

Design of Phosphorus Ligands with Deep Chiral Pockets: Practical Synthesis of Chiral β -Arylamines by Asymmetric Hydrogenation**

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Despite the significant advances in asymmetric hydrogenation, the development of novel and efficient chiral phosphorus ligands to solve new synthetic challenges continues to an important goal.^[1] C_2 -Symmetric chiral bisphosphorus ligands such as BINAP,^[2] DuPhos,^[3] and TangPhos^[4] are among the most versatile and important ligands for asymmetric hydrogenation, yet they are not universal. To expand their synthetic utilities, one common strategy is to develop structurally similar ligands, such as Tol-BINAP, Xyl-BINAP, Et-DuPhos, or *i*Pr-DuPhos by increasing the size of the substituents on the phosphorus centers (Figure 1 a). Such modifications lead to

strategy: 1) The R groups that protrude directly forward to the substrate coordination site can lead to a dramatic conformational variation of the chiral pocket; 2) the R groups are in close proximity to the metal center and the substrate, thereby providing a well-defined and deep chiral pocket. We herein report the development of WingPhos (**L5**) by using this strategy.

Chiral β -arylamines exist in numerous biologically interesting natural products and therapeutic agents. For examples, such moieties commonly exist in a series of naphthylisoquinoline alkaloids such as michellamine B and korupensamine A (Scheme 1).^[5] They also serve as pivotal structural units for

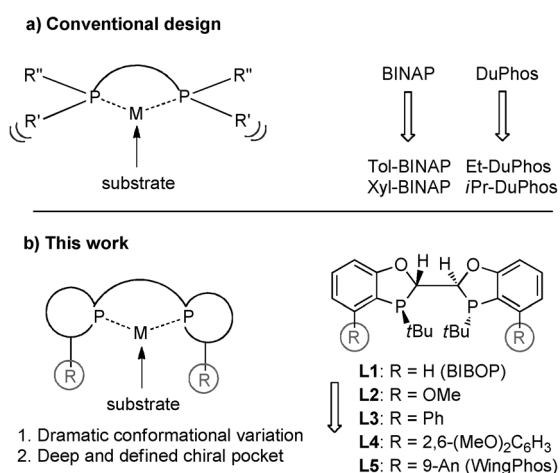
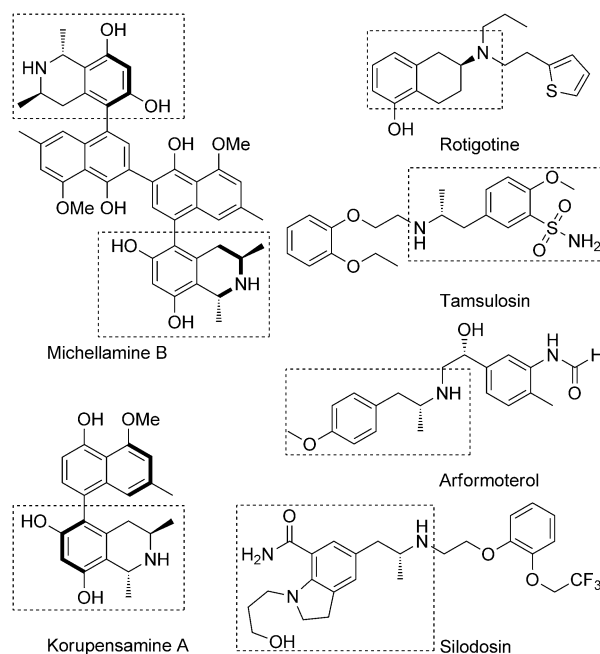


Figure 1. Design of novel chiral bisphosphorus ligand **L5** (WingPhos) with a deep chiral pocket (9-An = 9-anthracenyl).

the design of ligands with deeper chiral pockets mainly owing to the increased bulk of the R' groups, which protrude slightly forward to the substrate coordination. In this study we adopt a new strategy to design a ligand with a deep chiral pocket by installing R groups that protrude directly forward to the substrate coordination site. There are two advantages of this



Scheme 1. Selected natural products and therapeutic agents containing chiral β -arylamines.

many active pharmaceutical ingredients such as 3,4-methylenedioxymphetamine (MDA),^[6a] tamsulosin,^[6b] selegiline,^[6c] arformoterol,^[6d] rotigotine,^[6e] and silodosin.^[6f] Development of efficient asymmetric synthetic methods of chiral β -arylamines has thus become a subject of significant interest.^[7] However, the asymmetric hydrogenation of β -aryl enamides to prepare chiral β -arylamines remains underdeveloped. Zhang, Lei, and co-workers reported high enantioselectivities on the asymmetric hydrogenation of (*Z*)- β -aryl enamides by using a Rh–TangPhos catalyst.^[8] Nevertheless, low *ee* values were observed with thermodynamically more stable sub-

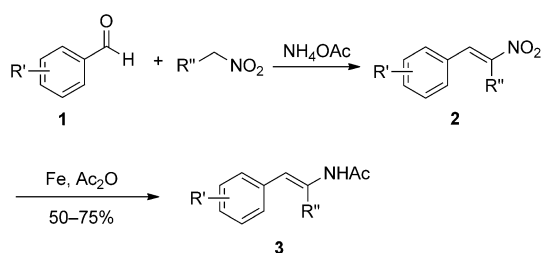
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strates, (*E*)- β -aryl enamides. Zhou and co-workers reported high *ee* values with (*Z*)- or (*E*)- β -aryl enamides when using a chiral monophosphane or phosphite ligand, albeit with limited turnover numbers (substrate/catalyst (s/c) ratio ≤ 100).^[9] For hydrogenation of cyclic^[10] or heterocyclic^[11] β -aryl enamides, few efficient chiral rhodium catalysts are available. We herein report an efficient method for the synthesis of acyclic, cyclic, or heterocyclic chiral β -arylamines by hydrogenation of readily accessible (*E*)- β -aryl enamides. Excellent reactivity (turnover number (TON) up to 10000) and enantioselectivities (up to $>99\%$ *ee*) have been achieved by employing the Rh-**L5** catalyst.

Although both (*Z*)- and (*E*)- β -aryl enamides have been studied for asymmetric hydrogenation, efficient asymmetric hydrogenation of (*E*)- β -aryl enamides is more desirable from a practical point of view, because they are more thermodynamically stable and can be selectively synthesized. Among various synthetic methods of β -aryl enamides,^[12] we chose to employ reductive acylation of nitroalkenes^[13] to prepare (*E*)- β -aryl enamides for synthetic easiness and cost effectiveness. Thus, Henry reaction between aryl aldehydes and nitroalkanes provided (*E*)-nitroalkenes in high yields. Reductive acylation of nitroalkenes according to a reported procedure led to the formation of **3** as *E/Z* isomeric mixture.^[15] By optimizing the reaction conditions, (*E*)- β -aryl enamides were formed preferentially and could be isolated in moderate to good yields without column chromatography (Scheme 2). This rapid and economical method holds promise for practical synthesis of (*E*)- β -aryl enamides.



Scheme 2. Syntheses of (*E*)- β -aryl-*N*-acetyl enamides from aldehydes and nitroalkanes. *R'* = substituents on the aromatic ring; *R''* = Me or Et.

The asymmetric hydrogenation of (*E*)-*N*-[1-(3,5-dimethoxyphenyl)prop-1-en-2-yl]acetamide (**3a**) was investigated with various chiral rhodium catalysts. The hydrogenations were conducted at room temperature at a hydrogen pressure of 300 psi for 12 h. It was found that well-known chiral ligands such as BINAP, Josiphos, and Tangphos^[8] did not provide superb enantioselectivities (Table 1, entries 1–2). Ligand BIBOP (**L1**), which was highly effective for hydrogenation of α -aryl-*N*-acetyl enamides in our previous study,^[14] proved to be inefficient (Table 1, entry 3). A low *ee* was also observed when MeO-BIBOP (**L2**) was applied (Table 1, entry 4). Gratifyingly, the enantioselectivity increased dramatically when ligands **L3–5** containing various aryl groups as *R* groups were employed (Table 1, entries 5–7). When **L5** with anthracenyl groups was applied, the enantioselectivity reached 97%. An excellent *ee* value was also achieved when a high

Table 1: Asymmetric hydrogenation of (*E*)-*N*-[1-(3,4-dimethoxyphenyl)prop-1-en-2-yl]acetamide.^[a]

Entry	Ligand	s/c	<i>ee</i> [%] ^[b]
1	(<i>R</i>)-BINAP	200	3
2	(<i>R,S</i>)-Josiphos	200	13
3	L1	200	27
4	L2	200	11
5	L3	200	35
6	L4	200	74
7	L5	200	97
8 ^[c]	L5	10000	97

[a] The hydrogenations were carried out in dichloromethane (2 mL) for 12 h with **3a** (0.1 mmol), [Rh(nbd)₂]BF₄ (0.5 μ mol; nbd = 3,5-norbornadiene), and ligand (0.6 μ mol) unless otherwise specified; all reactions proceeded completely; the absolute configuration was determined as *R* by comparing the optical rotation with reported data. [b] Determined by HPLC on a Chiralcel AD-H column. [c] **3a** (1 mmol), [Rh(nbd)₂](**L5**)BF₄ (0.1 μ mol), dichloromethane (2 mL), 80 °C, H₂ (750 psi), 20 h.

substrate/catalyst ratio (s/c = 10000) was employed (Table 1, entry 8), thus demonstrating the high reactivity and efficiency of ligand **L5** for this transformation.

With Rh-**L5** as the catalytic system, different substituted (*E*)- β -aryl-*N*-acetyl enamides were hydrogenated to provide an array of chiral β -arylamines in good to excellent enantioselectivities. High *ee* values were achieved regardless of the electronic property or the substitution pattern on the benzene ring (Table 2). An excellent *ee* value ($>99\%$ *ee*) was also achieved with a substrate containing a 4-methoxy substituent

Table 2: Asymmetric hydrogenation of (*E*)- β -aryl-*N*-acetyl enamides.^[a]

Entry	<i>R'</i>	<i>R''</i> (3)	<i>ee</i> [%] ^[b] (4)
1	Ph	Me (3b)	97 (4b)
2	2-MeOC ₆ H ₄	Me (3c)	99 (4c)
3	3-MeOC ₆ H ₄	Me (3d)	98 (4d)
4	4-MeOC ₆ H ₄	Me (3e)	>99 (4e)
5	2-MeC ₆ H ₄	Me (3f)	96 (4f)
6	3,5-(BnO) ₂ C ₆ H ₃	Me (3g)	99 (4g)
7	2-ClC ₆ H ₄	Me (3h)	98 (4h)
8	3-BrC ₆ H ₄	Me (3i)	98 (4i)
9	4-BrC ₆ H ₄	Me (3j)	98 (4j)
10	4-FC ₆ H ₄	Me (3k)	99 (4k)
11	1-naphthyl	Me (3l)	97 (4l)
12	2-naphthyl	Me (3m)	96 (4m)
13	3-thiophenyl	Me (3n)	93 (4n)
14	Ph	Et (3o)	98 (4o)
15	4-MeOC ₆ H ₄	Et (3p)	98 (4p)

[a] The hydrogenations were carried out in dichloromethane (0.5 mL) at 50 °C, under 750 psi of H₂ for 12 h with substrate (0.1 mmol) and [Rh(nbd)(**L5**)]BF₄ (0.5 μ mol); the absolute configuration was assigned as *R* by comparing the optical rotation with reported data^[8,9] or by analogy; the yields were $>99\%$. [b] Determined by chiral HPLC, see Supporting Information for details.

as the R' group, thereby providing an important chiral intermediate **4e** for the synthesis of β -adrenoceptor agonist drug arformoterol^[8d] and α_1 receptor antagonist tamsulosin (Table 2, entry 4).^[8b] Halogen substituents at various positions of the aromatic rings were tolerable (Table 2, entries 7–10). Substrates containing 1-naphthyl or 2-naphthyl moieties were well applicable (Table 2, entries 11, 12). A 3-thiophenyl substrate also provided a good *ee* value (Table 2, entry 13). Excellent enantioselectivities were also achieved on substrates with α -ethyl substituents (Table 2, entries 14–15).

Asymmetric hydrogenation of cyclic β -aryl-*N*-acetyl enamides constitutes an attractive method for the syntheses of chiral cyclic β -arylamines. Although a few ruthenium catalysts have been reported to be effective in the synthesis of cyclic β -aryl-*N*-acyl enamides,^[10] the enantioselectivities were often dependent on the structure of the acyl group.^[11a] In contrast, very limited success has been achieved with chiral rhodium catalysts.^[10c] We were pleased that the Rh–**L5** catalyst was equally effective for asymmetric hydrogenation of various substituted cyclic β -aryl-*N*-acetyl enamides, thereby leading to the formation of a series of chiral 2-aminotetralines and 3-aminochromanes in excellent enantioselectivities (Table 3). At a 1 mmol scale, hydrogenation of *N*-(5-methoxy-3,4-dihydronaphthalen-2-yl)acetamide yielded a key chiral intermediate for the dopamine agonist rotigotine^[6e] in 96% *ee* with up to 2000 TON (Table 3, entry 3). Heterocyclic substrates were equally effective (Table 3,

Table 3: Asymmetric hydrogenation of cyclic β -aryl-*N*-acetyl enamides **5**.^[a]

Entry	Substrate	s/c	Product	<i>ee</i> [%] ^[b]
1		200		96
2		200		96
3 ^[c]		2000		96
4		200		96
5		200		94
6		200		98
7		200		97

[a] The hydrogenations were carried out in dichloromethane (0.5 mL) for 12 h with substrate (0.1 mmol) and [Rh(nbd)(**L5**)]BF₄ (0.5 μ mol); complete conversion; the absolute configuration was assigned by comparing the optical rotation with reported data^[10,11] or by analogy; the yields were > 99%; [b] Determined by HPLC using a chiral stationary phase, see details in the Supporting Information; [c] **5b** (1 mmol), [Rh(nbd)(**L5**)]BF₄ (0.5 μ mol), dichloromethane (2 mL), 80 °C, H₂ (750 psi), 20 h.

entries 5–7), and the corresponding chiral 3-aminochromanes (up to 98% *ee*) are important intermediates for various therapeutic agents.^[11]

To understand the high enantioselectivity observed with the Rh–**L5** catalyst, a rhodium complex [Rh(nbd)(**L5**)]BF₄ was prepared, and a C₂-symmetric structure with a deep chiral pocket was revealed by X-ray crystallography.^[15] The two anthracenyl groups of **L5** protrude directly forward to the norbornadiene component and could have a steric effect on substrate coordination (Figure 2 a). The rhodium metal center is well sandwiched between the two anthracenyl groups, with a parallel distance of approximately 8 Å. The distance between the rhodium center and the *ipso* carbon atom of the anthracenyl group is approximately 4.4 Å, shorter than a phenyl substituent (ca. 5.2 Å). Thus, the orientation of an aromatic substrate could be well-defined when coordinating to the catalyst.

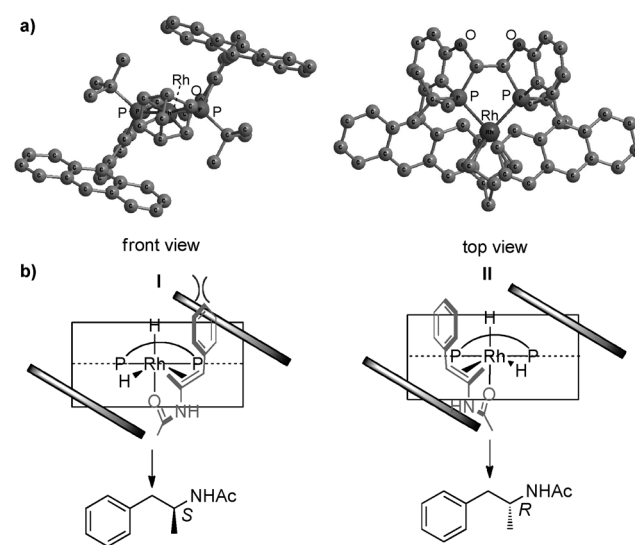
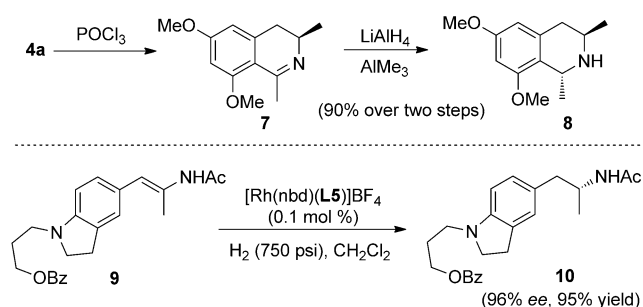


Figure 2. a) The X-ray structure of [Rh(nbd)(**L5**)]BF₄ (H atoms and BF₄ anion are omitted for clarity; selected parameters: $\angle$ P–Rh–P = 85.5°; bond length of Rh–P: 2.325 Å, Rh–*ipso*C of anthracenyl: 4.478, 4.411 Å); b) A stereochemical model for asymmetric hydrogenation of (*E*)- β -phenyl-*N*-acetyl enamides with the Rh–**L5** catalyst.

Owing to the structural similarity between (*E*)- β -aryl-*N*-acetyl enamides and (*E*)- β -(acylamino)acrylates, a reaction mechanism via monohydrides with the β -carbon atom bound to rhodium is proposed.^[16] Hence, substrate coordination of a Rh–**L5** dihydride complex^[17] provides two possible coordination modes I and II (Figure 2 b). Strong steric interaction is foreseen between the aromatic substituent of the substrate and an anthracenyl group of the ligand in mode I. Less steric interaction is expected in mode II, which could undergo insertion and reductive elimination to yield the chiral hydrogenation product with correct stereochemistry.

To further demonstrate the synthetic utility of this methodology, the chiral hydrogenation product **4a** was converted to a tetrahydroisoquinoline compound **8** in 90% overall yield through two simple transformations (Scheme 3). The chiral amine **8** is a key chiral building block for the



Scheme 3. Synthesis of useful intermediates **8** and **10** by using this hydrogenation methodology.

syntheses of michellamine B and korupensamine A.^[5a] A highly functionalized enamide **9** was also successfully hydrogenated in the presence of $[\text{Rh}(\text{nbd})(\text{L}5)]\text{BF}_4$ (0.1 mol %) to provide chiral amide **10** in 96 % *ee* and 95 % yield. Compound **10** is a key chiral intermediate for the α_1 adrenoceptor antagonist silodosin.^[6f]

In summary, we have successfully developed a novel C_2 -symmetric bisphosphorus ligand WingPhos with a deep and well-defined chiral pocket that has shown high efficiency in the rhodium-catalyzed asymmetric hydrogenation of (*E*)- β -aryl-*N*-acetyl enamides, cyclic β -aryl enamides, and heterocyclic β -aryl enamides. A series of chiral β -arylisopropylamines, 2-aminotetralines, and 3-aminochromanes can be synthesized with excellent *ee* values at high s/c ratios (up to 10000 TON). The methodology has been successfully applied to the syntheses of several key chiral intermediates of natural products and therapeutic agents. Since (*E*)- β -aryl-*N*-acetyl enamides can be easily synthesized from readily available materials, this method holds promise for practical syntheses of various chiral β -arylamine compounds. A study towards this end is actively under investigation.

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- [1] For selected reviews, see: a) *Comprehensive Asymmetric Catalysis* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**; b) *Asymmetric Catalysis on Industrial Scale: Challenges, Approaches and Solutions* (Eds.: H.-U. Blaser, E. Schmidt), Wiley-VCH, Weinheim, **2004**; c) W. Tang, X. Zhang, *Chem. Rev.* **2003**, *103*, 3029; d) J.-H. Xie, S.-F. Zhu, Q.-L. Zhou, *Chem. Rev.* **2011**, *111*, 1713; e) K. Gopalaiah, H. B. Kagan, *Chem. Rev.* **2011**, *111*, 4599; f) D.-S. Wang, Q.-A. Chen, S.-M. Lu, Y.-G. Zhou, *Chem. Rev.* **2012**, *112*, 2557.
- [2] R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, Wiley, New York, **1994**.
- [3] M. J. Burk, *Acc. Chem. Res.* **2000**, *33*, 363.
- [4] W. Tang, X. Zhang, *Angew. Chem.* **2002**, *114*, 1682; *Angew. Chem. Int. Ed.* **2002**, *41*, 1612.
- [5] a) G. Bringmann, T. Gulder, T. A. M. Gulder, M. Breuning, *Chem. Rev.* **2011**, *111*, 563; b) G. Bringmann, P. Frank in *Alkaloids, Vol. 46*, Academic Press, New York, **1995**, p. 127; c) K. P. Manfredi, J. W. Blunt, J. H. Cardellina II, J. B. McMahon, L. L. Pannell, G. M. Cragg, *J. Med. Chem.* **1991**, *34*, 3402; d) Y. F. Hallock, K. P. Manfredi, J. R. Dai, J. H. Cardellina II, R. J. Gulakowski, J. B. McMahon, M. Schaffer, M. Stahl, K. P. Gulden, G. Bringmann, G. Francois, M. R. Boyd, *J. Nat. Prod.* **1997**, *60*, 677.
- [6] a) S. H. Snyder, K. M. Tayler, *Science* **1970**, *168*, 1487; b) C. G. Roehrborn, P. Siami, J. Barkin, R. Damião, K. Major-Walker, B. Morrill, F. Montorsi, *J. Urol.* **2008**, *179*, 616; c) M. Sano, C. Ernesto, R. C. Thomas, M. R. N. Klauber, *N. Engl. J. Med.* **1997**, *336*, 1216; d) B. Barnes, *Formoterol, A New Generation of Beta-2-agonist*, Hogrefe and Huber Pub., Toronto, **1991**; e) D. Q. Pharm, A. Nogid, *Clin. Ther.* **2008**, *30*, 813; f) M. Yoshida, Y. Homma, K. Kawabe, *Expert Opin. Invest. Drugs* **2007**, *16*, 1955.
- [7] *Chiral Amine Synthesis: Methods, Developments and Applications* (Ed.: T. C. Nugent), Wiley-VCH, Weinheim, **2010**.
- [8] J. Chen, W. Zhang, H. Geng, W. Li, G. Hou, A. Lei, X. Zhang, *Angew. Chem.* **2009**, *121*, 814; *Angew. Chem. Int. Ed.* **2009**, *48*, 800.
- [9] S.-F. Zhu, T. Liu, S. Yang, S. Song, Q.-L. Zhou, *Tetrahedron* **2012**, *68*, 7685.
- [10] a) D. M. Tschaen, L. Abramson, D. Cai, R. Desmond, U.-H. Dolling, L. Frey, S. Karady, Y.-J. Shi, T. R. Verhoeven, *J. Org. Chem.* **1995**, *60*, 4324; b) P. Dupau, P. Le Gendre, C. Bruneau, P. H. Dixneuf, *Synlett* **1999**, 1832; c) X.-B. Jiang, L. Lefort, A. H. H. de Vries, P. W. N. M. van Leeuwen, J. G. de Vries, J. N. H. Reek, *Angew. Chem.* **2006**, *118*, 1245; *Angew. Chem. Int. Ed.* **2006**, *45*, 1223.
- [11] a) J. L. Renaud, P. Dupau, A.-E. Hay, M. Guingouain, P. H. Dixneuf, C. Bruneau, *Adv. Synth. Catal.* **2003**, *345*, 230; b) A. Beliaev, J. Wahnou, D. Russo, *Org. Process Res. Dev.* **2012**, *16*, 704.
- [12] For Beckmann rearrangement of ketoximes, see: a) R. Brett, S. M. Shibib, K. J. Wheeler, *J. Chem. Soc. Perkin Trans. 1* **1985**, 831; for reductive acylation of ketoximes, see: b) M. J. Burk, G. Casy, N. B. Johnson, *J. Org. Chem.* **1998**, *63*, 6084; c) G. Zhu, A. L. Casalnuovo, *J. Org. Chem.* **1998**, *63*, 8100; d) W. Tang, A. Capacci, M. Sarvestani, X. Wei, N. K. Yee, C. H. Senanayake, *J. Org. Chem.* **2009**, *74*, 9528; e) Z. Guan, Z. Zhang, Z. Ren, Y. Wang, X. Zhang, *J. Org. Chem.* **2011**, *76*, 339; for palladium-catalyzed cross-coupling, see: f) D. J. Wallace, D. J. Klauber, C.-Y. Chen, R. P. Volante, *Org. Lett.* **2003**, *5*, 4749.
- [13] N. M. Laso, B. Quiclet-Sire, S. Z. Zard, *Tetrahedron Lett.* **1996**, *37*, 1605.
- [14] a) W. Tang, B. Qu, A. G. Capacci, S. Rodriguez, X. Wei, N. Haddad, B. Narayanan, S. Ma, N. Grinberg, N. K. Yee, S. Krishnamurthy, C. H. Senanayake, *Org. Lett.* **2010**, *12*, 176; b) D. R. Fandrick, K. R. Fandrick, J. T. Reeves, Z. Tan, W. Tang, A. G. Capacci, S. Rodriguez, J. J. Song, H. Lee, N. K. Yee, C. H. Senanayake, *J. Am. Chem. Soc.* **2010**, *132*, 7600.
- [15] CCDC 921480 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
- [16] Gridnev and Imamoto first proposed this mechanism in hydrogenation of (*E*)- β -(acylamino)acrylates with BisP* as the ligand, see: a) M. Yasutake, I. D. Gridnev, N. Higashi, T. Imamoto, *Org. Lett.* **2001**, *3*, 1701; b) I. D. Gridnev, M. Yasutake, N. Higashi, T. Imamoto, *J. Am. Chem. Soc.* **2001**, *123*, 5268.
- [17] For hydrogenation mechanism through a "dihydride" pathway, see: a) I. D. Gridnev, N. Higashi, K. Asakura, T. Imamoto, *J. Am. Chem. Soc.* **2000**, *122*, 7183; b) I. D. Gridnev, N. Higashi, T. Imamoto, *J. Am. Chem. Soc.* **2000**, *122*, 10486; c) I. D. Gridnev, T. Imamoto, *Organometallics* **2001**, *20*, 545; d) I. D. Gridnev, T. Imamoto, *Acc. Chem. Res.* **2004**, *37*, 633; e) I. D. Gridnev, T. Imamoto, *Chem. Commun.* **2009**, 7447.