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Chiral monodentate phosphine ligands for the enantioselective α- and γ-arylation of aldehydes

Ivan Franzoni [a], Laure Guénée [b], Clément Mazet [a,*]

[a] Department of Organic Chemistry, University of Geneva, 30 quai Ernest Ansermet, 1211 Geneva 4, Switzerland
[b] Laboratoire de Cristallographie, University of Geneva, 24 quai Ernest Ansermet, 1211 Geneva 4, Switzerland

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ABSTRACT

The synthesis of chiral variants of monodentate trialkyl and dialkylbiaryl phosphine ligands elaborated on the binepine scaffold is described. Their application in the Pd-catalyzed intramolecular asymmetric α-arylation of aldehydes and the intermolecular asymmetric γ-arylation of α,β-unsaturated aldehydes provides a mean of validating the design of these ligands. For the first reaction, excellent reactivities have been obtained while only modest enantioselectivities were measured. Aside from enantioselectivity, the second reaction offers additional challenges associated with intramolecularity and regioselectivity. With the formal chiral trialkyl monodentate phosphine ligands, good yield, high olefin stereocontrol, and perfect γ-selectivity were obtained while the enantioselectivity remained in the low but promising range.

1. Introduction

Electron-rich and sterically demanding trialkyl (**A**) and dialkylbiaryl (**B**) monodentate phosphine ligands have had a tremendous impact on cross-coupling reactions over the last two decades, in particular in Pd-catalyzed C–C, C–N, and C–O bond forming processes (Fig. 1).[1] In several cases, coupling reactions that were recognized as highly challenging have been achieved successfully with these ligands under mild conditions, even with some of the least reactive coupling partners (e.g., typically aryl chloride or C(sp^3) alkyl halides or pseudohalides). Interestingly, the design of chiral ligands is often inspired by existing achiral structures that have found widespread applications in a variety of reactions that have the potential to be performed enantioselectively because they lead to chiral (but racemic) products. Indeed, often little structural modification of an existing scaffold by introduction of at least one element of chirality allows chiral ligands to be readily elaborated from an achiral motif. Despite some success story based on this approach, maintaining catalytic efficiency while imparting high level of enantioselectivity is not as trivial as it may appear at first sight.[2] In particular, there is to date only a limited number of chiral analogues of the sterically demanding trialkyl or dialkylbiaryl monodentate phosphine ligands (**C**–**F**).[3–6] Furthermore, these isolated examples have been employed in only a handful of catalytic reactions and high levels of enantioinduction have been rarely achieved.

In 2012 our group reported the synthesis of a novel class of chiral (P,N) ligands (**G**) elaborated on the ubiquitous binepine scaffold (**H**) (one of the few examples of chiral monodentate trialkyl phosphine ligand).[7,8] Originally inspired by the work of Wildhalm and Zhang,[9] these chelating ligands revealed particularly efficient in the Pd-catalyzed asymmetric intramolecular α-arylation of aldehydes and the Ir-catalyzed asymmetric hydrogenation of allylic alcohols. Importantly, during optimization of the ligand synthesis, we found that a single primary alkyl substituent could be introduced at the most accessible benzylic position with high levels of diastereoselectivity when a large secondary or tertiary alkyl group was attached to the phosphorus atom. Building on this observation, we set out to synthesize two novel and complementary classes of chiral monodentate phosphine ligands (**I** and **J**) articulated around a common binepine core structure. Whereas the first class (**I**) would represent a formal version of some of the ubiquitous electron-rich and sterically demanding trialkyl phosphine ligands, such as Cy_3P and $^tBu_3P$ (**A**), the second class (**J**) would

* Corresponding author. Tel.: +41 22 379 62 88; fax: +41 22 379 32 15; e-mail address: clement.mazet@unige.ch (C. Mazet).

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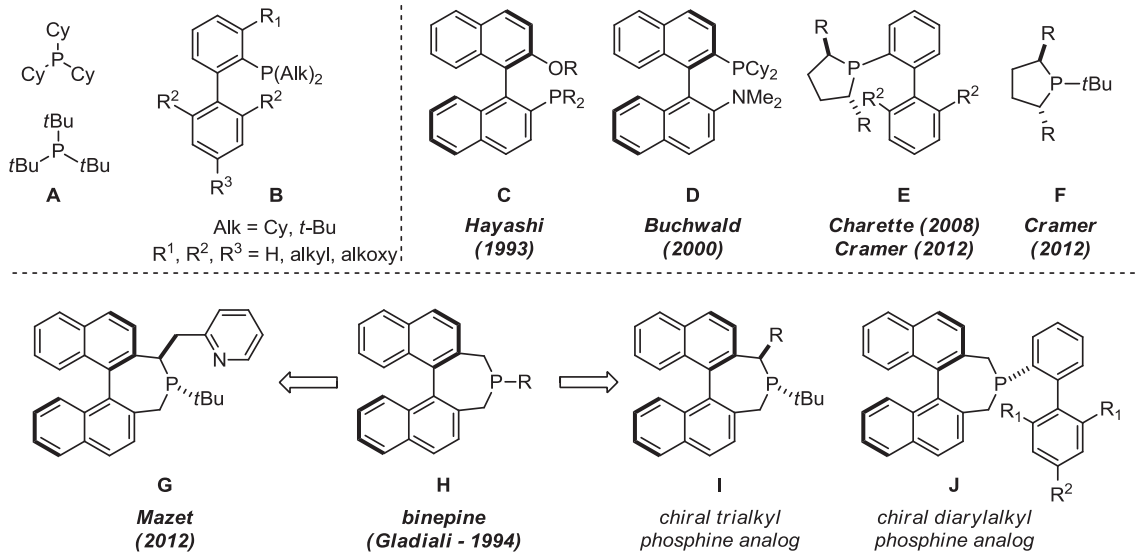


Fig. 1. Prototypical trialkyl (**A**) and dialkylbiaryl (**B**) phosphine ligands used in Pd-catalyzed cross-coupling. Representative chiral versions (**C**–**F**). Binepine (**H**) as a pivotal scaffold for the development of (P,N) ligands (**G**) and chiral trialkyl phosphine (**I**) and diarylalkyl phosphine (**J**) analogs of ligands of type **A** and **B**.

formally constitute a chiral version of the monodentate dialkylbiaryl phosphines (**B**).

2. Results and discussion

Over the years, the Buchwald group has developed a catalog of dialkylbiaryl monodentate phosphines, the design of which has been validated in an impressive number of Pd-catalyzed cross-coupling reactions.[10] Some key features that contribute to catalyst efficiency in mechanistically distinct transformations have been identified. For instance, large alkyl or alkoxy substituents on the *ortho* position of the lower aryl ring are thought to simultaneously promote reductive elimination, increase ligand stability, and prevent from undesired cyclometallation. Therefore, we commenced our synthesis from the commercially available 2′-bromo-2,6-dialkoxy-1,1′-biphenyl **1a** (R=Me) and **1b** (R=^{i}Pr) according to protocols reported in the literature.[11] In a one-pot operation, lithium/halogen exchange at low temperature followed by addition of 1 equiv of chlorophosphepine (R_a)-**3**[12] and final protection with an excess of BH_3·THF adduct delivered the corresponding ligand precursors (R_a)-**2a.BH$_3$** and (R_a)-**2b.BH$_3$** in moderate yields after purification by column chromatography as white crystalline solids. Ligand precursor (R_a)-**2c.BH$_3$** was prepared after in situ generation of the biaryl moiety starting from **1c**, followed by Cu-catalyzed coupling of the corresponding Grignard intermediate with chlorophosphepine (R_a)-**3** and subsequent borane protection. All three borane adducts were deprotected by refluxing in diethylamine for a 3–4 days period of time and the corresponding ligands (R_a)-**2a**–**c** were isolated in good yields as white crystalline solids (68–78%) (Fig. 2).

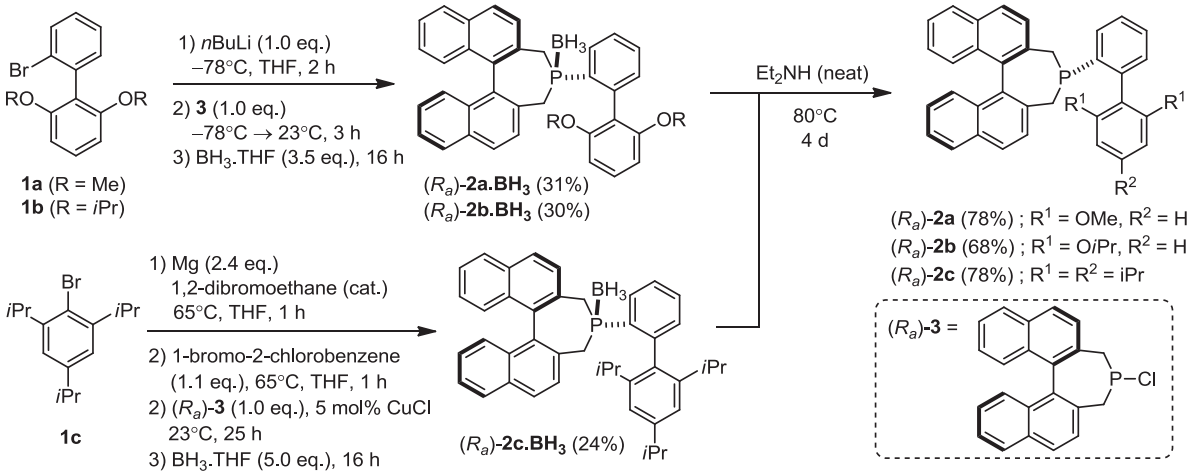


Fig. 2. Synthesis of three chiral monodentate dialkylbiaryl phosphine ligands (type **B**→**J**).

Chiral analogs of trialkyl monodentate phosphine ligands were prepared according to the protocol developed in our laboratory for the synthesis of (P,N) ligands of type **H** starting from (R_a)-**4.BH$_3$**.[7a,12] Seven different primary alkyl halides were selected to access a structurally varied library of these ligands (Fig. 3). Hence methylcyclohexyl (**2d**), benzyl (**2e**), mesitylmethyl (**2f**), 1,3,5-tris-*iso*-propylbenzyl (**2g**), 2-methylnaphthalene (**2h**), 3,5-dimethylbenzyl (**2i**), and 3,5-di-*tert*-butylbenzyl (**2j**) fragments were all introduced using the corresponding commercially available iodo-, bromo- or chloroalkyl precursors. The ligands were obtained in two steps as described on Fig. 3 in usually useful overall yields and essentially as single diastereoisomers (*dr*>50:1). As for their (P,N)

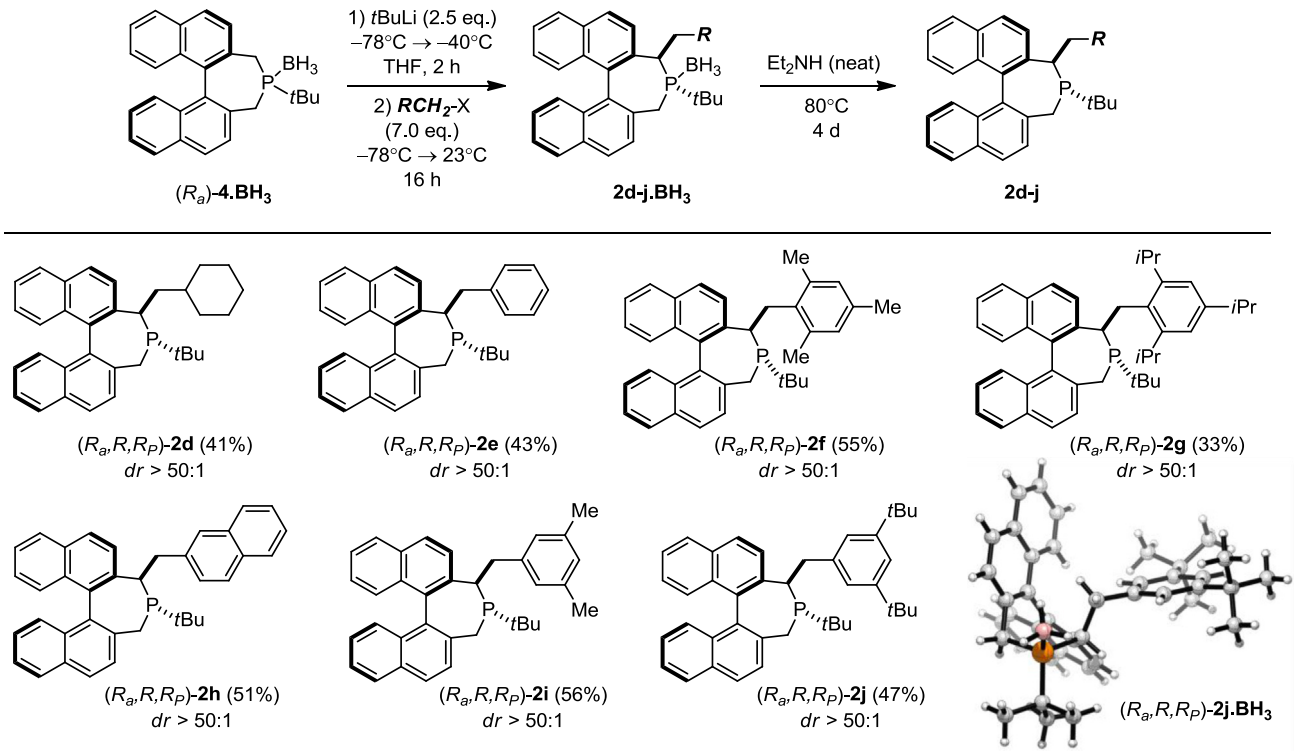


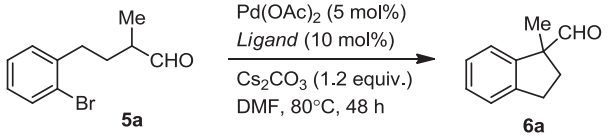
Fig. 3. Two-step synthesis of seven chiral monodentate trialkyl phosphine ligands (type **A**→**I**). Yields over two steps, diastereoselectivity determined by ^{1}H NMR of the crude reaction mixture after the first step. Bottom right: X-ray structure analysis of the borane-protected ligand precursor (R_a,*R*,R_P)-**2j.BH$_3$**.[13]

congeners, these compounds are characterized by three distinct elements of chirality: the axial chirality of the binepine core, the central chirality at the benzylic position and the central chirality at the phosphorus atom; the latter two being stereoselectively installed in the first step of the synthetic sequence. An X-ray diffraction study performed on (R_a,*R*,R_P)-**2j.BH$_3$** confirmed the absolute configuration of the borane-protected ligand and showed that the bulky aryl moiety projects away from the binaphthyl backbone in the solid state. Careful analysis by 2D NMR suggests that this arrangement is also conserved in solution.

The Pd-catalyzed intramolecular α-arylation of aldehydes was elected as benchmark reaction to evaluate the potential of ligands **2a**–**j** in asymmetric catalysis.[14] Among the various enantioselective α-arylation of carbonyl compounds reported, this reaction appears as one of the most challenging. This has been attributed to the inherent instability of aldehydes and to their tendency to undergo a variety of side-reactions under the necessary basic reaction conditions. Moreover, in contrast to amides, esters or ketones the carbon atom of the carbonyl group lacks gearing elements that may be needed to impart high levels of enantioinduction.[15]

To identify the best performer out of the library of 10 monodentate phosphine ligands **2a**–**j**, 4-(2-bromophenyl)-2-methylbutanal aldehyde **5a** was used as a model substrate under the reaction conditions optimized for the related (P,N) ligands (Cs_2CO_3 (1.2 equiv), DMF, 80 °C, 48 h) with a twofold excess of monodentate ligand relative to $Pd(OAc)_2$ (10 and 5 mol %, respectively). With the chiral dialkylbiaryl ligands (R_a)-**2a**–**c**, the cyclized product **6a** was obtained in excellent yield throughout the series while the enantioselectivity decreased with the increasing steric demand of the lower biaryl moiety (Table 1, Entry 1–3). In the chiral trialkyl series (R_a,*R*,R_P)-**2d**–**j**, conversions to product **6a** were usually excellent and the best level of enantioselectivity—albeit still modest—was obtained with ligand (R_a,*R*,R_P)-**2f** (95% conv., 35% ee). The scope was explored next using ligand (R_a,*R*,R_P)-**2f** and the corresponding cyclization product **6a**–**h** are all displayed on Fig. 4. Whereas variation of the alkyl substituent in the substrate or an

Table 1
Ligand screen for the intramolecular α-arylation of aldehydes



Entry	Ligand	Yield (%)[a]	ee (%)[b]
1	(R_a)-**2a**	96	29
2	(R_a)-**2b**	91	10
3	(R_a)-**2c**	97	<5
4	(R_a,*R*,R_P)-**2d**	87	9
5	(R_a,*R*,R_P)-**2e**	10	14[c]
6	(R_a,*R*,R_P)-**2f**	95	35
7	(R_a,*R*,R_P)-**2g**	97	24
8	(R_a,*R*,R_P)-**2h**	97	<5
9	(R_a,*R*,R_P)-**2i**	89	12

[a] Determined by ^{1}H NMR analysis of crude reaction mixture.
[b] Determined by chiral GC or chiral HPLC.
[c] In toluene for 24 h.

increase in electron density of the aromatic fragment had only minimal impact on the reaction outcome (58% yield and 28% ee for **6b**; 80% yield and 39% ee for **6c**), the use of an α-benzyl substituent afforded product **6d** in good yield but as a racemic mixture and the use of an α-phenyl substituent did not provide any cyclization product. In contrast, a 2-anisole α-substituent restored significant catalytic activity, **6f** being isolated in 75% yield and 15% ee. Similar selectivities were measured for the naphthyl derived aldehyde **6g** and the tetrahydronaphthalene product **6h**. Of note, no product formation could be detected in trying to develop an intermolecular version of this reaction (see Supplementary data).

We recently reported a very general protocol for the intermolecular Pd-catalyzed γ-arylation of γ-branched α,β-unsaturated aldehydes with electron-rich, electron-neutral, and electron-poor bromoarenes to efficiently forge remote quaternary

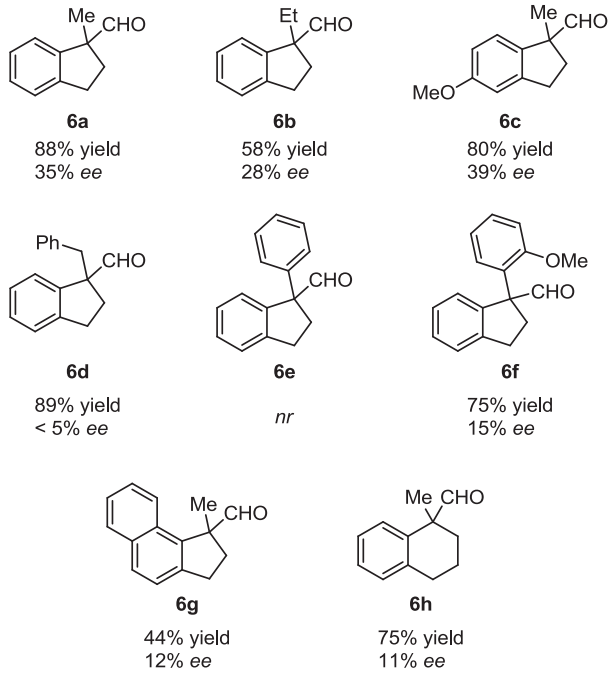


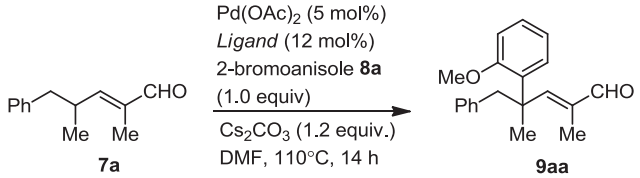
Fig. 4. Substrate scope using ligand (R_a,*R*,R_P)-**2f** and the optimized conditions of Table 1. Yields were assessed after purification by chromatography and ee values were determined using a chiral HLPC.

centers.[16,17] With the optimal protocol, the products were usually isolated in good yield with excellent γ regioselectivity and high levels of stereoselectivity (typically *E*/*Z*>9:1).

As a direct continuation of this study, we set out to develop an enantioselective version of this difficult cross-coupling reaction with aldehyde **7a** and 2- or 4-bromoanisole (**8a** and **8b**, respectively) in a model transformation using our initially optimized reaction conditions. A preliminary evaluation of a vast array of commercially available chiral ligands revealed that chelating (P,P) or (P,N) ligands were not suitable for this transformation as the cross-coupling products were usually isolated in low yield and marginal enantioselectivity (See Supplementary data for details). Surprisingly, when the dialkylbiaryl ligands (R_a)-**2a**–**c** were employed, the coupling between **7a** and 4-bromoanisole **8b** did not yield any product (Table 2, Entry 1–3). In contrast, good to very good conversions were obtained with the trialkyl ligands (R_a,*R*,R_P)-**2d**–**j** for the coupling between **7a** and **8a** (Table 2, Entry 4–10). We tentatively attribute this marked reactivity difference to an increased steric environment around the phosphorus atom in ligands **2d**–**j** when compared to ligands **2a**–**c**. The best results were obtained with ligands (R_a,*R*,R_P)-**2i** and (R_a,*R*,R_P)-**2j**, which delivered **9aa** in 57% yield and 23% ee and 70% yield and 26% ee, respectively; both with excellent stereoselectivity (*E*/*Z*>50:1 and 20:1, respectively). Although the enantioselectivities obtained with these two ligands are still modest, it is worth mentioning that the reactivity and stereoselectivity surpass those of the best achiral ligand (i.e., $^tBu_3P$) identified in our previous study.[16] Furthermore, examples of asymmetric intermolecular α and γ-arylations of carbonyls are still scarce (presumably due to reactivity issues prior to any selectivity consideration).[15]

A small set of other linear and cyclic α,β-unsaturated aldehydes was investigated with ligands (R_a,*R*,R_P)-**2i** and (R_a,*R*,R_P)-**2j** with either 2- or 4-bromoanisole as electrophilic component. The results of these investigations are summarized on Fig. 5. While the γ regioselectivity, the yield (average yield=74%; 5 examples) and the stereoselectivity (*E*/*Z*≥16:1) were consistently high, the enantioselectivities varied between 9 and 26%.

Table 2
Ligand screen for the intermolecular γ-arylation of aldehydes



Entry	Ligand	Yield (%)[a,b]	*E*/*Z*[c]	ee (%)[d]
1	(R_a)-**2a**[e]	nr[f]	nd[g]	nd
2	(R_a)-**2b**[e]	nr	nd	nd
3	(R_a)-**2c**[e]	nr	nd	nd
4	(R_a,*R*,R_P)-**2d**	76 (68)	30:1	12
5	(R_a,*R*,R_P)-**2e**	71 (64)	25:1	17
6	(R_a,*R*,R_P)-**2f**	87 (74)	14:1	−8
7	(R_a,*R*,R_P)-**2g**	91	12:1	<5
8	(R_a,*R*,R_P)-**2h**	66 (59)	30:1	14
9	(R_a,*R*,R_P)-**2i**	61 (57)	>50:1	23
10	(R_a,*R*,R_P)-**2j**	82 (70)	20:1	26

[a] Determined by ^1H NMR analysis of crude reaction mixture.
[b] In parenthesis: isolated yield of geometrically pure *E* isomer.
[c] Determined by ^1H NMR analysis of crude reaction mixture.
[d] Determined by chiral HPLC.
[e] 4-Bromoanisole **2b** was employed.
[f] No reaction.
[g] Not determined.

Using a ligand/metal stoichiometry similar to that employed for in situ catalysis, ligand (R_a,*R*,R_P)-**2i** was reacted with 0.5 equiv of [$(CH_3CN)_2PdCl_2$] at room temperature in dichloromethane in order to obtain structural information on the coordination mode of this ligand to palladium (Fig. 6). After 2 h, evaporation of the volatiles and purification by silica gel chromatography, an air-stable yellow solid was isolated. Mass spectrometric analyses showed molecular ion and fragmentation pics consistent with the formation of a complex of general formula [(R_a,*R*,R_P)-**2i**)$_2PdCl_2$], while NMR analyses indicated the presence of two distinct and non-exchangeable isomers in a 2:1 ratio ($^{31}P\{^1H\}$: δ=70.71 ppm (s) and 69.25 ppm (s) in $CDCl_3$). The coordination chemistry of monodentate binepine ligands to palladium has not been studied extensively. Among the very few examples reported, the *trans*-[(S_a)-**4**)$_2Pd(C_6H_5)Br$] complex has been crystallographically characterized by Baudoin and co-workers.[18,19] The singlet observed by $^{31}P\{^1H\}$ NMR (δ=67.6 ppm) was also consistent with the persistence of *trans* arrangement of the C_2-symmetric binepine (S_a)-**4** in solution. We propose that in the present study, the C_1-symmetry of ligand (R_a,*R*,R_P)-**2i** accounts for the formation of two air-stable, non-separable, isomeric palladium complexes where the monodentate ligands are *trans* disposed but in either a 'head-to-tail' (**10i**) or 'head-to-head' (**11i**) arrangement (Fig. 6). Slow evaporation of a concentrated solution of a mixture of the isomeric complexes gave crystals of suitable quality for an X-ray diffraction study for **10i** only. The nature of the 'head-to-tail' arrangement initially postulated was thus confirmed (Fig. 7).[20]

The neutral palladium complex is also characterized by a strongly distorted square planar geometry around the metal center as indicated by the angles between the mutually *trans* disposed donor atoms (P–Pd–P=168.27(8)°; Cl–Pd–Cl=168.48(8)°) and the torsion angle P–Cl–P–Pd=8.32°.

3. Conclusion

The design of novel chiral ligands and catalysts for asymmetric synthesis remains a formidable and contemporary challenge. Some categories of achiral ligands, such as sterically demanding and electron-rich trialkyl and dialkylbiaryl monodentate phosphines are still in need for efficient and broadly applicable chiral versions

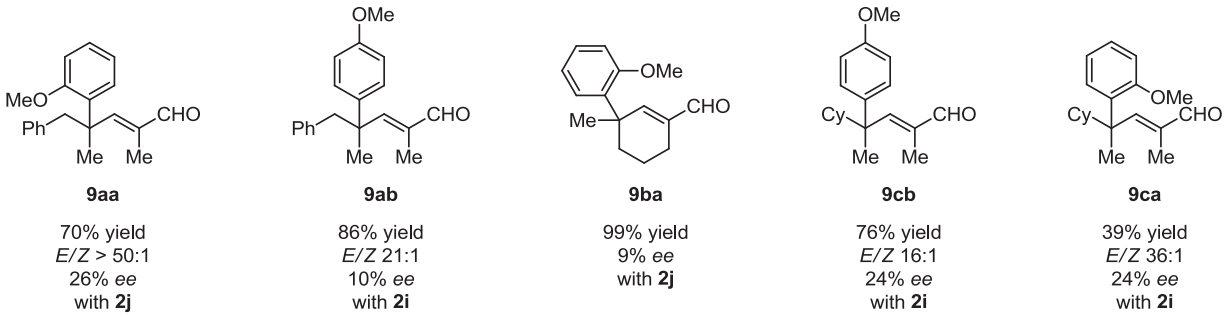


Fig. 5. Substrate scope using either ligand (R_a,*R*,R_P)-**2i** or ligand (R_a,*R*,R_P)-**2j** and the conditions described on Table 2. The *E*/*Z* ratio was determined by ^{1}H NMR of the crude reaction mixture. Yields of pure isomer *E* were assessed after purification by chromatography and ee values were determined using a chiral HLPC.

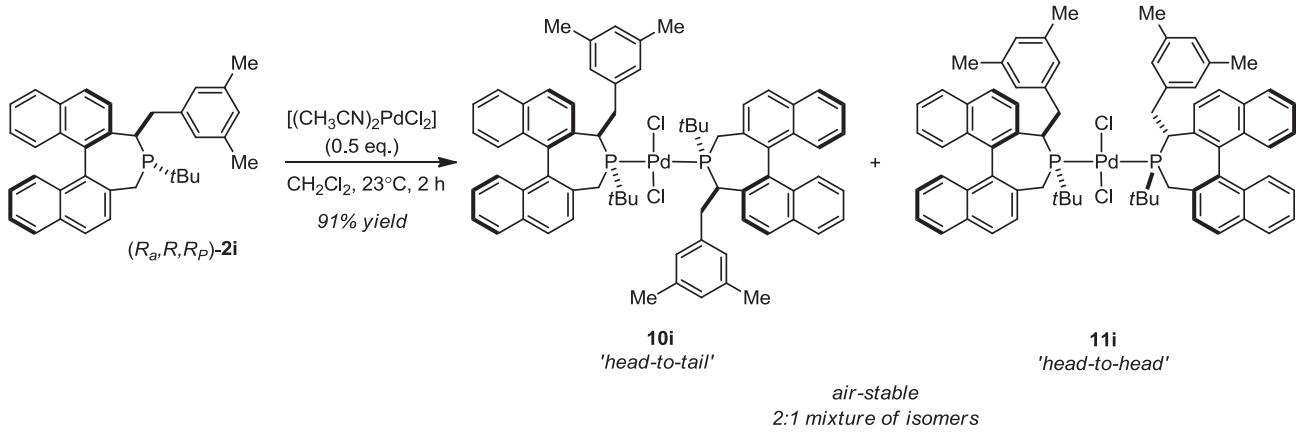


Fig. 6. Complexation of (R_a,*R*,R_P)-**2i** to palladium: formation of isomeric *trans*-coordinated Pd complexes **10i** and **11i**.

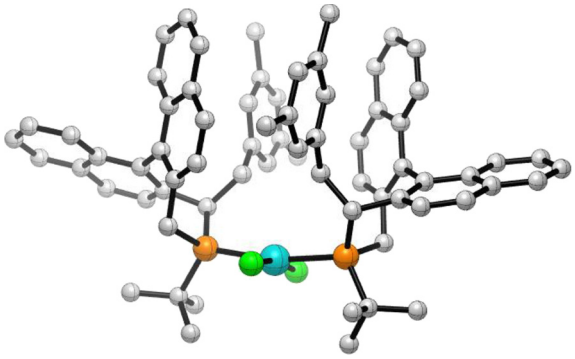


Fig. 7. CYLview representation of the crystal structure of complex **10i**.[13b] All hydrogen atoms have been omitted for clarity (color code: C *gray*; P *orange*; Cl *green*; Pd *cyan*).

to be developed. In this article we have presented our efforts in this direction using the ubiquitous binepine scaffold as the common core structure for the design of two novel classes of chiral ligands. The potential of these ligands was evaluated in two reputedly challenging cross-coupling reactions that enable the construction of congested quaternary stereocenters: (i) the intramolecular α-arylation of α-branched aldehydes and (ii) the intermolecular γ-arylation of γ-branched α,β-unsaturated aldehydes. In the first case, excellent reactivity was observed while the enantioselectivities remained modest for both ligand classes. In the second case,—which is by far more challenging (intermolecular process, regioselectivity issues)—excellent yields, regio- and stereoselectivities were observed in the chiral trialkyl series while again the ee were relatively low. We are nevertheless confident that the high degree of modularity of the binepine platform will allow the discovery of efficient chiral monodentate phosphine ligands for these transformations in a near future. Work in this direction is currently ongoing in our laboratories.

4. Experimental section

4.1. General

All reactions were carried out under an inert atmosphere of nitrogen using either two-manifold vacuum/inert gas lines or an MBraun glove-box, unless otherwise noted. Solvents were dried over activated alumina columns or by distillation from metallic sodium and further degassed by three successive 'freeze-pump-thaw' cycles. NMR spectra were recorded on AMX-400 and AMX-500 Bruker Avance spectrometers at 298 K unless otherwise noted. Deuterated solvents were purchased from Cambridge Isotope Laboratories. Spin multiplicities are reported as a singlet (s), doublet (d), triplet (t), quartet (q), and heptet (h) with coupling constants (*J*) given in Hertz, or multiplet (m). Broad signals are indicated as 'br'. ^{1}H and ^{13}C resonances were assigned with the aid of additional information from 1D and 2D NMR experiments (H,H-COSY, DEPT 135, HSQC, HMBC, and ROESY). ^{1}H and ^{13}C NMR chemical shifts are given in parts per million relative to $SiMe_4$, with the solvent resonance used as internal reference. ^{1}H NMR spectra were referenced to $CDCl_3$ (7.26 ppm) and ^{13}C NMR spectra were referenced to $CDCl_3$ (77.36 ppm) unless otherwise indicated. ^{31}P{^{1}H} NMR chemical shifts are reported in ppm relative to H_3PO_4. Infrared spectra were obtained on a Perkin–Elmer 1650 FT-IR spectrometer using neat samples on a diamond ATR Golden Gate sampler. Optical rotations were measured on a Perkin–Elmer 241 polarimeter equipped with a Na-lamp. The mass spectrometric data were obtained at the mass spectrometry facility of the University of

Geneva (http://www.unige.ch/sciences/sms/index.html). Chiral HPLC analyses were performed on Shimadzu CTO-20AA. Retention times are given in minutes. Chiral GC analyses were performed on HP6890 gas chromatograph. Commercial reagents were purchased from Aldrich, Acros or Strem and used without further purification, unless otherwise noted. Liquid reagents were transferred with stainless steel syringes or cannula. Thin layer chromatography (TLC) was performed on plates of silica pre-coated with 0.25 mm Kieselgel 60 F_{254}. Flash chromatography was performed using silica gel 60 (230–400 mesh ASTM) from SiliCycle. Precursor (R_a)-**3** and (R_a)-**4.BH$_3$** were prepared according to the procedure reported in the literature (*J. Am. Chem. Soc.* **2003**, *125*, 5139; *Org. Process Res. Dev.* **2007**, *11*, 568; *Angew. Chem., Int. Ed.* **2012**, *51*, 3826). Aldehydes **7a** and **7b** were prepared according to the procedure reported in the literature (*Chem. Sci.* **2013**, *4*, 2619). For additional experimental details (i.e., ligand screen, substrate synthesis) and for the precise assignments of all NMR signals, see the Supplementary data Files. Abbreviations used: THF (tetrahydrofuran), DMF (*N*,*N*-dimethylformamide).

4.2. General procedure for the preparation of borane-protected ligands (R_a)-2a–b.BH$_3$

In an oven-dry 5 mL Schlenk tube 2′-bromo-2,6-dialkoxybiphenyl (0.31 mmol, 1.0 equiv) was dissolved in 1.6 mL of THF. The resulting solution was cooled to −78 °C and ^{n}BuLi (0.33 mmol, 1.05 equiv) was added dropwise. After 1 h at −78 °C, a solution of (R_a)-**3** (0.33 mmol, 1.05 equiv) in 1.1 mL of dry and degassed THF was added dropwise and the resulting mixture stirred at −78 °C for additional 3 h. The reaction was quenched with 1.5 mL of degassed water and the aqueous phase was extracted with toluene (3×1 mL) under nitrogen. The combined organic layers were dried under vacuum and the resulting oil was dissolved in 1 mL of dry and degassed THF. The solution was cooled to 0 °C and BH_3–THF 1.0 M in THF (1.1 mmol, 3.5 equiv) was added dropwise. The resulting mixture was stirred at room temperature for 16 h. The excess of BH_3–THF was quenched by careful addition of few drops of methanol and all the volatiles were subsequently evaporated. The crude mixture was then purified by flash chromatography (pentane/CH_2Cl_2) to afford the protected ligand as a foamy solid.

*4.2.1. Protected ligand (R_a)-**2a.BH$_3$**.* The crude reaction mixture was purified by flash chromatography (pentane/CH_2Cl_2=2:1) to afford the desired compound as a white foamy solid (31% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm)=0.45 (br q, 3H), 2.43 (dd, $^2J_{HP}$=2.4 Hz, $^2J_{HH}$=12.9 Hz, 1H), 2.77–2.86 (m, 2H), 3.04 (s, 3H), 3.19 (dd, $^2J_{HP}$=5.4 Hz, $^2J_{HH}$=14.4 Hz, 1H), 3.81 (s, 3H), 6.32 (d, $^3J_{HH}$=8.4 Hz, 1H), 6.60 (d, $^3J_{HH}$=8.4 Hz, 1H), 7.04 (d, $^3J_{HH}$=8.3 Hz, 1H), 7.11–7.14 (m, 2H), 7.18–7.25 (m, 4H), 7.37 (br t, 1H), 7.40–7.43 (m, 2H), 7.47–7.55 (m, 3H), 7.72 (d, $^3J_{HH}$=8.3 Hz, 1H), 7.86–7.91 (m, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ (ppm)=28.9 (d, $^1J_{CP}$=32.6 Hz), 32.6 (d, $^1J_{CP}$=30.6 Hz), 55.3, 55.9, 103.6, 203.9, 118.2 (d, $^3J_{CP}$=2.8 Hz), 125.7, 125.8, 126.3, 126.4, 126.9, 127.1, 127.1 (d, $^3J_{CP}$=8.9 Hz), 127.8 (d, $^3J_{CP}$=2.4 Hz), 128.4, 128.5, 128.6, 128.7, 129.8 (d, $^3J_{CP}$=3.6 Hz), 130.3, 130.8 (d, $^4J_{CP}$=2.3 Hz), 131.3 (d, $^2J_{CP}$=6.3 Hz), 132.1 (d, $^2J_{CP}$=8.0 Hz), 132.2–132.3 (m), 133.0 (d, $^5J_{CP}$=1.6 Hz), 133.1 (d, $^3J_{CP}$=7.9 Hz), 133.4 (d, $^5J_{CP}$=2.6 Hz), 133.9 (d, $^3J_{CP}$=2.7 Hz), 133.9 (d, $^3J_{CP}$=4.2 Hz), 139.6 (d, $^2J_{CP}$=7.6 Hz), 158.2, 158.4; ^{31}P{^{1}H} NMR ($CDCl_3$, 162 MHz) δ (ppm)=49.3 (br m); IR spectrum (neat) ν (cm^{-1})=2931, 2381, 1590, 1470, 1430, 1248, 1108, 1054, 840, 820, 731; HRMS (ESI positive) calcd for 537.2149 $[M-H]^+$, found 537.2153; mp=150–152 °C; $[\alpha]_D^{23}$ +7.82 (*c* 1.0 in CH_2Cl_2).

*4.2.2. Protected ligand (R_a)-**2b.BH$_3$**.* The crude reaction mixture was purified by flash chromatography (pentane/CH_2Cl_2=2:1) to afford the desired compound as a white foamy solid (30% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm)=0.41 (br q, 3H), 0.49 (d, $^3J_{HH}$=6.0 Hz, 3H), 0.86 (d, $^3J_{HH}$=6.0 Hz, 3H), 1.11 (d, $^3J_{HH}$=6.0 Hz, 3H), 1.34 (d, $^3J_{HH}$=6.0 Hz, 3H), 2.56 (dd, $^2J_{HP}$=2.8 Hz, $^2J_{HH}$=13.0 Hz, 1H), 2.79 (dd, $^2J_{HP}$=7.2 Hz, $^2J_{HH}$=14.5 Hz, 1H), 3.01 (dd, $^2J_{HP}$=17.1 Hz, $^2J_{HH}$=13.0 Hz, 1H), 3.36 (dd, $^2J_{HP}$=5.8 Hz, $^2J_{HH}$=14.5 Hz, 1H), 4.12 and 4.45 (2hept, $^3J_{HH}$=6.0 Hz, 2×1H), 6.36 and 6.57 (2d, $^3J_{HH}$=8.3 Hz, 2×1H), 7.07 (ddd, *J*=1.0 Hz, *J*=3.4 Hz, $^3J_{HH}$=7.5 Hz, 1H), 7.12–7.14 (m, 2H), 7.17–7.21 (m, 4H), 7.28–7.31 (m, 1H), 7.39–7.44 (m, 4H), 7.47 (d, $^3J_{HH}$=8.4 Hz, 1H), 7.72 (d, $^3J_{HH}$=8.4 Hz, 1H), 7.85–7.90 (m, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$, 125 MHz) δ (ppm)=21.7, 22.1, 22.5, 22.8, 29.4 (d, $^1J_{CP}$=32.2 Hz), 32.7 (d, $^1J_{CP}$=30.7 Hz), 70.1, 71.5, 105.9, 106.5, 102.9 (d, $^3J_{CP}$=2.6 Hz), 125.7, 126.2, 126.3, 126.4 (d, $^3J_{CP}$=8.3 Hz), 127.0, 127.3, 128.1 (d, $^3J_{CP}$=2.5 Hz), 128.2, 128.4, 128.5, 128.6, 128.6 (d, $^1J_{CP}$=42.4 Hz), 129.7, 130.1 (d, $^3J_{CP}$=3.6 Hz), 130.3 (d, $^4J_{CP}$=6.0 Hz), 131.5–131.6 (m), 132.3 (d, $^4J_{CP}$=2.4 Hz), 132.4–132.5 (m), 133.1, 133.3 (d, $^3J_{CP}$=8.3 Hz), 133.4 (d, $^5J_{CP}$=2.1 Hz), 133.9 (d, $^3J_{CP}$=4.2 Hz), 134.0 (d, $^3J_{CP}$=2.7 Hz), 141.0 (d, $^2J_{CP}$=8.7 Hz), 157.2, 157.3; ^{31}P{^{1}H} NMR ($CDCl_3$, 162 MHz) δ (ppm)=47.7 (br m); IR spectrum (neat) ν (cm^{-1})=3050, 2975, 1385, 2317, 1591, 1457, 1371, 1246, 1113, 1057, 934, 837, 819, 738; HRMS (ESI positive) calcd for 593.2775 $[M-H]^+$, found 593.2794; mp=138–140 °C; $[\alpha]_D^{23}$ +2.96 (*c* 1.0 in CH_2Cl_2).

4.3. Preparation of borane-protected ligands (R_a)-2c.BH$_3$

In an oven-dry 25 mL Schlenk tube, 1-bromo-2,4,6-triisopropylbenzene (1.8 mmol, 1.0 equiv), and magnesium turnings (4.2 mmol, 2.4 equiv) were mixed in 2 mL of THF. One drop of 1,2-dibromoethane was added and the mixture was placed at 65 °C for 1 h. 2-Bromochlorobenzene (1.9 mmol, 1.1 equiv) was added slowly over 10 min and the reaction was stirred at 65 °C for 1.5 h. After cooling to room temperature, CuCl (0.089 mmol, 0.05 equiv) was added to the reaction followed by a solution of (R_a)-**3** (1.8 mmol, 1 equiv) in 2 mL of THF. The resulting mixture was stirred at room temperature for 25 h. After cooling to 0 °C, few drops of methanol were added to quench the remaining Grignard followed by the addition of BH_3–THF 1.0 M in THF (8.88 mmol, 5.0 equiv). The resulting mixture was stirred at room temperature for 16 h. The excess of BH_3–THF was quenched by careful addition of few drops of methanol and all the volatiles were evaporated. The crude mixture was then purified by flash chromatography (eluent pentane/CH_2Cl_2=2:1) to afford the protected ligand as a foamy solid (253 mg, 24% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm)=−0.36 (d, $^3J_{HH}$=6.8 Hz, 3H), 0.51 (br q, 3H), 0.73 (d, $^3J_{HH}$=6.8 Hz, 3H), 0.84 (d, $^3J_{HH}$=6.8 Hz, 3H), 1.17–1.20 (m, 6H), 1.41 (d, $^3J_{HH}$=6.8 Hz, 3H), 1.57 (hept, $^3J_{HH}$=6.8 Hz, 1H), 1.82 (dd, $^2J_{HP}$=2.5 Hz, $^2J_{HH}$=13.4 Hz, 1H), 2.50 (dd, $^2J_{HH}$=13.4 Hz, $^2J_{HP}$=18.7 Hz, 1H), 2.64 (hept, $^3J_{HH}$=6.8 Hz, 1H), 2.80 (hept, $^3J_{HH}$=6.8 Hz, 1H), 2.95 (dd, $^2J_{HP}$=6.8 Hz, $^2J_{HH}$=14.7 Hz, 1H), 3.40 (dd, $^2J_{HP}$=5.5 Hz, $^2J_{HH}$=14.7 Hz, 1H), 6.59 (d, $^4J_{HH}$=1.6 Hz, 1H), 7.08 (d, $^4J_{HH}$=1.6 Hz, 1H), 7.08–7.11 (m, 1H), 7.11–7.22 (m, 5H), 7.27 (dd partially overlapped with the signal of the solvent, $^4J_{HP}$=1.2 Hz); 7.39–7.47 (m, 3H), 7.55 (tt, *J*=1.5 Hz, $^3J_{HH}$=7.9 Hz, 1H), 7.75 (d, $^3J_{HH}$=8.4 Hz, 1H), 7.83–7.85 (m, 2H), 7.88 (d, $^3J_{HH}$=8.2 Hz, 1H), 7.96 (dd, $^3J_{HH}$=7.9 Hz, $^3J_{HP}$=11.6 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ (ppm)=21.1, 23.2, 24.2, 24.6, 25.9, 26.0, 28.5 (d, $^1J_{CP}$=30.3 Hz), 30.5, 30.8, 67.5 (d, $^1J_{CP}$=32.7 Hz), 34.5, 120.8, 120.9, 125.9, 126.4, 126.6, 127.1, 127.3, 127.5 (d, $^3J_{CP}$=10.1 Hz), 128.5, 128.7, 128.8 (d, $^1J_{CP}$=45.4 Hz), 128.9, 129.4 (d, $^3J_{CP}$=3.5 Hz), 129.8 (d, $^4J_{CP}$=30.3 Hz), 131.0 (d, $^2J_{CP}$=6.8 Hz), 131.8 (d, $^2J_{CP}$=10.0 Hz), 132.2 (d, $^4J_{CP}$=2.2 Hz), 132.5 (d, $^2J_{CP}$=11.5 Hz), 132.7, 133.4–133.5 (m), 133.7 (d, $^3J_{CP}$=4.5 Hz), 133.9 (d, $^3J_{CP}$=2.5 Hz), 135.3 (d, $^3J_{CP}$=2.0 Hz), 143.8 (d, $^2J_{CP}$=4.6 Hz), 146.3, 147.5, 149.9; ^{31}P{^{1}H} NMR ($CDCl_3$, 162 MHz) δ (ppm)=51.6 (br m); IR spectrum (neat) ν (cm^{-1})=3052, 2961, 2869, 2382, 1605, 1509, 1461, 1361, 1265,

1137, 1055, 935, 838, 820, 761, 735; HRMS (ESI positive) calcd for 603.3347 $[M-H]^+$, found 603.3342; mp=232–234 °C; $[\alpha]_D^{23}$ −38.96 (*c* 1.0 in CH_2Cl_2).

4.4. General procedure for the preparation of borane-protected ligands (R_a,*R*,R_P)-2d–j.BH_3

In a 10 mL Schlenk tube (R_a)-**4.BH_3** (0.35 mmol, 1.0 equiv) was dissolved in 5 mL of THF. After cooling to −78 °C, ^{t}BuLi (0.87 mmol, 2.5 equiv) was added dropwise and the reaction was slowly warmed to −40 °C over 2 h. After cooling again to −78 °C the appropriate electrophile (7–10 equiv) was added in one portion and the mixture was stirred at room temperature for 16 h. The reaction was quenched with 5 mL of water and the aqueous phase was extracted with CH_2Cl_2 (3×3 mL). The combined organic layers were dried over Na_2SO_4, the solvent was evaporated, and the resulting crude mixture was purified by flash chromatography (pentane/CH_2Cl_2) to afford the desired product as a foamy solid.

*4.4.1. Protected ligand (R_a,R,R_P)-**2d.BH_3**.* 10 equiv of bromomethylcylcohexane were employed. The crude reaction mixture was purified by flash chromatography (pentane/CH_2Cl_2=2:1) to afford the desired compound as a white foamy solid (63% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm)=0.11–0.15 and 0.28–0.37 (2m, 2×1H), 0.31 (br q, 3H), 0.41–0.52 (m, 1H), 0.65–0.71 (m, 3H), 0.83–0.93 (m, 2H), 1.13 and 1.16 (2s, 9H), 1.23–1.30 (m, 2H), 1.41 (m, 1H), 1.57 (m, 1H), 1.84 (m, 1H), 2.80 (dd, $^1J_{HP}$=2.8 Hz, $^1J_{HH}$=12.7 Hz, 1H), 3.14 (dd, $^1J_{HH}$=12.7 Hz, $^1J_{HP}$=16.2 Hz, 1H), 3.32 (ddd, *J*=4.5 Hz, *J*=9.5 Hz, *J*=13.5 Hz, 1H), 6.94 (br d, $^3J_{HH}$=8.2 Hz, 1H), 7.15 (ddd, $^4J_{HH}$=1.2 Hz, $^3J_{HH}$=6.8 Hz, $^3J_{HH}$=8.2 Hz, 1H), 7.21–7.25 (m, 2H), 7.37–7.41 (m, 1H), 7.43–7.48 (m, $^3J_{HH}$=8.4 Hz, 2H), 7.57 (dd, $^4J_{HP}$=1.1 Hz, $^3J_{HH}$=8.4 Hz, 1H), 7.89–7.94 (m, 4H); ^{13}C{^{1}H} NMR ($CDCl_3$, 400 MHz) δ (ppm)= 26.2, 26.3, 26.6 (d, $^1J_{CP}$=28.4 Hz), 26.7, 26.7, 30.7 (d, $^1J_{CP}$=25.3 Hz), 31.2, 33.6, 35.8, 35.9 (d, $^1J_{CP}$=13.9 Hz), 38.5 (d, $^3J_{CP}$=2.5 Hz), 125.7, 126.2, 126.6, 126.7, 127.1, 128.3, 128.4, 128.6–128.7 (m), 129.5 (d, $^2J_{CP}$=6.8 Hz), 129.7 (d, $^3J_{CP}$=3.4 Hz), 131.1 (d, $^3J_{CP}$=3.9 Hz), 132.7 (d, $^5J_{CP}$=2.3 Hz), 133.0, 133.2 (d, $^4J_{CP}$=2.1 Hz), 133.2, 133.8 (d, $^3J_{CP}$=4.6 Hz), 134.3 (d, $^3J_{CP}$=1.6 Hz), 136.8 (d, $^2J_{CP}$=7.5 Hz); ^{31}P{^{1}H} NMR ($CDCl_3$, 162 MHz) δ (ppm)=64.0 (br m); IR spectrum (neat) ν (cm^{-1})=2921, 2849, 2391, 2374, 1507, 1447, 1365, 1061, 1018, 844, 818, 745, 693, 624, 565; HRMS (ESI positive) calcd for 475.2721 $[M-3H]^+$, found 475.2705; mp=155–157 °C; $[\alpha]_D^{23}$ −215.73 (*c* 1.0 in CH_2Cl_2).

*4.4.2. Protected ligand (R_a,R,R_P)-**2e.BH_3**.* 10 equiv of benzyl bromide were employed. The crude reaction mixture was purified by flash chromatography (pentane/CH_2Cl_2=2:1) to afford the desired compound as a white foamy solid (72% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm)=0.51 (br, 3H), 1.17 (d, $^3J_{HH}$=13.2 Hz, 9H), 1.83 (t, $^3J_{HH}$=12.4 Hz, 1H), 2.88 (d, $^3J_{HH}$=12.6 Hz, 1H), 3.04 (t, $^3J_{HH}$=12.4 Hz, 1H), 3.37 (dd, $^2J_{HP}$=15.9 Hz, $^3J_{HH}$=12.6 Hz, 1H), 3.37 (t, $^3J_{HH}$=12.6 Hz, 1H), 6.66 (m, 2H), 6.96 (d, $^3J_{HH}$=8.3 Hz, 1H), 7.03 (m, 4H), 7.20 (m, 2H), 7.26 (t, $^3J_{HH}$=7.7 Hz, 1H), 7.44 (m, 2H), 7.65 (d, $^3J_{HH}$=8.3 Hz, 1H), 7.67 (d, $^3J_{HH}$=8.3 Hz, 1H), 7.84 (d, $^3J_{HH}$=8.1 Hz, 1H), 7.95 (d, $^3J_{HH}$=8.1 Hz, 1H), 7.99 (d, $^3J_{HH}$=8.3 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 400 MHz) δ (ppm)=26.2, 26.3 (d, $^1J_{CP}$=28.6 Hz), 30.7 (d, $^1J_{CP}$=25.8 Hz), 37.8 (d, $^2J_{CP}$=4.6 Hz), 41.5 (d, $^1J_{CP}$=22.1 Hz), 125.7, 126.0, 126.2, 126.3, 127.0, 128.0, 128.0, 128.1, 128.6, 128.7, 128.8, 129.6 (d, $^3J_{CP}$=6.5 Hz), 129.7 (d, $^3J_{CP}$=3.7 Hz), 131.3 (d, $^3J_{CP}$=3.7 Hz), 132.4 (d, $^2J_{CP}$=1.8 Hz), 132.8, 133.0, 133.1 (d, $^2J_{CP}$=1.8 Hz), 133.2 (d, $^2J_{CP}$=4.6 Hz), 134.0, 136.0 (d, $^3J_{CP}$=7.4 Hz), 140.6 (d, $^3J_{CP}$=13.8 Hz); ^{31}P{^{1}H} NMR ($CDCl_3$, 162 MHz) δ (ppm)=65.2 (br m); IR spectrum (neat) ν (cm^{-1})=3048, 2957, 2864, 2388, 2316, 2260, 1945, 1906, 1595, 1503, 1460, 1397, 1365, 1261, 1244, 1189, 1143, 1062, 1019, 956, 931, 845, 819, 750, 702, 657, 627; HRMS (ESI positive) calcd for 469.2250 $[M-3H]^+$, found 469.2342; mp=215–217 °C; $[\alpha]_D^{23}$ −658.4 (*c* 1.0 in CH_2Cl_2).

*4.4.3. Protected ligand (R_a,R,R_P)-**2f.BH_3**.* 8 equiv of α-chloroisodurene were employed. The crude reaction mixture was purified by flash chromatography (pentane/CH_2Cl_2=2:1) to afford the desired compound as a white foamy solid (78% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm)=0.73 (br q, 3H), 1.13 and 1.16 (2s, 9H), 1.80 (s, 6H), 2.15–2.21 (m and s, 1H+3H), 2.87 (dd, $^2J_{HP}$=3.1 Hz, $^2J_{HH}$=12.5 Hz, 1H), 3.04–3.23 (m, 3H), 6.64 (s, 2H), 7.05 (d, $^3J_{HH}$=8.4 Hz, 1H), 7.12 (br d, $^3J_{HH}$=8.5 Hz, 1H), 7.15–7.19 (m, 1H), 7.24–7.27 (m, 2H), 7.42 (br t, $^3J_{HH}$=7.1 Hz, 1H), 7.47 (ddd, J_{HH}=2.1 Hz, J_{HH}=5.9 Hz, $^3J_{HH}$=8.2 Hz, 1H), 7.68 (dd, $^4J_{HP}$=1.2 Hz, $^3J_{HH}$=8.4 Hz, 1H), 7.76 (d, $^3J_{HH}$=8.4 Hz, 1H), 7.90 (d, $^3J_{HH}$=8.2 Hz, 1H), 7.93 (d, $^3J_{HH}$=8.2 Hz, 1H), 7.99 (d, $^3J_{HH}$=8.4 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 400 MHz) δ (ppm)=21.1, 22.0, 26.7, 27.5 (d, $^1J_{CP}$=29.0 Hz), 31.7 (d, $^1J_{CP}$=25.0 Hz), 32.7 (d, $^2J_{CP}$=4.7 Hz), 41.5 (d, $^1J_{CP}$=19.2 Hz), 125.8, 125.9, 126.3, 126.4, 127.6, 127.9, 128.4, 128.5, 128.9, 129.0, 129.2, 129.9 (d, $^3J_{CP}$=3.3 Hz), 130.3 (d, $^2J_{CP}$=6.5 Hz), 131.4 (d, $^3J_{CP}$=4.0 Hz), 132.3 (d, $^4J_{CP}$=2.1 Hz), 133.0 (d, $^3J_{CP}$=4.9 Hz), 133.1, 133.4, 133.6 (d, $^5J_{CP}$=1.8 Hz), 134.5, 135.5, 136.5 (d, $^3J_{CP}$=10.9 Hz), 136.9, 138.8 (d, $^2J_{CP}$=7.1 Hz); ^{31}P{^{1}H} NMR ($CDCl_3$, 162 MHz) δ (ppm)=70.1 (br m); IR spectrum (neat) ν (cm^{-1})=2946, 2865, 2382, 1596, 1505, 1462, 1365, 1062, 846, 819, 748, 691, 659, 626; HRMS (ESI positive) calcd for 513.2877 $[M-H]^+$, found 513.2873; mp=222–224 °C; $[\alpha]_D^{23}$ −460.07 (*c* 1.0 in CH_2Cl_2).

*4.4.4. Protected ligand (R_a,R,R_P)-**2g.BH_3**.* 7 equiv of 2,4,6-triisopropylbenzyl chloride were employed. The crude reaction mixture was purified by flash chromatography (pentane/CH_2Cl_2=2:1) to afford the desired compound as a white foamy solid (59% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm)=0.74 (br s, 9H), 1.11–1.14 (2s, 9H), 1.19 (d, $^3J_{HH}$=6.9 Hz, 6H), 2.14–2.20 (m, 1H), 2.67 (br s, 2H), 2.79 (hept, $^3J_{HH}$=6.9 Hz, 1H), 2.88 (dd, $^2J_{HP}$=3.1 Hz, $^2J_{HH}$=12.5 Hz, 1H), 3.01–3.20 (m, 3H), 6.81 (br s, 2H), 7.02 (d, $^3J_{HH}$=8.4 Hz, 1H), 7.12 (d, $^3J_{HH}$=8.5 Hz, 1H), 7.22–7.26 (m, 3H), 7.41–7.48 (m, 2H), 7.68 (dd, $^3J_{HP}$=1.2 Hz, 1H), 7.73 (d, $^3J_{HH}$=8.4 Hz, 1H), 7.88 (d, $^3J_{HH}$=8.2 Hz, 1H), 7.94 (d, $^3J_{HH}$=7.9 Hz, 1H), 7.99 (d, $^3J_{HH}$=8.4 Hz, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ (ppm)=24.2, 24.4, 26.6, 27.5 (d, $^1J_{CP}$=29.1 Hz), 29.5, 29.8 (d, $^2J_{CP}$=4.8 Hz), 31.4 (d, $^1J_{CP}$=24.8 Hz), 34.2, 43.1 (d, $^1J_{CP}$=18.7 Hz), 121.2, 125.5, 126.2, 126.3, 127.1, 127.5, 128.3, 128.4, 129.0–129.1 (m), 129.8 (d, $^3J_{CP}$=3.4 Hz), 130.3 (d, $^2J_{CP}$=6.7 Hz), 132.0 (d, $^3J_{CP}$=4.3 Hz), 132.3 (d, $^4J_{CP}$=2.3 Hz), 133.0 (d, $^3J_{CP}$=4.9 Hz), 133.1, 133.4–133.5 (m), 133.7 (d, $^3J_{CP}$=11.3 Hz), 134.9 (d, $^3J_{CP}$=0.9 Hz), 137.8 (d, $^2J_{CP}$=7.1 Hz), 146.7, 147.2; ^{31}P{^{1}H} NMR ($CDCl_3$, 162 MHz) δ (ppm)=69.8 (br m); IR spectrum (neat) ν (cm^{-1})=2958, 2381, 1461, 1362, 1061, 816, 747; HRMS (ESI positive) calcd for 597.3816 $[M-H]^+$, found 597.3838; mp=155–157 °C; $[\alpha]_D^{23}$ −476.70 (*c* 0.51 in CH_2Cl_2).

*4.4.5. Protected ligand (R_a,R,R_P)-**2h.BH_3**.* 10 equiv of 2-(bromomethyl)naphthalene were employed. The crude reaction mixture was purified by flash chromatography (pentane/CH_2Cl_2=2:1) to afford the desired compound as a white foamy solid (75% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm)=0.79 (br q, 3H), 1.20 (2s, 9H), 1.94–2.01 (m, *J*=2.4 Hz, 1H), 2.91 (dd, $^1J_{HP}$=2.8 Hz, $^1J_{HH}$=12.9 Hz, 1H), 3.17–3.27 (m, 2H), 3.52–3.58 (ddd, *J*=3.2 Hz, *J*=10.1 Hz, *J*=13.0 Hz, 1H), 6.83 (br s, 1H), 6.97–7.01 (m, 2H), 7.06 (d, $^3J_{HH}$=8.5 Hz, 1H), 7.20–7.21 (m, 2H), 7.31–7.35 (m, 3H), 7.39–7.42 (m, 1H), 7.45–7.47 (m, 1H), 7.51–7.54 (m, 1H), 7.57–7.60 (m, 2H), 7.68–7.70 (m, 2H), 7.79 (d, $^3J_{HH}$=8.2 Hz, 1H), 8.00–8.05 (m, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ (ppm)=26.5, 26.6 (d, $^1J_{CP}$=28.4 Hz), 31.0 (d, $^1J_{CP}$=25.4 Hz), 38.1 (d, $^2J_{CP}$=4.4 Hz), 41.2 (d, $^1J_{CP}$=22.5 Hz), 125.5, 125.9, 126.0, 126.2, 126.4, 127.1, 127.1, 127.5, 127.7, 127.8, 127.9, 128.3, 128.3, 128.9 (d, $^4J_{CP}$=2.0 Hz), 129.0, 129.8 (d, $^2J_{CP}$=6.8 Hz), 129.9 (d, $^3J_{CP}$=3.4 Hz), 131.5 (d, $^3J_{CP}$=3.7 Hz), 132.2, 132.6 (d,

$^4J_{CP}$=2.4 Hz), 132.9, 133.1, 133.5, 133.6 (d, $^3J_{CP}$=4.7 Hz), 134.2, 136.0 (d, $^2J_{CP}$=7.0 Hz), 137.9 (d, $^3J_{CP}$=13.2 Hz); $^{31}P\{^1H\}$ NMR ($CDCl_3$, 162 MHz) δ (ppm)=65.1 (br m); IR spectrum (neat) ν (cm^{-1})=3052, 2958, 2384, 1597, 1507, 1463, 1365, 1246, 1062, 1019, 818, 804, 743, 691; HRMS (ESI positive) calcd for 545.2540 $[M+Na]^+$, found 545.2545; mp=125–127 °C; $[\alpha]_D^{23}$ −638.28 (*c* 1.0 in CH_2Cl_2).

*4.4.6. Protected ligand (R_a,R,R_P)-**2i.BH$_3$**.* 8 equiv of 3,5-dimethylbenzyl bromide were employed. The crude reaction mixture was purified by flash chromatography (pentane/CH_2Cl_2=2:1) to afford the desired compound as a white foamy solid (69% yield). ^1H NMR ($CDCl_3$, 500 MHz) δ (ppm)=0.10–0.70 (br q, 3H), 1.18 (d, 9H), 1.69–1.75 (m, *J*=12.75 Hz, *J*=2.5 Hz, 1H), 2.08 (s, 6H), 2.86 (dd, $^2J_{HH}$=12.7 Hz, $^2J_{HP}$=2.8 Hz, 1H), 2.85 (ddd, $^4J_{HH}$=14.1 Hz, $^3J_{HP}$=8.4 Hz, $^3J_{HH}$=3.1 Hz, 1H), 3.18 (dd, $^2J_{HH}$=12.7 Hz, $^2J_{HP}$=16.4 Hz, 1H), 3.41 (ddd, $^3J_{HH}$=13.0 Hz, $^2J_{HP}$=10.0 Hz, $^3J_{HH}$=13.0 Hz, 1H), 6.21 (s, 2H), 6.62 (s, 1H), 6.99 (d, $^3J_{HH}$=8.6 Hz, 1H), 7.03 (d, $^3J_{HH}$=8.4 Hz, 1H), 7.17–7.24 (m, 3H), 7.41–7.47 (m, 2H), 7.64 (dd, $^3J_{HH}$=8.4 Hz, $^4J_{HP}$=1.9 Hz, 1H), 7.68 (d, $^3J_{HH}$=8.4 Hz, 1H), 7.68 (d, $^3J_{HH}$=8.4 Hz, 1H), 7.84 (d, $^3J_{HH}$=8.2 Hz, 1H), 7.95 (d, $^3J_{HH}$=8.1 Hz, 1H), 7.99 (d, $^3J_{HH}$=8.4 Hz, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 125 MHz) δ (ppm)=21.5, 25.4 (d, $^1J_{CP}$=25.4 Hz), 26.6, 26.7 (d, $^1J_{CP}$=28.3 Hz), 37.7 (d, $^2J_{CP}$=4.2 Hz), 41.2 (d, $^1J_{CP}$=22.4 Hz), 125.9, 126.1, 126.3, 126.4, 126.9, 127.2, 127.5, 127.8, 128.1, 128.2, 128.8 (d, $^4J_{CP}$=1.7 Hz), 128.9, 129.8 (d, $^2J_{CP}$=6.7 Hz), 129.9 (d, $^3J_{CP}$=3.3 Hz), 131.8 (d, $^3J_{CP}$=3.7 Hz), 132.6 (d, $^4J_{CP}$=2.2 Hz), 132.9, 133.2, 133.4 (d, $^5J_{CP}$=1.8 Hz), 133.7 (d, $^3J_{CP}$=4.6 Hz), 134.2, 136.4 (d, $^2J_{CP}$=7.1 Hz), 137.5, 140.3 (d, $^3J_{CP}$=13.1 Hz); $^{31}P\{^1H\}$ NMR ($CDCl_3$, 162 MHz) δ (ppm)=64.8 (br m); IR spectrum (neat) ν (cm^{-1})=3056, 2961, 2865, 2383, 1605, 1509, 1461, 1362, 1057, 935, 840, 820, 739; HRMS (ESI positive) calcd for 497.2564 $[M-3H]^+$, found 497.2552; mp=132–134 °C; $[\alpha]_D^{23}$ −483.27 (*c* 1.0 in CH_2Cl_2).

*4.4.7. Protected ligand (R_a,R,R_P)-**2j.BH$_3$**.* 8 equiv of 3,5-ditertbutylbenzyl bromide were employed. The crude reaction mixture was purified by flash chromatography (pentane/CH_2Cl_2=2:1) to afford the desired compound as a white foamy solid (70% yield). ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm)=0.50 (br q, 3H), 1.13 (s, 18H), 1.16 (2s, 9H), 1.84 (t, *J*=13.1 Hz, 1H), 2.88 (dd, $^2J_{HP}$=2.8 Hz, $^2J_{HH}$=12.6 Hz, 1H), 2.93–2.99 (m, 1H), 3.18–3.28 (m, 2H), 6.48 (d, $^4J_{HH}$=1.75 Hz, 2H), 6.92 (d, $^3J_{HH}$=8.4 Hz, 1H), 7.07–7.11 (m, 2H), 7.18–7.25 (m, 3H), 7.40–7.47 (m, 2H), 7.65 (dd, $^4J_{HP}$=1.1 Hz, $^3J_{HH}$=8.4 Hz, 1H), 7.68 (d, $^3J_{HH}$=8.4 Hz, 1H), 7.86 (d, $^3J_{HH}$=8.2 Hz, 1H), 7.94 (d, $^3J_{HH}$=8.1 Hz, 1H), 7.98 (d, $^3J_{HH}$=8.4 Hz, 1H); $^{13}C\{^1H\}$ NMR ($CDCl_3$, 100 MHz) δ (ppm)=26.5, 26.6 (d, $^1J_{CP}$=28.5 Hz), 30.9 (d, $^1J_{CP}$=25.4 Hz), 31.7, 34.9, 38.4 (d, $^2J_{CP}$=4.1 Hz), 41.9 (d, $^1J_{CP}$=22.0 Hz), 119.9, 123.4, 125.8, 126.2, 126.4, 126.6, 127.0, 127.2, 128.1, 128.2, 128.9 (d, $^4J_{CP}$=2.0 Hz), 129.0, 129.9 (d, $^3J_{CP}$=3.4 Hz), 129.9 (d, $^2J_{CP}$=6.6 Hz), 131.9 (d, $^3J_{CP}$=3.8 Hz), 132.7 (d, $^4J_{CP}$=2.4 Hz), 132.9, 133.3, 133.4 (d, $^5J_{CP}$=2.2 Hz), 133.5 (d, $^3J_{CP}$=4.8 Hz), 134.1, 136.8 (d, $^2J_{CP}$=7.0 Hz), 140.1 (d, $^3J_{CP}$=12.8 Hz), 150.4; $^{31}P\{^1H\}$ NMR ($CDCl_3$, 162 MHz) δ (ppm)=65.4 (br m); IR spectrum (neat) ν (cm^{-1})=2957, 2370, 1597, 1463, 1363, 1247, 1203, 1062, 1017, 819, 736, 715; HRMS (ESI positive) calcd for 583.3660 $[M-H]^+$, found 583.3658; mp=122–124 °C; $[\alpha]_D^{23}$ −426.60 (*c* 1.0 in CH_2Cl_2).

4.5. General procedure for deprotection of ligands 2a–j.BH$_3$

In a 2 mL Schlenk tube the protected ligand (0.10 mmol) was dissolved in 0.25 mL of Et_2NH. The tube was sealed and placed at 80 °C for 4 days. The excess of amine was eliminated under vacuum and the residual was taken up in 0.5 mL of toluene. The Schlenk was brought back inside the glove box and the reaction mixture was filtered through a small pad of Celite©. The volatiles were evaporated under vacuum to afford the pure deprotected ligand as a foamy solid. As all deprotected ligands disclosed in this study are relatively air-sensitive, characterizations requiring long measuring time or exposure to air could not be performed without partial or complete oxidation of the free ligands. Hence, in the Supplementary data, only the ^1H NMR and ^{31}P NMR of all deprotected ligands are reported.

4.6. General procedure for the intramolecular α-arylation of aldehydes

Inside a glove box a 2 mL Schlenk tube was charged with $Pd(OAc)_2$ (1.1 mg, 0.005 mmol, 0.05 equiv), the appropriate ligand (0.012 mmol, 0.12 equiv), and Cs_2CO_3 (39.1 mg, 0.12 mmol, 1.2 equiv). The tube was sealed and taken out from the glove box and connected to a Schlenk line. After conditioning, 0.30 mL of DMF was added followed by the substrate (0.1 mmol, 1.0 equiv). The tube was placed in an oil bath preheated at 80 °C for 48 h. The reaction was diluted with 0.5 mL of Et_2O and washed with 0.5 mL of water. The aqueous phase was extracted with Et_2O (4×0.5 mL), the combined organic layers dried over Na_2SO_4, filtered, and the solvent evaporated. The crude mixture was purified by flash chromatography (pentane/CH_2Cl_2 or pentane/Et_2O). For all products spectrometric and spectroscopic analyses were consistent with the data reported in literature.

4.7. General procedure for the intermolecular γ-arylation of aldehydes

Inside a glove box a 5 mL Schlenk tube was charged with $Pd(OAc)_2$ (1.1 mg, 0.005 mmol, 0.05 equiv), the appropriate ligand (0.012 mmol, 0.12 equiv), and Cs_2CO_3 (39.1 mg, 0.12 mmol, 1.2 equiv). The tube was sealed and taken out from the glove box and connected to a Schlenk line. After conditioning, 0.30 mL of DMF, followed by the bromoarene (0.1 mmol, 1.0 equiv) and next the aldehyde (0.1 mmol, 1.0 equiv). The tube was placed an oil bath preheated at 110 °C for 14 h. The reaction was diluted with 0.5 mL of Et_2O and washed with 0.5 mL of water. The aqueous phase was extracted with Et_2O (4×0.5 mL), the combined organic layers dried over Na_2SO_4, filtered, and the solvent evaporated. The crude mixture was purified by flash chromatography (pentane/CH_2Cl_2 or pentane/Et_2O).

*4.7.1. (E)-4-(2-Methoxyphenyl)-2,4-dimethyl-5-phenylpent-2-enal **9aa**.* Prepared from **7a** and 2-bromoanisole **8a** using the general procedure. The *E*/*Z* ratio was determined to be >50:1 by ^1H NMR analysis of the crude reaction mixture. The crude residue was purified by flash chromatography (pentane/Et_2O=16:1). The enantiomeric excess was determined by chiral HPLC analysis (OJ-H, hexanes/^{i}PrOH 99:1, 1 mL/min, λ=278 nm): t_1=11.38 and t_2=12.44 min. ^1H NMR ($CDCl_3$, 500 MHz) δ (ppm)=1.24 (d, $^4J_{HH}$=1.3 Hz, 3H), 1.44 (s, 3H), 3.00 (d, $^2J_{HH}$=12.9 Hz, 1H), 3.57 (d, $^2J_{HH}$=12.9 Hz, 1H), 3.77 (s, 3H), 6.76–6.78 (m, 2H), 6.85 (td, $^3J_{HH}$=7.6 Hz, $^4J_{HH}$=1.0 Hz, 1H), 6.89–6.91 (m, 2H), 6.98 (dd, $^3J_{HH}$=7.7 Hz, $^4J_{HH}$=1.6 Hz, 1H), 7.11–7.14 (m, 3H), 7.23–7.27 (m, $^4J_{HH}$=1.7 Hz, 1H), 9.40 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm)= 9.8, 23.3, 43.7, 47.1, 55.7, 111.8, 120.9, 126.6, 127.7, 127.8, 128.5, 131.1, 133.7, 136.7, 137.9, 157.5, 165.4, 196.8; IR spectrum (neat) ν (cm^{-1})= 3024, 2964, 2843, 2730, 1676, 1634, 1599, 1491, 1467, 1452, 1435, 1374, 1288, 1243, 1221, 1180, 1124, 1080, 1020, 848, 746, 695; HRMS (ESI positive) calcd for 295.1692 $[M+H]^+$, found 295.1705; mp=84–86 °C.

*4.7.2. (E)-4-(4-Methoxyphenyl)-2,4-dimethyl-5-phenylpent-2-enal **9ab**.* Prepared from **7a** and 4-bromoanisole **8b** using the general procedure. The *E*/*Z* ratio was determined to be 21:1 by ^1H NMR

analysis of the crude reaction mixture. The crude residue was purified by flash chromatography (pentane/Et_2O=16:1). The enantiomeric excess was determined by chiral HPLC analysis (OJ-H, hexanes/*i*PrOH 95:5, 1 mL/min, λ=279 nm): t_1=16.22 and t_2=18.13 min. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm)=1.30 (d, $^4J_{HH}$=1.3 Hz, 3H), 1.47 (s, 3H), 3.05 (d, $^2J_{HH}$=12.9 Hz, 1H), 3.19 (d, $^2J_{HH}$=12.9 Hz, 1H), 3.81 (s, 3H), 6.77–6.83 (m, 4H), 6.85 (d, $^4J_{HH}$=1.3 Hz, 1H), 7.04–7.07 (m, 2H), 7.14–7.19 (m, 3H), 9.42 (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm)=10.7, 24.4, 44.8, 51.0, 55.4, 113.7, 126.7, 127.9, 128.3, 131.0, 137.1, 138.0, 140.3, 158.2, 163.3, 196.4; IR spectrum (neat) ν (cm^{-1})=3333, 3054, 3036, 3001, 2941, 2917.3, 2840, 2739, 2053, 1674, 1637, 1607, 1580, 1510, 1494, 1454, 1414, 1374, 1360, 1291, 1252, 1218, 1181, 1102, 1023, 954, 852, 826, 801, 760, 730, 705, 669, 640, 630, 555; HRMS (ESI positive) calcd for 295.1692 $[M+H]^+$, found 295.1692; mp=68–70 °C.

4.7.3. 2′-Methoxy-1-methyl-1,4,5,6-tetrahydro-[1,1′-biphenyl]-3-carbaldehyde ***9ba***. Prepared from **7b** and 2-bromoanisole **8a** using the general procedure. The crude residue was purified by flash chromatography (pentane/Et_2O=10:1). The enantiomeric excess was determined by chiral HPLC analysis (OD-H, hexanes/*i*PrOH 99:1, 1 mL/min, λ=233 nm): t_1=8.66 and t_2=10.80 min. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm)=1.54 (s, 3H), 1.58–1.72 (m, 3H), 2.13–2.38 (m, 3H), 3.80 (s, 3H), 6.84 (br t, 1H), 6.89–6.94 (m, 2H), 7.19 (dd, $^4J_{HH}$=1.6 Hz, $^3J_{HH}$=7.7 Hz, 1H), 7.22–7.25 (m, 1H), 9.50 (s, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ (ppm)=19.2, 21.7, 26.6, 35.1, 40.8, 55.4, 112.2, 120.8, 128.2, 128.3, 134.9, 139.5, 158.1, 159.9, 195.5; IR spectrum (neat) ν (cm^{-1})=2932, 2866, 2836, 1679, 1638, 1488, 1459, 1434, 1289, 1237, 1183, 1123, 1024, 802, 750, 696; HRMS (ESI positive) calcd for 231.1380 $[M+H]^+$, found 231.1380.

4.7.4. (E)-4-Cyclohexyl-4-(4-methoxyphenyl)-2-methylpent-2-enal ***9cb***. Prepared from **7c** and 4-bromoanisole **8b** using the general procedure. The *E*/*Z* ratio was determined to be 16:1 by ^{1}H NMR analysis of the crude reaction mixture. The crude residue was purified by flash chromatography (pentane/Et_2O=18:1). The enantiomeric excess was determined by chiral HPLC analysis (OD-H, hexanes/^{i}PrOH 99:1, 1 mL/min, λ=200 nm): t_1=7.35 and t_2=8.01 min. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm)=0.88–0.96 (m, 2H), 1.03–1.25 (m, 4H), 1.62–1.79 (m, 5H), 1.35 (d, $^4J_{HH}$=1.3 Hz, 3H), 1.48 (s, 3H), 3.80 (s, 3H), 6.81 (d, $^3J_{HH}$=8.9 Hz, 2H), 6.92 (br s, 1H), 7.09 (d, $^3J_{HH}$=8.9 Hz, 2H), 9.45 (s, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ (ppm)=11.0, 21.3, 26.9, 27.3, 27.3, 28.3, 28.3, 50.6, 47.2, 55.5, 113.6, 128.7, 137.4, 140.5, 158.0, 163.9, 196.8; IR spectrum (neat) ν (cm^{-1})=2926, 2854, 1685, 1511, 1454, 1377, 1293, 1249, 1182, 1029, 830; HRMS (ESI positive) calcd for 287.2006 $[M+H]^+$, found 287.1951.

4.7.5. (E)-4-Cyclohexyl-4-(2-methoxyphenyl)-2-methylpent-2-enal ***9ca***. Prepared from **7c** and 2-bromoanisole **8a** using the general procedure. The *E*/*Z* ratio was determined to be 36:1 by ^{1}H NMR analysis of the crude reaction mixture. The crude residue was purified by flash chromatography (eluent pentane/CH_2Cl_2=1:1). The enantiomeric excess was determined by chiral HPLC analysis (OJ-H, hexanes/^{i}PrOH 99:1, 1 mL/min, λ=225 nm): t_1=5.32 and t_2=6.09 min. ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm)=0.82–0.91 (m, 1H), 0.97–1.00 (m, 1H), 1.08–1.18 (m, 3H), 1.25 (d, $^4J_{HH}$=1.2 Hz, 3H), 1.25–1.33 (m, 1H), 1.43 (s, 3H), 1.64 (m, 2H), 1.82–1.86 (M, 1H), 1.93–1.96 (m, 1H), 2.18 (tt, $^3J_{HH}$=2.9 Hz, $^3J_{HH}$=11.8 Hz, 1H), 3.65 (s, 3H), 6.82 (dd, $^4J_{HH}$=1.0 Hz, $^3J_{HH}$=8.1 Hz, 1H), 6.94 (td, $^4J_{HH}$=1.2 Hz, $^3J_{HH}$=7.6 Hz, 1H), 7.11–7.12 (m, 1H), 7.19–7.26 (m, 2H), 9.42 (s, 1H); ^{13}C{^{1}H} NMR ($CDCl_3$, 100 MHz) δ (ppm)=9.9, 18.6, 27.1, 27.4, 27.6, 28.1, 29.1, 45.3, 46.1, 55.7, 112.4, 120.8, 127.9, 128.2, 134.7, 136.8, 157.5, 166.2, 197.1; IR spectrum (neat) ν (cm^{-1})=2926, 2852, 1679, 1488, 1452, 1238, 1020, 750; LRMS (ESI positive) calcd for 287.2 $[M+H]^+$, found 287.5.

4.8. Procedure for the complexation of (R_a,*R*,R_P)-2i with palladium

Inside a glove box a 2 mL oven-dry vial was charged with $[(CH_3CN)_2PdCl_2]$ (10 mg, 0.039 mmol, 1.0 equiv) and (R_a,*R*,R_P)-**2i** (37.5 mg, 0.077 mmol, 2.0 equiv). Next, 0.77 mL of CH_2Cl_2 was added and the resulting solution was stirred at room temperature for 2 h. After filtration through Celite© and evaporation of the solvent, the crude residue was purified by flash chromatography (pentane/CH_2Cl_2 1:1) to afford a 2:1 mixture of the isomeric complexes as crystalline yellow solids. ^{31}P{^{1}H} NMR ($CDCl_3$, 162 MHz) δ (ppm)=69.25 (s), 70.71 (s); IR spectrum (neat) ν (cm^{-1})=2931, 1598, 1505, 1463, 1367, 1245, 1174, 1245, 1174, 1018, 863, 829, 744, 690, 532; mp=220–222 °C. HRMS (ESI positive) calcd for 1155.3525 $[M+Li]^+$, found 1155.3650.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2014.02.079.

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