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Synthesis of Enantiomerically Enriched Imidazolidin-2-Ones via Asymmetric Pd-Catalyzed Alkene Carboamination Reactions

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Abstract

A catalyst composed of $\text{Pd}_2(\text{dba})_3$ and (*S*)-Siphos-PE is effective for the enantioselective coupling of *N*-allylureas with aryl bromides to afford 4-substituted imidazolidin-2-ones with up to 95% ee. Added water leads to significantly improved enantioselectivities with electron-poor aryl halide substrates. The mechanism of these transformations is discussed, and evidence is presented which suggests that, in contrast to other asymmetric alkene carboaminations, C–C bond-forming reductive elimination is the enantiodetermining step of these reactions.

Keywords

Asymmetric Catalysis; Asymmetric Synthesis; Heterocycles; Palladium; Stereoselective

Chiral 4-substituted imidazolidin-2-ones are displayed in a myriad of biologically active compounds, including potent HIV protease inhibitors.^[i] However, despite their significance, the preparation of these compounds via asymmetric catalysis has rarely been reported.^[ii] 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.^[iii,iv]

In this communication we describe the first catalytic asymmetric alkene carboamination reactions between *N*-allylurea derivatives and aryl or alkenyl halides.^[v,vi] 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*-allylurea substrates. This contrasts with other asymmetric metal-catalyzed alkene carboamination reactions, in which the absolute stereochemistry appears to be set during alkene aminometallation.^[vii]

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Supporting information for this article is available on the WWW under <http://www.angewandte.org> or from the author.

(1)

Our prior studies on Pd-catalyzed asymmetric carboaminations of *N*-Boc-pent-4-enylamine demonstrated that use of (*R*)-Siphos-PE^[viii] as a ligand provides 2-benzylpyrrolidine derivatives with good levels of enantioselectivity.^[viii] Thus in our efforts to generate enantiomerically enriched imidazolidin-2-ones we initially examined the use of a catalyst composed of Pd₂(dba)₃ and (*R*)-Siphos-PE for the asymmetric conversion of **1b** to **2b**. Unfortunately, this catalyst provided **2b** in only modest enantioselectivity [Eq. (1)].^[ix] 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 problem the reaction temperature was increased to 115–120 °C, and the desired products were generated in good chemical yield (entries 6–7) without a significant decrease in asymmetric induction.^[x] 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. We initially 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.^[xi] 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 16–17).

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 dr [Eq. (4)].^[xiii]

(2)

(3)

(4)

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)].

(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 catalyst provides (*S*)-imidazolidin-2-one products **2** in reactions of **1e–f**, whereas the same catalyst system afforded pyrrolidine enantiomer **8** from **7**.^[xiii] 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,^[xiv] and the water effect is considerably different for the imidazolidin-2-one vs. 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.^[xv]

Despite the differences in the absolute product stereochemistry in reactions of **1** vs. **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.^[viii] The mechanism of both reactions proceeds via oxidative addition of the aryl halide to Pd(0) followed by substrate deprotonation and substitution to provide alkene-bound palladium(aryl)(amido) complexes **9a–b** and **14a–b** (Scheme 2).^[vi] These complexes undergo *syn*-1,2-migratory insertion into the Pd–N bond to yield **10** and **16**,^[xvi] 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 vs. 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: (a) the migratory insertion step (e.g., **14b** to **16**); or (b) the subsequent reductive elimination step if migratory insertion is reversible (e.g., **10** to **2**).^[xvii] In our prior studies^[viii] we suggested that with the relatively electron-rich *N*-*boc* pentenylamine substrate **7**^[xviii] the aminopalladation is likely irreversible,^[xviii] and relatively fast reductive elimination from **16**^[xix] 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*-allylureas are consistent with a mechanism for imidazolidin-2-one formation that proceeds via 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**,^[xvii,c] and to promote β-amidate elimination (retro-aminopalladation) from these complexes.^[xvii] 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 via **9b** (as is the case for **14b** in the *N*-Boc series).

The observed influence of anionic ligands^[xx] (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**.^[xxi] Stereoselectivities 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.^[xxi] 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,^[xxii] 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 via 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 via 4-coordinate alkene-bound complexes such as **9a–b** or **14a–b**, and insertion from 5-coordinate species appears to be unfavorable.^[xvi]

In conclusion, we have developed a new catalytic asymmetric synthesis of 4-benzyl-imidazolidin-2-one derivatives via enantioselective carboamination reactions. The *N*-allylurea 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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- ix. Use of (*R*)-Siphos-PE as the ligand led to formation of (*R*)-2b in 25% ee.
- x. Replacement of the substrate *N*-methyl group with other substituents such as benzyl or *p*-methoxyphenyl did not lead to improved enantioselectivities.
- xi. 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.
- xii. The minor diastereomer likely arises through reversible β -hydride elimination/reinsertion pathways. For further details, see: Hay MB, Wolfe JP. J Am Chem Soc. 2005; 127:16468–16476. [PubMed: 16305233] Additional details are also provided in the Supporting Information.
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- xix. The observation that deuterated urea substrate (*Z*)-d-1f is converted to a 7:1 mixture of diastereomers whereas the analogous deuterated carbamate is transformed with >20:1 dr is consistent with relatively fast reductive elimination in the carbamate system as compared to the

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Scheme 1.
Stereochemistry of urea vs. pyrrolidine formation.

Scheme 2.
Mechanism of urea formation vs. pyrrolidine formation.

Table 1Electronic effects.^[a]

Entry	X	Yield (%) ^[b]	ee (%)
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*-^tBu-C₆H₄-Br, 2.0 equiv NaO^tBu, 2 mol % Pd₂(dba)₃, 6 mol % (*S*)-Siphos-PE Toluene (0.2 M), 90 °C, 12 h.

^[b] Isolated yield (average of two or more runs).

^[c] The reaction was conducted at 120 °C in xylenes.

Table 2

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

Entry	G	R-X	Additive ^[b]	Product	Yield (%) ^[c]	ee (%)
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> -Bu-C ₆ H ₄ -Br	–	2f	81	92
9	NO ₂	<i>p</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

Entry	G	R-X	Additive ^[b]	Product	Yield (%) ^[c]	ee (%)
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 were added to the reaction mixture prior to heating.

^[c] Isolated yield (average of two or more runs).

^[d] This material contained ca. 35% of an unidentified regioisomer.