

Synthesis of Enantiomerically Enriched Imidazolidin-2-Ones through Asymmetric Palladium-Catalyzed Alkene Carboamination Reactions**

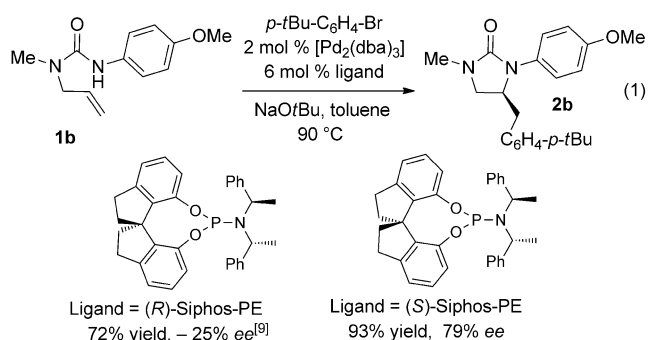
Brett A. Hopkins and John P. Wolfe*

Chiral 4-substituted imidazolidin-2-ones are displayed in a myriad of biologically active compounds, including potent HIV protease inhibitors.^[1] However, despite their significance, the preparation of these compounds by asymmetric catalysis has rarely been reported.^[2] In addition, no existing catalytic asymmetric reaction allows for the generation of a C–C bond during the course of imidazolidin-2-one formation. Most other routes to enantiopure imidazolidin-2-ones involve the synthesis of chiral 1,2-diamines, which often requires several synthetic steps and can be particularly lengthy when the two amino groups bear different substituents.^[3,4]

Here we describe the first catalytic asymmetric alkene carboamination reactions between *N*-allyl urea derivatives and aryl or alkenyl halides.^[5,6] These reactions provide a simple route to enantiomerically enriched 4-(arylmethyl)-imidazolidin-2-ones, and these studies illustrate the utility of water as an additive in an enantioselective Pd-catalyzed alkene difunctionalization reaction. Moreover, the results of these experiments suggest that C–C bond-forming reductive elimination may be the enantiodetermining step in transformations of *N*-allyl urea substrates. This contrasts with other asymmetric metal-catalyzed alkene carboamination reactions, in which the absolute stereochemistry appears to be set during alkene aminometallation.^[7]

Our prior studies on Pd-catalyzed asymmetric carboaminations of *N*-Boc-pent-4-enylamine (Boc = *tert*-butoxycarbonyl) demonstrated that use of (*R*)-Siphos-PE^[8] as a ligand provides 2-benzylpyrrolidine derivatives with good levels of enantioselectivity.^[7a] Thus in our efforts to generate enantiomerically enriched imidazolidin-2-ones we initially examined the use of a catalyst composed of [Pd₂(dba)₃] (dba = dibenzylideneacetone) and (*R*)-Siphos-PE for the asymmetric conversion of **1b** to **2b**. Unfortunately, this catalyst provided **2b** in only modest enantioselectivity [Eq. (1)].^[9] However, we were gratified to find that the diastereomeric ligand (*S*)-Siphos-PE provided **2b** in 93 % yield and 79 % *ee*. Despite this

promising result, a survey of other phosphine and phosphoramidite ligands did not lead to further improvements in asymmetric induction.



In efforts to both increase the asymmetric induction in Pd/(*S*)-Siphos-PE-catalyzed carboamination reactions of *N*-allyl ureas, and to explore the effect of nitrogen nucleophilicity on asymmetric induction, we prepared a series of substrates bearing different aromatic groups on the cyclizing nitrogen atom. As shown in Table 1, the level of asymmetric induction increased with the increasing electron-withdrawing ability of the *p*-substituent on the *N*-aryl moiety of **1**. Unfortunately, the chemical yields also decreased due to the diminished reactivity of these substrates, and unreacted starting material was observed in crude reaction mixtures. To address this

Table 1: Electronic effects.^[a]

Entry	X	Yield [%] ^[b]	<i>ee</i> [%]
1	N(Bn)Me (1a)	70 (2a)	73
2	OMe (1b)	93 (2b)	79
3	H (1c)	90 (2c)	78
4	Br (1d)	45 (2d)	83
5	CN (1e)	46 (2e)	89
6 ^[c]	CN (1e)	87 (2e)	86
7 ^[c]	NO ₂ (1f)	81 (2f)	92

[a] Conditions: 1.0 equiv **1**, 2.0 equiv *p*-*t*Bu-C₆H₄-Br, 2.0 equiv NaOtBu, 2 mol % [Pd₂(dba)₃], 6 mol % (*S*)-Siphos-PE, toluene (0.2 M), 90 °C, 12 h. [b] Yield of isolated products (average of two or more runs). [c] The reaction was conducted at 120 °C in xylenes.

[*] B. A. Hopkins, Prof. Dr. J. P. Wolfe
Department of Chemistry, University of Michigan
930 N. University Ave, Ann Arbor, MI 48109-1055 (USA)
E-mail: jpwolfe@umich.edu

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problem the reaction temperature was increased to 115–120 °C, and the desired products were generated in good chemical yield (entries 6 and 7) without a significant decrease in asymmetric induction.^[10] The best result was obtained with *p*-nitrophenyl-substituted substrate **1f**, which was converted to **2f** in 81 % yield and 92 % *ee*.

In order to explore the scope of the asymmetric carboamination reactions, substrate **1f** was coupled with a range of different aryl halide electrophiles (Table 2). We initially

Table 2: Scope of Pd-catalyzed asymmetric carboamination.^[a]

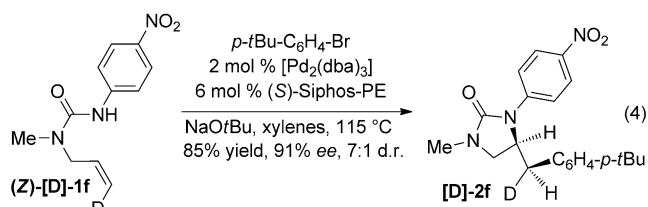
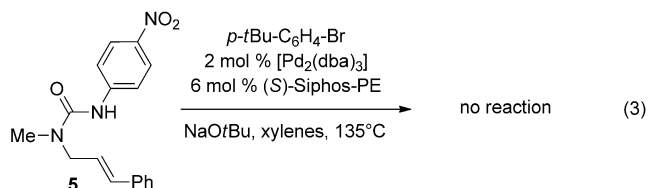
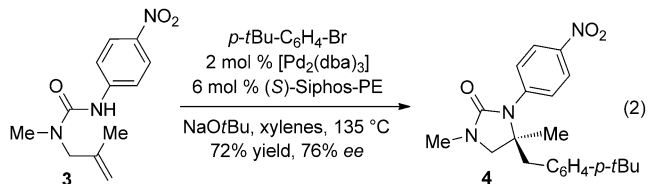
Entry	G	R-X	Additive ^[b]	Product	Yield [%] ^[c]	<i>ee</i> [%]
1	NO ₂	<i>p</i> -CF ₃ -C ₆ H ₄ -Br	–	2g	56	77
2	NO ₂	<i>p</i> -CF ₃ -C ₆ H ₄ -Br	H ₂ O	2g	72	95
3	NO ₂	<i>m</i> -CF ₃ -C ₆ H ₄ -Br	H ₂ O	2h	68	88
4	NO ₂	<i>o</i> -CF ₃ -C ₆ H ₄ -Br	H ₂ O	2i	56	83
5	NO ₂	<i>p</i> -PhC(O)-C ₆ H ₄ -Br	H ₂ O	2j	82	86
6	NO ₂	<i>p</i> -F-C ₆ H ₄ -Br	H ₂ O	2k	65	94
7	NO ₂	<i>p</i> -Cl-C ₆ H ₄ -Br	H ₂ O	2l	74	93
8	NO ₂	<i>p</i> - <i>t</i> Bu-C ₆ H ₄ -Br	–	2f	81	92
9	NO ₂	<i>p</i> - <i>t</i> Bu-C ₆ H ₄ -I	–	2f	60 ^[d]	47
10	NO ₂	Ph-Br	–	2m	83	89
11	NO ₂		–	2n	71	89
12	NO ₂		H ₂ O	2o	80	87
13	NO ₂	<i>p</i> -MeO-C ₆ H ₄ -Br	TFA	2p	80	90
14	NO ₂	<i>m</i> -MeO-C ₆ H ₄ -Br	–	2q	75	83
15	CN		–	2r	65	86
16	CN	<i>p</i> -CF ₃ -C ₆ H ₄ -Br	H ₂ O	2s	58	77
17	CN	<i>p</i> -CF ₃ -C ₆ H ₄ -I	H ₂ O	2s	77	80
18	CN	<i>p</i> -Me-C ₆ H ₄ -Br	–	2t	86	85
19	CN	<i>p</i> -Me-C ₆ H ₄ -I	–	2t	89	73
20	CN	<i>p</i> -MeO-C ₆ H ₄ -Br	–	2u	73	84

[a] Conditions: 1.0 equiv **1e** or **1f**, 2.0 equiv ArX, 2.0 equiv NaOtBu, 2 mol % [Pd₂(dba)₃], 6 mol % (S)-Siphos-PE, xylenes (0.2 M), 115 °C (substrate **1f**) or 120 °C (substrate **1e**), 14–18 h. [b] 2.0 Equiv water or 40 mol % TFA (trifluoroacetic acid) were added to the reaction mixture prior to heating. [c] Yield of isolated products (average of two or more runs). [d] This material contained ca. 35 % of an unidentified regioisomer.

encountered difficulty obtaining reproducible enantioselectivities in reactions of electron-deficient aryl bromides with **1f**. After some exploration, we discovered that addition of 2.0 equiv of water to the reactions led to significantly improved and reproducible enantioselectivities.^[11] The coupling of 2-bromonaphthalene or 3-bromoanisole with **1f** was not significantly influenced by the addition of water (entries 11 and 14). Addition of water had a negative

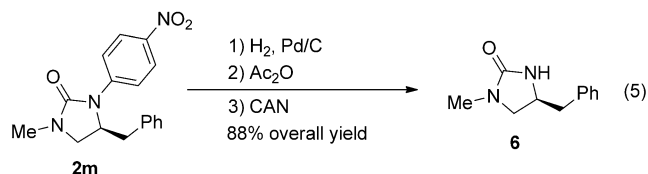
impact on the reaction of **1f** with 4-bromoanisole, but addition of 40 mol % of trifluoroacetic acid provided results superior to those obtained with either added water or no additive (entry 13). Efforts to employ alkenyl halides as electrophiles in the asymmetric carboamination of **1f** were unsuccessful. However, the reaction of substrate **1e** with 2-bromovinyltrimethylsilane proceeded in 65 % yield and 86 % *ee* (entry 15). The coupling of **1e** with aryl bromides generated cyclic urea products with lower enantioselectivities than were obtained in analogous reactions of **1f** (entries 16–20). Use of aryl iodides as electrophiles in reactions of **1e** and **1f** led to diminished enantioselectivities as compared to reactions of the corresponding aryl bromides (entries 8, 9 and 18, 19). However, addition of water to the reaction of 4-iodobenzotrifluoride led to a slightly higher *ee* than was obtained with the aryl bromide under similar conditions (entries 16 and 17).

The reactivity of substrates bearing disubstituted alkenes was also briefly explored. The 2-methylallyl urea derivative **3** was converted to cyclic urea **4** in 72 % yield and 76 % *ee* although a reaction temperature of 135 °C was required to effect complete conversion [Eq. (2)]. Addition of water or TFA did not have a positive effect on either the chemical yield or the enantioselectivity of this transformation. The 3-phenylallyl urea substrate **5** was unreactive at 135 °C, and only trace amounts of product were obtained at 160 °C [Eq. (3)]. In order to determine the stereochemistry of the 1,2-addition reaction, *Z*-deuterioalkene substrate (**Z**)-**[D]-1f** was subjected to the optimized reaction conditions. This transformation proceeded with *syn*-addition to the alkene to afford **[D]-2f** in 85 % yield, 91 % *ee*, and 7:1 d.r. [Eq. (4)].^[12]

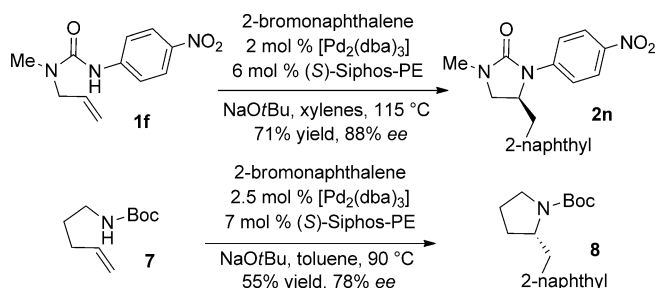


To illustrate the feasibility of deprotecting the *N*-aryl urea products we examined removal of the *p*-nitrophenyl group from **2m**. In this representative case, cleavage of the *N*-aryl substituent was cleanly accomplished using a three-step procedure that required only a single chromatographic

purification. As shown below, hydrogenation of **2m** followed by treatment with acetic anhydride and then oxidation with ceric ammonium nitrate provided **6** in 88% overall yield [Eq. (5)].



Several of the observations described above are quite surprising, particularly when results obtained in the Pd/Siphos-PE-catalyzed asymmetric carboaminations of ureas are compared to those for related asymmetric Pd-catalyzed carboamination reactions of *N*-Boc-pent-4-enylamines (Scheme 1). For example, the [Pd₂(dba)₃]/(*S*)-Siphos-PE

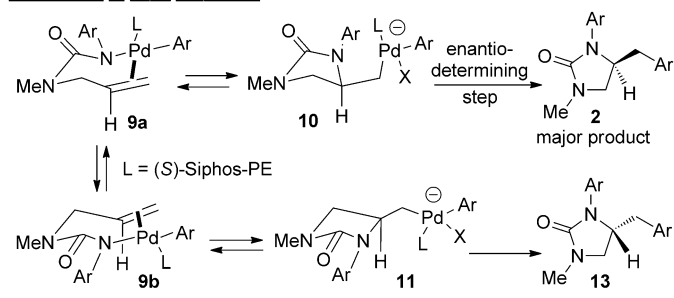


Scheme 1. Stereochemistry of urea versus pyrrolidine formation.

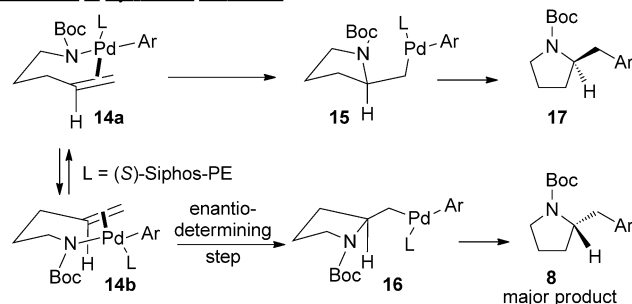
catalyst provides (*S*)-imidazolidin-2-one products **2** in reactions of **1e–f**, whereas the same catalyst system afforded pyrrolidine enantiomer **8** from **7**.^[13] Thus, despite the similarities of the two substrates, the two reactions proceed with the opposite absolute asymmetric induction. The positive effect of water on asymmetric induction in Pd-catalyzed reactions has rarely been observed,^[14] and the water effect is considerably different for the imidazolidin-2-one versus pyrrolidine systems. Addition of water in reactions of **1e** or **1f** with electron-deficient aryl bromides led to significantly improved asymmetric induction. In contrast, addition of water to reactions of *N*-Boc-pent-4-enylamine derivatives had a highly deleterious effect, as no desired product was obtained in these transformations.^[15]

Despite the differences in the absolute product stereochemistry in reactions of **1** versus **7**, these transformations appear to proceed through similar mechanisms and intermediates. In both cases *syn*-1,2-addition to the alkene is observed, and the ratio of ligand to Pd does not influence asymmetric induction in either case.^[7a] The mechanism of both reactions proceeds through oxidative addition of the aryl halide to Pd⁰ followed by substrate deprotonation and substitution to provide alkene-bound palladium(aryl)(amido) complexes **9a,b** and **14a,b** (Scheme 2).^[6] These complexes undergo *syn*-1,2-migratory insertion into the Pd–N bond to

Mechanism of Urea Formation



Mechanism of Pyrrolidine Formation



Scheme 2. Mechanism of urea versus pyrrolidine formation.

yield **10** and **16**,^[16] which then undergo reductive elimination to provide the observed major products **2** and **8**.

The differences in absolute stereochemistry of products obtained in reactions of the urea substrates versus the *N*-Boc pentenylamine derivatives are likely due to a change in the enantiodetermining step of the catalytic cycle. The product stereocenter is generated during the migratory insertion step, but two steps could potentially be enantiodetermining in this catalytic cycle: 1) the migratory insertion step (e.g., **14b** to **16**); or 2) the subsequent reductive elimination step if migratory insertion is reversible (e.g., **10** to **2**).^[16c] In our prior studies^[7a] we suggested that with the relatively electron-rich *N*-Boc pentenylamine substrate **7**^[17] the aminopalladation is likely irreversible,^[18] and relatively fast reductive elimination from **16**^[19] would provide the observed major pyrrolidine stereoisomer **8** following enantiodetermining aminopalladation (Scheme 2, bottom).

In contrast, the influence of *N*-aryl group electronic properties and anionic ligands on enantioselectivity in reactions of *N*-allyl ureas are consistent with a mechanism for imidazolidin-2-one formation that proceeds through reversible aminopalladation followed by enantiodetermining reductive elimination (Scheme 2, top). Electron-withdrawing *N*-substituents on the cyclizing nitrogen atom have been shown to decrease the rate of C–C bond-forming reductive elimination from complexes related to **10–11** and **15–16**,^[16a,c] and to promote β-amidate elimination (retro-aminopalladation) from these complexes.^[16c] Thus, equilibration of **11** ⇌ **9b** ⇌ **9a** ⇌ **10** is likely more facile for electron-poor substrates **1e,f**. Reductive elimination then occurs more rapidly from **10** rather than **11** due to the chirality of the ligand to yield the observed major enantiomer **2**. In contrast, equilibration (retro-aminopalladation) of **11** and **9b** may occur less readily for more electron-rich derivatives **1a–c**,

thus a greater amount of the minor enantiomer (i.e. lower enantioselectivity) is obtained with these substrates due to an inherent preference for insertion through **9b** (as is the case for **14b** in the N-Boc series).

The observed influence of anionic ligands^[20] (iodide from aryl iodides and hydroxide from added water) on these transformations may be due to their effect on the rate of the C–C bond-forming reductive elimination step, which could perturb the equilibration between **11** and **9b**.^[21] Enantioselectivities are improved for the combination of small hydroxide ligand and electron-poor aryl halides, which is consistent with the electron-rich hydroxide ligand slowing reductive elimination (and thereby facilitating equilibration) for these types of substrates that are otherwise prone to undergo relatively rapid C–C bond formation.^[21] This effect is minimized for electron-neutral or -rich aryl halides where reductive elimination is slow relative to electron-poor aryl halides. In contrast, the relatively large iodide ligand may increase the rate of reductive elimination through a steric effect,^[22] which is most pronounced with the electron-neutral or -rich aryl halides. This would be expected to disfavor equilibration of **11** and **9b** and lead to diminished enantioselectivities as observed. The positive effect of trifluoroacetic acid on the reaction of 4-bromoanisole with **1f** is also presumably due to coordination of a trifluoroacetate anion to **10** and **11**, although the precise nature of this effect is not clear. The pronounced effect of anionic ligands on the enantioselectivity of reactions of **1e,f** likely does not arise through anion binding to the metal prior to or during the aminopalladation step. The insertion of alkenes into Pd–N bonds has previously been shown to proceed through 4-coordinate alkene-bound complexes such as **9a,b** or **14a,b**, and insertion from 5-coordinate species appears to be unfavorable.^[16]

In conclusion, we have developed a new catalytic asymmetric synthesis of 4-benzyl-imidazolidin-2-one derivatives through enantioselective carboamination reactions. The *N*-allyl urea substrates are readily available (one step from commercially available materials), and products are generated in good yield and up to 95% *ee*. Importantly, these studies illustrate that the enantiodetermining step in asymmetric Pd-catalyzed carboamination reactions may be influenced by substrate structure, and that substrate electronics and anionic additives also greatly affect levels of asymmetric induction. These observations will likely be of significant utility in the future development of other enantioselective alkene difunctionalization reactions that involve potentially reversible alkene insertion processes.

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- c) W. M. Kazmierski, E. Furfine, Y. Gray-Nunez, A. Spaltenstein, L. Wright, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 5685–5687.
- [2] For other catalytic asymmetric syntheses of imidazolidin-2-ones, see: a) H. Du, B. Zhao, W. Yuan, Y. Shi, *Org. Lett.* **2008**, *10*, 4231–4234; b) H. Du, B. Zhao, Y. Shi, *J. Am. Chem. Soc.* **2008**, *130*, 8590–8591; c) B. Zhao, H. Du, Y. Shi, *J. Org. Chem.* **2009**, *74*, 4411–4413; d) B. M. Trost, D. R. Fandrick, *J. Am. Chem. Soc.* **2003**, *125*, 11836–11837.
- [3] G. Sartori, R. Maggi in *Science of Synthesis (Houben-Weyl Methods of Molecular Transformations)* Vol. 18 (Eds.: S. V. Ley, J. G. Knight), Thieme, Stuttgart, **2005**, pp. 665–758.
- [4] D. Lucet, T. L. Gall, C. Mioskowski, *Angew. Chem.* **1998**, *110*, 2724–2772; *Angew. Chem. Int. Ed.* **1998**, *37*, 2580–2627.
- [5] For the synthesis of racemic ureas by Pd-catalyzed alkene carboamination, see: a) J. A. Fritz, J. S. Nakhla, J. P. Wolfe, *Org. Lett.* **2006**, *8*, 2531–2534; b) J. A. Fritz, J. P. Wolfe, *Tetrahedron* **2008**, *64*, 6838–6852.
- [6] For recent reviews on Pd-catalyzed alkene carboamination reactions, see: a) D. M. Schultz, J. P. Wolfe, *Synthesis* **2012**, 351–361; b) J. P. Wolfe, *Synlett* **2008**, 2913–2937.
- [7] a) D. N. Mai, J. P. Wolfe, *J. Am. Chem. Soc.* **2010**, *132*, 12157–12159; b) T. W. Liwosz, S. R. Chemler, *J. Am. Chem. Soc.* **2012**, *134*, 2020–2023; c) W. Zeng, S. R. Chemler, *J. Am. Chem. Soc.* **2007**, *129*, 12948–12949; d) S. R. Chemler, *Org. Biomol. Chem.* **2009**, *7*, 3009–3019.
- [8] X. X. Guo, J. H. Xie, G. H. Hou, W. J. Shi, L. X. Wang, Q. L. Zhou, *Tetrahedron: Asymmetry* **2004**, *15*, 2231–2234.
- [9] Use of (R)-Siphos-PE as the ligand led to formation of (R)-**2b** in 25% *ee*.
- [10] Replacement of the substrate *N*-methyl group with other substituents such as benzyl or *p*-methoxyphenyl did not lead to improved enantioselectivities.
- [11] A similar effect was observed when substoichiometric amounts (50 mol %) of water or NaOH were added. However, the highest degree of reproducibility was obtained with 2.0 equiv of added water.
- [12] The minor diastereomer likely arises through reversible β -hydride elimination/reinsertion pathways. For further details, see: M. B. Hay, J. P. Wolfe, *J. Am. Chem. Soc.* **2005**, *127*, 16468–16476. Additional details are also provided in the Supporting Information.
- [13] D. N. Mai, Ph.D. Thesis, University of Michigan, Ann Arbor, MI, **2011**.
- [14] a) R. A. Fernandes, A. Stimac, Y. Yamamoto, *J. Am. Chem. Soc.* **2003**, *125*, 14133–14139; b) S. Rousseaux, J. Garcia-Fortanet, M. A. Del Aguila Sanchez, S. L. Buchwald, *J. Am. Chem. Soc.* **2011**, *133*, 9282–9285.
- [15] In contrast to asymmetric reactions of *N*-allyl ureas, transformations of *N*-Boc-pent-4-enylamine derivatives proceed with similar enantioselectivities for both aryl iodide and aryl bromide substrates. See Ref. [7a].
- [16] For studies on the mechanism of *syn*-migratory insertion of alkenes into Pd–N bonds, see: a) J. D. Neukom, N. S. Perch, J. P. Wolfe, *J. Am. Chem. Soc.* **2010**, *132*, 6276–6277; b) P. S. Hanley, D. Markovic, J. F. Hartwig, *J. Am. Chem. Soc.* **2010**, *132*, 6302–6303; c) J. D. Neukom, N. S. Perch, J. P. Wolfe, *Organometallics* **2011**, *30*, 1269–1277; d) P. S. Hanley, J. F. Hartwig, *J. Am. Chem. Soc.* **2011**, *133*, 15661–15673; e) P. B. White, S. S. Stahl, *J. Am. Chem. Soc.* **2011**, *133*, 18594–18597.
- [17] Our estimation of the relative electron-richness of the *N*-Boc pentenylamine versus the *p*-nitrophenyl urea are based on a comparison of pK_a values for N^1,N^1 -dimethyl- N^2 -(*p*-nitrophenyl)urea (pK_a = 15.9, DMSO) versus *N*-Boc-benzylamine (pK_a = 22.9, DMSO); the stronger acid possesses a less electron-rich nitrogen atom. See: a) J. P. Cheng, M. Xian, K. Wang, X. Zhu, Z. Yin, P. G. Wang, *J. Am. Chem. Soc.* **1998**, *120*, 10266–10267; b) T. Mita, J. Chen, M. Sugawara, Y. Sato, *Angew. Chem.*

- [1] a) J. Dumas, *Curr. Opin. Drug Discovery Dev.* **2002**, *5*, 718–727; b) E. DeClercq, *Biochem. Biophys. Acta.* **2002**, *1587*, 258–275;

- 2011**, 123, 1429–1432; *Angew. Chem. Int. Ed.* **2011**, 50, 1393–1396.
- [18] The *syn*-aminopalladation of *N*-aryl-pent-4-enylamines has been shown to be irreversible in Pd/dppf complexes.^[16c] Related migratory insertions of ethylene into LPd-NPh₂ complexes have also been shown to be irreversible.^[16b,d] The p*K*_a of diphenylamine (25.0) is comparable to that of *N*-Boc-benzylamine. See: J. N. Li, L. Liu, Y. Fu, Q. X. Guo, *Tetrahedron* **2006**, 62, 4453–4462.
- [19] The observation that deuterated urea substrate (**Z**)-**[D]**-**1 f** is converted to a 7:1 mixture of diastereomers whereas the analogous deuterated carbamate is transformed with >20:1 d.r. is consistent with relatively fast reductive elimination in the carbamate system as compared to the urea. See: a) Ref. [12]; b) M. B. Bertrand, J. D. Neukom, J. P. Wolfe, *J. Org. Chem.* **2008**, 73, 8851–8860.
- [20] a) For a review on the effects of anionic ligands in catalytic asymmetric reactions, see: K. Fagnou, M. Lautens, *Angew. Chem.* **2002**, 114, 26–49; *Angew. Chem. Int. Ed.* **2002**, 41, 26–47; b) for a review on the effect of anionic ligands on Pd-catalyzed asymmetric allylation reactions, see: B. M. Trost, T. Zhang, J. D. Sieber, *Chem. Sci.* **2010**, 1, 427–440.
- [21] Small anionic ligands increase the rate of C–C bond-forming reductive elimination from *five-coordinate* L₂Pd(Ar)(Ar₁) complexes. However, a small anionic ligand (Cl[−]) has been shown to dramatically *decrease* the rate of C–C bond-forming reductive elimination from *four-coordinate* anionic L₁Pd^{II}(aryl)(alkyl) complexes related to **10** and **11**. See: a) B. Pudasaini, B. G. Janesko, *Organometallics* **2011**, 30, 4564–4571; b) C. Amatore, A. Jutand, G. Le Duc, *Chem. Eur. J.* **2011**, 17, 2492–2503.
- [22] For a review, see: J. F. Hartwig, *Inorg. Chem.* **2007**, 46, 1936–1947.