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Palladacycle-Catalyzed Asymmetric Intermolecular Construction of Chiral Tertiary P-Heterocycles by Stepwise Addition of H−P−H Bonds to Bis(enones)

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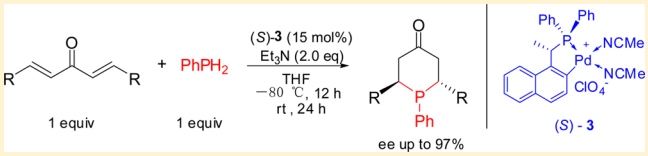
Supporting Information

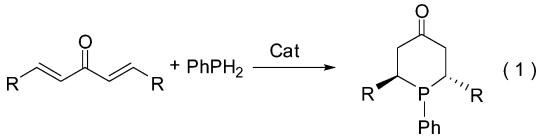
ABSTRACT: A palladacycle-catalyzed diastereo- and enantioselective stepwise double hydrophosphination of bis(enones) with $PhPH_2$ has been developed, allowing intermolecular construction of chiral tertiary bulky P-heterocycles in one pot in high yields. A catalytic cycle for the reaction is proposed as well.



INTRODUCTION

Chiral P-heterocycles containing phosphorus atom(s) in the ring such as DuPhos,[1] TangPhos,[2] *i*-Pr-BeePhos,[3] etc. have played important roles in asymmetric transformations.[4] However, most of these chiral P-heterocycles are predominantly prepared either via a tedious resolution process or by the synthetic manipulation of limited chiral pool starting materials.[5] Recently, a few efficient strategies for the catalytic synthesis of chiral phosphines have emerged and attracted great interest. These include the synthesis of P-stereogenic phosphines via cross-coupling reactions[6] and the synthesis of C-stereogenic phosphines via allylic phosphination[7] as well as hydrophosphination of Michael acceptors such as conjugated esters, nitriles,[8] enones,[9] enals,[10] and nitroalkenes.[11] Nevertheless, the products obtained via the aforementioned methods are usually confined to chain phosphines (containing phosphorus atom(s) in the chain). The methodology for catalytic synthesis of chiral P-heterocycles, on the other hand, remains a considerable challenge, especially when it involves the generation of multiple chiral centers from achiral acyclic substrates. Only Marks et al.[12] and Glueck et al.[13] have reported metal-catalyzed intramolecular cyclization to generate chiral P-heterocycles. Although syntheses of racemic P-heterocycles have been reported by thermal-/acid-mediated addition between primary phosphines and bis(enones) under high temperature (>100 °C),[14] the catalytic enantioselective intermolecular construction of chiral P-hetereocycles, to the best of our knowledge, has not been reported to date.

In connection with our continuous interest in the synthesis of chiral tertiary phosphines and motivated by our previous success in palladacycle-mediated[15] and -catalyzed[9b,e,g] asymmetric synthesis of chiral chain phosphines, herein we report the first diastereo- and enantioselective intermolecular construction of chiral P-heterocycles via a phosphapalladacycle-catalyzed stepwise double hydrophosphination between a primary phosphine and bis(enones) in one pot (eq 1).



(1)

It is indeed noteworthy that chiral tertiary P-heterocycles with sterically demanding groups are of interest as bulky ligands for several reasons:[14a] (1) the 2,6-substituents are in close proximity to the metal center, which may lead to unusual coordination chemistry and catalytic activity; (2) tuning of the 2,6-substituents on the ring enables manipulation of the ligand stereo- and electronic effects; (3) the carbonyl group allows further elaboration of the ligand at a site remote from the donor atom; (4) such ligands have been reported as efficient ligands for metal-catalyzed asymmetric hydrogenation reactions.[16]

RESULTS AND DISCUSSION

On the basis of previous studies, we employed the chiral palladacycles **1**−**3** (Figure 1) as catalysts toward the reaction of a primary phosphine $PhPH_2$ with dibenzylideneacetone (Table 1). Initially, the C,N-palladacycles (*S*)-**1** and (*S*)-**2** were used as the catalysts. However, the results showed that they are not efficient catalysts for this synthetic scenario. To our delight, the C,P-palladacycle (*S*)-**3** efficiently catalyzed the cyclization in high yields when it was employed as the catalyst. Various reaction conditions were subsequently screened, and the details are given in Table 1. The results showed that the best ee was achieved when THF was used as the solvent for the reaction. A

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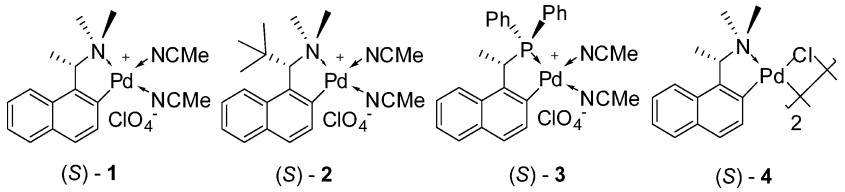
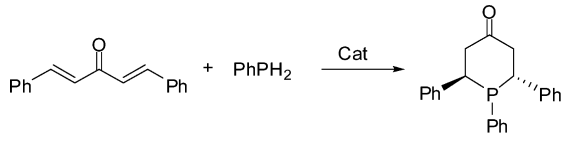


Figure 1. Palladacycles used in the study.

Table 1. Catalyst, Solvent, and Temperature Effects on the Reaction of $PhPH_2$ and Dibenzylideneacetone[a]



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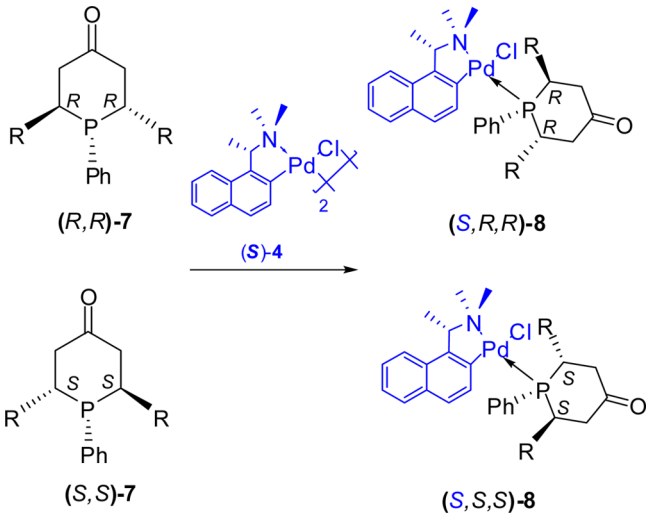
entry	cat.	solvent	temp (°C)	yield[b] (%)	dr[c]	ee(*R,R*)[d] (%)
1	(*S*)-**1**	THF	—80, 20	trace		
2	(*S*)-**2**	THF	—80, 20	trace		
3	(*S*)-**3**	THF	—80, 20	98	78:22	95
4	(*S*)-**3**	THF	20	messy		
5[e]	(*S*)-**3**	acetone	—80, 20	81	82:18	47
6	(*S*)-**3**	CH_2Cl_2	—80, 20	93	83:17	56
7	(*S*)-**3**	$CHCl_3$	—40, 20	93	83:17	72
8	(*S*)-**3**	NCMe	—40, 20	97	66:14	35
9[e]	(*S*)-**3**	benzene	20	99	70:30	41
10[f]	(*R*)-**3**	THF	—80, 20	98	78:22	—95

[a]Conditions: 0.35 mmol of $PhPH_2$, 15 mol % of cat., 1.0 equiv of bis(enone), 4 mL of solvent, 2.0 equiv of Et_3N. Reactions were started at the given low temperature for 12 h, and then the mixture was warmed to 20 °C with stirring for 24 h, unless otherwise noted. [b]Yield was calculated from $^{31}P\{^1H\}$ NMR of the crude product. [c]dr was calculated from $^{31}P\{^1H\}$ NMR of the crude product. [d]The ee (of the major product) was determined by $^{31}P\{^1H\}$ NMR; see the Supporting Information for details. [e]Stirring at 20 °C for 24 h. [f](*R*)-**3** was used as the catalyst.

Scheme 1. Protocol Adopted for the Determination of ee by Coordination of the P-Heterocycles to (*S*)-4



better dr with lower ee was observed when other solvents such CH_2Cl_2, acetone, $CHCl_3$, and NCMe were used.

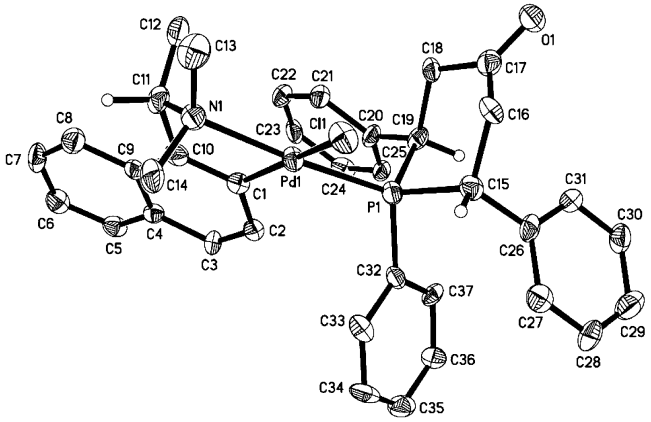
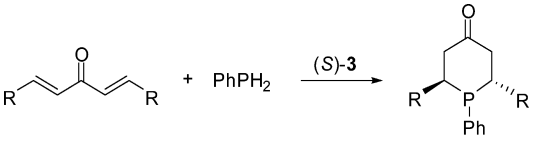


Figure 2. Molecular structure and absolute stereochemistry of (*S,R,R*)-**8a** with 50% probability thermal ellipsoids shown. Hydrogen atoms, except those on the chiral center, are omitted for clarity.

Table 2. Substrate Scope of the (*S*)-3-Catalyzed Asymmetric Hydrophosphination of Bis(enones) with $PhPH_2$[a]



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entry	R	7	yield[b] (%)	dr[c]	ee(*R,R*)[d] (%)
1	Ph	**7a**	98	78:22	95
2	4-FC_6H_4	**7b**	99	74:26	96
3	3-FC_6H_4	**7c**	97	83:17	94
4	4-ClC_6H_4	**7d**	99	65:35	93
5	3-ClC_6H_4	**7e**	98	82:18	97
6	4-BrC_6H_4	**7f**	99	64:36	91
7	3-BrC_6H_4	**7g**	90	82:18	97
8[e]		**7h**	99	82:18	93

[a]Conditions: 0.35 mmol of $PhPH_2$, 15 mol % of (*S*)-**3**, 4 mL of THF, 1.0 equiv of bis(enone), 2.0 equiv of Et_3N. The reactions were started at —80 °C for 12 h, and then the mixtures were warmed to 20 °C with stirring for another 24 h, unless otherwise noted. [b]Yield was calculated from $^{31}P\{^1H\}$ NMR of the crude product. [c]dr was calculated from $^{31}P\{^1H\}$ NMR of the crude product. [d]The ee (of the major product) was determined by $^{31}P\{^1H\}$ NMR: see the Supporting Information for details. [e]Stirring at —80 °C for 16 h and then at 20 °C for 3 days.

The reaction was conveniently monitored by $^{31}P\{^1H\}$ NMR spectroscopy. The diastereomeric ratio (dr = *rac*/*meso*) was determined from the $^{31}P\{^1H\}$ NMR spectrum of the crude

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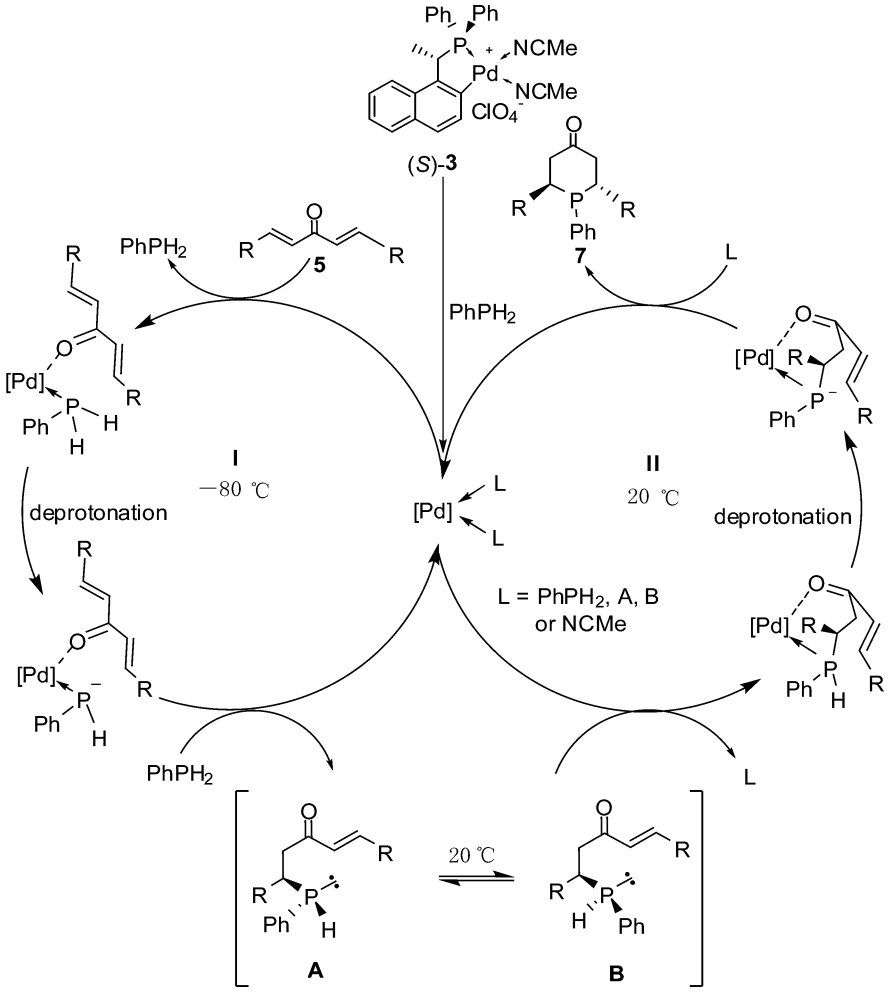
Scheme 2. Proposed Catalytic Cycle



product, and the enantiomeric excess (ee) of the *rac* isomers was determined from $^{31}P\{^{1}H\}$ NMR spectra of the derivatives **8** formed by treating the corresponding enantiomerically enriched **7** with the enantiopure palladacyclic complex (*S*)-/(*R*)-**4** (Scheme 1).[8f,g] Though *meso* and *rac* isomers involving two chiral centers were formed during the reaction, the corresponding derivatives for determination of ee could be conveniently and efficiently identified in $^{31}P\{^{1}H\}$ NMR spectroscopy by the use of a combination of (*R*)- and (*S*)-**4**.[17]

The single-crystal X-ray diffraction analysis of one such major derivative, **8a** (R = Ph), revealed that the absolute configuration at both chiral carbon centers of the major product is *R* (Figure 2).

With the optimal conditions established, a range of aromatic bis(enones) were screened for the asymmetric stepwise hydrophosphination reaction catalyzed by (*S*)-**3**. The results are presented in Table 2 and showed that the reaction proceeded to full conversion of $PhPH_2$ under the given conditions, allowing the intermolecular construction of a series of air-sensitive P-heterocyclic products. The process also tolerates a range of functional groups such as halogens (F, Cl, Br). Bis(enones) with electron-withdrawing substituents showed good reactivities with excellent enantioselectivities and concomitant high yields. However, those bearing electron-donating groups (such as MeO−) and more steric substituents (such as *o*-ClC_6H_4, 3,5-$Cl_2C_6H_3$) showed less reactivity and failed to give the expected products under the same conditions.

On the basis of the experimental results, a mechanism was proposed for the (*S*)-**3**-catalyzed asymmetric stepwise double hydrophosphination reaction (Scheme 2). Free $PhPH_2$ has a high affinity for palladium, and this leads to the facile displacement of the relatively weakly coordinated NCMe of the palladacycle and allows the formation of a bis(phosphine) complex. However, due to the strong π-accepting properties of the aromatic carbon donor, the P−Pd bond in the trans P−Pd−C moiety is labile and readily undergoes the ligand redistribution process, which provides the opportunity for the bis(enone) to coordinate to palladium. In comparison, the trans P−Pd−P moiety in the catalytic intermediate is more stable and allows the subsequent acidification of the P−H bond of the coordinated PPh(R′)H. In the presence of Et_3N as the external base, the coordinated PPh(R′)H is thus readily deprotonated to form the corresponding reactive phosphido species, which undergoes 1,4-addition with the coordinated bis(enone). The $^{31}P\{^{1}H\}$ NMR study of the reaction revealed that (*S*)-**3** can indeed catalyze the first addition of a P−H bond to bis(enone) at −80 °C quantitatively to give the secondary phosphine intermediate (**A** or **B**) with chiral centers at both carbon and phosphorus. Only one isomer was observed (^{31}P NMR δ −23.0), which means that the first addition indeed proceeds with excellent diastereoselectivity. However, the addition of

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another P−H bond (leading to cyclization) is significantly more challenging in terms of both electronic factors and stereocontrol and only occurred at a relatively higher temperature (20 °C). It is important to note that racemization at phosphorus also occurred as soon as the reaction temperature was raised, leading to the formation of a 1:1 equilibrium of the two diastereomers **A** and **B**. At 20 °C, the ^{31}P NMR spectrum therefore exhibited a new singlet at δ −27.7. However, due to the formation of the symmetrical products, the phosphorus atom in **7** is no longer stereogenic. Therefore, despite the undesired P inversion that occurs at the intermediate stage, the cyclic phosphines could still be obtained in high optical purity.

CONCLUSIONS

In summary, we have developed a novel method for the diastereo- and enantioselective intermolecular construction of tertiary P-heterocycles by a palladacycle-catalyzed stepwise double hydrophosphination of bis(enones) with a primary phosphine in high yields. A mechanism has been proposed for the reaction. We are currently investigating the applications of the chiral tertiary P-heterocycles in asymmetric transformations.

EXPERIMENTAL SECTION

General Procedure for Asymmetric Synthesis of P-Heterocycles. To a solution of $PhPH_2$ **6** (38.5 mg, 0.35 mmol, 1.0 equiv) in THF (4 mL) was added (*S*)-**3** (32.9 mg, 0.053 mmol, 15 mol %). The solution was stirred at room temperature for 5 min and then was cooled to −80 °C. Subsequently, the bis(enone) **5** (0.35 mmol, 1.0 equiv) was added. Et_3N (70.8 mg, 0.70 mmol, 2.0 equiv) in THF (0.5 mL) was then added dropwise. The solution was subsequently stirred at −80 °C for 12 h. Then, the mixture was warmed to room temperature (20 °C) gradually and stirred for 24 h. The reaction was monitored by $^{31}P\{^1H\}$ NMR. After the reaction was complete, the solvent (THF) was evaporated by vacuum pump to give the crude P-heterocyclic products. The diastereomeric ratio (dr) was measured by the $^{31}P\{^1H\}$ NMR spectrum of the crude products. For determination of the ee, the enantiopure dimeric palladacycle (*R*)-/(*S*)-**4** (in slight excess) was dissolved in the corresponding ligand solution, leading to the coordinated derivatives quantitatively. The ee was calculated from the $^{31}P\{^1H\}$ NMR spectra of the derivatives.[17]

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

ASSOCIATED CONTENT

Supporting Information

Text, figures, tables, and a CIF file giving experimental procedures, characterization data, and single crystal X-ray data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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