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Palladium-Catalyzed Asymmetric Quaternary Stereocenter Formation

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Abstract: An efficient palladium catalyst is presented for the formation of benzylic quaternary stereocenters by conjugate addition of arylboronic acids to a variety of β,β-disubstituted carbocyclic, heterocyclic, and acyclic enones. The catalyst is readily prepared from $PdCl_2$, PhBOX, and $AgSbF_6$, and provides products in up to 99% enantiomeric excess, with good yields. Based on this strategy, (−)-α-cuparenone has been prepared in only two steps.

Keywords: arylboronic acids · cuparenone · Michael addition · palladium · quaternary stereocenters

Introduction

Notwithstanding the significant advances in the field of transition-metal-catalyzed carbon–carbon bond formation,[1] the catalytic asymmetric synthesis of quaternary stereocenters remains a challenge and a crucial area of study in chemistry. Among the handful of methods available for construction of these units by metal catalysis,[2] conjugate addition to β,β-substituted[3] enones or Meldrum's acid derivatives[4] is of particular importance. This may be evidenced by the reports of Hoveyda[5] and Alexakis,[6] in which highly reactive organometallic nucleophiles (organozinc, organoaluminum, and organomagnesium reagents) were employed under copper catalysis, or, alternatively, by the recent studies of Shintani and Hayashi[7] on the use of boronates, catalyzed by rhodium. As a complementary procedure, asymmetric quaternary stereocenter formation that employs easily manipulated and readily available boronic acids under palladium catalysis would be an important addition to the toolbox of the synthetic chemist, especially in view of scaleup.

Given the precedent for the asymmetric Pd-catalyzed conjugate addition of arylboronic acids and their derivatives to α,β-unsaturated carbonyl compounds (for example, cyclohexenone),[8] combined with the abundant commercial availability of arylboronic acids, we decided to extend our approach[8a] to the enantioselective formation of quaternary stereocenters. A report by Lin and Lu in 2010,[9] confirmed our presumption that cationic Pd species are indeed capable of this transformation. Concurrent with our investigations, Stoltz et al.[10] recently disclosed the first report on Pd-catalyzed asymmetric conjugate additions of arylboronic acids to cyclic enones, which led to benzylic quaternary stereocenters in excellent yields and selectivities. Subsequently, a computational evaluation of the reaction mechanism was reported.[11]

Herein, we present the $PdCl_2$/(*R*,*R*)-2,2-bis(4-phenyl-2-oxazolin-2-yl)propane (PhBOX)/$AgSbF_6$ catalyzed conjugate addition of arylboronic acids to provide benzylic quaternary stereocenters for a variety of carbocyclic, heterocyclic, and acyclic enones.

Results and Discussion

The addition of phenylboronic acid (**2**) to 3-methyl-cyclohexenone (**1**) was investigated (Table 1) in the presence of various Pd precursors and chiral ligands **4**–**12**. Our quest to find an optimal catalyst system for the reaction began with MeDuPhos (**4**)/$Pd(O_2CCF_3)_2$ (Table 1, entry 1), a combination we have previously disclosed to be highly successful in the conjugate addition of arylboronic acids to cyclohexenone.[8a] However, the conversion obtained was very poor, despite achievement of an excellent enantiomeric excess (96% *ee*). Variations of temperature and solvent in this system did not prove beneficial. Analysis of other chiral phosphines, and cationic complexes thereof, also met with disappointing results.[12] This ensued a screen of various chiral nitrogen ligands. Interestingly, bidentate amine BINAM (**6**) provided a significant level of enantioinduction (72% *ee*), albeit with poor conversion (16%). Compelling

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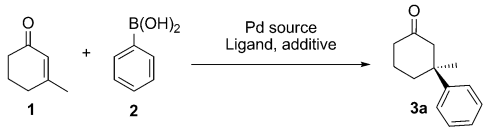
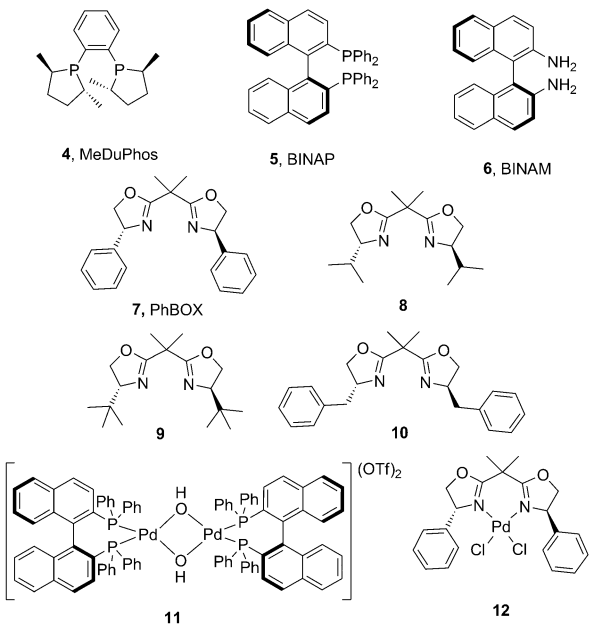
Table 1. Establishing the reaction parameters.[a]



Entry	Pd precursor	[mol%]	Ligand	[mol%]	Additive [20 mol%]	Conv[g] [%]	*ee*[h] [%]
1[b]	$Pd(O_2CCF_3)_2$	5	**4**	7	–	<5	96
2[c]	$[Pd(CH_3CN)_4(BF_4)_2]$	5	**5**	7	–	–	–
3[c]	**11**	5	–	–	–	<5	nd
4[c]	$[Pd(CH_3CN)_4(BF_4)_2]$	5	**6**	7	–	16	72
5[c]	$Pd(O_2CCF_3)_2$	5	**7**	7	–	22	92
6[d]	$Pd(O_2CCF_3)_2$	5	**7**	7	–	51	92
7[d]	$Pd(O_2CCF_3)_2$	5	**7**	7	$Cu(BF_4)_2{\cdot}6H_2O$	60	0
8[d]	$Pd(O_2CCF_3)_2$	5	**7**	27	$Cu(BF_4)_2{\cdot}6H_2O$	67	97
9[d]	$Pd(O_2CCF_3)_2$	5	**8**	27	$Cu(BF_4)_2{\cdot}6H_2O$	14	69
10[d]	$Pd(O_2CCF_3)_2$	5	**9**	27	$Cu(BF_4)_2{\cdot}6H_2O$	–	–
11[d]	$Pd(O_2CCF_3)_2$	5	**10**	27	$Cu(BF_4)_2{\cdot}6H_2O$	53	84
12[e]	**12**	8	–	–	$AgBF_4$	74	97
13[e]	**12**	8	–	–	$AgSbF_6$	100	96
14[e,f]	**12**	8	–	–	$AgSbF_6$	<10	97

[a] Reaction conditions: **1** (1 equiv), **2** (1.5 equiv), Pd precursor, ligand, additive, 40 °C, solvent, 24 h. [b] THF/water (10:1) as solvent [c] Solvent = MeOH. [d] Solvent = acetone. [e] Solvent = MeOH/water (4:1). [f] Reaction was performed with $PhBF_3K$ instead of $PhB(OH)_2$. [g] Conversion was determined by GC-NMR analysis of the crude reaction mixture. [h] Determined by chiral GC analysis of the crude reaction mixture.

improvements only began to appear, when bisoxazoline (BOX) ligands were studied. With **7** as ligand, a jump in conversion from 22 to 51% was observed when acetone was substituted for methanol as the solvent (Table 1, entries 5 and 6), and a high *ee* value of 92% was maintained. This result, together with the observation of Pd black when the reaction was performed in methanol, led us to assume that the reduction of Pd^{II} to Pd^0 by MeOH was the cause of the poor conversions.[13]



Because Pd^0 is catalytically inactive for the transformation, we sought methods to reoxidize Pd^0 to Pd^{II}. From the assay of potential oxidants, notable improvement in conversion was observed when $Cu(BF_4)_2{\cdot}6H_2O$ (20 mol%) was added. However, this came at the cost of complete loss of enantioselectivity, probably because **7** was scavenged from palladium by Cu^{II}. This warranted the addition of **7** (27 mol%) in subsequent runs to maintain the excellent enantioselectivity (97% *ee*) with 67% conversion (Table 1, entry 8).

Other BOX ligands showed no prominent improvement in conversion or enantioselectivity (Table 1, entries 9–11) and the reaction was found to be completely blocked by ligand **9** (Table 1, entry 10). At this stage, we scouted for alternative approaches to generate cationic Pd species in situ, with the goal to maintain the high enantioinduction rendered by **7** and improve the conversion. A reliable protocol to this end was the in situ dehalogenation of metal halides with silver salts.

We synthesized complex **12** (see Figure 1 for X-ray crystal structure) by heating $PdCl_2$ and **7** in acetonitrile at reflux temperature over 3 h (see the Experimental Section). Switching to MeOH/water (4:1) as the solvent, in situ dehalogenation with $AgBF_4$ resulted in a significant increase in conversion to 74% (Table 1, entry 12). However, a decisive improvement that led to full conversion with 96% *ee* after 24 h (Table 1, entry 13) was achieved by employment of $AgSbF_6$ as the silver salt.[15] It is fortunate that this superior catalyst is composed of commercially available and affordable PhBOX, $PdCl_2$, and $AgSbF_6$. Replacement of $PhB(OH)_2$ with $PhBF_3K$ (Table 1, entry 14) gave poor conversion (<10%) although the *ee* value remained excellent (97%).

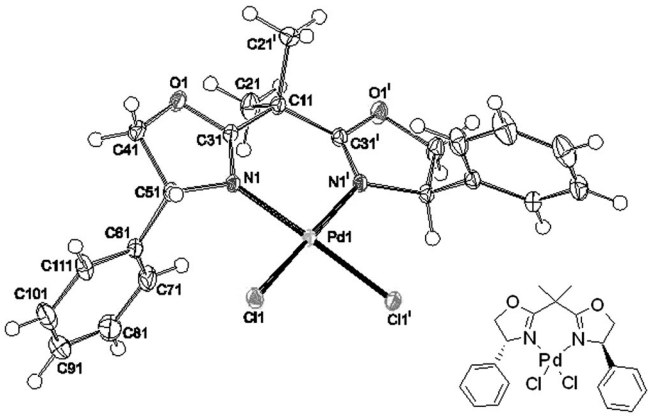
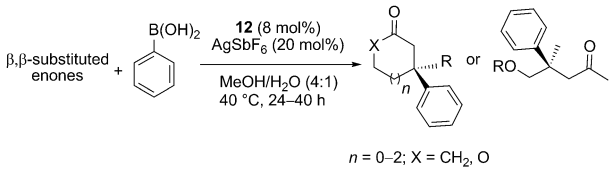


Figure 1. X-ray crystal structure of **12**.[14] Only one of two independent molecules is shown. Both molecules have twofold symmetry. The absolute structure was confirmed by the anomalous differences of X-ray intensities (see the Supporting Information).

Equipped with the **12**/$AgSbF_6$ system, we advanced to investigate the scope of the new reaction (Table 2). We were

delighted that the catalyst system was highly successful in the addition of **2** to five-, six- and seven-membered carbocycles; excellent enantioselectivities were uniformly delivered, along with high isolated yields. The reaction tolerates alkyl substituents at the β position, but not aryl substituents (Table 2, entries 2 and 3 vs. entry 4). Overall, this coincides with the results of Stoltz et al.,[10] but the *ee* values with the current **12**/$AgSbF_6$ catalyst system are essentially higher.

Table 2. Substrate scope in the conjugate addition of arylboronic acids.[a]



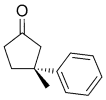
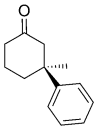
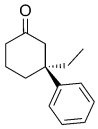
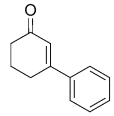
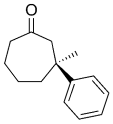
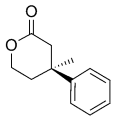
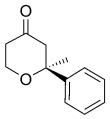
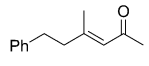
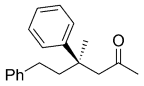
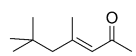
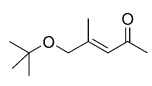
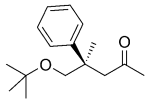
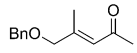
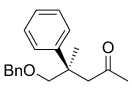
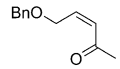
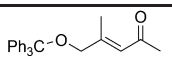
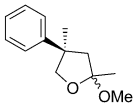
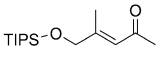
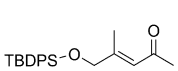
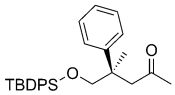
Entry	Substrate		Product		Yield [%][b]	*ee* [%][c]
1		**13**		**13a**	93	93
2		**1**		**3a**	95	96
3		**14**		**14a**	91	99
4		–		–	–	–
5		**15**		**15a**	80	94
6[d]		**16**		**16a**	57	88
7		**17**		**17a**	28	69
8[e]		**18**		**18a**	14	8
9[e]		**19**	–	–	<10	nd
10[e]		**20**		**20a**	84	23
11[e]		(*E*)-**21**		**21a**	81	25
12[e]		(*Z*)-**21**			78	36

Table 2. (Continued)

Entry	Substrate		Product		Yield [%][b]	*ee* [%][c]
13[e]		**22**		**22a**	53	51[f]
14[e]		**23**			68	27[f]
15[e]		**24**		**24a**	38	60

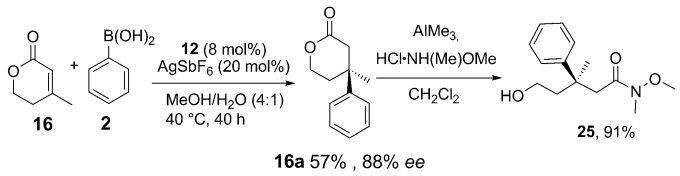
[a] Reaction conditions: substrate (0.5 mmol), **2** (0.75 mmol), **12** (8 mol%), $AgSbF_6$ (20 mol%), MeOH/water (4:1), 40 °C, 24–40 h. [b] Isolated yields. [c] Determined by chiral GC/HPLC analysis of the isolated products. [d] Boronic acid (3 equiv). [e] Reaction was performed at 60 °C. [f] The *ee* value was determined by ring opening of the acetal (see the Supporting Information). TBDPS = *tert*-butyldiphenylsilyl; Bn = benzyl; TIPS = triisopropylsilyl; nd = not determined.

Aside from carbocyclic enones, heterocycles that possess quaternary stereocenters are key building blocks in the synthesis of natural products and pharmaceuticals. In general, however, their synthesis is challenging and procedures that use catalytic asymmetric conjugate additions are limited. Lactone **16** turned out to be a suitable substrate for the catalyst system. Although the desired product **16a** was isolated with a reduced 57% yield, the *ee* value was respectable (88%; Table 2, entry 6). Cyclic ether **17a** was obtained in 28% yield and 69% *ee* from 6-methyl-2*H*-pyran-4(3*H*)-one (**17**; Table 2, entry 7). The lower activity may be a consequence of the poor electrophilicity of **17**, formally a vinylogous ester, which arises from electron donation by the lone pair of the oxygen atom in the ring.

Compared with cyclic enones, acyclic enones are known to be considerably more challenging substrates for conjugate addition; this reaction is no exception. Compound **18** underwent rapid *E*/*Z* isomerization, which, combined with poor conversion, resulted in low yield and *ee* value (Table 2, entry 8). Enone **19** met a similar fate. Realizing that success of the asymmetric addition to acyclic substrates rested in controlling this isomerization, several substrate classes were designed and studied. We were fortunate to discover that an allylic ether function in the substrate arrested the isomerization and led to considerably higher yields of the desired products. Product **20a** was obtained in a high yield of 84% from **20**, though with only 23% *ee*. Interestingly, benzyl ethers (*E*)-**21** and (*Z*)-**21** provided the same enantiomer of product **21a**, which suggests dominant catalyst control over the reaction, although a higher *ee* value was obtained from (*Z*)-**21** (Table 2, entries 11 and 12). This is in contrast to observations in the analogous Rh-catalyzed conjugate additions, in which *E* and *Z* isomers of the substrate provide the opposite enantiomers of the product.[7a–c] Trityl ether **22** (Table 2, entry 13) resulted in the formation of acetal **22a**, due to cleavage of the trityl moiety after conjugate addition. This is due to the acidic environment of the reaction. An im-

proved *ee* value of 51% was observed. Silyl ethers **23** and **24** also suffered cleavage of the protecting group. Reaction of **23** resulted in the formation of **22a**, but **24a**, which bore a *tert*-butyldiphenylsilyl (TBDPS) group, could be isolated from **24** in 38% yield (alongside the byproduct acetal **22a**) with a respectable *ee* value of 60% (Table 2, entry 15). The cleavage of the silyl ethers could be caused by fluoride, produced by the decomposition of SbF_6^-.

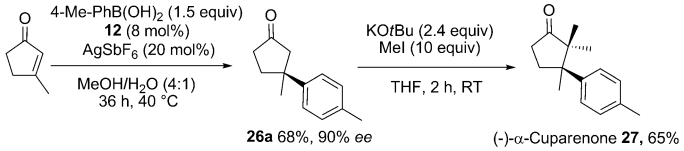
Complementary to the addition to linear substrates, we developed the one-step ring opening of **16a**, to provide **25** in high yield. Building block **25** offers two convenient handles for further functionalization (Scheme 1).



Scheme 1. Access to acyclic compounds with quaternary stereocenters through lactone ring-opening.

Further, we examined the scope of arylboronic acids that could be employed in the reaction. The scope turned out to be broad; phenylboronic acids substituted with both electron-donating and electron-withdrawing groups reacted readily. Excellent enantioselectivity (>95% *ee*) was observed with alkoxy-, alkyl-, or halide-substituted phenylboronic acids (Table 3). The steric encumbrance of *ortho* substituents was found to block the reaction (Table 3, entry 3). Once again, the enantioselectivities delivered were repeatedly higher than those reported previously[10] for the same substrates. Of particular mention is product **3g**, for which a 29% improvement in enantioselectivity was observed. Ferrocenylboronic acid, however, was found to be unreactive, even at 60°C (Table 3, entry 10).

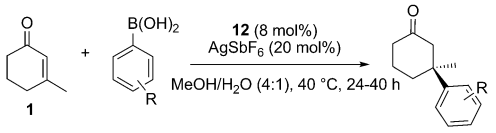
As an example of the impact of this new reaction, we completed the synthesis of sesquiterpene (−)-α-cuparenone,[16] isolated from *Thuja orientalis*, in just two steps; the shortest synthesis to date (Scheme 2). Compound **26a** was

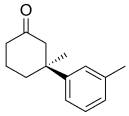
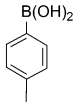
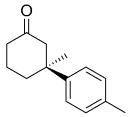
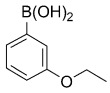
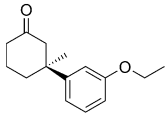
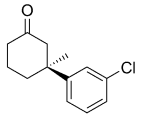
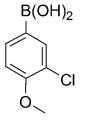
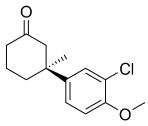
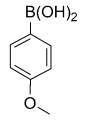
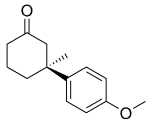
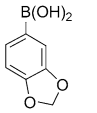
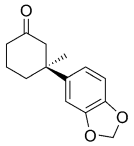
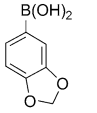
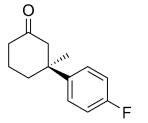
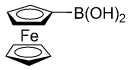


Scheme 2. A two-step synthesis of (−)-α-cuparenone (**27**).

obtained from 3-methylcylopentenone in 68% yield and 90% *ee*. Subsequent regioselective dimethylation could be performed in a single step by slow addition of KO*t*Bu in THF in the presence of MeI (a considerable improvement when compared to previous literature, see the Experimental Section).

Table 3. The conjugate addition of arylboronic acids to 3-methyl-cyclohexenone.[a]



Entry	Boronic acid	Product		Yield[b] [%]	*ee*[c] [%]
1			**3b**	89	97
2			**3c**	96	97
3		–	–	–	–
4[d]			**3d**	44	93
5[e]			**3e**	30	98
6			**3f**	98	>99
7			**3g**	85	98
8			**3h**	98	96
9			**3i**	88	98
10[e]		–	–	–	–

[a] Reaction conditions: **1** (0.5 mmol), arylboronic acid (0.75 mmol), **12** (8 mol%), $AgSbF_6$ (20 mol%), MeOH/water (4:1), 40°C, 24–40 h. [b] Isolated yields. [c] Determined by chiral GC/HPLC analysis of the isolated products. [d] Reaction did not proceed to completion, even after 72 h. [e] Reaction was performed at 60°C.

Conclusion

We have described **12**/$AgSbF_6$ as an efficient catalytic system for the conjugate addition of arylboronic acids to β,β-disubstituted enones. Benzylic quaternary stereocenters

are formed in excellent yields (up to 98%) and enantioselectivities (up to 99% *ee*) for carbocyclic enones, and with appreciable success for heterocyclic (up to 88% *ee*) and acyclic enones (up to 60% *ee*). This is the first example of a single catalytic system with the ability to address all these classes of substrates, which breaks the ground to further developments in this direction. An allylic ether moiety was found to be a key factor in the addition to acyclic substrates. The catalyst system has also been employed in the shortest synthesis to date of (−)-α-cuparenone. Further application of this methodology in natural product synthesis is currently underway.

Experimental Section

General: All experiments were carried out in flame-dried or oven-dried (150°C) glassware, under an atmosphere of nitrogen (unless otherwise specified) by standard Schlenk techniques. Schlenk reaction tubes with screw caps, equipped with a Teflon-coated magnetic stirrer bar were flame dried under vacuum and allowed to return to room temperature prior to being charged with reactants. A manifold permitting alternation between nitrogen atmosphere and vacuum was used to control the atmosphere in the reaction vessel. Reaction temperature refers to the temperature of the oil bath. Flash chromatography was performed with Merck silica gel type 9385 (230–400 mesh) and the indicated solvents or by using a Grace Revelaris automatic column machine equipped with silica gel column cartridges and an evaporative light scattering detector (ELSD) or UV detector. All solvents used for extraction, filtration and chromatography were of commercial grade and were used without further purification. Anhydrous methanol and acetonitrile were sourced from Sigma–Aldrich or Acros and stored under nitrogen. Reagents, ligands, and complex **11** were purchased from Sigma–Aldrich, Strem, or Acros and used without further purification. Silver hexafluoroantimonate was stored in a nitrogen dry-box. Bisoxazoline ligands **7**–**10** were stored at −20°C. Complex **12** was prepared as described below and stored under ambient conditions. TLC was performed on Merck silica gel 60, 0.25 mm plates and visualization was by UV and development with Seebach's reagent [phosphomolybdic acid (25 g), cerium(IV) sulfate (7.5 g), H_2O (500 mL), H_2SO_4 (25 mL)], vanillin stain [vanillin (6 g), concd sulfuric acid (1.5 mL), ethanol (95 mL)], or $KMnO_4$ stain. ^1H and ^{13}C NMR spectra were recorded with a Varian AMX400 instrument (400 and 100.59 MHz, respectively) in $CDCl_3$, unless otherwise specified. Chemical shift values (δ) are reported in ppm with the solvent resonance as the internal standard ($CHCl_3$: $\delta = 7.27$ ppm for ^1H NMR, $\delta = 77.1$ ppm for ^{13}C NMR). Data are reported as follows: δ, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (J [Hz]), and integration. GC-MS measurements were performed with a HP 6890 series gas chromatography system equipped with a HP 5973 mass sensitive detector. GC measurements were made performed with a Shimadzu GC 2014 gas chromatography system equipped with an AT5 column (Grace Alltech) and FID detector. Whenever GC conversion is reported, the quantification used cyclooctane as internal standard. Reactions for optimization of the reaction parameters (Table 1) were performed at a 0.1 mmol scale and reactions were performed with at least a 0.5 mmol scale when isolated yields were reported (Tables 2 and 3). Enantiomeric excess was determined by chiral HPLC analysis by using a Shimadzu LC-10ADVP HPLC instrument equipped with a Shimadzu SPD-M10AVP diode-array detector or by chiral GC analysis with Shimadzu GC-17A instrument equipped with a Chiraldex G-TA column (Grace Alltech nt. 4139, 30 m × 0.25 mm × 0.125 μm) and FID detector. The temperature program was: initial temperature (95°C); temperature gradient (4°C min^{-1}) up to 120°C; 5 min hold time; temperature gradient (1°C min^{-1}) up to 125°C; 7 min hold time; temperature gradient (0.5°C min^{-1}) up to 130°C 50 min hold time. Retention times (t_R) are given in min. Racemates were synthesized by using 2,2′-bipyridine instead of **7**, under the same reaction conditions. HRMS was performed by using a ThermoScientific LTQ Oribitrap XL spectrometer. Optical rotations were measured on a Schmidt+Haensch polarimeter (Polartronic MH8) with a 10 cm cell (c given in g/100 mL).

Synthesis of (*R*,*R*)-12: A flame dried Schlenk tube equipped with a magnetic stirrer bar was charged with $PdCl_2$ (135 mg, 0.762 mmol). The tube was closed with a rubber septum and alternated through three cycles of vacuum evacuation/nitrogen backfilling. Compound (*R*,*R*)-**7** (260 mg, 1.02 equiv, 0.777 mmol) was dissolved in dry acetonitrile (5 mL) and was introduced into the Schlenk by syringe. Dry acetonitrile (5 mL) was used to rinse the walls of the Schlenk tube. The septum was removed under a positive pressure of nitrogen and the Schlenk tube was connected to an Allihn condenser. The reaction mixture was alternated through three cycles of vacuum evacuation/nitrogen backfilling and heated at reflux temperature for 3 h under nitrogen. During this process, the reaction mixture turned from colorless to orange-red. The $PdCl_2$ that settled at bottom of vessel at the start of the reaction was completely consumed and an orange precipitate formed. The reaction was cooled to RT and filtered directly through a fritted funnel (pore size 4). The residue was washed with pentane and allowed to dry in air to yield the first crop of **12** (215 mg, 74%) as an orange-red solid. Upon concentration of the filtrate and layering with pentane, a second crop of **12** was obtained (overall yield = 241 mg, 83%). X-ray quality crystals were obtained by placing a concentrated solution of **12** in acetonitrile in a capped NMR tube and allowing it stand at 4°C for 72 h. $[\alpha]_D^{20} = -224.3$ ($c = 0.07$ in $CHCl_3$); ^1H NMR (400 MHz, [D$_6$]DMSO): δ = 7.54–7.40 (m, 10H), 5.81 (d, J = 8.6 Hz, 2H), 4.96 (t, J = 9.1 Hz, 2H), 4.55 (d, J = 8.2 Hz, 2H), 1.96 ppm (s, 6H); ^{13}C NMR (101.59 MHz, [D$_6$]DMSO): δ = 173.4, 142.0, 129.5, 129.4, 127.0, 78.0, 68.3, 26.0 ppm; HRMS (ESI+): m/z calcd: 439.06324 [M−2HCl]$^+$, found: 439.06324 [M−2HCl]$^+$; elemental analysis calcd (%) for $C_{21}H_{22}Cl_2N_2O_2Pd$: C 49.29, H 4.33, N 5.47; found: C 48.97, H 4.22, N 5.46.

General procedure for the conjugate addition: A flame-dried Schlenk tube equipped with a magnetic stirrer bar and penetrable screw cap was charged with **12** (20.5 mg, 8 mol%) and arylboronic acid (0.75 mmol). The Schlenk tube was alternated through three cycles of vacuum evacuation/nitrogen backfilling. The enone (0.5 mmol) was introduced by syringe, followed by methanol (2 mL). $AgSbF_6$ (38 mg, 20 mol%), dissolved in water (0.5 mL) was introduced by syringe. The Schlenk tube was placed in a preheated oil bath at 40°C and the reaction mixture was stirred for 24 h. Upon complete consumption of the enone (monitored by TLC/GC), the reaction mixture was allowed to cool to RT, diluted with diethyl ether, and filtered through a pad of silica. The filtrate was dried over anhydrous $MgSO_4$, concentrated in vacuo, and adsorbed on silica before being loaded on a silica gel column. Elution with a mixture of pentane/diethyl ether afforded the product.

Compound (*S*)-3a: Synthesized according to the general procedure and purified by flash chromatography (*n*-pentane/Et_2O = 4:1). Compound **3a** was obtained as a colorless oil (95%, 96% *ee*). $[\alpha]_D^{20} = +64.3$ ($c = 0.26$ in $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.28–7.13 (m, 5H), 2.84 (d, J = 14.2 Hz, 1H), 2.39 (d, J = 14.2 Hz, 1H), 2.27 (t, J = 6.8 Hz, 2H), 2.21–2.08 (m, 1H), 1.96–1.74 (m, 2H), 1.69–1.53 (m, 1H), 1.28 ppm (s, 3H); ^{13}C NMR (101.59 MHz, $CDCl_3$): δ = 211.5, 147.5, 128.6, 126.2, 125.6, 53.1, 42.9, 40.8, 38.0, 29.8, 22.1 ppm; HRMS (ESI+): m/z calcd: 189.12739 [M+H]$^+$, found: 189.12729 [M+H]$^+$; chiral GC: t_R = 24.7 (minor) and 25.2 min (major). Characterization matched with previously reported data.[6b,10]

Compound (*S*)-3b: Synthesized according to the general procedure and purified by flash chromatography (*n*-pentane/Et_2O = 4:1). Compound **3b** was obtained as a colorless oil (89%, 97% *ee*); ^1H NMR (400 MHz, $CDCl_3$): δ = 7.22 (t, J = 7.6 Hz, 1H), 7.13 (d, J = 7.7 Hz, 2H), 7.03 (d, J = 7.2 Hz, 1H), 2.88 (d, J = 14.2 Hz, 1H), 2.43 (d, J = 14.2 Hz, 1H), 2.36 (s, 3H), 2.32 (t, J = 6.8 Hz, 2H), 2.24–2.12 (m, 1H), 1.98–1.82 (m, 2H), 1.78–1.62 (m, 1H), 1.32 ppm (s, 3H); ^{13}C NMR (101.59 MHz, $CDCl_3$): δ = 211.6, 147.5, 138.0, 128.4, 126.9, 126.4, 122.6, 53.2, 42.7, 40.8, 38.0, 29.7, 22.1, 21.7 ppm; HRMS (ESI+): m/z calcd: 225.12496 [M+Na]$^+$; found: 225.12499 [M+Na]$^+$; chiral GC (GTA column): t_R = 32.6 (minor) and

33.3 min (major). Characterization matched with previously reported data.[6b,10]

Compound (*S*)-3c: Synthesized according to the general procedure and purified by flash chromatography (*n*-pentane/Et_2O = 4:1). Compound **3c** was obtained as a colorless oil (96%, 97% *ee*). $[\alpha]_D^{20} = +70.5$ ($c = 1.13$ in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.23$ (d, $J = 8.3$ Hz, 2H), 7.15 (d, $J = 8.4$ Hz, 2H), 2.88 (d, $J = 14.1$ Hz, 1H), 2.43 (d, $J = 14.1$ Hz, 1H), 2.33 (s, 3H), 2.23–2.14 (m, 2H), 1.99–1.82 (m, 2H), 1.76–1.59 (m, 2H), 1.32 ppm (s, 3H); ^{13}C NMR (101.59 MHz, $CDCl_3$): $\delta = 211.5$, 147.5, 128.6, 126.2, 125.6, 53.1, 42.9, 40.8, 38.0, 29.8, 22.0 ppm; HRMS (ESI+): *m*/*z* calcd: 225.12496 $[M+Na]^+$; found: 225.12499 $[M+Na]^+$; chiral GC (GTA column): $t_R = 38.3$ (minor) and 38.8 min (major). Characterization matched with previously reported data.[5b,6b,10]

Compound (*S*)-3d: Synthesized according to the general procedure and purified by flash chromatography (*n*-pentane/Et_2O = 9:1). Compound **3d** was obtained as a colorless oil (44%, 93% *ee*). $[\alpha]_D^{20} = M + > 49.1$ ($c = 1.45$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.21$ (t, $J = 8.0$ Hz, 1H), 6.87 (d, $J = 7.7$ Hz, 2H), 7.03 (d, $J = 8.1$ Hz, 1H), 4.0 (q, $J = 6.9$ Hz, 2H), 2.85 (d, $J = 14.2$ Hz, 1H), 2.41 (d, $J = 14.2$ Hz, 1H), 2.30 (t, $J = 10.6$ Hz, 2H), 2.18–2.13 (m, 1H), 1.92–1.83 (m, 2H), 1.70–1.61 (m, 1H), 1.40 (t, $J = 6.7$ Hz, 3H), 1.38 ppm (s, 3H); ^{13}C NMR (101.59 MHz, $CDCl_3$): $\delta =$ 211.5, 159.1, 149.3, 129.5, 118.0, 112.8, 111.5, 63.4, 53.2, 42.9, 40.9, 38.0, 29.8 ppm; HRMS: *m*/*z* calcd: 255.13555 $[M+Na]^+$; found: 255.13532 $[M+Na]^+$; chiral HPLC: Chiralpak AD-H column, *n*-heptane/*i*PrOH 99:1, 40 °C, detection at $\lambda = 210$ nm, $t_R = 21.3$ (minor) and 23.2 min (major). Characterization matched with previously reported data.[5b,6b,10]

Compound (*S*)-3e: Synthesized according to the general procedure and purified by flash chromatography (*n*-pentane/Et_2O = 4:1). Compound **3e** was obtained as a colorless oil (30%, 98% *ee*). The reaction did not proceed to completion even after 72 h. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta =$ 7.37–7.32 (m, 1H), 7.32–7.26 (m, 1H), 7.26–7.20 (m, 2H), 2.87 (d, $J =$ 14.1 Hz, 1H), 2.47 (d, $J = 14.1$ Hz, 1H), 2.36 (t, $J = 6.6$ Hz, 2H), 2.26–2.11 (m, 1H), 2.03–1.85 (m, 2H), 1.80–1.66 (m, 1H), 1.34 ppm (s, 3H); ^{13}C NMR (101.59 MHz, $CDCl_3$): $\delta = 210.8$, 149.8, 129.9, 126.5, 126.1, 123.9, 53.0, 43.0, 40.8, 37.9, 29.6, 22.1, 15.4 ppm; chiral HPLC analysis: Chiracel OJ-H column, *n*-heptane/*i*PrOH 99:1, 40 °C, detection at $\lambda =$ 210 nm, $t_R = 23.3$ (minor) and 24.7 min (major). Characterization matched with previously reported data.[5b,6b,10]

Compound (*S*)-3f: Synthesized according to the general procedure and purified by flash chromatography (*n*-pentane/Et_2O = 4:1). Compound **3f** was obtained as a colorless oil (98%, 99% *ee*). $[\alpha]_D^{20} = +65.4$ ($c = 1.93$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.35$ (d, $J = 2.5$ Hz, 1H), 7.19 (dd, $J = 2.5$, 8.6 Hz, 1H), 6.90 (d, $J = 8.6$ Hz, 1H), 2.83 (d, $J = 14.1$ Hz, 1H), 2.43 (d, $J = 14.1$ Hz, 1H), 2.33 (t, $J = 6.7$ Hz, 2H), 2.18–2.12 (m, 1H), 1.96–1.83 (m, 2H), 1.76–1.62 (m, 1H), 1.31 ppm (s, 3H); ^{13}C NMR (101.59 MHz, $CDCl_3$): $\delta = 210.9$, 153.1, 140.6, 127.5, 124.9, 122.3, 111.8, 56.0, 52.9, 42.2, 40.6, 37.8, 29.8, 21.9 ppm; HRMS (ESI+): *m*/*z* calcd: 275.08093 $[M+Na]^+$; found: 275.08096 $[M+Na]^+$; chiral HPLC: Chiracel OJ-H column, *n*-heptane/*i*PrOH 99:1, 40 °C, detection at $\lambda = 200$ nm, $t_R =$ 51.2 (minor) and 59.3 min (major).

Compound (*S*)-3g: Synthesized according to the general procedure and purified by flash chromatography (*n*-pentane/Et_2O = 4:1). Compound **3g** was obtained as a colorless oil (85%, 98% *ee*). $[\alpha]_D^{20} = +68.1$ ($c = 1.65$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.24$ (d, $J = 8.6$ Hz, 2H), 6.86 (d, $J = 8.6$ Hz, 2H), 3.79 (s, 3H), 2.85 (d, $J = 14.1$ Hz, 1H), 2.42 (d, $J =$ 14.2 Hz, 1H), 2.30 (t, $J = 6.7$ Hz, 2H), 2.21–2.10 (m, 1H), 1.94–1.82 (m, 2H), 1.71–1.60 (m,1H), 1.30 ppm (s, 2H); ^{13}C NMR (101.59 MHz, $CDCl_3$): $\delta = 211.7$, 157.7, 139.4, 126.7, 113.8, 55.2, 53.3, 42.3, 40.8, 38.1, 30.1, 22.0 ppm; HRMS (ESI+): *m*/*z* calcd: 241.11990 $[M+Na]^+$, found: 241.11961 $[M+Na]^+$; chiral HPLC: Chiracel OJ-H column, *n*-heptane/*i*PrOH 99:1, 40 °C, detection at $\lambda = 225$ nm, $t_R = 52.72$ (minor) and 57.04 min (major). Characterization matched with previously reported data.[5b,6b,10]

Compound (*S*)-3h: Synthesized according to the general procedure and purified by flash chromatography (*n*-pentane/Et_2O = 4:1). Compound **3h** was obtained as a colorless oil (98%, 96% *ee*). $[\alpha]_D^{20} = +73.5$ ($c = 0.80$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 6.82$ (s, 1H), 6.74 (brs, 2H), 5.93 (s, 2H), 2.81 (d, $J = 14.2$ Hz, 1H), 2.40 (d, $J = 14.2$ Hz, 1H), 2.30 (t, $J = 6.7$ Hz, 2H), 2.19–2.03 (m, 1H), 1.95–1.80 (m, 2H), 1.75–1.59 (m, 1H), 1.28 ppm (s, 3H); ^{13}C NMR (101.59 MHz, $CDCl_3$): $\delta = 211.3$, 147.9, 145.8, 141.5, 118.7, 108.0, 106.4, 101.0, 53.4, 42.8, 40.8, 38.2, 30.2, 22.0 ppm; HRMS (ESI+): *m*/*z* calcd: 255.09917 $[M+Na]^+$; found: 255.09913 $[M+Na]^+$; chiral HPLC: Chiracel OJ-H column, *n*-heptane/*i*PrOH 99:1, 40 °C, detection at $\lambda = 220$ nm, $t_R = 52.4$ (minor) and 62.1 min (major).

Compound (*S*)-3i: Synthesized according to the general procedure and purified by flash chromatography (*n*-pentane/Et_2O = 4:1). Compound **3i** was obtained as a colorless oil (88%, 99% *ee*). $[\alpha]_D^{20} = +68.2$ ($c = 1.57$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.36$–7.21 (m, 2H), 7.03–6.98 (m, 2H), 2.85 (d, $J = 14.1$ Hz, 1H), 2.44 (d, $J = 14.2$ Hz, 1H), 2.32 (t, $J =$ 6.7 Hz, 2H), 2.23–2.09 (m, 1H), 1.98–1.81 (m, 2H), 1.69 (m, 1H), 1.61 (m, 1H), 1.32 ppm (s, 3H); ^{13}C NMR: see ref. [7c]; HRMS (ESI+): *m*/*z* calcd: 229.10046 $[M+Na]^+$; found: 229.09966 $[M+Na]^+$; chiral GC (GTA column): $t_R = 30.5$ (minor) and 30.8 min (major). Characterization matched with previously reported data.[10]

Compound (*S*)-13a: Synthesized according to the general procedure and purified by flash chromatography (*n*-pentane/Et_2O = 9:1). Compound **13a** was obtained as colorless oil (93%, 93% *ee*). $[\alpha]_D^{20} = -10.8$ ($c = 1.19$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.36$–7.13 (m, 5H), 2.61 (d, $J =$ 17.6 Hz, 1H), 2.43 (d, $J = 17.5$ Hz, 1H), 2.39–2.16 (m, 2H), 2.33–2.26 (m, 2H), 1.34 ppm (s, 3H); ^{13}C NMR (101.59 MHz, $CDCl_3$): $\delta = 218.5$, 148.5, 128.6, 126.3, 125.4, 52.2, 43.8, 36.7, 35.8, 29.4 ppm; HRMS (ESI+): *m*/*z* calcd: 197.09423 $[M+Na]^+$; found: 197.09341 $[M+Na]^+$; chiral GC (GTA column): $t_R = 16.7$ (minor) and 17.2 min (major). Characterization matched with previously reported data.[6b,10]

Compound (*S*)-14a: Synthesized according to the general procedure and purified by flash chromatography (*n*-pentane/Et_2O = 4:1). Compound **14a** was obtained as a colorless oil (91%, 99% *ee*). $[\alpha]_D^{20} = +73.8$ ($c = 0.83$ in $CDCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.35$–7.26 (m, 4H), 7.22–7.18 (m, 1H), 2.93 (d, $J = 14.1$ Hz, 1H), 2.43 (d, $J = 14.1$ Hz, 1H), 2.31–2.28 (m, 2H), 2.21–2.1 (m, 1H), 2.02–1.95 (m, 1H), 1.88–1.72 (m, 2H), 1.69–1.53 (m, 2H), 0.6 ppm (t, $J = 7.4$ Hz, 3H); HRMS (ESI+): *m*/*z* calcd: 225.12553 $[M+Na]^+$; found: 225.12479 $[M+Na]^+$; chiral GC (GTA column): $t_R = 34.4$ (minor) and 34.8 min (major). Characterization matched with previously reported data.[6b,10]

Compound (*S*)-15a: Synthesized according to the general procedure and purified by flash chromatography (*n*-pentane/Et_2O = 4:1). Compound **15a** was obtained as a colorless oil (80%, 94% *ee*). $[\alpha]_D^{20} = +20.7$ ($c = 0.27$ in $CDCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.32$ (d, $J = 4.3$ Hz, 4H), 7.21–7.18 (m, 1H), 3.20 (d, $J = 14.4$ Hz, 1H), 2.71 (d, $J = 14.4$ Hz, 1H), 2.44–2.36 (m, 2H), 2.20–2.16 (m, 1H), 1.92–1.57 (m, 5H), 1.27 ppm (s, 3H); ^{13}C NMR (101.59 MHz, $CDCl_3$: $\delta = 213.8$, 147.9, 128.6, 126.0, 125.6, 55.7, 44.2, 43.5, 39.8, 31.9, 25.8, 23.9 ppm; HRMS (ESI+): *m*/*z* calcd: 225.12499 $[M+Na]^+$; found: 225.12484 $[M+Na]^+$; chiral GC (GTA column): $t_R = 34.8$ (minor) and 35.1 min (major). Characterization matched with previously reported data.[6b,10]

Compound (*S*)-16a: Synthesized according to the general procedure with boronic acid (3 equiv) and purified by flash chromatography (*n*-pentane/EtOAc = 7:2). Compound **16a** was obtained as a colorless oil (57%, 88% *ee*). $[\alpha]_D^{20} = +100.0$ ($c = 0.11$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.34$ (t, $J = 7.6$ Hz, 2H), 7.30–7.20 (m, 3H), 4.41–4.27 (m, 1H), 4.15–3.97 (m, 1H), 3.00 (dd, $J = 1.3$, 17.2 Hz, 1H), 2.57 (d, $J = 17.2$ Hz, 1H), 2.17–2.14 (m, 1H), 2.09–2.02 (m, 1H), 1.40 ppm (s, 3H); ^{13}C NMR (101.59 MHz, $CDCl_3$): $\delta = 170.9$, 145.6, 129.0, 126.9, 125.2, 66.8, 42.9, 37.3, 36.4, 29.8 ppm; HRMS (ESI+): *m*/*z* calcd: 213.0891 $[M+Na]^+$; found: 213.08838 $[M+Na]^+$; chiral HPLC: Chiralpak AS-H column, *n*-heptane/*i*PrOH 90:10, 40 °C, detection at $\lambda = 210$ nm, $t_R = 27.1$ (major) and 30.5 min (minor). Characterization matched previously reported data.[7b]

Compound (*S*)-17a: Synthesized according to the general procedure and purified by flash chromatography (*n*-pentane/EtOAc = 8:1). Compound **17a** was obtained as a colorless oil (28%, 69% *ee*). $[\alpha]_D^{20} = +78.6$ ($c = 0.35$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.42$–7.34 (m, 4H), 7.30–7.24 (m, 1H), 4.03 (ddd, $J = 3.5$, 6.9, 11.6 Hz, 1H), 3.67 (ddd, $J = 4.1$, 10.1, 11.7 Hz, 1H), 3.11 (dd, $J = 1.7$, 14.4 Hz, 1H), 2.69 (dd, $J = 1.0$, 14.4 Hz, 1H), 2.61–2.49 (m, 1H), 2.24 (dtd, $J = 1.8$, 3.8, 14.6 Hz, 1H), 1.57 ppm (s, 3H); ^{13}C NMR (101.59 MHz, $CDCl_3$): $\delta = 206.5$, 143.5, 128.6, 127.5, 125.8,

79.6, 61.4, 51.4, 41.4, 31.5 ppm; HRMS: *m/z* calc: 213.08915 $[M+Na]^+$; found: 213.08839 $[M+Na]^+$; chiral HPLC: Chiralpak AS-H column, *n*-heptane/*i*PrOH 90:10, 40 °C, detection at $\lambda = 210$ nm, $t_R = 9.7$ (major) and 10.8 min (minor).

Compound 18a: Synthesized according to the general procedure and purified by flash chromatography (*n*-pentane/Et_2O = 9:1). Compound **18a** was obtained as a colorless oil (14%, 8% *ee*). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.44$–6.83 (m, 10H), 2.85 (d, $J = 14.3$ Hz, 1H), 2.57 (d, $J = 14.3$ Hz, 1H), 2.43–2.35 (m, 1H), 2.10–1.94 (m, 2H), 1.97–1.81 (m, 1H), 1.71 (s, 3H), 1.46 ppm (s, 3H); ^{13}C NMR (101.59 MHz, $CDCl_3$): δ = 207.9, 146.1, 142.6, 128.5, 128.4, 128.3, 126.2, 126.1, 125.7, 56.2, 45.2, 40.7, 32.1, 30.6, 23.8 ppm; chiral HPLC: Chiracel AD-H column, *n*-heptane/*i*PrOH 99:1, 40 °C, detection at $\lambda = 210$ nm, $t_R = 9.8$ (minor) and 10.5 min (major). Characterization matched with previously reported data.[7a,c]

Compound 20a: Synthesized according to the general procedure and purified by flash chromatography (*n*-pentane/Et_2O = 9:1). Compound **20a** was obtained as a colorless oil (84%, 23% *ee*). $[\alpha]_D^{20} = +1$ ($c = 0.85$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.44$–7.36 (m, 2H), 7.35–7.30 (m, 2H), 7.25–7.18 (m, 1H), 3.52 (d, $J = 8.5$ Hz, 1H), 3.36 (d, $J = 8.5$ Hz, 1H), 2.92 (d, $J = 15.5$ Hz, 1H), 2.87 (d, $J = 15.5$ Hz, 1H), 1.92 (s, 3H), 1.44 (s, 3H), 1.15 ppm (s, 9H); ^{13}C NMR (101.59 MHz, $CDCl_3$): $\delta = 208.3$, 146.0, 128.15, 128.14, 126.3, 126.1, 72.7, 69.6, 51.6, 41.3, 31.8, 27.4, 23.5 ppm; chiral HPLC: Chiracel OJ-H column, *n*-heptane/*i*PrOH 99:1, 40 °C, detection at $\lambda = 210$ nm, $t_R = 12.6$ (minor) and 13.9 min (major).

Compound 21a: Synthesized according to the general procedure and purified by flash chromatography (*n*-pentane/Et_2O = 9:1). Compound **21a** was obtained as a colorless oil from (*E*)-**21** (81%, 25% *ee*) or from (*Z*)-**21** (78%, 36% *ee*). $[\alpha]_D^{20} = +2$ ($c = 0.51$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.51$–7.15 (m, 10H), 4.53 (s, 2H), 3.69 (d, $J = 8.9$ Hz, 1H), 3.61 (d, $J = 8.9$ Hz, 1H), 2.94 (q, $J = 15.5$ Hz, 2H), 1.93 (s, 3H), 1.52 ppm (s, 3H); ^{13}C NMR (101.59 MHz, $CDCl_3$): $\delta = 207.7$, 145.3, 138.4, 128.3, 128.2, 127.5, 127.4, 126.3, 126.1, 78.0, 73.2, 51.5, 41.7, 31.8, 23.5 ppm; HRMS (ESI+): *m/z* calcd: 305.1512 $[M+Na]^+$; found: 305.1511 $[M+Na]^+$; chiral HPLC: Chiralpak AD-H column, *n*-heptane/*i*PrOH 99:1, 40 °C, detection at $\lambda = 210$ nm, $t_R = 16.2$ (minor) and 16.8 min (major).

Compound 22a: Isolated from the reaction of **22** or **23**. Obtained as a mixture of diastereomers, which were subsequently converted to **22c** (see the Supporting Information) for determination of the *ee*. The diastereomeric ratio was determined by comparing the integrals of the methoxy signals in the ^{1}H NMR spectra [$\delta = 3.32$ (major) and 3.36 ppm (minor)]. Diastereomeric ratio (d.r.) obtained from **22** (trityl) was 1.9:1. d.r. obtained from **23** (TIPS) was 1.7:1. $[\alpha]_D^{20} = -26.5$ ($c = 2.2$ in $CHCl_3$) for the mixture of diastereomers that resulted from **22**; $[\alpha]_D^{20} = -12$ ($c = 0.85$ in $CHCl_3$,) for the mixture of diastereomers that resulted from **23**; ^{1}H NMR (400 MHz, $CDCl_3$, major diastereomer): $\delta = 7.42$–7.32 (m, 4H), 7.29–7.24 (m, 1H), 4.13–4.09 (m, 1H), 3.94 (d, $J = 8.2$ Hz, 1H), 3.32 (s, 3H), 2.53 (d, $J = 13.3$ Hz, 1H), 2.18 (d, $J = 13.3$ Hz, 1H), 1.62 (s, 3H), 1.52 ppm (s, 3H); ^{1}H NMR (400 MHz, $CDCl_3$, minor diastereomer): δ = 7.42–7.32 (m, 4H), 7.29–7.24 (m, 1H), 4.28 (d, $J = 8.6$ Hz, 1H), 4.01 (d, $J = 8.6$ Hz, 1H), 3.36 (s, 3H), 2.34 (d, $J = 3.8$ Hz, 2H), 1.64 (s, 3H), 1.48 ppm (s, 3H); ^{13}C NMR (101.59 MHz, $CDCl_3$, major diastereomer): $\delta = 147.3$, 128.5, 126.4, 125.7, 108.5, 78.5, 53.8, 48.7, 47.8, 29.8, 23.1 ppm; ^{13}C NMR (101.59 MHz, $CDCl_3$, minor diastereomer): $\delta = 149.8$, 128.5, 126.2, 126.1, 108.9, 79.9, 54.5, 48.7, 47.0, 27.8, 22.1 ppm; HRMS (ESI+): *m/z* calcd: 229.1199 $[M+Na]^+$; found: 227.1193 $[M+Na]^+$.

Compound 24a: Synthesized according to the general procedure and purified by flash chromatography (*n*-pentane/Et_2O = 9:1). Compound **24a** was obtained as a colorless oil (38%, 60% *ee*), In addition, **22a** (9%) was also isolated. $[\alpha]_D^{20} = +0.3$ ($c = 3.3$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.62$–7.50 (m, 4H), 7.47–7.19 (m, 11H), 3.76 (d, $J = 9.6$ Hz, 1H), 3.68 (d, $J = 9.6$ Hz, 1H), 3.08 (d, $J = 15.4$ Hz, 1H), 2.86 (d, $J = 15.4$ Hz, 1H), 1.92 (s, 3H),1.53 (s, 3H), 1.03 ppm (s, 9H); ^{13}C NMR (101.59 MHz, $CDCl_3$): $\delta = 207.78$, 144.85, 135.74, 135.70, 133.41, 133.36, 129.70, 129.66, 128.20, 127.68, 126.43, 126.30, 72.39, 51.05, 42.78, 31.94, 26.90, 22.34, 19.39 ppm; HRMS (ESI+): *m/z* calcd: 453.2220 $[M+Na]^+$; found: 453.2204 $[M+Na]^+$; chiral HPLC: Chiracel OJ-H column, *n*-heptane/*i*PrOH 95:5, 40 °C, detection at $\lambda = 210$ nm, $t_R = 9.3$ (major) and 11.5 min (minor).

Compound (*S*)-26a: Synthesized according to the general procedure and purified by flash chromatography (*n*-pentane/Et_2O = 9:1). Compound **26a** was obtained as an off-white solid (68%, 90% *ee*). $[\alpha]_D^{20} = -11.7$ ($c = 0.97$ in $CHCl_3$); m.p. 59–60 °C; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.19$ (dd, J = 8.7 Hz, 4H), 2.66 (d, $J = 17.6$ Hz, 1H), 2.51–2.38 (m, 3H), 2.36 (s, 3H), 2.35–2.25 (m, 2H), 1.40 ppm (s, 3H); ^{13}C NMR (101.59 MHz, $CDCl_3$): $\delta = 218.4$, 145.4, 135.7, 129.1, 125.3, 52.3, 43.4, 36.7, 35.8, 29.3, 20.8 ppm; HRMS (ESI+): *m/z* calcd: 211.10988 $[M+Na]^+$; found: 211.10922 $[M+Na]^+$; chiral GC (GTA column $t_R = 25.0$ (minor) and 25.8 min (major). Characterization matched previously reported data.[15d,16]

(*R*)-(−)-α-Cuparenone (27): Under nitrogen atmosphere at RT, a flame-dried Schlenk tube equipped with a magnetic stirrer bar, was charged with **26a** (250 mg, 1.33 mmol) in THF (6 mL) and MeI (0.897 mL, 14.4 mmol). Potassium *tert*-butoxide (543 mg, 4.84 mmol) in THF (3.0 mL) was added dropwise over 40 min. The mixture was stirred for an additional 2 h and progress was monitored by TLC. The reaction was quenched by the dropwise addition of an aqueous solution of HCl (1 M, 2 mL). The reaction was diluted with diethyl ether (5 mL). The aqueous layer was extracted with diethyl ether (5×2 mL) and the combined organic layers were washed with brine, dried over anhydrous $MgSO_4$, and concentrated in vacuo. The crude compound was purified by column chromatography (Et_2O/pentane 6:94) to give **27** (252 mg, 65%) as a colorless oil. $[\alpha]_D^{20} = -104.6$ ($c = 0.62$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 7.29$ (d, $J = 8.3$ Hz, 2H), 7.17 (d, $J = 8.2$ Hz, 2H), 2.72–2.64 (m, 1H), 2.53–2.45 (m, 1H), 2.36 (s, 3H), 1.95–1.90 (m, 1H), 1.27 (s, 3H), 1.19 (s, 3H), 0.63 ppm (s, 3H); ^{13}C NMR (101.59 MHz, $CDCl_3$): $\delta = 222.8$, 142.0, 135.9, 129.0, 126.5, 53.3, 48.4, 33.9, 29.7, 25.4, 22.2, 20.9, 18.5 ppm; HRMS (ESI+): *m/z* calcd: 239.14118 $[M+Na]^+$; found: 239.14123 $[M+Na]^+$. Characterization matched previously reported data.[16d,17]

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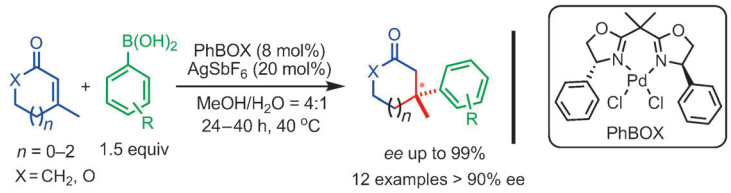

Jack of all trades: An efficient Pd catalyst for the formation of benzylic quaternary stereocenters by conjugate addition of arylboronic acids to a variety of β,β-disubstituted cyclic and acyclic enones is presented (see scheme). The catalyst provides product enantioselectivities up to 99%.

Stereochemistry

A. L. Gottumukkala, K. Matcha, M. Lutz, J. G. de Vries, A. J. Minnaard** ..... ▮▮▮▮–▮▮▮▮

Palladium-Catalyzed Asymmetric Quaternary Stereocenter Formation