylides are limited to maleates, fumarates, maleimides, acrylates, nitroalkenes, and vinyl phenyl sulfones in the synthesis of multisubstituted pyrrolidines. On the contrary, Mannich reaction of azomethine ylides with imine was documented,[4] while 1,3-dipolar cycloaddition of azomethine ylides to imine is rarely reported.[5]

Herein, we wish to report the synthesis of fluorinated tetrahydroimidazole by 1,3-dipolar cycloaddition of azomethine ylides with fluorinated imine catalyzed by silver(I) acetate. To begin our study, we selected azomethine ylides and *N*-aryl bromodifluoroethylimine, which was obtained by condensation of bromodifluoroacetaldehyde ethyl hemiacetal with arylamine, as the model reaction to optimize the reaction conditions. We found that AgOAc, AgOTf, Ag_2SO_4, $AgNO_3$, and Ag_2CO_3 catalyzed the 1,3-dipolar cycloaddition reaction (12 h, rt) affording the desired fluorinated tetrahydroimidazole in 70%, 60%, 64%, 20%, and 72% yield, respectively (Table 1, entries 1−5), in toluene. Then using

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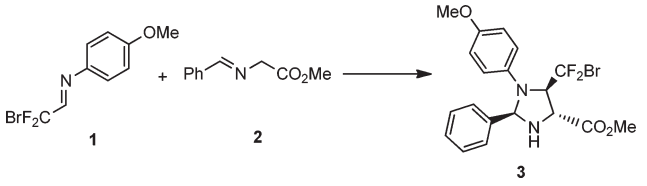
TABLE 1. Optimization of the Reaction Conditions[a]



entry	catalyst (5 mol %)	solvent	yield (%)[b]
1	AgOAc	toluene	70
2	AgOTf	toluene	60
3	Ag_2SO_4	toluene	64
4	$AgNO_3$	toluene	20
5	Ag_2CO_3	toluene	72
6	AgOAc	THF	94
7	Ag_2CO_3	THF	87
8	AgOAc	CH_2Cl_2	42
9	Ag_2CO_3	CH_2Cl_2	63

[a]The reactions all proceeded away from light. [b]Yields are of isolated products after column chromatography.

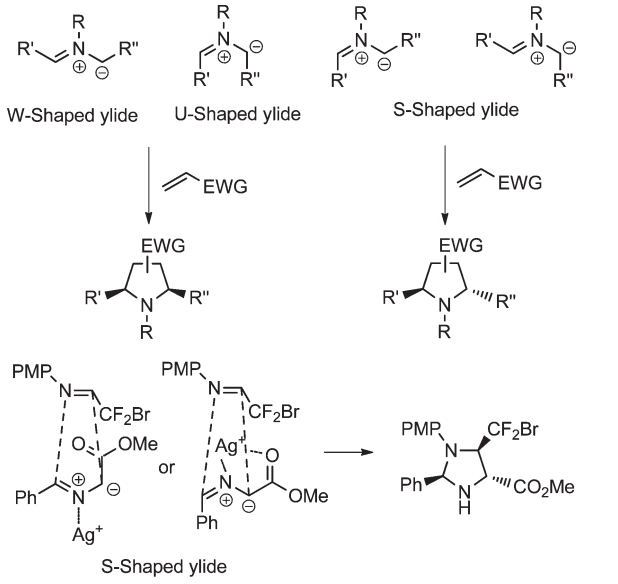


FIGURE 1. The stereochemistry of the cycloaddition.

AgOAc and Ag_2CO_3 as catalyst, various solvents were screened, and it was found that THF was the most desirable solvent for this reaction. Eventually, we determined the optimization condition was AgOAc (5 mol %) in THF at rt.

The stereochemistry of the cycloaddition of azomethine ylides is dependent on the geometries of the dipoles as well as dipolarophiles. The 2,5-stereochemistry of the resultant pyrrolidine ring is determined by the geometry of the ylide. The 2,5-cis-disubstituted pyrrolidine formed by intermediary W- and U-shaped dipole, while 2,5-trans-disubstituted product emerges from two possible S-shaped ylides (Figure 1).[6] However, the most catalytic 1,3-dipolar cycloaddition of azomethine ylides to electron-deficient alkenes formed 2,5-cis-disubstituted pyrrolidine, while 2,5-trans-disubstituted product is rare. From the X-ray of the product **3a**,[7] we found

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(7) See the Supporting Information.

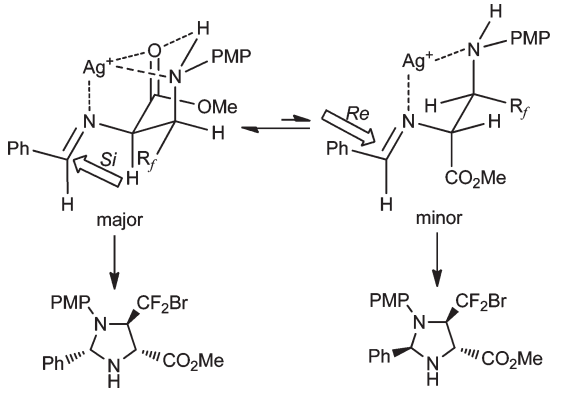
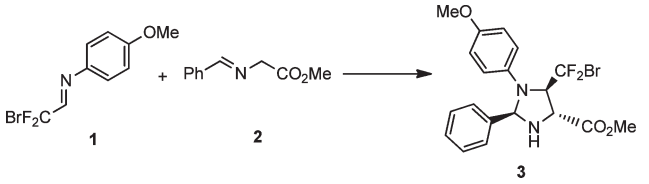


FIGURE 2. The conformational analysis of the stepwise mechanism.

TABLE 2. AgOAc-Catalyzed Synthesis of Fluorinated Tetrahydroimidazole[a]



entry	R_f	Ar	dr[b]	product/yield (%)[c]
1	CF_2Br	Ph	>20:1	**3a**/94
2	CF_3	Ph	>20:1	**3b**/91
3	CF_3	*p*-$CH_3C_6H_4$	>20:1	**3c**/87
4	CF_3	*p*-$CH_3OC_6H_4$	>20:1	**3d**/84
5	CF_3	3,5-$CH_3OC_6H_3$	>20:1	**3e**/42
6	CF_3	*o*-$CH_3OC_6H_4$	11:2:1:1	**3f**/65
7	CF_3	*p*-PhC_6H_4	>20:1	**3g**/96
8	CF_3	*p*-BrC_6H_4	>20:1	**3h**/94
9	CF_3	*p*-ClC_6H_4	>20:1	**3i**/96
10	CF_3	*p*-FC_6H_4	>20:1	**3j**/97
11	CF_3	*o*-ClC_6H_4	14:1:1:1	**3k**/95
12	CF_3	*o*-FC_6H_4	12:1:1:1	**3l**/96
13	CF_3	*m*-BrC_6H_4	>20:1	**3m**/94
14	CF_3	2-furyl	11:1:1:1	**3n**/80
15	CF_3	2-thienyl	14:1:1:1	**3o**/92
16	CF_3	2-naphthyl	>20:1	**3p**/93

[a]The reactions all proceeded away from light. [b]Determined by ^{19}F NMR signals in the crude precipitate. [c]Yields are of isolated products after column chromatography.

out that the 2 position phenyl group is trans to the 5 position ester group. There are two possible mechanisms for this reaction, concerted cycloaddition mechanism and stepwise mechanism, but we have not found a suitable experiment to distinguish these possibilities. We invoke an unusual S-shaped azomethine ylide to explain the unusual trans arrangement of the ylide aryl and ester substituents. We supposed this reaction is stepwise, but conformational analysis (Figure 2) indicated that the arrangement of the major product aryl and ester substituents should be cis, which is inconsistent with our experiment. In view of this indirect inference, we incline toward the concerted cycloaddition mechanism. However, the possibility of the stepwise mechanism cannot be excluded without direct experiment evidence.

Having established suitable reaction conditions, we explored the scope and generality of this methodology (Table 2). As shown in Table 2, most substrates examined provided excellent yields and high stereoselectivity under the standard reaction

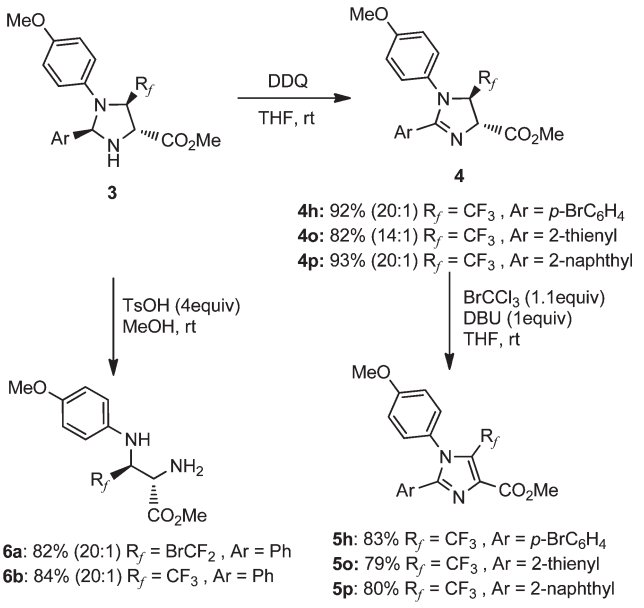


FIGURE 3. The derivatization of product **3**.

condition. In an effort to understand the limitation of the reaction, the effect of various substituents on the arene ring of the azomethine ylides was investigated. Generally, electron-donating substitutions on the benzene ring of the azomethine ylides, such as methoxy (Table 2, entries 4, 5, and 6) and methyl (Table 2, entry 3), would reduce the yield, while electron-withdrawing substitutions like the phenyl group (Table 2, entry 7), bromo (Table 2, entries 8 and 13), chloro (Table 2, entries 9 and 11), and fluoro (Table 2, entries 10 and 12) enhance the yield. Moreover, stereoselectivity is high except when the ortho position of the arene ring was substituted (Table 2, entries 6, 11, and 12) or the ortho position of the arene was a heteroatom (Table 2, entries 14 and 15). It is worthwhile to note that when the arene ring of the azomethine ylides is 2-furyl (Table 2, entry 14), 2-thienyl (Table 2, entry 15), or 2-naphthyl (Table 2, entry 16), they could also afford **3** in excellent yield.

The highly substituted tetrahydroimidazole products can be converted into a variety of other useful compounds and intermediates without erosion in dr (Figure 3). 1,2-Dihydroimidazole can be obtained in 90% yield with DDQ oxidation. Imidazole can be generated via treatment of 1,2-dihydroimidazole with $BrCCl_3$ and DBU.[8] Furthermore, acidic hydrolysis of tetrahydroimidazole products **3** with TsOH in methanol affords diamino esters **6** without erosion in dr.

In conclusion, we described here an instance of diastereoselective silver-catalyzed 1,3-dipolar cycloaddition of azomethine ylides with imine compounds. This new method provided synthetically useful, highly substituted tetrahydroimidazole derivatives with efficiency and high diastereoselectivity. We can conveniently obtain fluorinated dihydroimidazole, imidazole, and diamino esters through simple modification. Additional studies of asymmetric silver-catalyzed reactions of azomethine ylides with imine compounds are underway.

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Experimental Section

General Procedure for 3a−p. A Schlenk tube was charged with AgOAc (83 mg, 0.5 mmol), evacuated, and backfilled with nitrogen. THF (10 mL), azomethine ylide (1.772 g, 10 mmol), and 4-methoxy-*N*-(2-bromo-2,2-difluoroethylidene)aniline (2.641 g, 10 mmol) were successively added. Then the reaction mixture was stirred at rt and away from light for 24 h. The mixture was partitioned between ethyl acetate and water, then the organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica and then recrystallized from methanol to provide **3a**. White solid, mp 99−100 °C; ^{1}HNMR (300 MHz, $CDCl_3$) δ 7.58−7.56 (m, 2H), 7.38−7.36 (m, 3H), 6.74 (s, 4H), 5.43 (s, 1H), 4.79 (dd, J_1 = 16.3 Hz, J_2 = 4.2 Hz, 1H), 4.41 (s, 1H), 3.81 (s, 3H), 3.71 (s, 3H), 2.77 (br, 1H); ^{19}F NMR (282 MHz, CDCl3) δ −52.1 (dd, J_1 = 160.5 Hz, J_2 = 4.2 Hz, 1F), −57.8 (dd, J_1 = 160.5 Hz, J_2 = 16.3 Hz, 1F); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 154.4, 139.9, 139.0, 129.0, 127.0, 124.6 (t, J = 312.3 Hz), 118.4, 114.6, 83.3, 72.9 (t, J = 22.3 Hz), 62.1, 55.5, 53.0; IR (KBr) 3261, 2953, 2840, 1755, 1739, 1512, 1458, 1373, 1337, 1289, 1250, 1116, 1044, 936, 824, 698, 588; MS (EI) m/z (rel intensity) 440 (24) [M^+], 185 (67), 177 (100), 146 (37), 117 (88). Anal. Calcd for $C_{19}H_{19}BrF_2N_2O_3$: C, 51.72; H, 4.34; N, 6.35. Found: C, 51.62; H, 4.27; N, 6.25

General Procedure for 4h, 4o, and 4p. A Schlenk tube was charged with **3h** (459 mg, 1 mmol) and THF (3 mL). Then DDQ (227 mg, 1 mmol) was added. The reaction mixture was stirred at rt for 10 min. The mixture was partitioned between ethyl acetate and water, then the organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica and then recrystallized from methanol to provide **4h**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.50−7.36 (m, 4H), 7.10−6.77 (m, 4H), 4.93 (d, J = 5.3 Hz, 1H), 4.60 (qd, J_1 = 7.8 Hz, J_2 = 5.3 Hz, 1H), 3.88 (s, 3H), 3.75 (s, 3H); ^{19}F NMR (282 MHz, CDCl3) δ −76.7 (d, J = 7.8 Hz, 3F); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 166.0, 158.8, 135.4, 131.4, 131.1, 128.9, 128.0, 125.5, 124.8 (q, J = 278.7 Hz), 114.8, 69.0 (q, J = 30.9 Hz), 69.0, 55.4, 53.1; IR (KBr) 2955, 2839, 1745, 1620, 1511, 1401, 1337, 1237, 1167, 1133, 1037, 926, 835, 740; MS (EI) m/z (rel intensity) 456 (9) [M^+], 396 (100), 216 (80), 147 (53); HRMS calcd for $C_{19}H_{16}BrF_3N_2O_3$ 456.0294, found 456.0296.

General Procedure for 5h, 5o, and 5p. A Schlenk tube was charged with **3h** (229 mg, 0.5 mmol) and THF (4 mL). $BrCCl_3$ (109 mg, 0.55 mmol) and DBU (76 mg, 0.5 mmol) were successively added. Then the reaction mixture was stirred at rt for 4 h. The mixture was partitioned between ethyl acetate and water, then the organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by column chromatography on silica and then recrystallized from methanol to provide **5h**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39−7.37 (m, 2H), 7.26−7.19 (m, 4H), 6.97−6.94 (m, 2H), 3.98 (s, 3H), 3.84 (s, 3H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −55.4 (s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0, 160.7, 148.9, 134.1, 131.5, 130.6, 128.9, 127.7, 127.3, 125.6 (q, J = 39.1 Hz), 124.3, 119.6 (q, J = 270.5 Hz), 114.8, 55.5, 52.6; IR (KBr) 2954, 2841, 1736, 1608, 1568, 1512, 1466, 1421, 1350, 1300, 1225, 1132, 1036, 911, 843, 738, 645; MS (EI) m/z (rel intensity) 454 (100) [M^+], 369 (54), 288 (29), 183 (23), 77 (29); HRMS calcd for $C_{19}H_{14}BrF_3N_2O_3$ 454.0140, found 454.0139

General Procedure for 6a and 6b. A Schlenk tube was charged with **3a** (441 mg, 1 mmol) and methanol (5 mL). Next $TsOH\cdot H_2O$ (760 mg, 4 mmol) was added. Then the reaction mixture was stirred at rt over light. We neutralized the mixture by Na_2CO_3. Then the mixture was partitioned between ethyl acetate and water, then the organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was

purified by column chromatography on silica to provide **6a**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.78−6.67 (m, 4H), 4.72 (d, J = 10.1 Hz, 1H), 4.55−4.44 (m, 1H), 4.32 (s, 1H), 3.74 (s, 3H), 3.58 (s, 3H), 1.74 (br, 2H); ^{19}F NMR (282 MHz, $CDCl_3$) δ −51.5 to −53.3(m, 2F); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.6, 152.9, 139.8, 124.3 (t, J = 313.7 Hz), 115.7, 114.5, 65.0 (q, J = 21.3 Hz), 55.4, 53.1, 52.5; HRMS calcd for $C_{12}H_{16}BrF_2N_2O_3^+$ 353.0307, found 353.0316

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Supporting Information Available: Experimental details, characterization data, and the ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.