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An Enyne Cycloisomerization Approach to the Triple Reuptake Inhibitor GSK1360707F

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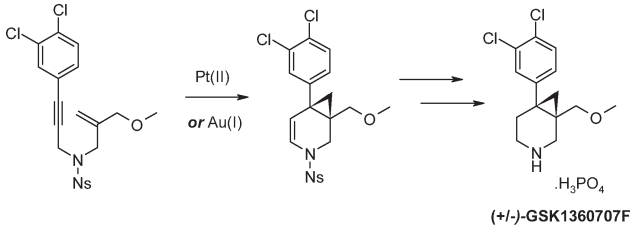

(+/-)-GSK1360707F

The triple reuptake inhibitor GSK1360707F was synthesized via an efficient and scalable route that features an enyne cycloisomerization reaction catalyzed by either Pt(II) or Au(I). Key aspects of this work such as the choice of the nitrogen protecting group and initial enantioselectivity studies are discussed.

GSK1360707F is a potent serotonin, noradrenaline, dopamine reuptake (triple reuptake) inhibitor under development at GlaxoSmithKline[1] for the treatment of major depressive disorder (MDD).[2] We recently disclosed our first generation route for the multikilogram scale synthesis of (−)-GSK-1360707F,[3] which took advantage of a novel double alkylation with a dihalomethane to construct the cyclopropane ring. While this route was utilized for the supply of 15 kg of drug substance, it had some potential long-term drawbacks, namely, the formation of polychlorinated biphenyl (PCB) byproducts in the Suzuki coupling, high cost of goods (COGs), and low atom efficiency. To address these issues, we have been exploring alternative approaches to the synthesis of GSK1360707F.

Transition metal-catalyzed enyne cycloisomerizations have emerged as powerful tools for the synthesis of carbocyclic and heterocyclic compounds.[4,5] In particular, we were intrigued by the possibility of isomerizing appropriately functionalized 1,6-enynes to arrive at the 3-azabicyclo[4.1.0]heptane[6] skeleton of GSK1360707F. Several recent examples of this type of transformation have appeared in the literature, typically utilizing Pt(II) or Au(I) catalysts. We were also encouraged by the likelihood of conducting these reactions in enantioselective fashion.[7]

We initially focused our attention on identifying a suitable nitrogen protecting group that would enable the synthesis and cycloisomerization of the desired enyne, and allow for ultimate conversion to GSK1360707F. While the vast majority of similar cyclization substrates in the literature employ *p*-toluenesulfonyl (*p*-Ts) nitrogen protecting groups, we reasoned (and later confirmed) that the late-stage removal of an *N*-tosylate would be difficult to accomplish chemoselectively. On the other hand, we surmised that a 2- or 4-nitrobenzenesulfonyl protecting group would meet our criteria.

To that end, reaction of propargyl amine with 2-nitrobenzenesulfonyl chloride gave propargyl sulfonamide **1** (Scheme 1). Sonogashira coupling[8] with 1,2-dichloro-4-iodobenzene generated **2** with no detected PCBs (by HPLC analysis). Allylation with 2-methoxymethylallyl chloride **3**[9] furnished the requisite cycloisomerization precursor **4**. Gratifyingly, heating **4** in toluene at 80 °C in the presence of catalytic $PtCl_2$ afforded the desired product **5** in high yield. Racemic GSK1360707F was then obtained after enamine reduction with TFA-triethylsilane,[10,11] protecting group removal under

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(11) Efficient removal of the platinum catalyst from the previous step was required to suppress competitive reduction of the nitro group.

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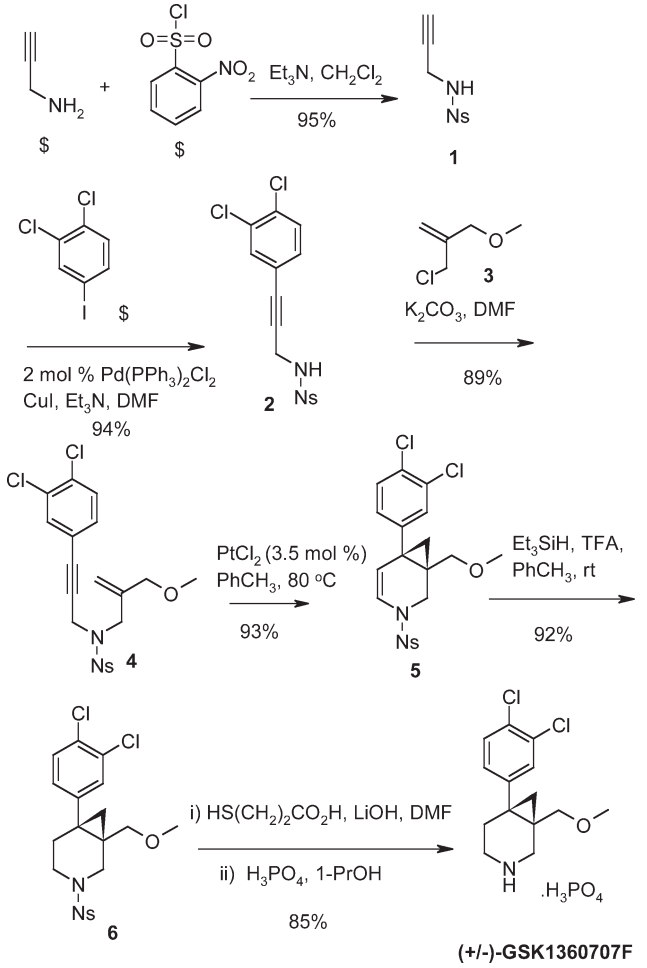
SCHEME 1. Synthesis of GSK1360707F[a]



[a]Ns = 2-nitrobenzenesulfonyl.

modified Fukuyama conditions,[12] and phosphate salt formation. The overall yield for this route was 58%.

Parallel reaction screening techniques were employed to investigate the enantioselective cycloisomerization of **4** with Au(I) catalysis.[13] Ligand, solvent, silver salt, and Ag/Au stoichiometry were assessed using a D-optimal experimental design. Statistical main effects indicated that (*R*)-tol-BINAP (**I**) was essential for good conversion and enantioselectivity. None of the remaining factors studied had significant impact upon the observed enantioselectivity. However, it was found that CH_2Cl_2 and $AgBF_4$ were beneficial to conversion overall. The highest ee observed was 59% with (*R*)-tol-BINAP as ligand (Table 1, entry 27).

In conclusion, we have demonstrated an efficient new route for the synthesis of GSK1360707F. This approach takes advantage of a highly selective enyne cycloisomerization reaction that elegantly assembles the 3-azabicyclo[4.1.0]heptane framework of the molecule, and offers the possibility of obtaining the product in enantioselective fashion. Additionally, no PCBs were detected during the incorporation of the dichlorophenyl fragment.

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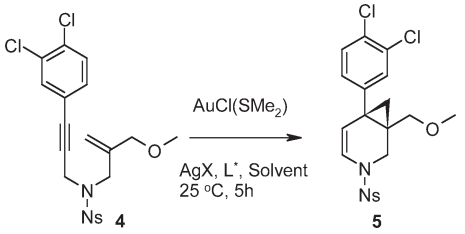
(13) Analogous enantioselectivity screens on a closely related substrate (4-nitrobenzenesulfonamide) with Pt(II) catalysts exhibited slow reaction rates at elevated temperatures.

TABLE 1. D-Optimal Screening for Enantioselective Cycloisomerization[a]



entry	ligand	AgX	solvent	Au:Ag molar ratio	% area (5)	ee[b]
1	A	$AgSbF_6$	CH_2Cl_2	1:1	100	0
2	H	$AgSbF_6$	CH_2Cl_2	1:2	63	5
3	C	$AgSbF_6$	CH_2Cl_2	1:1	17	21
4	B	$AgSbF_6$	CH_2Cl_2	1:2	99	−4
5	J	$AgSbF_6$	CH_2Cl_2	1:1	97	2
6	F	$AgSbF_6$	toluene	1:2	66	5
7	I	$AgSbF_6$	toluene	1:1	97	−51
8	E	$AgSbF_6$	toluene	1:1	18	0
9	G	$AgSbF_6$	toluene	1:2	0	
10	D	$AgSbF_6$	toluene	1:2	37	8
11	F	AgOTf	CH_2Cl_2	1:1	21	14
12	I	AgOTf	CH_2Cl_2	1:2	100	−48
13	D	AgOTf	CH_2Cl_2	1:2	92	19
14	B	AgOTf	CH_2Cl_2	1:2	37	−7
15	J	AgOTf	CH_2Cl_2	1:1	16	−7
16	A	AgOTf	toluene	1:2	43	33
17	H	AgOTf	toluene	1:1	36	−12
18	E	AgOTf	toluene	1:1	0	
19	C	AgOTf	toluene	1:1	0	
20	G	AgOTf	toluene	1:2	14	−1
21	H	$AgBF_4$	CH_2Cl_2	1:2	100	−1
22	E	$AgBF_4$	CH_2Cl_2	1:2	100	−2
23	C	$AgBF_4$	CH_2Cl_2	1:2	100	−6
24	G	$AgBF_4$	CH_2Cl_2	1:1	100	−3
25	D	$AgBF_4$	CH_2Cl_2	1:1	100	0
26	F	$AgBF_4$	toluene	1:2	80	13
27	I	$AgBF_4$	toluene	1:1	100	−59
28	A	$AgBF_4$	toluene	1:1	86	33
29	B	$AgBF_4$	toluene	1:1	13	−5
30	J	$AgBF_4$	toluene	1:2	40	−8
31	J	$AgBF_4$	toluene	2:3	37	−8
32	J	$AgBF_4$	toluene	2:3	36	−6

[a]Ligands: **A** (*R*)-Xylyl-P-Phos, **B** (*R*)-(*S*)-NMe_2-P(3,5-$CF_3Ph)_2$-Mandyphos, **C** (*R*)-(*S*)-NMe_2-Pcy_2-Mandyphos, **D** catASium MNXyl(R), **E** (*R*)-(*R*)-$Ph_2PPhFCHCH_3PPh_2$-Walphos, **F** (*R*)-MONOPHOS, **G** (*R*, *R*)-BDPP, **H** (*R*)-(*S*)-PPF-$PtBu_2$, **I** (*R*)-Tol-BINAP, **J** (*S*)-(+)-(3,5-dioxa-4-phosphacyclohepta[2,1-*a*;3,4-*a*′]dinapthalen-4-yl)[(1*R*)-1-phenylethyl]amine. [b]Plus ee indicates the fast eluting peak is in excess. For the purpose of this initial screen, the absolute configuration of **5** that relates to the respective peak by chiral HPLC was not determined. All the evaluated ligands may be procured in both antipodes allowing access to either enantiomer of **5**.

Experimental Section

2-Nitro-*N*-2-propyn-1-ylbenzenesulfonamide (1). In a 1 L jacketed laboratory reactor were charged triethylamine (91.9 g, 0.908 mol, 1 equiv), dichloromethane (994 g, 750 mL, 11.7 mol), and propargylamine (50 g, 0.908 mol, 1 equiv). The solution was cooled to about 0 °C and then treated with 2-nitrobenzenesulfonyl chloride (191.1 g, 0.862 mol, 0.95 equiv) portionwise over 15 min. The reaction was warmed to about 25 °C over 15 min, stirred for 3 h, and quenched with 1 M HCl (95 mL). The layers were separated. The organic layer was washed with water (200 mL) and saturated

aqueous $NaHCO_3$ (100 mL) and then concentrated under vacuum. The solids obtained were dried under vacuum at 40 °C for 12 h to give 201 g of **1** (97% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22−8.18 (m, 1H), 7.93−7.90 (m, 1H), 7.76 (J = Hz, 2H), 5.70 (s, 1H), 4.02 (dd, J = 6.1, 2.4 Hz, 2H), 1.97 (t, J = 2.5 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 134.2, 134.1, 133.2, 131.8, 125.8, 73.5, 33.6; IR (ATR) 3319 (w), 3296 (m), 1535 (s), 1415 (m), 1366 (m), 1330 (s), 1156 (s), 1127 (s), 1070 (s), 929 (w), 855 (w), 783 (s), 742 (s); HRMS m/z 241.0276 [(M+); calcd for $C_9H_9N_2O_4S$ 241.0278]; mp 90−92 °C.

***N*-[3-(3,4-Dichlorophenyl)-2-propyn-1-yl]-2-nitrobenzenesulfonamide (2).** In a 1 L jacketed laboratory reactor were charged 2-nitro-*N*-2-propyn-1-ylbenzenesulfonamide **1** (60 g, 0.250 mol, 1 equiv), 3,4-dichloroiodobenzene (62.02 g, 0.227 mol, 0.91 equiv), and DMF (397 g, 420 mL, 5.43 mol). After all the solids were dissolved, triethylamine (27.8 g, 0.275 mol, 1.1 equiv), $PdCl_2(PPh_3)_2$ (3.51 g, 0.005 mol, 0.02 equiv), and copper(I) iodide (1.9 g, 0.01 mol, 0.04 equiv) were added. Once the reaction was deemed complete, it was treated with MTBE (600 mL), 1 N HCl (100 mL), and water (200 mL). After separation of the layers, the aqueous layer was back extracted with MTBE (200 mL). The combined organic layers were washed with water (200 mL) and 1:1 water: saturated aqueous $NaHCO_3$ (300 mL). The organic layer was then partially concentrated to about 400 mL and the resulting slurry stirred at room temperature for about 72 h. The solid was filtered and dried at 40 °C under vacuum for 12 h to give 71 g of **2** (81% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24−8.22 (m, 1H), 7.89−7.87 (m, 1H), 7.73−7.67 (m, 2H), 7.29 (d, J = 8.2 Hz, 1H), 6.99 (d, J = 2 Hz, 1H), 6.88 (dd, J = 8.4, 2 Hz, 1H), 5.78 (s, 1H), 4.24 (d, J = 2.2 Hz, 2H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 134.6, 134.0, 133.5, 133.3, 133.2, 132.7, 131.8, 130.7, 130.6, 125.7, 121.7, 111.5, 85.1, 83.2, 34.4; IR (ATR) 3310 (w), 1534 (s), 1432 (m), 1337 (s), 1165 (s), 1125 (m), 1067 (s), 886 (w), 819 (w), 782 (s), 738 (s), 652 (s); HRMS m/z 384.9812 [(M+); calcd for $C_{15}H_{11}Cl_2N_2O_4S$ 384.9812]; mp 122−124 °C.

***N*-[3-(3,4-Dichlorophenyl)-2-propyn-1-yl]-*N*-{2-[(methyloxy)methyl]propen-1-yl}-2-nitrobenzenesulfonamide (4).** In a 2 L round-bottomed flask were charged *N*-[3-(3,4-dichlorophenyl)-2-propyn-1-yl]-2-nitrobenzenesulfonamide **2** (50 g, 0.130 mol, 1 equiv), DMF (378 g, 400 mL, 5.17 mol), and K_2CO_3 (19.7 g, 0.143 mol, 1.1 equiv). The reaction was stirred for 20 min followed by the addition of 3-chloro-2-[(methyloxy)methyl]-1-propene (**3**) (17.22 g, 0.143 mol, 1.1 equiv). After 2 h, the reaction was quenched with water (400 mL) and toluene (400 mL) and the layers were separated. The organic layer was washed successively with water (200 mL) and 1:1 water:saturated $NaHCO_3$ (200 mL). After concentration under vacuum, the material was purified by chromatography (gradient of 10 to 60% ethyl acetate/heptane) to give 49 g of oil **4** (80% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10−8.07 (m, 1H), 7.70−7.61 (m, 3H), 7.31 (d, J = 8.4 Hz, 1H), 7.20 (d, J = 2.0 Hz, 1H), 7.02 (dd, J = 8.2, 1.8 Hz, 1H), 5.27 (d, J = 23.5 Hz, 2H), 4.34 (s, 2H), 4.09 (s, 2H), 3.86 (s, 2H), 3.26 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 148.5, 139.6, 134.1, 133.5, 133.4, 132.9, 132.7, 131.9, 131.5, 130.9, 130.6, 124.4, 122.1, 117.3, 84.4, 83.6, 73.0, 58.5, 49.9, 36.9; IR (ATR) 2926 (w), 1541 (s), 1464 (m), 1357 (s), 1163 (s), 1125 (s), 1086 (s), 1032 (m), 906 (S), 851 (m), 820 (m), 774 (s), 740 (s), 683 (m); HRMS m/z 469.0383 [(M+); calcd for $C_{20}H_{19}Cl_2N_2O_5S$ 469.0387].

6-(3,4-Dichlorophenyl)-1-[(methyloxy)methyl]-3-[(2-nitrophenyl)sulfonyl]-3-azabicyclo[4.1.0]hept-4-ene (5). In a 250 mL round-bottomed flask were charged *N*-[3-(3,4-dichlorophenyl)-2-propyn-1-yl]-*N*-{2-[(methyloxy)methyl]propen-1-yl}-2-nitrobenzenesulfonamide **4** (10 g, 0.0213 mol, 1 equiv), toluene (43.3 g, 50 mL), and $PtCl_2$ (0.142 g, 0.5 mmol, 0.025 equiv). The reaction was heated to ~80 °C for 19.5 h. An additional charge of $PtCl_2$ (0.07 g, 0.26 mmol) was performed since the reaction did not reach completion. The reaction was stirred for another 2.5 h at which point it had reached completion. After cooling to room temperature, the reaction was filtered through Celite and concentrated. Purification by chromatography (ethyl acetate) through a plug of silica gel afforded 10 g of **5** as a yellow foam (100% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05−8.02 (m, 1H), 7.77−7.67 (m, 3H), 7.36−7.34 (m, 2H), 7.09 (dd, J = 8.4, 2.2 Hz, 1H), 6.44 (d, J = 8.0 Hz, 1H), 5.35 (d, J = 8 Hz, 1H), 4.10 (d, J = 12.3 Hz, 1H), 3.38 (d, J = 12.3 Hz, 1H), 3.08 (s, 3H), 3.07 (d, J = 8.4 Hz, 1H), 2.90 (d, J = 10.4 Hz, 1H), 1.36 (d, J = 5.5 Hz, 1H), 1.19 (d, J = 5.3 Hz, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 148.3, 140.9, 134.3, 132.4, 132.1, 131.7, 131.6, 131.2, 131.19, 130.4, 129.0, 124.6, 121.1, 116.8, 74.8, 59.0, 43.7, 36.8, 27.4, 22.4; IR (ATR) 2924 (w), 1541 (s), 1470 (m), 1397 (w), 1356 (s), 1287 (w), 1172 (s), 1128 (m), 1096 (s), 1030 (w), 978 (w), 956 (m), 851 (m), 756 (m), 742 (s), 681 (s); HRMS m/z 469.0382 [(M+); calcd for $C_{20}H_{19}Cl_2N_2O_5S$ 469.0387].

6-(3,4-Dichlorophenyl)-1-[(methyloxy)methyl]-3-[(2-nitrophenyl)sulfonyl]-3-azabicyclo[4.1.0]heptane (6). 6-(3,4-Dichlorophenyl)-1-[(methyloxy)methyl]-3-[(2-nitrophenyl)sulfonyl]-3-azabicyclo[4.1.0]-hept-4-ene **5** (8 g, 0.017 mol, 1 equiv) was dissolved in toluene (69 g, 80 mL). After addition of 5 wt % aqueous cysteine (40 mL), the mixture was heated to 60 °C for about 2 h and then cooled to room temperature. Toluene (40 mL), 1 N HCl (20 mL), and water (20 mL) were then added followed by phase separation. After the organic layer was washed with 1:1 water:saturated aqueous $NaHCO_3$ (100 mL), the aqueous layers were combined and extracted with toluene (100 mL). The combined organic layers were washed with water (100 mL), filtered, and then concentrated under vacuum to oil. The oil was dissolved in toluene (35 g, 40 mL) and then treated with triethylsilane (1.98 g, 2.72 mL, 1 equiv) and TFA (15.55 g, 10.1 mL, 8 equiv). After being stirred for 2 h, the reaction was quenched with 2 N NaOH (70 mL) and toluene (40 mL). After phase separation, the organic layer was washed with water (80 mL) and concentrated under vacuum. Purification by column chromatography (gradient of 30 to 40% ethyl acetate/heptane) gave 6.8 g of **6** as a yellow foam (84.8% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04−8.02 (m, H), 7.73−7.69 (m, H), 7.64−7.62 (m, H), 7.35 (s, H), 7.33 (d, J = 5.7 Hz, H), 7.10 (dd, J = 8.2, 2 Hz, H), 3.67 (t, J = 13.5 Hz, H), 3.37−3.21 (m, H), 3.10 (s, H), 2.99 (d, J = 10.0 Hz, H), 2.83 (d, J = 10.0 Hz, H), 2.15−1.99 (m, H), 1.07 (d, J = 5.7 Hz, H), 1.05 (d, J = 5.7 Hz, H); ^{13}C NMR (100.6 MHz, $CDCl_3$) δ 148.4, 144.1, 133.9, 132.4, 132.3, 131.9, 131.4, 131.3, 130.9, 130.6, 128.9, 124.3, 76.06, 58.9, 46.8, 43.0, 32.7, 28.7, 26.4, 19.1; IR (ATR) 2922 (m), 2853 (m), 1541 (s), 1467 (m), 1372 (s), 1343 (s), 1163 (s), 1128 (m), 1097 (s), 1059 (w), 1030 (w), 953 (m), 908 (w), 851 (m), 824 (w), 733 (s); HRMS m/z 471.0533 [(M+); calcd for $C_{20}H_{21}Cl_2N_2O_5S$ 471.0543].

(±)-GSK1360707F. In a 250 mL round-bottomed flask were charged 6-(3,4-dichlorophenyl)-1-[(methyloxy)methyl]-3-[(2-nitrophenyl)sulfonyl]-3-azabicyclo[4.1.0]heptane **6** (4 g, 0.0085 mol, 1 equiv), DMF (32.1 g, 34 mL), 3-mercaptopropionic acid (1.35 g, 1.11 mL, 0.0127 mol, 1.5 equiv), and LiOH (0.61 g, 0.0255 mol, 3 equiv). The reaction was stirred for 1 h and then quenched with MTBE (100 mL) and H_2O (50 mL). After phase separation, the organic layer was washed with 1 N NaOH (50 mL) and then H_2O (50 mL). Following concentration under vacuum, 1-propanol (17.7 g, 22 mL) was added. The solution was heated to about 80 °C and then treated with concentrated H_3PO_4 (0.53 mL, 0.0076 mol, 0.9 equiv). The slurry was then cooled to 25 °C over 5 h, and filtered. The wet solid was then dried at 60 °C under vacuum for 72 h to give 2.07 g of racemic GSK1360707F as a white solid (85% yield). The sample was identical by ^{1}H NMR to a sample of (−)-GSK1360707F, as reported previously.[3]

Enantioselective Isomerization of 4 to 5. D-Optimal Reaction Screen. To each of 32 individual 1.5 mL HPLC filter vials equipped with stir bars and assembled in a microtiter plate format were added $AuCl(SMe_2)$ (3.8 mg, 0.013 mmol, 0.1 equiv) and 25 mg of ultra-activated charcoal, using a solid dispensing robot. To each vial were added the appropriate ligand (0.1 equiv for monodentate or 0.05 equiv for bidentate phosphines) and silver salt, using the

solid dispensing robot followed by 750 μL of either toluene or CH_2Cl_2 as given in Table 1. The vials were sealed with parafilm and stirred at 25 °C for 1 h. The stir bars were now removed and a filter insert placed in each vial and depressed, transferring each filtrate to a fresh 1.5 mL HPLC vial equipped with a stir bar. To each vial was added a 0.5 M stock solution of **4** (250 μl, 0.13 mmol, 1 equiv) in either toluene or CH_2Cl_2 as given in Table 1. The vials were crimp sealed and stirred at 25 °C for 5 h. The conversion and enantioselectivity after this time were determined by HPLC and are reported in Table 1.

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Supporting Information Available: Experimental data, copies of spectra, and chromatograms for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.