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Article

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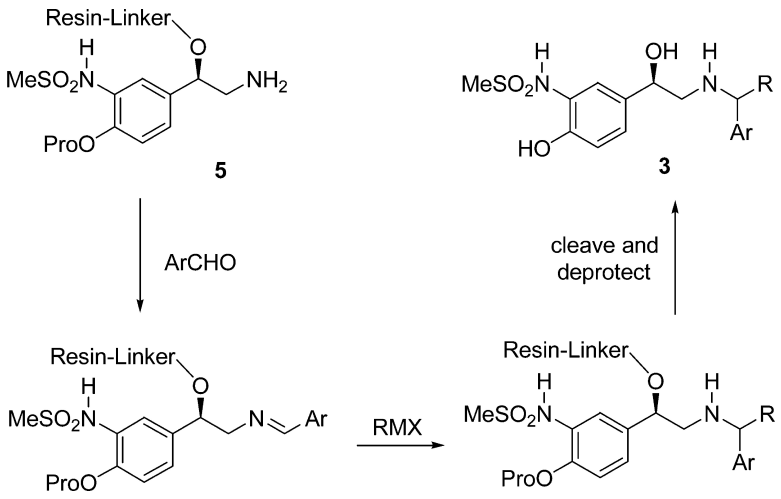

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Addition of Benzylic and Allylic Organozinc and Grignard Reagents to Resin-Bound Imines To Provide α-Branched Secondary Amines Bearing a Wide Variety of Functional Groups. Utility in the Synthesis of *β*-3 Adrenergic Receptor Agonists

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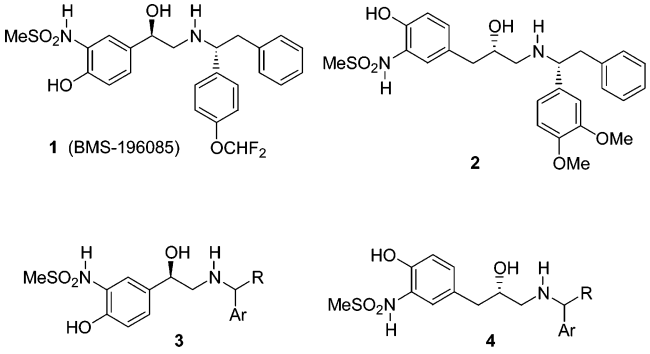
Benzylic and allylic organozinc and Grignard reagents have been added to resin-bound imines to provide α-branched secondary amines. Many functional groups, including electrophilic groups, were compatible with this methodology. Three modules—a resin-bound primary amine, an aromatic aldehyde, and the organometallic—were independently varied to produce a combinatorial library of α-branched secondary amines designed as *β*-3 adrenergic receptor agonists.

Introduction

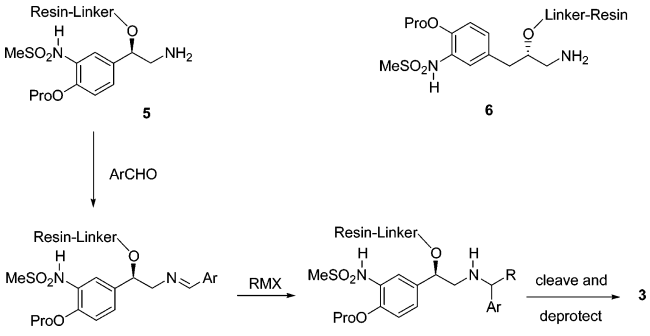
We have recently reported that 1,2-diarylethylamine-containing molecules **1** (BMS-196085) and **2** (Chart 1) are potent, selective *β*-3 adrenergic agonists.[1] To rapidly explore the SAR of the 1,2-diarylethylamine portion of these molecules, we required a convenient method for the synthesis of α-branched secondary amines **3** and **4** that would be compatible with a wide variety of functional groups. We imagined that condensation of resin-bound, primary amines **5** and **6** (Scheme 1) with a set of aromatic aldehydes, followed by addition of organometallic reagents to the resulting imines, and finally, cleavage from the resin (as illustrated for **5** to **3** in Scheme 1), would offer tremendous versatility and operational simplicity. Target molecules would be assembled from three independent modules that could be varied in combinatorial fashion, and with the imine formation and organometallic addition steps taking place on a resin, these reactions could be driven with excess reagents, and purification of their products could be accomplished by simple filtration and rinsing. This plan would require that the phenolic hydroxyl be protected in **5** in order to avoid through-ring elimination of the benzylic oxygen from the phenolate that would otherwise be generated upon exposure to organometallic reagents. However, careful choice of the protecting group (Pro) and the linker would allow deprotection and cleavage from the resin to be accomplished in one operation.

The preparation and reactions of imines on solid support have found widespread use in combinatorial synthesis.[2] Although nucleophilic addition of organometallics to imines in solution[3] has received a great deal of attention, the exploitation of this reaction on the solid phase[4] has only just begun. Utilization of organozinc reagents is of particular interest because of their compatibility with a wide range of functional groups.[5] We know of only one report describing reactions of organozinc reagents with imines immobilized on a resin, and this report discusses only allylic zinc reagents.[6a] We describe here the scope and limitations of organometallic additions to imines derived from resin-bound amines **5** and **6** and the use of this approach to independently vary the Ar and R moieties of **3** and **4**.[7]

Chart 1. *β*-3 Adrenergic Receptor Agonist Target Molecules



Scheme 1. Conceptual Strategy



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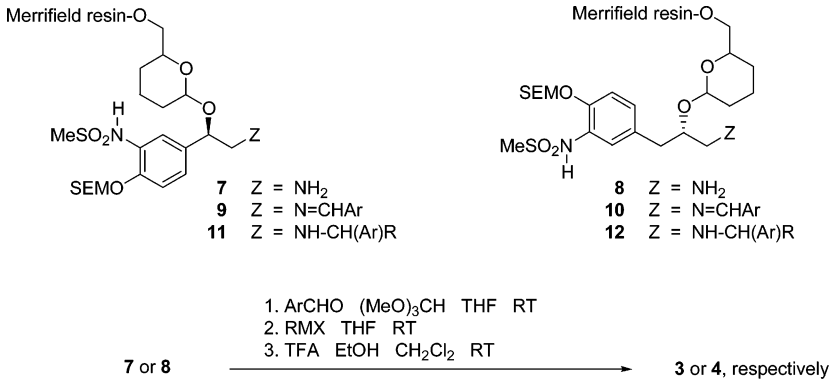
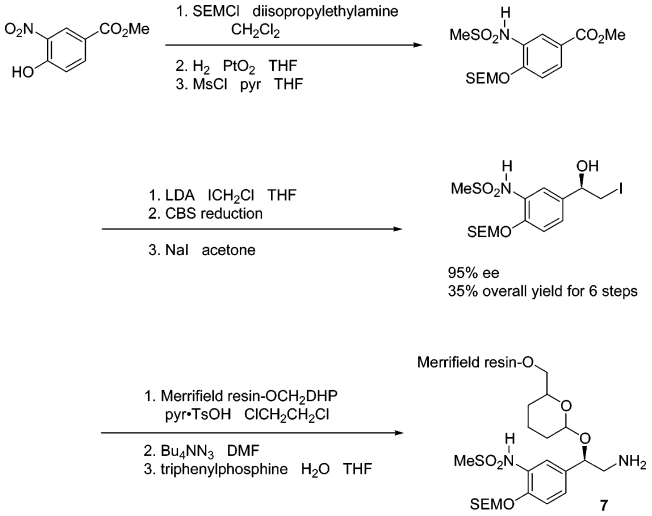
Scheme 2. Execution of Strategy



Scheme 3. Synthesis of Resin-Bound Amine **7**



Results and Discussion

Resin-bound, primary amines **7** and **8** (Scheme 2), in which a tetrahydropyranyl (THP) ether links the molecule to a Merrifield resin and a 2-(trimethylsilyl)ethoxymethyl (SEM) ether protects the phenol, were chosen to facilitate cleavage of both the linker and phenol protecting group in a single step. The syntheses of **7** and the previously disclosed synthesis of **8**[1d] are shown in Schemes 3 and 4, respectively. As planned, condensation of primary amines **7** and **8** with aromatic aldehydes (ArCHO) proceeded in tetrahydrofuran (THF) at room temperature with trimethyl orthoformate as dehydrating agent to produce the imines **9** and **10**, respectively (Scheme 2). Grignard reagents[8] (RMX, M = Mg, X = Cl or Br) were added in excess to the resin-bound imines **9** and **10** in THF at room temperature to produce adducts **11** and **12**, respectively. Organozinc reagents[9] (RMX, M = Zn, X = Br) were often employed in place of Grignard reagents, particularly in cases in which Ar or R contained sensitive functionality. The standard reaction time for these organometallic additions was 4 h when using Grignard reagents and 20 h when using the less reactive organozinc reagents. Cleavage from the resin and the phenol deprotection were accomplished in one operation by treatment with a mixture of trifluoroacetic acid, ethanol, and CH_2Cl_2 (7:5:5) at room temperature for 20 h. Following filtration and evaporation, the crude products **3** and **4** were obtained as TFA salts. In about half of the cases, the crude product was >70% pure (HPLC) as a mixture of diastereomers. In cases in which the organometallic addition reaction did not go to completion, the principal contaminant was typically the primary amine **13** or **14** (Chart 2). To eliminate any trace of **13** or **14**, all crude products **3** and **4** were routinely purified by automated preparative reversed-phase HPLC, which provided diastereomeric mixtures.[10] The entries in Table 1 demonstrate the scope of the reaction sequence. Overall yields are reported from resin-bound amines **7** and **8** to reversed-phase HPLC purified products **3** and **4**, respectively.

Chart 2. Principal Product Contaminants

Scheme 4. Synthesis of Resin-Bound Amine **8**

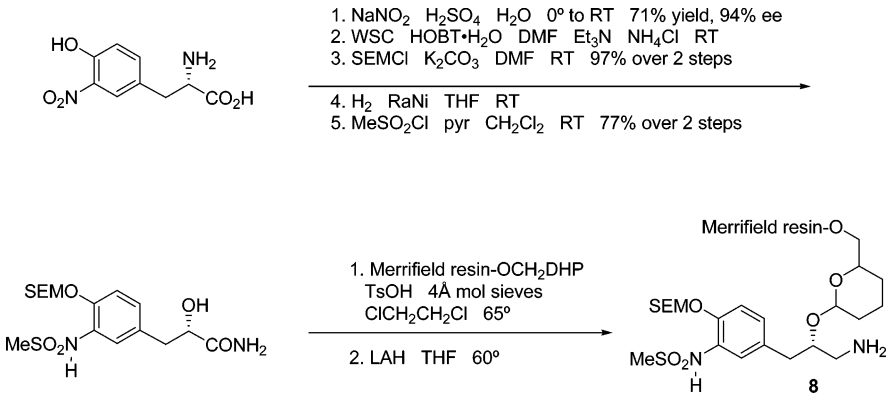
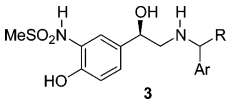
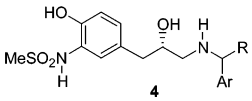


Table 1. α-Branched Secondary Amine Products **3** and **4** Prepared



3



4

entry	product	Ar	R	M	yield (%)	purity after prep HPLC (%)	crude purity before prep HPLC (%)	diastereomer ratio
1	**4a**	3,4-dichlorophenyl	benzyl	Mg	50	98	38	1:1 *SR* to *SS*
2	**4b**	4-fluoro-3-trifluoromethylphenyl	benzyl	Mg	26	98	29	1:1 *SR* to *SS*
3	**3a**	4-fluorophenyl	benzyl	Mg	27	98		1:2 *RR* to *RS*
4	**4c**	2-chloro-4,5-methylenedioxyphenyl	benzyl	Mg	50	95	70	2:1 *SR* to *SS*
5	**4d**	2-bromo-4,5-dimethoxyphenyl	benzyl	Mg	41	95	29	2:1 *SR* to *SS*
6	**4e**	2-methoxyphenyl	benzyl	Mg	52	94	38	4:1 *SR* to *SS*
7	**4f**	2,3-methylenedioxyphenyl	benzyl	Mg	71	90	65	3:1 *SR* to *SS*
8	**4g**	4-benzyloxyphenyl	benzyl	Mg	35	100	57	1:1 *SR* to *SS*
9	**4h**	3-benzyloxyphenyl	benzyl	Mg	44	100	66	1:1 *SR* to *SS*
10	**4i**	4-methoxy-3-methylphenyl	benzyl	Mg	52	90	42	1:1 *SR* to *SS*
11	**4j**	3,5-dimethoxyphenyl	benzyl	Mg	33	98		1:1 *SR* to *SS*
12	**4k**	3-methoxy-4,5-methylenedioxyphenyl	benzyl	Mg	58	90	61	1:1 *SR* to *SS*
13	**3b**	3,4-([3,6,9-trioxa-1,11-undecylenyl]dioxy)phenyl[a]	benzyl	Mg	27	96		2:3 *RR* to *RS*
14	**4l**	3,4-([3,6,9-trioxa-1,11-undecylenyl]dioxy)phenyl[a]	benzyl	Mg	53	95	60	1:1 *SR* to *SS*
15	**3c**	4-difluoromethoxyphenyl	2-methoxybenzyl	Mg	23	82		
16	**3d**	4-difluoromethoxyphenyl	2,4,6-trimethylbenzyl	Mg	9	90	32	2:3 *RR* to *RS*
17	**3e**	4-difluoromethoxyphenyl	2-phenylbenzyl	Mg	16	96	54	1:2 *RR* to *RS*
18	**3f**	4-difluoromethoxyphenyl	2-trifluoromethoxybenzyl	Mg	32	90		
19	**3g**	4-difluoromethoxyphenyl	3,5-dichlorobenzyl	Mg	37	99	81	
20	**4m**	3-hydroxy-4-methoxyphenyl	benzyl	Zn	33	98	33	1:1 *SR* to *SS*
21	**4n**	4-acetylaminophenyl	benzyl	Zn	38	98	50	1:1 *SR* to *SS*
22	**3h**	4-acetylaminophenyl	benzyl	Zn	30	99		1:1 *RR* to *RS*
23	**3i**	4-diethoxyphosphinylphenyl	benzyl	Zn	42	95		1:1 *RR* to *RS*
24	**3j**	4-methylsulfinylphenyl	benzyl	Zn	34	94		1:1 *RR* to *RS*
25	**4o**	4-cyanophenyl	benzyl	Zn	53	95	74	1:1 *SR* to *SS*
26	**4p**	3-cyanophenyl	benzyl	Zn	62	94	70	1:1 *SR* to *SS*
27	**3k**	4-difluoromethoxy-1-naphthyl	benzyl	Zn	35	94		1:1 *RR* to *RS*
28	**3l**	4-quinolinyl	benzyl	Zn	26	100	76	1:1 *RR* to *RS*
29	**3m**	2-thiazolyl	benzyl	Zn	19	84	69	1:1 *RR* to *RS*
30	**3n**	1-oxido-4-pyridyl	benzyl	Zn	10	86	86	1:1 *RR* to *RS*
31	**3o**	4-pyridyl	benzyl	Zn	25	80		1:1 *RR* to *RS*
32	**3p**	4-cyanophenyl	2-methylbenzyl	Zn	38	98	78	1:1 *RR* to *RS*
33	**3q**	4-difluoromethoxyphenyl	2-methylbenzyl	Zn	35	95	78	1:1 *RR* to *RS*
34	**3r**	4-difluoromethoxyphenyl	2-trifluoromethylbenzyl	Zn	30	97	75	
35	**3s**	4-difluoromethoxyphenyl	2-(phenylsulfonylmethyl)benzyl	Zn	34	98	81	1:1 *RR* to *RS*
36	**3t**	4-difluoromethoxyphenyl	2-cyanobenzyl	Zn	30	95	80	
37	**3u**	4-difluoromethoxyphenyl	3-carbomethoxybenzyl	Zn	31	96	84	1:1 *RR* to *RS*
38	**3v**	4-difluoromethoxyphenyl	4-carbomethoxybenzyl	Zn	38	90		
39	**3w**	4-difluoromethoxyphenyl	4-methylsulfonylbenzyl	Zn	48	98		
40	**3x**	4-difluoromethoxyphenyl	3-trifluoromethylbenzyl	Zn	37	97	80	
41	**3y**	4-difluoromethoxyphenyl	allyl	Mg	18	95		1:2 *RR* to *RS*
42	**4q**	3,4-dimethoxyphenyl	allyl	Mg	11	98	50	3:2 *SR* to *SS*
43	**4r**	3,4-dimethoxyphenyl	methallyl	Zn	18	95	80	4:1 *SR* to *SS*
44	**4s**	3,4-dimethoxyphenyl	1,1-dimethylallyl in **4** from 3,3-dimethylallyl in RMX	Zn	19	95		1:1 *SR* to *SS*
45	**3z**	4-difluoromethoxyphenyl	ethyl	Mg	7	85		

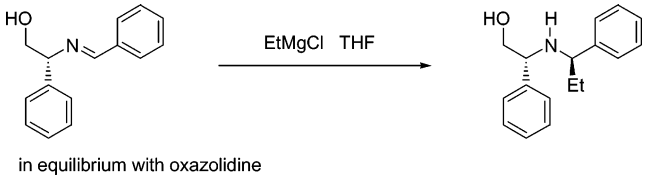
[a] ArCHO = 4′-formylbenzo-15-crown-5.

In cases in which closely eluting impurities were present, sacrificial cuts were sometimes made during purification, depressing reported yields. Purities are listed for preparative HPLC purified products based on HPLC chromatograms and in nearly all cases ^{1}H NMR spectra. All products were confirmed by HPLC/MS. Crude purities based on HPLC chromatograms of products before preparative HPLC purification are also listed. Diastereomeric ratios were determined by ^{1}H NMR.

When benzylmagnesium chloride was employed as the organometallic, the reaction sequence succeeded regardless of the electronic nature (Table 1 entries 1−14) or the steric hindrance (entries 4−7) of substituents on the benzaldehyde (ArCHO) used to prepare imines **9** and **10**. Entries 15−19 demonstrate that substituted benzylic Grignard reagents with either electron-donating or electron-withdrawing substituents added to an imine **9** despite the presence of its base-sensitive difluoromethoxy group. Reaction employing particularly hindered Grignard reagents (entries 16 and 17) proceeded sluggishly, resulting in incomplete reaction and, consequently, lower yields. The generally high reactivity of Grignard reagents precluded their use in cases in which either the imine or the organometallic itself bore electrophilic substituents.

Owing to their low reactivity toward many electrophilic groups, the use of organozinc reagents greatly expanded the scope of this methodology. For example, the reaction sequence succeeded with benzylzinc bromide (entries 20−

Scheme 5. Reported by Wu and Pridgen



in equilibrium with oxazolidine

26) regardless of the electronic nature, the electrophilic character, or the potential for deprotonation of the imine substituents. Thus, cyano (entries 25 and 26) and hydroxyl (entry 20) groups were tolerated. Additionally, other types of aromatic aldehydes, including more sterically demanding (entries 27 and 28) and heterocyclic (entries 28−31) aldehydes, gave useful yields of product with benzylzinc bromide. Substituted benzylic zinc reagents with either electron-donating or electron-withdrawing substituents were successfully added to imines derived from 4-cyanobenzaldehyde and 4-difluoromethoxybenzaldehyde (entries 32−40). Among these, entries 36−38, in which electrophilic cyano and ester groups substitute the organometallic, illustrate the versatility of the organozinc reagents. Entry 34 further demonstrates this versatility, since 2-trifluoromethylbenzylzinc bromide succeeded where the corresponding Grignard reagent failed due to its propensity to undergo through-ring elimination of fluoride.

Additions of allylic Grignard and allylic zinc reagents (entries 41−44) were also successful, albeit in lower yields. Interestingly, 3,3-dimethylallylzinc bromide gave the 1,1-dimethylallyl product (entry 44), resulting from nucleophilic attack by C-3 of the organometallic and producing a quaternary carbon.

Alkyl Grignard reagents, as well as aryl Grignard and arylzinc reagents failed completely, with the slight exception of ethyl Grignard (entry 45), which gave a low and unreproducible yield of desired product. One possible contributing factor in the failure of alkyl Grignard reagents is that they may be less reactive than allylic and benzylic Grignard reagents toward imines of aromatic aldehydes.[11] An additional factor may be that double deprotonation of the acidic methylsulfonylamino group generates a dianion that hinders addition of alkyl Grignard reagents to the imine by electrostatic repulsion.[12]

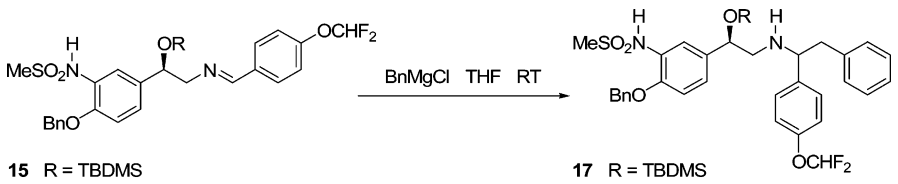
The relationship between this work and that of Wu and Pridgen deserves comment. Their 1991 report[13] disclosed the stereoselective synthesis of α-substituted benzylamines by organometallic addition to imines of benzaldehydes and enantiomerically pure phenylglycinol in solution. In contrast to our largely unsuccessful attempts to add alkyl Grignard reagents to our resin-bound imine, Wu and Pridgen reported the successful addition of several alkyl Grignard reagents in solution (Scheme 5). Their solution method differed from our solid phase work by the presence of a free, rather than etherified, hydroxyl group vicinal to the imine nitrogen in addition to lacking an acidic methylsulfonylamino substituent. After deprotonation of this hydroxyl, internal chelation of the magnesium ion to the imine nitrogen would increase the electrophilic reactivity of the imine.

Imine addition reactions of benzyl Grignard to solution analogues of our resin-bound imine were viable, though less convenient (Scheme 6). Both with and without benzylic hydroxyl protection, benzylmagnesium chloride (5 equiv) added to imines **15** and **16** in THF to produce adducts **17** and **18**, respectively.[14] The addition was somewhat faster with the benzylic hydroxyl unprotected (**16**), possibly reflecting either less steric hindrance or chelation of a magnesium atom between the imine nitrogen and the deprotonated benzylic hydroxyl, analogous to the method of Wu and Pridgen.

Given our success in adding benzylic zinc reagents to imines on solid support, we were surprised to find that in solution, these organometallics did not add to imines of phenylglycinol. Specifically, whereas 4-fluorobenzylmagnesium chloride readily added to the imine derived from phenylglycinol and 3,4-dimethoxybenzaldehyde at 0°, as would be predicted by Wu and Pridgen's report, attempted addition of 4-fluorobenzylzinc bromide (4 equiv) to the same imine in THF at temperatures up to reflux produced no more than a trace of the desired adduct. Even when 0.95 equiv of benzylmagnesium chloride was first added at 0° to chelate magnesium between the alcoholate and imine nitrogen, followed by 4 equiv of 4-fluorobenzylzinc bromide, no addition occurred at room temperature. We can offer no satisfying explanation for the failure of solution-phase benzylic zinc addition in light of its success on solid support. We merely note that there are three main differences between the two: the solution-phase case contains a free hydroxyl in the phenylglycinol moiety; the phenyl ring of the phenylglycinol moiety has no direct counterpart in the solid supported case; and of course, in the solution-phase case, there is no resin present.

The stereochemical outcome of the organometallic additions summarized in Table 1 shows some general trends.[15] All of the reactions employing a substituted or unsubstituted benzylzinc reagent produced diastereomers in a 1:1 ratio, regardless of which starting resin-bound amine (**7** or **8**) was used. The benzylic Grignard reagents, on the other hand, often showed a modest stereochemical bias. When amine **7** was used, the *RR*-to-*RS* ratio was between 2:3 and 1:2. When amine **8** was used, the *SR*-to-*SS* ratio was about 1:1 when the aromatic aldehyde had no ortho substituent, but increased when an ortho substituent was present (entry 4, 2:1; entry 5,

Scheme 6. Benzyl Grignard Addition to Solution Analogues of Resin-Bound Imine



15 R = TBDMS
16 R = H exists in equilibrium with oxazolidine

17 R = TBDMS
18 R = H, >85% yield

2:1; entry 6, 4:1; entry 7, 3:1). The fact that benzylic Grignard and benzylic zinc addition reactions produced different stereochemical results might be due to differences in transition state metal chelation effects or transition state progress along the reaction coordinate, assuming the product distribution is kinetically determined, or possibly due to radical mechanism intervention[6b] or reversibility in the addition of the organozinc reagents. Additions of allylic zinc reagents have been reported to be reversible,[16] and such reversibility may influence the ratios of diastereomers produced in entries 43 and 44.

Conclusion

A versatile synthesis of α-branched secondary amines that relies on the addition of benzylic and allylic organozinc and Grignard reagents to resin-bound imines has been described. Particularly when organozinc reagents were used, many functional groups were compatible with this methodology, including electrophilic cyano and ester groups, readily deprotonatable phenolic hydroxyl and anilinic methylsulfonylamino groups, and a variety of other electron-donating and electron-withdrawing groups. Three modules—a resin-bound primary amine, an aromatic aldehyde, and an organometallic reagent—were independently varied to produce a combinatorial library of α-branched secondary amines designed as β-3 adrenergic receptor agonists.

Experimental Section

General Methods. The following general experimental information is applicable wherever not specifically indicated otherwise in the experimental procedures described below. Benzylic halides, aromatic aldehydes, and all other reagents for which syntheses are not described herein were purchased at reagent grade from commercial suppliers (usually Aldrich Chemical Co.) and were used without prior purification. Two aromatic aldehydes that were not commercially available were prepared.[17] Silica gel column chromatography was carried out using Merck silica gel 60 (230−400 mesh), and analytical TLC was performed using Merck silica gel 60 F254 plates. Preparative HPLC and analytical HPLC were carried out on Shimadzu instruments using columns and solvent systems noted in the individual experimental procedures below. Unless otherwise indicated, analytical HPLC utilized a YMC S3 ODS 4.6 × 50 mm column, a 2.5 mL/min flow rate, and solvents A = 90% water/10% MeOH/0.2% phosphoric acid and B = 10% water/90% MeOH/0.2% phosphoric acid. ^{1}H NMR spectra are reported in parts per million downfield of the internal standard tetramethylsilane. ^{13}C NMR spectra are reported in parts per million downfield with $CDCl_3$ as the internal standard at 77.0 ppm. Solution NMR spectra were obtained with a JEOL CPF-270 spectrometer. Resin ^{13}C NMR spectra were obtained with a JEOL GX-270 spectrometer. Resin IR spectra were collected on a Nicolet Impact 420 FTIR spectrometer. HPLC/MS data were obtained on a Finnigan SSQ7000 single quadrupole mass spectrometer (positive electrospray ionization) interfaced to a Waters 600MS gradient HPLC (YMC S3 ODS 4.6 × 75 mm column, linear gradient 0−100% B solvent over 8 min at 2.5 mL/min, A = 90% water/10% MeOH/0.1% trifluoroacetic acid, B = 10% water/90% MeOH/0.1% trifluoroacetic acid).

Methyl 3-Nitro-4-(2-trimethylsilylethoxymethoxy)benzoate (Leading to 7 in Scheme 3). To a two-neck, 2-L round-bottom flask equipped with a magnetic stirbar, addition funnel with gas bubbler, and septum with a temperature probe, containing a stirred solution of methyl 4-hydroxy-3-nitrobenzoate (84.8 g, 430 mmol, Lancaster Synthesis) in CH_2Cl_2 (750 mL) under an argon atmosphere was added diisopropylethylamine (100 mL, 74.2 g, 574 mmol, 1.33 equiv). After cooling the mixture to 0 °C with an ice bath, 2-trimethylsilylethoxymethyl chloride (75.0 g, 450 mmol, 1.05 equiv) was added by addition funnel over 23 min, during which the temperature remained below 3 °C. The ice bath was removed 2 min after completion of the addition, and 20 min later, reversed-phase HPLC indicated complete reaction (linear gradient 0−100% B solvent over 10 min, detection at 220 nm, retention time for methyl 4-hydroxy-3-nitrobenzoate = 6.2 min, retention time for methyl 3-nitro-4-(2-trimethylsilylethoxymethoxy)benzoate = 10.3 min). The reaction mixture was washed sequentially with 5% w/v aqueous citric acid monohydrate (200 mL twice), water (200 mL), saturated aqueous sodium carbonate (200 mL twice), and saturated aqueous sodium chloride (200 mL). After the organic layer was dried over sodium sulfate, it was evaporated to obtain methyl 3-nitro-4-(2-trimethylsilylethoxymethoxy)-benzoate (141.4 g, 98% pure by HPLC, quantitative uncorrected yield) as a light orange liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.03 (s, 9H), 0.92 (m, 2H), 3.79 (m, 2H), 3.90 (s, 3H), 5.39 (s, 2H), 7.37 (d, 1H), 8.16 (dd, 1H), 8.44 (d, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ −1.6, 17.9, 52.4, 67.5, 93.5, 116.3, 123.2, 126.8, 134.7, 140.0, 153.7, 164.8.

Methyl 3-Amino-4-(2-trimethylsilylethoxymethoxy)benzoate (Leading to 7 in Scheme 3). To a three-neck, 2-L Morton flask equipped with mechanical stirrer, subsurface gas inlet, Claisen adapter, rubber septum with temperature probe, and gas outlet was added PtO_2 (5.09 g). After placing the catalyst under an argon atmosphere, a solution of methyl 3-nitro-4-(2-trimethylsilylethoxymethoxy)benzoate (137.1 g, 419 mmol) in MeOH (1.1 L) was added. The mixture was then degassed by addition of argon (bubbled in) while rapidly stirring for 10 min. An ambient temperature water bath was used to moderate the mildly exothermic reaction resulting from subsequent introduction of hydrogen gas (bubbled in). Internal temperature reached 36 °C. HPLC analysis after 40 min indicated complete reaction (linear gradient 0−100% B solvent over 10 min, detection at 220 nm, retention time for methyl 3-amino-4-(2-trimethylsilylethoxymethoxy)benzoate = 8.8 min). After a total of 90 min, hydrogen was purged by argon bubbling for 30 min. The mixture was then filtered (1.2-μm nylon membrane), and the filtrate was evaporated to provide methyl 3-amino-4-(2-trimethylsilylethoxymethoxy)benzoate (122.3 g, 97% pure by HPLC, 98% uncorrected yield) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.00 (s, 9H), 0.97 (m, 2H), 3.78 (m, 2H), 3.86 (s, 3H), 3.93 (bs, 2H), 5.30 (s, 2H), 7.05 (d, J = 8.1 Hz, 1H), 7.41 (s, 1H), 7.42 (dd, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ −1.5, 17.9, 51.7, 66.5, 93.1, 113.2, 115.9, 120.6, 123.6, 136.3, 148.6, 167.0.

Methyl 3-Methylsulfonylamino-4-(2-trimethylsilylethoxymethoxy)benzoate (Leading to 7 in Scheme 3). To a 2-L round-bottom flask equipped with mechanical stirrer, 3-way Claisen adapter, rubber septum with temperature probe, and gas bubbler was added methyl 3-amino-4-(2-trimethylsilylethoxymethoxy)benzoate (122.2 g, 411 mmol), dry THF (0.5 L), and pyridine (80 mL, 78.2 g, 989 mmol, 2.4 equiv). The resulting solution was placed under an atmosphere of nitrogen and, while stirring, cooled to 4 °C with an ice bath before methanesulfonyl chloride (40 mL, 59.2 g, 517 mmol, 1.26 equiv) was added in a single portion. The bath was removed after 1 min, and the mixture was allowed to gradually warm to ambient temperature. After 1 h, HPLC indicated roughly half conversion to desired product (linear gradient 0−100% B solvent over 10 min, detection at 220 nm, retention time for methyl 3-methylsulfonylamino-4-(2-trimethylsilylethoxymethoxy)benzoate = 9.2 min). The reaction was driven to completion by heating to 40 °C for 4 h, followed by addition of more methanesulfonyl chloride (20 mL, 29.6 g, 258 mmol, 0.63 equiv) and continued heating at 40 °C for 2 h. The reaction mixture was diluted with ethyl acetate (750 mL) and was washed sequentially with 5% w/v aqueous citric acid monohydrate (200 mL twice), saturated aqueous sodium bicarbonate (225 mL twice), and saturated aqueous sodium chloride (250 mL twice). The organic layer was dried over magnesium sulfate and filtered through a short silica gel plug (110 mm wide × 40 mm high) rinsing with ethyl acetate. Evaporation was followed by flash chromatography (413 g silica gel, 75 mm wide × 260 mm high, eluting with 100% CH_2Cl_2), which provided methyl 3-methylsulfonylamino-4-(2-trimethylsilylethoxymethoxy)benzoate (140.1 g, 100% pure by HPLC, 91% yield) as a light orange oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.03 (s, 9H), 0.94 (m, 2H), 3.00 (s, 3H), 3.75 (m, 2H), 3.87 (s, 3H), 5.34 (s, 2H), 7.01 (bs, 1H), 7.19 (d, 1H), 7.80 (dd, 1H), 8.15 (d, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ −1.6, 17.9, 39.4, 52.0, 67.2, 93.3, 113.6, 121.5, 124.1, 126.5, 127.3, 150.8, 166.1.

2-Chloro-1-[3-methylsulfonylamino-4-(2-trimethylsilylethoxymethoxy)phenyl]ethanone (Leading to 7 in Scheme 3) by the Kowalski Method.[18] To a heat-dried, two-neck, 2-L round-bottom flask equipped with magnetic stirbar, addition funnel with gas bubbler, and rubber septum with temperature probe was added diisopropylamine (100 mL, 72.2 g, 714 mmol, 5.34 equiv) and dry THF (625 mL) under a nitrogen atmosphere. The resulting solution was stirred while cooling to −60 °C before butyllithium (2.5 M in hexane, 250 mL, 625 mmol, 4.67 equiv) was added over 22 min by addition funnel while internal temperature remained below −45 °C. The resulting yellow solution was allowed to warm briefly to 5 °C before recooling to −76 °C. This solution of lithium diisopropylamide was used below. To a heat-dried, 3-L round-bottom flask equipped with magnetic stirbar, 3-way Claisen adapter, rubber septum with temperature probe, and gas bubbler was added methyl 3-methylsulfonylamino-4-(2-trimethylsilylethoxymethoxy)benzoate (50.2 g, 134 mmol), chloroiodomethane (47 mL, 113.8 g, 645 mmol, 4.83 equiv), and dry THF (625 mL) under a nitrogen atmosphere. The resulting light orange solution was stirred while cooling to −76 °C before the solution of lithium diisopropylamide prepared above was added via cannula, propelled by positive nitrogen pressure, over 95 min, during which the internal temperature remained below −72 °C. Stirring was continued at −76 °C for 20 min following completion of the addition, which resulted in an orange-red color. A solution of glacial acetic acid (185 mL) in THF (125 mL) was added over 20 min, during which the temperature was allowed to rise to −40 °C to facilitate stirring of the precipitating mixture. Subsequent rotoevaporation at up to 40 °C bath temperature removed 760 mL of volatiles. The mixture was diluted with ethyl acetate (750 mL). Sequential washing with 5% w/v aqueous citric acid monohydrate (500 mL twice), saturated aqueous sodium bicarbonate (500 mL twice), and saturated aqueous sodium chloride (500 mL), drying over sodium sulfate, and evaporation provided 86.1 g of crude product. This was chromatographed on a short silica gel plug (95 mm wide × 50 mm high) eluting with 0−50% ethyl acetate in CH_2Cl_2 to provide impure desired product (58.2 g). Flash chromatography (423 g silica gel, 75 mm wide × 245 mm high, eluting with 0−25% ethyl acetate in CH_2Cl_2) provided 2-chloro-1-[3-methylsulfonylamino-4-(2-trimethylsilylethoxymethoxy)phenyl]ethanone (34 g, 92% pure by HPLC, 64% uncorrected yield) as a light orange oil. The main impurity was starting material. ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.03 (s, 9H), 0.95 (m, 2H), 3.02 (s, 3H), 3.77 (m, 2H), 4.67 (s, 2H), 5.38 (s, 2H), 7.23 (bs, 1H), 7.26 (d, J = 9.0 Hz, 1H), 7.74 (dd, J = 9.0, 2.1 Hz, 1H), 8.07 (d, J = 2.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ −1.6, 17.8, 39.4, 45.6, 67.2, 93.3, 113.8, 120.7, 126.4, 126.9, 128.1, 151.7, 189.3. HPLC retention time = 8.9 min (linear gradient 0−100% B solvent over 10 min, detection at 220 nm).

(*R*)-2-Chloro-1-[3-methylsulfonylamino-4-(2-trimethylsilylethoxymethoxy)phenyl]ethanol (Leading to 7 in Scheme 3) by the CBS Reduction Method.[19] To a 2-L round-bottom flask equipped with magnetic stirbar, 3-way Claisen adapter, rubber septum with temperature probe, and gas bubbler was added 2-chloro-1-[3-methylsulfonylamino-4-(2-trimethylsilylethoxymethoxy)phenyl]ethanone (28.3 g, 72.0 mmol) and dry THF (485 mL) under a nitrogen atmosphere. The resulting orange solution was stirred at −14 °C while (*R*)-2-methyl-CBS-oxazaborolidine ((*R*)-tetrahydro-1-methyl-3,3-diphenyl-1*H*,3*H*-pyrrolo[1,2-*c*][1,3,2]oxazaborole, 8.6 mL, 1.1 M in toluene, 9.5 mmol) was added. Subsequently, borane dimethyl sulfide complex (14 mL, 11.2 g, 141 mmol) was added by syringe pump over 20 min while the internal temperature remained below −10 °C. TLC indicated complete reaction 15 min after the addition was complete (10% ethyl acetate in CH_2Cl_2, R_f of starting material = 0.78, R_f of product = 0.49). Careful addition of hydrogen chloride in MeOH (30 mL, 0.5 M, from acetyl chloride addition to MeOH) caused foaming for 10 min. More foaming occurred upon addition of saturated aqueous sodium bicarbonate (65 mL). The mixture was diluted with ethyl acetate (475 mL) and water (200 mL), and the pH was adjusted from 7.6 to 3.6 by addition of saturated aqueous citric acid (45 mL). The organic phase was separated and washed with saturated aqueous sodium bicarbonate (200 mL), then saturated

aqueous sodium chloride (200 mL), before drying over sodium sulfate and evaporation to provide 32 g of crude product. Flash chromatography (339 g silica gel, 75 mm wide × 205 mm high, eluting with 0−50% ethyl acetate in CH_2Cl_2), provided (*R*)-2-chloro-1-[3-methylsulfonylamino-4-(2-trimethylsilylethoxymethoxy)phenyl]ethanol (19.0 g, 95% pure by HPLC, 67% uncorrected yield) as a light orange oil. Chiral HPLC indicated 97.6% ee (Diacel Chiralcel OJ-R 4.6 × 150 mm column, linear solvent gradient 30−34% acetonitrile in water over 60 min at 0.7 mL/min, detection at 210 nm, retention time for *R* isomer = 53 min, retention time for *S* isomer = 48 min). Additional product was obtained from mixed fractions (5 g, 90% pure by HPLC). ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.00 (s, 9H), 0.96 (m, 2H), 2.98 (s, 3H), 3.63 (dd, J = 11.1, 8.5 Hz, 1H), 3.72 (m, 2H), 4.85 (m, 1H), 5.27 (s, 2H), 6.99 (bs, 1H), 7.17 (m, 2H), 7.53 (d, J = 2.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ −1.5, 18.0, 39.3, 50.6, 67.0, 73.3, 93.7, 114.6, 118.4, 123.0, 126.8, 134.4, 147.2. HPLC retention time = 8.7 min (linear gradient 0−100% B solvent over 10 min, detection at 220 nm).

(*R*)-2-Iodo-1-[3-methylsulfonylamino-4-(2-trimethylsilylethoxymethoxy)phenyl]ethanol (Leading to 7 in Scheme 3). To a foil-covered, 1-L round-bottom flask equipped with magnetic stirbar, rubber septum with temperature probe, and reflux condenser with gas bubbler was added sodium iodide (101 g) and a solution of (*R*)-2-chloro-1-[3-methylsulfonylamino-4-(2-trimethylsilylethoxymethoxy)phenyl]ethanol (19.0 g, 48.0 mmol) in acetone (350 mL, filtered through basic alumina) under a nitrogen atmosphere. The resulting suspension was stirred while heating at 61 °C for 74 h, after which HPLC indicated a 97:3 ratio of product to starting material (linear gradient 0−100% B solvent over 10 min, detection at 220 nm, retention time for (*R*)-2-iodo-1-[3-methylsulfonylamino-4-(2-trimethylsilylethoxymethoxy)phenyl]-ethanol = 9.1 min). After cooling to 50 °C, the mixure was diluted with hexane (200 mL) and ethyl acetate (150 mL) and filtered. The filtrate was evaporated, and the residue was slurried in ethyl acetate (350 mL). Sequential washes with 3 M aqueous sodium bisulfite (150 mL) and saturated aqueous sodium chloride (150 mL) were followed by drying over sodium sulfate and evaporation to provide crude product (21.3 g). Flash chromatography (443 g silica gel, 75 mm wide × 250 mm high, eluting with 0−20% ethyl acetate in CH_2Cl_2), followed by recrystallization from ethyl acetate/heptane provided (*R*)-2-iodo-1-[3-methylsulfonylamino-4-(2-trimethylsilylethoxymethoxy)phenyl]ethanol (13.6 g, pure, 58% yield) as a white powder. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.00 (s, 9H), 0.96 (m, 2H), 2.54 (d, J = 3.8 Hz, 1H), 2.98 (s, 3H), 3.39 (dd, J = 10.3, 8.6 Hz, 1H), 3.47 (dd, J = 10.3, 3.8 Hz, 1H), 3.74 (m, 1H), 4.78 (m, 1H), 5.27 (s, 2H), 6.92 (bs, 1H), 7.17 (m, 2H), 7.52 (d, J = 2.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ −1.4, 15.4, 18.1, 39.4, 67.1, 73.3, 93.8, 114.7, 117.9, 122.6, 126.9, 135.5, 147.1.

Resin-Bound Iodohydrin Leading to 7 (Scheme 3). A mixture of dihydropyran-derivatized Merrifield resin[20] (6.0 g, 7.05 mmol), (*R*)-2-iodo-1-[3-methylsulfonylamino-4-(2-trimethylsilylethoxymethoxy)phenyl]ethanol (8.6 g, 17.6 mmol), pyridinium 4-toluenesulfonate (1.5 g, 6.0 mmol), 3-Å molecular sieves (5 g), and dichloroethane (50 mL) was gently magnetically stirred at 65 °C under an argon atmosphere for 24 h. After cooling to room temperature, CH_2Cl_2 (100 mL) was added. The resin beads floated, while the molecular sieves did not. This allowed separation of the resin beads from the molecular sieves by decanting. The resin was then sequentially washed with CH_2Cl_2 (100 mL twice), *N*,*N*-dimethylformamide (50 mL, twice), and CH_2Cl_2 (50 mL twice) and dried under vacuum for 2 days to obtain resin-bound iodohydrin (8.0 g). The resin ^{13}C NMR spectrum ($CDCl_3$) indicated the absence of starting material and presence of a new C−I resonance at δ 12 ppm.

Resin-Bound Azide Leading to 7 (Scheme 3). Tetrabutylammonium azide (11.8 g, 41.4 mmol) was dissolved in *N*,*N*-dimethylformamide (80 mL) under an argon atmosphere, and 4-Å molecular sieves (20 g) were added. This mixture was gently magnetically stirred at room temperature for 30 min before resin-bound iodohydrin (16.6 g, 16.6 mmol) and *N*,*N*-dimethylformamide (80 mL) were added. The mixture was heated to 80 °C for 5 h, then cooled to room temperature before CH_2Cl_2 (100 mL) was added. The resin beads floated, while the molecular sieves did not. This allowed separation of the resin beads from the molecular sieves by decanting. The resin was then sequentially washed with CH_2Cl_2 (50 mL twice), *N*,*N*-dimethylformamide (50 mL twice), and CH_2Cl_2 (50 mL five times) and dried under vacuum for 16 h to obtain resin-bound azide (15 g). The resin ^{13}C NMR spectrum confirmed disappearance of the C−I resonance, and resin IR showed an azide stretch at 2100 cm^{-1}.

Resin-Bound Amine 7 (Scheme 3). A mixture of resin-bound azide (15 g, 15 mmol), triphenylphosphine (20 g, 76 mmol), THF (150 mL), and water (1.9 g, 105 mmol) was shaken at room temperature for 16 h in a closed vessel without inert atmosphere. The resin was filtered, then sequentially washed with THF (100 mL), *N*,*N*-dimethylformamide (100 mL), and CH_2Cl_2 (50 mL five times) and dried under vacuum for 24 h to obtain resin-bound amine (14.5 g). Resin IR confirmed disappearance of the azide stretch. A loading of 0.8 mmol/g was estimated on the basis of resin weight changes during the three steps leading to resin-bound amine **7**.

General Procedure for Preparation of Benzylic Grignard Reagents. To an oven-dried, Pyrex test tube (25 mm o.d. × 150 mm) containing a magnetic stirbar (Teflon-coated, 5/8-in., football-shaped) was added magnesium turnings (3 g, 123 mmol). The test tube was closed with a rubber septum (red, size for 24/40 joints) and purged with argon using a balloon and needle for argon inlet and a needle for gas outlet. After ∼2 L of argon had passed through the tube, the outlet needle was removed, and the tube was maintained under positive argon pressure from the balloon. The magnesium was stirred vigorously, dry, for 2 d, after which most of the turnings remained intact, but the bottom of the tube was coated with a mirror, and some gray powder was present. To this was added by syringe diethyl ether (10 mL, freshly distilled from potassium/benzophenone ketyl). The mixture was cooled to 0 °C, stirring rapidly. Until subsequent addition of benzylic halide, the ether phase remained clear and colorless. Benzylic chloride or bromide (10−20 mmol) was added neat, if a liquid, by syringe in roughly 10% portions

every 3−5 min over 30−45 min. If the benzylic halide was a solid, only ∼4 mL of ether was added to the magnesium initially, and a solution of the benzylic halide in ∼6 mL of ether was added about 10% at a time every 3−5 min over 30−45 min. In either case, stirring was continued for an additional 30 min at 0 °C before warming to room temperature. In no case was bubbling observed. In some cases, stirring was discontinued at this point, and the mixture was allowed to settle for 2 h before use. Typically, some black powder settled among the excess magnesium metal. The mirror was gone, and clear, tan, supernatant Grignard solution could then be removed by syringe for analysis and addition reactions. In many cases, to avoid crystallization of organometallic out of ether solution, prior to discontinuation of stirring, the reaction mixture was diluted with THF (10−20 mL, freshly distilled from sodium/benzophenone ketyl). Stirring was then stopped, followed by 2 h of settling before use. Approximate concentrations of organometallic were estimated by dividing the millimoles of benzylic halide used by the final solution volume, which was calculated by subtracting the calculated volume of the metal expected to remain after one equivalent is consumed from the total volume of the reaction mixture. Concentrations ranged from 0.3 to 1.5 M. Analysis of the Grignard reagents was performed by NMR after quenching to CD_3OD as follows. An aliquot of reagent was transferred by syringe to an NMR tube containing CD_3OD. The reagent was introduced below the surface of CD_3OD to minimize air oxidation, and introduction was carefully and slowly performed to avoid bumping from the exothermic reaction. The resulting cloudy mixture sometimes contained visible precipitate. Nevertheless, informative and sharp ^1H NMR spectra could be obtained, provided the *y* gain was high enough to see the relevant signals in the presence of much larger solvent peaks. The ^1H NMR spectrum was reviewed for the presence of benzylic halide, which was always absent, benzylic alcohol (δ 4.5−4.7, s), generally <10%, homocoupling bisbenzyl product (δ 2.8−3.0, s), generally <5%, and the expected α-monodeuteriotoluene (δ 2.2−2.4, narrow 1:1:1 triplet) generally >85%.

General Procedure for Preparation of Benzylic Organozinc Bromides (Allylic Organozinc Bromides Were Prepared Analogously). To an oven-dried, Pyrex test tube (25 mm o.d. × 150 mm) containing a magnetic stirbar (Teflon-coated, 5/8-in., football-shaped) was added zinc dust (<10 μm, 5 g, 76 mmol). The test tube was closed with a rubber septum (red, size for 24/40 joints) and purged with argon using a balloon and needle for argon inlet and a needle for gas outlet. After ∼2 L of argon had passed through the tube, the outlet needle was removed, and the tube was maintained under positive argon pressure from the balloon. No pretreatment of the zinc dust was performed before addition by syringe of THF (10 mL, freshly distilled from sodium/benzophenone ketyl). The mixture was cooled to 0 °C, stirring rapidly. Benzylic bromide (10−20 mmol) was added neat, if a liquid, by syringe in roughly 10% portions every 3−5 min over 30−45 min. If the benzylic bromide was a solid, only ∼4 mL of THF was added to the zinc initially, and a solution of the benzylic bromide in ∼6 mL of THF was added about 10% at a time every 3−5 min over 30−45 min. In either case, stirring was continued for an additional 30 min at 0 °C before warming to room temperature. Stirring was discontinued, and the mixture was allowed to settle for 2 h before clear or slightly cloudy supernatant organozinc solution was removed by syringe for analysis and addition reactions. Approximate concentrations of organometallic were estimated in a manner analogous to that described for the Grignard reagents. Concentrations ranged from 0.9 to 1.5 M. Analysis of the benzylic organozinc reagents was performed as described for the Grignard reagents by ^1H NMR after quenching to CD_3OD. Reaction of the organozinc reagents with CD_3OD was much slower than the reaction of Grignard reagents. Although the possible products were the same, collection of NMR spectra shortly after addition of reagent to CD_3OD often allowed observation of unreacted benzylic organozinc bromide. For example, unsubstituted benzylzinc bromide was roughly half consumed 10 min after addition to CD_3OD, as judged by the observation of a singlet at δ 1.77 ppm and aromatic proton resonances upfield of their corresponding chemical shifts in α-monodeuteriotoluene. By 2 h, these signals had vanished. The rate of reaction of organozinc with CD_3OD was structure-dependent, with the time required for half reaction of 2-trifluoromethylbenzylzinc bromide being ∼12 h. Once the organozinc had fully reacted, the relative abundance of species was very similar to that observed with the Grignard reagents: benzylic bromide was absent, benzylic alcohol and homocoupling bisbenzyl product together generally accounted for ∼10% of the material, and the expected α-monodeuteriotoluene accounted for the balance.

Formation of Resin-Bound Imines 9 and 10. To resin-bound amine **7** or **8** (150 mg, 0.12 mmol) in a rubber-septum-capped, fritted polypropylene tube was added dry THF (2 mL), trimethyl orthoformate (0.50 mL, 0.48 g, 4.6 mmol), and aromatic aldehyde (1.2 mmol). This mixture was vortexed vigorously for 20 h at room temperature without inert atmosphere. The liquid phase was drained under Ar pressure, and the resin was washed with dry THF (2 mL five times) before drying in the tube under vacuum for 2 h.

Addition of Grignard Reagents to Resin-Bound Imines to Form Adducts 11 and 12. To resin-bound imine **9** or **10** (from 150 mg of resin-bound amine **7** or **8**) in a rubber-septum-capped, fritted polypropylene tube flushed with argon was added dry THF (2 mL), followed by Grignard reagent (1.2 mmol) in THF, ether, or THF/ether solution. This mixture was vortexed vigorously for 4 h at room temperature. The liquid phase was drained under Ar pressure, and the resin was washed sequentially with dry THF (2.5 mL), MeOH (2.5 mL), and CH_2Cl_2 (2.5 mL) before drying in the tube under vacuum for 3 h.

Addition of Organozinc Bromides to Resin-Bound Imines to Form Adducts 11 and 12. To resin-bound imine **9** or **10** (from 150 mg of resin-bound amine **7** or **8**) in a rubber-septum-capped, fritted polypropylene tube flushed with argon was added only organozinc bromide in THF solution (typically 0.7 M, 3 mL, 2 mmol). This mixture was vortexed vigorously for 20 h at room temperature before the liquid phase was drained under Ar pressure, and the resin

was washed sequentially with MeOH (5 mL three times) and CH_2Cl_2 (5 mL twice) before drying in the tube under vacuum for 2 h.

Cleavage From the Resin and Phenol Deprotection to Form α-Branched Secondary Amines 3 and 4. To the resin-bound adduct **11** or **12** (from 150 mg of resin-bound amine **7** or **8**) in a rubber-septum-capped, fritted polypropylene tube flushed with argon was added a premixed solution of trifluoroacetic acid, ethanol, and CH_2Cl_2 (7:5:5, 5 mL). This mixture was vortexed vigorously for 24 h at room temperature. The liquid phase was drained under Ar pressure, and the resin was rinsed sequentially with CH_2Cl_2 (3 mL) and MeOH (3 mL). The combined reaction's liquid phase and rinses were evaporated under vacuum. Crude purities were determined at this point on the basis of HPLC peak area by UV detection at 215 nm without correcting for differences in extinction coefficient. In prototype reactions, reasonably pure products could be obtained by ion exchange chromatography in which the crude product was redissolved in MeOH (2 mL) and loaded onto a sulfonic acid cation exchange (SCX) resin column (United Chemical Technologies, CLEAN-UP Extraction Column, sorbent CUBCX1HL, *Synthesis* **1997**, 553−558). This column was then washed with MeOH (6 mL) before the desired product was eluted with ammonia in MeOH solution (2.0 M, 6 mL). However, out of concern that trace amounts of primary amine **13** or **14** might not be separated, purification was routinely accomplished instead by preparative reversed-phase HPLC (YMC S5 ODS 30 × 250 mm column, linear gradient 40−100% B solvent over 10 min at 25 mL/min, A = 90% water/10% MeOH/0.1% trifluoroacetic acid, B = 10% water/90% MeOH/0.1% trifluoroacetic acid, detection at 220 nm), which provided desired product as the trifluoroacetic acid salt. Overall yield from resin-bound amine **7** or **8** to reversed-phase HPLC purified product **3** or **4** was calculated on the basis of desired product weight and the estimated resin-bound amine **7** or **8** loading of 0.8 mmol/g. HPLC and HPLC/MS analyses, and in nearly all cases, ^{1}H NMR spectra were used to confirm structure, determine diastereomer ratio, and judge purity. For example, the mixture of diastereomers **3x** (Table 1 entry 40) exhibited the following HPLC and MS characteristics: HPLC retention time = 6.1 min (linear gradient 0−100% B solvent over 8 min, detection at 215 nm). MS (ESI) m/z = 561 ($M + H^+$). A diastereomer separation procedure and individual ^{1}H NMR spectra are given below.

Separation of Diastereomers 3x. A sample of **3x** (Table 1 entry 40) was separated into its component *RR* and *RS* diastereomers, each in >90% diastereomeric purity, using a porous graphite (Hypercarb by ThermoQuest Corp, Hypersil division) HPLC column. HPLC conditions used were Hypercarb 7-μm, 20 × 75 mm column, 83% B solvent isocratic at 15 mL/min, A = 90% water/10% MeOH/0.1% trifluoroacetic acid, B = 10% water/90% MeOH/0.1% trifluoroacetic acid, detection at 217 nm, 3 mg per injection, retention times for the *RR* and *RS* diastereomers = 10.9 and 13.1 min, respectively. *RR* isomer of **3x**: ^{1}H NMR (270 MHz, CD_3OD) δ 2.90 (s, 3H), 2.9 (m, 1H, overlapping resonance at 2.90), 3.16 (dd, 1H), 3.3 (m, 1H, overlapping NMR solvent resonance), 3.67 (dd, 1H), 4.58 (dd, 1H), 4.76 (dd, 1H), 6.83 (t, 1H), 6.85 (d, 1H), 7.05 (dd, 1H), 7.18 (d, 2H), 7.22−7.49 (m, 7H). *RS* isomer of **3x**: ^{1}H NMR (270 MHz, CD_3OD) δ 2.81 (dd, 1H), 2.88 (s, 3H), 3.08 (dd, 1H), 3.36 (dd, 1H), 3.59 (dd, 1H), 4.71 (dd, 1H), 4.9 (m, 1H, overlapping NMR solvent resonance), 6.83 (t, 1H), 6.85 (d, 1H), 7.01 (dd, 1H), 7.18 (d, 2H), 7.22−7.49 (m, 7H). Diastereomer assignments for products **3** were most easily made by comparing the ^{1}H NMR chemical shifts of the methylsulfonyl resonances at $\delta \sim 2.9$ ppm. The methylsulfonyl resonances of the *RR* diastereomers appeared slightly downfield of those of the *RS* diastereomers. Other diagnostic resonances were those between the δ 3.3 and 4.9 ppm solvent resonances in spectra taken in CD_3OD.

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(15) In most cases, stereochemical assignments were made by ^{1}H NMR comparison to the same or closely related analogues prepared in solution as previously described.[1a,c,d] See also Separation of Diastereomers **3x** in the Experimental Section.

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