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PAPER

Access to chiral α-bromo and α-H-substituted tertiary allylic alcohols *via* copper(I) catalyzed 1,2-addition of Grignard reagents to enones†

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The catalytic asymmetric synthesis of tertiary alcohols by the addition of organometallic reagents to ketones is of central importance in organic chemistry. The resulting quaternary stereocentres are difficult to prepare selectively by other means despite their widespread occurrence in natural products and pharmaceuticals. Here we report on a new methodology which allows access to both α-bromo-substituted and α-H-substituted allylic tertiary alcohols with excellent yields, and enantioselectivities of up to 98% using the copper(I)-catalysed 1,2-addition of Grignard reagents to enones. As an example, the methodology is applied in the synthesis of a chiral dihydrofuran.

Introduction

Chiral secondary and tertiary alcohols are important structural motifs in organic chemistry and are ubiquitous in natural products and pharmaceuticals.[1] Chiral allylic alcohols are an important subset of this class and function as extremely versatile synthetic intermediates. The possible transformations of these important compounds are numerous, *e.g.* allylic epoxidation, sigmatropic rearrangement, and other substrate-directed chemical reactions.[2] As a result, chiral allylic alcohols appear frequently as key precursors in asymmetric total syntheses, emphasizing the need for efficient and benign methods of their formation.[2] A variety of synthetic methods have been developed to obtain optically pure secondary alcohols; the synthesis of chiral tertiary alcohols, however, remains very challenging.[1–4] Catalytic asymmetric carbon–carbon bond formation *via* 1,2-addition of organometallics to carbonyl compounds is in principle one of the most direct methods to access single enantiomers of chiral secondary and tertiary alcohols.[3–5] The metal-catalyzed version of this key transformation has been studied extensively using dialkylzinc, organoboron, and silicon reagents.[5] However, until recently, despite the versatility and ready availability of Grignard reagents for organic synthesis, there have been no examples for the catalytic asymmetric 1,2-addition of Grignard reagents to ketones reported.[5]

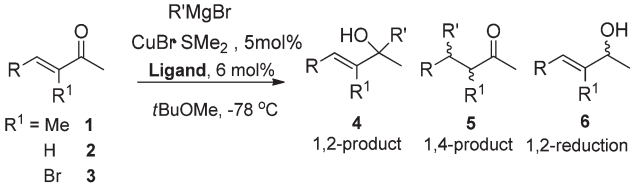
Recently, we showed that the combination of a Cu(I) salt with a specific chiral ferrocenyl diphosphine ligand[6] catalyses the 1,2-addition of Grignard reagents to α,β-unsaturated ketones providing tertiary alcohols with enantioselectivities of up to 96%.[7]

Here we report on the copper catalysed enantioselective synthesis of chiral tertiary allylic alcohols *via* addition of Grignard reagents to α-bromo substituted α,β-unsaturated ketones. This methodology allows access to functionalised α-bromo-substituted and α-H-substituted allylic tertiary alcohols with very high levels of enantioselectivity and excellent yields. Furthermore, the current methodology was applied in the synthesis of chiral tertiary dihydrofuran compounds.

Results and discussion

When highly reactive organometallic reagents are used in addition reactions to α,β-unsaturated ketones, regioselectivity is an important issue. In addition to the formation of the desired 1,2-product **4**, the 1,4-product **5**, expected to be formed *via* conjugate addition of Grignard reagents and secondary alcohol **6**, *via* β-hydride transfer can be formed. Furthermore enolisation of a ketone *via* highly reactive Grignard reagents is another side reaction pathway that is expected (Scheme 1).

In the absence of a catalyst a mixture of all possible products is formed with a prevalence of the 1,2- and 1,4-addition



Scheme 1 Product distribution in the 1,2-addition of Grignard reagents to α,β-unsaturated ketones.

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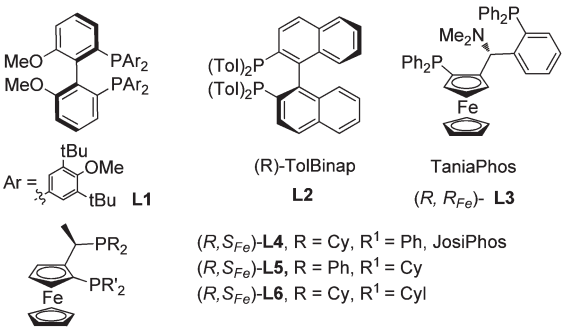
Table 1 Substrate **1–3** (R = Ph) studied in the 1,2-addition reactions of Grignard reagents

Entry[a]	R^1	Ligand	R′MgBr	**4** : **5** : **6**[b] (%)	**4**, ee[c] (%)
1	Me	**L5**	EtMgBr	97 : 2 : 1	40
2	Me	**L5**	iBuMgBr	98 : 1 : 1	84
3	H	—	EtMgBr	21 : 79 : 0	—
4	H	**L5**	EtMgBr	16 : 84 : 0	14
5	H	**L5**	iBuMgBr	51 : 49 : 0	32
6	Br	**L5**	EtMgBr	98 : 1 : 1	42
7	Br	**L5**	iBuMgBr	97 : 1 : 2	90

[a] Reaction conditions: addition of 1.2 equiv. R′MgBr to a 0.15 M solution of **1–3** in *t*BuOMe at −78 °C in the presence of 6 mol% of **L5** and 5 mol% of $CuBr{\cdot}SMe_2$. [b] Ratio of **4** : **5** : **6** was determined by GC analysis. [c] Enantioselectivity of **4** was determined by HPLC analysis (see ESI†).

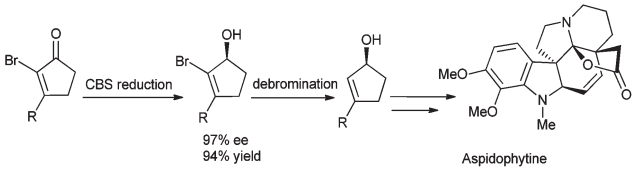
products. Research over the last 80 years has firmly established that copper(I) based reagents and catalysts are the primary synthetic tool to obtain 1,4-selectivity in addition reactions of organometallic reagents.[8,9] Recently we have shown, however, that when Grignard reagents are used in the addition to α-methyl substituted enones **1**, complete 1,2-selectivity can be achieved using chiral Cu(I) based catalysts (Table 1, entry 1).[7] From several ligands screened in our earlier studies we found that ligand **L5** provides the best 1,2-regioselectivity and enantioselectivity in these reactions. Importantly, all other ligands screened provided racemic 1,2-addition products.

To access α-H-substituted tertiary allylic alcohols, we investigated the behaviour of the same catalytic system CuBr/**L5** in the addition of Grignard reagents to α-H-substituted enone **2**. Initially, the regioselectivity of the non-catalysed background reaction was investigated. In the presence of 5 mol% of a copper (I) salt, in the absence of chiral ligand, the addition of EtMgBr to substrate **2** proceeded to full conversion providing a mixture of 1,2- and 1,4-addition product in 21 : 79 ratio (Table 1, entry 3).

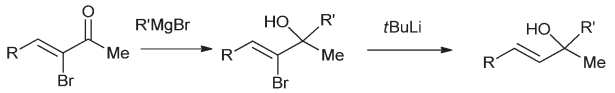


The use of ligand **L5** in combination with the copper salt and EtMgBr, led to higher 1,4-selectivity. The 1,2-addition product was formed with a regioselectivity of 16% and low 14% ee (entry 4). Changing the Grignard reagent to β-branched iBuMgBr increased both the 1,2-selectivity and the enantioselectivity (to 51% and 32%, respectively, entry 5). These results clearly demonstrate that both the α-substituent present in the substrate, as well as steric hindrance of the Grignard reagent play an important role in obtaining high regio- and enantioselectivity.

Access to tertiary alcohols without a substituent at the α-position can be achieved using strategy reminiscent of that



Scheme 2 Corey's approach used in the synthesis of *Aspidophytine*.[10]



Scheme 3 Access to α-H-substituted allylic tertiary alcohols.

developed by Corey *et al.* in their total synthesis of *Aspidophytine* (Scheme 2). In this synthesis, an α-bromo-substitution was employed to increase the enantioselectivity in a CBS reduction. Subsequently, the bromo substituent was removed to give the desired non-substituted product.[10]

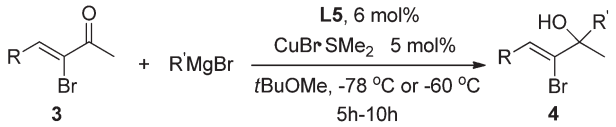
α-Bromo substituted enones are readily accessible from the corresponding enone by dibromination/elimination. The latter compounds were used as substrates in the asymmetric 1,2-addition, followed by debromination (Scheme 3), thus providing access to α-H-substituted tertiary allylic alcohols.

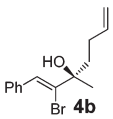
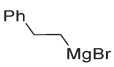
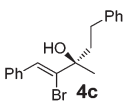
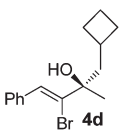
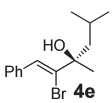
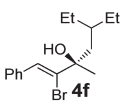
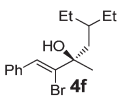
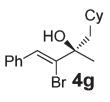
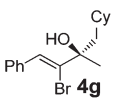
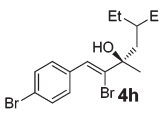
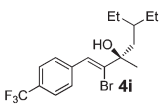
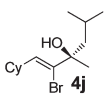
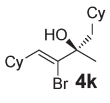
Furthermore, α-bromo substituted enones are useful building blocks in themselves and provide a platform for testing functional group tolerance using our catalyst system. Therefore, bromo-enone **3** was studied in the addition reactions of EtMgBr and iBuMgBr (entries 6 and 7). Remarkably, both reactions proceeded with excellent yields and almost perfect regioselectivity towards the 1,2-addition product. In the case of iBuMgBr, the ee was 90%, 6% higher than that of the methyl-substituted analogue **1** (entries 2 and 7). Notably, magnesium-bromide exchange did not occur under the reaction conditions.

A range of α-bromo substituted enones were investigated in the $CuBr{\cdot}SMe_2$/**L5** catalyzed 1,2-addition reaction, which provided 1,2-products with excellent yields and ees of up to 98% (Table 2). The scope of the reaction was studied using different Grignard reagents. The use of the less reactive MeMgBr resulted in complete recovery of the starting material while addition of PhMgBr led to a racemic 1,2-product. Excellent yields, nearly complete 1,2-selectivity and high ee were obtained with a variety of other Grignard reagents, although, a somewhat decreased enantioselectivity was obtained with linear Grignard reagents (entries 1–3). Increasing the sterics of the Grignard reagents provided higher enantioselectivity. Addition of a Grignard reagent bearing a cyclobutyl moiety furnished the 1,2-addition product with an ee of 82% and a yield of 96% (entry 4). An excellent enantioselectivity and high yield were obtained, also when the reaction was scaled up to 3 mmol (entry 7). Using cyclohexylmethylmagnesium bromide, the corresponding 1,2-addition product was obtained with 94% ee and 96% yield (entry 8).

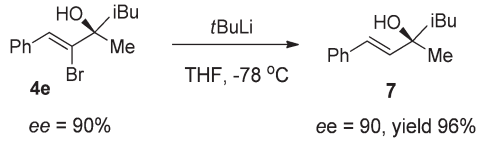
Increasing the reaction temperature to −60 °C furnished the 1,2-addition products in high yields albeit with lower enantioselectivity (entry 9). Substrates with substituted phenyl rings also led to **4** in high yields and with high ee (entries 10 and 11). Tertiary alcohol **4i** containing an electron withdrawing

Table 2 Scope of the CuBr·SMe_2/**L5** catalyzed 1,2-addition of Grignard reagents to α-bromo substituted enones

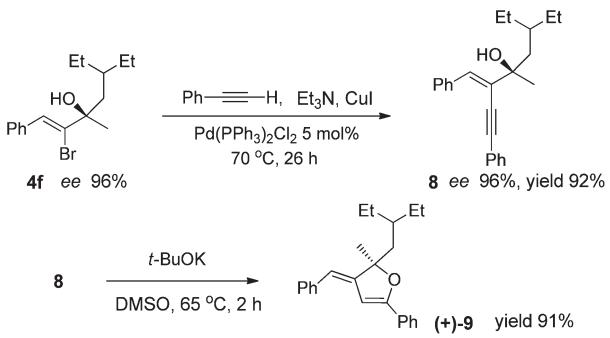


Entry[a]	R, **3**	R′MgBr	**4**	ee (yield)[b,c] (%)
1	Ph		 **4a**	39 (96)
2	Ph		 **4b**	66 (95)
3	Ph		 **4c**	72 (94)
4	Ph		 **4d**	82 (96)
5	Ph		 **4e**	90 (94)
6	Ph		 **4f**	96 (94)
7[d]	Ph		 **4f**	98 (92)
8	Ph		 **4g**	94 (96)
9[e]	Ph		 **4g**	86 (94)
10	*p*BrC_6H_4		 **4h**	92 (94)
11	*p*$CF_3C_6H_4$		 **4i**	94 (96)
12	Cy		 **4j**	94 (95)
13	Cy		 **4k**	94 (94)

[a] Conditions: addition of 1.2 equiv. R′MgBr to a 0.15 M solution of **3** (0.3 mmol) in *t*BuOMe at −78 °C. [b] Yield of the isolated product **4**. [c] ee of **4** was determined by chiral HPLC analysis (see ESI†). [d] Reaction was performed on a larger scale (3 mmol). [e] Reaction was performed at −60 °C.



Scheme 4 Debromination of the addition product **4e**.



Scheme 5 Application of the methodology in the synthesis of chiral furan derivative.

trifluoromethyl group was synthesized with 94% ee (entry 11). It is worth mentioning that this catalytic system is also applicable to aliphatic substrates providing high yields and an enantioselectivity of 94% for the 1,2-addition products (entries 12 and 13).

Debromination of the 1,2-addition product, here shown for **4e**, is readily achieved using *t*BuLi, providing **7**, the formal 1,2-addition product to the α-H-substituted enone, in excellent yield and with retention of ee (Scheme 4).

An application of the current methodology is demonstrated by the subsequent conversion of the 1,2-addition product into a highly functionalized building block.[11a] Exposure of **4f** to phenylacetylene under Sonogashira conditions provided **8** in excellent yield (92%) and with retention of ee (Scheme 5). Product **8** was readily cyclized to the chiral dihydrofuran **9** in 91% yield.[11b]

Conclusions

In summary, we have established a new methodology for the catalytic asymmetric synthesis of α-bromo- and α-H-substituted chiral tertiary allylic alcohols *via* copper catalysed 1,2-addition of Grignard reagents to α,β-unsaturated ketones. The corresponding tertiary allylic alcohols were obtained with excellent regioselectivity and enantioselectivities of up to 98%. The versatility of the α-bromo-tertiary alcohol products is exemplified in their transformation to enantiopure dihydrofuran compounds containing a quaternary stereocenter.

Experimental procedures

General

All reactions were carried out under a nitrogen atmosphere using oven dried glassware and using standard Schlenk techniques. *t*BuOMe and dichloromethane were dried and distilled from

calcium hydride; toluene, THF and n-hexane were dried and distilled from sodium. All copper salts were purchased from Aldrich, and used without further purification. Starting materials were prepared following literature procedures.[12d,e] Grignard reagents were purchased from Aldrich (iBuMgBr (2 M in Et_2O), EtMgBr (3 M in Et_2O)). Ligands **L1–L6** were purchased from Aldrich. Racemic products were synthesized by reaction of the α,β-unsaturated ketones (**1–3**) and the corresponding Grignard reagent at rt in Et_2O. All Grignard reagents were prepared from the corresponding alkyl bromides and Mg activated with I_2 in Et_2O.

Procedure A: addition to α-bromo α,β-unsaturated ketones

A Schlenk tube equipped with a septum and stirring bar was charged with CuBr·SMe_2 (0.015 mmol, 3.08 mg, 5 mol%) and ligand **L5** (0.018 mmol, 6 mol%). Dry *t*BuOMe (3 mL) was added and the solution was stirred under nitrogen at room temperature for 15 min. Then, corresponding ketone (0.3 mmol in 1 mL *t*BuOMe) was added and the resulting solution was cooled to −78 °C. The corresponding Grignard reagent (0.36 mmol, 1.2 eq., in Et_2O) was diluted with *t*BuOMe (combined volume of 1 mL) under nitrogen and added to the reaction mixture over 15 min. Once the addition was complete, the reaction mixture was monitored by TLC and GCMS. The reaction was quenched by the addition of MeOH (1 mL) and saturated aqueous NH_4Cl (2 mL) and the mixture was warmed to room temperature, diluted with Et_2O and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organic layers were dried with anhydrous Na_2SO_4, filtered and the solvent was evaporated *in vacuo*. The crude product was purified by flash chromatography on silica gel using mixtures of n-pentane and Et_2O as the eluent. **Note**: Gas chromatography analysis was carried out to determine the 1,2-addition, 1,4-addition and 1,2-reduction ratio on a sample obtained after aqueous workup and extraction with Et_2O, which was passed through a short plug of silica gel to remove copper residues.

Procedure B: addition to α-bromo α,β-unsaturated ketones

A Schlenk tube equipped with a septum and stirring bar was charged with CuBr·SMe_2 (0.015 mmol, 3.08 mg, 5 mol%) and ligand **L5** (0.018 mmol, 6 mol%). Dry *t*BuOMe (3 mL) was added and the solution was stirred under nitrogen at room temperature for 15 min. Then, corresponding ketone (0.3 mmol in 1 mL *t*BuOMe) was added and the resulting solution was cooled to −78 °C. In a separate Schlenk, the corresponding Grignard reagent (0.36 mmol, 1.2 eq.) was diluted with *t*BuOMe (combined volume of 1 mL) under nitrogen and added dropwise to the reaction mixture over 3 hours using a syringe pump. For the rest follow procedure A.

Procedure C: addition to α-bromo α,β-unsaturated ketones

A Schlenk tube equipped with a septum and stirring bar was charged with CuBr·SMe_2 (0.015 mmol, 3.08 mg, 5 mol%) and ligand **L5** (0.018 mmol, 6 mol%). Dry *t*BuOMe (3 mL) was added and the solution was stirred under nitrogen at room temperature for 15 min. Then, corresponding ketone (0.3 mmol in 1 mL *t*BuOMe) was added and the resulting solution was cooled to −60 °C. The corresponding Grignard reagent (0.36 mmol, 1.2 eq., in Et_2O) was diluted with *t*BuOMe (combined volume of 1 mL) under nitrogen and added to the reaction mixture over 15 min. For the rest follow procedure A.

(+)-(*E*)-3-Methyl-1-phenylpent-1-en-3-ol (4aa). Using method A: The reaction was performed with ligand **L5**, (*E*)-4-phenylbut-3-en-2-one and EtMgBr. Colorless oil obtained as a 16 : 84 : 0 mixture of **4aa**, **5aa**, and **6aa** after column chromatography (SiO_2, n-pentane–Et_2O 90 : 10), **4aa** [11% yield, 14% ee]. The physical data were identical in all respects to those previously reported.[12a] $[\alpha]_D^{20}$ = +5.4 (*c* = 1.4, $CHCl_3$). Enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel AD-H column, n-heptane–i-PrOH 98 : 02, 40 °C, detection at 240 nm, retention times (min): 32.5 (major) and 34.6 (minor).

(+)-(*Z*)-2-Bromo-3-methyl-1-phenylpent-1-en-3-ol (4a). Using method B: Reaction was performed with ligand **L5** and EtMgBr. Colorless oil obtained as a 98 : 1 : 1 mixture of **4a**, **5a**, and **6a** after column chromatography (SiO_2, n-pentane–Et_2O 90 : 10), **4a** [96% yield, 42% ee]. ^1H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.5, 2H), 7.33 (m, 3H), 7.18 (s, 1H), 1.86 (m, 3H), 1.56 (s, 3H), 0.92 (t, *J* = 7.5, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.14, 134.05, 129.03, 128.04, 127.69, 126.77, 77.45, 33.69, 27.10, 8.08.

$[\alpha]_D^{20}$ = +2.2 (*c* = 0.9, $CHCl_3$). HRMS (ESI+, *m*/*z*): calcd for $C_{12}H_{15}BrO$–OH $[M - OH]^+$: 237.0279; found: 237.0274. Enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel AD-H column, n-heptane–i-PrOH 98 : 2, 40 °C, detection at 240 nm, retention times (min): 29.8 (minor) and 31.7 (major). The absolute configuration of this compound is assumed to be (*R*), analogous to the other products.

(+)-(*Z*)-2-Bromo-3-methyl-1-phenylhepta-1,6-dien-3-ol (4b). Using method B: Reaction was performed with ligand *ent*-**L5** and but-3-en-1-ylmagnesium bromide. Colorless oil obtained as a 99 : 1 : 0 mixture of **4b**, **5b**, and **6b** after column chromatography (SiO_2, n-pentane–Et_2O 90 : 10), **4b** [95% yield, 66% ee]. ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, *J* = 7.9, 2H), 7.45–7.27 (m, 3H), 7.21 (s, 1H), 5.88 (m, 1H), 5.19–4.83 (m, 2H), 2.21–2.10 (m, 3H), 2.10–1.98 (m, 1H), 1.82 (m, 1H), 1.57 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.43, 136.05, 133.71, 129.03, 128.07, 127.75, 126.75, 115.12, 77.26, 39.73, 28.43, 27.88. $[\alpha]_D^{20}$ = −4.3 (*c* = 1, $CHCl_3$). HRMS (ESI+, *m*/*z*): calcd for $C_{14}H_{17}BrO$–OH $[M - OH]^+$: 263.0436; found: 263.0431. Enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel AD-H column, n-heptane–i-PrOH 98 : 2, 40 °C, detection at 240 nm, retention times (min): 25.9 (minor) and 29.0 (major). The absolute configuration of this compound is assumed to be (*S*), analogous to the other products.

(−)-(*Z*)-2-Bromo-3-methyl-1,5-diphenylpent-1-en-3-ol (4c). Using method A: Reaction was performed with ligand *ent*-**L5** and phenethylmagnesium bromide. Colorless oil obtained as a 97 : 2 : 1 mixture of **4c**, **5c**, and **6c** after column chromatography (SiO_2, n-pentane–Et_2O 90 : 10), **4c** [94% yield, 72% ee]. ^1H NMR (400 MHz, $CDCl_3$) δ 7.64–7.54 (m, 2H), 7.38 (dd, *J* = 10.0, 4.8, 2H), 7.35–7.26 (m, 4H), 7.21 (dd, *J* = 15.1, 7.0, 3H),

2.68 (m, 2H), 2.1 (s, 1H), 2.14–1.98 (m, 2H), 1.62 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.79, 136.01, 133.54, 129.06, 128.47, 128.41, 128.10, 127.80, 126.94, 125.94, 77.16, 42.72, 30.39, 28.00. $[\alpha]_D^{20} = -8.0$ (c = 0.3, $CHCl_3$). HRMS (ESI+, m/z): calcd for $C_{18}H_{19}BrO$–OH [M − OH]$^+$: 313.0592; found: 313.0590. Enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel AD-H column, n-heptane–i-PrOH 98 : 2, 40 °C, detection at 240 nm, retention times (min): 43.8 (major) and 47.7 (minor).

(+)-(*Z*)-3-Bromo-1-cyclobutyl-2-methyl-4-phenylbut-3-en-2-ol (4d). Using method A: Reaction was performed with ligand **L5** and (cyclobutylmethyl)magnesium bromide. Colorless oil obtained as a 98 : 1 : 1 mixture of **4d**, **5d**, and **6d** after column chromatography (SiO_2, n-pentane–Et_2O 90 : 10), **4d** [96% yield, 82% ee]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61–7.51 (m, 2H), 7.43–7.26 (m, 3H), 7.15 (s, 1H), 2.48 (m, 1H), 2.19–1.71 (m, 8H), 1.55 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.18, 134.68, 129.01, 128.05, 127.67, 126.21, 77.45, 47.79, 32.04, 29.66, 27.60, 19.49. $[\alpha]_D^{20} = +13.3$ (c = 0.9, $CHCl_3$). HRMS (ESI+, m/z): calcd for $C_{15}H_{19}BrO$–OH [M − OH]$^+$: 277.0592; found: 277.0583. Enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel AD-H column, n-heptane–i-PrOH 98 : 2, 40 °C, detection at 240 nm, retention times (min): 23.4 (minor) and 28.2 (major).

(+)-(*Z*)-2-Bromo-3,5-dimethyl-1-phenylhex-1-en-3-ol (4e). Using method B: Reaction was performed with ligand **L5** and iBuMgBr. Colorless oil obtained as a 97 : 1 : 2 mixture of **4e**, **5e**, and **6e** after column chromatography (SiO_2, n-pentane–Et_2O 90 : 10), **4e** [94% yield, 90% ee]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (m, 2H), 7.40–7.26 (m, 3H), 7.24 (s, 1H), 1.99 (s, 1H), 1.97–1.74 (m, 2H), 1.65 (m, 1H), 1.61–1.54 (s, 3H), 0.99 (2d, J = 6.7, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.22, 134.69, 129.02, 128.05, 127.66, 126.25, 77.61, 49.12, 28.76, 24.49, 24.24. $[\alpha]_D^{20} = +17.4$ (c = 0.9, $CHCl_3$). HRMS (ESI+, m/z): calcd for $C_{14}H_{19}BrO$–OH [M − OH]$^+$: 265.0592; found: 265.0487. Enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel AD-H column, n-heptane–i-PrOH 98 : 2, 40 °C, detection at 240 nm, retention times (min): 22.0 (minor) and 27.1 (major).

(+)-(*Z*)-2-Bromo-5-ethyl-3-methyl-1-phenylhept-1-en-3-ol (4f). Using method A: Reaction was performed with ligand **L5** and (2-ethylbutyl)magnesium bromide. Colorless oil obtained as a 96 : 2 : 2 mixture of **4f**, **5f**, and **6f** after column chromatography (SiO_2, n-pentane–Et_2O 90 : 10), **4f** [94% yield, 96% ee]. ^{1}H NMR (201 MHz, $CDCl_3$) δ 7.53 (d, J = 7.4, 2H), 7.35 (m, 3H), 7.22 (s, 1H), 1.99 (s, 1H) 1.97–1.66 (m, 2H), 1.59 (s, 3H), 1.50–1.24 (m, 5H), 0.87 (t, J = 6.6, 6H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 136.28, 134.95, 129.00, 128.06, 127.63, 126.34, 77.58, 43.79, 36.36, 28.59, 26.46, 10.79. $[\alpha]_D^{20} = +17.1$ (c = 1.2, $CHCl_3$). HRMS (ESI+, m/z): calcd for $C_{16}H_{23}BrO$–OH [M − OH]$^+$: 293.0905; found: 293.0879. Enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel AD-H column, n-heptane–i-PrOH 99 : 1, 40 °C, detection at 240 nm, retention times (min): 25.6 (minor) and 27.3 (major). The same above reaction was performed by using method B on 3 mmol scale: Colorless oil obtained as a 94 : 2 : 4 mixture of **4f**, **5f**, and **6f** after column chromatography (SiO_2, n-pentane–Et_2O 90 : 10), **4f** [92% yield, 98% ee].

(–)-(*Z*)-3-Bromo-1-cyclohexyl-2-methyl-4-phenylbut-3-en-2-ol (4g). Using method **A**: Reaction was performed with ligand *ent*-**L5** and (cyclohexylmethyl)magnesium bromide. Colorless oil obtained as a 99 : 1 : 0 mixture of **4g**, **5g**, and **6g** after column chromatography (SiO_2, n-pentane–Et_2O 90 : 10), **4g** [96% yield, 94% ee]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (d, J = 7.3, 2H), 7.41–7.27 (m, 3H), 7.23 (s, 1H), 1.99 (s, 1H), 1.90–1.74 (m, 3H), 1.74–1.60 (m, 4H), 1.58 (s, 3H), 1.52–1.39 (m, 1H), 1.33–0.94 (m, 5H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.31, 134.89, 129.01, 128.08, 127.64, 126.24, 77.63, 47.94, 34.88, 33.89, 28.71, 26.41, 26.25. $[\alpha]_D^{20} = -12.4$ (c = 2.8, $CHCl_3$). HRMS (ESI+, m/z): calcd for $C_{17}H_{23}BrO$–OH [M − OH]$^+$: 305.0905; found: 305.0917. Enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel AD-H column, n-heptane–i-PrOH 98 : 2, 40 °C, detection at 240 nm, retention times (min): 25.9 (major) and 26.7 (minor).

The same above reaction was performed by using method C: colorless oil obtained as a 96 : 2 : 2 mixture of **4g**, **5g**, and **6g** after column chromatography (SiO_2, n-pentane–Et_2O 90 : 10), **4g** [94% yield, 86% ee].

(+)-(*Z*)-2-Bromo-1-(4-bromophenyl)-5-ethyl-3-methylhept-1-en-3-ol (4h). Using method A: Reaction was performed with ligand **L5** and (2-ethylbutyl)magnesium bromide. Colorless oil obtained as a 97 : 2 : 1 mixture of **4h**, **5h**, and **6h** after column chromatography (SiO_2, n-pentane–Et_2O 90 : 10), **4h** [94% yield, 92% ee]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (dd, J = 8.7, 2.0, 2H), 7.40 (d, J = 8.6, 2H), 7.15 (s, 1H), 1.92 (s, 1H), 1.83 (dd, J = 14.5, 3.7, 1H), 1.69–1.60 (m, 1H), 1.57 (s, 3H), 1.47–1.31 (m, 5H), 0.86 (t, J = 7.1, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 135.68, 135.15, 131.23, 130.62, 125.29, 121.59, 77.67, 43.70, 36.43, 28.68, 26.50, 10.80. $[\alpha]_D^{20} = +16.7$ (c = 3.5, $CHCl_3$). HRMS (ESI+, m/z): calcd for $C_{16}H_{22}Br_2O$–OH [M − OH]$^+$: 371.0010; found: 371.0013. Enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel AD-H column, n-heptane–i-PrOH 99 : 1, 40 °C, detection at 240 nm, retention times (min): 26.2 (major) and 30.4 (minor).

(+)-(*Z*)-2-Bromo-5-ethyl-3-methyl-1-(4-(trifluoromethyl) phenyl)hept-1-en-3-ol (4i). Using method B: Reaction was performed with ligand **L5** and (2-ethylbutyl)magnesium bromide. Colorless oil obtained as a 98 : 1 : 1 mixture of **4i**, **5i**, and **6i** after column chromatography (SiO_2, n-pentane–Et_2O 90 : 10), **4i** [96% yield, 94% ee]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (s, 4H), 7.27 (s, 1H), 1.90 (s, 1H), 1.86 (dd, J = 14.5, 3.9, 1H), 1.65 (dd, J = 14.5, 4.8, 1H), 1.59 (s, 3H), 1.46–1.32 (m, 5H), 0.86 (t, J = 7.2, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 139.98, 136.90, 129.25, 125.28, 124.99, 77.72, 43.65, 36.34, 28.78, 26.50, 10.78. $[\alpha]_D^{20} = +11.3$ (c = 1.8, $CHCl_3$). HRMS (ESI+, m/z): calcd for $C_{17}H_{22}BrF_3O$–OH [M − OH]$^+$: 361.0779; found: 361.0776. Enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel AD-H column, n-heptane–i-PrOH 99 : 1, 40 °C, detection at 240 nm, retention times (min): 17.9 (major) and 21.2 (minor).

(+)-(*Z*)-2-Bromo-1-cyclohexyl-3,5-dimethylhex-1-en-3-ol (4j). Using method B: Reaction was performed with ligand **L5** and

iBuMgBr. Colorless oil obtained as a 98 : 2 : 0 mixture of **4j**, **5j**, and **6j** after column chromatography (SiO_2, n-pentane–Et_2O 90 : 10), **4j** [95% yield, 94% ee]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.85 (d, J = 8.6, 1H), 2.48–2.37 (m, 1H), 1.85 (s, 1H), 1.68 (m, 7H), 1.56 (m, 1H), 1.44 (s, 3H), 1.35–1.24 (m, 2H), 1.24–1.05 (m, 3H), 0.93 (2d, J = 6.4, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.32, 132.64, 76.58, 49.15, 40.60, 31.76, 28.14, 25.96, 25.65, 24.44, 24.14. $[\alpha]_D^{20}$ = +1.6 (c = 1.9, $CHCl_3$). HRMS (ESI+, m/z): calcd for $C_{14}H_{25}BrO$–OH $[M - OH]^+$: 271.1062; found: 271.1065. Enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel AD-H column, n-heptane–i-PrOH 99 : 1, 40 °C, detection at 240 nm, retention times (min): 13.1 (minor) and 17.3 (major).

(+)-(*Z*)-3-Bromo-1,4-dicyclohexyl-2-methylbut-3-en-2-ol (4k). Using method A: Reaction was performed with ligand **L5** and (cyclohexylmethyl)magnesium bromide. Colorless oil obtained as a 97 : 2 : 1 mixture of **4k**, **5k**, and **6k** after column chromatography (SiO_2, n-pentane–Et_2O 90 : 10), **4k** [94% yield, 94% ee]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.84 (d, J = 8.6, 1H), 2.49–2.36 (m, 1H), 1.84 (s, 1H), 1.77–1.59 (m, 10H), 1.52 (dd, J = 14.3, 5.7, 1H), 1.43 (s, 3H), 1.39–1.04 (m, 10H), 0.96 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 133.29, 132.64, 76.63, 47.88, 40.58, 34.74, 33.94, 31.72, 28.09, 26.39, 25.97, 25.65. $[\alpha]_D^{20}$ = +1.8 (c = 1.5, $CHCl_3$).

HRMS (ESI+, m/z): calcd for $C_{17}H_{29}BrO$–OH $[M - OH]^+$: 311.1375; found: 311.1372. Enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel AD-H column, n-heptane–i-PrOH 99 : 1, 40 °C, detection at 240 nm, retention times (min): 19.1 (minor) and 19.7 (major).

(+)-(*E*)-3,5-Dimethyl-1-phenylhex-1-en-3-ol (7). Using *t*BuLi: Reaction was performed with **4e**, 2 mmol in Et_2O (2 mL) cooled to −80°C. After 15 min at that temperature, 1.2 eq. of *t*-BuLi was added and the mixture was stirred for another 30 min at −80 °C. The reaction was quenched with saturated aqueous NH_4Cl (2 mL) and the mixture was warmed up to room temperature, diluted with Et_2O and the layers were separated. The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organic layers were dried with anhydrous Na_2SO_4, filtered and the solvent was evaporated *in vacuo*. Product **7**[12b] was obtained as a colorless oil after column chromatography (SiO_2, n-pentane–Et_2O 90 : 10) [96% yield, 90% ee]. $[\alpha]_D^{20}$ = +21.5 (c = 1.1, $CHCl_3$). Enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel AD-H column, n-heptane–i-PrOH 98 : 02, 40 °C, detection at 240 nm, retention times (min): 21.9 (major) and 23.2 (minor).

(+)-(*E*)-3-Benzylidene-6-ethyl-4-methyl-1-phenyloct-1-yn-4-ol (8). 8 was prepared from compound **4f** on 0.3 mmol scale, according to a literature procedure.[12c] Colorless oil obtained after column chromatography (SiO_2, n-pentane–Et_2O 90 : 10), **8** [92% yield, 96% ee]. ^{1}H NMR (201 MHz, $CDCl_3$) δ 8.02–7.84 (m, 2H), 7.59–7.26 (m, 8H), 7.07 (s, 1H), 2.06–1.88 (m, 2H), 1.78 (s, 1H), 1.60 (s, 3H), 1.54–1.28 (m, 5H), 0.88 (t, J = 7.2, 3H), 0.72 (t, J = 7.1, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 136.56, 131.81, 131.30, 129.17, 128.85, 128.44, 128.37, 128.18, 128.07, 127.92, 123.43, 97.41, 88.20, 76.45, 44.69, 36.28, 29.33, 26.86, 10.79. $[\alpha]_D^{20}$ = +51.6 (c = 1.8, $CHCl_3$). HRMS (ESI+, m/z): calcd for $C_{24}H_{28}O$–OH $[M - OH]^+$: 315.2113; found: 315.2107. Enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel AD-H column, n-heptane–i-PrOH 98 : 2, 40 °C, detection at 240 nm, retention times (min): 35.0 (major) and 41.3 (minor).

(+)-(*E*)-3-Benzylidene-2-(2-ethylbutyl)-2-methyl-5-phenyl-2,3-dihydrofuran (9). 9 prepared from compound **8** on 0.25 mmol scale, according to a literature procedure.[11b] Colorless oil obtained after column chromatography (SiO_2, n-pentane), **9** [91% yield]. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82–7.65 (m, 2H), 7.37 (m, 7H), 7.17 (t, J = 7.1, 1H), 6.64 (s, 1H), 5.73 (s, 1H), 1.76 (m, 2H), 1.50 (s, 3H), 1.42–1.24 (m, 5H), 0.89–0.69 (t, J = 7.1, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.95, 150.53, 139.06, 130.74, 129.25, 128.45, 128.41, 127.49, 125.66, 125.42, 111.64, 98.68, 92.00, 44.49, 36.37, 28.06, 26.78, 26.51, 10.85. $[\alpha]_D^{20}$ = +37.7 (c = 0.9, $CHCl_3$). HRMS (ESI+, m/z): calcd for $C_{24}H_{28}O$ + H $[M + H]^+$: 333.2140; found: 333.2213.

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