Synthesis of Homoallylic Alcohols via Lewis Acid Assisted Enantioselective Desymmetrization

Bing Yu, Frederic Menard, Naohiro Isono, Mark Lautens*

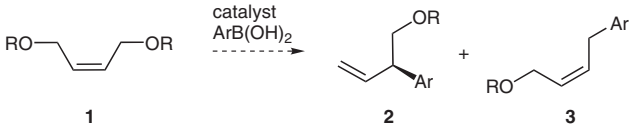
Davenport Laboratories, Department of Chemistry, University of Toronto, 80 St. George Street, Toronto, ON, M5S 3H6, Canada
Fax +1(416)9468185; E-mail: mlautens@chem.utoronto.ca

Received 30 October 2008; revised 3 November 2008

Abstract: A highly enantioselective allylic substitution of (*Z*)-but-2-ene-1,4-diol derivatives was developed using a rhodium(I) catalyst and arylboronic acids as nucleophiles. The reaction yields versatile homoallylic alcohols from readily available linear biscarbonates.

Key words: homoallylic alcohols, rhodium, boronic acids, desymmetrization, asymmetric allylic substitution

Chiral small molecules are of interest for their use as building blocks in total synthesis and in medicinal chemistry. As part of our program aimed at developing stereoselective addition reactions to alkenes, we sought to extend our rhodium-catalyzed methodology to linear allylic derivatives **1**.[1,2] Thus, versatile chiral synthons **2** could be accessed, which bear three differentiated functional groups for use as synthetic handles: a terminal alkene, a protected alcohol, and a substituted arene (Equation 1).[3] We report herein a simple, useful protocol that effects the desymmetrization of allylic carbonates with arylboronic acids in high selectivity using a rhodium(I) catalyst and P-Phos as chiral ligand.[4,5]



Equation 1

Symmetrical linear butenediol derivatives **1** are attractive because of their ease of preparation and commercial availability. A number of palladium-catalyzed asymmetric allylic substitutions (AAS) are known,[6] but only a few allow AAS with hard carbon nucleophiles[7] and most are conducted with more reactive cyclic substrates.[8] Unsymmetrical allylic systems that either bear a single leaving group or are electronically biased have led to exceptional results with rhodium,[9] iridium,[10] and copper[11,12] catalysts.[13] Importantly, Murakami and co-workers reported a simple transformation whereby free alcohols of **1** reacted with triarylboroxines to give alcohol **2b** regioselectively.[14] Although the present reaction is very similar in appearance to Murakami's based on the products, experimental evidence suggests that the two reactions in fact proceed by different mechanisms.

Under our previously reported conditions, the desired branched product **2a** was obtained with the best combined yield and selectivity using Chan's bispyridyl bisphosphine ligand **L5** (P-Phos; Figure 1 and Table 1).[15]

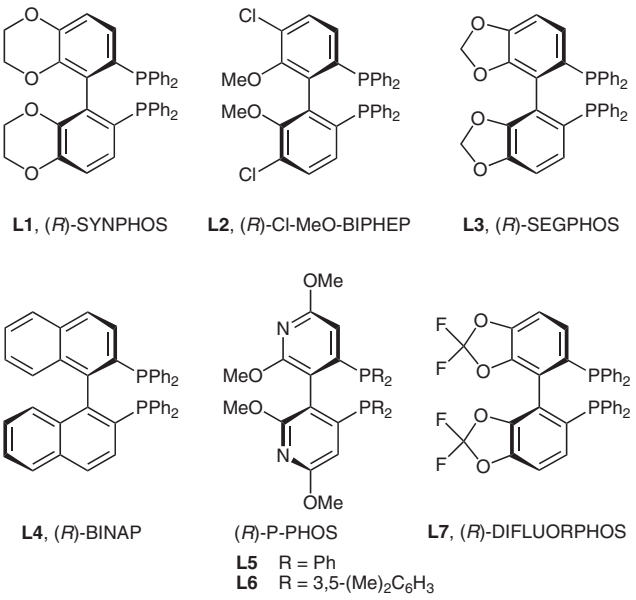


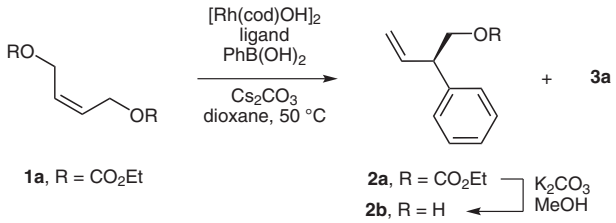
Figure 1 Ligands tested in this study

However, the regioselectivity was highly variable and depended strongly on the nature of the ligand. Specifically, P-Phos and DiFluorPhos[16] (Figure 1), ligands that are electron-donating by π-resonance but electron-deficient by σ-induction, gave optimal selectivity (entries 6 and 7). Whereas cyclic substrates reacted best with Xyl-P-Phos (**L6**) in our previous report,[2] here the bulky groups on phosphorus atoms of this ligand led to low selectivity, although the yield was high (entry 4). DiFluorPhos showed selectivities slightly higher than those obtained with P-Phos, but we pursued our studies with P-Phos, mostly owing to its availability. It should be noted that the reaction needs to be conducted under a strictly inert atmosphere.[17]

The effect of additives was investigated with P-Phos in order to improve the conversion while maintaining the regio- and enantioselectivity. When Lewis acids that might activate the carbonate leaving groups were screened, it was found that a substoichiometric amount of zinc triflate

SYNTHESIS 2009, No. 5, pp 0853–0859
Advanced online publication: 11.02.2009
DOI: 10.1055/s-0028-1083368; Art ID: Z23208SS

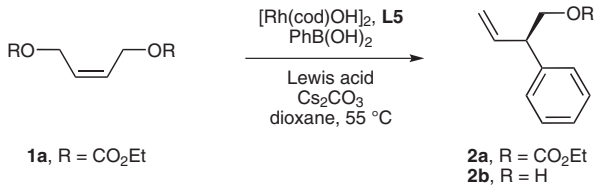
Table 1 Ligand Screening[a]



Entry	Ligand	Yield (%)[b]	**2a/3a**[c]	ee (%)[d]
1	**L1**	57	1:1.5	50
2	**L2**	41	1.2:1	50
3	**L3**	24	1.2:1	62
4	**L6**	80	2:1	70
5	**L4**	40	5:1	40
6	**L5**	50	8:1	91
7	**L7**	45	10:1	93

[a] Reagents and conditions: $[Rh]_2$ (5 mol%), ligand (12 mol%), $PhB(OH)_2$ (2.0 equiv), Cs_2CO_3 (1.0 equiv).
[b] Isolated yield of combined branched **2** and linear **3** carbonates.
[c] Regioisomeric ratio (branched/linear) determined by ^1H NMR.
[d] Determined by chiral HPLC or GC analyses of deprotected **2b** (K_2CO_3, MeOH, r.t., 3 h).

Table 2 Effect of Lewis Acids[a]



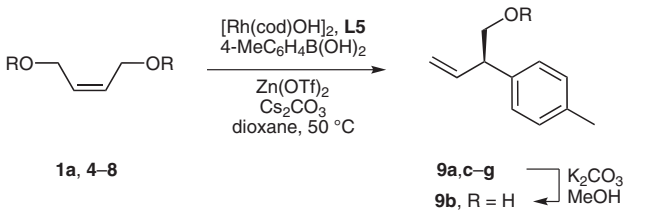
Entry	Lewis acid	Yield (%)[b]	**2a/3a**[c]	ee (%)[d]
1	–	42	10:1	87
2	AgOTf	65	17:1	81
3	CuOTf	55	8:1	95
4	$Zn(OTf)_2$	85	10:1	94
5	$La(OTf)_3$	76	10:1	88

[a] Reagents and conditions: $[Rh]_2$ (5 mol%), ligand (12 mol%), $ArB(OH)_2$ (2.0 equiv), Cs_2CO_3 (1.0 equiv), Lewis acid (20 mol%).
[b] Isolated yield of combined branched **2** and linear **3** carbonates.
[c] Regioisomeric ratio (branched/linear) determined by ^1H NMR.
[d] Determined by chiral HPLC or GC analyses of deprotected **2b**.

proved to be most effective (Table 2). Its presence was crucial to get full conversion of the substrate. Other Lewis acids were tested ($TiCl_4$, BF_3, $AlCl_3$ and TBSOTf), but none afforded the desired products. With an acceptable catalytic system in hand, we looked at the influence of the leaving groups.

A range of substrates were prepared in quantitative yield by bis-acylation of (*Z*)-but-2-ene-1,4-diol. 4-Tolylboronic acid was used as nucleophile because its moderate reactivity would provide a reference point in seeking better conditions. Ethyl biscarbonate **1** remained the best substrate (Table 3). Substrates bearing weakly coordinating leaving groups led to low regio- and enantioselectivity (entries 3 and 4), whereas more electron-rich leaving groups led to higher ee (entries 2 and 6). In view of the clean reaction profile, we settled on the use of ethyl carbonates to explore the scope of the reaction. It should be noted that unreacted **1a** was always recovered along with the desired products (yields were >90% when based on recovered starting material).

Table 3 Influence of the Leaving Group[a]



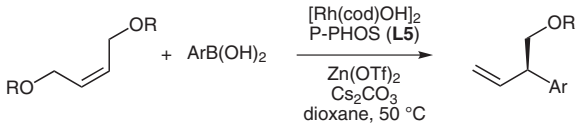
Entry	R	Yield (%)[b]	r.r.[c]	ee (%)[d]
1	CO_2Et (**1a**)	59	>20:1	93
2	CO_2i-Pr (**4**)	50	10:1	90
3	$CO_2CH_2CF_3$ (**5**)	76	1:1	53
4	CO_2Ph (**6**)	64	4:1	68
5	COPh (**7**)	35	7:1	90
6	COC_6H_4(4-OMe) (**8**)	36	7:1	93

[a] Reagents and conditions as described in Table 2.
[b] Isolated yield of combined branched **2** and linear **3** products.
[c] Regioisomeric ratio (branched:linear) determined by ^1H NMR.
[d] Determined by chiral HPLC or GC analyses of deprotected **9b**.

A selection of arylboronic acids tested in this reaction is shown in Table 4. The reaction is highly enantioselective, and we observed that electron-rich aryl groups are best suited for this transformation in terms of regioselectivity. Substitution at the *meta*- or *para*-position on the boronic acid is also tolerated. However, *ortho*-substituents lead to significantly diminished yields when compared to the *para*-isomers. Nucleophiles that did not react under these conditions included boronic acids bearing functional groups such as a protected amine, aldehyde, nitro, and bromide.

Two proposed mechanistic scenarios are illustrated in Scheme 1. Our results suggest that pathway (a) may be dominant. An ionization mechanism is distinctly different from the one proposed by Murakami.[14] Pathway (a) involves oxidative ionization of the catalyst to form a Rh(III) σ–enyl intermediate **A**, which can slowly isomerize to **B**, as described by Nelson and Evans.[18] Reductive elimination from either **A** or **B** then yields products **2** or **3**, respectively. Therefore, the product distribution may be dictated by the competing rates of reductive elimination

Table 4 Scope of Boronic Acids[a]

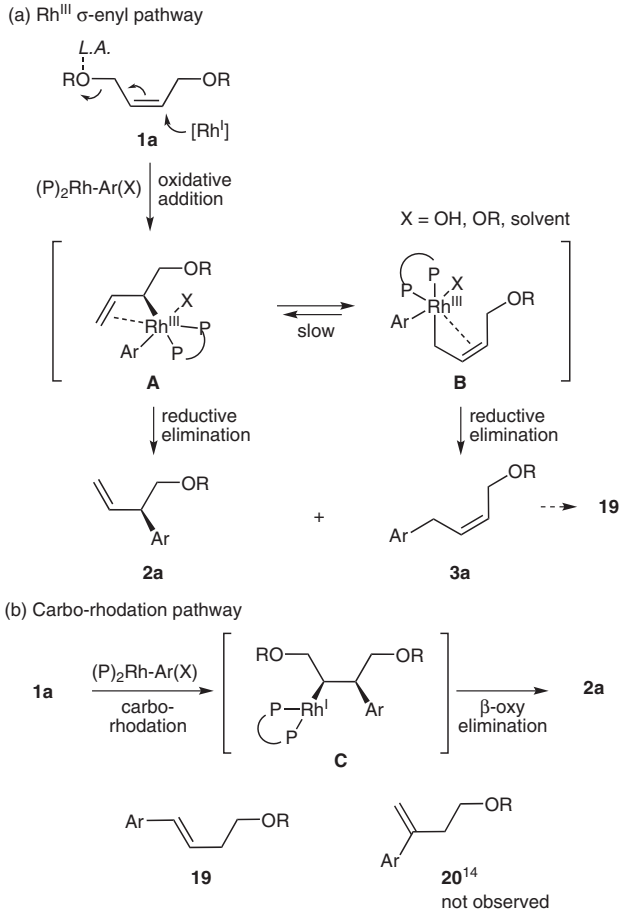


1a

2a, **9a**–**18a**, R = CO_2Et
2b, **9b**–**18b**, R = H

Entry	Ar	Product	Yield (%)[b]	r.r.[c]	ee (%)[d]
1	Ph	**2a**	85	10:1	94
2	4-MeC_6H_4	**9a**	59	>20:1	93
3	4-$MeOC_6H_4$	**10a**	60	>20:1	93
4	4-ClC_6H_4	**11a**	65	10:1	95
5	4-FC_6H_4	**12a**	66	4:1	67
6	3,4-$(MeO)_2C_6H_3$	**13a**	68	7:1	92
7	3-Me-4-$MeOC_6H_3$	**14a**	45	10:1	87
8	3-MeC_6H_4	**15a**	38	10:1	88
9	3-ClC_6H_4	**16a**	66	4:1	70
10	1-naphthyl	**17a**	32	>20:1	65
11	2-naphthyl	**18a**	61	>20:1	90

[a] Reagents and conditions as described in Table 2.
[b] Isolated yield of combined branched **2** and linear **3** carbonates.
[c] Regioisomeric ratio (branched/linear) determined by ^1H NMR.
[d] Determined by chiral HPLC or GC analyses of deprotected **2b** and **9b**–**18b** (K_2CO_3, MeOH, r.t., 3 h).



Scheme 1 Possible mechanistic pathways

versus isomerization, and may depend on the species coordinated to the σ–enyl complex.

Alternatively, carbometalation of the alkene leading to **C**, followed by simple elimination, cannot be ruled out (pathway b), although it would not explain the formation of linear product **3**. Notably, we did not observe by-product **20**, which was previously reported and can only occur by pathway (b).[14] The only side-product sometimes formed was **19**, which can arise from isomerization of **3**. Importantly, pathway (a) may not be accessible by Murakami's protocol, based on stereoelectronic aspects. Indeed, these authors have shown through control experiments that a cyclic intermediate tying up both oxygens of **C** is necessary for their system, and the seven-membered ring thus formed does not allow the required alignment of allylic oxygens with the alkene to form Rh(III) complexes **A** or **B**. It may also explain why, in contrast to Murakami's report, carbonates are suitable substrates.

The marked increase in yield when a metal-based Lewis acid is used may be due to activation of the leaving groups of **1a**, thereby facilitating an ionization process (pathway a). We showed that the leaving groups are clearly involved, and their influence on regio- and enantioselectivity suggests that the released counterions may be bound to rhodium complexes **A** and **B**, and influence the relative rates of isomerization/reductive elimination. The fact that electron-rich leaving groups lead to higher ee and regioselectivity provides experimental support for pathway (a).

The current study shows that symmetrical, linear allylic biscarbonates are good substrates for enantioselective desymmetrizations. The method complements alternative procedures, as it provides enantioenriched, protected homoallylic alcohols. Although conversion could be improved, the commercial availability of starting materials and reagents makes this system useful, yielding important chiral building blocks in one step with high ee.

In conclusion, we report a highly enantioselective rhodium-catalyzed arylative allylic substitution reaction, assisted by Lewis acids. The reaction generates optically active 2-arylbut-3-enyl carbonates in high regio- and enantioselectivity from easily accessible substrates and reagents.

$[Rh(cod)OH]_2$ was prepared from $[Rh(cod)Cl]_2$ following a literature procedure.[19] Dioxane was purified by distillation under N_2 from Na/benzophenone immediately prior to use. Pentane and EtOAc used for chromatographic purification were purchased from Caledon Laboratories Ltd. and used without further purification. Microwave sealed tubes (1.0–4.0 mL tubes with Teflon septa and aluminum crimps) were purchased from Biotage. All reactions were performed under either N_2 or argon. All solvents used were freshly distilled and degassed. Organic solvents were removed by rotary evaporation using the house vacuum (40 torr) or a water aspirator.

Analytical TLC plates were used (glass or aluminum-backed E.M. Merck plates; 0.25 mm, 60 Å pore size). TLC visualization: 254 nm UV light, then immersion in acidic vanillin solution, followed by heating with a heatgun. Purification was performed by flash chromatography with Silicycle™ Ultra-pure 230–400 mesh silica gel. ^{1}H NMR and ^{13}C NMR spectra were recorded at 25 °C either on a Varian 400 (400/100 MHz) spectrometer with an ATB8123-400 probe, or on a Varian Mercury 400 (400/100 MHz) with a Nalorac4 N-400 probe. Chemical shifts (δ) for ^{1}H and ^{13}C NMR spectra are reported in ppm relative to TMS using residual solvent signal as an internal reference. Data is represented as follows: chemical shift (multiplicity, coupling constant and integration). Infrared spectra were recorded using a Shimadzu FTIR-8400S spectrometer. High-resolution EI mass spectra were obtained with a SI2 Micromass 70S-250 mass spectrometer (EI) or an ABI/Sciex Qstar mass spectrometer (ESI).

(*Z*)-But-2-ene-1,4-bis(ethylcarbonate) (1a); Typical Procedure

(*Z*)-But-2-ene-1,4-diol (5.0 g, 56.7 mmol) was suspended in CH_2Cl_2 (280 mL) and the flask was capped with a septum, then purged with a stream of N_2, and cooled to 5 °C using an ice bath. $ClCO_2Et$ (16.0 mL, 3.0 equiv) was added via syringe, followed by careful addition of pyridine (16.0 mL, 4.0 equiv), ensuring a controlled exothermic reaction. The solution turned from colorless to bright pink, together with the formation of a white precipitate. The reaction was allowed to warm to r.t. until completion (~4 h, reaction monitored by TLC; longer stirring, i.e. overnight, did not affect the reaction). The reaction was extracted successively with sat. aq NH_4Cl (200 mL, 100 mL then 50 mL). The combined aqueous layer was extracted with Et_2O (200 mL) and the combined organic layer was dried with brine (50 mL), then $MgSO_4$, filtered and concentrated under reduced pressure to yield an amber fluid (17 g). The crude oil was purified by silica gel chromatography (EtOAc–pentane, 10%) to give **1a**. Characterization data for **1a** matched those in literature reports.[20]

Yield: 13.2 g (99% yield); colorless fluid oil.

(*Z*)-But-2-ene-1,4-bis(isopropylcarbonate) (4)

Prepared according to the typical procedure described for **1a**.

Yield: 100%; colorless oil.

IR (NaCl, neat): 2965, 1747, 1471, 1400, 1381, 1377, 1371, 1244, 970 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.91–5.72 (m, 2 H), 4.83–4.66 (m, 4 H), 3.92 (m, 2 H), 0.94 (d, *J* = 6.7 Hz, 12 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.3, 128.2, 63.2, 28.0, 19.1.

Compound was unstable under MS conditions.

(*Z*)-But-2-ene-1,4-bis(2′,2′,2′-trifluoroethylcarbonate) (5)

(*Z*)-But-2-ene-1,4-diol (2.0 g, 0.023 mol) along with *N*,*N*-carbonyldiimidazole (CDI; 11.1 g, 0.0681 mol, 3 equiv) were weighed in a 150 mL round-bottom flask. CH_2Cl_2 (100 mL) was then added and the solution was stirred at r.t. for 3 h. The reaction was washed with 1 N HCl (50 mL, 30 mL and 20 mL), and the organic layer was dried with $MgSO_4$, filtered and the solvent removed under reduced pressure. The resulting solid was dissolved in CH_2Cl_2 (100 mL) and DMAP (20 mg, cat.) and CF_3CH_2OH (9.08 g, 4.0 equiv) were added. The resulting mixture was stirred at r.t. overnight then washed with 1 N HCl (50 mL, 30 mL and 20 mL). The combined aqueous layers were extracted with CH_2Cl_2 (25 mL) and the combined organic layers were washed with H_2O (20 mL), followed by brine (20 mL), dried with $MgSO_4$, and the solvents were removed under reduced pressure. The crude oil was purified by flash chromatography (hexane–EtOAc, 90:10).

Yield: 100%; colorless oil.

IR (NaCl, neat): 2983, 1770, 1454, 1417, 1354, 1381, 1354, 1171, 1021, 968 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.86 (ddd, *J* = 1.2, 4.1, 5.2 Hz, 2 H), 4.82 (dd, *J* = 1.3, 4.1 Hz, 4 H), 4.51 (q, *J* = 8.2 Hz, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.9, 128.1, 64.2, 63.9, 63.5.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –74.67 (t, *J* = 8.2 Hz, 1 H).

HRMS-EI: *m*/*z* [M]$^+$ calcd for $C_{10}H_{10}O_6F_6$: 340.0382; found: 340.0385.

(*Z*)-But-2-ene-1,4-bis(phenylcarbonate) (6)

Prepared according to the typical procedure described for **1a**.

Yield: 96%; colorless oil.

IR (NaCl, neat): 3061, 2966, 1761, 1593, 1492, 1348, 1236, 1205, 1058 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.35 (m, 4 H), 7.29–7.22 (m, 2 H), 7.21–7.14 (m, 4 H), 5.94 (m, 2 H), 4.90 (t, *J* = 7.6 Hz, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.7, 151.2, 129.7, 128.2, 126.3, 121.2, 63.9.

HRMS-EI: *m*/*z* [M + Na]$^+$ calcd for $C_{18}H_{16}O_6Na$: 351.0839; found: 351.0839.

(*Z*)-But-2-ene-1,4-bisbenzoate (7)

Prepared according to the typical procedure described for **1a**.

Yield: 94%; colorless crystals; mp 83–84 °C.

IR (NaCl, neat): 3061, 3034, 2966, 1748, 1601, 1448, 1346, 1267, 1107, 1095, 1070, 1024, 966, 940 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.09–7.99 (m, 4 H), 7.59–7.52 (m, 2 H), 7.43 (t, *J* = 7.7 Hz, 4 H), 5.98–5.89 (m, 2 H), 5.00 (d, *J* = 5.2 Hz, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.6, 133.3, 130.2, 129.9, 128.6, 128.6, 60.8.

HRMS-EI: *m*/*z* [M]$^+$ calcd for $C_{18}H_{16}O_2$: 296.1049; found: 296.1042.

(*Z*)-But-2-ene-1,4-bis(4-methoxybenzoate) (8)

Prepared according to the typical procedure described for **1a**.

Yield: 86%; yellow solid; mp 101–103 °C.

IR (NaCl, neat): 2960, 1776, 1712, 1604, 1579, 1510, 1460, 1255, 1167, 1099, 1026 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.03–7.95 (m, 4 H), 6.95–6.85 (m, 4 H), 5.96–5.89 (m, 2 H), 4.97 (d, *J* = 5.1 Hz, 4 H), 3.86 (s, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.3, 133.1, 131.9, 128.6, 122.6, 114.3, 113.8, 60.6, 55.6.

HRMS-EI: *m*/*z* [M + Na]$^+$ calcd for $C_{20}H_{20}O_6Na$: 379.1152; found: 379.1152.

2-Phenylbut-3-enyl Ethyl Carbonate (2a); Typical Procedure

In a glove box, $[Rh(cod)OH]_2$ (3.9 mg, 0.0086 mmol, 0.05 equiv), ligand (0.0206 mmol, 0.12 equiv), Cs_2CO_3 (56 mg, 0.172 mmol) and $Zn(OTf)_2$ (12.5 mg, 0.0344 mmol, 0.20 equiv) were weighed into an 8 mL oven-dried microwave tube. The tube was sealed with a septum and a crimp, and taken out of the glove box. Dioxane was added (1.0 mL) and the resulting mixture was then stirred at r.t. for 10–15 min. Meanwhile, allylic carbonate **1a** (0.172 mmol) and phenyl boronic acid (0.344 mmol) were weighed into a 4 mL vial. The vial was sealed, purged with argon, and dioxane (1.00 mL) was added. The substrate and boronic acid solution was transferred via syringe into the sealed tube containing the premixed catalyst solution. The reaction mixture was then heated at 50 °C for 20 h, then diluted with EtOAc (10 mL), filtered through a silica pad (~2 g), and

washed with EtOAc (~50 mL). The filtrate was concentrated under reduced pressure and purified by flash chromatography (EtOAc–pentane, 5→15%). The branched and linear products **2a** and **3a** were isolated as an inseparable mixture. Regioselectivity was determined by ^{1}H NMR analysis.

IR (NaCl, neat): 3007, 2986, 1750, 1467, 1449, 1373, 1258, 1018, 920 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.86–5.65 (dt, *J* = 4.0, 1.2 Hz, 2 H), 4.82–4.62 (m, 4 H), 4.17 (d, *J* = 5.3 Hz, 4 H), 1.27 (t, *J* = 7.1 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.1, 128.2, 64.3, 63.1, 14.4.

2-Phenylbut-3-en-1-ol (2b); Typical Procedure

In order to obtain the desired branched product, the carbonate mixture (**2a** and **3a**) and K_2CO_3 (10 equiv) were weighed into a 4 mL vial. MeOH (2 mL) was added and the solution was stirred at r.t. for 3 h. The solvent was then concentrated under reduced pressure and the residue was taken into EtOAc (15 mL). The organic layer was washed with sat. aq NH_4Cl (15 mL) and the aqueous layer was extracted with Et_2O (15 mL and 10 mL), and the combined organic layers were concentrated under reduced pressure. The crude oil was purified by flash chromatography (EtOAc–pentane, 10→25%) to give a colorless oil. Some compounds were found to be sensitive to silica in the alcohol form.

Yield: quant.; colorless oil; 94% ee determined by HPLC (Chiralcel AD; *i*-PrOH–Hexanes, 0.5%; 1.0 mL/min; 208 nm; t_R = 28.2 min, t_R' = 32.4 min); $[\alpha]_D^{25}$ +118.7 (*c* 0.62, $CHCl_3$).

IR (NaCl, neat): 3368, 3070, 2928, 2875, 1633, 1599, 1492, 1452, 1055, 1030, 955, 918 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.29 (m, 2 H), 7.28–7.19 (m, 3 H), 6.00 (ddd, *J* = 7.7, 10.4, 17.2 Hz, 1 H), 5.19 (m, 2 H), 3.81 (dd, *J* = 1.4, 7.1 Hz, 2 H), 3.52 (q, *J* = 7.3 Hz, 1 H), 1.55 (s, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.8, 138.4, 129.0, 128.2, 127.2, 117.3, 66.3, 52.7.

HRMS-EI: *m*/*z* $[M]^+$ calcd for $C_{10}H_{12}O$: 148.0888; found: 148.0886.

2-(4-Tolyl)but-3-en-1-ol (9b)

The carbonates were isolated in 59% yield as a colorless oil. The mixture was treated with K_2CO_3 in MeOH according to the typical procedure for **2b** and the desired branched product was characterized as the free alcohol.

Colorless oil; 93% ee determined by HPLC (Chiracel AD-H; *i*-PrOH–hexane, 0.9%; 0.3mL/min; 208 nm; t_R = 74.9 min, t_R' = 80.6 min); $[\alpha]_D^{25}$ +140.5 (*c* 0.61, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21–7.06 (m, 4 H), 5.99 (ddd, *J* = 7.7, 10.5, 17.1 Hz, 1 H), 5.24–5.12 (m, 2 H), 3.80 (t, *J* = 6.4 Hz, 2 H), 3.50 (q, *J* = 7.3 Hz, 1 H), 2.33 (s, 3 H), 1.46 (t, *J* = 6.3 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.6, 137.7, 136.8, 129.7, 128.0, 117.1, 66.3, 52.3, 21.2.

IR (NaCl, neat): 3366, 3020, 2872, 1739, 1638, 1510, 1460, 1412, 1040, 914 cm^{-1}.

HRMS-EI: *m*/*z* $[M^+]$ calcd for $C_{11}H_{14}O$: 162.1045; found: 162.1044.

2-(4-Methoxyphenyl)but-3-en-1ol (10b)

The carbonates were isolated in 60% yield as a colorless oil. The mixture was treated with K_2CO_3 in MeOH according to the typical procedure for **2b** and the desired branched product was characterized as the free alcohol.

Colorless solid; 93% ee determined by HPLC (Chiralcel AD-H; *i*-PrOH–hexane, 0.5%; 1.0 mL/min; 208 nm; t_R = 81.7 min, t_R' = 87.8 min); $[\alpha]_D^{25}$ +83.7 (*c* 0.64, $CHCl_3$).

IR (NaCl, neat): 3375, 3078, 2933, 1610, 1412, 1464, 1302, 1248, 1178, 1035, 918 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21–7.08 (m, 2 H), 6.96–6.79 (m, 2 H), 5.96 (ddd, *J* = 7.6, 10.4, 17.2 Hz, 1 H), 5.26–5.08 (m, 2 H), 3.78 (s, 3 H), 3.77 (d, *J* = 7.12 Hz, 2 H), 3.47 (q, *J* = 7.3 Hz, 1 H), 1.24 (t, *J* = 7.1 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.8, 138.7, 132.7, 129.1, 117.0, 114.4, 66.3, 55.5, 51.8.

HRMS-EI: *m*/*z* $[M]^+$ calcd for $C_{11}H_{14}O_2$: 178.0994; found: 178.0994.

2-(4-Chlorophenyl)but-3-en-1-ol (11b)

The carbonates were isolated in 65% yield as a colorless oil. The mixture was treated with K_2CO_3 in MeOH according to the typical procedure for **2b** and the desired branched product was characterized as the free alcohol.

Colorless oil; 96% ee determined by GC (Shuzimi column; 2 min at 130 °C, then 130→200 °C at 4 °C/min; t_R = 11.55 min, t_R' = 11.63 min); $[\alpha]_D^{25}$ –19.6 (*c* 0.76, $CHCl_3$).

IR (NaCl, neat): 3365, 3082, 2928, 2878, 1637, 1491, 1406, 1093, 1057, 922 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.27 (m, 2 H), 7.21–7.14 (m, 2 H), 5.97 (m, 1 H), 5.20 (m, 2 H), 3.81 (dd, *J* = 6.6 Hz, 2 H), 3.51 (q, *J* = 7.2 Hz, 1 H), 1.46 (t, *J* = 6.3 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.1, 137.7, 132.7, 129.3, 128.9, 117.5, 65.9, 51.8.

HRMS-EI: *m*/*z* $[M]^+$ calcd for $C_{10}H_{11}OCl$: 182.0498; found: 182.0498.

2-(4-Fluorophenyl)but-3-en-1-ol (12b)

The carbonates were isolated in 66% yield as a colorless oil. The mixture was treated with K_2CO_3 in MeOH according to the typical procedure for **2b** and the desired branched product was characterized as the free alcohol.

Colorless oil; 67% ee determined by HPLC (Chiralcel AD-H; *i*-PrOH–hexane, 0.9%; 0.5 mL/min; 208 nm; t_R = 47.5 min, t_R' = 50.1 min); $[\alpha]_D^{25}$ +54.8 (*c* 0.25, $CHCl_3$).

IR (NaCl, neat): 3368, 3080, 2926, 2875, 1637, 1602, 1508, 1467, 1225, 1159, 1225, 1057, 1028, 922 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.18–7.08 (m, 2 H), 7.01–6.89 (m, 2 H), 5.90 (ddd, *J* = 7.6, 10.4, 17.3 Hz, 1 H), 5.20–5.05 (m, 2 H), 3.74 (d, *J* = 7.0 Hz, 2 H), 3.45 (q, *J* = 5.5, 10.9 Hz, 1 H), 0.95 (t, *J* = 7.9 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.2, 160.8, 138.2, 136.5, 136.5, 129.6, 129.6, 117.5, 115.9, 115.6, 66.2, 66.2, 51.8.

^{19}F NMR (376 MHz, $CDCl_3$): δ = –116.4 (tt, *J* = 5.4, 8.7 Hz, 1 H).

HRMS-EI: *m*/*z* $[M]^+$ calcd for $C_{10}H_{11}OF$: 166.0794; found: 166.0791.

2-(3,4-Dimethoxyphenyl)but-3-en-1-ol (13b)

The carbonates were isolated in 68% yield as a colorless oil. The mixture was treated with K_2CO_3 in MeOH according to the typical procedure for **2b** and the desired branched product was characterized as the free alcohol.

Colorless oil; 92% ee determined by HPLC (Chiracel AD-H; *i*-PrOH–hexanes, 1%; 1.00 mL/min; 208 nm; t_R = 73.41 min, t_R' = 80.90 min); $[\alpha]_D^{25}$ +64.50 (*c* 0.11, $CHCl_3$).

IR (NaCl, neat): 3387, 2999, 2955, 1736, 1591, 1516, 1464, 1262, 1142, 1028 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 6.88 (d, *J* = 8.3 Hz, 1 H), 6.83 (d, *J* = 8.2 Hz, 1 H), 6.79 (s, 1 H), 6.10–5.94 (m, 1 H), 6.03 (m, 1 H),

5.23 (m, 2 H), 3.91 (dd, J = 2.4, 7.1 Hz, 2 H), 3.85 (d, J = 7.2 Hz, 3 H), 3.85 (d, J = 7.2 Hz, 3 H), 3.52 (d, J = 7.3 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 169.2, 149.2, 148.0, 138.3, 133.0, 119.8, 116.9, 111.5, 111.2, 66.1, 55.9, 52.0.

HRMS-EI: m/z $[M]^+$ calcd for $C_{12}H_{16}O_3$: 208.1099; found: 208.1099.

2-(4-Methoxy-3-methylphenyl)but-3-en-1-ol (14b)
The carbonates were isolated in 45% yield as a colorless oil. The mixture was treated with K_2CO_3 in MeOH according to the typical procedure for **2b** and the desired branched product was characterized as the free alcohol.

Colorless oil; 88% ee determined by HPLC (Chiralcel AD; *i*-PrOH–hexanes, 2%; 1.00 mL/min; 208 nm; t_R = 24.4 min, t_R' = 26.7 min); $[\alpha]_D^{25}$ +116.40 (c 0.92, $CHCl_3$).

IR (NaCl, neat): 3384, 3080, 2924, 1635, 1608, 1504, 1464, 1254, 1136, 1034, 916 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.06–6.97 (m, 2 H), 6.79 (d, J = 8.2 Hz, 1 H), 5.98 (ddd, J = 7.7, 10.5, 17.1 Hz, 1 H), 5.21–5.11 (m, 2 H), 3.81 (s, 3 H), 3.78 (d, J = 7.1 Hz, 2 H), 3.45 (q, J = 7.3 Hz, 1 H), 2.21 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.0, 138.8, 132.3, 130.4, 127.2, 126.3, 116.8, 110.4, 66.4, 55.6, 51.9, 16.5.

HRMS-EI: m/z $[M]^+$ calcd for $C_{12}H_{16}O_2$: 192.1150; found: 192.1155.

2-(2-Tolyl)but-3-en-1-yl Ethyl Carbonate (15a)
Yield: 38%; colorless oil; 88% ee determined by HPLC (Chiralcel AD; *i*-PrOH–hexanes, 0.4%; 1.00 mL/min; 208 nm; t_R = 34.8 min, t_R' = 42.1 min); $[\alpha]_D^{25}$ +24.8 (c 0.83, $CHCl_3$).

IR (NaCl, neat): 3080, 2982, 2920, 2872, 1745, 1607, 1466, 1396, 1259, 1115, 1009, 922, 877 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21 (m, 1 H), 7.13–6.95 (m, 3 H), 6.12–5.91 (m, 1 H), 5.22–5.10 (m, 2 H), 4.35 (dd, J = 3.6, 7.3 Hz, 1 H), 4.17 (m, 2 H), 3.68 (q, J = 7.3 Hz, 2 H), 2.34 (s, 3 H), 1.28 (t, J = 7.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.1, 139.8, 138.3, 137.5, 128.7, 128.5, 127.8, 124.9, 116.8, 70.1, 64.0, 48.7, 21.4, 14.2.

HRMS-EI: m/z $[M]^+$ calcd for $C_{14}H_{18}O_3Na$: 257.1148; found: 257.1143.

2-(2-Chlorophenyl)but-3-en-1-ol (16b)
The carbonates were isolated in 66% yield as a colorless oil. The mixture was treated with K_2CO_3 in MeOH according to the typical procedure for **2b** and the desired branched product was characterized as the free alcohol.

Colorless oil; 70% ee determined by HPLC (Chiralcel AD-H; *i*-PrOH–hexane, 0.9%; 0.30 mL/min; 208 nm; t_R = 74.9 min, t_R' = 80.6 min); $[\alpha]_D^{25}$ +80.7 (c 0.13, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.27–7.12 (m, 3 H), 7.09–7.02 (m, 1 H), 5.90 (m, 1 H), 5.22–5.08 (m, 2 H), 3.76 (d, J = 7.0 Hz, 2 H), 3.44 (q, J = 7.1 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 143.0, 137.7, 134.8, 130.2, 128.3, 127.3, 126.4, 117.9, 66.1, 52.3.

IR (NaCl, neat): 3335, 3080, 2926, 1595, 1574, 1478, 1431, 1057, 922 cm^{-1}.

HRMS-EI: m/z $[M]^+$ calcd for $C_{11}H_{14}O$: 162.1045; found: 162.1044.

2-(Naphthalen-1-yl)but-3-en-1-ol (17b)
The carbonates were isolated in 32% yield as a colorless oil. The mixture was treated with K_2CO_3 in MeOH according to the typical procedure for **2b** and the desired branched product was characterized as the free alcohol.

Colorless oil; 65% ee determined by HPLC (Chiralcel AD; *i*-PrOH–hexanes, 2%; 1.0 mL/min; 254 nm; t_R = 42.3 min, t_R' = 50.4 min); $[\alpha]_D^{25}$ –11.3 (c 0.54, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.07 (d, J = 8.8 Hz, 1 H), 7.83–7.78 (m, 1 H), 7.70 (d, J = 8.0 Hz, 1 H), 7.51–7.31 (m, 4 H), 6.08 (ddd, J = 7.3, 10.7, 16.9 Hz, 1 H), 5.19 (m, 2 H), 4.34 (dd, J = 7.2, 13.5 Hz, 2 H), 3.95 (qd, J = 6.7, 10.9 Hz, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.5, 136.6, 134.3, 132.0, 129.2, 127.7, 126.4, 125.9, 125.7, 124.6, 123.4, 117.7, 65.7, 47.3.

IR (NaCl, neat): 3363, 3047, 2926, 2874, 1637, 1597, 1510, 1396, 1259, 1167, 1035, 798 cm^{-1}.

HRMS-EI: m/z $[M]^+$ calcd for $C_{14}H_{14}O$: 198.1045; found: 198.1045.

2-(Naphthalen-2-yl)but-3-en-1-ol (18b)
The carbonates were isolated in 61% yield as a colorless oil. The mixture was treated with K_2CO_3 in MeOH according to the typical procedure for **2b** and the desired branched product was characterized as the free alcohol.

Colorless oil; 90% ee determined by HPLC (Chiralcel AD; *i*-PrOH–hexane, 1.25%; 1.00 mL/min; 215 nm; t_R = 32.0 min, t_R' = 37.5 min); $[\alpha]_D^{25}$ +25.6 (c 0.46, $CHCl_3$).

IR (NaCl, neat): 3364, 2055, 2924, 2870, 1634, 1599, 1506, 1464, 1376, 1055, 1028, 914 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79–7.68 (m, 3 H), 7.62 (s, 1 H), 7.45–7.34 (m, 2 H), 7.30 (dd, J = 1.7, 8.5 Hz, 1 H), 6.03 (ddd, J = 7.5, 10.4, 17.2 Hz, 1 H), 5.26–5.05 (m, 2 H), 4.01–3.75 (m, 2 H), 3.64 (q, J = 7.2 Hz, 1 H), 1.20 (s, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 138.1, 138.0, 133.5, 132.5, 128.4, 127.6, 127.6, 126.6, 126.1, 125.7, 117.3, 66.0, 52.6, 31.0.

HRMS-EI: m/z $[M]^+$ calcd for $C_{14}H_{14}O$: 198.1045; found: 198.1045.

Acknowledgment

We gratefully acknowledge NSERC (Canada), Merck-Frosst Canada, and the University of Toronto for financial support, as well as Solvias AG, Digital Specialty Chemicals and Takasago for generous gifts of ligands. F.M. thanks the Ontario government for a postgraduate scholarship (OGS). N.I. thanks Otsuka Pharmaceuticals Co. for financial support.

References

(1) (a) Lautens, M.; Dockendorff, C.; Fagnou, K.; Malicki, A. *Org. Lett.* **2002**, *4*, 1311. (b) Tseng, N.-W.; Mancuso, J.; Lautens, M. *J. Am. Chem. Soc.* **2006**, *128*, 5338. (c) Cho, Y.; Zunic, V.; Senboku, H.; Olsen, M.; Lautens, M. *J. Am. Chem. Soc.* **2006**, *128*, 6837. (d) McManus, H. A.; Fleming, M. J.; Lautens, M. *Angew. Chem. Int. Ed.* **2007**, *46*, 433. (e) Menard, F.; Lautens, M. *Angew. Chem. Int. Ed.* **2008**, *47*, 2085.
(2) Menard, F.; Chapman, T. M.; Dockendorff, C.; Lautens, M. *Org. Lett.* **2006**, *8*, 4569.
(3) (a) van Zijl, A. W.; Lopez, F.; Minnaard, A. J.; Feringa, B. L. *J. Org. Chem.* **2007**, *72*, 2558. (b) Davies, H. M. L.; Yang, J. *Adv. Synth. Catal.* **2003**, *345*, 1133.
(4) For recent examples, see: (a) Shintani, R.; Duan, W.; Hayashi, T. *J. Am. Chem. Soc.* **2006**, *128*, 5628. (b) Mariz, R.; Luan, X.; Gatti, M.; Linden, A.; Dorta, R. *J. Am. Chem. Soc.* **2008**, *130*, 2172.

(5) For reviews, see: (a) Yoshida, K.; Hayashi, T. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; Wiley-VCH Verlag GmbH: Weinheim, **2005**, 55–77. (b) Tomioka, K.; Nagaoka, Y. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer Verlag: Berlin / Heidelberg, **1999**, Chap. 31.1. (c) Fagnou, K.; Lautens, M. *Chem. Rev.* **2003**, *103*, 169. (d) Hayashi, T.; Yamasaki, K. *Chem. Rev.* **2003**, *103*, 2829.

(6) (a) Godleski, S. A. In *Comprehensive Organic Synthesis*, Vol. 4; Trost, B. M.; Fleming, I.; Semmelhack, M. F., Eds.; Pergamon Press: Oxford, **1990**, Chap. 3.3. (b) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395. (c) Helmchen, G. *J. Organomet. Chem.* **1999**, *576*, 203. (d) Tsuji, J. *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*; Wiley: New York, **1996**. (e) Paquin, J.-F.; Lautens, M. In *Comprehensive Asymmetric Catalysis*, Vol. 2; Jacobsen, E. N.; Pfaltz, A.; Yamamoto, H., Eds.; Springer: Berlin, **2004**, 73.

(7) (a) Kobayashi, Y.; Murugesh, M. G.; Nakano, M.; Takahisa, E.; Usmani, S. B.; Ainai, T. *J. Org. Chem.* **2002**, *67*, 7110. (b) Piarulli, U.; Daubos, P.; Claverie, C.; Roux, M.; Gennari, C. *Angew. Chem. Int. Ed.* **2003**, *42*, 234.

(8) (a) Marino, J. P.; Fernández de la Pradilla, R.; Laborde, E. *J. Org. Chem.* **1987**, *52*, 4898. (b) Stille, J. K.; Tueting, D. R.; Echavarren, A. M. *Tetrahedron* **1989**, *45*, 5052. (c) Ernst, M.; Helmchen, G. *Synthesis* **2002**, 1953. (d) Kobayashi, Y.; Ainai, T.; Ito, M. *Tetrahedron Lett.* **2003**, *44*, 3983.

(9) (a) Evans, P. A.; Leahy, P. K. *J. Am. Chem. Soc.* **2002**, *124*, 7882. (b) Evans, P. A.; Leahy, P. K. *J. Am. Chem. Soc.* **2003**, *125*, 8974. (c) Evans, P. A.; Leahy, P. K.; Andrews, W. J.; Uraguchi, D. *Angew. Chem. Int. Ed.* **2004**, *43*, 4788.

(10) (a) Alexakis, A.; Polet, D. *Org. Lett.* **2004**, *6*, 3529. (b) Lipowski, G.; Miller, N.; Helmchen, G. *Angew. Chem. Int. Ed.* **2004**, *43*, 4595. (c) Graening, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 17192.

(11) Reviews on copper-catalyzed allylic substitution reactions with alkyl nucleophiles: (a) Yorimitsu, H.; Oshima, K. *Angew. Chem. Int. Ed.* **2005**, *44*, 4435. (b) Alexakis, A.; Malan, C.; Lea, L.; Tissot-Croset, K.; Polet, D.; Falciola, C. *Chimia* **2006**, *60*, 124.

(12) (a) Tissot-Croset, K.; Polet, D.; Alexakis, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 2426. (b) Breit, B.; Demel, P.; Studte, C. *Angew. Chem. Int. Ed.* **2004**, *43*, 3786. (c) Hoveyda, A. H.; Kacprzynski, M. A. *J. Am. Chem. Soc.* **2004**, *126*, 10676. (d) Lopez, F.; Zijl, A. W.; Minnaard, A. J.; Feringa, B. L. *Chem. Commun.* **2006**, 409. (e) Geurts, K.; Fletcher, S. P.; Feringa, B. L. *J. Am. Chem. Soc.* **2006**, *128*, 15572. (f) Sebesta, R.; Pizzuti, M. G.; Minnaard, A. J.; Feringa, B. L. *Adv. Synth. Catal.* **2007**, *349*, 1931.

(13) Pineschi, M. *New J. Chem.* **2004**, *28*, 657.

(14) Miura, T.; Takahashi, Y.; Murakami, M. *Chem. Commun.* **2007**, 595.

(15) (a) Wu, J.; Chen, H.; Zhou, Z.; Yeung, C. H.; Chan, A. S. C. *Synlett* **2001**, 1050. (b) Wu, J.; Chan, A. S. C. *Acc. Chem. Res.* **2006**, *39*, 711.

(16) (a) Jeulin, S.; Duprat De Paul, S.; Ratovelomanana-Vidal, V.; Genet, J.-P.; Champion, N.; Dellis, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 320. (b) Jeulin, S.; Duprat De Paul, S.; Ratovelomanana-Vidal, V.; Grenet, J.-P.; Champion, N.; Dellis, P. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5799. (c) Touati, R.; Gimza, T.; Jeulin, S.; Deport, C.; Ratovelomanana-Vidal, V.; Ben Hassine, B.; Genet, J.-P. *Synlett* **2005**, 2478.

(17) P-Phos is stable to air in the solid state; however, it is highly sensitive to oxygen once in solution.

(18) Evans, P. A.; Nelson, J. D. *J. Am. Chem. Soc.* **1998**, *120*, 5581.

(19) Urson, T.; Oro, L. A.; Cabeza, J. A. *Inorg. Synth.* **1985**, *23*, 126.

(20) Tsuda, T.; Kiyoi, T.; Seagusa, T. *J. Org. Chem.* **1990**, *55*, 3388.