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Highly Enantioselective Pd-Catalyzed Synthesis of P-Stereogenic Supramolecular Phosphines, Self-Assembly, and Implication

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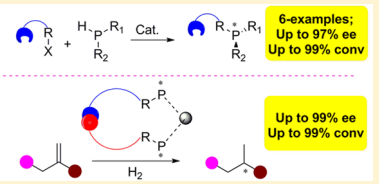
Supporting Information

ABSTRACT: Metal-catalyzed asymmetric addition of a secondary phosphine to an aryl halide is one of the most efficient and reliable approaches for the construction of enantiopure carbon−phosphorus bonds. An isolated Pd(II) complex (**5**) catalyzes the carbon−phosphorus coupling reaction between tolylphenylphosphine (**1a**) and 3-iodophenylurea (**2b**), which proceeds with an unprecedented enantiomeric excess (ee) of 97%. The generality of the strategy has been demonstrated by preparing a small library of a new class of P-stereogenic phosphines with an in-built hydrogen bonding motif for the first time. The P-stereogenic phosphines self-assemble on a metal template via deliberately installed hydrogen-bonding motifs and mimic the bidentate ligand coordination. Interestingly, when it was employed in asymmetric hydrogenation, the supramolecular phosphine {1-(3-(phenyl(*o*-tolyl)phosphanyl)phenyl)urea} (**6b**) produced the corresponding hydrogenated product with the highest enantiomeric excess of 99% along with excellent conversion, demonstrating the potential of these enantioenriched P-chirogenic supramolecular phosphines in asymmetric catalysis.



Metal-catalyzed asymmetric synthesis depends on chiral ligands, among which phosphines play a prominent role.[1] Although P-chiral phosphines were the first chiral ligands applied in homogeneous catalysis,[2,3] they have been supplanted by phosphines having chirality on the backbone and the development of P-chiral phosphines has been incredibly slow.[4] This is most likely due to the difficulty of synthesis of P-chiral compounds, which are traditionally generated with a stoichiometric amount of the chiral auxiliary or through resolution techniques.[5] A paradigm shift could be achieved if enantiopure P-stereogenic ligands could be catalytically prepared. Although highly desirable, the transition-metal-catalyzed synthesis of P-stereogenic ligands is still in its infancy,[6] and only a handful of ligands with enantioselectivities up to 88%[6c] have been synthesized using this concept. Furthermore, to the best of our knowledge there have been no reports on the catalytic synthesis of enantiopure P-stereogenic ligands equipped with an additional supramolecular bonding motif.

In spite of the increasing knowledge of homogeneous catalysis, the current discovery and design of an efficient and selective catalyst still relies on a tedious and time-consuming trial and error methodology.[7] To shorten the time needed to identify a suitable catalyst, combinatorial screening techniques have been devised. However, these techniques still make use of covalently synthesized ligands. To address this synthetic bottleneck, strategies based on the formation of bidentate ligands held together by noncovalent interactions have recently emerged.[8] Thus, the catalytic synthesis of P-stereogenic supramolecular phosphines should significantly increase the chemical space within which an optimal ligand set can be identified. However, currently there is no precedent in the literature on the catalytic synthesis of enantiopure P-stereogenic supramolecular phosphines, although supramolecular phosphines (C-chiral or -achiral) have found a wide range of applications in industrially important transformations such as hydrogenation,[9] hydroformylation,[10] hydrocyanation,[11] and hydrosilylation.[12]

Herein we disclose the first example of a highly enantioselective C−P coupling (asymmetric phosphination) reaction that generates enantioenriched P-stereogenic supramolecular phosphines. The generality of the strategy is demonstrated by preparing a small library of enantioenriched P-stereogenic supramolecular phosphines. Furthermore, the self-assembly of these P-stereogenic supramolecular phosphines and their implication in asymmetric hydrogenation is reported.

P-stereogenic phosphines have attracted significant attention in recent years, and various synthetic methodologies have been deployed in the past decade.[13] We anticipated that a palladium-catalyzed C−P coupling reaction between a racemic phosphine and aryl halide equipped with urea would produce the desired P-stereogenic supramolecular phosphine via path-III (Figure 1, top).

In our pursuit to realize the synthesis of enantioenriched P-stereogenic supramolecular phosphines, we set out to prepare the three components of the phosphination reaction. Phenyl(*o*-tolyl)phosphine (**1a**) and mesityl(phenyl)phosphine (**1b**) were prepared using literature protocols.[14] Whereas, the hydrogen bonding motifs 2-iodophenylurea (**2a**), 3-iodophenylurea (**2b**), and 4-iodophenylurea (**2c**) were synthesized using modified literature methods.[15] The third component, palladium catalyst,

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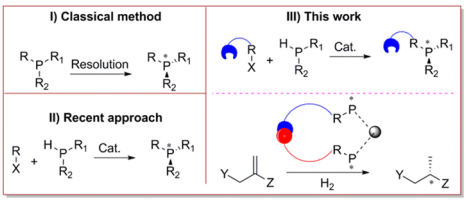
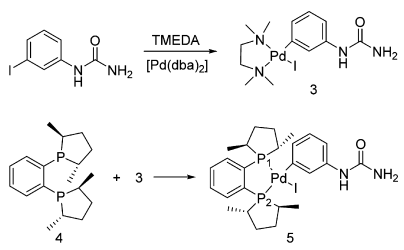


Figure 1. Synthesis of P-stereogenic phosphines: (I) classical method; (II) recent approach; (III) this work.

was prepared by a two-step synthetic protocol. The stoichiometric reaction of 3-iodophenylurea (**2b**), $[Pd(dba)_2]$, and tetramethylethylenediamine (tmeda) produced the anticipated precatalyst [Pd(tmeda)(3-phenylurea)(I)] (**3**) in good yield (63%). The existence of **3** was unambiguously ascertained using a combination of analytical and spectroscopic methods. Electrospray ionization mass spectroscopic analysis revealed a pseudomolecular ion peak at m/z 357.09 ($[M-I]^+$), confirming the presence of **3**. The spectroscopic results were further corroborated by single-crystal X-ray diffraction. Complex **3** crystallizes in the monoclinic crystal system with the $P1$ space group. The geometry around palladium is distorted square planar with regular bond angles and bond lengths. A notable difference is a short N2−Pd bond of 2.118 Å, in comparison to the N1−Pd bond distance of 2.205 Å. This difference can be attributed to the trans effect imparted by iodide (Figure S17 in the Supporting Information).[16] Addition of (*S*,*S*)-Me-DuPHOS to complex **3** in acetonitrile at room temperature and tracking the reaction progress by ^{31}P NMR indicated completion of the reaction within 2 h.[17] After 2 h, volatiles were evaporated under reduced pressure to give a gray residue, which after *n*-hexane washing produced pure complex **5**. ^{31}P NMR of the isolated compound displayed a doublet of doublets due to the magnetically nonequivalent phosphorus centers. The doublet at 69.4 ($^2J_{PP}$ = 25 Hz) can be assigned to P1, and the second doublet at 65.1 ppm ($^2J_{PP}$ = 25 Hz) can be readily assigned to P2 (see Scheme 1,

Scheme 1. Synthesis of Palladium Complex 5



compound **5**). Electrospray ionization mass spectroscopic analysis revealed a pseudomolecular ion peak at m/z 547.12 ($[M-I]^+$), confirming the presence of the anticipated complex **5** (see Figure S22 in the Supporting Information).[15,18] After having established the existence of complex **5**; we set out to evaluate the performance of **5** in catalytic asymmetric C−P coupling (phosphination) reactions. A general phosphination reaction leading to P-stereogenic supramolecular phosphine is depicted in Scheme 2, and Table 1 summarizes the most important findings. THF was found to be the solvent of choice, as it provided optimal solubility for all the reaction components. Surprisingly, complex **5** failed to catalyze the reaction between **1a** and **2a**.[19] In our pursuit to understand the failures, we performed stoichiometric reaction; which suggested C═O chelation and suppression of C−P coupling (see section 2.4.1 in the Supporting Information).

Scheme 2. Catalytic Synthesis of Enantioenriched P-Stereogenic Supramolecular Phosphines 6a−c and 7a−c

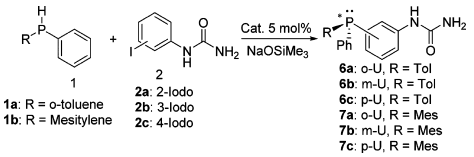


Table 1. Palladium-Catalyzed Asymmetric Phosphination of Racemic Phosphines with Phenylurea[a]

run	product (b[b])	T (°C)	time (h)	conversn (%)[c]	ee (%)[d]
1	**6b** (1)	room temp	24	~8	ND
2	**6b** (2)	room temp	24	31	ND
3	**6b** (3)	room temp	24	>99	00
4	**6b** (3)	20	144	22	46
5	**6b** (3)	0	72	7	83
6[e]	**6b** (3)	0	360	>99	79 (−)
7[e]	**6b** (3)	−5[f]	168	65	97 (−)
8	**6c** (3)	room temp	60	>99	4
9	**6c** (3)	0	432	50	11
10	**6c** (3)	−5[e,f]	144	25	40
11	**7b** (3)	room temp	64	>99	ND
12	**7b** (3)	0	152	42	11
13	**7b** (3)	−5[e,f]	168	42	11
14	**7c** (3)	0	168	25	11
15	**7c** (3)	−5[e,f]	168	38	11

[a]Conditions: catalyst 0.005 mmol, **1a** 0.1 mmol, **2a** 0.1 mmol, total 1 mL of THF. T denotes the temperature. [b]b denotes the equivalents of $NaOSiMe_3$. [c]Determined by ^{31}P NMR;. [d]Determined by chiral HPLC after protection of **6**/**7** by sulfur. [e]15 mol % catalyst loading. [f]±5 °C. ND denotes not determined.

On the basis of these investigations we anticipated that installing the urea group away from the metal center might overcome C═O chelation and might catalyze the phosphination. Indeed, initial catalyst optimization studies using **2b** indicated completion of the reaction within 12 h. The effect of catalyst loading on conversion was investigated, and the optimal catalyst loading was found to be 5 mol %. The effect of various bases was investigated, and $NaOSiMe_3$ outperformed the other common bases (Table S2 in the Supporting Information). Increasing the amount of base from 1 to 3 equiv progressively led to better conversions (Table 1, runs 1−3),[20] but only racemic product was observed. Decreasing the reaction temperature led to a much better stereocontrol. Performing the reaction at 20 °C resulted into a moderate enantiomeric excess of 46% with a lower conversion of 22%. Decreasing the temperature further to 0 °C resulted in 83% enantiomeric excess (run 5). A prolonged reaction time at 15 mol % catalyst loading increased the conversion to **6b** (>99%) without significantly affecting the selectivity (run 6). To our delight, performing the reaction at −5 °C produced **6b** with an unprecedented enantiomeric excess of 97% (run 7) along with significant (65%) conversion. To the best of our knowledge, the enantiomeric excess of 97% reported for **6b** is the highest ever reported in any asymmetric phosphination/hydrophosphination reaction.

Motivated by the excellent performance of **5**, we further expanded the substrate scope and phosphination of **1a** with 4-iodophenyurea (**2c**) was attempted. Only 40% ee could be obtained using **5**, even after extensive screening of various reaction parameters (Table 1, runs 8−10). We then explored the

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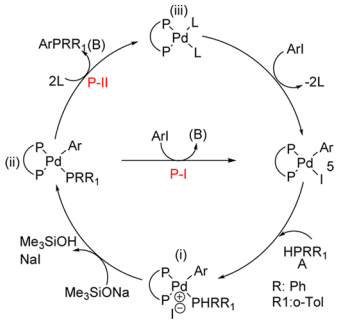
scope of phosphines, and the performance of **5** in the phosphination of **2b,c** with mesitylphenylphosphine (**1b**) was evaluated. Mesitylphenylphosphine (**1b**) smoothly reacts with 3-iodophenylurea (**2b**) under the optimized conditions to produce the corresponding phosphines in good yields and decent enantiomeric excess (4−11%) (run 11−13). Similar reactivity was witnessed with 4-iodophenylurea, and decent ee's (11%) were recorded (run 15).

In our quest to understand the mechanism of the C−P coupling reaction, we investigated the reactivity of **5** in a stoichiometric NMR-tube reaction. Complex **5** was dissolved in THF-d_8, and 1 equiv of **A** (Scheme 3) was placed in the NMR

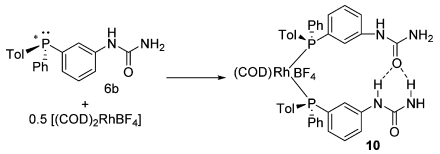
Scheme 3. Proposed Mechanism for the Phosphination Reaction



tube. Apart from the Pd-DuPHOS resonances, the ^{31}P NMR spectrum of this mixture displayed a broad singlet at −49.4 ppm that can be easily assigned to free phosphine **A**. This broad signal disappeared instantaneously after addition of $NaOSiMe_3$ with concomitant appearance of a broad resonance at −23.9 and a sharp peak at −13 ppm (Figure S59 in the Supporting Information). The former broad resonance can be attributed to the phosphido species **ii** and the latter sharp singlet to the reductive elimination product **B**. At the same time the doublet of doublets originating from **5** diminished and a broad resonance at 44 ppm emerged. This resonance can be easily assigned to Me-DuPHOS phosphorus in species **ii**.[21] The existence of intermediates **i** and **ii** could be detected only at low temperature. At −40 °C, species **i** displayed a broad doublet at −22.2 (J_{P-P} = 353 Hz), whereas addition of base to this solution revealed two doublets of doublets (−18.3 (dd, $^2J_{P-P}$ = 40 Hz, 106 Hz) and −26.1 ppm (dd, $^2J_{P-P}$ = 56 Hz, 117 Hz)) at −40 °C (Figure S60 in the Supporting Information). These resonances can be attributed to the phosphido-Pd intermediate **ii** (**iia** ⇌ **iib**; Scheme S3 in the Supporting Information). This spectroscopic evidence suggests that path P-I is more likely than path P-II (see Scheme 3).[22]

The thus prepared P-stereogenic supramolecular phosphines were found to self-assemble on a metal template to produce self-assembled metal complexes (see **10** in Scheme 4).

Scheme 4. Hydrogen Bonding Induced Self-Assembly of 6b on a Metal



Multinuclear NMR and IR spectroscopy indicates the existence of hydrogen bonding interactions (section 2.7 in the Supporting Information). Such metal complexes have been found to catalyze asymmetric reactions (hydrogenation, hydroformylation, etc.) of a range of olefins.[23] The performance of supramolecular phosphine ligand **6b** with the highest ee of 97% was evaluated in asymmetric hydrogenation of dimethyl itaconate and *N*-acetyldehydrophenylalanine. Preliminary asymmetric hydrogenation of dimethyl itaconate at 0 °C revealed a modest enantiomeric excess of 36%. Interestingly, testing **6b** in the asymmetric hydrogenation of *N*-acetyldehydrophenylalanine led to a preliminary ee of 67% (Table S6 in the Supporting Information) at room temperature within 5 h. Performing the reaction at 0 °C revealed 99% ee, importantly, along with 91% isolated yields, within 5 h.[24] Changing the solvent did not affect the selectivity, and a 98% enantiomeric excess could be recorded in THF. Thus, asymmetric hydrogenation of *N*-acetyldehydrophenylalanine was aptly catalyzed by **6b** in the presence of $[(COD)_2RhBF_4]$ (1 mol %), resulting in an excellent (99%) enantiomeric excess along with 91% conversion.

In summary, we report the catalytic asymmetric synthesis of a new class of P-stereogenic supramolecular phosphines for the first time. The isolated Pd-DuPHOS complex **5** catalyzes phosphination of urea-substituted aryl halides and secondary phosphines to produce the corresponding C−P coupling products. A judicious selection of substrate and tuning of reaction parameters led to an unprecedented enantioselectivity of 97% in **6b**, along with significant conversion (65%). Preliminary mechanistic investigations failed to spot the Pd(0) species **iii**, whereas spectroscopic observation of the phosphido intermediate **ii** suggests that the phosphination reaction most likely proceeds via path P-I. Moreover, the thus prepared enantioenriched P-stereogenic supramolecular phosphines self-assemble upon simple mixing with $[(COD)_2RhBF_4]$. When it was employed in the asymmetric hydrogenation of *N*-acetyldehydrophenylalanine, **6b** displayed an excellent enantiomeric excess of 99%, along with 91% conversion. These findings demonstrate the potential of the P-stereogenic supramolecular phosphines in asymmetric catalysis. We are currently exploring the mechanism of asymmetric phosphination and are investigating the application of the thus-prepared P-stereogenic supramolecular phosphines in asymmetric catalysis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organomet.5b00664.

Synthetic protocols for **1a,b**, **2a−c**, **6a−c**, and **7a−c**, method to determine percent enantioselectivity, spectroscopic and analytical data, and crystallographic data (PDF)

Crystallographic data for **3** (CCDC 1046371) (CIF)

Crystallographic data for **8b** (CCDC 1046370) (CIF)

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Notes

The authors declare no competing financial interest.

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(15) The synthesis of 3-iodophenylurea (**2b**) has been reported.[9a] A modified protocol has been developed for the synthesis of **2b**,**c**. A detailed synthetic procedure is reported in the Supporting Information.

(16) A detailed synthesis procedure and characterization data are described in the Supporting Information.

(17) The choice of a ligand is a very crucial parameter in asymmetric phosphination. Our ligand choice is based on the following criteria: (a) the ligand should resist displacement from the metal; (b) the ligand to metal coordination should be robust (preferably more than monodentate); (c) donor atoms on the ligand should be electron rich.

(18) The desired complex **5** was found to be unstable in solution over an extended period of time. However, it is stable in the solid state over months and does not decompose. Our attempts to crystallize **5** failed, and only the undesired diiodo complex could be isolated.

(19) Phosphination with an ortho-substituted aryl group has been reported by Glueck et al.[6b] However, in our case, ortho-substituted iodophenylurea failed to provide the anticipated coupling product.

(20) It is most likely that the urea protons interact with base and might consume 2 equiv of base per urea group.

(21) Similar ^{31}P chemical shifts and mechanisms were presented by Glueck et al. See: (a) Moncarz, J. R.; Brunker, T. J.; Glueck, D. S.; Sommer, R. D.; Rheingold, A. L. *J. Am. Chem. Soc.* **2003**, *125*, 1180−1181. (b) Detailed spectroscopic evidence supporting the proposed mechanism is presented in the Supporting Information..

(22) Although the existence of species **iii** cannot be completely ruled out, no evidence supporting the existence of **iii** could be obtained.

(23) (a) Wieland, J.; Breit, B. *Nat. Chem.* **2010**, *2*, 832−837. (b) Meeuwissen, J.; Reek, J. N. H. *Nat. Chem.* **2010**, *2*, 615−621. (c) Meeuwissen, J.; Detz, R. J.; Sandee, A. J.; De Bruin, B.; Reek, J. N. H. *Dalton Trans.* **2010**, *39*, 1929−1931. (d) Laungani, A. C.; Breit, B. *Chem. Commun.* **2008**, 844−846. (e) Birkholz, M. N.; Dubrovina, N. V.; Jiao, H.; Michalik, D.; Holz, J.; Paciello, R.; Breit, B.; Borner, A. *Chem. - Eur. J.* **2007**, *13*, 5896−5907. (f) Weis, M.; Waloch, C.; Seiche, W.; Breit, B. *J. Am. Chem. Soc.* **2006**, *128*, 4188−4189.

(24) Asymmetric hydrogenation of *N*-acetyldehydrophenylalanine has been reported earlier. See: Boyd, D. R.; Bell, M.; Dunne, K. S.; Kelly, B.; Stevenson, P. J.; Malone, J. F.; Allen, C. A. R. *Org. Biomol. Chem.* **2012**, *10*, 1388−1395.

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