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Palladium-catalyzed allylic alkylation using chiral P,O-ligands synthesized via sulfonamide directed *ortho*-lithiation

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ABSTRACT

An efficient approach for the synthesis of chiral P,O-ligands containing sulfonamide and phosphine moieties is designed. The introduction of the chirality is achieved through different stereogenic groups attached to the sulfonamide nitrogen. The highly effective sulfonamide directed *ortho*-lithiation and the subsequent reaction with $ClPPh_2$ is the key step in the synthesis of the ligands. The prepared P,O-compounds are applied in Pd-catalyzed asymmetric allylic alkylation (AAA) under optimized conditions, to obtain high degrees of enantioselectivity.

Phosphine ligands have been used in numerous catalytic applications. In particular, phosphines possessing chirality are of great importance in different types of transition metal catalyzed transformations (e.g., hydrogenations, isomerizations, C—C coupling reactions, etc.).[1] A growing interest has been directed toward the synthesis and application of phosphine ligands containing additional functionality, as in the case of the mixed amido-phosphine compounds that combine the properties of hard and soft donor ligands. These types of ligands offer the opportunity of 'fine-tuning' of ligand-to-metal binding properties and thus have significant influence on the catalytic activity of the corresponding complexes. A comprehensive review analyzing the results in this area was published in 2012.[2] In previous studies, we were interested in the synthesis of chiral amido-phosphine derivatives for two reasons: firstly, to use them as chiral ligands for Pd-catalyzed C—C bond-forming reactions, and secondly to study the *ortho*-directing ability, and in some cases the diastereoselectivity induced by the chiral amido group in lithiation reactions.[3] Considering the literature data in respect of *ortho*-directing groups for lithiation reactions the application of the sulfonamide group attracts considerable interest as a powerful auxiliary for Directed *ortho* Metalation (DoM) of aromatic compounds.[4] This selective metalation reaction using butyllithium reagents offers various synthetic opportunities to obtain sulfonamide ligands in a subsequent treatment of the lithiated intermediate with suitable phosphorus-containing electrophiles. The DoM by means of a sulfonamide group has been utilized in different types of synthetic applications.[5] It is interesting to note that the sulfonamide functionality has not been used as a directing group for the synthesis of chiral phosphine ligands. There is only one report on the synthesis of a nonchiral sulfonamide-phosphine ligand through DoM, and its subsequent application in Suzuki–Miyaura cross-couplings.[6] On the other hand, there are several reports on the application of sulfonamide–phosphine derivatives possessing chirality.[7] However, these ligands have been synthesized by other synthetic methods and not using the DoM approach. Herein, we present a viable synthesis of a series of chiral sulfonamide-phosphine ligands via highly efficient DoM and their application in Pd-catalyzed asymmetric allylic substitutions.

The chiral tertiary sulfonamides serving as precursors of the chiral P,O-ligands were synthesized in two steps, starting from benzenesulfonyl chloride (**1**). In the first step, the sulfonamides **3a–f** were prepared using **1** and a series of chiral amines **2a–f** (Scheme 1).[8] The reactions were carried out under standard conditions (DIPEA/CH_2Cl_2) leading to almost quantitative conversions.

The selected chiral amines were commercially available with the exception of **2c** and **2d**. The synthesis of amines **2c** and **2d** was realized utilizing known procedures.[9,10] Amine **2c** was formed as a mixture of two diastereoisomers in 86:14 ratio. It was not possible to separate them by column chromatography, therefore the mixture was applied directly in the reaction with **1** forming the desired sulfonamide in high yield (Scheme 2). The separation of *exo*-**3c** and *endo*-**3c** was performed effectively by column chromatography without mixed fractions. It is worth mentioning

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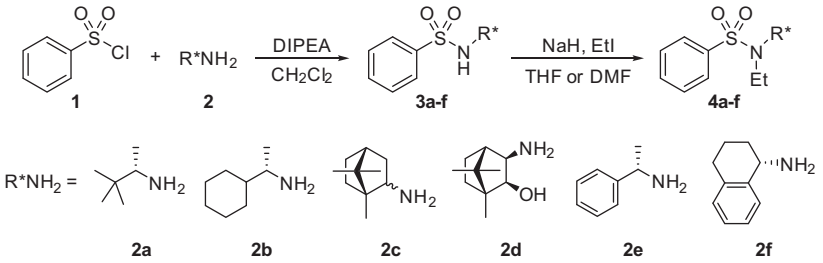
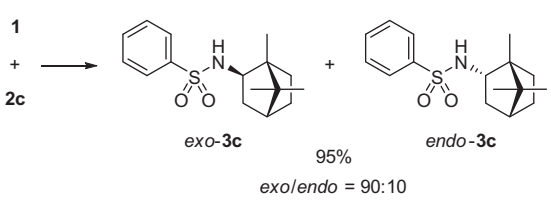
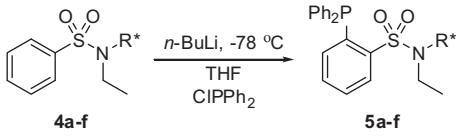


Scheme 1. Synthesis of chiral tertiary sulfonamides **4a–f**.



Scheme 2. Synthesis of secondary sulfonamides with camphene-based amine **2c**.



Scheme 3. Synthesis of phosphine derivatives **5a–f** by directed *ortho*-lithiation.

that during the formation/separation process of **3c**, the ratio of the *exo*/*endo* diastereoisomers changed slightly in favor of *exo*-**3c**.

For the preparation of amine **2d** an efficient procedure providing the amino alcohol in two steps in high yield and ca. 90% diastereomeric purity of the di-*exo*-diastereoisomer was utilized.[10] We were able to synthesize the target compound in 90% diastereomeric purity (by NMR) in accordance with the published data. It is necessary to mention that in the literature[11] the formation of all possible diastereoisomers of **2d** has been described. The crude amino alcohol **2d** was used for the synthesis of the sulfonamide **3d**, which was isolated in 52% yield after column chromatography.

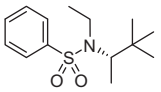
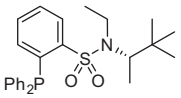
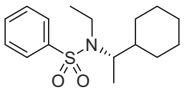
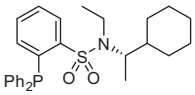
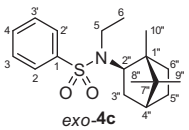
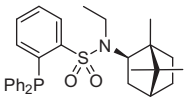
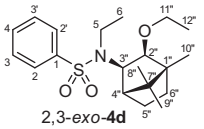
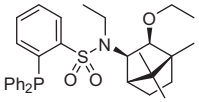
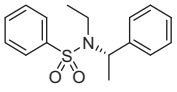
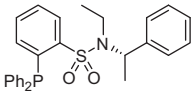
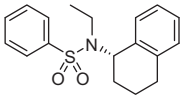
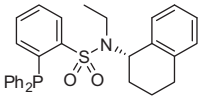
The subsequent alkylation of the secondary sulfonamides **3a–f** with EtI, using NaH as the deprotonating agent, afforded compounds **4a–f** in excellent yields (Scheme 1).[8] All the reactions were carried out under reflux conditions with a large excess of alkylating reagent. The reactions performed at room temperature required longer reaction times. The N-ethylation of sulfonamide **3c** bearing the camphane moiety proceeded very slowly in THF and the isolated yield of **4c** was relatively low (28%). However, performing the reaction in dry DMF afforded the desired product in a considerably higher yield (72%). The sulfonamide **3d** was also alkylated using DMF, but unexpectedly, in this case, the alkylation led to the formation of two products: *N*-ethyl- and *N,O*-diethyl-derivatives, and even a large excess of the alkylating reagent and a prolonged reaction time (24 h) did not lead to a higher yield of the dialkylated product. Both products, *N*-ethyl-**4d** (65%) and *N,O*-diethyl-**4d** (35%), were isolated in pure form by column chromatography. The isolated N-alkylated product was applied in a subsequent ethylation reaction to give an additional quantity of *N,O*-diethyl-**4d**. Remarkably, the alkylation of *N*-ethyl-**4d** was accomplished much faster, compared to its formation from **3d** in a mixture with the dialkylated product.

The key stage of our synthetic strategy to produce chiral bidentate ligands was the introduction of a phosphine group. The property of the sulfonamide moiety as an *ortho*-directing group in aromatic systems[4] was efficiently applied in the case of compounds **4a–f**. Thus, we successfully prepared chiral diphenylphosphine ligands **5a–f** by reacting **4a–f** with 1.2 equiv of *n*-BuLi and subsequent treatment of the formed organolithium intermediate with two equivalents of $ClPPh_2$ (Scheme 3).[12] In all cases, the reactions proceeded in excellent yields (Table 1). No experimental results have been obtained in respect of possible deprotonation at the benzylic position in the case of **4e** and **4f**. However, this side reaction could not be excluded, considering the observed decrease of the yield in transforming **4e** into **5e**.

The next step in our work was to evaluate the synthesized chiral diphenylphosphine sulfonamides as P,O-ligands in Pd-catalyzed asymmetric allylic alkylation (AAA) of racemic (*E*)-1,3-diphenyl-2-propenyl acetate. The active palladium(II) catalyst was generated by the reaction of 6 mol % of the corresponding chiral ligand **5a–f** with 3 mol % of allylpalladium(II) chloride dimer. The reactions were performed by varying the conditions with respect to the base, solvent, and temperature (Table 2).[13] Initially, following Trost's procedure,[14] the nucleophile was generated in situ using *N,O*-bis(trimethylsilyl)acetamide (BSA) and a catalytic amount of potassium acetate in dichloromethane at room temperature. Under these conditions, the reactions proceeded with excellent conversions with all of the tested ligands **5a–f** (Table 2). Ligand *exo*-**5c** induced the highest enantioselectivity in favor of the (*S*)-enantiomer (58% ee, Table 2, entry 5). Aiming toward the achievement of higher enantioselectivity, *exo*-**5c** was used for optimization of the reaction conditions. Catalytic reactions in two different solvents (toluene and THF) were performed, however, the resulting enantioselectivities were lower (15% and 31% ee, respectively, Table 2, entries 6 and 7). Further, Cs_2CO_3 was employed as a base[15] instead of BSA/KOAc and the reaction was conducted at room temperature in CH_2Cl_2. These reaction conditions led to a promising result, that is, 77% ee (Table 2, entry 8). This encouraged us to test the activity of *exo*-**5c** with the same base at −5 °C which led to an increase of the enantioselectivity to 83%. At this temperature, the reaction proceeded considerably slower, 0.5 h versus 24 h (Table 2, entries 8 and 9), while at −40 °C the product was not formed at all. Following the Cs_2CO_3 protocol, further catalytic reactions were performed at room temperature, using ligands **5a**, **5b**, and **5d–f**. In all cases, a slight increase in the enantioselectivity was achieved (see Table 2).

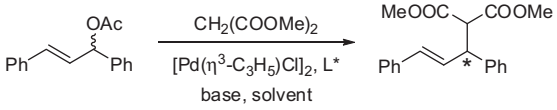
In conclusion, we have described a very efficient and viable approach for the synthesis of chiral P,O-ligands based on introduction of chirality within the sulfonamide group and Directed *ortho* Metalation (DoM). The application of these ligands in Pd-catalyzed allylic alkylation was high yielding leading, in some cases, to high degrees of enantioselectivity (up to 83%). These promising results should lead to further development in respect of chirality modifications of the ligands and further catalytic processes.

Table 1
Synthesis of chiral P,O-ligands via directed *ortho*-lithiation

Entry	Sulfonamide	Time[a] (h)	Product	Yield[b] (%)
1	 **4a**	1	 **5a**	70
2	 **4b**	2	 **5b**	93
3[c]	 *exo*-**4c**	3	 *exo*-**5c**	68
4[c]	 2,3-*exo*-**4d**	2	 2,3-*exo*-**5d**	84
5	 **4e**	0.7	 **5e**	69
6	 **4f**	4	 **5f**	98

[a] Reaction time after addition of the electrophile, $ClPPh_2$.
[b] Isolated yield after purification by chromatography.
[c] The arbitrary numbering given in entries 3 and 4 is used for NMR analysis.

Table 2
Palladium-catalyzed AAA of racemic (*E*)-1,3-diphenyl-2-propenyl acetate with dimethyl malonate



Entry	L*	Solvent	Base	Temp (°C)	Time (h)	Yield[c] (%)	ee[d] (%)
1	**5a**	CH_2Cl_2	BSA, KOAc[a]	rt	2	99	13 (*R*)
2	**5a**	CH_2Cl_2	Cs_2CO_3[b]	rt	1	99	19 (*R*)
3	**5b**	CH_2Cl_2	BSA, KOAc[a]	rt	3	99	0
4	**5b**	CH_2Cl_2	Cs_2CO_3[b]	rt	4	99	8 (*S*)
5	*exo*-**5c**	CH_2Cl_2	BSA, KOAc[a]	rt	1	99	58 (*S*)
6	*exo*-**5c**	$PhCH_3$	BSA, KOAc[a]	rt	13	99	15 (*S*)
7	*exo*-**5c**	THF	BSA, KOAc[a]	rt	4	99	31 (*S*)
8	*exo*-**5c**	CH_2Cl_2	Cs_2CO_3[b]	rt	0.5	99	77 (*S*)
9	*exo*-**5c**	CH_2Cl_2	Cs_2CO_3[b]	−5	24	95	83 (*S*)
10	*exo*-**5c**	CH_2Cl_2	Cs_2CO_3[b]	−40	—	—	—
11	**2,3**-*exo*-**5d**	CH_2Cl_2	BSA, KOAc[a]	rt	3	99	9 (*R*)
12	**2,3**-*exo*-**5d**	CH_2Cl_2	Cs_2CO_3[b]	rt	3	99	12 (*R*)
13	**4e**	CH_2Cl_2	BSA, KOAc[a]	rt	1	99	5 (*S*)
14	**4e**	CH_2Cl_2	Cs_2CO_3[b]	rt	1	99	22 (*S*)
15	**4f**	CH_2Cl_2	BSA, KOAc[a]	rt	2	99	5 (*R*)
16	**4f**	CH_2Cl_2	Cs_2CO_3[b]	rt	2	99	8 (*R*)

[a] Method **A**: 1 equiv substrate, 0.03 equiv $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, 0.06 equiv ligand, 3 equiv BSA, 3 equiv dimethylmalonate.
[b] Method **B**: 1 equiv substrate, 0.03 equiv $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$, 0.06 equiv ligand, 3 equiv Cs_2CO_3, 3 equiv dimethylmalonate.
[c] Isolated yield of pure product after column chromatography.
[d] Enantiomeric excess determined by HPLC analysis (Chiralpak IC chiral column). The absolute configuration was determined by comparison of the specific rotation with the literature value.[16]

Acknowledgements

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8. *General procedure for the synthesis of chiral sulfonamides **3a–f** and **4a–f***: To a stirred, cold (ice bath) solution of benzenesulfonyl chloride (1 equiv) in CH_2Cl_2 were added DIPEA (1 equiv) and the corresponding chiral amine **2a–f** (1.1 equiv). The ice bath was removed and the mixture was allowed to warm to room temperature and stirred until the sulfonyl chloride had been completely consumed (TLC). The mixture was washed with H_2O (100 mL), and the organic phase dried (Na_2SO_4), and concentrated. The residue was purified by flash chromatography on silica gel to give the corresponding target products (sulfonamides **3a–f**). A solution of the corresponding secondary sulfonamide **3a–f** (1 equiv) in THF was cooled in an ice bath and then NaH (2.2 equiv) was added, followed by EtI (20 equiv). After 5 min, the ice bath was removed, and the mixture was allowed to warm to room temperature and stirred until the starting material had been completely consumed (TLC). The mixture was quenched with sat. aq NH_4Cl, and extracted with CH_2Cl_2. The organic phase was dried (Na_2SO_4) and concentrated. The crude product was purified by flash chromatography. Data for *exo*-**4c**: Yield 72%; colourless oil; $[\alpha]_D^{20} = -28.26$ (*c* 1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.80 (s, 3H, 10″-H), 0.84 (s, 3H, 8-H), 0.91 (s, 3H, 9-H), 1.12–1.17 (m, 1H, 5″-H_{endo}), 1.20–1.22 (m, 1H, 6″-H_{endo}), 1.28 (t, 3H, 6-H, J = 7.0 Hz), 1.40 (dd, 1H, 3″-H_{endo}, J = 12.6, 9.5 Hz), 1.51–1.56 (m, 1H, 6″-H_{exo}), 1.67–1.75 (m, 2H, 4″-H, 5″-H_{exo}), 1.78–1.83 (m, 1H, 3″-H_{exo}), 3.19 (q, 1H, 5-H, J = 7.0 Hz), 3.40 (q, 1H, 5-H, J = 7.0 Hz), 3.95–3.98 (m, 1H, 2″-H), 7.47–7.50 (m, 2H, 2-H), 7.53–7.56 (m, 1H, 4-H) 7.80–7.82 (m, 2H, 2-H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 12.01 (C-10″), 17.54 (C-6), 21.15 (C-8″), 21.61 (C-9″), 26.30 (C-5″), 34.64 (C-3″), 39.16 (C-6″), 39.44 (C-5), 44.65 (C-4″), 46.30 (C-7″), 49.85 (C-1″), 65.97 (C-2″), 127.00 (C-2, C-2′), 128.93 (C-3, C-3′), 132.13 (C-4), 141.15 (C-1); MS (ESI) *m*/*z* (rel. int.): 322 (20, M+1), 137 (100); Anal. Calcd for $C_{18}H_{27}NO_2S$: C, 67.25; H, 8.47; N, 4.36; Found: C, 67.48; H, 8.18; N, 4.33. Data for 2,3-*exo*-**4d**: Yield 35%; colourless oil; $[\alpha]_D^{20} = +6.37$ (*c* 0.80, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.76 (s, 3H, 9″-H), 0.92 (s, 3H, 10″-H), 0.94–0.98 (m, 1H, 6″-H_{endo}), 1.05 (t, 3H, 6-H, J = 7.0 Hz), 1.09–1.14 (m, 1H, 5″-H_{endo}), 1.12 (s, 3H, 8″-H), 1.29 (t, 3H, 12″-H, J = 6.9 Hz), 1.43–1.48 (m, 1H, 5″-H_{exo}), 1.65–1.71 (m, 1H, 6″-H_{exo}), 1.76 (d, 1H, 4″-H, J = 4.2 Hz), 3.16 (q, 1H, 11″-H_a, J = 6.9 Hz), 3.26 (q, 1H, 11″-H_b, J = 6.9 Hz), 3.28 (d, 1H, 3″-H, J = 7.2 Hz), 3.46 (q, 1H, 5-H_a, J = 7.0 Hz), 3.74 (q, 1H, 5-H_b, J = 7.0 Hz), 3.86 (d, 1H, 2″-H, J = 7.2 Hz), 7.47–7.50 (m, 2H, 3-H, 3′-H), 7.52–7.55 (m, 1H, 4-H), 7.86–7.87 (m, 2H, 2-H, 2′-H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 11.71 (C-10″), 15.25 (C-6), 16.11 (C-12″), 21.68 (C-9″), 21.97 (C-8″), 29.36 (C-6″), 32.37 (C-5″), 42.19 (C-5), 47.25 (C-7″), 47.71 (C-4″), 49.57 (C-1″), 68.89 (C-2″), 68.53 (C-11″), 90.80 (C-3″), 127.06 (C-2, C-2′), 128.84 (C-3, C-3′), 132.07 (C-4), 140.62 (C-1); MS (ESI) *m*/*z* (rel.int): 366 (100, M+1); Anal. Calcd for $C_{20}H_{31}NO_3S$: C, 65.72; H, 8.55; N, 3.83; Found: C, 65.48; H, 8.18; N, 3.63.
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12. *General procedure for the synthesis of ortho-diphenylphosphino-benzene sulfonamides **5a–f***: To a stirred solution of chiral sulfonamide **4a–f** (1 equiv) in THF at −78 °C, *n*-BuLi (1.1 equiv, 1.6 M solution in *n*-hexane) was added dropwise. The solution was stirred at −78 °C for 1 h and quenched with $ClPPh_2$ (2 equiv). The mixture was stirred at this temperature until completion of the reaction, as monitored by the consumption of the starting sulfonamide (TLC). The mixture was worked-up by filtration through Celite, which was then washed with Et_2O. The collected organic filtrates were concentrated and the residue chromatographed. Data for *exo*-**5c**: Yield 68%; colorless crystals; mp 150–153 °C; $[\alpha]_D^{20} = -31.50$ (*c* 1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.84 (s, 3H, 10″-H), 0.86 (s, 3H, 8″-H), 0.97 (s, 3H, 9″-H), 1.19 (t, 3H, 6-H, J = 7.0 Hz), 1.21–1.27 (m, 2H, 5″-H_{endo}, 6″-H_{endo}), 1.47–1.53 (m, 1H, 6″-H_{exo}), 1.66–1.76 (m, 3H, 3″-H_{endo}, 4″-H, 5″-H_{exo}), 1.94–1.99 (m, 1H, 3″-H_{exo}), 3.30–3.37 (m, 1H, 5-H), 3.73–03.79 (m, 1H, 5-H), 4.41–4.47 (m, 1H, 2″-H), 7.11 (ddd, 1H, 2′-H, J = 7.7, 3.1, 1.3 Hz), 7.18–7.21 (m, 2H, PPh_2) 7.22–7.26 (m, 2H, PPh_2), 7.30–7.34 (m, 6H, PPh_2), 7.37 (ddd, 1H, 3′-H, J = 8.8, 7.5, 1.4 Hz), 7.43 (ddd, 1H, 4-H, J = 8.8, 7.5, 1.3 Hz), 8.02 (ddd, 1H, 3-H, J = 7.8, 3.6, 1.3 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 12.24 (C-10″), 17.31 (C-6), 21.42 (C-8″), 21.65 (C-9″), 26.30 (C-5″), 35.14 (C-3″), 38.82 (C-6″), 39.78 (C-5), 44.72 (C-4″), 46.57 (C-7″), 50.08 (C-1″), 65.76 (C-2″), 128.44–128.59 (m, 6C, PPh_2), 128.77 (d, C-4, J_{CP} = 21.9 Hz), 130.01 (d, C-2′, J_{CP} = 21.9 Hz), 131.71 (C-3′), 133.65 (d, 2C, PPh_2, J_{CP} = 14.9 Hz), 133.79 (d, 2C, PPh_2, J_{CP} = 14.7 Hz), 136.26 (C-3), 136.85 (d, C-2, J_{CP} = 11.2 Hz), 137.38 (d, 1C, PPh_2, J_{CP} = 28.96 Hz), 137.82 (d, 1C, PPh_2, J_{CP} = 14.01 Hz), 145.96 (d, C-1, J_{CP} = 24.93 Hz); ^{31}P NMR (250 MHz, $CDCl_3$): δ −6.10 (s); MS (ESI) *m*/*z* (rel.int): 506 (94, M+1), 370 (100). Data for 2,3-*exo*-**5d**: Yield 84%; colorless crystals; mp 51–56 °C; $[\alpha]_D^{20} = +20.30$ (*c* 1, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.70 (s, 3H, 9″-H), 0.75 (t, 3H, 6-H, J = 6.36 Hz), 1.07 (s, 3H, 10″-H), 1.01–1.06 (m, 2H, 5″-H_{endo}, 6″-H_{endo}), 1.07 (s, 3H, 8″-H), 1.23 (t, 3H, 12″-H, J = 6.9 Hz), 1.34–1.43 (m, 1H, 5″-H_{exo}), 1.59–1.66 (m, 1H, 6″-H_{exo}), 1.89 (d, 1H, 4″-H, J = 4.2 Hz), 3.17 (d, 1H, 3″-H, J = 7.3 Hz), 3.22 (q, 1H, 5-H_a, J = 7.1 Hz), 3.30 (q, 1H, 11″-H_a, J = 7.0 Hz), 3.36–3.44 (m, 2H, 5-H_b, 11″-H_b), 4.11 (dd, 1H, 2″-H, J = 7.3, 1.7 Hz), 7.11 (ddd, 1H, 3-H, J = 7.5, 3.1, 1.3 Hz), 7.14–7.17 (m, 2H, PPh_2) 7.20–7.25 (m, 8H, PPh_2), 7.29 (ddd, 1H, 4-H, J = 8.9, 7.5, 1.4 Hz), 7.34 (ddd, 1H, 3′-H, J = 8.8, 7.9, 1.4 Hz), 7.90 (ddd, 1H, 2′-H, J = 7.8, 3.7, 1.3 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 11.76 (C-10″), 15.12 (C-6), 15.61 (C-12″), 21.68 (C-9″), 21.80 (C-8″), 28.95 (C-6″), 32.33 (C-5″), 42.31 (C-11″), 47.26 (C-7″), 48.01 (C-4″), 49.77 (C-1″), 66.22 (C-2″), 68.27 (C-5), 90.61 (C-3″), 128.42 (d, 6C, PPh_2, J_{CP} = 6.9 Hz), 128.66, (d, C-3′, J_{CP} = 7.1 Hz), 128.88 (d, C-2′, J_{CP} = 4.5 Hz), 131.27 (C-4), 133.65 (d, 2C, PPh_2, J_{CP} = 20.1 Hz), 133.85 (d, 2C, PPh_2, J_{CP} = 20.5 Hz), 136.67 (C-3), 136.98 (d, 1C, PPh_2, J_{CP} = 13 Hz), 137.30 (d, 1C, PPh_2, J_{CP} = 13 Hz), 137.75 (C-2), 146.53 (C-1); ^{31}P NMR (250 MHz, $CDCl_3$): δ −9.22 (s); MS (ESI) *m*/*z* (rel.int): 550 (89, M+1), 325 (100).
13. *General procedure for the palladium-catalyzed allylic alkylation; **Method A***: A solution of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (3 mol %), ligand **4a–f** (6 mol %), and anhydrous KOAc (5 mol %) in dry CH_2Cl_2 (2 mL) was stirred at room temperature in a Schlenk tube for 1 h. Then *rac*-1,3-diphenylprop-2-en-1-yl acetate (1 equiv), BSA (3 equiv), and dimethyl malonate (3 equiv) were added. ***Method B***: A solution of $[Pd(\eta^3\text{-}C_3H_5)Cl]_2$ (3 mol %) and ligand **4a–f** (6 mol %) in dry CH_2Cl_2 (2 mL) was stirred at room temperature in a Schlenk tube for 1 h. Then *rac*-1,3-diphenylprop-2-en-1-yl acetate (1 equiv), dimethyl malonate (3 equiv), and Cs_2CO_3 were added. The mixture was stirred at room temperature and monitored by TLC. The mixture was diluted with Et_2O (30 mL) and washed with sat. aq. NH_4Cl solution. The organic phase was dried (Na_2SO_4), filtered, and concentrated. The residue was purified by flash chromatography (silica gel, hexane/EtOAc = 4.6:0.4). The enantioselectivity was determined by HPLC analysis on a chiral column Chiralpak IC; hexane/*i*-PrOH, 96:4; flow rate, 1 mL/ min; $t_{(R)}$ = 9.421 min; $t_{(S)}$ = 10.817 min.
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