ORGANOMETALLICS
Note

*Organometallics* **2010,** *29,* 6125–6128 6125
DOI: 10.1021/om1006984

# Platinum-Catalyzed Alkene Cyclohydroamination: Evaluating the Utility of Bidentate P,N/P,P Ligation and Phosphine-Free Catalyst Systems

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*Received July 15, 2010*

*Summary: The efficacy of phosphine-free Pt precatalysts including $PtCl_2$ and $(COD)PtCl_2$ in promoting the cyclohydroamination of primary as well as secondary alkyl/arylamines tethered to α-olefins is demonstrated for the first time. Further catalytic studies examining the use of phenylene-P,N co-ligands, as well as neutral, cationic, and formally zwitterionic complexes derived from the new ligand precursor 1-$PPh_2$-2-P($tBu)_2$-indene, revealed comparable reactivity in Pt-catalyzed cyclohydroamination catalysis relative to these phosphine-free catalysts.*

## Introduction

Notwithstanding the significant advances that have been achieved in Buchwald−Hartwig amination in recent years,[1] the inherent lack of atom economy associated with such procedures has prompted the continued development of hydroamination techniques, including cyclohydroamination protocols that enable concomitant ring closure and C−N bond formation via the direct addition of N−H bonds to unsaturated substrates.[2] In this context, the pursuit of general methods for promoting the cyclization of rather simple aminoalkene substrates featuring primary (−$NH_2$) or secondary (−NHR; R = alkyl or aryl) amino substituents tethered to α-olefins represents an active area of inquiry in the field of organometallic catalysis. While a diversity of catalysts for cyclohydroamination have been reported,[2] those based on the late transition metals have proven to be particularly effective for the cyclization of the aforementioned aminoalkene substrate classes. The first late metal catalyst system of this type was described in 2005 by Bender and Widenhoefer,[3] who reported the use of a catalyst mixture comprised of $[PtCl_2(H_2C{=}CH_2)]_2$ (2.5 mol %) and $PPh_3$ (5 mol %) (or alternatively 2.5 mol % $[PtCl_2(PPh_3)]_2$) for the cyclization of secondary alkylaminoalkenes at 120 °C. Spectroscopic data obtained in the course of this investigation support a reaction pathway involving nucleophilic attack by a pendant amine fragment on a Pt-coordinated alkene, followed by rapid and reversible protonation at Pt and rate-limiting C−H reductive elimination.[3] Encouraged by these mechanistic observations, Widenhoefer and co-workers[4] surveyed a more broad collection of sterically demanding monodentate phosphines and N-heterocyclic carbenes in this chemistry, in anticipation that such bulky co-ligands might promote the key C−H reductive elimination step. In the course of this investigation, it was discovered that mixtures of $PtCl_2$ and biarylphosphines including tBu-DavePhos (2-di-*tert*-butylphosphino-2′-*N*,*N*-dimethylaminobiphenyl) offer improved substrate scope under less harsh conditions (60−80 °C) for the cyclohydroamination of alkylaminoalkenes relative to the Pt(II)/$PPh_3$ catalyst system.[4] While further advances in the late metal-mediated cyclohydroamination of primary and/or secondary alkyl/arylamines and terminal or internal alkenes have been achieved by use of rhodium,[5] iridium,[5b,6] and copper[7] catalysts, the identification of increasingly effective late metal catalysts for use in promoting the cyclohydroamination of simple aminoalkene substrates under mild conditions and with broad substrate scope remains an important and significant challenge.

Intrigued by the apparent reactivity benefits derived from the use of bulky monodentate phosphines in Pt-mediated cyclohydroamination,[4] we became interested in examining the influence of sterically demanding bidentate ancillary ligands on such catalytic chemistry, including P,N ligands recently developed in our group that feature a phenylene backbone,[8] as well as a new P,P-indene ligand that enables the construction of neutral, cationic, and formally zwitterionic complexes.[9] Herein we report on the results of our synthetic and catalytic studies in this area, including the observation that $PtCl_2$ and $(COD)PtCl_2$ alone are capable of promoting the cyclohydroamination of primary as well as secondary alkyl/arylamines tethered to α-olefins.[10]

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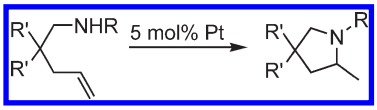
(9) For a review featuring our work in the area of zwitterionic catalyst design, see: Stradiotto, M.; Hesp, K. D.; Lundgren, R. J. *Angew. Chem., Int. Ed.* **2010**, *49*, 494.

(10) For related studies examining phosphine-free Pt catalysts for the hydroamination of ethylene with aniline, see: Dub, P. A.; Rodriguez-Zubiri, M.; Daran, J.-C.; Brunet, J.-J.; Poli, R. *Organometallics* **2009**, *28*, 4764.



Published on Web 10/07/2010

**Table 1. Cyclohydroamination of Aminoalkenes Employing Platinum Pre-catalysts[a]**



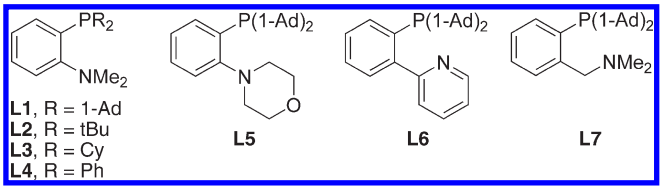

| entry | precatalyst | R, (R′)$_2$ | temp (°C) | conv (%)[b] |
|---|---|---|---|---|
| 1 | (COD)PtCl$_2$ | Bn, (CH$_2$)$_5$ | 110 | 82 |
| 2 | PtCl$_2$ | Bn, (CH$_2$)$_5$ | 110 | 79 |
| 3 | PtCl$_2$ + PPh$_3$ | Bn, (CH$_2$)$_5$ | 110 | 82 |
| 4 | (COD)PtCl$_2$ | Bn, (CH$_2$)$_5$ | 65 | 28 |
| 5 | (COD)PtCl$_2$ | Bn, (CH$_2$)$_5$ | 80 | 42 |
| 6 | PtCl$_2$ + PPh$_3$ | Bn, (CH$_2$)$_5$ | 80 | 13 |
| 7 | (COD)PtCl$_2$ | *p*-tolyl, (Ph)$_2$ | 110 | 92 |
| 8 | PtCl$_2$ + tBu-DavePhos[c] | *p*-tolyl, (Ph)$_2$ | 110 | >95 |
| 9 | (COD)PtCl$_2$ | H, (Ph)$_2$ | 110 | 61 |
| 10 | PtCl$_2$ + tBu-DavePhos[c] | H, (Ph)$_2$ | 110 | 90 |
| 11 | PtCl$_2$ + **L1** | Bn, (CH$_2$)$_5$ | 110 | 59 |
| 12 | PtCl$_2$ + **L2** | Bn, (CH$_2$)$_5$ | 110 | 8 |
| 13 | PtCl$_2$ + **L3** | Bn, (CH$_2$)$_5$ | 110 | <5 |
| 14 | PtCl$_2$ + **L4** | Bn, (CH$_2$)$_5$ | 110 | <5 |
| 15 | PtCl$_2$ + **L5** | Bn, (CH$_2$)$_5$ | 110 | 38 |
| 16 | PtCl$_2$ + **L6** | Bn, (CH$_2$)$_5$ | 110 | 11 |
| 17 | PtCl$_2$ + **L7** | Bn, (CH$_2$)$_5$ | 110 | 8 |
| 18 | (**L1**)PtCl$_2$ | Bn, (CH$_2$)$_5$ | 110 | 83 |
| 19 | **2** | Bn, (CH$_2$)$_5$ | 110 | 76 |
| 20 | **2** + AgOTf | Bn, (CH$_2$)$_5$ | 110 | 81 |
| 21 | **3a** | Bn, (CH$_2$)$_5$ | 110 | 86[d] |

[a] Reaction conditions: 0.25 mmol of aminoalkene in 0.50 mL of 1,4-dioxane, 5 h. See the Supporting Information for complete experimental details. [b] Except where noted, clean conversion to the pyrrolidine was monitored by use of GC techniques with less than 3% byproduct observed in each case; product identity was confirmed by comparison with authentic samples. [c] tBu-DavePhos = 2-di-*tert*-butylphosphino-2′-*N*,*N*-dimethylaminobiphenyl. [d] Complete consumption of the starting aminoalkene observed, along with ca. 14% conversion to an alkene isomerization byproduct.

## Results and Discussion

Given our previous observation that [Ir(COD)Cl]$_2$ is an active precatalyst for the intramolecular addition of primary (using HNEt$_3$Cl as a cocatalyst) as well as secondary alkyl/arylamines to unactivated olefins,[6a] we sought to establish the catalytic abilities of the phosphine-free species (COD)PtCl$_2$ and PtCl$_2$ prior to exploring the influence of P,N and P,P ligands on Pt-mediated cyclohydroamination. Preliminary experiments of this type were conducted using a representative secondary benzylamine substrate under conditions similar to those that proved effective for the Pt(II)/PPh$_3$ catalyst system[3] (5 mol % Pt, 110 °C, 1,4-dioxane, 5 h; Table 1). Notably, under these reaction conditions each of (COD)PtCl$_2$ (entry 1) and PtCl$_2$ (entry 2) was found to be a competent precatalyst for the cyclohydroamination of this alkylamine substrate, affording conversions to the corresponding pyrrolidine (ca. 80%) that were comparable to those reported previously[3] and to those obtained in our laboratory (entry 3), when using a Pt(II)/PPh$_3$ catalyst system. Furthermore, while diminished conversions were achieved when using (COD)PtCl$_2$ at lower temperatures (65 °C, 28%, entry 4; 80 °C, 42%, entry 5), the performance of PtCl$_2$/PPh$_3$ (80 °C, 13%, entry 6) was found to be inferior to that of (COD)PtCl$_2$.[11a] The ability of Pt complexes lacking phosphine or carbene ligation to mediate such alkylamine cyclohydroamination reactions had not previously been demonstrated in the literature, and collectively the observations reported herein bring into question the direct involvement of PPh$_3$ in supporting a catalytically active Pt(II) species in this particular reaction system. Nonetheless, the outstanding catalytic behavior exhibited by the PtCl$_2$/tBu-DavePhos catalyst system[4] with this test substrate (e.g., 80 °C, diglyme, 6 h, >99%) as well as with alternative alkylamines featuring a range of substitution patterns demonstrates that appropriately designed (dialkyl)phosphine co-ligands can indeed offer reactivity advantages in Pt-catalyzed cyclohydroamination.

**Chart 1**

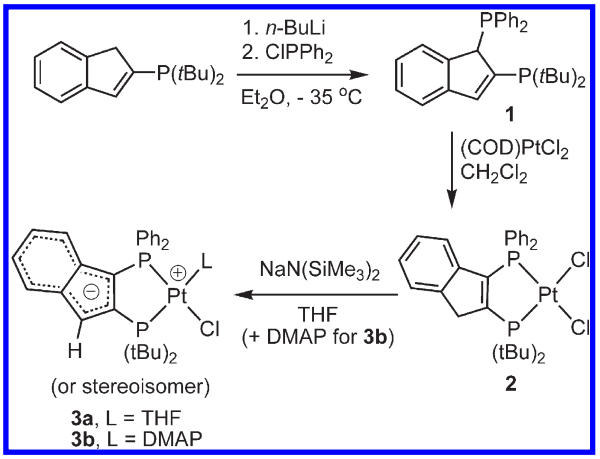



Despite recent progress in late-metal hydroamination catalyst design, the identification of catalysts that can promote the intramolecular addition of primary amines as well as secondary alkyl- and arylamines to unactivated olefins has proven difficult; to the best of our knowledge, such scope has only been demonstrated by the [Ir(COD)Cl]$_2$/HNEt$_3$Cl system.[6a] In this context, and given that previous examinations of cyclohydroamination employing the PtCl$_2$/tBu-DavePhos catalyst system are limited almost exclusively to secondary alkylamines,[4,11b] we sought to conduct proof-of-principle experiments using (COD)PtCl$_2$ (entries 7 and 9) and PtCl$_2$/tBu-DavePhos (entries 8 and 10) as precatalysts for the cyclization of secondary arylamine and primary amine test substrates under similar experimental conditions (Table 1). Gratifyingly, each catalyst proved capable of promoting the cyclohydroamination of these test substrates to a significant extent, with the PtCl$_2$/tBu-DavePhos system offering substantially improved catalytic performance in the case of the primary amine substrate (61% versus 90%).

Previous research in the Stradiotto group has established the utility of appropriately designed $\kappa^2$-*P*,*N* ligands featuring bulky (dialkyl)phosphino substituents in the Ir-mediated transfer hydrogenation of ketones (**L2**), as well as in the Pd-catalyzed amination of aryl and heteroaryl halides and pseudohalides (**L1**, Me-DalPhos; **L5**, Mor-DalPhos; Chart 1).[8] In an effort to evaluate if bulky co-ligands of this type might provide improved catalytic performance in Pt-catalyzed cyclohydroamination relative to phosphine-free catalysts, the cyclization of a representative secondary benzylamine substrate was examined under the conditions employed for PtCl$_2$ (entry 2), but with the inclusion of 6 mol % of **L1**-**L7** (entries 11−17). In all cases, the in situ-prepared PtCl$_2$/**L** catalyst mixture proved significantly inferior to PtCl$_2$ alone, with **L1** affording the most active catalyst among the P,N ligands surveyed (59%). While improvements in conversion relative to those obtained when using the PtCl$_2$/**L1** mixture were achieved by using the preformed coordination complex (**L1**)PtCl$_2$ (83%, entry 18), these catalytic results are still only on par with those obtained when using PtCl$_2$ in the absence of a co-ligand (79%, entry 2). Further efforts to improve the catalytic activity of (**L1**)PtCl$_2$ through the addition of halide-abstracting agents (5 mol % AgOTf or AgB(C$_6$F$_5$)$_4$) or

(11) (a) In keeping with our observations, Widenhoefer and co-workers have reported that a mixture of [PtCl$_2$(H$_2$C=CH$_2$)]$_2$ (2.5 mol %) and PPh$_3$ (5 mol %) under similar conditions using diglyme as the solvent exhibits negligible catalytic activity for this cyclohydroamination reaction.[4] (b) The use of PtCl$_2$/tBu-DavePhos as a catalyst for the cyclohydroamination of one secondary arylamine substrate has been reported.[6c]

**Scheme 1. Synthesis of 1 and the Derived Coordination Complexes 2 and 3a,b[a]**




[a] DMAP = 4-dimethylaminopyridine.

Brønsted acids (5 mol % HOTf or $HNEt_3Cl$) were unsuccessful, affording inferior results. Moreover, attempts to employ (**L1**)$PtCl_2$ (as well as **2**, **2**/AgOTf, or **3a**, vide infra) for the cyclization of secondary arylamine and primary amine test substrates under conditions similar to those featured in entries 7−10 in each case resulted in <15% consumption of the aminoalkene substrate.

With an aim toward evaluating the influence of sterically demanding and potentially strongly chelating bis(phosphine) ancillary ligands on Pt-catalyzed cyclohydroamination, we turned our attention to the study of neutral, cationic, and formally zwitterionic complexes derived from the new ligand precursor 1-$PPh_2$-2-P$(tBu)_2$-indene **1** (Scheme 1). Our inspiration for studying Pt precatalysts of this type comes from our prior observations that formally zwitterionic complexes supported by donor-substituted indenide ligands in some cases exhibit stoichiometric and catalytic reactivity patterns that are divergent from more conventional neutral and cationic complexes of related donor-substituted indenes, owing to the apparent involvement of the indenide framework in substrate activation.[9,12] Furthermore, a recent report by Ikariya and coworkers[6b] focusing on $(C_5Me_5)$Ir(pyrazolato) precatalysts supports the viability of metal−ligand bifunctional catalysis in cyclohydroamination chemistry. Lithiation of 2-P$(tBu)_2$-indene followed by quenching with $ClPPh_2$ afforded **1** in 85% isolated yield, which in turn was transformed into the isolable chelate complex **2** (89%) upon treatment of **1** with (COD)$PtCl_2$. The connectivity within **2** in solution was confirmed by use of NMR techniques, including the observation of two doublets (65.9 and 17.6 ppm, with accompanying Pt satellites) in the $^{31}P\{^1H\}$ NMR spectrum. The solid-state structure of **2** was confirmed on the basis of single-crystal X-ray diffraction data,[13] and an ORTEP diagram[14] of **2** is presented in Figure 1. Whereas the more electron-rich (indene)P$(tBu)_2$ fragment in **2** (versus the (indene)$PPh_2$ fragment) might be predicted to result in a longer corresponding *trans* Pt−Cl linkage, the Pt−Cl distances in **2** (Pt−Cl1, 2.3574(8) Å; Pt−Cl2, 2.3618(9) Å) are indistinguishable. Furthermore, the $Ph_2$P−Pt distance (2.2155(8) Å) is significantly shorter than the $(tBu)_2$P−Pt distance (2.2534(8) Å) linkage, which may be attributable to the greater steric demands of the (dialkyl)phosphino fragment.

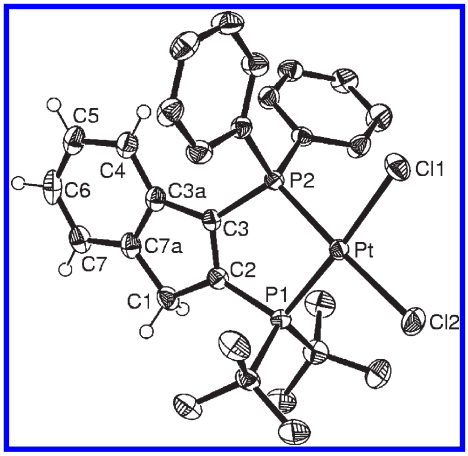



**Figure 1.** ORTEP diagram for **2** depicting the atomic numbering scheme and shown with 50% displacement ellipsoids. Selected hydrogen atoms have been removed for clarity. Selected interatomic distances (Å): Pt−Cl1, 2.3574(8); Pt−Cl2, 2.3618(9); Pt−P1, 2.2534(8); Pt−P2, 2.2155(8); P1−C2, 1.823(3); P2−C3, 1.808(3); C1−C2, 1.524(5); C2−C3, 1.348(5).

In an effort to prepare a formally zwitterionic bis(phosphine) Pt complex of the type ($\kappa^2$-*P*,*P*-indenide)Pt(THF)Cl **3a**, dehydrohalogenation of **2** in THF using $NaN(SiMe_3)_2$ was undertaken. While clean conversion to a new product that we tentatively assign as **3a** was observed over the course of 20 min when monitoring by use of NMR techniques in THF-$d_8$ ($^{31}P$ NMR: 55.5 and 7.8 ppm, with accompanying Pt satellites), we have thus far not been able to isolate **3a** in analytically pure form, due to decomposition upon removal of solvent or other workup. However, support for the identity of **3a** comes from the isolation of the corresponding 4-dimethylaminopyridine (DMAP) adduct **3b** upon treatment of solutions of putative **3a** with DMAP. Complex **3b** was isolated as an analytically pure yellow solid in 86% yield and was characterized by use of $^1H$, $^{13}C$, and $^{31}P$ NMR techniques.

In surveying the ability of each of **2**, **2**/AgOTf, and **3a** (cleanly generated in situ) to promote the cyclization of a representative secondary benzylamine substrate (entries 19−21, Table 1), only minor differences in catalytic performance were observed among these complexes, as well as between these bis(phosphine) species and either (COD)$PtCl_2$ or $PtCl_2$ under similar experimental conditions. One differentiating characteristic associated with the catalytic behavior of **3a** is that among all of the Pt precatalysts investigated herein, only this putative zwitterion exhibited a propensity for alkene isomerization within the α-olefinic secondary benzylamine substrate.

(12) For representative examples, see: (a) Hesp, K. D.; McDonald, R.; Ferguson, M. J.; Stradiotto, M. *J. Am. Chem. Soc.* **2008**, *130*, 16394. (b) Lundgren, R. J.; Rankin, M. A.; McDonald, R.; Schatte, G.; Stradiotto, M. *Angew. Chem., Int. Ed.* **2007**, *46*, 4732.

(13) (a) Selected crystallographic data for **2**: Empirical formula, $C_{29}H_{34}Cl_2P_2Pt_1$; formula weight, 710.49; crystal dimensions, 0.36 × 0.26 × 0.04; crystal system, orthorhombic; space group, $Pca2_1$ (No. 29); *a* (Å), 19.1456(9); *b* (Å), 8.5058(4); *c* (Å), 16.9601(8); *V* (Å$^3$), 2761.9(2); *Z*, 4; $\rho_{calcd}$ (g cm$^{-3}$), 1.709; $\mu$ (mm$^{-1}$), 5.406; 2$\theta$ limit (deg), 55.30 with $-24 \le h \le 24$, $-11 \le k \le 11$, $-22 \le l \le 22$; total data collected, 23 404; independent reflections, 6387; $R_{int}$ = 0.0304; observed reflections, 5934; absorption correction, Gaussian integration (face-indexed); range of transmission, 0.8048−0.2436; data/restraints/parameters, 6387/0/307; Flack absolute structure parameter, 0.001(4); $R_1$ [$F_o^2 \ge 2\sigma(F_o^2)$], 0.0193; $wR_2$ [$F_o^2 \ge 3\sigma(F_o^2)$], 0.0437; goodness-of-fit, 1.020; largest peak, hole (e Å$^{-3}$), 1.471, −0.321.

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## Summary and Conclusions

The proof-of-principle catalytic results featured herein establish the ability of phosphine-free Pt complexes including $PtCl_2$ and (COD)$PtCl_2$ to function as effective precatalysts for the cyclohydroamination of primary as well as secondary alkyl/arylamines tethered to α-olefins. These observations have important implications with respect to the design of Pt catalysts for use in such synthetic transformations, most notably asymmetric variants, in that the contributions from phosphine-free Pt species may figure significantly in the observed product distribution. The reactivity benefits associated with the use of sterically demanding monophosphine co-ligands such as tBu-DavePhos in the Pt-catalyzed cyclohydroamination of secondary alkylamine substrates is well established,[4] and herein we confirm that such precatalysts are also capable of mediating the cyclization of secondary arylamine and primary amine substrates. However, improved catalytic activity relative to $PtCl_2$ and (COD)$PtCl_2$ was not achieved through the use of complexes supported by the bidentate co-ligands featured in our study, which included precatalysts featuring phenylene-P,N ligands as well as neutral, cationic, and formally zwitterionic complexes derived from the new ligand precursor 1-$PPh_2$-2-P(tBu)$_2$-indene. Collectively, the observations featured in this report highlight the complexities associated with design of Pt catalysts for cyclohydroamination and will contribute to the further development of increasingly effective catalysts for this atom-economical transformation.

**Acknowledgment** is made to Dalhousie University and the Natural Sciences and Engineering Research Council of Canada (including a Discovery Grant for M.S. and a Canada Graduate Scholarship for C.B.L.). We also thank Dr. Michael Lumsden (NMR3, Dalhousie) for technical assistance in the acquisition of NMR data.

**Supporting Information Available:** Complete experimental details (PDF) and single-crystal X-ray diffraction data in CIF format for **2** are available free of charge via the Internet at http://pubs.acs.org.

**Note Added in Proof.** Following the acceptance of this manuscript for publication, a highly effective rhodium catalyst for the cyclohydroamination of unbiased and functionalized primary aminoalkenes was reported: Julian, L. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2010**, *132*, 13813.