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Highly Enantio- and Diastereoselective One-Pot Reactions in Aqueous Media: Combined Asymmetric Rh-Catalyzed Conjugate Addition/Metal-Mediated Allylation

Sara Källström,[a] Richard B. C. Jagt,[b] Reijo Sillanpää,[c][‡] Ben L. Feringa,[b] Adriaan J. Minnaard,*[b] and Reko Leino*[a]

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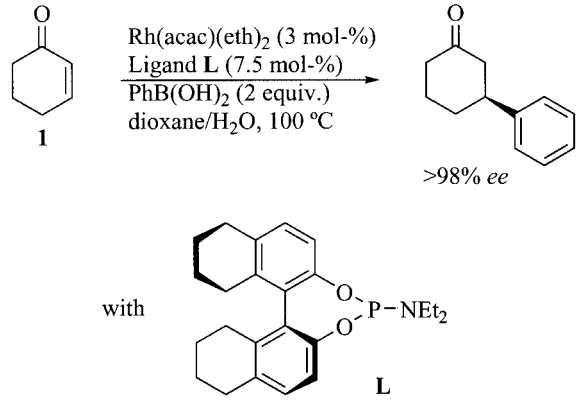
1,3-Disubstituted, enantiopure cyclohexanols have been prepared in very high diastereoselectivities and good yields by a concise one-pot method combining the enantioselective rhodium-catalyzed conjugate addition of arylboronic acids with indium-mediated allylation into a highly efficient one-pot reaction in aqueous media.

Introduction

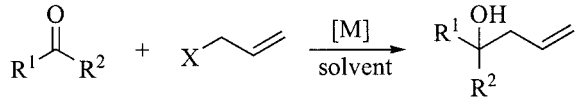
Carbon–carbon bond-forming methods provide the means for generating more complicated organic compounds from simpler ones, and constitute the essence of organic synthesis.[1] Due to the great demand for stereochemically defined products, such as medicines and pesticides, asymmetric C–C bond formation has become one of the most important areas of organic synthesis.[2] An essential goal in asymmetric synthesis is the development of tandem, one-pot and cascade reactions giving a rapid increase in molecular complexity with minimal isolation and purification.[3]

During the past decade, the rhodium-catalyzed conjugate addition of aryl- and alkenyl boronic acids, pioneered by Miyaura and Hayashi,[4] has emerged as an impressive tool for stereoselective chemical synthesis.[5] A number of chiral ligands, the majority being bidentate in nature, has been introduced for these reactions.[6] Monodentate phosphoramidite ligands[7–9] have recently shown to give excellent enantioselectivities and fast reactions (Scheme 1).[10] This class of cheap and easily tunable ligands has also proven to be successful in the rhodium-catalyzed conjugate addition of aryl- and vinyltrifluoroborates.[8]



Scheme 1.

Another important and much scrutinized C–C bond forming method is the Barbier-type metal-mediated allylation in aqueous media.[11] Due to the relatively high reactivity of allyl halides, the allylation reaction has turned out to be the most successful among the large amount of different nucleophilic addition reactions to carbonyl compounds. Various metals have been found to be effective in mediating this particular reaction (Scheme 2) and among them, indium has emerged as the most reactive and effective one.[12]



Scheme 2.

[a] Laboratory of Organic Chemistry, Åbo Akademi Univeristy, 20500 Åbo, Finland
Fax: +358-2-2154866
E-mail: reko.leino@abo.fi
[b] Department of Organic and Molecular Inorganic Chemistry, Stratingh Institute, University of Groningen, Nijenborgh 4, 9747 AG Groningen, The Netherlands
Fax: +31-50-3634296
E-mail: a.j.minnaard@rug.nl
[c] Department of Chemistry, Univeristy of Jyväskylä, 40351 Jyväskylä, Finland
[‡] X-ray crystallography.
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Herein we report our initial efforts in combining these two well-known carbon–carbon bond-forming methods presented above, namely the rhodium-catalyzed asymmetric conjugate addition of arylboronic acids and the indium-mediated allylation into a highly efficient one-pot reaction sequence in aqueous media. Because the conjugate addition step is highly enantioselective, this one-pot protocol offers excellent means for the controlled creation of a second stereogenic center in the molecule. The diastereomerically pure homoallylic alcohols obtained may then serve as valuable chiral building blocks by further functionalization of the alcohol moiety or the C–C double bond of the allylic unit, as briefly demonstrated in the present work.

Results and Discussion

In the conjugate addition step of the one-pot reaction sequence presented in this study, the monodentate phosphoramidite **L** was applied and the cyclic ketones **1**–**4** were investigated (Figure 1). As reported previously, this particular ligand **L** provides full conversion and excellent enantioselectivity when used in combination with $Rh(acac)(eth)_2$ in dioxane/water at 100 °C.[10b]

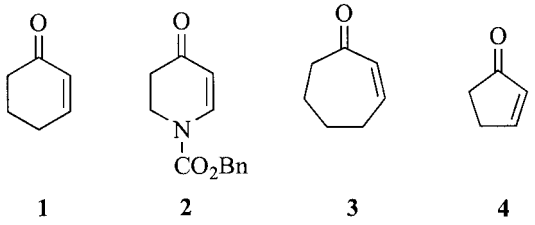
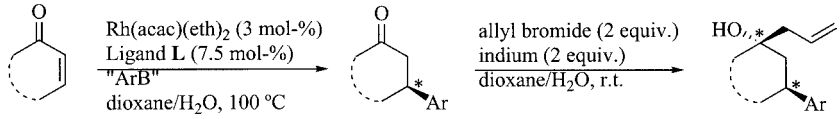


Figure 1. Structures of the substrates used in the rhodium-catalyzed conjugate addition.

The one-pot allylation of the conjugate addition products **5**–**9** (Table 1), directly following the conjugate addition step, was performed by in situ formation of the allylindium species from indium powder and allyl bromide added to the reaction mixture after cooling it to room temperature. We were pleased to find that this second step of the one-pot protocol indeed proceeded in a highly diastereoselective fashion and with excellent conversions for ketones **5** and **6** (Table 1, Entries 1–2).[13] The one-pot indium-mediated allylation of ketone **7** also proceeded with excellent conversion (Table 1, Entry 3). This case, however, showed only moderate diastereoselectivity. Quite surprising, only moderate conversions were obtained in the one-pot allylation of **8** and **9** (Table 1, Entries 4 and 5). The complete lack of diastereoselectivity found in the allylation of ketone **9** is not surprising given the fact that the envelope conformation of saturated five-membered rings is very flexible and often behaves as if the two positions on any carbon atom are the same.[14] Nevertheless, it must be emphasized that the yields reported in Table 1 refer to those of pure *single diastereoisomers.*

In order to examine the scope of the second step of the consecutive conjugate addition/allylation reactions, we decided to continue our study by a further examination of different allylating agents for the allylation of **5** (Table 2). The indium-mediated allylation and methallylation of this ketone occurred in 2–3 hours at room temperature yielding **10a**–**b** with full conversion, high yields and very high diastereoselectivities (Table 2, Entries 1 and 2). Unfortunately, though not surprising,[3c,11b] we found a complete lack of diastereoselectivity for the third additional stereocenter in the homoallylic alcohol **10c** of the indium-mediated crotylation. In all other aspects, this reaction showed similar results compared to the indium-mediated allylation and methallylation reactions (Table 2, Entry 3). The indium-medi-

Table 1. The conjugate addition–allylation sequence evaluating different keto substrates for the first part of the one-pot reaction.



1
1
2
3
4

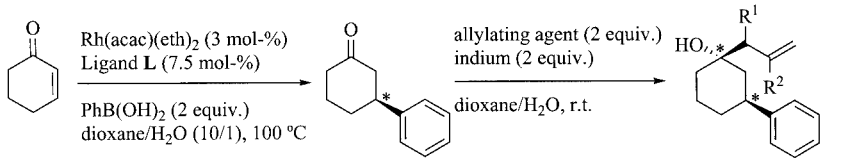
5, substrate **1**
6, substrate **1**
7, substrate **2**
8, substrate **3**
9, substrate **4**

10, substrate **1**
11, substrate **1**
12, substrate **2**
13, substrate **3**
14, substrate **4**

Entry	"ArB" (equiv.)	Cond.[a]	Product	Conv.[b] [%]	*ee*[c] [%]	*dr*[d] [a/b]	Yield[e] [%]
1	$PhB(OH)_2$ (2.0)	A	**10**	100	>98	94:6	62
2	*m,p*-$(MeO)_2C_6H_3B(OH)_2$ (2.0)	A	**11**	100	96	>99:<1	84
3	$(PhBO)_3$ (3.0)	B	**12**	100	99	73:27	35
4	$PhB(OH)_2$ (2.0)	A	**13**	68	96	82:18	38
5	$PhB(OH)_2$ (2.0)	A	**14**	69	85	50:50	32

[a] Conjugate additions were performed on a 0.2-mmol scale with 3 mol-% $Rh(acac)(eth)_2$ and 7.5 mol-% **L** at 100 °C for 3 h. Condition A: 1.0 mL of dioxane, 0.1 mL of H_2O as reported in ref.[10b]. Condition B: 0.5 mL of dioxane, slow addition of water by syringe pump (100 °C, 2 h), as reported in ref.[5h]. Allylations were performed at room temp. for 3 h with 2.0 equiv. of indium and allyl bromide, respectively. [b] Conversions were determined by ^1H NMR spectroscopy. [c] *ee* Values were determined by chiral HPLC. [d] a: axial OH group; b: equatorial OH group. *dr* values were determined by GC or ^1H NMR spectroscopy. [e] Isolated yields of pure single diastereoisomers shown in Scheme.

Table 2. The conjugate addition–allylation sequence testing different substrates for the second part of the one-pot reaction.[a]



1 **5**

10a, R^1 = H, R^2 = H
10b, R^1 = H, R^2 = Me
10c, R^1 = Me, R^2 = H
10d, R^1 = *i*Pr, R^2 = H

Entry	Allylating agent	R^1	R^2	Conv.[b] [%]	*dr*[c] [a/b]	Yield[d] [%]
1	allyl bromide	H	H	100	94:6	62
2	methallyl bromide	H	Me	100	95:5	75
3	crotyl bromide	Me	H	100	98:2	71
4	prenyl bromide	*i*Pr	H	65	>99:<1	46

[a] Conjugate additions were performed on a 0.2-mmol scale in dioxane/H_2O, 10:1 with 3 mol-% Rh(acac)(eth)$_2$ and 7.5 mol-% **L** at 100 °C for 3 h. Allylations were performed at room temp. for 3 h with 2.0 equiv. of indium and allyl bromide, respectively. [b] Conversions were determined by ^{1}H NMR spectroscopy. [c] a: axial OH group; b: equatorial OH group. *dr* values were determined by GC or ^{1}H NMR spectroscopy. [d] Isolated yields of pure single diastereoisomers are shown in the Scheme.

ated prenylation giving **10d** showed the highest diastereoselectivity after a reaction time of 3 hours, however at the expense of conversion and yield (Table 2, Entry 4).[15]

The stereochemistry of the homoallylic alcohol products could be ascertained by NMR analysis. For the minor equatorial-OH alcohol **10a′**, formed by an axial attack of the allylindium, a NOESY cross-peak between the C(7) protons of the allyl group and the C(3) proton in the cyclohexane ring is clearly observed (Figure 2). This interaction is not observed for the major alcohol **10a** with an axial OH group, which is formed through the preferred equatorial approach of the allylindium. The configuration of the major and minor diastereomer, respectively, is also supported by coupling constant data where the C(7) protons of the *freely rotating* allyl group of the major diastereomer **10a** give rise to a doublet with a coupling of J = 8.0 Hz, while the same *sterically hindered* protons of the minor diastereomer **10a′** give two distinct doublet-of-doublets with J = 8.0 Hz and J = 14.4 Hz.

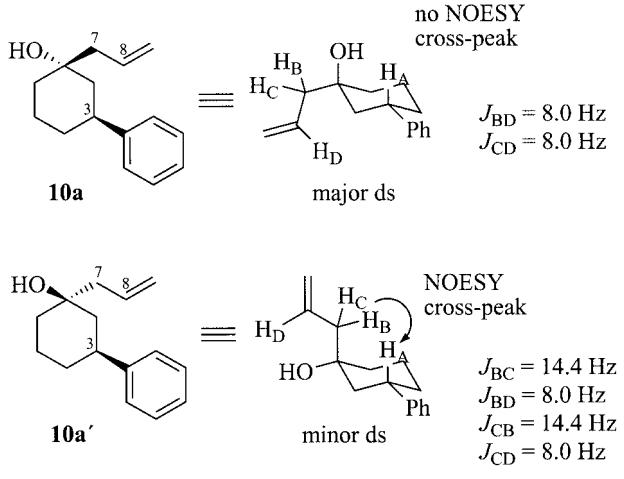


Figure 2. Assignment of the stereochemistry of the products by NMR analysis.

The stereochemical assignment of the chiral cyclohexanols **10a** and **10a′** was further supported by single-crystal X-ray analysis of **10a**, confirming the equatorial positioning of the allyl group (Figure 3).[16] Compound **10a** crystallizes with three molecules in the asymmetric unit, H-bonded as shown in Figure 3. From HO3 there is an intermolecular H-bond to O1^i (i = x, y + 1, x). This results in the formation of H-bonded columns connected only by van der Waals forces and explains the fiber-like appearance of the crystals of **10a**.

The preferred equatorial attack of the allylindium reagent leading to the axial-OH alcohol **10a** (Figure 4) conforms to the stereoselectivity previously observed for both allylindium as well as other allylmetal reagents.[17] Formation of the minor equatorial-OH alcohol **10a′** by axial attack of the allylindium is believed to be hindered by 1,3-diaxial interactions with bulky reagents.[17b] This is supported by the increase in diastereoselectivity found in this study upon switching from allyl bromide to prenyl bromide (Table 2). Another possibility is that the rather large van der Waals radius of indium dictates the stereocontrol in cyclic systems of this kind, making an axial approach of the allylindium species sterically unfavorable, as previously discussed by Paquette and co-workers.[17c]

Despite the successful nature of indium-promoted reactions, their precise mechanism remains unclear. One possible mechanism is a single electron transfer process proposed by Chan and Li (Figure 5, I).[11d,18] This reaction pathway involves a radical anion/indium radical cation pair which is generated by the SET process at the surface of the indium metal as allyl bromide approaches it. An alternative pathway involving an allylindium sesquibromide (Figure 5, II) might overrun the SET mechanism when preformed allylindium reagents are used.[17d–17e,19]

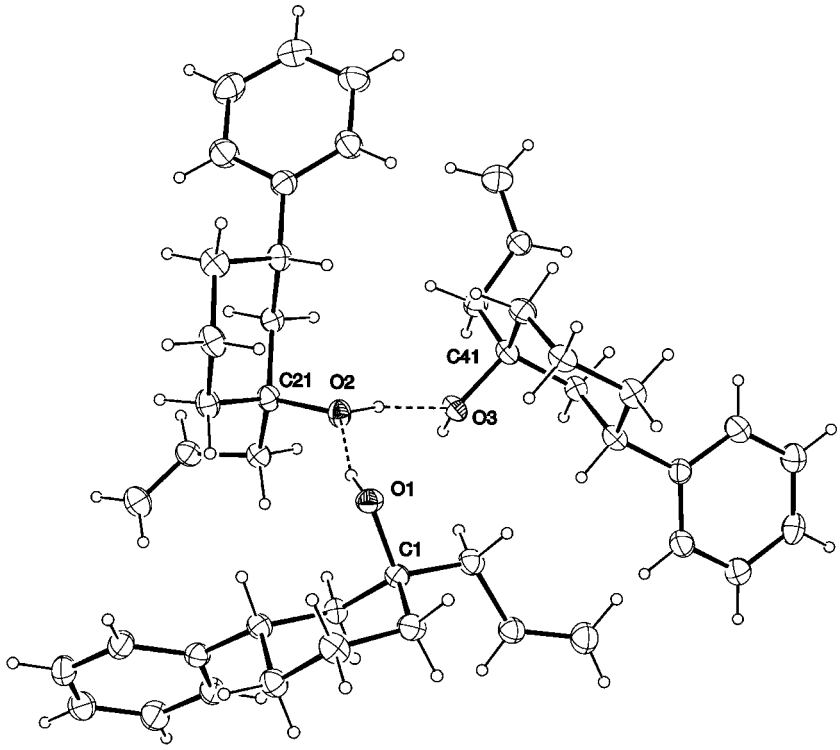


Figure 3. ORTEP drawing of **10a**.

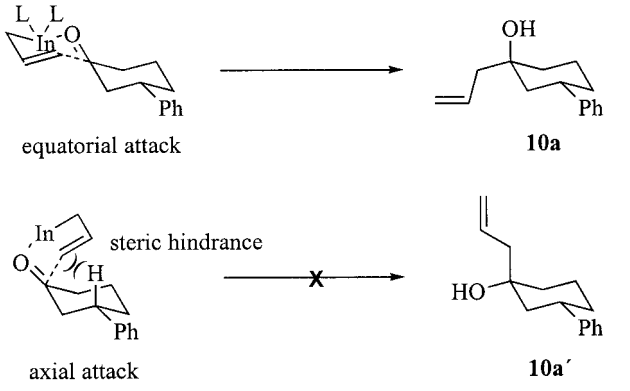


Figure 4. Equatorial attack of the allylindium reagent is preferred over axial attack due to steric reasons.

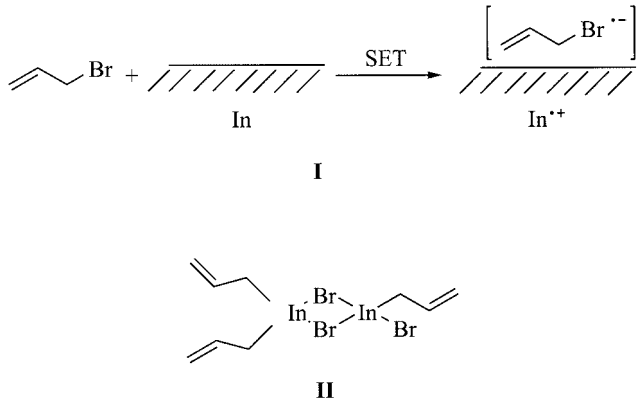
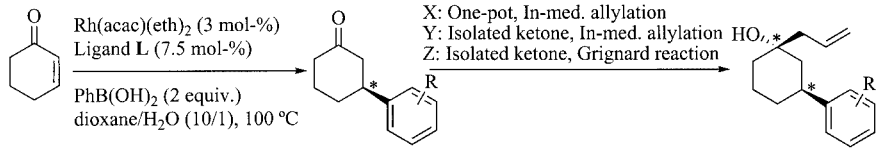


Figure 5. I: Single electron-transfer mechanism. II: Allylindium sesquibromide.

After demonstrating the efficiency of the one-pot protocol described above, the outcome of the combined method was compared with the one carried out in the traditional two-step fashion.[20] We also wished to compare the outcome of an indium-mediated allylation vs. a Grignard reaction using allylmagnesium bromide in the second step.[21] The results unambiguously demonstrate the advantages of the one-pot approach (Table 3) in terms of isolated yield. Furthermore, the indium-mediated allylation proved to be far more selective than the Grignard reaction (Table 3, Entries 1, 2 and 4 vs. 3 and 5). This is most likely due to the properties of the indium metal, as also previously shown by Reetz and co-workers in the diastereoselective allylation of 3-methylcyclohexanone using indium-ate complexes.[17d]

Thus, the one-pot protocol reported here provides an attractive and efficient route to chiral cyclohexanol building blocks with two asymmetric centers formed in excellent diastereoselectivities. As a demonstration of the further derivatization of these compounds, we converted the homoallylic alcohol **10a** into the corresponding allyl ether **15** in good yield by deprotonation with sodium hydride and subsequent reaction with excess allyl bromide at room temperature (Scheme 3).[21] Upon treating a degassed dichloromethane solution of **15** with the Grubbs' second-generation ruthenium catalyst at room temperature, chiral spirocyclic ether **16** was obtained in 60% yield after purification by column chromatography, leaving a double bond in the ring for further derivatization by e.g. dihydroxylation or epoxid-

Table 3. One-pot protocol vs. traditional methodologies.

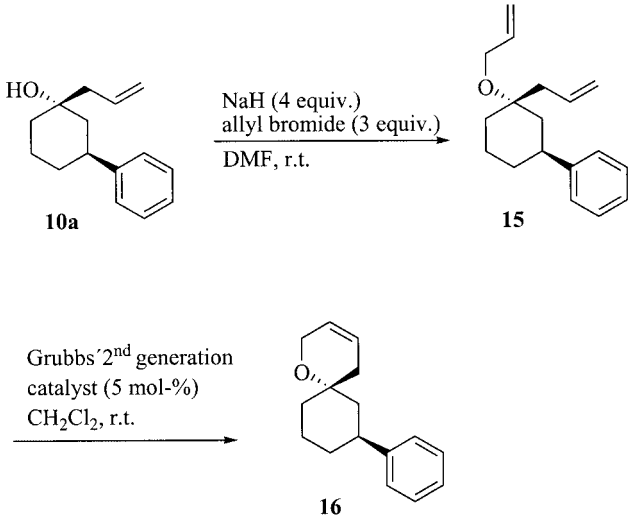


1 **5**, R = H; **6**, R = *m,p*-$(MeO)_2$ **10a**, R = H; **11**, R = *m,p*-$(MeO)_2$

Entry	Method[a]	Product	Conv.[b] [%]	*dr*[c] [a/b]	Yield[d] [%]
1	X	**10a**	100	94:6	62
2	Y	**10a**	100	94:6	39
3	Z	**10a**	100	65:35	33
4	X	**11**	100	>99:<1	84
5	Z	**11**	84	53:47	22

[a] Conjugate additions were performed on a 0.2 mmol scale in dioxane/H_2O, 10:1 with 3 mol-% Rh(acac)(eth)$_2$ and 7.5 mol-% **L** at 100 °C for 3 h. Method X: One-pot allylation was performed in dioxane/H_2O, 10:1 at room temp. for 3 h with 2.0 equiv. of indium and allyl bromide, respectively. Method Y: Following isolation of 5, allylation was performed in THF/hexane, 3:1 at room temp. for 3 h with 2.0 equiv. of indium and allyl bromide, respectively, as reported in ref.[20]. Method Z: Following isolation of 5, allylation was performed in Et_2O at room temp. for 12 h with 1.2 equiv. of allylmagnesium bromide, as reported in ref.[21]. [b] Conversions were determined by ^{1}H NMR spectroscopy. [c] a: axial OH group; b: equatorial OH group. *dr* values were determined by GC or ^{1}H NMR spectroscopy. [d] Isolated yields of pure single diastereoisomers shown in Scheme.

ation.[22] Further work on the utilization of these one-pot reaction products is currently in progress.



Scheme 3.

Conclusions

To summarize, we have developed a viable method for the highly diastereoselective construction of two new stereocenters in an efficient manner by consecutive, one-pot rhodium-catalyzed asymmetric conjugate addition and indium-mediated allylation in aqueous media. Furthermore, we have shown that the indium-mediated allylation is far more selective in this particular reaction than the corresponding Grignard reaction with allylmagnesium bromide. Finally, the one-pot reaction products obtained may be further utilized as chiral building blocks. Subsequent etherification followed by ring-closing metathesis gives chiral spirocyclic ethers in good yield, providing an example of the possibilities emerging from the products of this new one-pot protocol.

Experimental Section

General Remarks: All reactions were performed under dry nitrogen or argon using standard Schlenk techniques. 1,4-Dioxane was distilled from Na and stored under nitrogen. Reagents were used as received. ^{1}H NMR, ^{13}C NMR and NOESY spectra were recorded at room temperature in $CDCl_3$ on Varian or Bruker instruments at 200 MHz, 400 MHz, 500 MHz or 600 MHz. Chemical shifts were determined relative to residual solvent peaks ($CHCl_3$, δ = 7.26 ppm for proton atoms, δ = 77.23 ppm for carbon atoms). HRMS were recorded on an AEI MS-902 or a Fisons ZABSpec-oaTOF instrument. Optical rotations were measured with a Schmidt and Haensch Polartronic MH8 or a Perkin–Elmer 343 polarimeter. Flash chromatography was performed using silica gel 60 Å (Merck, 230–400 mesh).

Synthesis of Starting Materials: Substrate **2** was synthesized from 4-piperidone monohydrate hydrochloride and benzyl chloroformate, following the literature procedure for ethyl 3,4-dihydro-4-oxo-1(2*H*)-pyridinecarboxylate, and was obtained as a white solid in 64% yield.[23] Spectral data were in accordance with literature.[24] Arylboroxines were prepared from the corresponding arylboronic acids by heating at 300 °C in vacuo.[25] Phosphoramidite ligand (*S*)-**L** was prepared from the corresponding H8-bis-β-naphthol, PCl_3, and diethylamine according to a previously reported procedure.[10b]

One-pot Procedure: Standard reaction for Table 2; In a Schlenk tube flushed with nitrogen, Rh(acac)(eth)$_2$ (1.55 mg, 6 μmol) and phosphoramidite **L** (5.93 mg, 15 μmol) were dissolved in dioxane (1 mL). Water (0.1 mL) was added, and the resulting solution was stirred 5 min at room temperature. Cyclohexenone (20 μL, 0.2 mmol) and phenylboronic acid (48.8 mg, 0.4 mmol) were added to the solution, and the mixture was heated to 100 °C. The resulting solution was stirred for 3 hours at 100 °C and subsequently cooled to room temperature. Indium (46 mg, 0.4 mmol) and allyl bromide

(35 μL, 0.4 mmol) were added. The mixture was stirred for an additional 3 hours at room temperature followed by quenching with satd. $NaHCO_3$, extraction with diethyl ether and washing with water. The organic phase was passed through a pad of silica gel. The crude mixture was purified by flash chromatography and subjected to analysis.

(1*R*,3*S*)-1-Allyl-3-phenylcyclohexanol (10a): White solid. M.p. 52–54 °C. R_f = 0.63 (10% EtOAc in pentane). $[\alpha]_D$ = +10.0 ($CHCl_3$, *c* = 0.10). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.34–1.53 (m, 4 H), 1.67–1.93 (m, 5 H), 2.25 (d, *J* = 8.0 Hz, 2 H), 2.97 (tt, *J* = 3.2, 12.4 Hz, 1 H), 5.14 (dd, *J* = 1.2, 17.2 Hz, 1 H), 5.17 (dd, *J* = 1.2, 10.4 Hz, 1 H), 5.91 (ddt, *J* = 8.0, 10.0, 17.2 Hz, 1 H), 7.18–7.33 (m, 5 H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 20.3, 32.0, 35.1, 37.7, 43.4, 47.4, 69.8, 117.7, 124.5, 125.4, 126.9, 131.8, 145.6 ppm. HRMS calcd. for 216.1514, found 216.1520. $C_{15}H_{20}O$: calcd. C 83.28, H 9.32; found C 83.40, H 9.46.

(1*S*,3*S*)-1-Allyl-3-phenylcyclohexanol (10a′): White solid. M.p. 62–65 °C. R_f = 0.35 (10% EtOAc in pentane). $[\alpha]_D$ = –9.8 ($CHCl_3$, *c* = 0.10). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.24–1.61 (m, 5 H), 1.81–1.96 (m, 4 H), 2.41 (dd, *J* = 8.0, 14.4 Hz, 1 H), 2.47 (dd, *J* = 8.0, 14.4 Hz, 1 H), 2.66 (tt, *J* = 3.2, 12.4 Hz, 1 H), 5.19 (dd, *J* = 1.2, 18.0 Hz, 1 H), 5.21 (dd, *J* = 1.2, 10.8 Hz, 1 H), 5.92 (dddd, *J* = 7.2, 10.8, 14.8, 18.4 Hz, 1 H), 7.20–7.32 (m, 5 H) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 23.7, 33.8, 38.1, 41.5, 41.8, 45.8, 72.5, 119.4, 126.4, 127.0, 128.7, 133.6, 146.4 ppm. HRMS calcd. for 216.1514, found 216.1517.

(1*S*,3*S*)-1-(2-Methylallyl)-3-phenylcyclohexanol (10b): Colorless oil. R_f = 0.27 (10% EtOAc in hexane). $[\alpha]_D$ = +13.3 ($CHCl_3$, *c* = 1.04). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.35–1.43 (m, 2 H), 1.48–1.52 (m, 1 H), 1.62 (br. s, 1 H), 1.69–1.74 (m, 2 H), 1.77–1.85 (m, 2 H), 1.85 (s, 3 H), 1.88–1.92 (m, 1 H), 2.22 (d, *J* = 2.0 Hz, 1 H), 2.97 (tt, *J* = 3.4, 12.5 Hz, 1 H), 4.78 (br. s, 1 H), 4.95 (br. s, 1 H), 7.18–7.31 (m, 5 H) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 22.1, 25.7, 33.7, 37.3, 39.5, 45.6, 52.1, 71.6, 115.3, 126.2, 127.2, 128.6, 142.4, 147.4 ppm. HRMS calcd. for 230.1671, found 230.1691.

(1*S*,3*S*)-1-(1-Methylallyl)-3-phenylcyclohexanol (10c): Colorless oil. R_f = 0.56 (10% EtOAc in pentane). $[\alpha]_D$ = +1.7 ($CHCl_3$, *c* = 1.04). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.05 (d, *J* = 1.6 Hz, 3 H), 1.07 (d, *J* = 2.0 Hz, 3 H), 1.33–1.90 (m, 18 H), 2.18 (m, 2 H), 2.97 (tt, *J* = 3.2, 10.4 Hz, 2 H), 5.07–5.12 (m, 4 H), 5.79–5.87 (m, 2 H), 7.18–7.32 (m, 10 H) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 14.5, 14.6, 22.0, 22.1, 33.5, 33.6, 33.7, 34.4, 39.4, 39.5, 42.2, 42.9, 49.9, 73.3, 73.4, 116.7, 116.8, 126.1, 126.2, 127.1, 127.2, 128.5, 128.6, 140.3, 147.4, 147.5 ppm. HRMS calcd. for 230.1671, found 230.1680.

(1*S*,3*S*)-1-(1,1-Dimethylallyl)-3-phenylcyclohexanol (10d): Colorless oil. R_f = 0.79 (10% EtOAc in pentane). $[\alpha]_D$ = +6.7 ($CHCl_3$, *c* = 1.34). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.06 (s, 3 H), 1.07 (s, 3 H), 1.30–1.88 (m, 9 H), 2.94 (tt, *J* = 3.2, 12.4 Hz, 1 H), 5.07 (dd, *J* = 1.2, 17.2 Hz, 1 H), 5.12 (dd, *J* = 1.6, 11.2 Hz, 1 H), 6.01 (dd, *J* = 10.8, 17.6 Hz, 1 H), 7.18–7.33 (m, 5 H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 20.3, 20.5, 29.4, 31.7, 38.0, 38.2, 42.8, 73.6, 112.5, 124.5, 125.5, 126.9, 143.7, 145.9 ppm. HRMS calcd. for 244.1827, found 244.1855.

(1*R*,3*S*)-1-Allyl-3-(3,4-dimethoxyphenyl)cyclohexanol (11): Colorless oil. R_f = 0.53 (30% EtOAc in pentane). $[\alpha]_D$ = +10.3 ($CHCl_3$, *c* = 1.74). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.33–1.47 (m, 4 H), 1.65–1.90 (m, 5 H), 2.24 (d, *J* = 7.2 Hz, 2 H), 2.90 (tt, *J* = 3.2, 12.4 Hz, 1 H), 3.85 (s, 3 H), 3.87 (s, 3 H), 5.13 (dd, *J* = 1.2, 18.0 Hz, 1 H), 5.16 (dd, *J* = 1.2, 9.2 Hz, 1 H), 5.90 (ddt, *J* = 6.8, 9.6, 17.2 Hz, 1 H), 6.74 (s, 1 H), 6.75 (d, 1 H, *J* = 7.6 Hz), 6.81 (d, *J* = 8.0 Hz, 1 H) ppm. ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 20.3, 32.1, 35.1, 37.4, 43.7, 47.3, 54.3, 69.9, 109.1, 109.7, 116.9, 117.7, 131.8, 138.4, 145.7, 147.3 ppm. HRMS calcd. for 276.1725, found 276.1734.

Procedure for the Synthesis of 12: In a Schlenk tube flushed with nitrogen, $Rh(acac)(eth)_2$ (1.55 mg, 6 μmol) and phosphoramidite **L** (5.93 mg, 15 μmol) were dissolved in dioxane (0.5 mL). After stirring for 15 min at room temperature, substrate **2** (46.2 mg, 0.2 mmol) and phenylboroxine (187.0 mg, 0.6 mmol) were added, and the resulting mixture was stirred at reflux with slow addition of a 20 vol.-% solution of water in 1,4-dioxane by syringe pump (0.1 mL/h). After 2 h it was cooled to room temperature and indium (46 mg, 0.4 mmol) and allyl bromide (35 μL, 0.4 mmol) were added. The mixture was stirred for an additional 3 hours at room temperature after which it was diluted with diethyl ether (2 mL) and passed through a pad of silica gel. The crude mixture was purified by flash chromatography and subjected to analysis.

Benzyl (2*S*,4*S*)-4-Allyl-4-hydroxy-2-phenylpiperidine-1-carboxylate (12): Light yellow oil. R_f = 0.43 (hexane/Et_2O, 1:2). $[\alpha]_D$ = –27.6 ($CHCl_3$, *c* = 2.10). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.18 (s, 1 H), 1.56–1.66 (m, 2 H), 2.02 (dd, *J* = 7.0, 14.7 Hz, 1 H), 2.22 (d, *J* = 7.4 Hz, 1 H), 2.37 (d, *J* = 14.7 Hz, 1 H), 3.37 (dt, *J* = 3.4, 13.3 Hz, 1 H), 4.21 (d, *J* = 13.6 Hz, 1 H), 5.11–5.19 (m, 4 H), 5.53 (br. s, 1 H), 5.86 (ddt, *J* = 7.7, 10.2, 17.7 Hz, 1 H), 7.22–7.38 (m, 10 H) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 36.2, 36.8, 39.4, 48.2, 52.3, 67.5, 69.9, 119.6, 125.6, 126.8, 128.0, 128.1, 128.6, 128.9, 132.9, 136.9, 156.2 ppm. HRMS calcd. for 351.1834, found 351.1842.

(1*R*,3*S*)-1-Allyl-3-phenylcycloheptanol (13): Colorless oil. R_f = 0.69 (10% EtOAc in pentane). $[\alpha]_D$ = +1.1 ($CHCl_3$, *c* = 1.14). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.39–1.44 (m, 2 H), 1.60–1.67 (m, 2 H), 1.72–1.85 (m, 5 H), 1.92–1.97 (m, 2 H), 2.20 (dd, *J* = 7.9, 13.5 Hz, 1 H), 2.30 (dd, *J* = 7.2, 13.2 Hz, 1 H), 3.06 (tt, *J* = 2.8, 11.2 Hz, 1 H), 5.11 (dd, *J* = 1.2, 16.4 Hz, 1 H), 5.14 (dd, *J* = 1.6, 10.8 Hz, 1 H), 5.86 (ddt, *J* = 7.2, 10.0, 16.8 Hz, 1 H), 7.14–7.29 (m, 5 H) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 22.5, 29.2, 38.1, 39.4, 40.8, 49.3, 49.7, 74.3, 119.5, 125.8, 126.9, 128.6, 134.0, 150.1 ppm. HRMS calcd. for 230.1671, found 230.1680.

(1*R*,3*S*)-1-Allyl-3-phenylcyclopentanol (14): Colorless oil. R_f = 0.69 (10% EtOAc in pentane). $[\alpha]_D$ = +12.2 ($CHCl_3$, *c* = 0.56). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.61 (br. s, 1 H), 1.68–1.75 (m, 2 H), 1.78–1.83 (m, 1 H), 1.96–2.01 (m, 1 H), 2.06 (dd, *J* = 6.8, 13.1 Hz, 1 H), 2.29 (m, 1 H), 2.43 (d, *J* = 7.4 Hz, 1 H), 3.44–3.50 (m, 1 H), 5.18–5.20 (m, 2 H), 5.92 (ddt, 1 H, *J* = 7.2, 9.2, 16.8 Hz), 7.18–7.31 (m, 5 H) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 32.9, 39.6, 43.8, 46.7, 48.5, 81.4, 119.3, 126.2, 127.2, 128.6, 134.3, 145.7 ppm. HRMS calcd. for 202.1358, found 202.1370.

Procedure for the Synthesis of 16: A Schlenk tube flushed with argon was charged with NaH (14.4 mg, 0.6 mmol) and anhydrous DMF (0.5 mL) and cooled in an ice bath. To this slurry a solution of **10a** (33.7 mg, 0.2 mmol) in anhydrous DMF (0.5 mL) was added. The reaction mixture was warmed to room temperature over the course of 1 h and then recooled on an ice bath and treated with freshly purified allyl bromide (42 μL, 0.5 mmol, filtered through a basic alumina column). The reaction mixture was stirred at room temperature overnight. After 15 h it was again cooled on an ice bath and quenched by a slow addition of water. The resulting mixture was extracted with diethyl ether, washed with water and brine, and the organic extracts were dried with $MgSO_4$. Filtration through a pad of silica followed by concentration in vacuo gave **15** as a colorless liquid, which was used for the next reaction without further purification.

In the second step of preparing **16**, a Schlenk tube flushed with argon was charged with a solution of **15** (32.5 mg, 0.13 mmol) in anhydrous CH_2Cl_2 (0.7 mL) and degassed using three evacuation/argon-fill cycles. In a separate tube a degassed solution of Grubbs' second-generation catalyst in anhydrous CH_2Cl_2 (0.3 mL) was prepared. The solution of **15** was cooled on an ice bath and treated dropwise with the solution of catalyst over the course of approximately 5 min. The reaction mixture was then removed from the ice bath, warmed to room temperature and stirred overnight. After 12 h the reaction product was purified by flash chromatography by passing the reaction mixture as such through a silica column affording **16** (21.4 mg, 60%) as a light yellow oil.

(6*R*,8*S*)-8-Phenyl-1-oxaspiro[5,5]undec-3-ene (16): Light yellow oil. R_f = 0.50 (10% EtOAc in hexane). $[\alpha]_D$ = +9.8 ($CHCl_3$, c = 1.02). ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.24 (dt, J = 4.2, 13.7 Hz, 1 H), 1.33–1.45 (m, 2 H), 1.64–1.69 (m, 1 H), 1.75–1.83 (m, 1 H), 1.89–2.03 (m, 4 H), 2.10–2.13 (m, 1 H), 2.94 (tt, J = 3.3, 12.7 Hz, 1 H), 4.13–4.15 (m, 2 H), 5.67–5.70 (m, 1 H), 5.72–5.76 (m, 1 H), 7.17–7.31 (m, 5 H) ppm. ^{13}C NMR (150.9 MHz, $CDCl_3$): δ = 21.8, 34.1, 34.3, 37.1, 39.1, 42.3, 60.5, 71.1, 123.0, 125.3, 126.1, 127.2, 128.6, 147.5 ppm. HRMS calcd. for 228.1514, found 228.1513.

X-ray Crystallographic Study of 10a: CCDC-298839 contains the supplementary crystallographic data for crystals of **10a**. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.data_request/cif.

Supporting Information (see also the footnote on the first page of this article): ^{1}H and ^{13}C NMR spectra of **10a**, **10a′**, **10b**, **10c**, **10d**, **11**, **12**, **13**, **14**, and **16**. NOESY NMR spectra of **10a** and **10a′**.

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[1] E. J. Corey, X. M. Cheng, *The Logic of Chemical Synthesis*, John Wiley & Sons, New York, **1989**.

[2] a) S. R. Buxton, S. M. Roberts, *Guide to Organic Stereochemistry from Methane to Macromolecules*, Addison Wesley Longman, Singapore, **1996**; b) C. Bolm, J. A. Gladysz, *Chem. Rev.* **2003**, *103*, 2761–2762; Special Issue on Enantioselective Catalysis.

[3] a) T.-L. Ho, *Tandem Organic Reactions*, John Wiley & Sons, New York, **1992**; b) J. G. Kim, K. M. Waltz, I. F. Garcia, D. Kwiatkowski, P. J. Walsh, *J. Am. Chem. Soc.* **2004**, *126*, 12580–12585; c) S. Källström, A. Erkkilä, P. M. Pihko, R. Sjöholm, R. Sillanpää, R. Leino, *Synlett* **2005**, 751–756; d) H.-C. Guo, J.-A. Ma, *Angew. Chem. Int. Ed.* **2006**, *45*, 354–366; e) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115–136.

[4] a) M. Sakai, H. Hayashi, N. Miyaura, *Organometallics* **1997**, *16*, 4229–4231; b) Y. Takaya, M. Ogasawara, T. Hayashi, M. Sakai, N. Miyaura, *J. Am. Chem. Soc.* **1998**, *120*, 5579–5580.

[5] a) P. Mauléon, J. C. Carretero, *Org. Lett.* **2004**, *6*, 3195–3198; b) M. Lautens, J. Mancuso, *J. Org. Chem.* **2004**, *69*, 3478–3487; c) M. Lautens, T. Marquardt, *J. Org. Chem.* **2004**, *69*, 4607–4614; d) Y. Otomaru, T. Senda, T. Hayashi, *Org. Lett.* **2004**, *6*, 3357–3359; e) G. De la Herrán, M. Mba, M. Carmen Murcia, J. Plumet, A. G. Csákÿ, *Org. Lett.* **2005**, *7*, 1669–1671; f) M. P. Sibi, H. Tatamidani, K. Patil, *Org. Lett.* **2005**, *7*, 2571–2573; g) G. Chen, N. Tokunaga, T. Hayashi, *Org. Lett.* **2005**, *7*, 2285–2288; h) R. B. C. Jagt, J. G. de Vries, B. L. Feringa, A. J. Minnaard, *Org. Lett.* **2005**, *7*, 2433–2435.

[6] a) T. Hayashi, *Bull. Chem. Soc. Jpn.* **2004**, *77*, 13–21; b) M. T. Reetz, D. Moulin, A. Gosberg, *Org. Lett.* **2001**, *3*, 4083–4085; c) M. Kuriyama, K. Tomioka, *Tetrahedron Lett.* **2001**, *42*, 921–923; d) Y. Otomaru, K. Okamoto, R. Shintani, T. Hayashi, *J. Org. Chem.* **2005**, *70*, 2503–2508; e) Y. Otomaru, A. Kina, R. Shintani, T. Hayashi, *Tetrahedron: Asymmetry* **2005**, *16*, 1673–1679; f) C. Defieber, J.-F. Paquin, S. Serna, E. M. Carreira, *Org. Lett.* **2004**, *6*, 3873–3876; g) R. Shintani, K. Ueyama, I. Yamada, T. Hayashi, *Org. Lett.* **2004**, *6*, 3425–3427; h) T. Hayashi, *Synlett* **2001**, 879–887; i) K. Fagnou, M. Lautens, *Chem. Rev.* **2003**, *103*, 169–196; j) T. Hayashi, K. Yamasaki, *Chem. Rev.* **2003**, *103*, 2829–2844.

[7] a) M. Van den Berg, A. J. Minnaard, E. P. Schudde, J. Van Esch, A. H. M. de Vries, J. G. de Vries, B. L. Feringa, *J. Am. Chem. Soc.* **2000**, *122*, 11539–11540; b) D. Peña, A. J. Minnaard, J. G. de Vries, B. L. Feringa, *J. Am. Chem. Soc.* **2002**, *124*, 14552–14553; c) M. Van den Berg, A. J. Minnaard, R. M. Haak, M. Leeman, E. P. Schudde, A. Meetsma, B. L. Feringa, A. H. M. de Vries, C. E. P. Maljaars, C. E. Willans, D. Hyett, J. A. F. Boogers, H. J. W. Henderickx, J. G. de Vries, *Adv. Synth. Catal.* **2003**, *345*, 308–323.

[8] a) A. Duursma, J.-G. Boiteau, L. Lefort, J. A. F. Boogers, A. H. M. de Vries, J. G. de Vries, A. J. Minnaard, B. L. Feringa, *J. Org. Chem.* **2004**, *69*, 8045–8052; b) A. Duursma, L. Lefort, J. A. F. Boogers, A. H. M. de Vries, J. G. de Vries, A. J. Minnaard, B. L. Feringa, *Org. Biomol. Chem.* **2004**, *2*, 1682–1684.

[9] a) B. L. Feringa, *Acc. Chem. Res.* **2000**, *33*, 346–353; b) R. Naasz, L. A. Arnold, A. J. Minnaard, B. L. Feringa, *Angew. Chem. Int. Ed.* **2001**, *40*, 927–930; c) L. A. Arnold, R. Naasz, A. J. Minnaard, B. L. Feringa, *J. Am. Chem. Soc.* **2003**, *125*, 3700–3701.

[10] a) J.-G. Boiteau, R. Imbos, A. J. Minnaard, B. L. Feringa, *Org. Lett.* **2003**, *5*, 681–684; b) J.-G. Boiteau, A. J. Minnaard, B. L. Feringa, *J. Org. Chem.* **2003**, *68*, 9481–9484; c) Y. Iguchi, R. Itooka, N. Miyaura, *Synlett* **2003**, 1040–1042.

[11] a) B. Cornils, W. A. Herrmann, *Aqueous-Phase Organometallic Catalysis*, Wiley-VCH, Weinheim, **1998**; b) Y. Yamamoto, N. Asao, *Chem. Rev.* **1993**, *93*, 2207–2293; c) D. A. Russo, *Chem. Ind. N. Y.* **1996**, *64*, 405–439; d) C.-J. Li, *Tetrahedron* **1996**, *52*, 5643–5668; e) L. A. Paquette, *Green Chem.* **1998**, 250–264; f) J. Podlech, T. C. Maier, *Synthesis* **2003**, 633–655; g) S. E. Denmark, J. Fu, *Chem. Rev.* **2003**, *103*, 2763–2794; h) C.-J. Li, *Chem. Rev.* **2005**, *105*, 3095–3166. On related reactions in aqueous media, see, for example; i) K. H. Shaughnessy, R. B. DeVasher, *Curr. Org. Chem.* **2005**, *9*, 585–604.

[12] C.-J. Li, T. H. Chan, *Tetrahedron Lett.* **1991**, *32*, 7017–7020.

[13] In addition to indium, tin and zinc were also screened as metals for the allylation step of the one-pot reaction. Tin provided similar selectivities but lower yields and zinc both lower selectivities and yields.

[14] J. Clayden, N. Greeves, S. Warren, P. Wothers, *Organic Chemistry*, Oxford University Press, New York, **2001**.

[15] The indium-mediated prenylation was also performed at 50 °C and with a reaction time of 20 hours to see if an elevated temperature or an increase in reaction time would have any effect on the conversion. This did not turn out to be the case.

[16] Crystal data for compound **10a**: $C_{15}H_{20}O$, M = 216.31, monoclinic, space group $P21$, a = 14.8329(14), b = 6.6067(7), c = 19.8548(19) Å, β = 98.472(5)°, V = 1924.5(3) Å3, Z = 6, $D_{calcd.}$ = 1.120 Mg/m^{-3}, $F(000)$= 708, μ(Cu-K_a) = 0.519 mm^{-1}, T = 173 K, 5223 independent reflections measured on a Nonius Kappa CCD using Cu-K_a radiation (χ = 1.54184 Å). Refinement using SHELXL-97. Final residues were R_1 = 0.078, wR_2 = 0.182 [for reflections $I > 2\sigma(I)$], R_1 = 0.124, wR_2 = 0.228 for all reflections. CCDC reference number 298839.

[17] a) Y. Yamamoto, N. Asao, *Chem. Rev.* **1993**, *93*, 2207–2293; b) E. C. Ashby, J. T. Laemmle, *Chem. Rev.* **1975**, *75*, 521–546; c) Indium: L. A. Paquette, P. C. Lobben, *J. Org. Chem.* **1998**, *63*, 5604–5616; d) Indium: M. T. Reetz, H. Haning, *J. Organomet. Chem.* **1997**, *541*, 117–120; e) Indium: S. Araki, H. Ito, Y. But-

sugan, *J. Org. Chem.* **1988**, *53*, 1831–1833; f) Aluminium, magnesium, lithium, potassium, and sodium: M. Gaudemar, *Tetrahedron* **1976**, *32*, 1689–1691; g) Chromium: T. Hiyama, Y. Okude, K. Kimura, H. Nozaki, *Bull. Chem. Soc. Jpn.* **1982**, *55*, 561–568; h) Tin: Y. Naruta, S. Ushida, K. Maruyama, *Chem. Lett.* **1979**, 919–922; i) Zinc: S. R. Wilson, M. E. Guazzaroni, *J. Org. Chem.* **1989**, *54*, 3087–3091.

[18] T.-H. Chan, C. J. Li, M. C. Lee, Z. Y. Wei, *Can. J. Chem.* **1994**, *72*, 1181–1192.

[19] a) C. Elschenbroich, A. Salzer, *Organometallics – A Concise Introduction*, VCH Verlagsgesellschaft, Weinheim, and VCH Publishers, New York, **1992**; b) L. A. Paquette, T. M. Mitzel, *J. Am. Chem. Soc.* **1996**, *118*, 1931–1937.

[20] T.-P. Loh, J.-R. Zhou, X.-R. Li, *Tetrahedron Lett.* **1999**, *40*, 9333–9336.

[21] M. A. Walters, F. La, P. Deshmukh, D. O. Omecinsky, *J. Comb. Chem.* **2002**, *4*, 125–130.

[22] M. E. Maier, M. Bugl, *Synlett* **1998**, 1390–1392.

[23] A. P. Kozikowski, P.-U. Park, *J. Org. Chem.* **1990**, *55*, 4668–4682.

[24] R. Shintani, N. Tokunaga, H. Doi, T. Hayashi, *J. Am. Chem. Soc.* **2004**, *126*, 6240–6241.

[25] T. Hayashi, T. Senda, T. Yoshiaki, M. Ogasawara, *J. Am. Chem. Soc.* **1999**, *121*, 11591–11592.

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