1,4-Asymmetric Induction in the Chromium(II)- and Indium-Mediated Coupling of Allyl Bromides to Aldehydes

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A series of allyl bromides bearing an ethereal stereogenic substituent at C-2 were synthesized from methyl acrylate. These were coupled with a range of aldehydes under chromium(II) chloride-mediated conditions to afford *syn*-4-alkoxyalkan-1-ols in good yield and diastereoselectivity. The effect of altering the nature of the ethereal group and alkyl substituent upon the diastereoselectivity of the reaction was also investigated. The relative stereochemistry was proved by X-ray structure analysis. The work was extended to replace the chromium(II) chloride with indium metal, and this also afforded *syn*-4-alkoxyalkan-1-ols in good yield and diastereoselectivity.

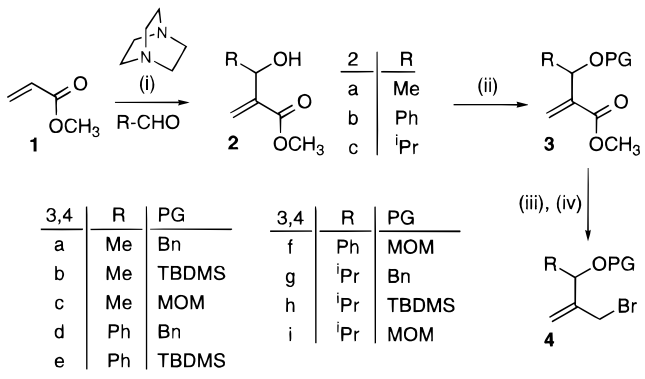
Introduction

Since the initial description of the chromium(II) chloride-mediated coupling of allyl halides to aldehydes in the late 1970s,[1] the "Nozaki−Hiyama" reaction and its variations have proved to be powerful synthetic operations.[2] The reaction features almost exclusive 1,2-*anti*-diastereoselectivity, excellent chemoselectivity, and the mild Lewis acidity of the chromium(II) species allows the process to be performed on relatively sensitive substrates. These advantages have been demonstrated in the synthesis of a wide range of natural products.[3] Further work in this field has led to the development of 1,2-asymmetric induction reactions, either by the use of chiral aldehydes[4] or chiral allyl bromides,[5] but little attention has been paid to extending the range of the stereochemical communication in this reaction. This paper describes a general method for achieving 1,4-asymmetric induction in the Nozaki−Hiyama reaction and efforts to optimize the stereochemical outcome of the reaction. This approach was extended, in a similar manner, to indium metal as the coupling agent.

Results and Discussion

Initial studies in the use of allylmetallic reagents for 1,4-asymmetric induction have been limited to the use of allylsilanes[6] and allylstannanes[7] and one specific example of a chromium(II)-mediated coupling of an aldehyde to a cyclic allyl iodide.[8] In these reports, the diastereoselectivity is postulated to arise from chelation between a chiral oxygenated function and the Lewis acidic element, which then dictates the facial selectivity of the reaction between the activated allyl species and the aldehyde. We decided to adopt a similar approach and to take advantage of the strong affinity of chromium toward oxygen. The allyl bromides were readily accessible in racemic form in a four-step sequence from methyl acrylate (**1**), Scheme 1. Thus, methyl acrylate was treated with the required aldehyde in the presence of DABCO according to literature procedure.[9] The hydroxy esters **2a−c** were then protected as either a benzyl ether (**3a,d,j**),[10] *tert*-butyldimethylsilyl ether (**3b,e,h**),[11] or methoxymethyl ether (**3c,f,i**).[12] Reduction at low temperature with DIBAL-H, followed by the Nicolaou bromination of the resulting alcohols,[13] afforded the requisite 2-substituted allyl bromides **4**, which, due to their lability, were

Scheme 1



(i) 7d, rt (40-50%); (ii) either (a) $BnO(C{=}NH)CCl_3$, TfOH, rt, (85-98%) or TBDMS-Cl, Imid., DMF, rt (65-89%) or MOM-Cl, DIPEA, Bu_4NI, rt, (77-86%); (iii) DIBAL-H, CH_2Cl_2, -78°C, 4h, (87-97%); (iv) NBS, PPh_3, CH_2Cl_2, -18°C, 5h (65-71%)

† X-ray structural analysis.

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Scheme 2

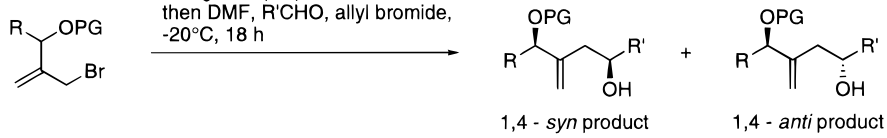


Table 1

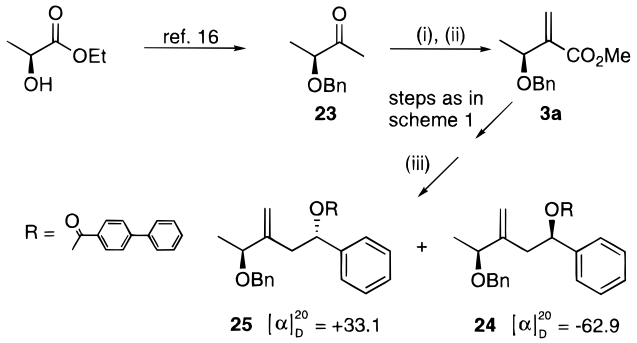
entry	ally bromide	R	PG	R′	% yield	syn:anti[a]	compound no.[b]
1	**4a**	Me	Bn	Ph	64	87:13	5
2	**4a**	Me	Bn	Me	75	83:17	6
3	**4a**	Me	Bn	Et	68	85:15	7
4	**4a**	Me	Bn	^{i}Pr	71	81:19	8
5	**4a**	Me	Bn	^{t}Bu	69	81:19	9
6	**4a**	Me	Bn	vinyl	26[c]	85:15	10
7	**4a**	Me	Bn	CO_2Et	complex	mixture	–
8	**4d**	Ph	Bn	Ph	71	91:9	11
9	**4d**	Ph	Bn	Et	70	85:15	12
10	**4d**	Ph	Bn	^{i}Pr	68	87:13	13
11	**4g**	^{i}Pr	Bn	Ph	60	95:5	14
12	**4g**	^{i}Pr	Bn	Et	66	91:9	15
13	**4g**	^{i}Pr	Bn	^{i}Pr	51[d]	91:9	16
14	**4b**	Me	TBDMS	Ph	34	83:17	17
15	**4e**	Ph	TBDMS	Ph	75	89:11	18
16	**4h**	^{i}Pr	TBDMS	Ph	64	90:10	19
17	**4c**	Me	MOM	Ph	61	81:19	20
18	**4f**	Ph	MOM	Ph	75	83:17	21
19	**4i**	^{i}Pr	MOM	Ph	72	88:12	22

[a] Determined by ^{1}H NMR. [b] Refers to compound number in experimental section; c: 47% allyl chloride returned; d: 34% allyl chloride returned.

not further characterized, but used directly in the chromium-mediated coupling reaction.

With a reliable route to the allyl bromides in hand, attention was turned to attempting the chromium-mediated coupling reactions. Early work showed that reactions of allyl bromide **4a** with benzaldehyde, performed in THF, afforded a degree of diastereoselectivity, but were complicated by an Oppenauer-type oxidation of the product homoallylic alcohol.[14] Fortunately, the formation of the ketone was completely suppressed when the reaction was performed in DMF, and superior yields and selectivities were obtained, see Scheme 2 and Table 1. Further studies showed that the optimum temperature for performing the reactions was −20 °C; below this, the reaction became sluggish and afforded little improvement in selectivity. Difficulties in isolating the product, attributed to hydrolysis of the strong chromium-oxygen bond, were overcome by adopting the procedure of Takai and Utimoto.[15] A range of aldehydes were reacted with **4a** under these conditions and afforded homoallylic alcohols in good yield and selectivity; the results are presented in Table 1 (entries 1−7). It is notable that pivalaldehyde (entry 5) gave a high degree of selectivity, despite being notorious for performing badly in Nozaki−Hiyama reactions. Less stable aldehydes (entries 6 and 7) decomposed before coupling, maybe this is due to the long reaction time under Lewis acid conditions. The reaction also returned significant quantities (ca. 10−25%) of bromide/chloride exchange product, which unfortunately did not react under these conditions. This problem is ameliorated by the potential to "recycle" the allyl chloride species by halide exchange.

Scheme 3



(i) LDA, THF, -78 - 0°C then $PhN(Tf)_2$; (ii) $Pd(OAc)_2$, CO, MeOH, Et_3N, PPh_3, DMF (60% two steps); (iii) 4-phenylbenzoyl chloride, Et_3N, DMAP, CH_2Cl_2 (82-90%)

The major and minor isomers could be clearly distinguished by ^{1}H-NMR. In all cases, the carbinol proton signal for the major product appeared downfield (ca. 0.1−0.2 ppm) of the corresponding signal for the minor isomer. The diastereoisomers could also be differentiated by the chemical shift and coupling patterns of the allylic and vinylic protons. The relative configuration of the major diastereoisomer was determined to be 1,4-*syn* by X-ray analysis of 4-phenylbenzoate derivative **24**, furnished from a homoenantiomeric synthesis of allyl bromide **4a**, Scheme 3. Thus, using literature procedures, (*S*)-ethyl lactate was protected using the Bundle procedure[10] and the ester function converted to a methyl ketone (**23**) *via* the method outlined by Weinreb.[16] Formation of the enol triflate,[17] followed by palladium(II) acetate catalyzed

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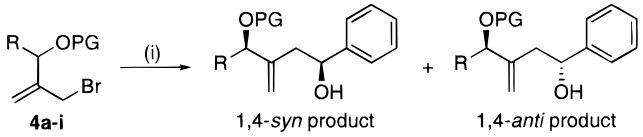
methoxycarbonylation,[18] furnished homoenantiomeric ester **3a** in good overall yield, which then led through to the required allyl bromide. Hence, reaction with benzaldehyde afforded a mixture of C-1 epimers which could be separated by bench-top chromatography and acylated with 4-phenylbenzoyl chloride.[19] The benzoate derivative of the major product **24** crystallized as colorless needles and allowed its structure to be determined by single crystal X-ray analysis (supporting information). Unfortunately, the derivative of the minor isomer **25** did not prove to be so obliging.

Having established the stereochemical outcome of the reaction, we proceeded to determine the effect of altering the alkyl residue and ethereal protecting group. Substituting the methyl group of the allyl bromide with either phenyl (**4d**) or isopropyl (**4g**) produced a profound effect on the level of asymmetric induction (entries 8−13), affording consistently superior diastereoselectivities in the range 74−82% de and 82−90% de, respectively. These results draw the conclusion that the steric demands of the allyl bromide far outweigh those of the aldehyde in determining the level of 1,4-asymmetric induction furnished by the reaction. The use of allyl bromides (**4b,e,h** and **4c,f,i**) provided information about the effect of the ethereal protecting group on the product profile (entries 14−19). The *tert*-butyldimethylsilyl- and methoxymethyl-protecting groups were chosen to alter the "accessibility" of the oxygen atom, either reducing or enhancing any interaction it may have with the chromium species. Neither group had any effect in improving the level of stereoselectivity and actually led to reduced values, particularly in the case of the methoxymethyl group. If chromium−oxygen chelation was an important factor in determining the reaction diastereoselection, it would be expected that the MOM group would improve the selectivity and the silyl group reduce it; this is not the case, and it could well be that the ethereal oxygen cannot compete with the DMF solvent molecules in chelating to the chromium species.

After establishing the results of the chromium(II) chloride reactions, we turned our attention to developing an alternative coupling system. In recent times, the metal indium has begun to sparkle in the limelight of organometallic chemistry, affording such advantages as low toxicity of the metal and its salts, reactions that can be performed in "wet" conditions, and the relative ease of product purifiction.[20] Contemporary work by Paquette and Mitzel, using α- and *β*-oxygenated aldehydes afforded useful levels of 1,2- and 1,3-asymmetric induction, respectively,[21] and this led to our investigation into whether the variety of allyl bromide species we have developed, bearing a stereogenic ether function, will provide asymmetric induction under similar conditions. To our delight, exposing allyl bromide **4a** to benzaldehyde in the presence of indium, in THF/water mix, afforded the 1,4-*syn*-adduct **5** as the major product. Further experimentation showed that the yield and reaction rate could be improved by the addition of tetra-*n*-butylammonium iodide, probably through *in situ* generation of the more reactive allyl iodide species (the addition of tetraethylammonium bromide gave little improvement to the system without added phase-transfer agents). Thus, taking advantage of our supply of allyl bromides, we investigated the effect of protecting group and allylic substituent on the product profile, Scheme 4 and Table 2.

Scheme 4



4a-i 1,4-*syn* product 1,4-*anti* product

(i) Indium powder, THF: H_2O (1:1), Bu_4NI, PhCHO, rt, 8-18 h

Table 2

allyl bromide	R	PG	% yield	syn:anti[a]	ref[b]
4a	Me	Bn	72	86:14	5
4d	Ph	Bn	79	88:12	11
4g	^{i}Pr	Bn	59	96:4	14
4b	Me	TBDMS	67	86:14	17
4e	Ph	TBDMS	75	90:10	18
4h	^{i}Pr	TBDMS	71	97:3	19
4c	Me	MOM	89	73:27	20
4f	Ph	MOM	83	79:21	21
4i	^{i}Pr	MOM	85	82:18	22

[a] Determined by ^{1}H NMR. [b] Compound number in Experimental Section.

The reactions were generally complete after 8 h, but some cases (PG = TBDMS) required stirring overnight. In these extended reactions, the indium showed a tendency to coagulate into small balls, due to the action of the stirrer bar; the addition of a small quantity of indium powder (*ca.* 0.1−0.2 equiv) to the reaction helped the reaction to completion. As can be seen from the table, the results are comparable to those found for the Nozaki−Hiyama conditions, furnishing similar levels of 1,4-asymmetric induction and generally better yields. In one system (R = ^{i}Pr, PG = TBDMS), the product diastereoselection proved to be superb, emphasizing the steric demands of the hydrocarbocarbon substituent on the reaction selectivity.

Mechanistic Rationale

The stereochemical outcome of the coupling reactions can be rationalized by considering the approach of the aldehyde to the preferred conformation of the allyl bromide function, Scheme 5. Whether it is an aldehyde−metal complex reacting with the allyl bromide function, or the aldehyde reacting with an allylmetal species, is open to debate (hence the use of "M" in the Scheme 5), but the approach of the carbonyl species is postulated to occur in a manner antiperiplanar to the oxygenated function, drawing an analogy to the Felkin−Anh model.[3a] The allyl species prefers to adopt the conformation shown in **26** rather than **27**, where the 1,3-allylic strain with the allylic hydrocarbon residue is minimized and the steric interaction with the "incoming" aldehyde is also reduced (R *vs* H). The facial selection with respect to the aldehyde is determined by the aldehyde residue (R′) to reside in the least sterically demanding position, away from the substituted allylic carbon. A metallo-ene reaction then proceeds *via* a six-membered chairlike transi-

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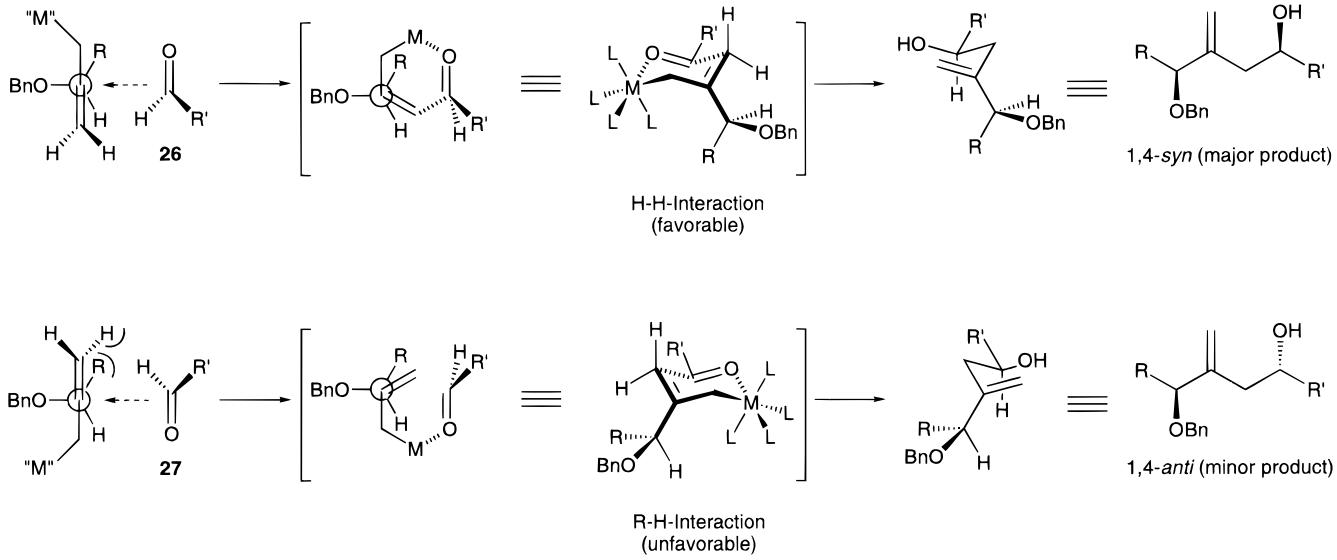
Scheme 5



tion state, in which the aldehyde substituent attains an equatorial position, to afford the 1,4-*syn*-product. This hypothesis is supported by the increase in the bulk of the allylic hydrocarbon residue (R) furnishes improved diastereoselectivity, and that little difference in reaction selectivity is observed by altering the nature of the ether function, which in this model is essentially removed from the interaction with the aldehyde.

Conclusion

To conclude, this paper outlines the development of long range stereochemical communication techniques in the Nozaki−Hiyama reaction and investigates the effect of altering the nature of the controlling stereogenic center. The reaction affords good to excellent 1,4-*syn*-asymmetric induction, comparable to those observed for the 1,2-diastereoselective reactions.[3] This paper also outlines the first example of 1,4-asymmetric induction in indium-mediated allyl transfer chemistry, *featuring the stereocontrolling element on the allyl bromide.* It is our hope that this work will receive further attention in the solution of synthetic problems.

Experimental Section

All reagents and solvents were of commercial quality or purified by literature procedures.[22] Chromium(III) chloride was purchased from Merck, Darmstadt, and dried over P_2O_5 at reduced pressure overnight. Anhydrous DMF, lithium aluminum hydride solution in THF, and indium powder (Mg free) were purchased from Aldrich Chemical Co. All temperatures refer to the external bath temperature. Anhydrous reactions were performed under an atmosphere of argon. The ^{1}H-NMR and ^{13}C-NMR spectra were run in chloroform-*d* and measured on 250, 270, 400, or 600 MHz machines.

Typical Procedure for DIBAL-H Reactions. Diisobutylaluminum hydride (160 mL, 1 M in hexane) was added dropwise to a solution of methyl (3*RS*)-3-(benzyloxy)-2-methylidenebutanoate (16.71 g, 76 mmol) in dry CH_2Cl_2 at −78 °C, and stirring was maintained at −78 °C for 3 h. To this was added methanol (27 mL), and the solution was allowed to warm to 0 °C, followed by the dropwise addition of saturated ammonium chloride solution (81 mL). The mixture was stirred rapidly for 3 h and then left to stand for 18 h. The mixture was filtered, the filter cake was washed with ethyl acetate, and the combined filtrates were concentrated at reduced pressure. Chromatography on silica gel, using hexane−ethyl acetate (3:1) as eluent, afforded (3*RS*)-3-(benzyloxy)-2-methylidene-1-butanol as a colorless oil (13.15 g, 90%).

Typical Procedure for Bromination Reactions. To a solution of (3*RS*)-3-(benzyloxy)-2-methylidene-1-butanol (2.14 g, 11.1 mmol) in dry CH_2Cl_2 (24 mL) at −18 °C were added portionwise triphenylphosphine (3.36 g, 12.8 mmol) and *N*-bromosuccinimide (2.08 g, 11.7 mmol) and stirring was maintained at −18 °C for 5 h. To this were added diethyl ether (50 mL) and water (50 mL), and the mixture was partitioned. The organic phase was washed with brine, dried (Na_2SO_4), and preabsorbed onto silica at reduced pressure. Chromatography on silica gel, using hexane−ethyl acetate (30:1) as eluent, afforded (3*RS*)-3-(benzyloxy)-1-bromo-2-methylidenebutane (**4a**) as a colorless oil (1.99 g, 70%).

Typical Procedure for Chromium(II) Chloride-Mediated Coupling Reactions. To a suspension of chromium(III) chloride (0.402 g, 2.54 mmol) in dry THF (10 mL) at 0 °C was added dropwise lithium aluminum hydride solution (1.27 mL, 1 M in THF, 1.27 mmol), and the mixture was allowed to warm to ambient temperature and stirred for 30 min. The THF was evaporated by gently warming the solution in a stream of argon and replaced by dry DMF (10 mL). The suspension was cooled to −20 °C, and benzaldehyde (0.138 mL, 1.36 mmol) was added dropwise followed by a solution of (3*RS*)-1-bromo-3-(methoxymethoxy)-3-phenyl-2-methylidenepropane (**4f**) (0.246 g, 0.91 mmol) in dry DMF (2 mL). The solution was stirred at −20 °C for 18 h and then poured into a rapidly stirred mixture of water (20 mL), brine (20 mL), and diethyl ether (20 mL), with a wash of ethyl acetate (20 mL), and stirred at ambient temperature for 48 h. The mixture was extracted with diethyl ether (×3), and the combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated at reduced pressure. Chromatography on silica gel, using hexane−diethyl ether (8:1) as eluent, afforded (1*RS*,4*SR*)-1,4-diphenyl-4-(methoxymethoxy)-3-methylidene-1-butanol (**21**) as a mixture of diastereoisomers (0.202 g, 75%).

The major and minor diastereoisomers could be partially separated by further bench-top chromatography. The analytical data for the syn diastereomers are presented in the supporting information.

(1*R*,4*S*)-4-Benzyloxy-3-methylidene-1-phenyl-1-pentenyl 4-Phenylbenzoate (24). 4-Phenylbenzoyl chloride (110 mg, 0.51 mmol) was added to a stirred solution of (1*R*,4*S*)-4-(benzyloxy)-3-methylidene-1-phenyl-1-pentanol (**9**) (57 mg, 0.20 mmol), triethylamine (82 μL 0.59 mmol), and DMAP (7 mg, 0.06 mmol) in dry CH_2Cl_2 (2 mL) at ambient temperature, and the solution was stirred for 18 h. The mixture was diluted with diethyl ether and washed with water (×2) and brine,

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dried ($MgSO_4$), and concentrated at reduced pressure. Chromatography on silica gel, using hexane−diethyl ether (20:1) as eluent, afforded the title compound as a colorless oil (75 mg, 80%). Trituration of this oil with *n*-pentane at 0 °C afforded fine white crystals. Recrystallization from pentane−CH_2Cl_2 afforded colorless needles.

Mp: 89−91 °C; $[\alpha]^{20}_D$ −62.9 (*c* 0.68, $CHCl_3$); ν_{max} 3031, 2926, 1715, 1608, 1268, 1100, 746, 670; δ_H 1.34 (3H, d, J = 6.5), 2.71 (1H, dd, J = 15.2, 5.4), 2.84 (1H, dd, J = 15.2, 8.7), 3.98 (1H, q, J = 6.5), 4.23 and 4.41 (each 1H, d, J = 12), 5.08 (1H, d, J = 1.1), 5.13 (1H, s), 6.25 (1H, dd, J = 8.7, 5.4), 7.29 (9H, m), 7.43 (4H, m), 7.63 (4H, m), 8.13 (2H, m); δ_C 165.5, 145.6, 145.2, 140.5, 139.9, 138.4, 130.0, 129.0, 128.8, 128.4, 128.2, 127.9, 127.5, 127.3, 127.1, 127.0, 126.5, 114.2, 78.2, 75.2, 69.9, 37.4, 20.1. Anal. $C_{32}H_{30}O_3$ (M_r 462.59) Calcd C: 83.09 H: 6.54. Found C: 82.82 H: 6.72

(1S,4S)-4-Benzyloxy-3-methylidene-1-phenyl-1-pentenyl 4-Phenylbenzoate (25). The title compound was prepared from (1*S*,4*S*)-4-(benzyloxy)-3-methylidene-1-phenyl-1-pentanol (30 mg, 0.11 mmol) in the manner described above. This afforded the title compound as an opaque, colorless glass (45 mg, 92%).

$[\alpha]^{20}_D$ +33.1 (*c* 0.72, $CHCl_3$); ν_{max} 3031, 2926, 1716, 1608, 1451, 1267, 1100, 1029, 747; δ_H 1.30 (3H, d, J = 6.5), 2.64 (1H, dd, J = 15.7, 4.8), 2.95 (1H, dd, J = 15.7, 9.4), 3.95 (1H, q, J = 6.5), 4.27 and 4.52 (each 1H, d, J = 12.0), 5.16 (1H, s), 5.18 (1H, s), 6.30 (1H, dd, J = 9.3, 4.8), 7.33 (9H, m), 7.48 (4H, m), 7.63 (4H, m), 8.12 (2H, m); δ_C 165.5, 145.6, 145.0, 140.5, 139.9, 138.6, 130.0, 128.9, 128.8, 128.4, 128.2, 128.0, 128.0, 127.4, 127.3, 127.1, 127.0, 126.5, 113.9, 78.3, 74.7, 69.9, 37.3, 20.3.

Typical Procedure for the Indium Metal-Mediated Coupling Reactions. Indium metal powder (0.225 g, 1.96 mmol) was added to a rapidly stirred solution of **4c** (0.228 g, 1.09 mmol) and tetra-*n*-butylammonium iodide (0.725 g, 1.96 mmol) in THF (1 mL) and water (1 mL) at ambient temperature. The mixture was stirred rapidly for 8 h, diluted with ethyl acetate, and preabsorbed onto silica gel at reduced pressure. The silica powder was washed with diethyl ether (×3), and the combined filtrates were concentrated at reduced pressure. Chromatography on silica gel, using hexane−ethyl acetate (5:1) as eluent, afforded 20 (0.231 g, 89%).

X-ray Crystallographic Data of Compound 24:[23] $C_{32}H_{30}O_3$, M_r = 462.59, orthorhombic, $P2_12_12_1$, a = 6.0796(5), b = 14.579(3), c = 29.305(8) Å, V = 2597(1) Å^3, Z = 4, D_c = 1.183 g cm^{-3}, linear absorption coeff = 5.5 cm^{-1}, radiation = Cu Kα, scan mode = ω, total no. of reflections = 3058 at scan range $+h,\pm k,+l$ quadrant at rt. $2\theta_{max}$ = 100°, $R(F)$ = 0.052, $wR(F)$ = 0.052.

A single crystal was measured on an ENRAF-NONIUS CAD4 diffractometer. Three standard reflections remeasured every 5500 s remained stable. No absorption correction was made. No averaging of equivalent reflections was performed. The structure was determined by direct methods using program SIR92. The H atoms were placed at calculated positions and were not refined. The C and O atoms were refined with anisotropic thermal parameters. The structure was refined on F values using weighting scheme: $w(F) = 4\times F^2/[\sigma^2(F^2) + (0.03\times F^2)^2]$. The final difference density was between −0.12 and +0.11 e Å^{-3}. A refinement of the Flack parameter gave x = −0.4(4) (x = 0 for the correct and 1 for the wrong absolute structure). The calculations were performed with the SHELX and MolEN program systems.

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Supporting Information Available: Characterization data for **5**−**22**; ORTEP diagram of 24 (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(23) The authors have deposited full details of the X-ray structure determination of compound **24** with the Cambridge Crystallographic Data Centre. These data can be obtained, on request, from the Director, Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK.