Asymmetric Synthesis and Organometallic Chemistry of Functionalized Phosphines Containing Stereogenic Phosphorus Centers

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ABSTRACT
A series of organometallic reagents containing orthometalated chiral amine auxiliaries have been utilized as chiral templates to activate phospholes, vinylphosphines, and alkynylphosphines toward asymmetric ligand transformations via cycloaddition and hydroamination reactions. By a systemic manipulation of the subtle stereoelectronic properties of the auxiliaries and the metal centers, the template properties could be modified and the origins of stereoselectivity revealed. The chiral templates are able to control the disposition of selected functionalities into designated locations on the transformed P-stereogenic mono- and diphosphine ligands. This Account provides an overview of our recent work in this area.

Introduction

Enantiomerically pure phosphines and diphosphines containing stereogenic phosphorus centers and selected functionalities have long been considered as powerful auxiliaries for metal-based homogeneous asymmetric catalysis.[1] These chiral ligands have also been used extensively in chemotherapy, biochemistry, and asymmetric organic synthesis.[2] Unfortunately, numerous synthetic challenges including the lack of a natural pool of chirality as well as the high chemical reactivity and configurational instability[3] of the phosphorus stereocenters had hindered the asymmetric synthesis of these important ligands. So far, most of the reported P-stereogenic phosphines have been prepared via their borane complexes[4] or by optical resolution. To date, palladium(II) complexes containing enantiomerically pure forms of orthometalated [1-(dimethylamino)ethyl]naphthalene are considered the most efficient resolving agents for certain types of heterobidentate phosphines.[5] When monodentates or other resolving agents are involved, however, the resolution process could become rather tedious and inefficient. Furthermore, separation of diastereomers is a prerequisite when the target ligand contains more than one stereogenic center. This Account reviews our recent work on the asymmetric synthesis of functionalized P-stereogenic phosphines by means of metal template-promoted [4+2] cycloaddition and hydroamination reactions. In several cases, up to six stereogenic centers could be generated stereospecifically in a single step.

Pak-Hing Leung obtained his B.Sc.(Hons) degree from the Polytechnic of North London (1982) and Ph.D. (1986) from the Australian National University, advised by Professor S. Bruce Wild. He continued his postdoctoral training with Professor Brice Bosnich both at the University of Toronto and later at the University of Chicago. He joined the faculty at the National University of Singapore in 1989 and was recipient of the Outstanding University Researcher Award in 1998. Currently he is a Professor and the Deputy Head in the Chemistry Department. His research interests include stereochemistry of organometallic compounds, asymmetric synthesis, and development of gold-based anti-cancer drugs.

Chiral Metal Templates Promoted Cycloaddition Reactions

Choice of Chiral Templates. The asymmetric Diels−Alder reaction is one of the most efficient and elegant methods for the construction of chiral six-membered rings. Recently, we have been able to apply this synthetic methodology for the asymmetric synthesis of functionalized mono- and diphosphines. One of our approaches involves the activation of the five-membered heterocycle 3,4-dimethyl-1-phenylphosphole (DMPP)[6] as a cyclic diene for the cycloaddition reaction. A key conceptual feature in this synthetic approach is that DMPP itself is not a reactive cyclic diene but becomes reactive when it is coordinated onto a transition metal ion.[7] This feature provides a unique opportunity for controlling the stereochemistry of the cycloaddition reaction by incorporating an appropriate chiral auxiliary onto the activating metal ion. We have chosen the orthometalated dimethyl-[1-(α-naphthyl)ethyl]-amine as the chiral auxiliary in most of our phosphine syntheses, as shown in the palladium complex **1**[8,9] (Scheme 1). Both enantiomeric forms of the naphthylamine auxiliary are commercially available and they have been used for the asymmetric synthesis of selected enantiomers of the targeted ligands. For clarity, only the *R* enantiomer is used for stereochemical illustrations in this Account. It is noteworthy that the enantiomeric forms of all the chiral phosphine compounds in the discussion have been prepared similarly by use of the *S* form of the naphthylamine as the auxiliary.

A unique stereochemical feature of the chiral naphthylamine chelate ring in (R_c)-**1** is that there is an internal steric repulsion between the methyl substituent on the stereogenic carbon and its neighboring naphthylene proton.[10] The crystallographic determinations and rotating Overhauser effect (ROESY) NMR investigations confirmed that the organometallic ring is locked into the static δ conformation, both in the solid state and in solution.[11] Thus the prochiral NMe groups are fixed into the nonequivalent axial and equatorial positions. These NMe groups control the stereochemistry of the neighboring coordination sites. Electronically, the σ-donating nitrogen and the π-accepting naphthylene carbon of the organopalladium ring control the regioselectivity of the incoming ligands: DMPP and other ligands with soft donors prefer to take up the coordination position trans to the NMe_2 moiety. On the other hand, the weak and labile perchlorato−palladium bond in (R_c)-**1** can be displaced by most electron-rich functionalities in the reacting dienophiles to form a cationic intermediate such that both DMPP and

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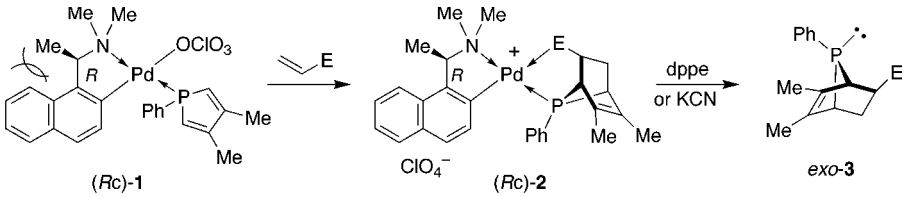
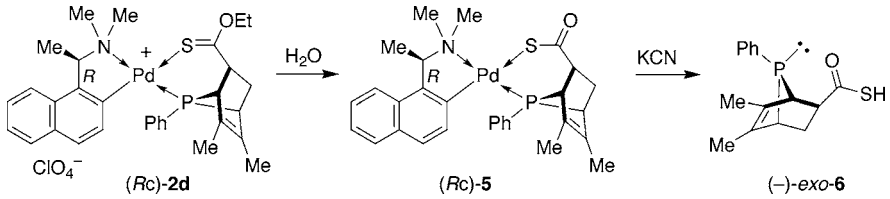
Scheme 1



(*Rc*)-**1** (*Rc*)-**2** *exo*-**3**

		temp °C	time	isolated yield %
(*Rc*)-**2a**	E = –C(O)NMe$_2$	25	3 d	85
(*Rc*)-**2b**	E = –C(O)Et	25	9 d	73
(*Rc*)-**2c**	E = –C(O)OMe	75	14 d	48
(*Rc*)-**2d**	E = –C(S)OEt	75	15 h	15 (unstable)
(*Rc*)-**2e**	E = –C(S)NMe$_2$	25	6 d	58
(*Rc*)-**2f**	E = –SPh	75	17 d	65
(*Rc*)-**2g**	E = –S(O)CH=CH$_2$	75	4 d	40
(*Rc*)-**2h**	E = –2-pyridyl	75	20 d	60

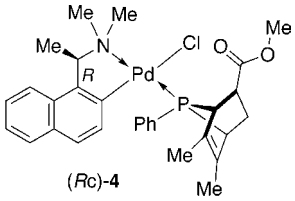
Scheme 2



(*Rc*)-**2d** (*Rc*)-**5** (–)-*exo*-**6**

the reacting dienophile are coordinated simultaneously onto the chiral template during the course of cycloaddition reaction. Due to these special steric and electronic features, *exo*-cycloadducts are always formed with high stereoselectivity when (R_c)-**1** is used as the reaction template (Scheme 1).

Synthesis of Monophosphines via *exo*-*Cycloaddition Reaction.* The amido group in *N*,*N*-dimethylacrylamide displaced the perchlorato ligand in (R_c)-**1**, thus allowing the intramolecular cycloaddition reaction to take place on the chiral template.[12,13] The amidophosphine *exo*-cycloadduct was generated stereospecifically on the cationic template complex (R_c)-**2a**. The ambidentate amido functional group in the cycloadduct coordinated to the palladium template via its oxygen atom to form a stable P−O chelate, while the amido−nitrogen atom is not involved in metal complexation. The selective formation of the stable P−O chelate in (R_c)-**2a** is interesting as such Pd−O bonds in amido complexes are usually unstable and readily displaced by water. Under similar conditions, the *exo*-cycloaddition reaction between (R_c)-**1** and ethyl vinyl ketone gave the stable keto-substituted *exo*-cycloadduct (R_c)-**2b**.[14] Apparently, ethyl vinyl ketone is less reactive than *N*,*N*-dimethylacrylamide toward the chiral template as it required longer reaction time to form (R_c)-**2b**. On the other hand, prolonged heating was required for the reaction between methyl acrylate and (R_c)-**1**.[15] Unlike those observed in the cycloadducts **2a** and **2b**, the C═O−Pd bond in the ester-substituted complex (R_c)-**2c** is unstable and readily displaced by other donor atoms. The formation of this *exo*-cycloadduct, however, indicated that a weak ester C═O−Pd interaction must be involved in the reaction intermediate. Clearly, the intrinsic electronic delocalization between the two oxygen atoms in the ester group renders the carbonyl oxygen a poor electron donor and thus hampers the formation of a stable C═O−Pd bond. In contact with an aqueous sodium chloride solution, (R_c)-**2c** was converted quantitatively to the stable monodentate *exo*-cycloadduct (R_c)-**4**.

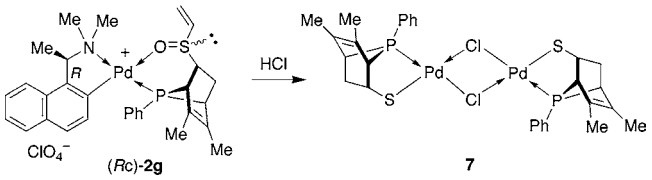


(*Rc*)-**4**

Structurally, the C═S-substituted dienophile ethyl-*trans*-crotonthiolate is analogous to methyl acrylate. Interestingly, the synthesis of the *exo*-thionoester cycloadduct (R_c)-**2d** was markedly faster (15 h) than the formation of the ester complex (R_c)-**2c** (14 days), despite the fact that both reactions were conducted under similar conditions.[15] Evidently, the strength of the dienophile−template interactions affects the rate of the cycloaddition reactions. However, the stronger EtO−C═S−Pd coordination in (R_c)-**2d** also renders the thionoester function highly susceptible to hydrolysis. Upon contact with water, removal of the EtO group in the thionoester function occurred rapidly and resulted in the formation of a stable O═C−S−Pd moiety (Scheme 2). Treatment of the thiocarboxylate complex (R_c)-**5** with aqueous cyanide liberated the thiocarboxylate-substituted ligand (−)-*exo*-**6**.

Interestingly, substitution of the C═O group with a C═S moiety in the dienophile and the formation of a strong C═S−Pd bond do not always warrant a faster cycloaddition reaction. For example, the formation of the amido-substituted cycloadduct (R_c)-**2a** was completed in only 3 days. Under similar reaction conditions, however, it requied 6 days to generate the P−S cycloadduct (R_c)-**2e** from the reaction between (R_c)-**1** and *N*,*N*-dimethylthio-

Scheme 3



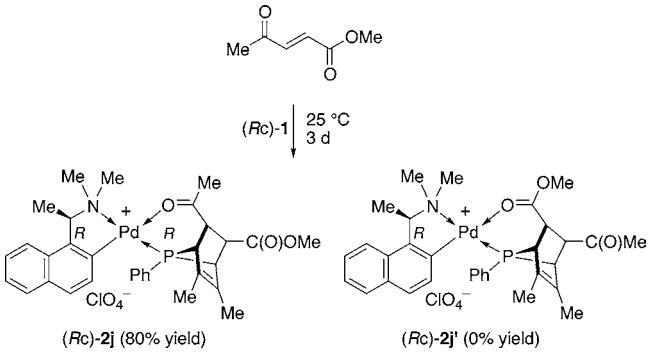
acrylamide.[16] Interestingly, the thiocarbamoyl group in (R_c)-**2e** is stable toward hydrolysis.

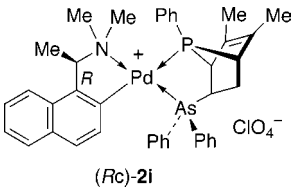
Unlike the sulfur atom in the C═S moiety, thioethers form weak and labile S−Pd bonds. Due to the weak template−dienophile interaction, it took 17 days for the reaction between (R_c)-**1** and phenyl vinyl sulfide to completely generate (R_c)-**2f**, despite the fact that the reaction was conducted in refluxing 1,2-dichloroethane.[17] It is noteworthy that the coordinated sulfur atom in the sulfanyl-substituted P−S cycloadduct (R_c)-**2f** is a chiral center, but it equilibrates rapidly between the two configurations in solution.

The synthesis of the *exo*-cycloadducts in complexes (R_c)-**2a**−**f** illustrates that the palladium template (R_c)-**1** is able to interact with both thia- and oxa-substituted dienophiles through the S−Pd and O−Pd bonds. In general, palladium(II) is considered as a "soft" metal ion and prefers to coordinate to the softer sulfur donor than the harder oxygen atom. Surprisingly, (R_c)-**1** was found to interact only with the oxygen atom in the ambidentate sulfoxide moiety. The P−O cycloadduct (R_c)-**2g** was generated chemoselectively from the reaction between (R_c)-**1** and divinyl sulfoxide.[18,19] It is noteworthy that the uncoordinated sulfinyl sulfur atom in (R_c)-**2g** is a stable stereogenic center. Unfortunately, due to the prolonged heating conditions, the sulfinyl S chirality could not be generated stereoselectively. The cycloadduct (R_c)-**2g** was obtained as a 1:1 diastereomeric mixture, which could be separated by silica gel chromatography or by fractional crystallization. Interestingly, the S═O−Pd coordination renders the sulfinyl function unstable toward acid hydrolysis.[19] In contact with dilute HCl, a reductive cleavage of the S═O and the vinylic S−C bonds in the diastereomeric complexes occurred, thus generating a single optically pure thiolato-substituted cycloadduct **7** (Scheme 3). Both the chiralities at the sulfur atom and the naphthylamine auxiliary were removed during the acid hydrolysis.

Apart from the oxo- and thia-substituted dienophiles, the chiral template (R_c)-**1** is also reactive toward aza-substituted dienophiles, although strong reaction conditions are usually required. For example, the reaction between (R_c)-**1** and 2-vinylpyridine in refluxing 1,2-dichloroethane for 20 days generated the P−N cycloadduct (R_c)-**2h** as the sole product in a moderate yield.[20] Interestingly, the template (R_c)-**1** is found to be even more reactive toward vinylarsines than the well-known dienophile 2-vinylpyridine, despite the fact that vinylarsines were unknown to react as dienophiles previously. For example, the reaction between diphenylvinylarsine and template (R_c)-**1** at room temperature was completed in 3 days to give the optically pure As−P cycloadduct (R_c)-**2i** in 50% yield.[21] A unique structural feature in (R_c)-**2i** is that the phosphanorbornene-P donor is coordinated on the template in the position trans to the strong π-accepting naphthylene carbon. The regiochemistry observed in (R_c)-**2i** suggested that the arsenic atom in diphenylvinylarsine is a stronger π-acceptor than the phosphorus atom in DMPP. The ligand redistribution process between the two precursors is clearly faster than the cycloaddition reaction. Recently, Wild and Nelson and their co-workers[22] observed a similar regioselectivity when they reacted (R_c)-**1** with dicyclohexylvinylarsine. The enantiomerically pure *exo*-phosphanorbornenes *exo*-**3** could be liberated in 70−90% yields from the corresponding template complexes by treatment with aqueous cyanide or by displacement with dppe.[5a]

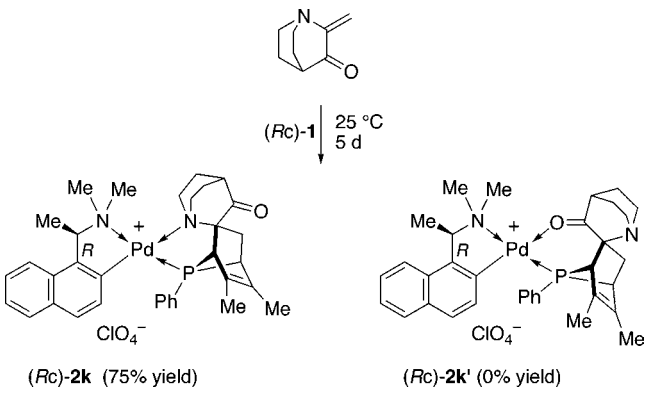
Scheme 4





Molecular Recognition in the *exo*-Cycloaddition Reaction. The synthesis of the *exo*-cycloadducts **2a**−**i** involves various types of template−dienophile interactions. Thus, competition for the coordination site in the chiral template may occur when a dienophile containing two or more types of functional groups is used for the *exo*-cycloaddition reaction. This competition, if it occurs, will increase the number of possible isomeric products and thus hamper the potential application of (R_c)-**1** for the asymmetric synthesis of multifunctional phosphines. Amazingly, (R_c)-**1** shows a high degree of recognition toward different functionalities. For example, when the template complex was treated with methyl-*trans*-4-oxo-2-pentenoate, the keto C═O−Pd cycloadduct (R_c)-**2j** was generated exclusively (Scheme 4).[23] The other possible ester C═O−Pd complex (R_c)-**2j′** was not generated in this reaction. A similar selectivity was observed when 2-methylene-3-quinuclidinone was used as the dienophile (Scheme 5).[24] According to its structure, the dienophile may interact with the template either via its keto oxygen or the amino nitrogen donor to form (R_c)-**2k** or (R_c)-**2k′**, respectively. However, only the N−Pd cycloadduct (R_c)-**2k** was formed in the synthesis. In view of the selective

Scheme 5

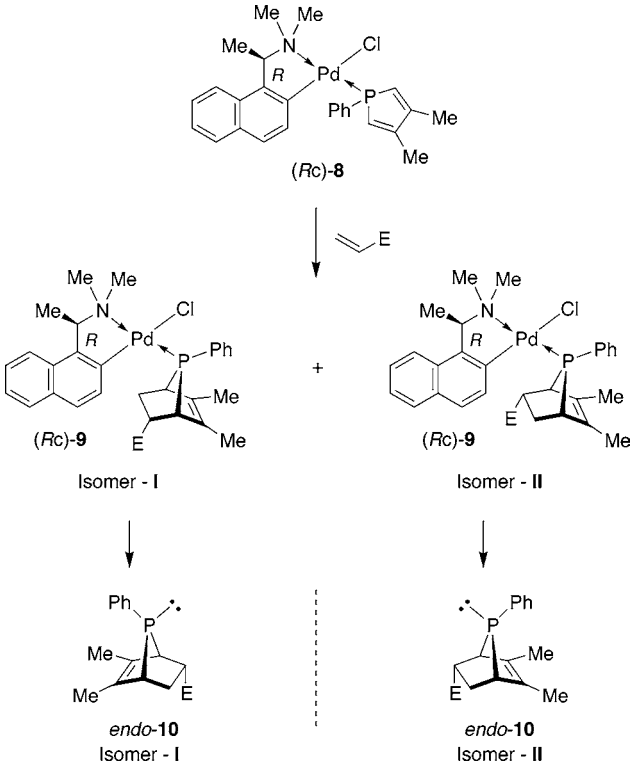


formation of the C═O−Pd coordination in the amido complex (R_c)-**2a**, the adoption of the sterically unfavorable N−Pd bond in (R_c)-**2k** is surprising. Undoubtedly the chiral template is sensitive toward the subtle electronic properties of the nitrogen and oxygen atoms in various functionalities.

Synthesis of Monophosphines via *endo*-Cycloaddition Reaction. The readily available template site in the complex (R_c)-**1** can be sealed off effectively by replacing the perchlorato ligand with the chloro counterpart. Thus the weaker donors in most organic dienophiles are not able to cleave the thermodynamically stable and kinetically inert Pd−Cl bond in (R_c)-**8** for interaction with the palladium center,[25] which therefore deters the formation of any bidentate *exo*-cycloadduct. However, the activated DMPP ligand in the chloro complex can undergo an intermolecular *endo*-cycloaddition reaction. As shown in Scheme 6, (R_c)-**8** is reactive toward a range of dienophiles, including styrene[13] and 1-methyl-2-vinylpyrrole.[26] Stereochemically, the *endo*-cycloaddition reaction is controlled by the chiral template via only a single and rotatable P−Pd bond. Thus this intermolecular process does not show high stereoselectivity and produces a pair of diastereomeric *endo*-cycloadducts, i.e., isomers **I** and **II** of (R_c)-**9**. In most syntheses, however, the two diastereomers are obtained in nonequivalent ratios and they can be separated by fractional crystallization or by column chromatography. With the exception of (R_c)-**9h**,[27] all the phosphanorbornene cycloadducts described in this Account are stable toward the retro Diels−Alder reaction.

Several interesting reactivity patterns were observed in the present chiral template-promoted *endo*- and *exo*-cycloaddition reactions. When reactive dienophiles were involved, the *endo*-cycloaddition reactions usually proceeded at notably faster rates than the corresponding *exo* processes. For example, under similar reaction conditions, the formation of the ester-substituted *endo*- and *exo*-cycloadducts required 3 and 14 days, respectively.[12] Similarly, it took only 4 days to form the pyridyl-substituted *endo*-cycloadduct but the corresponding *exo*-cycloaddition reaction required 20 days to complete.[17] In a contradicting observation, the *exo*-cycloaddition reactions proceeded at significantly faster rates than the corresponding *endo* processes when the less reactive dienophiles were utilized. For example, the formation of

Scheme 6

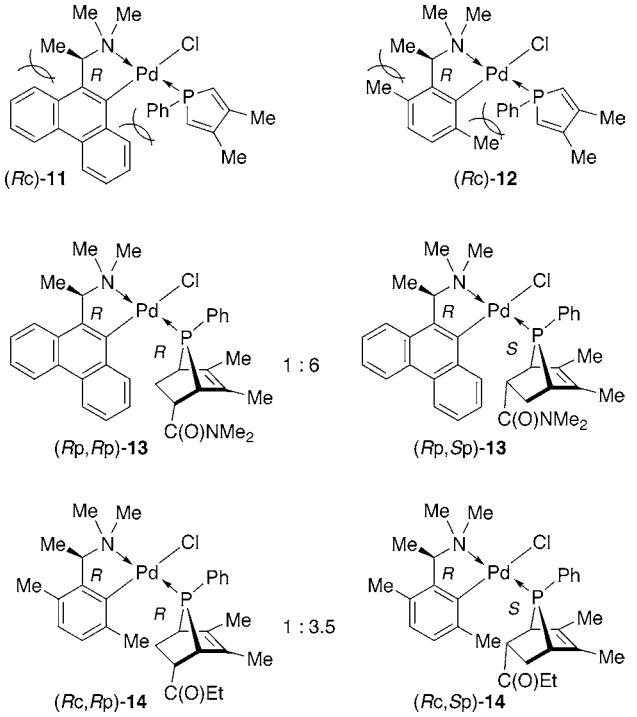


	E	temp °C	time	isomeric ratio I : II
(*Rc*)-**9a**	C(O)NMe$_2$	25	32 d	2 : 1
(*Rc*)-**9b**	C(O)Et	25	6 d	1 : 2.5
		70	16 h	1 : 1
(*Rc*)-**9c**	C(O)OMe	75	3 d	1 : 1.5
(*Rc*)-**9d**	C(S)NMe$_2$	25	60 d	3 : 1
(*Rc*)-**9e**	2-pyridyl	75	4 d	1 : 1
(*Rc*)-**9f**	Ph	80	3 d	1 : 1.5
(*Rc*)-**9g**	N-methyl-2-pyrrole	85	5 d	1 : 1
(*Rc*)-**9h**	S(O)$_2$Ph	80	2 d	1 : 3

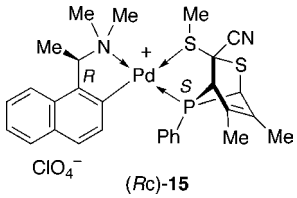
the amido-[12,13] and thioamido-[16] substituted *exo*-cycloadducts is at least 10 times faster than their *endo* analogues. From a mechanistic standpoint, the intramolecular *exo*-cycloaddition reaction involves a cationic intermediate in which both DMPP and the reacting dienophile are coordinated simultaneously onto the chiral template during the course of reaction. On the other hand, a neutral transition state is involved in the intermolecular *endo*-cycloaddition reaction. Classically, the faster reaction rates in the intermolecular reactions are attributed to the higher degree of electronic activation offered by the neutral metal template to the coordinated cyclic diene. Therefore the coordinated DMPP ligand in (R_c)-**8** is indeed expected to be more reactive toward various dienophiles than its counterpart in (R_c)-**1**. The prolonged reaction time observed in the *endo*-cycloaddition reactions involving the amido- and thioamido-substituted dienophiles was merely due to the intrinsic electronic resonance features within these two functional groups. The C═C bonds in *N*,*N*-dimethylacrylamide and *N*,*N*-dimethylthioacrylamide are less polarized than their counterparts in methyl acrylate

and in 2-vinylpyridine. Considering these classical electronic-reactivity factors, it may be rather intriguing, at first glance, to record some relatively fast *exo*-cycloaddition reactions in which the presumably less reactive cyclic diene and dienophiles were involved. The metal−dienophile interactions in these intramolecular processes must have provided significant activation to these less reactive dienophiles. These dienophile interactions occur at the electronically deficient template position that is trans to the strong π-accepting orthometalated naphthylene carbon. The formation of the O−Pd and the S−Pd bonds in the cationic intermediates, for example, dramatically enhances the polarization of the vinylic moieties in *N*,*N*-dimethylacrylamide and *N*,*N*-dimethylthioacrylamide, respectively. A similar S−Pd coordination activated the dienophilicity of ethyl-*trans*-crotonthiolate in the *exo*-cycloaddition reaction with (R_c)-**1**. Such a dienophile activation is not allowed by the chloro template (R_c)-**8**, and the thionoester-substituted dienophile is therefore not reactive toward the *endo*-cycloaddition reaction. On the other hand, both styrene and 1-methyl-2-vinylpyrrole do not have any suitable donor atoms for the metal−dienophile interactions. Accordingly, they do not react with the heterocyclic diene in (R_c)-**1**, despite the fact that a coordination site is readily available. The DMPP ligand in (R_c)-**1** does not show sufficient reactivity toward the alternative intermolecular *endo*-cycloaddition reactions with the dienophiles.

Enhanced Stereoselectivity in *endo*-Cycloaddition Reaction. As discussed earlier, the two *endo*-diastereomers of (R_c)-**9** could usually be separated by fractional crystallization or by column chromatography. In several syntheses, however, the separation process was somewhat tedious and resulted in lower yields of a targeted enantiomer. To improve their stereoselectivity, two new complexes **11**[28] and **12**[29] have been utilized as the chiral templates in these *endo*-cycloaddition reactions. Both enantiomeric forms of the phenanthrylamine and the dimethylbenzylamine auxiliaries were obtained via optical resolutions. The two new complexes exhibit the major stereoelectronic properties of the original naphthylamine template. For example, the static δ organometallic ring conformation in both (R_c)-**11** and (R_c)-**12** has been locked by a spacer. Furthermore, a second spacer is introduced on the aromatic carbon, which is adjacent to the Pd−C bond on each template complex. The second spacers were designed to project the stereochemistry of the chiral amine auxiliaries to their neighboring template sites. Unlike (R_c)-**1**, all the template sites in (R_c)-**11** and (R_c)-**12** are efficiently controlled by the new chiral auxiliaries. The new chiral templates indeed generated the *endo*-cycloadducts with significantly higher stereoselectivities. For example, the reaction between (R_c)-**11** and *N*,*N*-dimethylacrylamide generated a 1:6 mixture of the two expected diastereomers (R_c, R_p)- and (R_c, S_p)-**13**, respectively. When the naphthylamine template (R_c)-**1** was used, however, the diastereomeric complexes (R_c, R_p)- and (R_c, S_p)-**9a** were obtained in a 2:1 ratio, despite the fact that the synthesis was conducted at a lower temperature with a prolonged reaction time. Similarly, (R_c)-**1** produced equal quantities of the keto complexes (R_c, R_p)- and (R_c, S_p)-**9b** when the corresponding *endo*-cycloaddition was conducted at 70 °C. Under such conditions, the reaction between (R_c)-**12** and ethyl vinyl ketone gave the diastereomeric complexes (R_c, R_p)- and (R_c, S_p)-**14** in an improved ratio of 1:3.5.

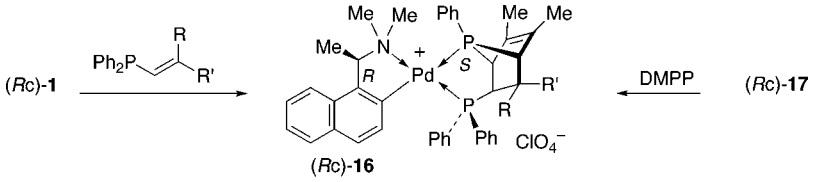


Asymmetric Hetero Diels−Alder Reaction. Apart from the stereoselective formation of two carbon−carbon bonds, the heterocyclic diene in (R_c)-**1** is also reactive toward the C═S bond in cyanodithioformate.[30] At room temperature, the heterodienophile reacted with (R_c)-**1** within 24 h to generate the stable 6-thia-7-phospha-substituted cycloadduct (R_c)-**15**. The 6-thia sulfur atom in the phosphanorbornene backbone and the attached nitrile function are not involved in metal complexation. Experimentally, cyanodithioformate is a more reactive dienophile than phenyl vinyl sulfide since shorter reaction time and lower temperature were required for the heterocycloaddition reaction. However, both dienophiles are not reactive toward the coordinated DMPP in the chloro complex (R_c)-**8**. Apparently, the S−Pd coordination is essential for the dienophiles to activate their dienophilicity toward the cycloaddition reaction.



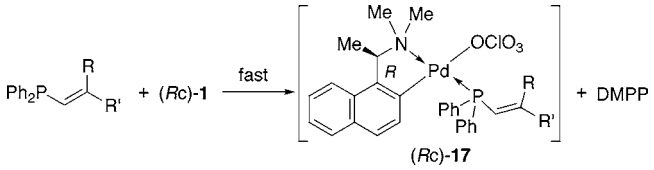
Synthesis of Diphosphines via *exo*-Cycloaddition Reaction. Similar to DMPP, uncoordinated vinylphosphines do not show the necessary dienophilicity toward cycloaddition reaction. When they are coordinated on the same transition metal ion, however, DMPP and vinylphosphines

Scheme 7

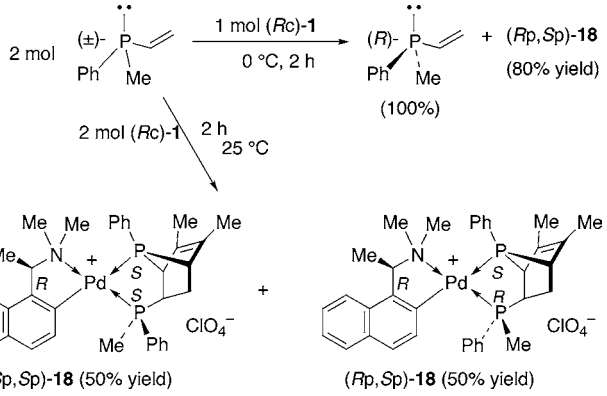


		temp °C	time	isolated yields %
(*Rc*)-**16a**	R = H, R' = H	25	3 h	70
(*Rc*)-**16b**	R = H, R' = Me	25	3 h	61
(*Rc*)-**16c**	R = Me, R' = H	25	3 h	76
(*Rc*)-**16d**	R= H, R' = CO_2Et	25	3 h	90

Scheme 8



Scheme 9



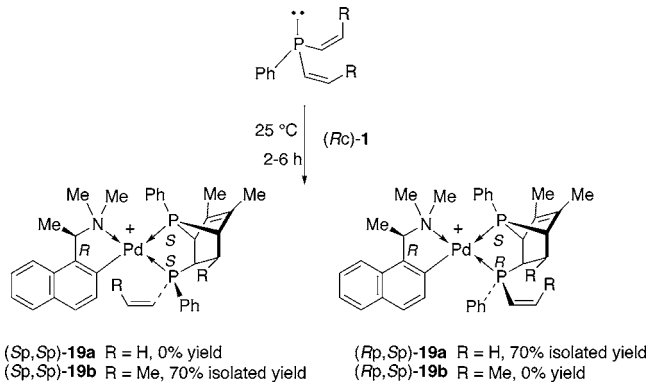
undergo the *exo*-cycloaddition reaction under mild reaction conditions to form the corresponding diphosphine cycloadducts in high yields (Scheme 7). Accordingly, the treatment of the chiral template (R_c)-**1** with diphenylvinylphosphine[31] and (*E*)-diphenyl-1-propenylphosphine[32] for 2−3 h gave the diphosphine cycloadducts (R_c)-**16a** and (R_c)-**16b**, respectively. Under similar conditions, however, the reaction was found to be significantly slower (50 h) when (*Z*)-diphenyl-1-propenylphosphine was used as the dienophile.[32] Nevertheless, the desired cycloadduct (R_c)-**16c** was also obtained in high yield. The 2D-ROESY NMR studies of complexes (R_c)-**16a**−**c** revealed that the slow formation of complex (R_c)-**16c** was due to a severe steric repulsion between the naphthylamine auxiliary and the (*Z*)-substituted methyl group in the vinylphosphine dienophile. Selected functionalities can be conveniently introduced into the diphosphine cycloadducts by utilizing the appropriate functionalized vinylphosphines. For example, the ester-substituted diphosphine complex (R_c)-**16d** was generated efficiently from the reaction between (R_c)-**1** and diphenyl-[(*E*)-2-(ethoxycarbonyl)vinyl]phosphine.[33] The formation of diphosphine cycloadducts in complexes (R_c)-**16b**−**d** involved the stereospecific generation of one phosphorus and four carbon stereogenic centers within the chiral phosphanorbornene frameworks.

Due to a rapid ligand redistribution process that occurred between the phosphorus precursors, the same cycloadducts (R_c)-**16a**−**d** were produced when the corresponding vinylphosphine complexes (R_c)-**17a**−**d**, respectively, were treated with DMPP. Experimentally, the phosphorus atoms in vinylphosphines are stronger π-acceptors than their counterparts in DMPP. Consequently, the vinylphosphine precursors always displace the DMPP ligand from the template position trans to the NMe_2 group (Scheme 8). These regio-orientations remained unchanged in the product complex as, once formed, the diphosphine−palladium chelates are kinetically stable.

Surprisingly, the stereospecific formation of the chiral phosphanorbornene frameworks would not be disturbed when chiral vinylphosphine prescursors were employed. For example, in the reaction between (R_c)-**1** and 1 equiv of the racemic dienophile (±)-methylphenylvinylphosphine, a 1:1 diastereomeric mixture of complexes (R_p, R_p)- and (R_p, S_p)-**18** was generated quantitatively (Scheme 9).[34] The absolute stereochemistry of phosphanorbornene frameworks in both (R_p, S_p)- and (S_p, S_p)-**18** is the same, and the two isomers are diastereomeric only at the phosphorus centers that are attached to C-5 of the cycloadduct. Thus the absolute orientations of the diene and the dienophiles during the course of cycloaddition reactions are being controlled stereospecifically by the naphthylamine auxiliary and would not be disturbed by the contradicting chiralities associated with the racemic dienophile. Furthermore, a highly efficient chiral discrimination process occurred when (R_c)-**1** was treated with 2 equiv of (±)-methylphenylvinylphosphine.[35] The chiral template reacted exclusively with only the (*S*)-methylphenylvinylphosphine to form (R_p, S_p)-**18**. The excess dieneophile, (*R*)-methylphenylvinylphosphine, was subsequently recovered quantitatively in its optically pure form via silica gel chromatography. It is noteworthy that the optical resolution of monodentate P-stereogenic phosphines remains tedious and inefficient, despite improved resolving agents being available. The above chiral discrimination process is able to generate the enantiomerically pure forms of methylphenylvinylphosphine within several hours.

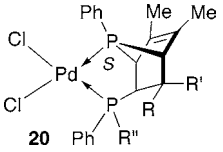
The chiral template (R_c)-**1** can be further employed to control formation of stereogenic centers outside the rigid backbone. For example, the reaction between (R_c)-**1** and the prochiral dienophile phenyldivinylphosphine may

Scheme 10

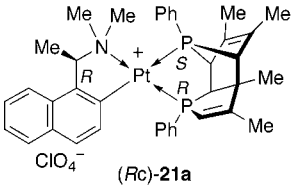


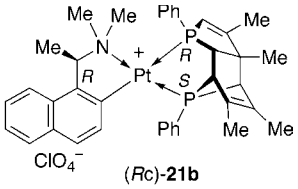
generate two possible diastereomers, (R_p, S_p)- and (S_p, S_p)-**19a**, arising from the phosphorus stereogenic center generated outside the phosphanorbornene skeleton (Scheme 10). Experimentally, the reaction proceeded with high stereoselectivity, generating only (R_p, S_p)-**19a** in high yields.[36] Interestingly, the reaction between (R_c)-**1** and di-[(*Z*)-prop-1-enyl]phenylphosphine generated (S_p, S_p)-**19b** stereospecifically.[37] All six new stereogenic centers in (S_p, S_p)-**19b** have been generated stereospecifically in a single step. The isolation of complexes **19a**−**b** confirmed that stereogenic centers could be generated stereoselectively both within and outside the norbornene framework in a [4+2] cycloaddition reaction. It is noteworthy, however, that mild reaction conditions are crucial for controlling formation of these external chiralities. Indeed, the sulfinyl S chiral center in (R_c)-**2g** could not be generated stereoselectively as prolonged heating was required for the cycloaddition reaction.

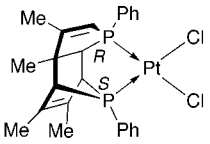
All the stable diphosphine cycloadducts were liberated efficiently from their template complexes in two steps: first, removal of the naphthylamine auxiliary from the complexes by treatment with HCl to form the corresponding dichloro complexes **20**; and second, decomposition of the dichloro complexes with aqueous cyanide to liberate the chiral diphosphines as highly air-sensitive oils in 70−90% yields.



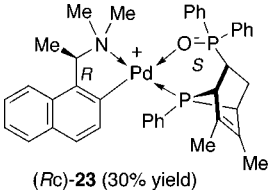
Asymmetric Dimerization of DMPP. In principle, a simple asymmetric [4+2] *exo*-cycloaddition reaction between two DMPP molecules produces a rigid chiral diphosphine containing two phosphorus and four carbon stereogenic centers. This asymmetric synthesis, however, could not be achieved when (R_c)-**1** was used as the chiral template. Apparently, the palladium(II) ion activates DMPP as a cyclic diene but failed to promote its dienophilicity. Upon the replacement of the palladium(II) center in (R_c)-**1** with a platinum(II) ion, however, the dimerization reaction proceeded smoothly at room temperature to give the two regioisomers (R_c)-**21a** and (R_c)-**21b** in quantitative yield.[38] The diphosphine cycloadducts in these isomers are of the same absolute stereochemistry and differ only in their regio-orientations on the asymmetric platinum template. Accordingly, both platinum template sites are able to activate DMPP either as a cyclic diene or as a dienophile. Treatments of (R_c)-**21a** and (R_c)-**21b** with HCl gave the same dichloro complex **22** from which the enantiomerically pure diphosphine ligand could be liberated by the standard cyanide treatment.

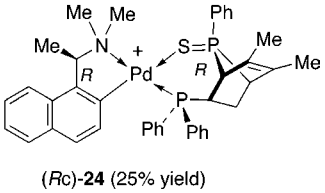






Mixed P(III)−P(V) Ligands. The cycloaddition reaction between (R_c)-**1** and vinylphosphines may be used as a general approach to synthesize P-stereogenic diphosphine monoxides. For example, treatment of diphenylvinylphosphine oxide with (R_c)-**1** in refluxing 1,2-dichloroethane for 4 days generated the P−O bidentate cycloadduct (R_c)-**23**.[39] Comparatively, diphenylvinylphosphine oxide is less reactive than its P(III) analogue for the *exo*-cycloaddition reaction since strong reaction conditions were required for the synthesis of (R_c)-**23**. Nevertheless, both vinyl phosphines and their oxides are not reactive toward the *endo*-cycloaddition reaction with the coordinated cyclic diene in the chloro template (R_c)-**8**. Interestingly, the combination of DMPP═O and the vinylphosphine complexes (R_c)-**17** also failed to generate the mixed P(III)−P(O) donor ligands, as DMPP═O itself is highly reactive and dimerizes rapidly to form the corresponding racemic P(O)−P(O) *endo*-cycloadduct. On the other hand, DMPP═S is not a reactive cyclic diene and it does not dimerize readily. Thus the asymmetric cycloaddition reaction between the vinylphosphine complex (R_c)-**17a** and DMPP═S gave the P−P(S) cycloadduct (R_c)-**24**.[40]

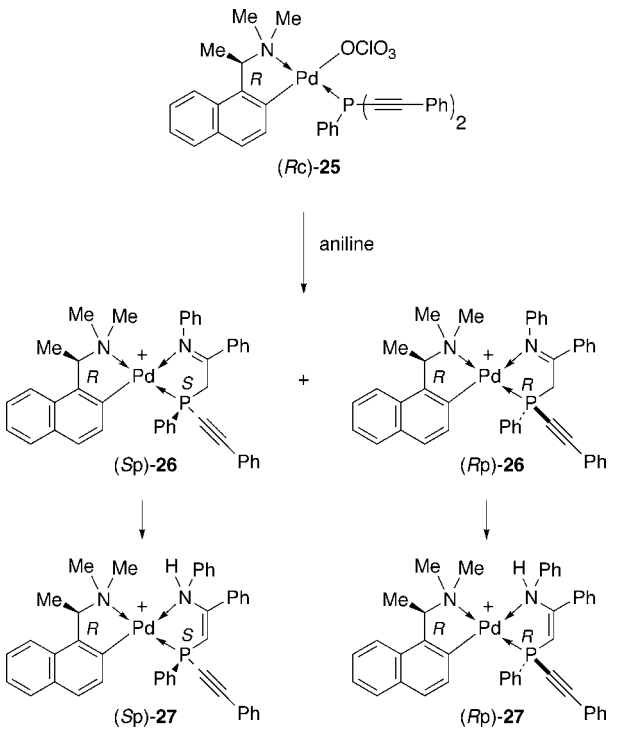




Chiral Iminophosphines and Enaminophosphines from Alkynylphosphines

The coordinated phosphinoalkyne PhP(C≡CPh)$_2$ in complex (R_c)-**25** is chemically reactive toward the hydroamination reaction with aniline. Treatment of (R_c)-**25** with excess aniline gave a 1:4 mixture of diastereomeric iminophosphine complexes (R_p)- and (S_p)-**26**. (Scheme 11).[41] The diastereomers could be separated efficiently by silica

Scheme 11



gel chromatography or fractional crystallization. In the solid state, the iminophosphine chelates in both diastereomers are stable. In solution, however, the chelating iminophosphines transformed slowly into the corresponding thermodynamically stable enamino species. Treatments of both resolved imino and enamino complexes with aqueous cyanide liberated the same enantiomerically pure P-stereogenic iminophosphines. In solution, the liberated iminophosphines are air-sensitive but adopt only the stable imino forms. Clearly the imine−enamine tautomerism observed in the template complexes was triggered by the metal complexation.

Summary and Outlook

By virtue of their unique electronic and stereochemical properties, orthometalated amine complexes constitute a new family of impressive reagents for the asymmetric synthesis of functionalized phosphines and diphosphines. By subtle variations of metal centers and the ancillaries, one can readily manipulate the delicate stereochemical control over the chiral ligand formation reactions. Through a direct visualization of the various metal−functional group interactions and some understanding of metal ion effects on the ligand activation, this Account provides insights to readers on the development of chiral organometallic reagents and functionalized phosphorus ligands. We have recently reported that, among other applications, the new chiral functionalized phosphines are efficient controllers for the cytotoxicity of gold-based anti-cancer drugs.[42] The drug activities and selectivities are critically controlled by the selected functionalities and their locations within a particular chiral phosphine supporter.[43] In this drug design, the functional groups can interact either internally with the gold(I) drug center or externally with other chiral biomolecules. To elucidate this structure−activity relationship in a systematic manner, we are currently developing a large family of the functionalized chiral gold drugs.

I am indebted to my students and collaborators whose names appear in the joint publications listed here.

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