

A Chiral Cyclohexanone Linked to Polystyrene for Solid-Phase Synthesis of Chiral α -Carbonyls

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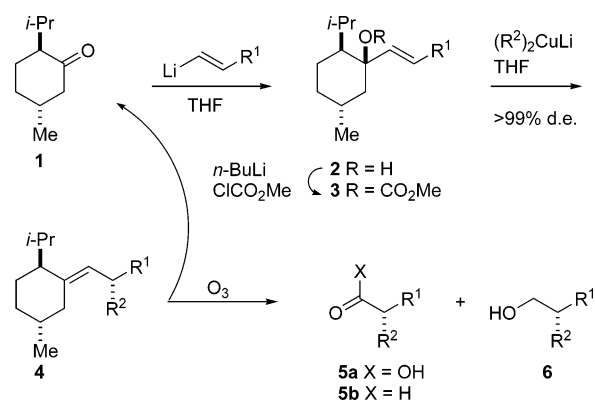
Two chiral cyclohexanones were linked to polystyrene resin. The polymer-bound auxiliaries were subjected to a sequence of four reactions, the last of which cleaves the desired α -chiral carbonyl compound off the resin, concurrently regenerating the resin-bound auxiliary in its original form. The resin can then be reused.⁷

Introduction

Polymer-bound reagents and catalysts have proven very useful for organic synthesis.¹ Among the several advantages they may provide are ease of removal, recyclability, and utilization of large excess without waste. The same advantages apply to resin-bound auxiliaries,² yet relatively few have been developed in the past decade or so,³ and many were derivatives of Evans' oxazolidinones used in alkylation,⁴ aldol additions,⁵ Diels–Alder,⁶ and 1,3-dipolar cycloadditions.⁷ Many of the disadvantages of using auxiliaries on a solid support vanish if their removal can coincide with the cleavage of the substrate from the resin and if the resin-bound auxiliary can be reused. However, to be able to fix a chiral auxiliary to a resin, it may be necessary to modify its original structure substantially, which may result in a decreased performance.

We have reported a method to make α -chiral carbonyl compounds based on menthone as a chiral auxiliary (Scheme 1).⁸ The method is equivalent to the alkylation of chiral enolates,⁹ and it enables the preparation of carbonyl compounds usually in >99% ee, some that cannot be prepared by the more classical approach of chiral enolate alkylation. In this 4-step sequence, the addition of vinylolithiums to menthone (**1**) proceeds with complete selectivity. The resulting axial alcohol **2** is difficult to derivatize but it was possible to convert it to a carbonate **3** quantitatively. The subsequent displacement by cuprate reagents proceeds with complete regioselectivity and total transfer of chirality (stereospecificity) to give exocyclic alkene **4**. The nature of the cuprate reagent does not affect the regioselectivity and stereospecificity.^{8,10} One minor drawback was that some aryl-substituted carbonates (**3**, R¹ = Ar) gave lower stereoselectivities with large cuprate reagents (e.g., **4**, R² = *tert*-butyl). Ozonolysis provides the desired carboxylic acid **5a**, aldehyde **5b**, or primary alcohol **6**, depending on workup conditions used. In addition, the chiral auxiliary is recovered in good overall yield. *p*-Menthane-3-carboxaldehyde, prepared in two steps from menthone, allows the synthesis of quaternary carbons of high optical purity.¹¹

Scheme 1



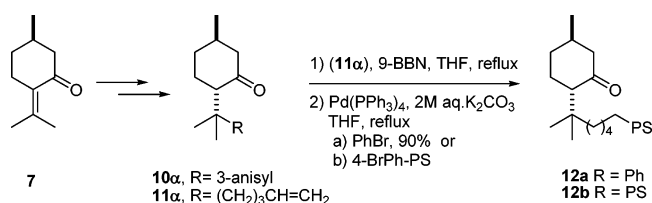
We deemed possible to fix a menthone-like molecule on a polymer resin to allow the same sequence of reactions to be conducted on solid support. Libraries of chiral carbonyl compounds could be prepared with three stages of divergence: the vinylolithiums, the cuprate reagents, and the ozonolysis workup. Importantly, the resin is in principle reusable, since the oxidative cleavage regenerates the initial carbonyl on the auxiliary. Moreover, there would be no need for chromatographic separation of the auxiliary from the desired compound, which is not the case in the solution-phase sequence. We did not anticipate problems in terms of the regio- and stereoselectivity of the key cuprate displacement step in the solid-phase sequence. However, the nature of the menthone-like auxiliary would greatly affect the stereoselectivity of the vinylolithium addition step. This is why we elected to start with molecules with structures as close as possible to the menthone skeleton.

Results and Discussion

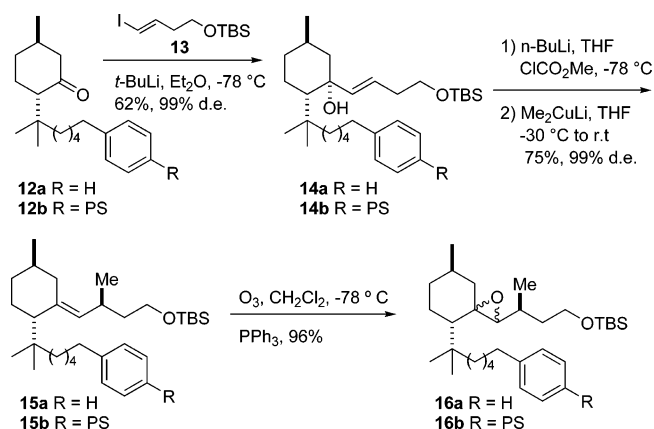
Auxiliaries Based on Pulegone. The first auxiliaries we built possessed a structure close to that of menthone and were made from the commercially available (+)-pulegone **7** (Scheme 2). We figured that a cuprate addition on pulegone would allow the introduction of a linker for its subsequent attachment to a resin. The extra bulk around the ring ketone was not a concern, initially. However, it turned out to be fatal to this type of auxiliary (*vide infra*). Ozone is a harsh

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Scheme 2



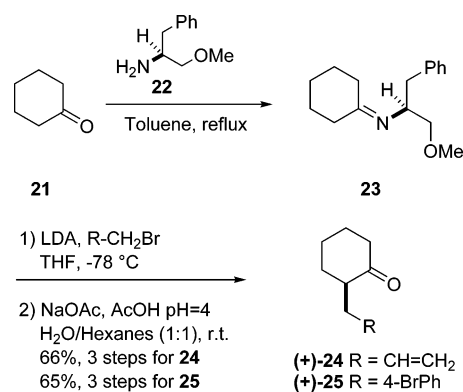
Scheme 3



oxidant, and we wanted as few functionalities as possible on the linker. Heteroatoms in general were to be avoided if possible, though ethers are fairly unreactive and were considered relatively safe, even if they can be oxidized by ozone in some instances.¹² Kakiuchi and co-workers have linked a menthol-based auxiliary on a PEG–Wang resin via the phenolic hydroxyl.¹³ Benzyls and aromatics could be tolerated on the linker, since many resins are made up largely of these groups, and ozone has been shown to be useful for solid-phase chemistry.¹⁴ The syntheses of **10** and **11** are described in the Supporting Information. Compound **11 α** was subjected to hydroboration with 9-BBN, and the resulting borane was coupled with bromobenzene under the Suzuki conditions¹⁵ to afford **12 a** in good yield (Scheme 2). Compound **12 a** was to serve as a solution-phase model for **12 b** . Auxiliary **11 α** was coupled to BrPS under the same reaction conditions to give **12 b** , but no effort was made to characterize the resulting solid-supported auxiliary, since it eventually proved unusable (vide infra).

Scheme 3 displays the sequence of reactions that were performed starting with auxiliary **12 a** . Vinyl iodide **13** underwent a lithium–iodide exchange with *t*-BuLi, and the resulting vinyllithium added, as expected, with complete stereoselectivity to ketone **12 a** to give alcohol **14 a** . The carbonate derived from **14 a** was subjected to a reaction with lithium dimethyl cuprate, which to our delight proceeded to give adduct **15 a** with complete transfer of chirality. However, we were disappointed to find that ozonolysis of **15 a** did not cleave the auxiliary at all, but instead, gave an excellent yield of epoxide **16 a** . Epoxides are known to arise from the ozonolysis of sterically crowded double bonds.¹⁶ This was a disastrous result because two extra steps would be required to open the epoxide to a diol and cleave the auxiliary with periodate. We did not investigate this possibility, as the total number of steps would become prohibitively high. Just in case the outcome would be different, we repeated

Scheme 4



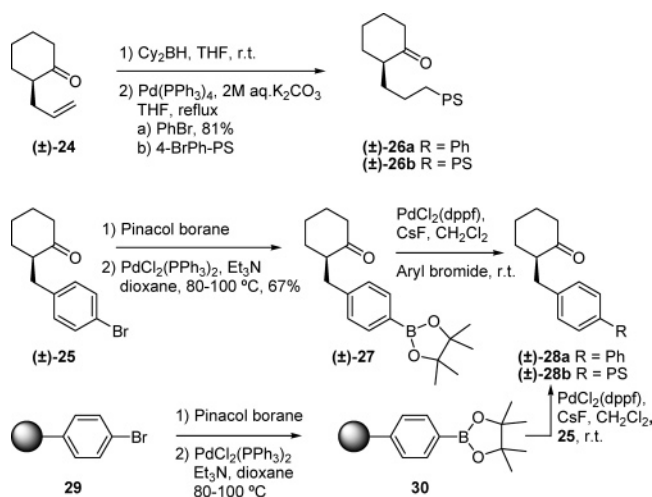
this same sequence on solid phase using **12 b** , but no product came out of the resin upon ozonolysis, confirming our fear that here, too, the corresponding epoxide was probably the major product (Scheme 3, **12 b** → **16 b**).

Auxiliary **10 α** suffered a similar fate starting with vinyl iodide **17** where the sequence before ozonolysis went very well but the ozonolysis furnished only 20% of the desired product (shown in the Supporting Information). It is important to note that other oxidizing agents do not cleave double bonds in compounds such as **4**, **15**, or **19**, including OsO₄ and RuO₄. Even ozone cleaves the double bond rather slowly in menthone-derived compounds, such as **4**. Therefore, at that point, we decided to use auxiliaries with less steric bulk next to the ketone in order to allow the ozonolysis step to take place normally.

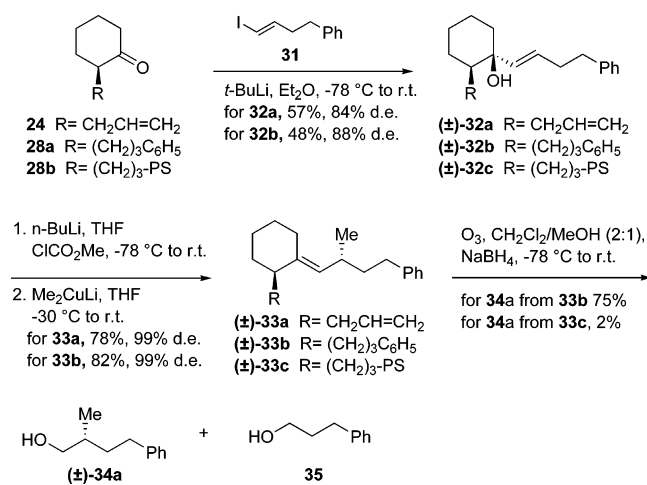
Other Cyclohexanone Auxiliaries. After considering several alternatives, we elected to prepare (+)-2-allyl-1-cyclohexanone **24** as described in the literature¹⁷ and (+)-2-(4-bromophenyl)-1-cyclohexanone **25** (Scheme 4). Compound **24** was obtained optically pure, as reported, whereas compound **25** was only 72% ee. However, after three recrystallizations in 2-propanol, auxiliary **25** was isolated in >99% ee in a remarkably high overall yield of 52%. It was then converted to the boronate **27** without racemization. Although both auxiliaries were prepared in >99% ee, the initial trials were actually conducted on the racemic material for economic reasons. Altered conditions were necessary to fix auxiliary **24** to the resin via the Suzuki coupling because of competing reduction of the ketone in the hydroboration step (Scheme 5). Unapparent in Scheme 5 is the fact that these conditions were, in fact, racemizing the starting ketone **24**. Auxiliary **25** was converted to the boronate **27** and coupled to bromobenzene to give **28 a** . Those two reactions were nonracemizing when the conditions shown in Scheme 5 were utilized, as we later demonstrated. We successfully coupled boronate **27** to bromopolystyrene **29**, too, and obtained **28 b** . Alternatively, bromide **25** could be converted directly to **28 b** using pinacolboratopolystyrene **30**, which was made from bromopolystyrene **29** following the conditions developed by Y. Masuda.¹⁸

The sequence of reactions was first tested with racemic **26 a** in solution (Scheme 6). We noticed a decrease in the selectivity in the addition of the vinyllithium **31** to **26 a** . The ratio of 94:6 corresponds closely to the calculated ratio of the equilibrium between the two chair conformations of **26 a** , if we assume a preference for equatorial attack on both

Scheme 5



Scheme 6



conformations (Figure 1). In comparison, the methyl and isopropyl groups in menthone **1** ensure a single conformation onto which the vinyl lithium may attack, resulting in a completely selective equatorial addition. We decided to make do with this small decrease in selectivity because adding an extra alkyl group on the cyclohexanone did not appear particularly easy. The desired isomer of **32b** was separated from its epimer by normal silica gel column chromatography, and the S_N2' displacement by cuprate reagents of the carbonate derived from **32b** gave a single diastereomer **33b**. Ozonolysis proceeded uneventfully to afford racemic **34a**. The overall yield of the unoptimized sequence in solution was 30% for four steps from auxiliary **26a**, or an average of 74% yield per step. We repeated the sequence on solid phase

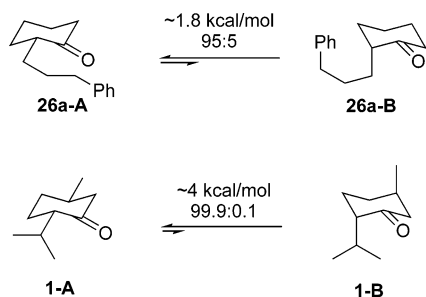
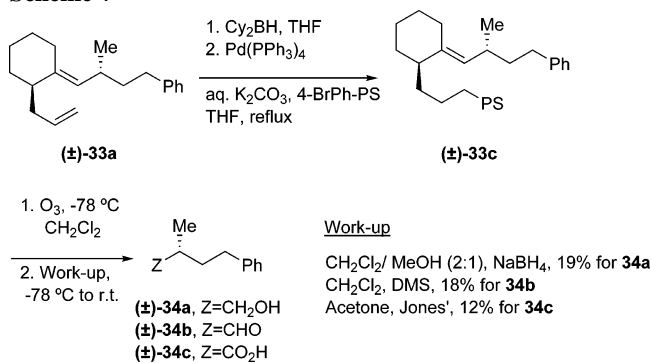


Figure 1. Calculated energy difference between the two chair conformations for **1** and **26a**.

Scheme 7



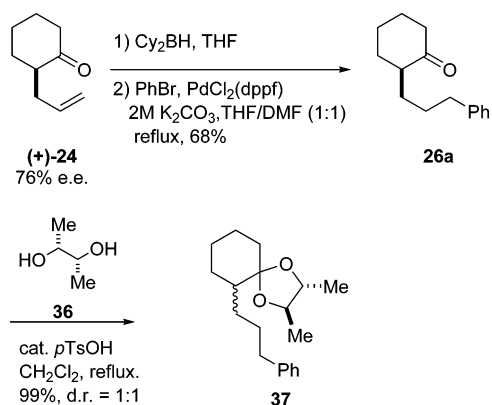
using **26b** and obtained an overall yield of 2% of alcohol **34a** for 5 steps, which corresponds to a 46% yield per step (Scheme 6). Although the overall yield was seemingly low, this was an unoptimized pass, and the isolated compound was very clean (estimated >80% pure by ¹H NMR), the only other contaminant being alcohol **35** (~3% of the mixture). We considered this result as very positive. The formation of alcohol **35** was not surprising and likely emanates from an incomplete carbonate formation on the solid support, giving **33c** contaminated with leftover **32c**. The latter will react with ozone to give **35**. This problem can be circumvented with excess base and carbonate, although we cannot monitor the reaction. Incomplete carbonate formation is seldom observed when conducted in solution. It can be monitored by TLC, and the leftover **32b** would be removed chromatographically.

We elected to first optimize the ozonolysis step on solid phase. To that end, intermediate **33a** was prepared in solution (Scheme 6) and then fixed to the resin (Scheme 7) using the hydroboration/Suzuki coupling protocol to give **36**. A single large batch of **36** was used to optimize the ozonolysis step to remove the effect of the coupling step on the overall yield. Solvent, reaction time and temperature, and workup conditions were varied systematically. Scheme 7 shows the optimized conditions for the formation of the primary alcohol **34a**, the aldehyde **34b**, and the carboxylic acid **34c**. The yield shown was that obtained for both the coupling and ozonolysis steps, and at this stage, we could not determine the yield of each individual step, although we suspected the coupling step to be the culprit of the modest yields.

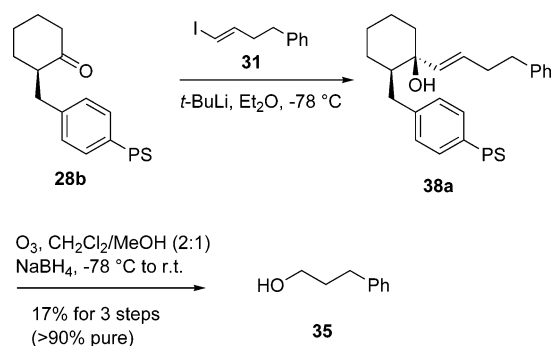
We were now ready to try the whole sequence of reactions on solid phase. As alluded to earlier, repeating the whole sequence of reaction starting with the optically enriched auxiliary **24** (76% ee) furnished alcohol **34a** in racemic form. We were able to determine that the optimized conditions for the Suzuki coupling were, in fact, responsible for the racemization of the ketone **24** prior to its linking to the resin. Indeed, treating (+)-**24** (76% ee) with the conditions shown in Scheme 8 gave (\pm)-**26a**, which was converted to the chiral acetal **37**. The latter was isolated as a 1:1 mixture of diastereomers. By contrast, **24** (76% ee) was converted under the same reaction conditions to the corresponding cyclic acetal (not shown), yielding an 88:12 ratio of diastereomers and, therefore, establishing that the acetal formation was not racemizing **26a**. For this reason, further development with auxiliary **24** was stopped.

In the meantime, the sequence of reactions was also being optimized for solid phase with auxiliary **28b** (cf. Scheme

Scheme 8



Scheme 9



5). The optimized conditions for the ozonolysis shown in Scheme 7 were also optimal for this auxiliary. Optimizing the other steps individually was not easy because of our choice of using a noncleavable, chemically unreactive linker. However, we could optimize the vinylolithium addition reaction as shown in Scheme 9. A single large batch of **28b** was submitted to the addition reaction of vinylolithium derived from **31**, and the resulting resin-bound allylic alcohol was ozonolyzed. The number of equivalents of **31** and *t*-BuLi, the solvent, temperature, and reaction time were varied systematically while the ozonolysis step was kept identical for all trials. We were satisfied to reproducibly get 17% of alcohol **35** under those conditions (note that the Suzuki coupling reaction to make **28b** was not yet optimized).

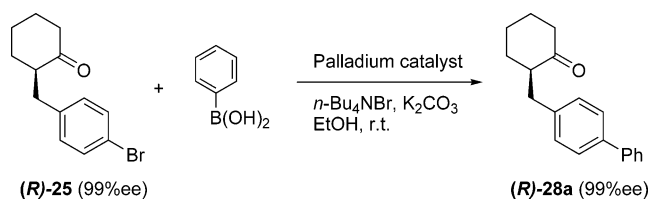
We decided to test the overall yield of the whole five-step sequence. A small library of compounds was made to test the efficiency of our system and is reported in Table 1. A single batch of **28b** was prepared by Suzuki coupling of **27** with 4-bromopolystyrene. Initial attempts to apply the Suzuki coupling conditions to 4-bromopolystyrene beads in individual IRORI Kans gathered inside a larger vessel gave us ~60% yield of **28b** on the basis of recovered starting boronate **27**. We surmised that the problem could be due to inadequate mixing compounded by the low solubility of CsF in dichloromethane. Instead, the same reaction was carried out on the free resin inside a single flask, and we obtained linkage of the auxiliary in >95% on the basis of recovered starting boronate **27** and the weight of the resin. The beads of resin-bound **28b** were then separated into three unequal portions and charged in separate flasks of vials. In each vessel was added a different vinylolithium reagent, giving rise to alcohols **38a–c** (cf. Scheme 11). Each of the three batches was further divided again in six, two, and four portions,

Table 1. Small Library of Compounds Made from One Batch of **28b** with Three Points of Divergence^a

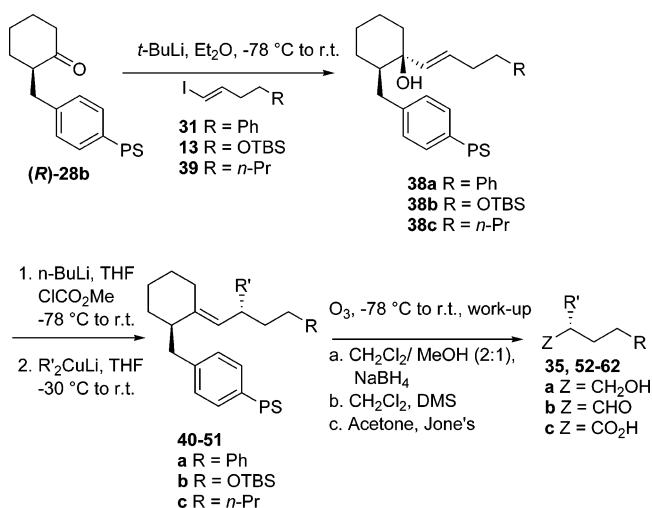
entry	S.M.	Prd	R	R'	Z	yield (%) ^b	yield/step (%)
1	40a	34a	Ph	Me	CH_2OH	8	60
2	40a	34b	Ph	Me	CHO	18	71
3	40a	34c	Ph	Me	COOH	9	62
4	41a	52a	Ph	Ph	CH_2OH	14	68
5	41a	52b	Ph	Ph	CHO	10	63
6	41a	52c	Ph	Ph	COOH	9	62
7	42a	53a	Ph	<i>t</i> -Bu	CH_2OH	3	50
8	42a	53b	Ph	<i>t</i> -Bu	CHO	9	62
9	42a	53c	Ph	<i>t</i> -Bu	COOH	10	63
10	43a	54a	Ph	<i>s</i> -Bu	CH_2OH	9	62
11	43a	54c	Ph	<i>s</i> -Bu	COOH	11	64
12	44a	55a	Ph	<i>n</i> -Bu	CH_2OH	4	53
13	44a	55b	Ph	<i>n</i> -Bu	CHO	7	59
14	44a	55c	Ph	<i>n</i> -Bu	COOH	10	63
15	45a	56a	Ph	1-naphth	CH_2OH	6	57
16	45a	56b	Ph	1-naphth	CHO	4	53
17	46b	57a	OTBS	Me	CH_2OH	8	60
18	46b	57b	OTBS	Me	CHO	12	66
19	47b	58a	OTBS	Ph	CH_2OH	4	53
20	47b	58b	OTBS	Ph	CHO	8	60
21	48c	59a	<i>n</i> -Pr	Me	CH_2OH	5	55
22	49c	60a	<i>n</i> -Pr	<i>s</i> -Bu	CH_2OH	8	60
23	50c	61a	<i>n</i> -Pr	$\text{CH}_2\text{Si}(\text{Me})_3$	CH_2OH	7	59
24	51c	62a	<i>n</i> -Pr	Ph	CH_2OH	8	60
25	51c	62b	<i>n</i> -Pr	Ph	CHO	16	69
26	51c	62c	<i>n</i> -Pr	Ph	COOH	5	55

^a cf. Scheme 11. ^b Yield of isolated pure products after chromatography, calculated for five steps.

Scheme 10



Scheme 11



respectively. Each of the 12 stacks of beads, bearing one of three different alcohols, was treated with 5 equiv of *n*-BuLi and 7 equiv of methyl chloroformate and then 5 equiv of different cuprate reagents (Table 1). Finally, the resulting cuprate adducts were treated with ozone, followed by one of three different workup conditions to give a primary

alcohol, an aldehyde, or a carboxylic acid. Not all of these three combinations were carried out, but in total, a small library of 26 compounds was obtained. Overall yields varied from 4 to 18%, with a median yield of \sim 10%. This corresponded to more than 60% yield per step, a result that satisfied us, given the relatively high purity of the compounds obtained as judged by ^1H NMR (after chromatography). The chemical purity of the crude products was generally acceptable: alcohols were obtained between 80 and 90% purity; aldehydes were around 80% purity; the purity of the carboxylic acids was more variable but $>70\%$ in the crude mixtures.

Nonracemizing Suzuki Coupling Conditions. There have been few reports in the literature regarding the investigation of mild (room temperature) Suzuki coupling reaction conditions.^{19,20} However, no generally applicable set of reaction conditions has yet been found to effect this reaction. In many cases, the reaction conditions and, in particular, the base that is necessary are not entirely compatible with the functional groups present in the desired substrate, especially those that can lead to racemization of the substrate. Aqueous carbonate is the most frequently employed.²¹ Recent efforts to solve this difficulty have focused on the use of less basic reagents, such as tripotassium phosphate²² and fluoride salts²³ in hydrocarbon solvents.

To the best of our knowledge, there has been only one report by Shieh and co-workers in which racemization issue of the starting substrate was addressed.²⁴ They have carried out the Suzuki coupling of *N*-Boc-(*S*)-tyrosine triflate with phenylboronic acid using heterogeneous conditions and 3 mol % of tetrakis(triphenylphosphine)palladium(0) and anhydrous potassium carbonate in toluene at 90 °C and obtained the corresponding biaryl product in 94% yield without racemization. However, the same reaction conditions gave racemized biaryl Suzuki product **28a** in our case, starting from chiral substrate (*R*)-**27** (99% ee). We therefore initiated a preliminary study aimed at finding conditions that would not racemize (*R*)-**25** or (*R*)-**27**, first in solution, then on solid phase, by carrying out the whole sequence of reactions and analyzing **34a** for stereochemical purity.

An initial screen of various Pd catalysts (2–10 mol %), including Pd(OAc)₂, PdCl₂, Pd₂(dba)₃, PdCl₂(PPh₃)₂, Pd(PPh₃)₄, PdCl₂(C₆H₆CN)₂, and PdCl₂(dppf), with K₃PO₄ (3 equiv) as a base and Bu₄NBr (5 mol %) as an additive suggested that PdCl₂(dppf) was superior in terms of yield for the Suzuki coupling of (*R*)-**25** with phenylboronic acid (Scheme 10). In addition, ethanol as solvent gave the best yield of **28a**. However, under these conditions, all catalysts, including PdCl₂(dppf) were giving complete or partial racemization. We therefore screened different bases and solvents for this reaction (Table 2). Carbonate bases gave significant racemization in ethanol (entries 1–2) and lower conversions in CH₂Cl₂ (entry 3). The PdCl₂(dppf)/K₃PO₄ system in ethanol gave a good yield of biaryl product **28a** at room temperature but with some racemization (entry 4). The best combination was PdCl₂(dppf)/CsF or KF catalyst system in dry CH₂Cl₂ (entries 6 and 8), which catalyzed the Suzuki coupling of aryl bromide **29** with arylboronic acid at room temperature without racemization. Other bases and

Table 2. Effect of Base and Solvent on the Suzuki Cross Coupling of Aryl Bromide **25** with Phenylboronic Acid^a

entry	base (equiv)	solvent	time (h)	yield (%) ^c of (<i>R</i>)- 28a (% ee) ^d	yield (%) ^c of (<i>R</i>)- 25 (% ee) ^b
1	K ₂ CO ₃ (3)	EtOH	4	91 (30)	0
2	CsCO ₃ (3)	EtOH	4	95 (30)	0
3	CsCO ₃ (3)	CH ₂ Cl ₂	48	76	24 (98)
4	K ₃ PO ₄ (2)	EtOH	26 ^e	100 (93)	0
5	CsF (3)	EtOH	4	86 (98)	08 (98)
6	CsF (3)	CH ₂ Cl ₂	48	97 (98)	02 (98)
7	KF (3)	EtOH	26 ^e	91 (98)	03 (98)
8	KF (3)	CH ₂ Cl ₂	48	88 (98)	12 (98)
9	NEt ₃ (10)	EtOH	48	73 (92)	27 (92)
10	ⁱ Pr ₂ NH (3)	EtOH	48	70	30 (82)
11	Na ₃ PO ₄ ·12H ₂ O (3)	EtOH	26 ^e	55	45 (98)
12	KOAc (3)	EtOH	26 ^e	23	77 (98)
13	NaOAc (3)	EtOH	26 ^e	12	88 (98)

^a Conditions: **25** (1 equiv), PhB(OH)₂ (1.5 equiv), Bu₄NBr (5 mol %), and PdCl₂(dppf) (10 mol %). ^b Percent enantiomeric excess of recovered auxiliary **25**, determined by HPLC (Chiralcel OD column). ^c Isolated yield. ^d Percent enantiomeric excess of **28a**, determined by converting it into the corresponding ketal form with chiral (*R,R*)-2,3-butanediol. ^e No further conversion up to 48 h.

Table 3. Homochiral Compounds **52–54** and **60** Made from **28b**

entry	S.M.	Prd	R	R'	Z	yield (%) ^a	er ^b
1	41a	52a	Ph	Ph	CH ₂ OH	14	93:7
2	41a	52b	Ph	Ph	CHO	10	91:9
3	41a	52c	Ph	Ph	COOH	9	90:10
4	42a	53a	Ph	<i>t</i> -Bu	CH ₂ OH	9	92:8
5	42a	53c	Ph	<i>t</i> -Bu	COOH	10	95:5
6	43a	54a	Ph	<i>s</i> -Bu	CH ₂ OH	11	95:5 ^c
7	43a	54c	Ph	<i>s</i> -Bu	COOH	11	92:8 ^c
8	43c	60a	<i>n</i> -Pr	<i>s</i> -Bu	CH ₂ OH	8	95:5 ^c

^a Yield of isolated pure products, calculated for five steps. ^b Determined by HPLC using a Chiralcel OD column. ^c Determined by GC/MS of the corresponding Mosher ester.

conditions gave lower yields, racemization, or both (see entries 5, 7, and 9–13).

With these nonracemizing Suzuki coupling conditions in hand, the resin-bound auxiliary **28b** was prepared and subjected to the four-step sequence (Scheme 11, Table 3). Agreeably, the overall yield of the sequence was as high with these new conditions (between 4 and 14% yield for 5 steps), and the purity of the crude compounds was close to 90%, as estimated by ^1H NMR. The optical purity of compounds in Table 3 was satisfactory. We judged that a small library of eight homochiral compounds was enough to demonstrate unambiguously that the chirality of the auxiliary is efficiently transferred to the final product. Knowing that the addition step procures an \sim 94:6 mixture²⁵ of alcohols **38** (vide supra) every other step proceeded with preservation of the stereochemical integrity of the starting auxiliary. Several compounds were made, including alcohols (entries 1, 4, 6, and 8), aldehydes (entry 2), and acids (entries 3, 5, and 7) in a library-style synthesis starting from a single batch of **28b**.

Conclusion

We have successfully developed a novel polystyrene-based resin bearing a chiral auxiliary capable of producing chiral

carbonyl compounds and alcohols in high enantiomeric excess. The sequence is short (four steps from the auxiliary-bearing resin) and affords good overall yields of material in an acceptable level of purity.

Experimental Section

All reactions were carried out under an atmosphere of argon. Ethyl ether, toluene, and benzene were dried over metallic sodium using benzophenone as an indicator; tetrahydrofuran was dried over both sodium and potassium using the same indicator. Dichloromethane, dimethyl formamide, triethylamine, acetonitrile, and diisopropylamine were distilled over calcium hydride. Hexanes were purchased anhydrous from Aldrich. Thin-layer chromatography was performed using 0.25-mm Silica Gel 60 F254 (EM Science-Merck), and flash chromatography using silica gel Kieselgel 60 (230–400 mesh ASTM). Hewlett Packerd (HP 1100 series) HPLC was used for checking optical purity of synthetic analogues (Chiralcel OB and Chiralcel OD column, 0.46 cm × 25 cm, 1–20% *i*PrOH/hexane as a gradient eluent, flow rate 1 mL/min, 10 μ m, λ = 220, 230, 254, and 270 nm).

All nuclear magnetic resonance spectra were taken in deuterated chloroform on a Bruker AC-300 (¹H, 300 MHz; ¹³C, 75 MHz). Chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane. The splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and ABq, AB quartet. The infrared spectra (IR) were determined on a Perkin-Elmer 1600 Fourier transform spectrometer. The IR spectra were determined neat, unless otherwise stated. The melting points were performed on a Mettler Toledo model 62. High- and low-resolution mass spectra (HRMS and LRMS) were obtained with a Micromass spectrometer ZAB-1F model VG. $[\alpha]_D$ were measured with a Perkin-Elmer Polarimeter 343.

2-(4-Bromobenzyl)cyclohexanone (25). To a stirred solution of anhydrous diisopropylamine (4.62 g, 6.4 mL, 45.70 mmol) in dry THF (85 mL) was added *n*-butyllithium (1.78 M solution in pentane, 25.8 mL, 45.90 mmol) slowly over a 15-min period at 0 °C, and the reaction mixture was stirred for 15 min at that temperature. After that time, it was cooled to –30 °C, and imine **23** (10.68 g, 43.52 mmol) in dry THF (45 mL) was added slowly over a period of 20 min. Stirring was continued at that temperature for 2 h. The reaction was then cooled to –78 °C and 4-bromobenzyl bromide (11.41 g, 45.67 mmol) in dry THF (30 mL) was added over a period of 45 min. The mixture was allowed to stir at that temperature for 2 h, then it was poured in a saturated solution of aqueous NaCl (500 mL) and extracted in diethyl ether (3 × 200 mL) to yield a sensitive imine product (18.40 g, 100%). The product was hydrolyzed immediately without further purification. ¹H NMR (300 MHz, CDCl₃): δ 7.5–7.35 (m, 5H), 7.25–6.95 (m, 4H), 3.65–3.45 (m, 2H), 3.4–3.32 (m, 2H), 3.28 (s, 3H), 3.2 (m, 1H), 3.0 (dd, 1H, *J* = 13.1, 3.3 Hz), 2.78–2.6 (m, 2H), 2.6–2.2 (m, 4H), 1.85 (m, 1H), 1.5 (m, 1H), 1.4–1.2 (m, 2H). LRMS (*m/z*): 413 (M⁺), 415 (M⁺).

To a stirred solution of the imine (18.37 g) in pentane (250 mL) was added a buffer solution [NaOAc (14.36 g), AcOH (33.0 mL), distilled H₂O (152 mL)], and the reaction

mixture was stirred at room temperature for 1.5 h. After that time, the pentane layer was separated, and the aqueous portion was extracted with pentane (2 × 200 mL). The combined pentane layers were washed with 1 N HCl (200 mL); water (200 mL); 5% aqueous NaHCO₃ (200 mL); water (200 mL); and, finally, with brine. Flash chromatography on silica gel using hexane and then 5% ethyl acetate/hexane as eluent gave a white solid (7.98 g, 65%). Compound **25** was determined to be 72% ee by chiral HPLC. It was then recrystallized three times in warm 2-propanol. The auxiliary was obtained in 52% (6.38 g) overall yield after three recrystallizations, and the percent ee was >99% as determined by chiral HPLC. **25**: mp = 50–52 °C. ¹H NMR (300 MHz, CDCl₃): δ 7.38 (d, 2H, *J* = 8.2 Hz), 7.03 (d, 2H, *J* = 8.8 Hz), 3.15 (dd, 1H, *J* = 13.75, 4.95 Hz), 2.55–2.25 (m, 4H), 2.1 (m, 2H), 1.85 (m, 1H), 1.6 (m, 2H), 1.3 (m, 1H). ¹³C NMR (75 MHz, CDCl₃): δ 139.4 (s), 131.3 (d), 130.9 (d), 119.7 (s), 52.3 (d), 42.1 (t), 34.9 (t), 33.5 (t), 28.0 (t), 25.1 (t). HRMS calcd for C₁₃H₁₅BrO: 266.0306. Found: 266.0301. LRMS (*m/z* (relative intensity)): 266 (M⁺, 60), 268 (M⁺, 60), 237 (15), 239 (15), 209 (15), 171 (15), 169 (100), 171 (100). IR (CHCl₃): 3059, 3025, 2928, 2857, 1705 (s), 1588, 1497 cm⁻¹. $[\alpha]_D$ = +32.59 (*c* = 2.47, CHCl₃).

2-[4-(4,4,5,5-Tetramethyl-[1,3,2]dioxaborolan-2-yl)benzyl]cyclohexanone (27). To a stirred solution of starting bromide **25** (15.0 g, 56.17 mmol) in anhydrous 1,4-dioxane (225 mL) was added dichlorobis(triphenylphosphine) palladium(II). CH₂Cl₂ adduct (1.83 g, 2.24 mmol) and the reaction mixture was stirred at room temperature for 15 min. Anhydrous triethylamine (17.05 g, 23.49 mL, 168.53 mmol), followed by pinacolborolane (10.78 g = 12.22 mL, 84.26 mmol), was added to the reaction. The reaction mixture was then heated at 80–100 °C for 3 h. After that time, it was cooled to ambient temperature, dioxane was removed under vacuum, and water (250 mL) was poured in. The aqueous phase was extracted with diethyl ether (3 × 150 mL), and the combined ether layers were washed with water and brine, dried over anhydrous MgSO₄, filtered, and concentrated under vacuum to yield the crude compound. The product was purified by flash chromatography on silica gel using 5–15% ethyl acetate/hexane as eluent to yield boronate **27** as a low-melting white solid (11.86 g, 67%) and some dehalogenated compound (1.8 g, 17%). **27**: mp = 66–68 °C. ¹H NMR (300 MHz, CDCl₃): δ 7.71 (d, 2H, *J* = 7.69 Hz), 7.15 (d, 2H, *J* = 7.69 Hz), 3.23 (dd, 1H, *J* = 13.75, 4.4 Hz), 2.55–2.25 (m, 4H), 2.0 (m, 2H), 1.8–1.5 (m, 4H), 1.32 (s, 12H). ¹³C NMR (75 MHz, CDCl₃): δ 212.1 (s), 143.7 (s), 134.6 (d), 128.4 (d), 83.5 (s), 52.2 (d), 41.9 (t), 35.5 (t), 33.2 (t), 27.8 (t), 24.9 (t), 24.7 (q). HRMS calcd for C₁₉H₂₇BO₃: 314.2053. Found: 314.2063. LRMS (*m/z* (relative intensity)): 314 (M⁺, 100), 295, 271, 217. IR (CHCl₃): 3086, 3054, 2957, 1702 (s), 1605, 1358 cm⁻¹. $[\alpha]_D$ = +17.40 (*c* = 1.58, CHCl₃).

Synthesis of Resin-Bound Auxiliary 28b. To an oven dried round-bottomed flask was added 4-bromopolystyrene (1.59 g, 3.18 mmol, 2.0 mmol/g) in anhydrous dichloromethane (50 mL). The resin was allowed to swell by letting it stir for 10 min. PdCl₂(dppf)·CH₂Cl₂ (0.259 g, 0.318 mmol) catalyst was added, and the reaction mixture was stirred at

room temperature for 15 min. Pinacolboronate ester **27** (1.49 g, 4.77 mmol) in dry dichloromethane (10 mL) was added to the reaction mixture, followed by anhydrous cesium fluoride (1.45 g, 9.55 mmol). The mixture was stirred at room temperature for 40 h, after which time the resin was filtered out and successively washed with CH_2Cl_2 , H_2O , DMF, H_2O , THF, MeOH, CH_2Cl_2 , and MeOH (30–40 mL of each \times 3–5 min stirring). The resin was dried under high vacuum for 6 h to yield the resin-bound auxiliary **28b**.

Solid-Phase Sequence To Obtain Resin-Bound Allylic Alcohol 38a. To a stirred solution of vinyl iodide **31** (2.46 g, 9.54 mmol) in dry ether (50 mL) was slowly added *tert*-butyllithium (1.7 M in pentane, 11.23 mL, 19.1 mmol) over a period of 15–20 min at -78°C under an argon atmosphere. The reaction mixture was then stirred at -78°C for 1.5 h and at room temperature for 45 min, then the reaction mixture was again chilled to -78°C and was transferred via cannula to a precooled (-78°C) solution of the resin-bound auxiliary **28b** (1.59 g, 3.18 mmol) in dry THF (30 mL). Stirring was continued for 20 h while slowly warming to room temperature. After that time, the resin was filtered out and copiously washed with THF, THF/ H_2O (1:1), H_2O , THF, CH_2Cl_2 , and MeOH (30–40 mL, with 3–5 min stirring each wash). The resin was dried under high vacuum for 6 h to yield the alcohol intermediate **38a**.

Solid-Phase Sequence To Obtain The Carbonate Intermediate. To an oven dried round-bottomed flask was added alcohol **38a** (1.59 g, 3.18 mmol) in dry THF (40 mL), and it was stirred at room temperature for 10 min to swell the resin. *n*-Butyllithium (2.3 M solution in hexane, 6.91 mL, 15.91 mmol) was added slowly over a period of 10 min at -78°C , and the reaction was stirred at the same temperature for 2 h. Then methylchloroformate (2.09 g, 1.71 mL, 22.27 mmol) was added to the above reaction mixture at that same temperature, and stirring was continued for 20 h while allowing the mixture to slowly warm to room temperature. Then the resin was filtered and generously washed with THF, THF/ H_2O (1:1), H_2O , THF, CH_2Cl_2 , and MeOH (30–40 mL of each \times 3–5 min stirring). The resin was dried under high vacuum for 6 h to yield the corresponding carbonate compound.

Solid-Phase Sequence To Obtain Cuprate Adduct 41a. To a stirred solution of anhydrous LiI (2.12 g, 19.10 mmol) and CuI (3.02 g, 15.91 mmol) in dry THF (100 mL) was slowly added phenyllithium (1.72 M solution in cyclohexanes-ether, 18.5 mL, 31.82 mmol) over a period of 20 min at -65°C . The reaction mixture was then stirred for 2 h while it was allowed to warm slowly to -30°C . It was again chilled to -65°C and was cannulated to a precooled (-78°C) solution of the resin-bound carbonate compound. The reaction was then stirred for 20 h while allowing the mixture to slowly warm to room temperature. Then the resin was filtered and washed with a 9:1 mixture of $\text{NH}_4\text{Cl}/\text{NH}_4\text{OH}$, then H_2O , THF/ H_2O (1:1), THF, CH_2Cl_2 , and MeOH (40–50 mL of each \times 3–5 min stirring). The resin was dried under high vacuum for 6 h to yield the cuprate compound **41a** (R and R' = Ph).

Procedure for Ozonolysis on Solid Phase To Obtain 2,4-Diphenylbutan-1-ol (52a). Alkene compound **41a** (R

and R' = Ph) (0.75 g, 1.50 mmol) was dissolved in dry CH_2Cl_2 (40 mL) and stirred at room temperature for 10 min to allow the resin to swell, and ozone was bubbled in the cold (-78°C) mixture. When the solution remained light blue (nearly 3–5 min), indicating the excess ozone, the flow was stopped, and nitrogen was bubbled to remove excess ozone. The solution was then diluted with dry MeOH (15 mL), and NaBH_4 (0.28 g, 7.50 mmol) was added at -78°C and continued stirring for 20 h while allowing the mixture to slowly warm to room temperature. The resin was filtered and washed with CH_2Cl_2 and MeOH (30–40 mL each). The combined filtrates were concentrated under vacuum, poured into water, and extracted with diethyl ether. The combined ether layers were washed with water and brine, dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The ^1H NMR of the crude product showed the required compound in more than 90% purity. The crude compound was purified by flash chromatography on silica gel to obtain pure chiral alcohol **52a** as a colorless thick liquid (93:7 er) in 14% isolated overall yield for five steps. ^1H NMR (300 MHz, CDCl_3): δ 7.4–7.11 (m, 10H), 3.8–3.69 (m, 2H), 2.86–2.77 (m, 1H), 2.59–2.43 (m, 2H), 2.09–1.86 (m, 2H), 1.36 (brd, 1H). ^{13}C NMR (75 MHz, CDCl_3): δ 141.89 (s), 131.15 (s), 128.75 (d), 128.3 (d), 128.17 (d), 126.88 (d), 125.78 (d), 67.61 (t), 48.07 (d), 33.58 (t), 33.39 (t). HRMS calcd for $\text{C}_{16}\text{H}_{18}\text{O}$: 226.1358. Found: 226.1353. LRMS (m/z (relative intensity)): 226 (M^+ , 10), 208 ($\text{M} - \text{H}_2\text{O}$, 15), 117 (40), 104 (25), 91 (100). IR (neat): 3500–3300 (brd), 3061, 2929, 2863, 1602, 1493, 1453 cm^{-1} . $[\alpha]_D = +6.92$ ($c = 1.82$, CHCl_3).

Procedure for Ozonolysis on Solid Phase To Obtain 2,4-Diphenylbutyaldehyde (52b). Alkene **41a** (R' = Ph) (0.75 g, 1.50 mmol) was dissolved in dry CH_2Cl_2 (40 mL) and stirred at room temperature for 10 min to allow the resin to swell, and ozone was bubbled in the cold (-78°C) mixture. When the solution remained light blue (nearly 3–5 min), indicating the excess ozone, the flow was stopped, and nitrogen was bubbled to remove excess ozone. Dimethyl sulfide (10 equiv) was added at -78°C and continued stirring for 20 h while allowing the mixture to slowly warm to room temperature (by removing the cooling bath). The resin was filtered out, and the resin was washed with CH_2Cl_2 and MeOH (30–40 mL each). The combined filtrates were concentrated under vacuum, poured into water, and extracted with diethyl ether. The combined ether layers were washed with water and brine, dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The ^1H NMR of the crude product showed the required aldehyde in $\sim 80\%$ purity. The crude compound was purified through flash silica gel chromatography to obtain the pure chiral aldehyde **52b** as a colorless liquid (91:9 er) in 10% isolated yield for five steps. ^1H NMR (300 MHz, CDCl_3): δ 9.68 (d, 1H, $J = 2.2$ Hz), 7.43–7.14 (m, 10H), 3.74–3.5 (t, 1H, $J = 8.25$ Hz), 2.68–2.38 (m, 3H), 2.2–2.0 (m, 1H). ^{13}C NMR (75 MHz, CDCl_3): δ 200.57 (d), 141.05 (s), 136.1 (s), 129.14 (d), 128.95 (d), 128.43 (d), 127.66 (d), 126.04 (d), 58.23 (d), 32.87 (t), 31.06 (t). HRMS calcd for $\text{C}_{16}\text{H}_{20}\text{NO}$ ($\text{M} + \text{NH}_4$): 242.1545. Found: 242.1540. LRMS (m/z (relative intensity)): 242 (MNH_4^+ , 45), 207 (8), 120 (100),

91 (65). IR: 3029, 2931, 2863, 1720 (s), 1602, 1494, 1453 cm^{-1} . $[\alpha]_{\text{D}} = -0.66^{\circ}$ ($c = 1.8$, CHCl_3).

Procedure for Ozonolysis on Solid Phase To Obtain 2,4-Diphenylbutyric Acid (52c). Alkene **41a** ($R' = \text{Ph}$) (0.75 g, 1.50 mmol) was dissolved in acetone (40 mL) and stirred at room temperature for 10 min to allow the resin to swell, and ozone was bubbled in the cold (-78°C) mixture. When the solution remained light blue (nearly 3–5 min), indicating the excess ozone, the flow was stopped, and nitrogen was bubbled to remove excess ozone. Jones' reagent (5 equiv) was added at -78°C and continued stirring for 20 h while allowing the mixture to slowly warm to room temperature. The resin was filtered out, and the resin was washed with acetone, CH_2Cl_2 , and MeOH (30–40 mL each). The combined filtrates were concentrated under vacuum, poured into water, and extracted with diethyl ether. The combined ether layers were washed with water and brine, dried over anhydrous MgSO_4 , filtered, and concentrated under reduced pressure. The ^1H NMR of the crude product showed the required acid compound in $\sim 80\%$ purity. The crude compound was purified through flash silica gel chromatography to obtain pure chiral acid **52c** as a colorless thick liquid (90:10 er) in 9% isolated yield for five steps. ^1H NMR (300 MHz, CDCl_3): δ 11.8 (brd, 1H), 7.39–7.15 (m, 10H), 3.59 (t, 1H, $J = 8.25$ Hz), 2.61 (t, 2H, $J = 8.25$ Hz), 2.59–2.39 (m, 1H), 2.2–2.08 (m, 1H). ^{13}C NMR (75 MHz, CDCl_3): δ 180.26 (s), 141.05 (s), 138.07 (s), 128.75 (d), 128.43 (d), 128.17 (d), 127.59 (d), 126.04 (d), 50.73 (d), 34.42 (t), 33.45 (t). HRMS calcd for $\text{C}_{16}\text{H}_{16}\text{O}_2$: 240.1150. Found: 240.1147. LRMS (m/z (relative intensity)): 240 (M^+ , 8), 178 (3), 148 (3), 136 (100), 105 (25), 91 (68). IR: 3400–3027, 2951, 2863, 1702 (s), 1601, 1495, 1453 cm^{-1} . $[\alpha]_{\text{D}} = +23.35$ ($c = 2.0$, CHCl_3).

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Supporting Information Available. Experimental details and copies of ^1H NMR spectra for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

References and Notes

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