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Synthesis of Stereoprojecting, Chiral N-C(sp^3)-E Type Pincer Complexes

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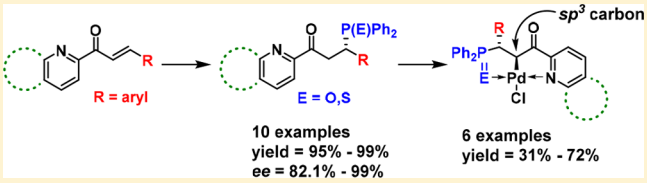
Supporting Information

ABSTRACT: A synthetic strategy to generate chiral N-C(sp^3)-E (E = S, O) pincer complexes incorporating enhanced stereoprojecting groups at the N-arm site has been established. The synthesis of the tridentate pincer ligand was carried out via palladacycle-catalyzed asymmetric hydrophosphination of N-chelating enones. The chelation properties of the substrates were initially demonstrated on C(sp^2)-N type palladacycles. The extended substrate scope allows versatile structural modifications on the ligand backbone. Subsequent cyclometalation provided N-C(sp^3)-E complexes in a diastereoselective reaction.



INTRODUCTION

The development of palladacyclic compounds, bearing either a bidentate or a tridentate pincer ligand scaffold, has attracted interest in the last few decades, due to the extensive application of these useful organometallic complexes.[1] Among these materials, the chiral derivatives have attracted interest since their first discovery in asymmetric synthesis scenarios. Their application in the chiral template-promoted cycloadditions and hydrofunctionalization reactions has been extensively explored over the past decade.[2] In this methodology, the metal complex is required in stoichiometric amount for the reaction. However, it allows the generation of synthetically challenging P,P- and P,N-bidentate ligands, which can develop five- or six-membered-ring chelation with the metal center, circumventing the hurdle of catalyst poisoning.[3] Optically pure C(sp^2)-E (E = electron donor atom) type palladacycle complexes can be also successfully applied in catalytic amounts for asymmetric Michael-type addition reactions,[4] including P−H addition,[5] Hayashi−Miyaura arylboronic acid addition,[6] [3,3]-sigmatropic aza-Claisen rearrangement,[7] and ring-opening reactions[8] just to name a few.

One of the most important features of the palladacyclic complexes is the extensive synthetic opportunities to modify the ligand backbone. This in turn allows enormous possibilities for the fine tuning of the electronic properties of the metal center as well as control of the stereochemistry around the coordination sites. Both of these factors can have a direct effect on reactivity as well as stereoselectivity when these complexes are employed in asymmetric synthesis. In the aforementioned examples, it has already been proven that each individual complex has its own structural and electronic features that lead to a unique performance in catalysis. Thus, some derivatives may be more efficient in one particular catalytic reaction, while analogues work better in another reaction. While the importance of ligand modifications is evident, in most of the cases it is quite difficult, since each alteration requires an individual, multistep ligand synthesis procedure. For instance, one of the most commonly used chiral C(sp^2)-N palladacycles, the bis(μ-chloro) (1-naphthyl)dimethylamine palladacycle **1**, is relatively easy to synthesize; however, its structural modifications, reported by our group, require multistep syntheses, including the need for kinetic resolution (Figure 1).[9] On the basis of these considerations, the development of a more direct and efficient ligand synthesis for extended structural modifications is unquestionably needed for all kinds of complex families.

The generation of achiral N-C(sp^2)-E pincer palladacycles has already been established, and their catalytic activity was tested in Suzuki−Miyaura cross-coupling reactions.[10] The aliphatic derivatives of those pincer complexes were also reported previously with the N-C(sp^3)-O pincer backbone.[11] However, in these early studies the catalytic activity was not explored. Our group recently reported the synthesis of chiral N-C(sp^3)-E (E = O, S) type complexes, including bimetallic derivatives, and the catalytic performance was evaluated in asymmetric hydrophosphination reactions.[12] The new compounds provided the desired chiral phosphine products with high enantioselectivities and regioselectivities. However, the structural modifications of the catalyst have not yet been investigated and the steric control around the catalytic site still can be improved by building up projecting groups at the N site of the complex (Figure 2). Our group is interested in exploring further the chemistry of the relatively less explored chiral N-C(sp^3)-E pincer complexes and therefore embarked upon developing an effective and robust synthetic strategy, which also allows easy and convenient structural modifications on the ligand backbone.

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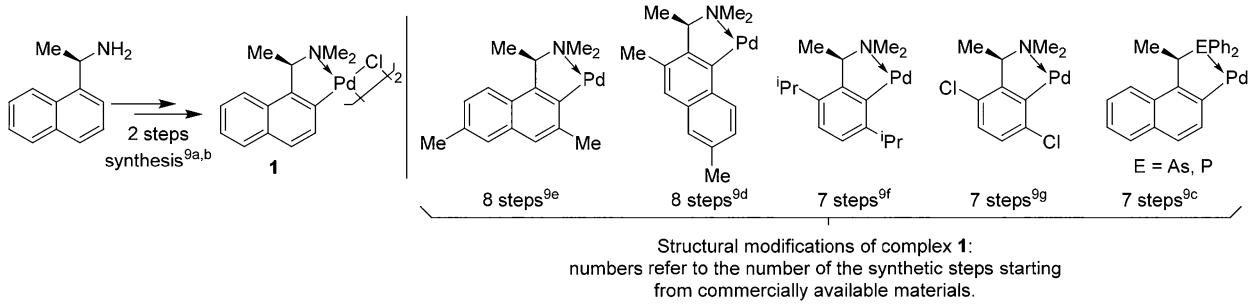


Figure 1. Structural modifications of C(sp^2)-N type palladacycles.

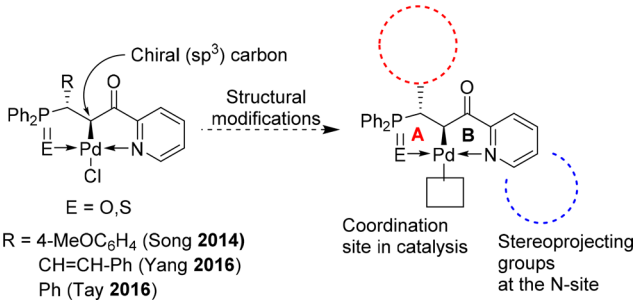


Figure 2. Structural modifications of N-C(sp^3)-E complexes.

In addition, varying the groups connected to the chiral carbon adjacent to the phosphorus atom may also have some influence on the catalytic performance via alteration of the conformation of the five-membered palladacyclic ring (ring A in Figure 2). It needs to be reiterated that such sterically enhanced, optically pure N-C(sp^3)-E complexes have not yet been reported in the literature, nor has a relatively concise and universal synthetic strategy been found that provides easy structural modifications on this new class of complexes. Herein we report an effective and simple method for structural modification, in which the first C(sp^3) stereocenter is generated in asymmetric hydrophosphination, followed by cyclometalation which creates the second stereocenter in a highly diastereoselective manner. This method allows us to generate a wide range of new, optically pure N-C(sp^3)-E complexes bearing enhanced stereoprojecting units without the need for a time-consuming and often inefficient kinetic resolution step.

RESULTS AND DISCUSSION

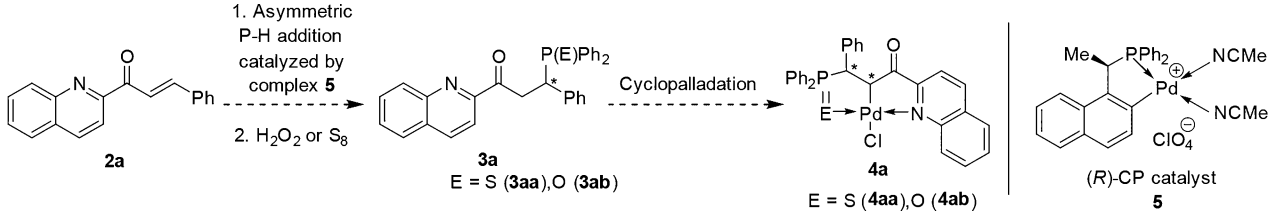
In order to build up the steric projection at the N-site of the N-C(sp^3)-E complexes, our first attempt was to change the pyridyl group to a quinolyl ring. For this purpose, the synthesis route was initiated with an asymmetric P−H addition step onto an α,β-unsaturated enone (**2a**) bearing a quinolyl ring adjacent to the carbonyl functionality (Scheme 1). In this step, the first stereocenter is generated via an asymmetric hydrophosphination reaction, catalyzed by complex **5**. On the basis of our previous studies, complex **5** is still one of the most powerful and well-established catalysts in asymmetric hydrophosphination reactions.[5,13] In the following step, a diastereoselective cyclometalation leads us to the desired, optically active final product (**4a**). The cyclometalation of the synthesized ligand is also a crucial part of our strategy, since the synthesis of these compounds is known to be exceptionally challenging.

One of the most important components of this aliphatic pincer ligand scaffold is the C(sp^3) unit, which is connected directly to the metal center and imparts entirely different features to the complexes in comparison to the C(sp^2) counterpart. These include, but are not limited to, higher electron density around the metal center and a stereogenic carbon donor which is directly coordinated to the metal, thus allowing a more efficient transmission of chiral information. These structural features may have a strong influence on the stereochemistry when the complex is applied in a particular catalytic transformation.

It is generally accepted that intramolecular cyclometalation via C−H activation is preferentially favored in the case of the aromatic ligands in comparison to the aliphatic ligands.[14] One explanation is that, although the alkylic C(sp^3)−H bond is generally weaker than the aromatic C(sp^2)−H bond, the strength of the generated M−C(sp^2) bond is significantly higher than that of the M−C(sp^3) bond.[15] Another important factor in the C(sp^2)−H bond activation is the possible coordination of the π aromatic system to the metal, before the C−H bond cleavage takes place. In the case of aliphatic C(sp^3)−H bond activation, such precoordination does not occur.[1f,c,16] In addition, the enhanced flexibility of the aliphatic backbone complicates the selective generation of the well-defined compounds. There are indeed only a few reports in the literature in which the M−C(sp^3) bond formation was promoted over the M−C(sp^2) formation.[17]

Therefore, while initiating our ligand synthesis, we took all the possible difficulties in the P−H addition into consideration.

Scheme 1. Synthetic Plan To Generate the Quinolyl-Based N-C(sp^3)-E Complex (4ab)



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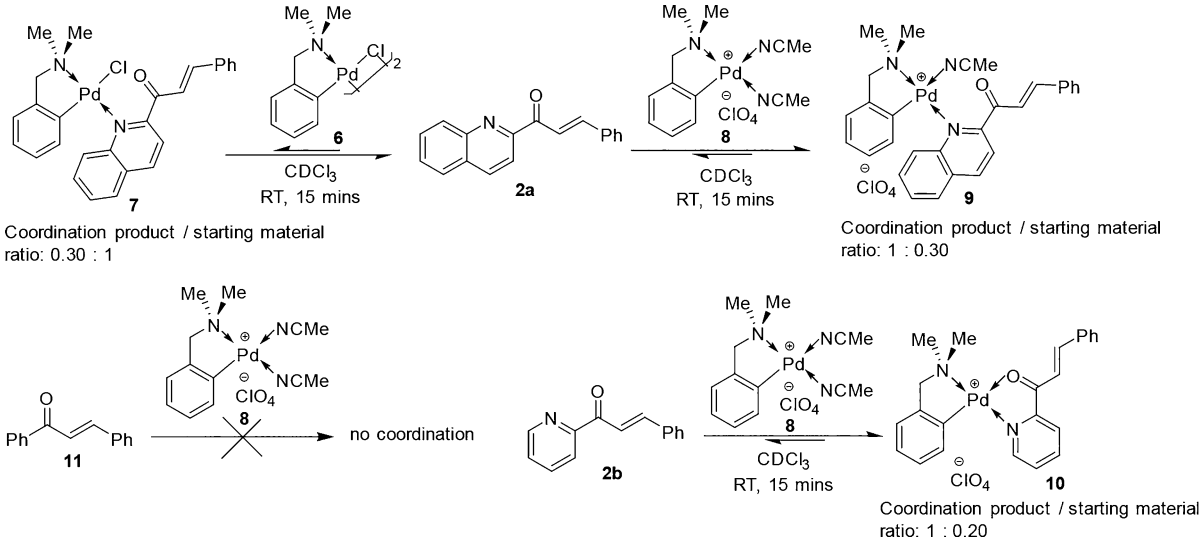
Scheme 2. Coordination Properties of N-Chelating Enones



It has been demonstrated previously that the P,N-chelating phosphine ligands, which are generated in asymmetric hydrophosphination, can alter the catalytic performance of complex **5** by acting as a catalyst poison.[18] However, in our P−H addition reactions the source of the problem was not the generated ligands but the N-chelating enone starting materials themselves. Since the synthesis of N-C(sp^3)-E pincer complexes requires the use of these types of N-chelating substrates during the ligand synthesis, the effect of N-chelation also plays a crucial role in the development of our synthetic strategy and provides fundamental insights into this aspect of coordination in this class of compounds.

With the N-chelating enones, the source of the difficulty is the lone pair of the N-moiety that takes part in the final coordination in the N-C(sp^3)-E complexes, as well as in the chelation to the palladium before the P−H addition. To explore the coordination behavior of the selected N-chelating substrates, compound **2a** was treated with 1 equiv of complex **6** and stirred at room temperature in $CDCl_3$ for 15 min (Scheme 2, top left).

Within this time, a dynamic equilibrium was set up between the starting materials and the product (**7**). Compound **7** was generated by N chelation via the nitrogen of the quinolyl ring to the metal center. The ratio between complex **7** and the starting materials was found to be 0.30:1 as determined by ^{1}H NMR. The coordination product can be isolated via crystallization from the solvent, and it was found to be stable in the solid state. However, when the isolated product was redissolved in $CDCl_3$, the same equilibrium was reestablished.

Another proof for the existence of the equilibrium was the presence of the same amount of complex **7** in the mixture even after more than 10 days, without any changes in the ratio. This experiment excludes the possibility of a one-way coordination reaction. The single-crystal X-ray diffraction analysis of complex **7** confirmed its structure (Figure 3).

In the bis(chloro)-C(sp^2)-N dimer **6**, which was used for the coordination test, the bridging chlorides make a stronger X-type and a weaker L-type coordination to the palladium centers. On the basis of the findings, the quinolyl enone (**2a**) is strong enough to replace the L-type chloride, but the X-type chloride stays intact. According to the NMR measurements, significant coordination via the carbonyl oxygen was not

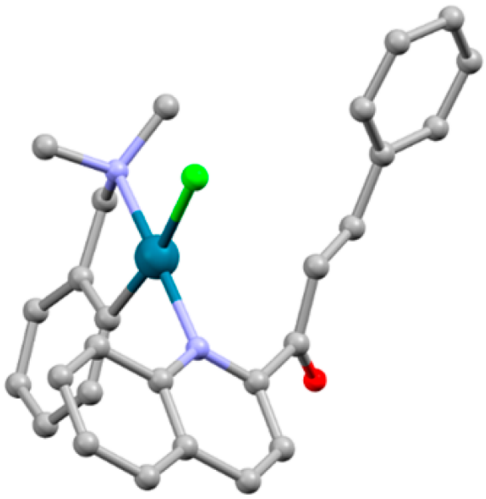


Figure 3. ORTEP structure of complex **7**. All hydrogen atoms are omitted for clarity.

recognized under the mentioned reaction conditions (for NMR spectra, see the Supporting Information).

Complex **8** was generated from complex **6** by mixing it with 1 equiv of $AgClO_4$ in acetonitrile.

After the chloride atoms were removed, the two acetonitrile molecules provided a more hemilabile coordination to the metal center. Introducing a stoichiometric amount of enone **2a** to compound **8** leads to the formation of complex **9** (Scheme 2, top right). After isolation of the coordination product, the ORTEP structure revealed that the quinolyl substrate **2a** can indeed replace one acetonitrile in a position trans to the nitrogen of the C(sp^2)-N ligand while the other acetonitrile remains coordinated to the palladium (Figure 4). Coordination complex **9** exists in equilibrium in $CDCl_3$, giving a 1:0.30 ratio with the starting materials.

In a subsequent experiment, the coordination ability of the pyridyl ring was tested by treatment of complex **8** with enone **2b** (Scheme 2, bottom right). The equilibrium was also observed in this case, giving a 1:0.20 ratio between the coordination product and the starting materials in the same solvent system at the same temperature. According to an X-ray

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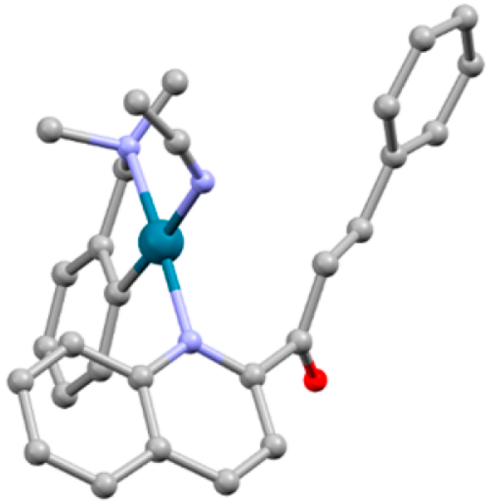

Figure 4. ORTEP structure of complex **9**. All hydrogen atoms are omitted for clarity.

analysis, in this case both coordinated acetonitrile molecules were replaced by the substrate, leading to N,O-chelation to the palladium center (Figure 5). Single coordination by the nitrogen or the oxygen was not observed under the experimental conditions.

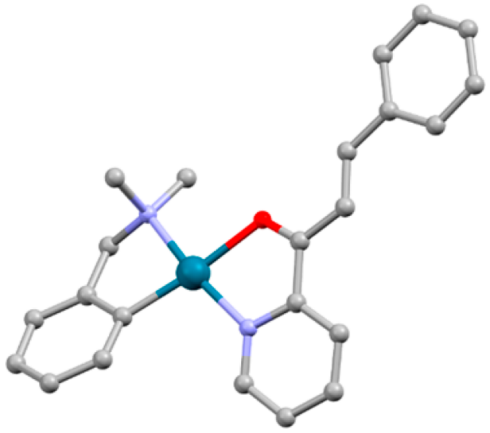

Figure 5. ORTEP structure of complex **10**. All hydrogen atoms are omitted for clarity.

Treatment of the *trans*-chalcone (**11**) with the CN-bis(acetonitrile) complex **8** did not show any coordination at ambient temperature on the basis of ^{1}H NMR measurements in $CDCl_3$. This means that, without a stronger electron donor atom, coordination does not take place between the substrate and the metal.

To sum up, on the basis of these experimental studies, the nitrogen atom in the heterocyclic ring has a crucial role in coordination to the palladium center. Coordination via the oxygen atom was observed only upon mixing enone **2b** and complex **8**, thus generating an N,O-type chelation.

The different coordination properties of the pyridyl- and quinolyl-based substrates were thus established in these experiments, and on the basis of these findings, their different performances in the palladacycle-catalyzed asymmetric hydrophosphination were surmised.

In order to synthesize the tridentate pincer ligands for the N-C(sp^3)-E type complexes, the first P−H addition step was carried out in an asymmetric fashion using chiral catalysts (Table 1). As previously reported by us, a wide range of α,β-unsaturated ketones can be effectively transformed into the corresponding chiral phosphine ligands, catalyzed by the C(sp^2)-P type palladacycle **5**. This transformation included the pyridyl enone derivative **2b**, which successfully went through the P−H addition with 92% enantiomeric excess and provided the desired product in quantitative yield.[19] In accordance with this study, we started our synthesis plan with the addition reaction under the same conditions using the quinolyl-based enone derivative **2a**. In the addition reaction the phosphine product **3aa** was produced in quantitative yield; however, the enantioselectivity dropped drastically (ee = 52.3%) (Table 1, entry 2).

By changes in the reaction conditions, several attempts were made to improve the stereoselectivity in the reaction, but no increase in enantioselectivity was achieved (Table 1, entries 1−10). The optimization study was continued by using the P-C(sp^2)-P type pincer complex **12**, which was also reported by our group previously.[20]

For complex **5**, the addition of a base was necessary for the reaction to be completed; however, complex **12** does not require the use of triethylamine in the transformation (Table 1, entries 12 and 13). The reason is the presence of acetate ion, coordinated to the palladium, which can take the role of the internal base.

The amount of the catalyst was also optimized, and according to the results, the best conditions require 10 mol % catalyst loading (Table 1, entries 12, 14, and 15). A higher catalyst loading of 15 mol % significantly accelerated the reaction (2 times faster than that of with 5 mol % loading); however, the faster transformation slightly decreased the enantioselectivity.

Modification of the temperature revealed that the highest enantiomeric excess can be achieved at −40 °C (Table 1, entries 11, 14, and 16−18). In general, the choice of the lower temperature is more advantageous in asymmetric hydrophosphination reactions, however in this case −60 °C was found to be too low for the transformation in terms of selectivity. After trying out different conditions, eventually the usage of complex **12** with 10 mol % catalyst loading at −40 °C in acetone gave the best overall result (Table 1, entry 17).

The desired phosphine ligand was generated after 1 h reaction time in quantitative yield with excellent (ee = 96.6%) enantioselectivity. After a single recrystallization from the DCM/Et_2O solvent system, the enantiomerically pure (ee > 99%) compound was observed in 76% isolated yield.

The optimization showed that substrate **2a**, bearing the quinolyl ring instead of the pyridyl moiety, acts in an entirely different way from substrate **2b** during the catalysis. We have reported the reaction mechanism of similar hydrophosphination reactions using (*R,R*)-**12** as the catalyst for other pyridyl-substituted substrates.[20a] The aforementioned coordination studies with the C(sp^2)-N palladacycles demonstrated the different chelating properties of these two enone derivatives, which may be one of the reasons for the unusual performance in the addition reaction catalyzed by complex **5**. However, this finding still does not provide an explanation for the different behavior in the hydrophosphination reactions catalyzed by complexes **5** and **12**.

In order to examine this aspect, substrate **2a** and complex **5** were mixed in $CDCl_3$ in equivalent amounts and stirred for 15 min. The same experiment was carried out with 1 equiv of

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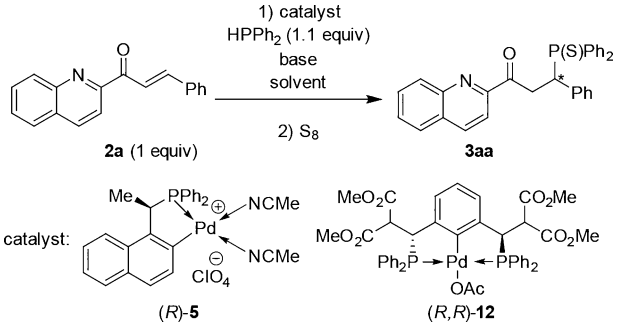
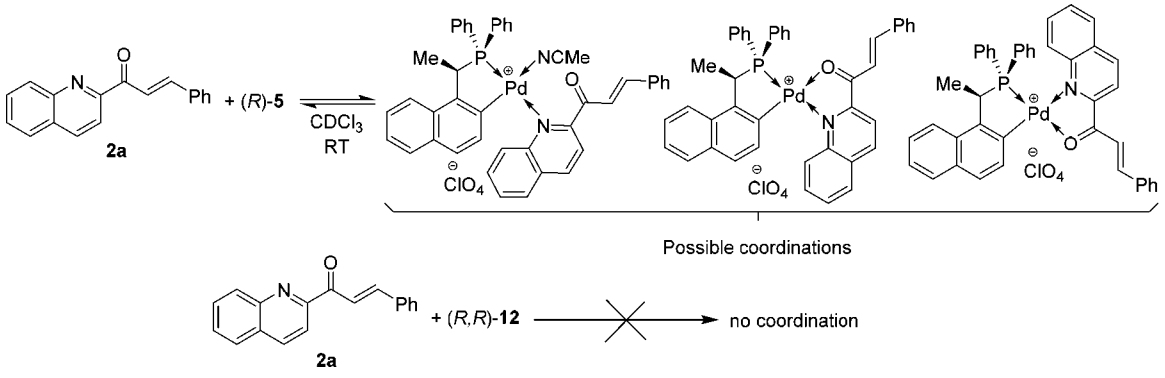
Table 1. Optimization of P−H Addition onto Enone 2a[a]



entry	catalyst	solvent	T (°C)	t (h)	yield[b] (%)	ee[c] (%)
1[d]	(*R*)-**5**	THF	−40	20	99	6.3
2[d]	(*R*)-**5**	THF	−80	20	99	52.3
3[d]	(*R*)-**5**	MeCN	−40	20	99	12.3
4[d]	(*R*)-**5**	toluene	−40	21	99	0.5
5[d]	(*R*)-**5**	toluene	−80	20	99	0
6[d]	(*R*)-**5**	$CHCl_3$	−40	14	99	25.6
7[d]	(*R*)-**5**	DCM	−40	22	99	14.0
8[d]	(*R*)-**5**	DCM	−80	20	99	41.8
9[d]	(*R*)-**5**	DCM/MeOH (10/1)	−80	20	99	3.2
10[d,e]	(*R*)-**5**	acetone	−40	1	99	27.1
11	(*R,R*)-**12**	acetone	room temp	1.5	99	48.9
12	(*R,R*)-**12**	acetone	0	1.5	99	51.0
13[d]	(*R,R*)-**12**	acetone	0	1.5	99	52.6
14[e]	(*R,R*)-**12**	acetone	0	1	99	67.8
15[f]	(*R,R*)-**12**	acetone	0	0.5	99	22.6
16[e]	(*R,R*)-**12**	acetone	−20	1	99	81.1
17[e]	(*R,R*)-**12**	acetone	−40	1	99 (76)	96.6 (>99)
18[e]	(*R,R*)-**12**	acetone	−60	2	99	84.6
19	(*R,R*)-**12**	$CHCl_3$	0	20	99	28.9
20	(*R,R*)-**12**	toluene	0	20	99	−40.6

[a]Reaction conditions unless specified otherwise: enone **2a** (85 μmol, 1.0 equiv), $HPPh_2$ (93.5 μmol, 1.1 equiv), catalyst (4.25 μmol, 5 mol %), solvent (2.6 mL). [b]The yield was calculated from $^{31}P\{^1H\}$ NMR. Isolated yields after a single recrystallization are given in parentheses. [c]The ee was determined by chiral HPLC. The ee values after a single recrystallization are given in parentheses. [d]Triethylamine (85 μmol, 1.0 equiv) was added to the reaction. [e]In the reaction, 10 mol % of catalyst was used. [f]In the reaction 15 mol % of catalyst was used.

Scheme 3. Coordination Behavior of Enone 2a with (*R*)-5 and (*R,R*)-12



complex **12** as well. According to $^{31}P\{1H\}$ and ^1H NMR measurements, complex **5** and substrate **2a** develop a dynamic connection, a continuous coordination, and decoordination between the reactants, providing different possible coordination products (Scheme 3).

While coordination between compound **2a** and the C(sp^2)-N type complex **8** developed a well-defined equilibrium (see above), in the case of the C(sp^2)-P palladacycle (**5**), the coordination is far more flexible and the chelation is fairly hemilabile (for NMR spectra, see the Supporting Information). However, mixing enone **2a** and complex **12** did not show any coordination at all, which can be explained by the steric repulsion between the phenyl groups in the P-C(sp^2)-P pincer complex and enone **2a** (Figure 6). The metal center in compound **12** is evidently much less accessible than that in **5**.

We have reported previously that catalysts (*R,R*)-**12** and (*R*)-**5** operate via different reaction mechanisms.[13,18b]

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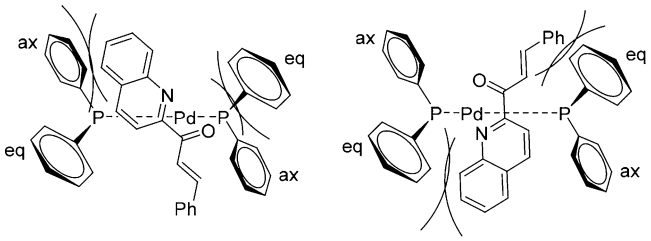


Figure 6. Steric repulsion between enone **2a** and P-C(sp^2)-P complex **12**. The structure of **12** is simplified for clarity.

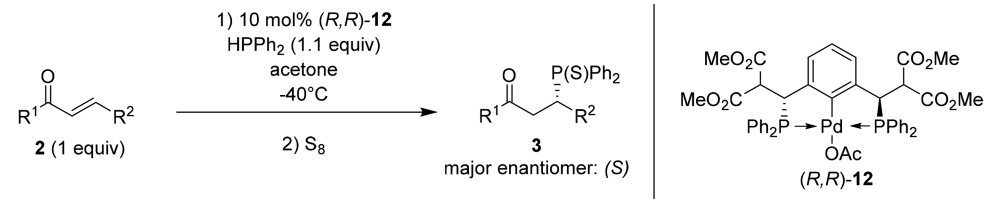
Catalyst **5** involves an intramolecular mechanism in which the reacting phosphine and the substrate coordinate simultaneously on the palladium catalyst. On the other hand, catalyst (*R,R*)-**12** adopts an intermolecular mechanism in which only the phosphine coordinates to the palladium during the course of the addition reaction. The substrate chelation to complex **5** might be one explanation for the suppressed catalytic performance in the P−H addition reaction. Since we did not experience such chelation with complex **12**, the transfer of the chiral information is much more effective.

On application of the optimized conditions, a series of tridentate N-C(sp^3)-E type ligands were synthesized bearing an extended group at the N-site (Scheme 4). To make a comparison between the new ligand synthesis route and the previously reported systems, at first, pyridyl enone **2b** was used in the addition reaction. The generated ligand **3b** was observed with 97.4% enantiomeric excess in quantitative isolated yield after 5 h reaction time. This result is slightly better than those in earlier studies on this substrate.[21] In order to enhance the projection in the N-C(sp^3)-E complexes, not only the quinolyl derivatives but also the 6-Me- and 6-anisyl-substituted pyridyl enones (**2c,d**) were applied in the hydrophosphination reaction.

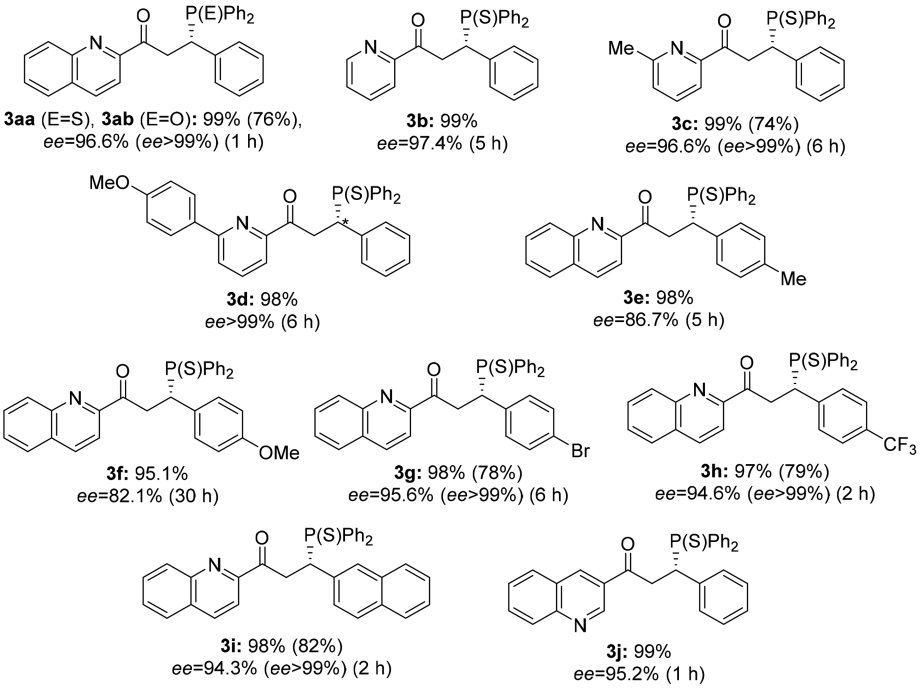
The former enone **2c** provided the corresponding ligand **3c** in quantitative yield with high enantiomeric excess (ee = 96.6%), and the latter enone **2d** was transformed into the desired product **3d** in an enantiomerically pure transformation. In the next step, the effect of different substituents on the R^2 aryl ring was tested. These modifications may also alter the catalytic performance of the final complexes, by changing the ring conformation in the N-C(sp^3)-E pincer palladacycles.

Among the modified structures (**2e−i**), the 4-methoxy-substituted compound turned out to be the most challenging in this series. The reaction proceeded with high 95.1% yield with a longer 30 h reaction time and the enantiomeric excess was slightly lower at 82.1%. If the substituent was changed to another electron-donating group, such as 4-bromo, the reaction provided high ee and yield in 6 h.

Scheme 4. Extension of N-C(sp^3)-E Pincer Ligand Synthesis



2a: R^1 = 2-quinolyl R^2 = Ph, **2b**: R^1 = 2-pyridyl R^2 = Ph, **2c**: R^1 = 2-(6-Me)pyridyl R^2 = Ph,
2d: R^1 = 2-(6-anisyl)pyridyl R^2 = Ph, **2e**: R^1 = 2-quinolyl R^2 = 4-MeC_6H_4, **2f**: R^1 = 2-quinolyl R^2 = 4-$MeOC_6H_4$,
2g: R^1 = 2-quinolyl R^2 = 4-BrC_6H_4, **2h**: R^1 = 2-quinolyl R^2 = 4-$CF_3C_6H_4$, **2i**: R^1 = 2-quinolyl R^2 = 2-naphthyl,
2j: R^1 = 3-quinolyl R^2 = Ph.



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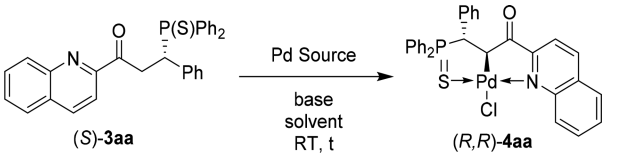
The presence of an electron-withdrawing group, such as a *p*-trifluoromethyl substituent on the aryl ring, also did not change the efficiency of the synthesis. A sterically more hindered group (2-naphthyl) in the R^2 position was also tested in the addition reaction onto enone **2i**, and the transformation was complete, giving similar results. Altering the position of the N donor atom on the aryl ring also did not cause any drawbacks to the reaction; the corresponding phosphine **3j** was observed with excellent selectivity and yield within a short reaction time.

On the basis of our findings, the new synthesis system has a very high tolerance toward substrate modifications. Overall, all of the tridentate ligands were produced in a short reaction (less than 6 h) in quantitative or nearly quantitative yield (97–99%), with good to excellent enantiomeric excesses (ee = 82.1% to ee > 99%). It is worth mentioning that, after a single recrystallization, the enantiomerically pure ligands **3aa,c,g–i** were observed in good (up to 82%) yield.

Asymmetric hydrophosphination is an extraordinary tool to generate the chiral phosphine ligands in a single step with high atom economy. This transformation makes our synthetic plan certainly powerful. After the first stereocenter is generated in this addition step, the second step is the cyclometalation of the tridentate ligand.

During the optimization process of the metalation step, various solvents and palladium sources were tried out (Table 2). The best palladium source was found to be Li_2PdCl_4 in a methanol/chloroform (2/1) solvent mixture, which gave a moderate 40% isolated yield after 40 h at ambient temperature. Under the same conditions, a longer reaction time did not improve the conversion significantly (Table 2, entries 4 and 8). However, if 1 equiv of triethylamine was introduced to the system, the yield increased to 72% after a reaction time of 5 days (Table 2, entry 9). Applying $Pd(MeCN)_4(ClO_4)_2$ as a metal source accelerated the reaction, and after 2 h the isolated yield was 45%. However, this result could not be further improved by extending the reaction time or by adding an additional amount of base (Table 2, entry 7).

Table 2. Optimization of Cyclometalation of (*S*)-3aa[a]



entry	palladium source	solvent	*t*	yield (%)
1	Li_2PdCl_4	DCM	40 h	23
2	Li_2PdCl_4	MeOH	40 h	26
3	Li_2PdCl_4	acetone	40 h	21
4	Li_2PdCl_4	MeOH/$CHCl_3$ (2/1)	40 h	40
5	K_2PdCl_4	MeOH/$CHCl_3$ (2/1)	40 h	25
6[b]	$PdCl_2(MeCN)_2$	DCM	40 h	33
7[c]	$Pd(MeCN)_4(ClO_4)_2$	MeCN	2 h	45
8	Li_2PdCl_4	MeOH/$CHCl_3$ (2/1)	5 days	44
9[d]	Li_2PdCl_4	MeOH/$CHCl_3$ (2/1)	5 days	72

[a]Reaction conditions: ligand (*S*)-**3aa** (42 μmol, 1.0 equiv), reagent (42 μmol, 1.0 equiv), solvent (20 mL), room temperature. [b]NaOAc (42 μmol, 1.0 equiv) was added to the reaction mixture. [c]After completion of the metalation, LiCl (42 μmol, 1.0 equiv) was added to the reaction mixture. [d]Triethylamine (42 μmol, 1.0 equiv) was added to the reaction mixture.

The structure and the absolute stereochemistry of (*R,R*)-**4aa** in the solid state was confirmed by single-crystal X-ray crystallographic analysis (Figure 7). The obtained structure

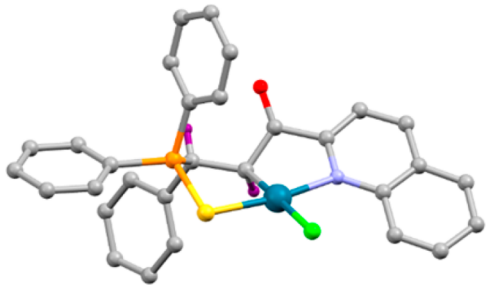
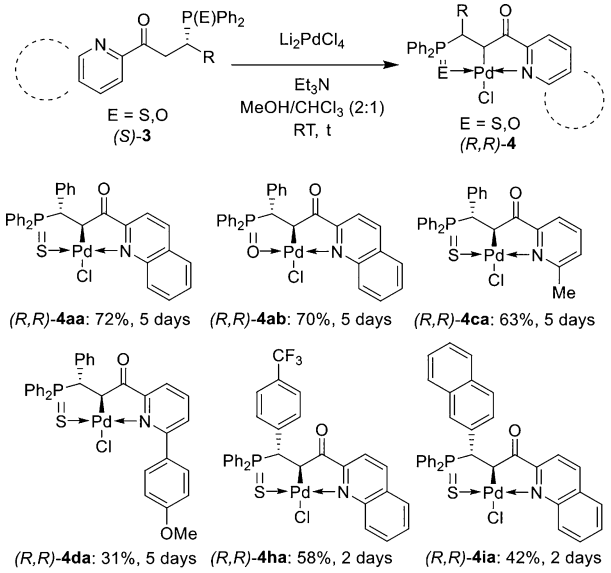


Figure 7. ORTEP structure of (*R,R*)-**4aa**. Hydrogen atoms are omitted from the structure for clarity (except on chiral carbons).

revealed that the C1–C12–P1–S1 chelate adopted the λ conformation with the C-Ph group occupying the sterically less favorable axial position. One of the explanations for this aspect may be the possible steric repulsion between the C-Ph and the P-Ph(eq) units. It needs to be noted that, while the first stereocenter is generated via the asymmetric hydrophosphination, during cyclometalation a second chiral center is created in a diastereoselective manner.

On application of the optimal conditions, several new N-C(sp^3)-E complexes were synthesized with enhanced steric projection at the N site (Scheme 5). To test the extent of the synthetic route, the N-C(sp^3)-O derivative of the quinolyl ligand **3ab** was also successfully utilized in the cyclometalation reaction, giving 70% yield in the reaction. The N-C(sp^3)-S type ligand bearing the 6-methylpyridyl ring **3c** provided the final complex with a slightly lower isolated yield (63%); however, the generation of the 6-anisylpyridyl complex **4da** was found to be even more difficult. In the test reactions, different modifications on the aryl group, connected to the carbon

Scheme 5. Synthesis of Stereoprojecting N-C(sp^3)-E Complexes



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Organometallics XXXX, XXX, XXX–XXX

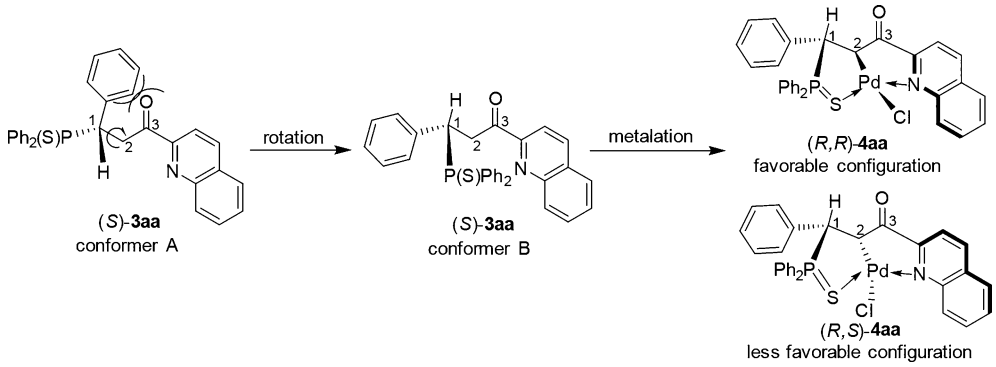

Figure 8. Explanation of diastereoselectivity in cyclometalation.

next to phosphorus, were also performed by introducing 4-CF_3-phenyl and naphthyl groups in the ligands **3h,i**. These reactions were carried out in a shorter time and generated the desired complexes in moderate to good yields. In all syntheses, the applied pincer ligands were used in their enantiomerically pure form and the transformation provided only one of the possible diastereomers without loss of enantiopurity.

On the basis of the experimental results, if the generated N-C(sp^3)-E type ligands are enantiomerically pure, the diastereoselective metalation step provides the optically pure complexes without the loss of chiral purity. The diastereoselectivity can be explained by steric effects during the metalation process (Figure 8). The chiral phosphine ligands in solution may exist as different conformers (A and B). Due to the steric repulsion between the phenyl group on C1 and the oxygen of the carbonyl group, the bond between C1 and C2 may undergo rotation to develop the sterically more favorable conformer B. In the cyclometalation step, as a result of the Pd−C σ-bond formation and the rotation between C3 and the quinolyl ring, two five-membered palladacycle rings are generated. Since the stereochemistry of the ligand is fixed, after metalation, one stereocenter out of two is always fixed, corresponding to the chirality on C1. In other words, when the synthesis is started with the *S* ligand, the possible diastereomers have the *R,X* general chirality (*R* defines the stereochemistry on C1 and *X* belongs to C2, which can be either *R* or *S*). Considering the structure of the two possible diastereomers *R,R* or *R,S*, complex **4** with the same configuration on C1 and C2 chiral centers has a much more favorable orientation, in comparison to that having alternate stereochemistry. On the basis of experimental results, the *R,S* diastereomer is not generated during the syntheses.

If the metalation step was carried out by using the phosphine sulfide ligand (*R*)-**3** with the opposite chirality, the obtained N-C(sp^3)-E complex acquired the reverse *S,S* stereochemistry. The transformation of (*R*)-**3ab** to (*S,S*)-**4ab** established the simple switch between the different enantiomers. The X-ray structure of (*S,S*)-**4ab** confirmed the structure and the chirality (Figure 9). In this case, the C11−C12−P1−O1 chelate developed the δ conformation, once again with the C-Ph moiety located in the unexpected axial position.

The result of the cyclometalation is the generation of two slightly distorted square planar palladacycle rings. The metalation of ligand **3j**, bearing a 3-quinolyl ring instead of the 2-quinolyl moiety, could provide the formation of a six-membered palladacycle ring, on the basis of the structural features. However, even after trying different palladium sources, such a transformation was not observed.

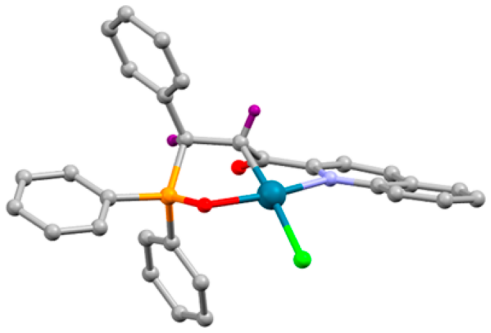

Figure 9. ORTEP structure of (*S,S*)-**4ab**. Hydrogens are omitted from the structure for clarity (except on chiral carbons).

The tridentate pincer backbone provides extraordinary stability to the generated N-C(sp^3)-E complexes. Complex **4aa** was dissolved and heated to reflux temperature in toluene for more than 10 h without any observed thermal decomposition.

If we consider the stereochemical stability, it is known in the literature that aliphatic C(sp^3)-type pincer complexes can undergo α-hydrogen abstraction, which results in the formation of palladium carbene complexes,[22] as well as α- or β-H elimination.[1b,d−f,l,j] These transformations could result in racemization in our case (since the two chiral centers in the final complexes are located exactly in the positions α and β to the palladium center), if a reversible elimination/insertion or abstraction/C−H bond activation would occur. In order to examine this possibility, the optical rotation of the final complexes was monitored over a 2 week period, and no such process was observed. As a result of a reversible α- or β-H elimination, the possible generation of the other diastereomer, with the alternate chirality, could take place. In a test of the stability of pure (*R,R*)-**4aa** in this regard, the $^{31}P\{^1H\}$ NMR was monitored over a period of 1 month with once again no formation of the other *R,S* diastereomer.

CONCLUSIONS

In conclusion, an effective and extensive synthetic methodology was demonstrated to produce new, stereoprojecting N-C(sp^3)-E complexes. The first step of our strategy, the catalytic asymmetric hydrophosphination reaction, was carried out on the more challenging, N-chelating substrates, giving the desired chiral phosphine ligands in quantitative yield with up to ee > 99%. The N-chelating effect was examined by coordination studies on C(sp^2)-N, C(sp^2)-P, and P-C(sp^2)-P palladacycles. The different chelation properties between the **2b** pyridyl and

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2a quinolyl enones were established, as well as the different performances in catalytic asymmetric hydrophosphination, leading to the reported **3b** and the new **3a** chiral ligands. The complexation of the new N-C(sp^3)-E type tridentate ligands was also discussed, and all of the generated complexes bear a sterically enhanced group at the N site of the compound. This enhanced stereoprojection may alter the catalytic performance of the N-C(sp^3)-E compounds, and studies on this aspect are currently in progress. Overall, the newly developed synthetic pathway allows us to perform easy structural modifications on the enantiomerically pure chiral complexes, within a relatively fast, selective transformation, without the need for time-consuming and wasteful resolution.

EXPERIMENTAL SECTION

All air-sensitive manipulations were carried out under a positive pressure of nitrogen using Schlenk techniques. Solvents were degassed prior to use. Solvents were obtained from the following sources: chloroform (AR), acetonitrile (AR), methanol (AR), dichloromethane (HPLC), acetone (AR), ethyl acetate (AR), and *n*-hexane (HPLC) VWR; 2-propanol (HPLC), *n*-hexane (AR), and toluene (AR) from Avantor; diethyl ether (AR) from Fischer Scientific; THF from TEDIA Co. THF was distilled from sodium/benzophenone before use. NMR spectra were recorded on Bruker AV 300, AV 400, AV 500, and BBFO 400 spectrometers. Chemical shifts are reported in ppm and referenced to an internal $SiMe_4$ standard (0 ppm) for ^1H NMR, chloroform-*d* (77.22 ppm) for ^{13}C NMR, and external 85% H_3PO_4 for $^{31}P\{^1H\}$ NMR. A PSL-1800 Low Temp Pairstirrer was used for low-temperature reactions. Column chromatography was performed with silica gel 60 (purchased from Merck). Melting points were measured using the SRS Optimelt Automated Point System SRS MPA100. Elemental analysis was performed on the EuroVector Euro EA elemental analyzer. In case if elemental analysis measurements were not performed, the purity was determined by other measurements stated below. HRMS using electrospray ionization (ESI) was performed on the Waters Q-Tof Premier spectrometer. Optical rotations were examined with the JASCO P-1030 polarimeter in DCM in a 0.1 dm cell at the specified temperatures. The enantioselectivities of the asymmetric hydrophosphination reactions were determined with an Agilent 1200 Series HPLC machine fitted with the specified Daicel Chiralpak columns with an *n*-hexane/2-propanol mixture as eluent at 23 °C.

(*R*)-C(sp^2)-P complex **5**,[5c,9c] C(sp^2)-N achiral palladacycles **6**[23] and **8**,[24] and (*R*,*R*)-P-C(sp^2)-P pincer complex **12**[20] were prepared according to literature methods. The N-chelating chalcone derivatives **2** were prepared according to modified literature procedures[25] (for details see the Supporting Information). All other reactants and reagents were used as supplied without further purification unless stated otherwise.

Typical Experimental Procedure of N-C(sp^3)-E Pincer Ligand Synthesis via Asymmetric Hydrophosphination. A nitrogen-flushed two-neck flask was charged with diphenylphosphine (17.4 mg, 93.5 μmol, 1.1 equiv) and degassed solvent (2 mL) at room temperature, followed by the addition of (*R*)-**5** (2.7 mg, 4.25 μmol, 5 mol %) or (*R*,*R*)-**12** catalyst (7.6 mg, 8.5 μmol, 10 mol %). The setup was brought to −40 °C and the mixture stirred for 10 min before introducing enone **2** (85 μmol, 1.0 equiv). In case of the (*R*)-**5**-catalyzed reactions, triethylamine (8.6 mg, 85 μmol, 1.0 equiv), dissolved in 0.5 mL of degassed solvent, was added dropwise to the mixture. The reaction mixture was stirred at low temperature and monitored by $^{31}P\{^1H\}$ NMR. Upon completion, H_2O_2 (31% w/w, 0.1 mL) or S_8 (10.9 mg, 42.5 μmol, 0.5 equiv) was placed in the flask and the reaction mixture was warmed to room temperature and stirred for 30 min. Evaporation of the solvent under reduced pressure generated a crude mixture, which was purified by silica gel column chromatography, with an *n*-hexane/EtOAc (97/3 to 70/30) solvent system as eluent.

*(S)-3-(Diphenylphosphorothioyl)-3-phenyl-1-(quinolin-2-yl)-propan-1-one ((S)-**3aa**).* White solid material was produced in 99% yield and ee = 96.6%. $[\alpha]_D^{20}$ = −230 (*c* 0.5, CH_2Cl_2) for ee > 99%. Mp: 203.5−204.0 °C. $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ 51.52 (s, 1P). ^1H NMR (400 MHz, $CDCl_3$): δ 8.32−8.22 (m, 3H, ArH), 8.16 (d, *J* = 8.5 Hz, 1H, ArH), 7.91 (d, *J* = 8.5 Hz, 1H, ArH), 7.83−7.78 (m, 2H, ArH), 7.64 (t, *J* = 7.3 Hz, 1H, ArH), 7.58−7.49 (m, 4H, ArH), 7.36−7.20 (m, 6H, ArH), 7.08 (s, 3H, ArH), 4.94 (td, *J* = 10.7, 2.0 Hz, 1H, PC*H*CH$_2$), 4.73−4.59 (m, 1H, C(O)C*H*$_2$), 3.66 (ddd, *J* = 17.6, 11.1, 2.2 Hz, 1H, C(O)C*H*$_2$). ^{13}C NMR (101 MHz, $CDCl_3$): δ 199.38 (d, *J* = 15.5 Hz, 1C, C═O), 152.59−118.32 (27C, Ar), 42.56 (d, $^1J_{PC}$ = 52.4 Hz, 1C, PCH), 38.83 (d, $^2J_{PC}$ = 3.5 Hz, 1C, C(O)*C*H$_2$). Anal. Calcd for $C_{30}H_{24}NOPS$: C, 75.45; H, 5.07; N, 2.93. Found: C, 75.31; H, 4.93; N, 2.81. HRMS (+ESI) *m*/*z*: $(M + H)^+$ calcd for $C_{30}H_{25}NOPS$, 478.1394; found, 478.1389.

*(S)-3-(Diphenylphosphoryl)-3-phenyl-1-(quinolin-2-yl)propan-1-one ((S)-**3ab**).* White solid material was produced in 99% yield and ee = 96.6%. $[\alpha]_D^{20}$ = −121 (*c* 0.5, CH_2Cl_2) for ee > 99%. Mp: 172.0−173.0 °C (dec). $^{31}P\{^1H\}$ NMR (162 MHz, $CDCl_3$): δ 34.04 (s, 1P). ^1H NMR (400 MHz, $CDCl_3$): δ 8.21 (d, *J* = 8.4 Hz, 1H, ArH), 8.16 (d, *J* = 8.5 Hz, 1H, ArH), 8.09−8.01 (m, 2H, ArH), 7.92 (d, *J* = 8.5 Hz, 1H, ArH), 7.83−7.75 (m, 2H, ArH), 7.63 (t, *J* = 7.4 Hz, 1H, ArH), 7.56−7.44 (m, 5H, ArH), 7.39−7.32 (m, 3H, ArH), 7.29−7.22 (m, 2H, ArH), 7.16−7.04 (m, 3H, ArH), 4.69−4.57 (m, 1H, PC*H*CH$_2$), 4.54−4.48 (m, 1H, C(O)C*H*$_2$), 3.71 (ddd, *J* = 17.9, 10.7, 2.4 Hz, 1H, C(O)C*H*$_2$). ^{13}C NMR (101 MHz, $CDCl_3$): δ 199.33 (d, *J* = 13.7 Hz, 1C, C═O), 151.82−118.22 (27C, Ar), 41.49 (d, $^1J_{PC}$ = 77.3 Hz, 1C, PCH), 38.26 (s, 1C, C(O)*C*H$_2$). Anal. Calcd for $C_{30}H_{24}NO_2P$: C, 78.08; H, 5.24; N, 3.04. Found: C, 78.27; H, 5.35; N, 3.24. HRMS (+ESI) *m*/*z*: $(M + H)^+$ calcd for $C_{30}H_{25}NO_2P$, 462.1623; found, 462.1625.

*(S)-3-(Diphenylphosphorothioyl)-3-phenyl-1-(pyridin-2-yl)-propan-1-one ((S)-**3b**).* White solid material was produced in 99% yield and ee = 97.4%. The obtained characterization data were consistent with the literature report.[12b] $[\alpha]_D^{20}$ = −241 (*c* 0.1, CH_2Cl_2) for ee > 99%. Mp: 94.0−96.0 °C. $^{31}P\{^1H\}$ NMR ($CDCl_3$, 162 MHz): δ 51.5 (s, 1P). ^1H NMR ($CDCl_3$, 400 MHz): δ 8.63−8.61 (m, 1H, ArH), 8.23−8.18 (m, 2H, ArH), 7.80 (d, 1H, *J* = 7.8 Hz, ArH), 7.68 (td, 1H, *J* = 7.7 Hz, *J* = 1.7 Hz, ArH), 7.54−7.49 (m, 5H, ArH), 7.39−7.35 (m, 1H, ArH), 7.33−7.25 (m, 3H, ArH), 7.23−7.19 (m, 2H, ArH), 7.08−7.05 (m, 3H, ArH), 4.87 (td, 1H, *J* = 10.6 Hz, *J* = 2.6 Hz, PC*H*CH$_2$), 4.51 (ddd, 1H, *J* = 18.2 Hz, *J* = 10.9 Hz, *J* = 6.2 Hz, C(O)C*H*$_2$), 3.51 (ddd, 1H, *J* = 18.4 Hz, *J* = 11.6 Hz, *J* = 2.7 Hz, C(O)C*H*$_2$). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 198.8 (d, *J* = 15.1 Hz, 1C, C═O), 152.9−121.8 (23C, Ar), 42.1 (d, $^1J_{PC}$ = 52.9 Hz, 1C, PCH), 38.6 (s, 1C, C(O)CH$_2$). Anal. Calcd for $C_{26}H_{22}NOPS$: C, 73.05; H, 5.19; N, 3.28. Found: C, 72.87; H, 5.02; N, 3.60. HRMS (+ESI) *m*/*z*: $(M + H)^+$ calcd for $C_{26}H_{23}NOPS$, 428.1238; found, 428.1235.

*(S)-3-(Diphenylphosphorothioyl)-1-(6-methylpyridin-2-yl)-3-phenylpropan-1-one ((S)-**3c**).* White solid material was produced in 99% yield and ee = 96.6%. $[\alpha]_D^{20}$ = −245 (*c* 1.0, CH_2Cl_2) for ee > 99%. Mp: 144.0−146.0 °C. $^{31}P\{^1H\}$ NMR ($CDCl_3$, 162 MHz): δ 51.59 (s, 1P). ^1H NMR (400 MHz, $CDCl_3$): δ 8.27−8.18 (m, 2H, ArH), 7.60 (d, *J* = 7.6 Hz, 1H, ArH), 7.57−7.45 (m, 6H, ArH), 7.33−7.24 (m, 3H, ArH), 7.24−7.14 (m, 3H, ArH), 7.10−7.01 (m, 3H, ArH), 4.91 (td, *J* = 10.7 Hz, *J* = 2.3 Hz, 1H, PC*H*CH$_2$), 4.46 (ddd, *J* = 17.5, 11.0, 6.1 Hz, 1H, C(O)C*H*$_2$), 3.50 (ddd, *J* = 17.7, 11.4, 2.1 Hz, 1H, C(O)C*H*$_2$), 2.58 (s, 3H, ArC*H*$_3$). ^{13}C NMR (101 MHz, $CDCl_3$): δ 199.00 (d, *J* = 15.5 Hz, 1C, C═O), 158.09−119.01 (23C, Ar), 42.17 (d, $^1J_{PC}$ = 52.5 Hz, 1C, PCH), 38.84 (d, $^2J_{PC}$ = 3.4 Hz, 1C, C(O)*C*H$_2$), 24.44 (s, 1C, ArCH$_3$). Anal. Calcd for $C_{27}H_{24}NOPS$: C, 73.45; H, 5.48; N, 3.17. Found: C, 73.76; H, 5.84; N, 3.30. HRMS (+ESI) *m*/*z*: $(M + H)^+$ calcd for $C_{27}H_{25}NOPS$, 442.1394; found, 442.1390.

*(S)-3-(Diphenylphosphorothioyl)-1-(6-(4-methoxyphenyl)-pyridin-2-yl)-3-phenylpropan-1-one ((S)-**3d**).* White solid material was produced in 98% yield and ee > 99%. $[\alpha]_D^{20}$ = −259 (*c* 0.5, CH_2Cl_2) for ee > 99%. Mp: 210.8−211.2 °C. $^{31}P\{^1H\}$ NMR ($CDCl_3$, 162 MHz): δ 51.38 (s, 1P). ^1H NMR (400 MHz, $CDCl_3$): δ 8.18 (ddd, *J* = 12.0, 7.5, 1.9 Hz, 2H, ArH), 8.04 (d, *J* = 8.8 Hz, 2H, ArH),

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7.79 (dd, J = 7.7, 1.2 Hz, 1H, ArH), 7.76−7.65 (m, 2H, ArH), 7.58−7.43 (m, 5H, ArH), 7.37−7.27 (m, 3H, ArH), 7.27−7.19 (m, 2H, ArH), 7.13−7.02 (m, 5H, ArH), 4.89 (td, J = 10.5, 2.8 Hz, 1H, PC*H*CH_2), 4.64 (ddd, J = 17.6, 10.8, 6.5 Hz, 1H, C(O)CH_2), 3.90 (s, 3H, OCH_3), 3.58 (ddd, J = 18.2, 11.6, 2.8 Hz, 1H, C(O)CH_2). ^{13}C NMR (101 MHz, $CDCl_3$): δ 199.46 (d, J = 14.9 Hz, 1C, C═O), 161.14−114.53 (29C, Ar), 55.64 (s, 1C, OCH_3), 42.43 (d, $^1J_{PC}$ = 52.5 Hz, 1C, PCH), 38.70 (d, $^2J_{PC}$ = 3.6 Hz, 1C, C(O)CH_2). Anal. Calcd for $C_{33}H_{28}NO_2PS$: C, 74.28; H, 5.29; N, 2.62. Found: C, 74.06; H, 5.11; N, 2.40. HRMS (+ESI) m/z: (M + H)$^+$ calcd for $C_{33}H_{29}NO_2PS$, 534.1657; found, 534.1652.

*(S)-3-(Diphenylphosphorothioyl)-1-(quinolin-2-yl)-3-(p-tolyl)-propan-1-one ((S)-**3e**).* White solid material was produced in 98% yield and ee = 86.7%. $[\alpha]_D^{20}$ = −273 (c 1.0, CH_2Cl_2) for ee = 86.7%. Mp: 167.6−168.0 °C. $^{31}P\{^1H\}$ NMR ($CDCl_3$, 162 MHz): δ 51.37 (s, 1P). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31−8.20 (m, 3H, ArH), 8.15 (d, J = 8.5 Hz, 1H, ArH), 7.90 (d, J = 8.5 Hz, 1H, ArH), 7.84−7.76 (m, 2H, ArH), 7.66−7.60 (m, 1H, ArH), 7.60−7.50 (m, 5H, ArH), 7.34 (td, J = 7.2, 1.6 Hz, 1H, ArH), 7.29−7.20 (m, 2H, ArH), 7.16 (dd, J = 8.2, 2.1 Hz, 2H, ArH), 6.87 (d, J = 8.0 Hz, 2H, ArH), 4.92 (td, J = 10.8, 2.7 Hz, 1H, PC*H*CH_2), 4.62 (ddd, J = 17.6, 11.1, 6.3 Hz, 1H, C(O)CH_2), 3.64 (ddd, J = 17.9, 11.1, 2.7 Hz, 1H, C(O)CH_2), 2.18 (d, J = 1.8 Hz, 3H, ArCH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ 199.43 (d, J = 16.2 Hz, 1C, C═O), 152.60−118.33 (27C, Ar), 42.16 (d, $^1J_{PC}$ = 52.5 Hz, 1C, PCH), 38.78 (d, $^2J_{PC}$ = 4.0 Hz, 1C, C(O)CH_2), 21.22 (s, 1C, ArCH_3). Anal. Calcd for $C_{31}H_{26}NOPS$: C, 75.74; H, 5.33; N, 2.85. Found: C, 75.93; H, 5.64; N, 3.02. HRMS (+ESI) m/z: (M + H)$^+$ calcd for $C_{31}H_{27}NOPS$, 492.1551; found, 492.1554.

*(S)-3-(Diphenylphosphorothioyl)-3-(4-methoxyphenyl)-1-(quinolin-2-yl)propan-1-one ((S)-**3f**).* White solid material was produced in 95.1% yield and ee = 86.7%. $[\alpha]_D^{20}$ = −225 (c 0.5, CH_2Cl_2) for ee = 82.1%. Mp: 137.6−138.0 °C. $^{31}P\{^1H\}$ NMR ($CDCl_3$, 162 MHz): δ 51.27 (s, 1P). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32−8.22 (m, 3H, ArH), 8.16 (d, J = 8.5 Hz, 1H, ArH), 7.91 (d, J = 8.5 Hz, 1H, ArH), 7.85−7.76 (m, 2H, ArH), 7.64 (t, J = 7.5 Hz, 1H, ArH), 7.59−7.50 (m, 5H, ArH), 7.34 (td, J = 7.0, 1.2 Hz, 1H, ArH), 7.29−7.26 (m, 1H, ArH), 7.25−7.22 (m, 1H, ArH), 7.19 (dd, J = 8.8, 2.2 Hz, 2H, ArH), 6.61 (d, J = 8.6 Hz, 2H, ArH), 4.90 (td, J = 11.1, 2.6 Hz, 1H, PC*H*CH_2), 4.60 (ddd, J = 17.6, 11.2, 6.3 Hz, 1H, C(O)CH_2), 3.67 (s, 3H, OCH_3), 3.61 (ddd, J = 17.7, 10.7, 2.7 Hz, 1H, C(O)CH_2). ^{13}C NMR (101 MHz, $CDCl_3$): δ 199.52 (d, J = 15.8 Hz, 1C, C═O), 159.03−113.40 (27C, Ar), 55.26 (s, 1C, OCH_3), 41.81 (d, $^1J_{PC}$ = 53.0 Hz, 1C, PCH), 38.83 (d, ^{2}JPC = 4.1 Hz, 1C, C(O)CH_2). Anal. Calcd for $C_{31}H_{26}NO_2PS$: C, 73.35; H, 5.16; N, 2.76. Found: C, 73.27; H, 5.09; N, 2.62. HRMS (+ESI) m/z: (M + H)$^+$ calcd for $C_{31}H_{27}NO_2PS$, 508.1500; found, 508.1495.

*(S)-3-(4-Bromophenyl)-3-(diphenylphosphorothioyl)-1-(quinolin-2-yl)propan-1-one ((S)-**3g**).* White material was produced in 98% yield and ee = 95.6%. $[\alpha]_D^{20}$ = −291 (c 1.0, CH_2Cl_2) for ee > 99%. Mp: 203.5−204.0 °C. $^{31}P\{^1H\}$ NMR ($CDCl_3$, 162 MHz): δ 50.93 (s, 1P). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.31−8.20 (m, 3H, ArH), 8.17 (d, J = 8.5 Hz, 1H, ArH), 7.91 (d, J = 8.5 Hz, 1H, ArH), 7.84−7.75 (m, 2H, ArH), 7.68−7.61 (m, 1H, ArH), 7.61−7.50 (m, 5H, ArH), 7.41−7.33 (m, 1H, ArH), 7.33−7.23 (m, 2H, ArH), 7.23−7.12 (m, 4H, ArH), 4.90 (td, J = 11.0, 2.6 Hz, 1H, PC*H*CH_2), 4.62 (ddd, J = 17.6, 11.2, 6.1 Hz, 1H, C(O)CH_2), 3.61 (ddd, J = 17.9, 10.7, 2.7 Hz, 1H, C(O)CH_2). ^{13}C NMR (101 MHz, $CDCl_3$): δ 199.20 (d, J = 15.4 Hz, 1C, C═O), 152.39−118.25 (27C, Ar), 42.10 (d, $^1J_{PC}$ = 52.4 Hz, 1C, PCH), 38.61 (d, $^2J_{PC}$ = 3.4 Hz, 1C, C(O)CH_2). Anal. Calcd for $C_{30}H_{23}NOPSBr$: C, 64.75; H, 4.17; N, 2.52. Found: C, 64.90; H, 4.39; N, 2.77. HRMS (+ESI) m/z: (M + H)$^+$ calcd for $C_{30}H_{24}NOPSBr$, 556.0500; found, 556.0493.

*(S)-3-(Diphenylphosphorothioyl)-1-(quinolin-2-yl)-3-(4-(trifluoromethyl)phenyl)propan-1-one ((S)-**3h**).* White solid material was produced in 97% yield and ee = 94.6%. $[\alpha]_D^{20}$ = −226 (c 1.0, CH_2Cl_2) for ee > 99%. Mp: 121.9−122.6 °C. $^{31}P\{^1H\}$ NMR ($CDCl_3$, 162 MHz): δ 51.27 (s, 1P). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.32−8.21 (m, 3H, ArH), 8.17 (d, J = 8.5 Hz, 1H, ArH), 7.91 (d, J = 8.5 Hz, 1H, ArH), 7.88−7.74 (m, 2H, ArH), 7.64 (t, J = 7.5 Hz, 1H, ArH), 7.61−7.48 (m, 5H, ArH), 7.45−7.30 (m, 5H, ArH), 7.30−7.19 (m, 2H, ArH), 4.99 (td, J = 10.9, 2.4 Hz, 1H, PC*H*CH_2), 4.70 (ddd, J = 17.6, 11.2, 6.0 Hz, 1H, C(O)CH_2), 3.65 (ddd, J = 18.1, 11.0, 2.5 Hz, 1H, C(O)CH_2). ^{13}C NMR (101 MHz, $CDCl_3$): δ 199.08 (d, J = 15.2 Hz, 1C, C═O), 152.31−118.22 (28C, Ar + CF_3), 42.51 (d, $^1J_{PC}$ = 51.9 Hz, 1C, PCH), 38.62 (d, $^2J_{PC}$ = 3.1 Hz, 1H, C(O)CH_2). Anal. Calcd for $C_{31}H_{23}NOPSF_3$: C, 68.25; H, 4.25; N, 2.57. Found: C, 68.12; H, 4.19; N, 2.44. HRMS (+ESI) m/z: (M + H)$^+$ calcd for $C_{31}H_{24}NOPSF_3$, 546.1268; found, 546.1267.

*(S)-3-(Diphenylphosphorothioyl)-3-(naphthalen-2-yl)-1-(quinolin-2-yl)propan-1-one ((S)-**3i**).* White solid material was produced in 98% yield and ee = 94.3%. $[\alpha]_D^{20}$ = −294 (c 1.0, CH_2Cl_2) for ee > 99%. Mp: 208.0−210.0 °C (dec). $^{31}P\{^1H\}$ NMR ($CDCl_3$, 162 MHz): δ 51.24 (s, 1P). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.35−8.24 (m, 3H, ArH), 8.12 (d, J = 8.5 Hz, 1H, ArH), 7.86 (d, J = 8.5 Hz, 1H, ArH), 7.83−7.77 (m, 2H, ArH), 7.74 (s, 1H, ArH), 7.69−7.59 (m, 3H, ArH), 7.58−7.49 (m, 6H, ArH), 7.41 (d, J = 8.5 Hz, 1H, ArH), 7.38−7.32 (m, 2H, ArH), 7.32−7.26 (m, 1H, ArH), 7.17 (td, J = 7.6, 3.1 Hz, 2H, ArH), 5.11 (td, J = 10.8, 2.7 Hz, 1H, PC*H*CH_2), 4.79 (ddd, J = 17.6, 11.1, 6.2 Hz, 1H, C(O)CH_2), 3.74 (ddd, J = 18.0, 11.0, 2.7 Hz, 1H, C(O)CH_2). ^{13}C NMR (101 MHz, $CDCl_3$): δ 199.33 (d, J = 15.5 Hz, 1C, C═O), 152.52−118.28 (31C, Ar), 42.77 (d, $^1J_{PC}$ = 52.3 Hz, 1C, PCH), 38.88 (d, $^2J_{PC}$ = 3.5 Hz, 1C, C(O)CH_2). Anal. Calcd for $C_{34}H_{26}NOPS$: C, 77.40; H, 4.97; N, 2.65. Found: C, 77.45; H, 5.13; N, 2.76. HRMS (+ESI) m/z: (M + H)$^+$ calcd for $C_{34}H_{27}NOPS$, 528.1551; found, 528.1552.

*(S)-3-(Diphenylphosphorothioyl)-3-phenyl-1-(quinolin-3-yl)-propan-1-one ((S)-**3j**).* White solid material was produced in 99% yield and ee = 95.2%. $[\alpha]_D^{20}$ = −268 (c 1.0, CH_2Cl_2) for ee = 95.2%. Mp: 194.6−195.0 °C. $^{31}P\{^1H\}$ NMR ($CDCl_3$, 121 MHz): δ 51.67 (s, 1P). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.28 (d, J = 2.2 Hz, 1H, ArH), 8.63 (d, J = 2.0 Hz, 1H, ArH), 8.25−8.14 (m, 2H, ArH), 8.10 (d, J = 8.5 Hz, 1H, ArH), 7.90 (d, J = 8.2 Hz, 1H, ArH), 7.86−7.75 (m, 1H, ArH), 7.65−7.57 (m, 1H, ArH), 7.57−7.46 (m, 5H, ArH), 7.40−7.30 (m, 3H, ArH), 7.29−7.19 (m, 2H, ArH), 7.16−7.06 (m, 3H, ArH), 4.90 (td, J = 10.0, 2.8 Hz, 1H, PC*H*CH_2), 4.20 (ddd, J = 17.9, 10.1, 6.2 Hz, 1H, C(O)CH_2), 3.49 (ddd, J = 18.0, 12.1, 2.8 Hz, 1H, C(O)CH_2). ^{13}C NMR (75 MHz, $CDCl_3$): δ 196.05 (d, J = 14.6 Hz, 1C, C═O), 150.00−126.77 (27C, Ar), 41.69 (d, $^1J_{PC}$ = 52.9 Hz, 1C, PCH), 40.03 (d, $^2J_{PC}$ = 3.9 Hz, 1C, C(O)CH_2). Anal. Calcd for $C_{30}H_{24}NOPS$: C, 75.45; H, 5.07; N, 2.93. Found: C, 75.22; H, 4.93; N, 2.88. HRMS (+ESI) m/z: (M + H)$^+$ calcd for $C_{30}H_{25}NOPS$, 478.1394; found, 478.1393.

Typical Experimental Procedure of N-C(sp^3)-E Complex Synthesis via Cyclometalation of Ligand 3. A mixture of $PdCl_2$ (7.4 mg, 42 μmol, 1.0 equiv) and LiCl (7.1 mg, 168 μmol, 4.0 equiv) in 20 mL of solvent was stirred for 30 min. Then, the ligand (*S*)-**3** (42 μmol, 1.0 equiv) was added and this mixture was stirred at room temperature for 2−5 days. The reaction was monitored by thin-layer chromatography (ethyl acetate/*n*-hexanes 2/1) and confirmed by $^{31}P\{^1H\}$ NMR. After completion the solvent was removed under reduced pressure and the crude material was purified via column chromatograpy by using an *n*-hexane/ethyl acetate (from 80/20 to 20/80) eluent system.

*((1R,2R)-1-(Diphenylphosphorothioyl)-3-oxo-1-phenyl-3-(quinolin-2-yl)propan-2-yl)palladium(II) Chloride ((R,R)-**4aa**).* Yellow solid material was produced in 72% yield. $[\alpha]_D^{20}$ = −90 (c 1.0, CH_2Cl_2). Mp: 214.2−215.5 °C (dec). $^{31}P\{^1H\}$ NMR ($CDCl_3$, 162 MHz): δ 67.23 (s, 1P). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.47 (d, J = 8.8 Hz, 1H, ArH), 8.37 (d, J = 8.3 Hz, 1H, ArH), 7.97−7.88 (m, 3H, ArH), 7.85 (d, J = 7.8 Hz, 1H, ArH), 7.76 (d, J = 8.3 Hz, 1H, ArH), 7.71−7.62 (m, 4H, ArH), 7.62−7.51 (m, 3H, ArH), 7.42 (td, J = 7.8, 3.3 Hz, 2H, ArH), 7.25−7.19 (m, 1H, ArH), 7.15 (t, J = 7.6 Hz, 2H, ArH), 7.02 (d, J = 7.4 Hz, 2H, ArH), 5.34 (dd, J = 14.8, 8.8 Hz, 1H, PC*H*), 4.96 (dd, J = 8.7, 6.1 Hz, 1H, PdC*H*). ^{13}C NMR (101 MHz, $CDCl_3$): δ 189.15 (d, J = 14.6 Hz, 1C, C═O), 158.23−118.33 (27C, Ar), 57.53 (d, $^2J_{PC}$ = 5.9 Hz, 1C, PdCH), 53.37 (d, $^1J_{PC}$ = 58.8 Hz, 1C, PCH). Anal. Calcd for $C_{30}H_{23}NOPPdSCl$: C, 58.27; H, 3.75; N, 2.26. Found: C, 58.04; H, 3.65; N, 2.41. HRMS (+ESI) m/z: (M + H)$^+$ calcd for $C_{30}H_{24}NOP^{108}PdSCl$, 620.0044; found, 620.0032.

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*((1R,2R)-1-(Diphenylphosphoryl)-3-oxo-1-phenyl-3-(quinolin-2-yl)propan-2-yl)palladium(II) Chloride ((R,R)-**4ab**).* Yellow solid material was produced in 70% yield. $[\alpha]_D^{20}$ = −117 (*c* 1.0, CH_2Cl_2). Mp: 179.0−180.0 °C (dec). $^{31}P\{^1H\}$ NMR ($CDCl_3$, 162 MHz): δ 73.24 (s, 1P). ^1H NMR (400 MHz, $CDCl_3$): δ 9.44 (d, *J* = 8.8 Hz, 1H, ArH), 8.36 (d, *J* = 8.3 Hz, 1H, ArH), 8.01 (dd, *J* = 11.2, 7.9 Hz, 2H, ArH), 7.91 (t, *J* = 7.7 Hz, 1H, ArH), 7.81 (d, *J* = 8.0 Hz, 1H, ArH), 7.72−7.48 (m, 8H, ArH), 7.44−7.33 (m, 2H, ArH), 7.21−7.06 (m, 5H, ArH), 5.27 (dd, *J* = 7.4, 5.4 Hz, 1H, PdC*H*), 4.96 (dd, *J* = 14.1, 7.7 Hz, 1H, PC*H*). ^{13}C NMR (101 MHz, $CDCl_3$): δ 188.58 (d, *J* = 10.1 Hz, 1C, C═O), 159.52−118.20 (27C, Ar), 59.70 (s, 1C, PdCH), 48.06 (d, *J* = 71.7 Hz, 1C, PCH). Anal. Calcd for $C_{30}H_{23}NO_2PPdCl$: C, 59.82; H, 3.85; N, 2.33. Found: C, 59.99; H, 4.05; N, 2.58. HRMS (+ESI) *m*/*z*: (M + H)$^+$ calcd for $C_{30}H_{24}NO_2P^{106}PdCl$, 602.0268; found, 602.0281.

*((1R,2R)-1-(Diphenylphosphorothioyl)-3-(6-methylpyridin-2-yl)-3-oxo-1-phenylpropan-2-yl)palladium(II) Chloride ((R,R)-**4ca**).* Yellow material was produced in 63% yield. $[\alpha]_D^{20}$ = −77 (*c* 1.0, CH_2Cl_2). Mp: 210.5−212.0 °C (dec). $^{31}P\{^1H\}$ NMR ($CDCl_3$, 162 MHz): δ 67.30 (s, 1P). ^1H NMR (400 MHz, $CDCl_3$): δ 7.94−7.85 (m, 2H, ArH), 7.75 (t, *J* = 7.7 Hz, 1H, ArH), 7.69−7.50 (m, 7H, ArH), 7.42 (td, *J* = 7.9, 3.3 Hz, 2H, ArH), 7.29 (d, *J* = 7.8 Hz, 1H, ArH), 7.24−7.17 (m, 1H, ArH), 7.14 (t, *J* = 7.6 Hz, 2H, ArH), 7.02−6.97 (m, 2H, ArH), 5.28 (dd, *J* = 14.9, 8.8 Hz, 1H, PC*H*), 4.79 (dd, *J* = 8.7, 6.1 Hz, 1H, PdC*H*), 3.09 (s, 3H, ArCH_3). ^{13}C NMR (101 MHz, $CDCl_3$): δ 189.04 (d, *J* = 14.7 Hz, 1C, C═O), 162.46−119.61 (23C, Ar), 56.37 (d, $^2J_{PC}$ = 6.0 Hz, 1C, PdCH), 53.59 (d, $^1J_{PC}$ = 59.0 Hz, 1C, PCH), 26.04 (s, 1C, ArCH_3). Anal. Calcd for $C_{27}H_{23}NOPPdSCl$: C, 55.68; H, 3.98; N, 2.41. Found: C, 55.51; H, 3.86; N, 2.69. HRMS (+ESI) *m*/*z*: (M + H)$^+$ calcd for $C_{27}H_{24}NOPPdSCl$, 582.0040; found, 582.0022

*((1R,2R)-1-(Diphenylphosphorothioyl)-3-(6-(4-methoxyphenyl)pyridin-2-yl)-3-oxo-1-phenylpropan-2-yl)palladium(II) Chloride ((R,R)-**4da**).* Yellow solid material was produced in 31% yield. $[\alpha]_D^{20}$ = −94 (*c* 1.0, CH_2Cl_2). Mp: 200.0−201.5 °C (dec). $^{31}P\{^1H\}$ NMR ($CDCl_3$, 162 MHz): δ 67.35 (s, 1P). ^1H NMR (400 MHz, $CDCl_3$): δ 8.04 (d, *J* = 8.8 Hz, 2H, ArH), 7.93−7.84 (m, 3H, ArH), 7.83−7.74 (m, 2H, ArH), 7.69−7.57 (m, 4H, ArH), 7.57−7.44 (m, 4H, ArH), 7.25−7.15 (m, 3H, ArH), 7.12 (d, *J* = 8.8 Hz, 2H, ArH), 7.10−7.04 (m, 2H, ArH), 5.29 (dd, *J* = 14.9, 8.7 Hz, 1H, PCH), 4.93 (dd, *J* = 8.7, 6.4 Hz, 1H, PdCH), 3.93 (s, 3H, OCH_3). ^{13}C NMR (75 MHz, $CDCl_3$): δ 187.81 (d, *J* = 14.7 Hz, 1C, C═O), 161.72−114.28 (29C, Ar), 56.27 (d, $^2J_{PC}$ = 5.6 Hz, 1C, PdCH), 55.57 (s, 1C, OCH_3), 53.51 (d, $^1J_{PC}$ = 59.3 Hz, 1C, PCH). Anal. Calcd for $C_{33}H_{27}NO_2PPdSCl$: C, 58.77; H, 4.04; N, 2.08. Found: C, 58.76; H, 3.96; N, 2.09. HRMS (+ESI) *m*/*z*: (M + H)$^+$ calcd for $C_{33}H_{28}NO_2P^{108}PdSCl$, 676.0306; found, 676.0338.

*((1R,2R)-1-(Diphenylphosphorothioyl)-3-oxo-3-(quinolin-2-yl)-1-(4-(trifluoromethyl)phenyl)propan-2-yl)palladium(II) Chloride ((R,R)-**4ha**).* Yellow solid material was produced in 58% yield. $[\alpha]_D^{20}$ = −82 (*c* 1.0, CH_2Cl_2). Mp: 203.0−204.0 °C (dec). $^{31}P\{^1H\}$ NMR ($CDCl_3$, 162 MHz): δ 67.63 (s, 1P). ^1H NMR (300 MHz, $CDCl_3$): δ 9.47 (d, *J* = 8.7 Hz, 1H, ArH), 8.39 (d, *J* = 8.4 Hz, 1H, ArH), 8.01−7.89 (m, 3H, ArH), 7.86 (d, *J* = 8.1 Hz, 1H, ArH), 7.76 (d, *J* = 8.3 Hz, 1H, ArH), 7.74−7.54 (m, 7H, ArH), 7.51−7.38 (m, 4H, ArH), 7.15 (d, *J* = 7.4 Hz, 2H, ArH), 5.38 (dd, *J* = 15.1, 8.7 Hz, 1H, PCH), 4.91 (dd, *J* = 8.6, 6.3 Hz, 1H, PdCH). ^{13}C NMR (101 MHz, $CDCl_3$): δ 189.37 (d, *J* = 14.1 Hz, 1C, C═O), 157.96−118.33 (28C, Ar + CF_3), 56.86 (d, $^2J_{PC}$ = 5.7 Hz, 1C, PdCH), 53.03 (d, $^1J_{PC}$ = 58.9 Hz, 1C, PCH). Anal. Calcd for $C_{31}H_{22}NOPPdSF_3Cl$: C, 54.24; H, 3.23; N, 2.04. Found: C, 54.56; H, 3.49; N, 2.30. HRMS (+ESI) *m*/*z*: (M + H)$^+$ calcd for $C_{31}H_{23}NOP^{108}PdSF_3Cl$, 687.9918; found, 687.9921.

*((1R,2R)-1-(Diphenylphosphorothioyl)-1-(naphthalen-2-yl)-3-oxo-3-(quinolin-2-yl)propan-2-yl)palladium(II) Chloride ((R,R)-**4ia**).* Yellow solid material was produced in 42% yield. $[\alpha]_D^{20}$ = −81 (*c* 1.0, CH_2Cl_2). Mp: 200.5−202.0 °C (dec). $^{31}P\{^1H\}$ NMR ($CDCl_3$, 162 MHz): δ 68.07 (s, 1P). ^1H NMR (500 MHz, $CDCl_3$): δ 9.49 (d, *J* = 8.8 Hz, 1H, ArH), 8.36 (d, *J* = 8.3 Hz, 1H, ArH), 7.96−7.88 (m, 3H, ArH), 7.85 (d, *J* = 8.1 Hz, 1H, ArH), 7.78−7.72 (m, 4H, ArH), 7.69 (t, *J* = 7.6 Hz, 1H, ArH), 7.66−7.62 (m, 2H, ArH), 7.61−7.51 (m, 4H, ArH), 7.47−7.37 (m, 4H, ArH), 7.34 (s, 1H, ArH), 7.15 (d, *J* = 8.5 Hz, 1H, ArH), 5.51 (dd, *J* = 15.3, 9.3 Hz, 1H, PCH), 5.06 (dd, *J* = 9.3, 5.4 Hz, 1H, PdCH). ^{13}C NMR (126 MHz, $CDCl_3$): δ 189.11 (d, *J* = 15.5 Hz, 1C, C═O), 158.22−118.38 (31C, Ar), 57.97 (d, $^2J_{PC}$ = 6.3 Hz, 1C, PdCH), 54.04 (d, $^1J_{PC}$ = 59.0 Hz, PCH). Anal. Calcd for $C_{34}H_{25}NOPPdSCl$: C, 61.09; H, 3.77; N, 2.10. Found: C, 61.36; H, 3.90; N, 2.24. HRMS (+ESI) *m*/*z*: (M + H)$^+$ calcd for $C_{34}H_{26}NOP^{106}PdSCl$, 668.0196; found, 668.0215.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organomet.8b00262.

General methods, NMR spectra, coordination study, HPLC spectra, and X-ray measurement data (PDF)

Accession Codes

CCDC 1835818−1835819, 1835822−1835827, 1836590, and 1836617 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(19) Optimized conditions on the basis of Huang's report: 0.30 mmol of $HPPh_2$, 5 mol % of (*R*)-**5**, 5 mL of THF, 1.0 equiv of enone **10**, 0.5 equiv of Et_3N reacted at −80 °C for 20 h; yield 99%; ee = 92%; after single recrystallization, yield 71%, ee ≥ 99%.[5c]
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