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Evaluation of Palladacycles as a Non-Rhodium Based Alternative for the Asymmetric Conjugate 1,4-Addition of Arylboronic Acids to α,β-Unsaturated Enones

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Abstract: The asymmetric conjugate 1,4-addition of arylboronic acids to α,β-unsaturated carbonyl compounds is an extremely versatile and widely used organic transformation. While the rhodium(I)-catalysed reaction has been thoroughly explored, the asymmetric palladium-catalysed protocol is far less developed and understood, particularly with acyclic enones as substrates. Herein, we report the systematic evaluation of a series of metallacycles for this reaction and the conjugate addition of arylboronic acids to a wide range of α,β-unsaturated enones, catalysed by an easily accessible and robust chiral phosphapalladacycle in high yields and enantioselectivities.

Keywords: addition reactions; asymmetric synthesis; boronic acids; metallacycles; phosphapalladacycles

Introduction

Since the discovery of the Suzuki coupling in 1979,[1] the employment of boronic acids in organic synthesis has shown a prolific development in both synthetic utility and functional group tolerance.[2] The allure of boronic acids can be simultaneously attributed to their thermal stability, as well as their ability to resist oxidation in the absence of an inert environment.[3] These exceptional qualities allow boronic acids to be exploited as a convenient, commercially available, nucleophilic carbon source in the presence of a transition metal catalyst, without the need for forcing conditions. With these outstanding advantages, it is therefore not surprising that chemists have used boronic acids in organic synthesis as well as in the total synthesis of natural products.[2f,4] Since the introduction of the Hayashi–Miyaura reaction in 1998,[5] the asymmetric 1,4-conjugate addition of arylboronic acids to α,β-unsaturated carbonyl compounds has become a component in the synthetic repertoire of organic chemists. Such a protocol has the dual benefit of forming a chiral centre at the β-position, as well as leaving a carbon skeleton capable of further functional group transformation in lieu of the low pK_a of the α-proton[6] and the presence of the carbonyl functionality.[6] While the rhodium-catalysed asymmetric conjugate addition reaction on enones has been quite thoroughly developed,[7] the high cost of rhodium prohibits its implementation on a large scale.[8]

In light of the prohibitive cost of rhodium, we directed our attention towards the search for a more cost-efficient modus of asymmetric carbon-carbon bond formation *via* the Hayashi–Miyaura addition reaction. In spite of the obvious dominance of rhodium, other metals such as palladium[9] and platinum[9g,10] have also been used for the addition of boronic acids to enones. However, these protocols have drawbacks of lengthened reaction times (18 h,[9e] 23 h,[9a,d] 24 h,[9j] 40 h[9i] *vs.* 10 h), elevated temperatures (50 °C,[9e] 60 °C,[9b] 80 °C[9j] *vs.* room temperature), onerous additives [$Cu(BF_4)^2$,[9a] $SbCl_3$[9b] *vs.* PPh_3), high catalyst loading (10 mol%[9b] *vs.* 5 mol% of metal) or poor enantioselectivity (42%,[9j] 76%[9k] *vs.* 92%).[11] In other works, the asymmetric variant was not studied.[9a-d, f-i,10] A major challenge in the use of palladium is posed by the competitive β-hydride elimination in place of protonolysis, which leads to the formation of catalytically inactive palladium(0), thus imparing the catalytic potential of the system.[12] Recently, the palla-

dium-catalysed addition of boronic acids has been gaining momentum as evidenced by the addition of boronic acids to imines,[13] aldehydes[10,14] as well as the formation of all-carbon quaternary centres.[15] However, the addition of arylboronic acids onto acyclic enones *via* palladium-based catalysts is largely undeveloped, disregarding key structural elements such as the β,β-diaryl skeleton which is of utility in further transformations.

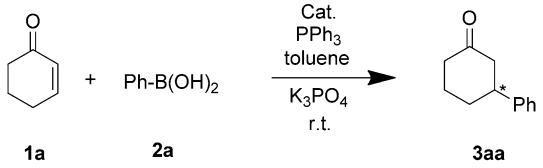
In view of the aforementioned factors and as part of our continuing interest in metallacycle-based catalysts for C–C,[16] C–N[17] and C–P[18] bond formations, we decided to explore the development of an efficient metallacycle-based protocol for this important reaction. A metallacycle can be loosely defined as an organometallic complex with at least one carbon-metal covalent bond, intramolecularly stabilised by a donor atom (N, P, As etc), forming a chelate.[19] The presence of this C–M bond reduces the propensity of the metal to undergo reduction, preferring to remain in a positive oxidation state. Metallacycles incorporating metals such as palladium and platinum have shown unprecedented reactivity in a myriad of addition and substitution reactions.[16–18,19b,20] As a complement to the convenient nature of boronic acids, metallacycles also possess a high degree of air/moisture stability as well as tolerance to elevated temperatures due to their structural rigour.[21] In addition, asymmetry in the reaction can be induced *via* chiral elements located on the organic backbone.[20c]

While the metal of choice has a profound impact on the efficacy of the catalytic system, the constitutional provisions of the ligand backbone to the reaction cannot be discounted.[22] Although a multitude of chiral ligands has been successfully employed in the Hayashi–Miyaura reaction, a void exists in the comparison of ligand structures and its impact on the reaction outcome.

Herein, a range of metallacycles was synthesised and their competence in the asymmetric conjugate addition of arylboronic acids to enones was systematically compared. Following which, the protocol was extended to include acyclic enones with high yields and enantioselectivities.

Results and Discussion

Using 2-cyclohexen-1-one **1a** and phenylboronic acid **2a** as representative substrates, a catalyst screening was carried out (Scheme 1, Table 1) using metallacycles (*S*)-**4** to (*S*)-**10** (Figure 1) to catalyse the above reaction. It was observed that a platinacycle with the chiral naphthylamine ligand backbone (*S*)-**4** was catalytically inactive, with starting materials being quantitatively recovered after 24 h (Table 1, entry 1). However, when the same ligand backbone was coordinated onto a palladium centre in (*S*)-**5**, the reaction proceeded, albeit with low yield and enantioselectivity (entry 2). The introduction of the phosphino moiety in place of the amino moiety on the naphthyl core in



Scheme 1. Preliminary screening of metallacycles.

Table 1. Catalyst screening for the asymmetric conjugate 1,4-addition of phenylboronic acid to 2-cyclohexenone.[a]

Entry	Catalyst	Time [h]	Yield [%][b]	*ee*[c]
1	(*S*)-**4**	24	not observed	–
2	(*S*)-**5**	24	39	9
3	(*S*)-**6**	10	89	92 (+)[d]
4	(*S*)-**7**	10	87	75
5	(*S*)-**8**	10	62	54
6	(*S*)-**9**	24	23	75
7	(*S*)-**10**	24	45	67
8	$Pd(OAc)_2$	24	not observed	–

[a] The reaction was carried out with 2-cyclohexen-1-one (0.1 mmol), phenylboronic acid (0.5 mmol), metallacycle/catalyst (5 mol% of metal), PPh_3 (5.0 mol%) and K_3PO_4 (0.05 mmol) in 1 mL of toluene at room temperature.
[b] Isolated percentage yield.
[c] The *ee* % was determined by chiral HPLC. (+/−) was determined by optical rotation and is shown in parentheses.
[d] Chiral centre has the *R* configuration.[5]

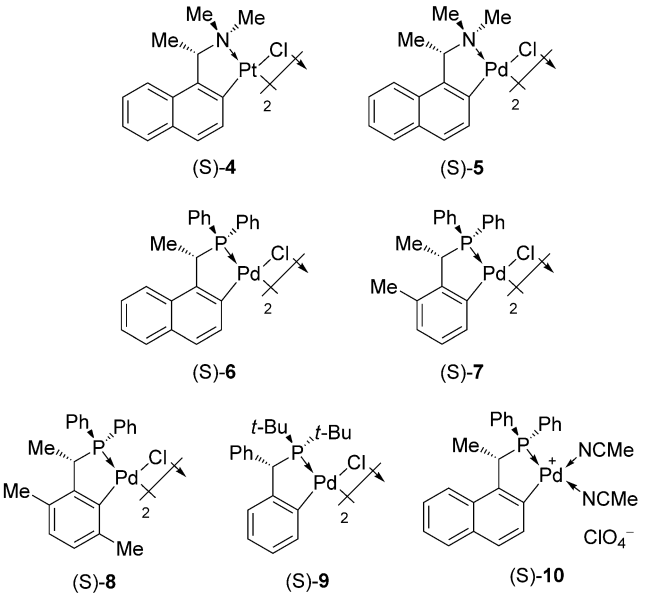
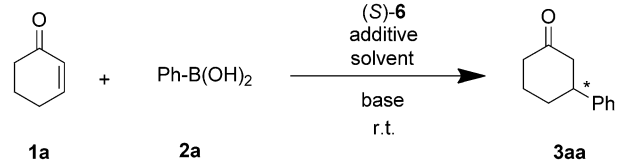


Figure 1. Evaluated metallacycles.

(*S*)-**6** drastically improved the reactivity of the palladium centre affording the addition product in 89% yield and 91% *ee* (entry 3). This is in line with current literature which suggests that a phosphine donor on the palladium is needed for the asymmetric conjugate addition of boronic acids to proceed and a similar trend has been observed by us with palladacycles in C–P bond formation scenarios.[18b,c,e,f] Taking into account this additional consideration, three more phosphapalladacycles, (*S*)-**7** to (*S*)-**9** were tested. The benzyl skeleton of (*S*)-**7** proved to be equally reactive to the detriment of enantioselectivity (entry 4). The latter can be attributed to the lack of conformational rigidity of the metallacycle which is usually imparted by a locking of the conformation *via* the steric interaction between the methyl moiety on the chiral centre and a protruding hydrogen on the naphthyl skeleton.[23] The introduction of a methyl group *ortho* to the palladium atom in (*S*)-**8** was intended to increase the steric bulk of the catalyst within the coordination sphere, thereby increasing enantioselectivity. However, when (*S*)-**8** was used as a catalyst, the yield of the reaction dropped to 61% (entry 5). While the previous phosphino moieties were diphenylphosphino groups, (*S*)-**9** used the sterically more demanding, electron-donating, di(*tert*-butyl)phosphino group. The yield of the reaction dropped to 23%, suggesting that this reaction is very sensitive to the steric environment of the catalyst (entry 6). As (*S*)-**6** proved to be the most effective catalyst, the dimeric compound was converted into the monomeric, cationic form with a perchlorate counterion, (*S*)-**10**. The monomeric form was found to be inefficient, yielding the desired addition adduct in low yields after 24 h (entry 7). In order to showcase the catalytic potential of the phosphapalladacycle (*S*)-**6**, palladium(II) acetate was utilised. The reaction yielded no observable product after 24 h under similar conditions (entry 8).

With the catalyst design optimised, further optimisation of the other reaction conditions was carried out (Scheme 2, Table 2). Firstly, a range of solvents was screened to determine the appropriate reaction medium (Table 2, entries 1–8). It appears that the reaction favours relatively non-polar, aprotic solvents with toluene (entry 1) yielding the best results. DMF, being an extremely polar aprotic solvent did not provide a suitable reaction environment for the addition to take place, with no product being formed (entry 6).



Scheme 2. Screening of reaction conditions.

Table 2. Condition screening for the phosphapalladacycle-catalysed asymmetric conjugate 1,4-addition of phenylboronic acid to 2-cyclohexenone.[a]

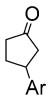
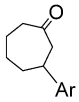
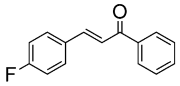
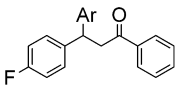
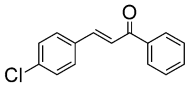
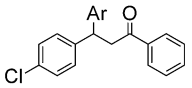
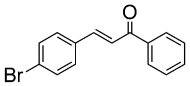
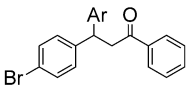
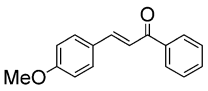
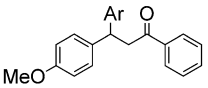
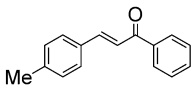
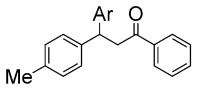
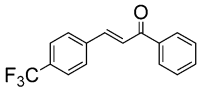
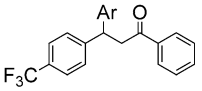
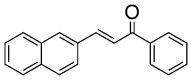
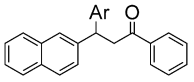
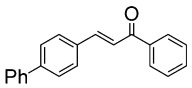
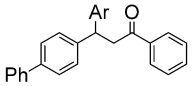
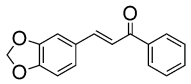
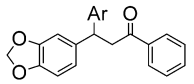
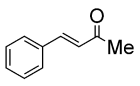
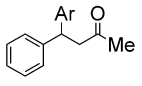
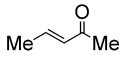
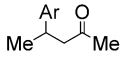
Entry	Solvent	Base	Additive	Yield[b]	*ee*[c]
1	toluene	K_3PO_4	PPh_3	89	92
2	*p*-xylene	K_3PO_4	PPh_3	79	79
3	dioxane	K_3PO_4	PPh_3	22	>99
4	DCM	K_3PO_4	PPh_3	79	85
5	1,2-DCE	K_3PO_4	PPh_3	82	85
6	DMF	K_3PO_4	PPh_3	–	–
7	MeCN	K_3PO_4	PPh_3	23	34
8	MeOH	K_3PO_4	PPh_3	38	53
9	toluene	–	PPh_3	11	63
10	toluene	Cs_2CO_3	PPh_3	21	79
11	toluene	Et_3N	PPh_3	23	76
12	toluene	KF	PPh_3	62	85
13	toluene	K_3PO_4	–	45	73
14	toluene	K_3PO_4	P(*o*-Tol)$_3$	20	73
15	toluene	K_3PO_4	DMPP[d]	–	–

[a] The reaction was carried out with 2-cyclohexen-1-one (0.1 mmol), phenylboronic acid (0.5 mmol), (*S*)-**6** (2.5 mol%), PPh_3 (5.0 mol%) and K_3PO_4 (0.05 mmol) in 1 mL of toluene at room temperature.
[b] Isolated percentage yield.
[c] The *ee* % was determined by chiral HPLC. (+/−) was determined by optical rotation and shown in parentheses.
[d] 3,4-Dimethyl-1-phenylphosphole.

Methanol was also used but the product was only formed in low yields and enantioselectivity (entry 8). While 1,4-dioxane yielded the product in extremely high enantioselectivity, the yield of the reaction was poor at 22% (entry 3). Following the solvent selection, we proceeded to analyse the impact of bases (entries 9–12). When the reaction was run in the absence of a base, the enantiomerically-enriched product was isolated in 11% yield (entry 9). A modification of the base to cesium carbonate or potassium fluoride did not enhance either the isolated yield or the enantioselectivity (entries 10 and 12) and the deployment of an organic base lowered the yield to 23% (entry 11), suggesting that it functioned more as a ligand instead of a base. Lastly, additives were screened. It was found that in the absence of an additional additive, the catalyst decomposed rapidly, with significant amounts of palladium(0) being deposited on the walls of the reaction vessel. This suggests that in the absence of an additional phosphine, the system tended to undergo β-hydride elimination more rapidly, reducing the catalyst and leading to low yields (entry 13). It was also found that a bulkier phosphine did not afford the product in a higher yield (entry 14) and the introduction of a planar phosphorus ligand in the form of DMPP did not yield any observable product (entry 15).

With reaction conditions optimised, the functional group tolerance of the protocol was tested and the re-

Table 3. Substrate screening for the asymmetric conjugate 1,4-addition of arylboronic acids on different a,ß-unsaturated ketones.[a]

Entry	Enone		Ar	Product		Yield[b]	*ee*[c]
1		(**1b**)	Ph (**2a**)		(**3ba**)	64	50 (–)[d]
2		(**1c**)	Ph (**2a**)		(**3ca**)	72	87 (+)[e]
3		(**1d**)	Ph (**2a**)		(**3da**)	88	81 (–)
4		(**1e**)	Ph (**2a**)		(**3ea**)	92	78 (+)[f]
5		(**1f**)	Ph (**2a**)		(**3fa**)	88	78 (+)
6		(**1g**)	Ph (**2a**)		(**3ga**)	95	81 (+)[f]
7		(**1h**)	Ph (**2a**)		(**3ha**)	97	81 (+)[f]
8		(**1i**)	Ph (**2a**)		(**3ia**)	92	69 (+)[f]
9		(**1j**)	Ph (**2a**)		(**3ja**)	88	85 (+)[f]
10		(**1k**)	Ph (**2a**)		(**3ka**)	85	79 (+)
11		(**1l**)	Ph (**2a**)		(**3la**)	95	81 (+)
12		(**1m**)	4-Me-C_6H_4 (**2b**)		(**3mb**)	63	87 (-)
13		(**1n**)	Ph (**2a**)		(**3na**)	56	93 (–)

[a] The reaction was carried out with enone (0.1 mmol), boronic acid (0.5 mmol), (*S*)-**6** (2.5 mol%), PPh_3 (5.0 mol%) and K_3PO_4 (0.05 mmol) in 1 mL of toluene at room temperature.
[b] Isolated percentage yield.
[c] The *ee*% was determined by chiral HPLC. (+/−) was determined by optical rotation and is shown in parentheses.
[d] Chiral centre has *S* configuration.[5]
[e] Chiral centre has *R* configuration.[5]
[f] Chiral centre has *S* configuration.[9e]

sults are shown in Table 3. It can be seen that the protocol is applicable to various cyclic enones with both five- and seven-membered rings showing promising results (Table 3, entries 1 and 2). The dimished yield and lowered enantioselectivity of the five-membered enone can be attributed to the extreme reactivity of the molecule and the planarity of the molecule respectively.[24] Following the conjugate addition of the aryl group onto cyclic enones, the substrate scope was further expanded to include acyclic enones. The asymmetric addition onto acyclic enones poses an additional problem as the transition state of the reaction can exist in both the *s-cis* and *s-trans* forms,[24] thereby lowering the enantioselectivity. However, the addition of arylboronic acids onto a wide variety of substrates proved to be successful, with the catalytic system tolerating a wide range of functional groups. Introduction of highly electron-withdrawing groups such as trifluoromethyl (entry 8) on the phenyl ring do not seem to have much of an impact on the reactivity of the reaction as evidenced from the high yields. A similar trend was observed with electron-donating substituents such as the methyl and methoxy moieties (entries 7 and 6, respectively) which should have hindered the reaction progress.

Interestingly, the reaction also proceeded smoothly with halogens (entries 3–5), yielding the addition adducts in high yields and enantioselectivities. This result was particularly surprising, especially for the bromo-substituted enone, where the coupling product was not observed. This suggests that palladium(0) was not being produced *via* the β-hydride elimination pathway, showing that the system remains catalytically active through the reaction duration. It is noteworthy that this system can be extended to aliphatic, acyclic enones, albeit with a slightly diminished yield (entries 12 and 13).

Having screened a range of enones, a selection of boronic acids was reacted with *trans*-chalcone in order to investigate the efficacy of the catalytic protocol and the results are compiled in Table 4. Electron-rich boronic acids show excellent reactivity yielding the desired product in high yields (entries 5 and 6). Naphthalen-2-ylboronic acid also shows a high degree of reactivity, giving the addition adduct in almost quantitative yield (entry 1). When 4-bromobenzeneboronic acid was reacted with *trans*-chalcone, the 1,4-product was obtained in 88% yield, with no homocoupling product observed (entry 4). Also, electron-deficient boronic acids such as 4-trifluoromethylbenzeneboronic acid are able to furnish the product, but in lower yields and poorer enantioselectivities. It is noteworthy that the same product produced by altering the substrates show opposite enantioselectivities, providing a variety of synthetic routes to the same product (Table 3 entry 6 *vs.* Table 4 entry 6; Table 3 entry 3 *vs.* Table 4 entry 2, etc.).

Proposed Reaction Mechanism

The proposed mechanism of the reaction is shown in Figure 2 and is analogous to the Rh(I) catalytic cycle based on mechanistic studies done by Hayashi et al. in 2002[25] with modifications made based on DFT studies done by Houk et al.[26] and Wu et al.[27] The cycle starts with a hydroxo-palladium species (**11**). Transmetallation occurs between **11** and phenylboronic acid, forming a phenyl-palladium bond. Upon coordination of the enone onto the palladium centre, the metal-bound phenyl group inserts into the carbon-carbon double bond of the enone, forming **13**. While Hayashi found evidence for the existence of a oxa-π-allylrhodium species,[25] other researchers determined that there was a preference for palladium complexes to form in a C-bound fashion (**13a**) instead of an O-bound manner (**13c**), although it is believed all three exist in equilibrium.[28] However, the earlier mentioned DFT studies[26,27] have shown that while the alkene insertion reaction generates the C-bound eno-

Table 4. Substrate screening for the asymmetric conjugate 1,4-addition of various arylboronic acids on *trans*-chalcone.[a]

Entry	Enone	Ar	Product	Yield[b]	*ee*[c]
1	(**1o**)	2-naphthyl (**2c**)	(**3oc**)	97	77 (−)[d]
2	(**1o**)	4-F-C_6H_4 (**2d**)	(**3od**)	92	79 (+)
3	(**1o**)	4-Cl-C_6H_4 (**2e**)	(**3oe**)	56	82 (−)[d]
4	(**1o**)	4-Br-C_6H_4 (**2f**)	(**3of**)	88	56 (−)
5	(**1o**)	4-Me-C_6H_4 (**2b**)	(**3ob**)	89	69 (−)[d]
6	(**1o**)	4-MeO-C_6H_4 (**2g**)	(**3og**)	83	85 (−)[d]
7	(**1o**)	4-CF_3-C_6H_4 (**2h**)	(**3oh**)	47	80 (−)[d]

[a] The reaction was carried out with 2-cyclohexen-1-one (0.1 mmol), phenylboronic acid (0.5 mmol), (*S*)-**6** (2.5 mol%), PPh_3 (5.0 mol%) and K_3PO_4 (0.05 mmol) in 1 mL of toluene at room temperature.
[b] Isolated percentage yield.
[c] The *ee* % was determined by chiral HPLC. (+/−) was determined by optical rotation and is shown in parentheses.
[d] Chiral centre has *R* configuration.[9e]

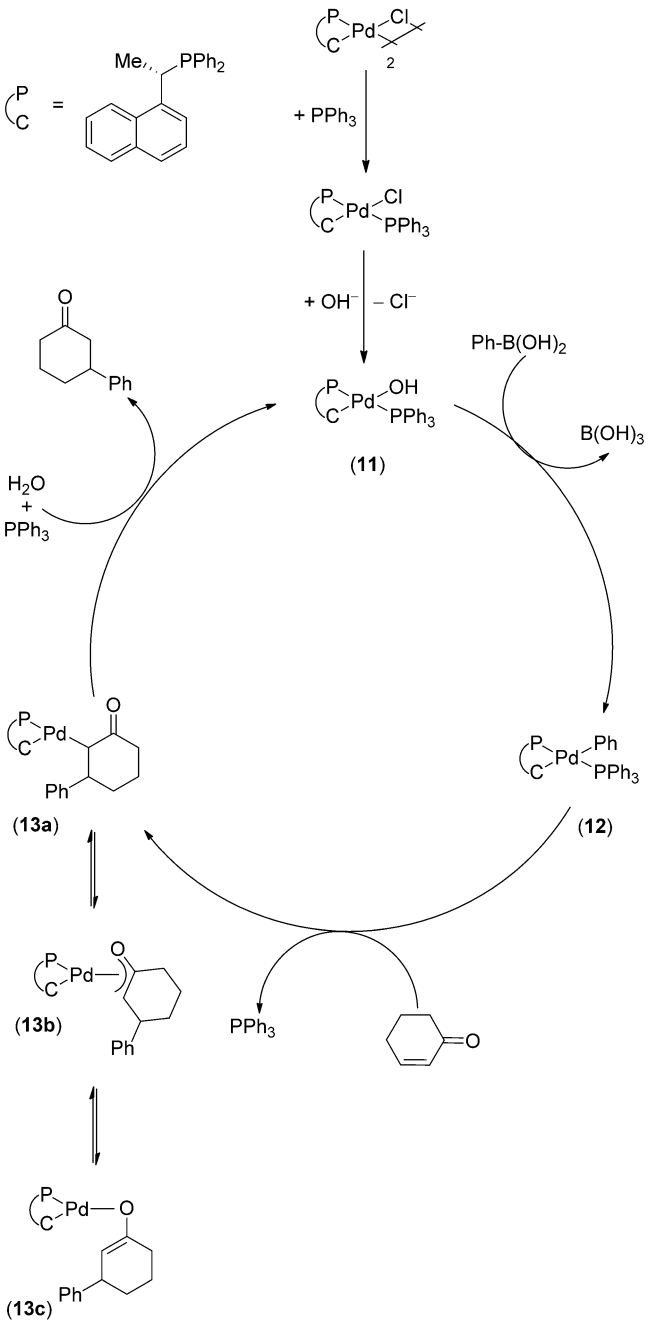


Figure 2. Proposed catalytic cycle.

late (**13a**), the rate-determining transition state for protonolysis to occur is the O-bound enolate. Evidently, the stability of the O-bound enolate is essential for promoting protonolysis, yielding the addition product and surpressing β-hydride elimination, giving the substitution product. Furthermore, it is plausible that the addition of triphenylphosphine in the system limited the availability of a vacant site, hindering the β-hydride elimination which would have generated a Heck-type product. Following the alkene insertion, protonolysis of the palladium-enolate bond yielded the addition product, regenerating catalytically active **11**.[29] It has been mentioned by Wu and co-workers that the ligand has a profound, but yet only partially understood impact on the reactivity of the catalyst, potentially explaining the vast difference in results between the different metallacycles previously screened.

Conclusions

Herein, we have reported a phosphapalladacycle-catalysed asymmetric conjugate 1,4-addition onto enones, utilising boronic acids as an aryl source. This protocol has the advantages of tolerating a wide range of functional groups, both on the enone and on the boronic acid, yielding the addition products in high yields and enantioselectivities. Furthermore, the reaction takes place at room temperature without the need for onerous additives within a short amount of time. In addition, key structural features of the catalyst that aid in reaction progress were identified. We believe that this protocol will be a useful addition in the field that has so far been dominated by rhodium-based catalysts. Research is currently being undertaken in our group to extend this protocol to a wider range of α,β-unsaturated compounds.

Experimental Section

All reactions with air- or moisture-sensitive manipulations were carried out under positive pressure of nitrogen using standard Schlenk techniques. All solvents were used as received and where necessary, dried and distilled according to literature methods.[30] Column chromatography was performed on Silica Gel 60 (Merck). NMR spectra were recorded on Bruker AV300 spectrometer (300 MHz for ^{1}H, 75 MHz for ^{13}C, 282 MHz for ^{19}F). Chemical shifts are reported in δ (ppm), referenced to an internal standard of $SiMe_4$ ($\delta = 0.00$ ppm) for ^{1}H NMR and chloroform-*d* ($\delta =$ 77.00 ppm) for ^{13}C NMR. Multiplicities are given as: s (singlet), brs (broad singlet), d (doublet), dd (doublet of doublets), t (triplet), q (quartet), m (multiplet). The number of protons (n) for a given resonance are given by n H and coupling constants are given as a *J* value in Hz. Optical rotations were measured on the specific solution on a 0.1 dm cell at 23 °C with a Jusco P-1030 polarimeter equipped with a sodium vapour lamp at 589 nm. Enantiomeric excesses (*ee*s) were determined by chiral HPLC using an Agilent 1200 Series instrument or Shimatsu LC-20AD instrument using Diacel Chiracel columns. HR-MS (ESI) were recorded on a time-of-flight (TOF) machine. Commercially unavailable enones[31] and chiral palladacycles[18f,32] were prepared according to literature methods. Other chemicals were used as received from the supplier without any further purification.

Caution! Perchlorate salts of metal complexes are potentially explosive compounds and should be handled with care.

Typical Procedure for Phosphapalladacycle-Catalysed Asymmetric Conjugate 1,4-Addition of Arylboronic Acids on α,β-Unsaturated Ketones

To a reaction vessel was added enone (0.1 mmol), boronic acid (0.5 mmol), K_3PO_4 (10.6 mg, 0.05 mmol), (*S*)-**6** (2.4 mg, 0.0025 mmol) and PPh_3 (1.3 mg, 0.0050 mmol) and dissolved in toluene (1 mL). The reaction was stirred and monitored by TLC. Upon reaction completion, the crude reaction mixture was chromatographed over silica (hexanes/EtOAc), yielding the analytically pure product.

(+)-3-Phenylcyclohexanone (3aa): yield: 89%; colourless oil; 92% *ee*; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.82–1.93 (m, 2H), 2.11–2.18 (m, 2H), 2.32–2.64 (m, 4H), 2.96–3.05 (m, 1H), 7.21–7.36 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.5, 32.8, 41.2, 44.7, 48.9, 126.6 (2C), 126.7, 128.7 (2C), 144.3, 211.0: HPLC (Diacel Chiralcel AD-H, *n*-hexane:2-propanol = 98:2, 1.0 mL min^{-1}, 270 nm): retention time = 10.2 (minor), 12.0 (major); HR-MS (ESI): *m/z* = 175.1110, calcd. for $C_{12}H_{15}O$ (M^++H): 175.1123.

(−)-3-Phenylcyclopentanone (3ba): yield: 64%; colourless oil; 50% *ee*; ^{1}H NMR (300 MHz, $CDCl_3$): = 1.96–2.07 (m, 1H), 2.24–2.51 (m, 4H), 2.63–2.71 (m, 1H), 3.37–3.49 (m, 1H), 7.22–7.37 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 31.2, 38.8, 42.2, 45.8, 126.70 (2C), 126.71, 128.6 (2C), 143.0, 218.3; HPLC (Diacel Chiralcel OB-H, *n*-hexane:2-propanol = 98:2, 0.8 mL min^{-1}, 230 nm): retention time = 55.3 (major), 64.6 (minor); HR-MS (ESI): *m/z* = 161.0973, calcd. for $C_{11}H_{13}O$ (M^++H): 161.0966.

(+)-3-Phenylcycloheptanone (3ca): yield: 72%; colourless oil; 87% *ee*; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.44–1.51 (m, 1H), 1.64–1.81 (m, 2H), 1.95–2.11 (m, 3H), 2.57–2.67 (m, 3H), 2.85–2.98 (m, 2H), 7.16–7.33 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.2, 29.2, 39.2, 42.7, 43.9, 51.2, 126.3, 126.4 (2C), 128.6 (2C), 146.9, 213.4; HPLC (Diacel Chiralcel AD-H, *n*-hexane:2-propanol = 98:2, 0.5 mL min^{-1}, 254 nm): retention time = 19.1 (minor), 21.5 (major); HR-MS (ESI): *m/z* = 189.1273, calcd. for $C_{17}H_{17}O$ (M^++H): 189.1279.

(−)-3-(4-Fluorophenyl)-1,3-diphenylpropan-1-one (3da): yield: 88%; white solid; 81% *ee*; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.71 (d, $^3J_{H,H}$ = 7.2 Hz, 2H), 4.81 (t, $^3J_{H,H}$ = 7.2 Hz, 1H), 6.90–6.98 (m, 2H), 7.15–7.30 (m, 7H), 7.40–7.57 (m, 3H), 7.91 (d, $^3J_{H,H}$ = 1.5, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 44.8, 45.2, 115.3 (d, $^2J_{C,F}$ = 21.0 Hz, 2C), 126.5, 127.7 (2C), 128.0 (2C), 128.6 (3C), 129.27 (d, $^3J_{C,F}$ = 8.3 Hz, 2C), 133.1 (2C), 137.0, 139.3 (d, $^4J_{C,F}$ = 3.8 Hz), 161.4 (d, $^1J_{C,F}$ = 243.0 Hz), 197.8; ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$): δ = −116.8; HPLC (Diacel Chiralcel AD-H, *n*-hexane:2-propanol = 98:2, 0.5 mL min^{-1}, 280 nm, retention time: 38.9 min (minor), 42.1 min (major); HR-MS (ESI): *m/z* = 305.1335, calcd. for $C_{21}H_{18}FO$ (M^++H): 305.1342.

(+)-3-(4-Chlorophenyl)-1,3-diphenylpropan-1-one (3ea): yield: 92%; white solid; 78% *ee*; H NMR (300 MHz, $CDCl_3$): δ = 3.70 (dd, $^3J_{H,H}$ = 7.3 Hz, $^3J_{H,H}$ = 0.9, 2H), 4.78 (t, $^3J_{H,H}$ = 7.3 Hz, 1H), 7.16–7.30 (m, 9H), 7.41–7.46 (m, 2H), 7.52–7.58 (m, 1H), 7.91–7.94 (m, 2H); ^{13} C NMR (75 MHz, CDCl3): δ = 44.6, 45.3, 126.6, 127.7 (2C), 128.0 (2C), 128.6–128.7 (6C), 129.2 (2C), 132.1, 133.2, 136.9, 142.6, 143.7, 197.7; HPLC (Diacel Chiralcel AD-H, *n*-hexane:2-propanol = 98:2, 0.5 mL min^{-1}, 280 nm): retention time = 40.2 min (minor), 49.2 min (major); HR-MS (ESI): *m/z* = 321.1060, calcd. for $C_{21}H_{18}ClO$ (M^++H): 321.1046.

(+)-3-(4-Bromophenyl)-1,3-diphenylpropan-1-one (3fa): yield: 88%; white solid; 78% *ee*; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.71 (dd, $^3J_{H,H}$ = 7.2 Hz, $^3J_{H,H}$ = 0.9, 2H), 4.79 (t, $^3J_{H,H}$ = 7.2 Hz, 1H), 7.12–7.58 (m, 13H), 7.90–7.91 (m, 2H); ^{13} C NMR (75 MHz, $CDCl_3$): δ = 44.5, 45.3, 120.2, 126.6, 127.7 (2C), 128.0 (2C), 128.6 (2C), 128.7 (2C), 129.6 (2C), 131.6 (2C), 133.2, 136.9, 143.1, 143.6, 197.6; HPLC (Diacel Chiralcel AD-H, *n*-hexane:2-propanol = 98:2, 0.5 mL min^{-1}, 240 nm): retention time = 43.1 min (minor), 53.5 min (major); HR-MS (ESI): *m/z* = 365.0554, calcd. for $C_{21}H_{18}BrO$ (M^++H): 365.0541.

(+)-3-(4-Methoxyphenyl)-1,3-diphenylpropan-1-one (3ga): yield: 95%; white solid; 81% *ee*; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.71 (d, $^3J_{H,H}$ = 7.4 Hz, 2H), 3.87 (s, 3H), 4.79 (t, $^3J_{H,H}$ = 7.5 Hz, 1H), 6.80–6.83 (m, 2H), 7.14–7.20 (m, 3H), 7.27–7.31 (m, 4H), 7.41–7.47 (m, 2H), 7.50–7.60 (m, 1H), 7.92–7.95 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 44.9, 45.2, 55.2, 113.9 (2C), 126.3, 127.3 (2C), 128.1 (2C), 128.5 (2C), 128.6 (2C), 128.8 (2C), 133.0, 136.3, 137.1, 144.5, 158.1, 198.2; HPLC (Diacel Chiralcel AD-H, *n*-hexane:2-propanol = 98:2, 0.5 mL min^{-1},270 nm): retention time = 66.4 min (minor), 71.0 min (major); HR-MS (ESI): *m/z* = 317.1540, calcd. for $C_{22}H_{21}O_2$ (M^++H): 317.1542.

(+)-1,3-Diphenyl-3-(*para*-tolyl)propan-1-one (3ha): yield: 97%; white solid; 81% ee; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.30 (s, 3H), 3.74 (d, $^3J_{H,H}$ = 7.2 Hz, 2H), 4.82 (t, $^3J_{H,H}$ = 7.2 Hz, 1H), 7.08–7.11 (m, 2H), 7.15–7.22 (m, 3H), 7.25–7.63 (m, 8H), 7.94–7.96 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 20.9, 44.8, 45.6, 126.3, 127.7 (2C), 127.8 (2C), 128.0 (2C), 128.5 (2C), 129.3 (2C), 133.0, 135.9, 137.1, 141.1, 144.4, 198.1; HPLC (Diacel Chiralcel AD-H, *n*-hexane:2-propanol = 98:2, 0.5 mL min^{-1}, 270 nm): retention time = 32.0 min (minor), 39.3 min (major); HR-MS (ESI): *m/z* = 301.1587, calcd. for $C_{22}H_{21}O$ (M^++H): 301.1592.

(+)-1,3-Diphenyl-3-[4-(trifluoromethyl)phenyl]propan-1-one (3ia): yield: 92%; white solid; 69% *ee*; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.75 (dd, $^3J_{H,H}$ = 7.3 Hz, $^3J_{H,H}$ = 2.1 Hz, 2H), 4.89 (t, $^3J_{H,H}$ = 7.2 Hz, 1H), 7.17–7.58 (m, 12H), 7.92–7.95 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 44.4, 45.7, 124.2 (q, $^1J_{C,F}$ = 270.0 Hz), 125.5 (q, $^3J_{C,F}$ = 3.8 Hz, 2C), 126.8, 127.8 (2C), 128.0 (2C), 128.2 (2C), 128.66 (q, $^2J_{C,F}$ = 31.5 Hz), 128.67 (2C), 128.8 (2C), 133.3, 136.8, 143.3, 148.2, 197.4; ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$): δ = −62.4; HPLC (Diacel Chiralcel AD-H, *n*-hexane:2-propanol = 98:2, 0.5 mL min^{-1}, 240 nm): retention time = 30.3 min (minor), 34.4 min (major); HR-MS (ESI): *m/z* = 355.1318, calcd. for $C_{22}H_{18}F_3O$ (M^++H): 355.1310.

(+)-3-(Naphthalen-2-yl)-1,3-diphenylpropan-1-one (3ja): yield: 88%; yellow solid; 85% *ee*; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.86 (dd, $^3J_{H,H}$ = 7.5 Hz, $^3J_{H,H}$ = 2.7 Hz, 2H), 5.02 (t, $^3J_{H,H}$ = 7.2 Hz, 1H), 7.17–7.58 (m, 11H), 7.74–7.79 (m, 4H), 7.93–7.96 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 44.6, 46.0, 125.5, 125.8, 126.0, 126.4, 126.7, 127.6, 127.8, 128.0 (2C), 128.1 (2C), 128.3, 128.58 (2C), 128.59 (2C), 132.2, 133.1, 133.5, 137.1, 141.5, 144.0, 198.0; HPLC (Diacel Chiralcel AD-H, *n*-hexane:2-propanol = 98:2, 0.5 mL min^{-1}, 270 nm): retention time = 58.7 min (minor), 62.8 min (major); HR-MS (ESI): *m/z* = 337.1583, calcd. for $C_{25}H_{21}O$ (M^++H): 337.1592.

(+)-3-([1,1′-Biphenyl]-4-yl)-1,3-diphenylpropan-1-one (3ka): yield: 85%; yellow solid; 79% *ee*; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.77 (dd, $^3J_{H,H}$ = 7.4 Hz, $^3J_{H,H}$ = 0.9 Hz, 2H), 4.87 (t, $^3J_{H,H}$ = = 7.5 Hz, 1H), 7.16–7.57 (m, 17H), 7.93–7.96 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 44.7, 45.6, 126.4, 127.0 (2C), 127.1, 127.3 (2C), 127.8 (2C), 128.1 (2C), 128.2 (2C), 128.6 (3C), 128.7 (2C), 133.1, 137.0, 139.3, 140.8, 143.2, 144.1, 197.9; HPLC (Diacel Chiralcel AD-H, *n*-hexane:2-propanol = 98:2, 0.5 mL min^{-1}, 230 nm): retention time = 57.3 min (minor), 68.6 min (major); HR-MS (ESI): *m/z* = 363.1785, calcd. for $C_{27}H_{23}O$ (M^++H): 363.1749.

(+)-3-(Benzo[*d*][1,3]dioxol-5-yl)-1,3-diphenylpropan-1-one (3la): yield: 95%; yellow oil; 81% *ee*; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.77 (d, $^3J_{H,H}$ = 7.2 Hz, 2H), 4.74 (t, $^3J_{H,H}$ = 6.9 Hz, 1H), 5.87 (s, 2H), 6.68–6.75 (m, 3H), 7.15–7.19 (m, 1H), 7.23–7.29 (m, 4H), 7.41–7.45 (m, 2H), 7.51–7.57 (m, 1H), 7.91–7.94 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 44.8, 45.6, 100.9, 108.2, 108.4, 120.7, 127.4, 127.6 (2C), 128.0 (2C), 128.56 (2C), 128.58 (2C), 133.1, 138.1, 133.2, 146.0, 147.7, 198.0; HPLC (Diacel Chiralcel AD-H, *n*-hexane:2-propanol = 98:2, 0.5 mL min^{-1}, 230 nm): retention time = 77.7 min (minor), 83.8 min (major); HR-MS (ESI): *m/z* = 311.1337, calcd. for $C_{22}H_{19}O_3$ (M^++H): 331.1334.

(−)-4-Phenyl-4-(*para*-tolyl)butan-2-one (3mb): yield: 63%; colourless oil; 87% ; ^{1}H NMR (300 MHz, $CDCl_3$): *d* = 2.07 (s, 3H), 2.28 (s, 3H), 3.16 (d, $^3J_{H,H}$ = 7.5 Hz, 2H), 4.54 (t, $^3J_{H,H}$ = 7.5 Hz, 1H), 7.06–7.29 (m, 9H); ^{13}C NMR (75 MHz, $CDCl_3$): *d* = 20.9, 30.6, 45.7, 49.8, 126.4, 127.5 (2C), 127.6 (2C), 128.6 (2C), 129.3 (2C), 136.0, 140.8, 144.1, 207.0; HPLC (Diacel Chiralcel AD-H, *n*-hexane:2-propanol = 98:2, 0.5 mL min^{-1}, 270 nm): retention time = 16.2 min (major), 18.0 min (minor); HR-MS (ESI): *m/z* = 239.1442; calcd. for $C_{17}H_{19}O$ (M^++H): 239.1436.

(−)-4-Phenylpentan-2-one (3na): yield: 66%; yellow oil; 93% *ee*; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27 (d, $^3J_{H,H}$ = 7.2 Hz, 3H), 2.06 (s, 3H), 2.71 (m, 2H), 3.30 (m, 1H), 7.16–7.32 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.0, 30.5, 35.5, 126.3, 127.8 (2C), 128.5 (2C), 146.2, 207.8; HPLC (Diacel Chiralcel AS-H, *n*-hexane:2-propanol = 98:2, 0.5 mL min^{-1}, 200 nm): retention time = 13.3 min (minor), 14.5 min (major); HR-MS (ESI): *m/z* = 163.1121, calcd. for $C_{11}H_{15}O$ (M^++H): 163.1123.

(−)-3-(Naphthalen-2-yl)-1,3-diphenylpropan-1-one (3oc): yield: 97%; yellow solid; 77% *ee*; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.86 (dd, $^3J_{H,H}$ = 7.5 Hz, $^3J_{H,H}$ = 2.7 Hz, 2H), 5.02 (t, $^3J_{H,H}$ = 7.2 Hz, 1H), 7.17–7.58 (m, 11H), 7.74–7.79 (m, 4H), 7.93–7.96 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 44.6, 46.0, 125.5, 125.8, 126.0, 126.4, 126.7, 127.6, 127.8, 128.0 (2C), 128.1 (2C), 128.3, 128.58 (2C), 128.59 (2C), 132.2, 133.1, 133.5, 137.1, 141.5, 144.0, 198.0; HPLC (Diacel Chiralcel AD-H, *n*-hexane:2-propanol = 98:2, 0.5 mL min^{-1}, 210 nm): retention time = 58.8 min (major), 63.0 min (minor); HR-MS (ESI): *m/z* = 337.1586, calcd. for $C_{25}H_{21}O$ (M^++H): 337.1592.

(+)-3-(4-Fluorophenyl)-1,3-diphenylpropan-1-one (3od): yield: 92%; white solid; 79% *ee*; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.71 (d, $^3J_{H,H}$ = 7.2 Hz, 2H), 4.81 (t, $^3J_{H,H}$ = 7.2 Hz, 1H), 6.90–6.98 (m, 2H), 7.15–7.30 (m, 7H), 7.40–7.57 (m, 3H), 7.91 (d, $^3J_{H,H}$ = 1.5, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): *d* = 44.8, 45.2, 115.3 (d, $^2J_{C,F}$ = 21.0 Hz, 2C), 126.5, 127.7 (2C), 128.0 (2C), 128.6 (3C), 129.27 (d, $^3J_{C,F}$ = 8.3 Hz, 2C), 133.1 (2C), 137.0, 139.3 (d, $^4J_{C,F}$ = 3.8 Hz), 161.4 (d, $J_{C,F}$ = 243.0 Hz), 197.8; ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$): δ = −116.8; HPLC (Diacel Chiralcel AD-H, *n*-hexane:2-propanol = 98:2, 0.5 mL min^{-1}, 280 nm): retention time = 38.3 min (major), 40.5 min (minor): HR-MS (ESI): *m/z* = 305.1345, calcd. for $C_{21}H_{18}FO$ (M^++H): 305.1342.

(−)-3-(4-Chlorophenyl)-1,3-diphenylpropan-1-one (3oe): yield: 56%; white solid; 82% *ee*; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.70 (dd, $^3J_{H,H}$ = 7.3 Hz, $^3J_{H,H}$ = 0.9, 2H), 4.78 (t, $^3J_{H,H}$ = 7.3 Hz, 1H), 7.16–7.30 (m, 9H), 7.41–7.46 (m, 2H), 7.52–7.58 (m, 1H), 7.91–7.94 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 44.6, 45.3, 126.6, 127.7 (2C), 128.0 (2C), 128.6–128.7 (6C), 129.2 (2C), 132.1, 133.2, 136.9, 142.6, 143.7, 197.7; HPLC (Diacel Chiralcel AD-H, *n*-hexane:2-propanol = 98:2, 0.5 mL min^{-1}, 280 nm): retention time = 37.7 min (major), 45.4 min (minor); HR-MS (ESI): *m/z* = 321.1032, calcd. for $C_{21}H_{18}ClO$ (M^++H): 321.1046.

(−)-3-(4-Bromophenyl)-1,3-diphenylpropan-1-one (3of): yield: 88%; white solid; 56% *ee*; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.71 (dd, $^3J_{H,H}$ = 7.2 Hz, $^3J_{H,H}$ = 0.9, 2H), 4.79 (t, $^3J_{H,H}$ = = 7.2 Hz, 1H), 7.12–7.58 (m, 13H), 7.90–7.91 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 44.5, 45.3, 120.2, 126.6, 127.7 (2C), 128.0 (2C), 128.6 (2C), 128.7 (2C), 129.6 (2C), 131.6 (2C), 133.2, 136.9, 143.1, 143.6, 197.6; HPLC (Diacel Chiralcel AD-H, *n*-hexane:2-propanol = 98:2, 0.5 mL min^{-1}, 254 nm): retention time = 41.6 min (major), 51.6 min (minor); HR-MS (ESI): *m/z* = calcd. for $C_{21}H_{18}BrO$ (M^++H): 365.0541.

(−)-1,3-Diphenyl-3-(*para*-tolyl)propan-1-one (3ob): yield: 89%; white solid; 69% *ee*; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.30 (s, 3H), 3.74 (d, $^3J_{H,H}$ = 7.2 Hz, 2H), 4.82 (t, $^3J_{H,H}$ = 7.2 Hz, 1H), 7.08–7.11 (m, 2H), 7.15–7.22 (m, 3H), 7.25–7.63 (m, 8H), 7.94–7.96 (m, 2H); ^{13} C NMR (75 MHz, $CDCl_3$): δ = 20.9, 44.8, 45.6, 126.3, 127.7 (2C), 127.8 (2C), 128.0 (2C), 128.5 (2C), 129.3 (2C), 133.0, 135.9, 137.1, 141.1, 144.4, 198.1; HPLC (Diacel Chiralcel AD-H, *n*-hexane:2-propanol = 98:2, 0.5 mL min^{-1}, 254 nm): retention time = 30.3 min (major), 39.3 min (minor); HR-MS (ESI): *m/z* = 301.1593, calcd. for $C_{22}H_{21}O$ (M^++H): 301.1592.

(−)-3-(4-Methoxyphenyl)-1,3-diphenylpropan-1-one (3og): yield: 83%; white solid; 85% *ee*; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.71 (d, $^3J_{H,H}$ = 7.4 Hz, 2H), 3.87 (s, 3H), 4.79 (t, $^3J_{H,H}$ = 7.5 Hz, 1H), 6.80–6.83 (m, 2H), 7.14–7.20 (m, 3H), 7.27–7.31 (m, 4H), 7.41–7.47 (m, 2H), 7.50–7.60 (m, 1H), 7.92–7.95 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 44.9, 45.2, 55.2, 113.9 (2C), 126.3, 127.3 (2C), 128.1 (2C), 128.5 (2C), 128.6 (2C), 128.8 (2C), 133.0, 136.3, 137.1, 144.5, 158.1, 198.2: HPLC (Diacel Chiralcel AD-H, *n*-hexane:2-propanol = 98:2, 0.5 mL min^{-1}, 270 nm): retention time = 68.4 min (major), 71.6 min (minor); HR-MS (ESI): *m/z* = 317.1546, calcd. for $C_{22}H_{21}O_2$ (M^++H): 317.1542.

(−)-1,3-Diphenyl-3-(4-(trifluoromethyl)phenyl)propan-1-one (3oh): yield: 47%; white solid; 93% *ee*; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.75 (dd, $^3J_{H,H}$ = 7.3 Hz, $^3J_{H,H}$ = 2.1 Hz, 2H), 4.89 (t, $^3J_{H,H}$ = = 7.2 Hz, 1H), 7.17–7.58 (m, 12H), 7.92–7.95 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): *d* = 44.4, 45.7, 124.2 (q, $^1J_{C,F}$ = 270.0 Hz), 125.5 (q, $^3J_{C,F}$ = 3.8 Hz, 2C), 126.8, 127.8 (2C), 128.0 (2C), 128.2 (2C), 128.66 (q, $^2J_{C,F}$ = 31.5 Hz), 128.67 (2C), 128.8 (2C), 133.3, 136.8, 143.3, 148.2, 197.4; ^{19}F{^{1}H} NMR (282 MHz, $CDCl_3$): δ = −62.4; HPLC (Diacel Chiralcel IC, *n*-hexane:2-propanol = 98:2, 0.5 mL min^{-1}, 254 nm): retention time = 12.9 min (major),

13.6 min (minor); HR-MS (ESI): $m/z = 355.1340$, calcd. for $C_{22}H_{18}F_3O$ ($M^+ + H$): 355.1310.

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