



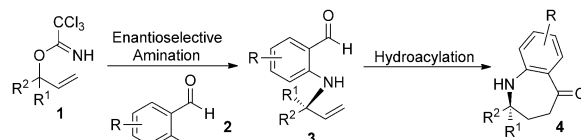
# Rhodium-Catalyzed Sequential Allylic Amination and Olefin Hydroacylation Reactions: Enantioselective Synthesis of Seven-Membered Nitrogen Heterocycles\*\*

Jeffrey S. Arnold, Edward T. Mwenda, and Hien M. Nguyen\*

**Abstract:** Dynamic kinetic asymmetric amination of branched allylic acetimidates has been applied to the synthesis of 2-alkyl-dihydrobenzoazepin-5-ones. These seven-membered-ring aza ketones are prepared in good yield with high enantiomeric excess by rhodium-catalyzed allylic substitution with 2-amino aryl aldehydes followed by intramolecular olefin hydroacylation of the resulting alkenals. This two-step procedure is amenable to varied functionality and proves useful for the enantioselective preparation of these ring systems.

Chiral nitrogen-containing heterocycles are important structural motifs embedded in a wide variety of bioactive natural products and pharmaceuticals.<sup>[1]</sup> Despite many efficient strategies toward their construction,<sup>[2,3]</sup> methods that allow the catalytic asymmetric synthesis of medium-sized-ring aza ketones remain underdeveloped.<sup>[2,3]</sup> Transition-metal-catalyzed intramolecular alkene hydroacylation with 2-aminobenzaldehydes would be a novel way to prepare this motif.<sup>[4,5]</sup> This strategy has not been fully investigated, in part because of strong metal–nitrogen bonding. Other less-basic heteroatoms, however, have been utilized to assist the intramolecular hydroacylation of alkenes.<sup>[6–8]</sup> Dong and co-workers reported the first example of a chiral rhodium-catalyzed amine-directed hydroacylation of alkenal ketones for the enantioselective preparation of seven- and eight-membered-ring nitrogen-containing lactones.<sup>[9]</sup> Recently, Bendorf et al. demonstrated the feasibility of amine-directed intramolecular alkene hydroacylation, which provided the corresponding racemic medium-size aza heterocycles.<sup>[10]</sup> Herein, we describe a new strategy for the catalytic enantioselective synthesis of 2-alkyl-dihydrobenzoazepin-5-ones **4** by a sequential rhodium-catalyzed asymmetric allylic amination followed by an intramolecular alkene hydroacylation reaction (Scheme 1).

Our group recently reported the chiral-diene-ligated rhodium-catalyzed dynamic kinetic asymmetric transformation (DYKAT) of racemic allylic trichloroacetimidates with a range of anilines.<sup>[11]</sup> This method allows the high-yielding



**Scheme 1.** Sequential amination and alkene hydroacylation.

and enantioselective synthesis of allylic arylamines.<sup>[12–16]</sup> Herein, we extend our DYKAT process to challenging anilines **2** bearing an *ortho*-aldehyde functionality to form enantioenriched allylic amines **3** (Scheme 1), which could participate in an intramolecular alkene hydroacylation. The resulting two-step process, based on allylic trichloroacetimidates **1** with 2-aminobenzaldehydes **2**, would provide chiral medium-sized-ring aza ketones **4**. The unique feature of this approach is that the asymmetric induction is controlled during the amination step, rather than during the hydroacylation step.<sup>[5–9]</sup>

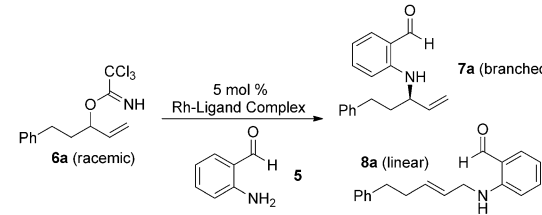
Although the use of 2-aminobenzaldehydes **2** as nucleophiles in the sequential reactions highlights the efficacy of our DYKAT method, this approach could be challenging. It is well-established that Rh<sup>I</sup> catalysts undergo oxidative addition of aldehydes to form the acyl-Rh<sup>III</sup> complexes.<sup>[17]</sup> This pathway would be more favorable because of the presence of the *ortho*-nitrogen atom.<sup>[6–8]</sup> To our knowledge, there is only one example of the use of 2-aminobenzaldehydes **2** as substrates for hydroacylation with alkynes.<sup>[18]</sup> To test our hypothesis, the regioselective amination of allylic trichloroacetimidate **6a** with 2-aminobenzaldehyde (**5**) was investigated (Table 1). We discovered that the neutral rhodium catalyst  $[\text{RhCl}(\text{cod})_2]$ , was more effective than cationic rhodium complexes at promoting the reaction (entries 1–3). Allylic arylamine **7a** (entry 3) was formed in 77 % yield with excellent regioselectivity (b/l > 99:1). Next, we focused on the rhodium(I)-catalyzed DYKAT of imidate **6a** with aniline **5**. Under previously optimized conditions,<sup>[11a]</sup> the amination product **7a** was isolated in 14 % yield (entry 4) and with poor selectivities (b/l = 2:1, 29 % *ee*). Decreasing the reaction temperature to 25 °C (entry 5) significantly improved the selectivity (b/l = 2:1 → 29:1, 29 → 67 % *ee*). The outcome of this result can be rationalized in terms of competition between the rate of  $\pi$ -allylrhodium interconversion and nucleophilic attack by aniline **5**.<sup>[11a]</sup> Changing to MTBE as the solvent (entry 8) afforded **7a** in higher yield (11 → 61 %), while retaining the selectivity. To further optimize the reaction conditions, a number of Hayashi's chiral diene ligand analogues were examined (entries 9–13).<sup>[19,20]</sup> As expected

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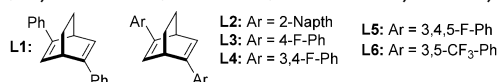
Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201310354>.

**Table 1:** Studies of rhodium-catalyzed asymmetric amination.<sup>[a]</sup>


Entry	Rh-ligand complex	Solvent	T [°C]	t [h]	Yield [%] <sup>[b]</sup>	[b/l] <sup>[c]</sup>	ee [%] <sup>[d]</sup>
1	[Rh(cod) <sub>2</sub> ]OTf	THF	25	3	66	10:1	—
2	[Rh(cod) <sub>2</sub> ]BF <sub>4</sub>	THF	25	3	59	6:1	—
3	{[RhCl(cod)] <sub>2</sub> }	THF	25	3	77	> 99:1	—
4	{[RhCl(ethylene) <sub>2</sub> ] <sub>2</sub> }/L1	dioxane	40	22	14	2:1	29
5	{[RhCl(ethylene) <sub>2</sub> ] <sub>2</sub> }/L1	dioxane	25	22	11	29:1	67
6	{[RhCl(ethylene) <sub>2</sub> ] <sub>2</sub> }/L1	THF	25	22	44	82:1	71
7	{[RhCl(ethylene) <sub>2</sub> ] <sub>2</sub> }/L1	toluene	25	22	22	30:1	53
8	{[RhCl(ethylene) <sub>2</sub> ] <sub>2</sub> }/L1	MTBE	25	22	61	29:1	67
9	{[RhCl(ethylene) <sub>2</sub> ] <sub>2</sub> }/L2	MTBE	25	22	34	26:1	59
10	{[RhCl(ethylene) <sub>2</sub> ] <sub>2</sub> }/L3	MTBE	25	22	35	20:1	70
11	{[RhCl(ethylene) <sub>2</sub> ] <sub>2</sub> }/L4	MTBE	25	22	46	53:1	65
12	{[RhCl(ethylene) <sub>2</sub> ] <sub>2</sub> }/L5	MTBE	25	22	64	> 99:1	84
13	{[RhCl(ethylene) <sub>2</sub> ] <sub>2</sub> }/L6	MTBE	25	22	59	6:1	62

[a] All amination reactions were conducted at 0.2 M with 1 equiv imidate **6a**.

[b] Yields of isolated products. [c] The branched to linear ratio (b/l) was determined by <sup>1</sup>H NMR spectroscopy. [d] Determined by HPLC on a chiral stationary phase. cod = 1,5-cyclooctadiene, Tf = triflate, MTBE = methyl *tert*-butyl ether.

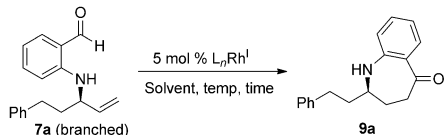


on the basis of our previous studies,<sup>[11a]</sup> electron-deficient ligands induced excellent asymmetric induction. The best result was achieved using chiral ligand **L5** (entry 12) with 3,4,5-trifluorophenyl groups (b/l > 99:1, 84% ee), thus demonstrating the successful extension of the DYKAT method<sup>[11]</sup> to challenging 2-aminobenzaldehydes in the asymmetric amination. In no case was the decarbonylation of alkenal **7a** observed. In addition, the hydroacylation product (e.g. **4**, Scheme 1) was not formed even at elevated temperatures or when the neutral rhodium-**L5** complex was converted into a more reactive cationic rhodium species with silver salts.

Next, we focused on evaluating rhodium catalysts to effect the intramolecular hydroacylation of alkenal **7a** (Table 2). We anticipated that coordination of the amine group in **7a** to a rhodium center to form a five-membered amino-acyl rhodacycle is important to promote olefin hydroacylation over aldehyde decarbonylation.<sup>[9,10]</sup> Accordingly, we tested a number of bisphosphine-ligated rhodium catalysts (Table 2) in various solvents at elevated temperatures.<sup>[6–10]</sup> Table 2 demonstrates that the ligand bite angle plays a critical role in the hydroacylation.<sup>[7b]</sup> The efficiency of the cyclization of **7a** decreased (96% versus 72%, entries 2 and 1, respectively) as the bite angle of the bisphosphine ligand becomes smaller. This result is consistent with the reported rhodium-catalyzed enantioselective hydroacylation of ketones.<sup>[7b]</sup> Even though rhodium-bisphosphine complexes (entries 1–5) performed well in the reaction, the need to generate them by the hydrogenation of [Rh(nbd)<sub>2</sub>]BF<sub>4</sub>/bisphosphine complexes

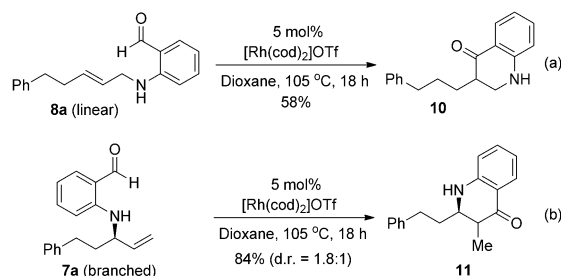
(nbd = 2,5-norbornadiene) detracts from their utility.<sup>[7]</sup> Commercially available [Rh(cod)(dppb)]BF<sub>4</sub> (entry 6) was equally effective, affording seven-membered-ring aza ketone **9a** in 99% yield after 1 h at 105 °C. On the other hand, cyclization to form nitrogen heterocycle **9a** progressed slowly at 70 °C (entry 7), and full conversion was observed after 20 h. In all cases, **9a** was produced without any observable racemization.<sup>[21]</sup> The results in Table 2 highlights that cyclization can take place effectively in the absence of additional substituents on the nitrogen atom of allylic amines; such amines are unsuitable substrates under Bendorf's conditions.<sup>[10]</sup>

We also subjected linear allylic amine **8a** to the hydroacylation reaction (Scheme 2a). Cyclization of the minor amination isomer **8a** did not proceed in the presence of the [Rh(cod)(dppb)]BF<sub>4</sub> catalyst, which effectively promoted hydroacylation of the branched allylic arylamine **7a** (Table 2). Alternatively, the use of [Rh(cod)<sub>2</sub>]OTf provided six-membered-ring aza ketone **10** in 58% yield.<sup>[22]</sup> Encouraged by this result, we performed the cyclization of branched amination isomer **7a** (Scheme 2b), which afforded six-membered-ring product **11** in 84% yield, albeit with low diastereoselectivity (d.r. = ca. 2:1).

**Table 2:** Hydroacylation of branched allylic arylamine.<sup>[a]</sup>


Entry	Rh <sup>I</sup> catalyst	Solvent	T [°C]	t [h]	Yield [%] <sup>[b]</sup>	ee [%] <sup>[c]</sup>
1	[Rh(dppe)] <sub>2</sub> (BF <sub>4</sub> ) <sub>2</sub>	PhCF <sub>3</sub>	105	1	72	84
2	[Rh(dppp)] <sub>2</sub> (BF <sub>4</sub> ) <sub>2</sub>	PhCF <sub>3</sub>	105	1	96	84
3	[Rh(dppb)] <sub>2</sub> (BF <sub>4</sub> ) <sub>2</sub>	PhCF <sub>3</sub>	105	1	82	84
4	[Rh(dppp)] <sub>2</sub> (BF <sub>4</sub> ) <sub>2</sub>	toluene	105	1	99	84
5	[Rh(dppp)] <sub>2</sub> (BF <sub>4</sub> ) <sub>2</sub>	dioxane	105	1	99	84
6	[Rh(cod)(dppb)]BF <sub>4</sub>	dioxane	105	1	99	84
7	[Rh(cod)(dppb)]BF <sub>4</sub>	dioxane	70	20	99	84

[a] All reactions, except for entries 6 and 7, were conducted in the presence of 5 mol % [Rh(nbd)<sub>2</sub>]BF<sub>4</sub>, 5.5 mol % bisphosphine ligand, and H<sub>2</sub> (g).<sup>[7b]</sup> [b] Yield of isolated product. [c] Determined by HPLC on a chiral stationary phase. dppe = ethane-1,2-diylbis(diphenylphosphane), dppp = propane-1,3-diylbis(diphenylphosphane), dppb = butane-1,4-diylbis(diphenylphosphane).


**Scheme 2.** Formation of six-membered-ring aza ketones.

To illustrate the scope of the sequential process, we turned our attention to assessing the rhodium-catalyzed asymmetric amination of racemic secondary allylic imidates **6b–h** (Table 3, entries 1–7), which contain a variety of functional groups, and found that they were able to react with 2-aminobenzaldehyde (**5**). The allylic amines **7b–h** were isolated in 40–95 % yield and 80–92 % *ee*, with complete selectivity for the branched product. Notably,  $\alpha$ -substituted imidate **6h** (entry 7) reacted efficiently to afford amine **7h** with excellent regioselectivity; this substrate was previously reported to form amination products with low regioselectivity.<sup>[13a]</sup> Furthermore, the amination is compatible with electron-donating and electron-deficient 2-amino aryl aldehydes (entries 8–10), thereby giving access to **7i–k** in 61–91 % yield with excellent enantioselectivity (84–94 % *ee*). A cyclic aniline nucleophile (entry 11) also provides allylic amine **7l** in 83 % yield and 88 % *ee*. To establish the generality of the process, we examined the amination with disubstituted olefin **6j** (entry 12), which had not previously been explored under our DYKAT conditions. This imidate presents an additional challenge in that both the *syn*- and *anti*- $\pi$ -allylrhodium intermediates need to be considered.<sup>[23]</sup> Although the 2-methyl group on the  $\pi$ -allyl system destabilizes the *syn* isomer through a 1,2 steric interaction, the *anti* isomer suffers from A(1,3)interaction. As expected, allylic arylamine **7m** was isolated in 10 % yield with 13 % *ee* (entry 12). This low selectivity suggests that the Rh-L5 complex was not effective at controlling the relative population of the *syn* and *anti* isomers.<sup>[23]</sup> Overall, Table 3 illustrates the generality of this class of 2-amino aryl aldehydes with our DYKAT method.

With alkenyl aldehydes **7b–m** in hand, we subsequently subjected these amination products to the intramolecular olefin hydroacylation conditions of 5 mol % [Rh(cod)-(dppb)]BF<sub>4</sub> at 105 °C for 1 h (Table 3). The cyclization of alkenals **7b–m** proceeded smoothly to afford seven-membered aza heterocycles **9b–m** in high yields (50–99 %) without any observable racemization. A range of functional groups are tolerated in the  $\beta$ -substituted alkenal. Notably, the  $\alpha$ -substituted cyclohexyl alkenal **7h** (entry 7) efficiently underwent cyclization to provide seven-membered-ring aza ketone **9h** in nearly quantitative yield. In the case of amine substrate **7j** (entry 9), we observed that the hydroacylation occurred preferentially at the allyl position at 105 °C to yield a nitrogen-containing heterocycle, with simultaneous isomerization of the  $\gamma$ -vinyl substituent.<sup>[24]</sup> On the other hand, cyclization of arylamine **7j** at 70 °C provided aza ketone **9j** (entry 9) and the exclusive *Z*-isomerization product as a 1:1 inseparable mixture of isomers.<sup>[25]</sup> Electron-deficient alkenal **7k** (entry 10) significantly slowed down the cyclization process. Even after 24 h, only 62 % yield of the nitrogen-containing heterocycle **9k** (entry 10) was obtained in the reaction. Cyclization of substrate **7l**, which contains a secondary aniline functionality, also reacted slowly and took 24 h to reach completion (entry 11). Seven-membered-ring product **9l** was obtained in 66 % yield. Interestingly, intramolecular hydroacylation of the challenging allylic arylamine **7m** (entry 12) proceeded smoothly to afford aza heterocycle **9m** in 99 % yield with d.r. = 4:1 and without racemization. Although the major diastereomer of **9m** was isolated with 15 % *ee*, the minor

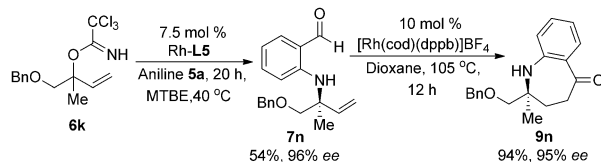
**Table 3:** Scope of sequential amination and hydroacylation.<sup>[a]</sup>

Trichloroacetimidates	Allylic amines yield [%] <sup>[b]</sup> ( <i>ee</i> [%]) <sup>[c]</sup>	Aza ketones yield [%], <sup>[b]</sup> ( <i>ee</i> [%]) <sup>[c]</sup>
1 <b>6b</b> : R = BnOCH <sub>2</sub>	<b>7b</b> : 95 (87)	<b>9b</b> : 99 (89)
2 <b>6c</b> : R = TBSOCH <sub>2</sub>	<b>7c</b> : 67 (83)	<b>9c</b> : 90 (83)
3 <b>6d</b> : R = BnO	<b>7d</b> : 81 (86)	<b>9d</b> : 99 (86)
4 <b>6e</b> : R = 4-F-PhO	<b>7e</b> : 77 (80)	<b>9e</b> : 99 (80)
5 <b>6f</b> : R = Ph	<b>7f</b> : 59 (92)	<b>9f</b> : 95 (92)
6 <b>6g</b> : R = (CH <sub>3</sub> ) <sub>2</sub> CH	<b>7g</b> : 40 (80) <sup>[e]</sup>	<b>9g</b> : 96 (78)
7 <b>6h</b>	<b>7h</b> : 41 (80) <sup>[e]</sup>	<b>9h</b> : 99 (80)
8 <b>6f</b>	<b>7i</b> : 91 (94)	<b>9i</b> : 92 (95)
9 <b>6i</b>	<b>7j</b> : 61 (84)	<b>9j</b> : 50 (86) <sup>[d]</sup>
10 <b>6b</b>	<b>7k</b> : 64 (93) <sup>[e]</sup>	<b>9k</b> : 62 (94) <sup>[f]</sup>
11 <b>6d</b>	<b>7l</b> : 83 (88)	<b>9l</b> : 66 (84) <sup>[g]</sup>
12 <b>6j</b>	<b>7m</b> : 10 (13) <sup>[e]</sup>	<b>9m</b> : 99, d.r. = 4:1

[a] All amination reactions were conducted with 1 equiv allylic acetimidate and 1.5 equiv 2-amino aryl aldehyde. [b] Yield of isolated product. [c] Determined by HPLC on a chiral stationary phase. [d] Reaction conducted at 70 °C for 18 h. [e] Reaction carried out with 7.5 mol % Rh-L5 complex at 40 °C for 24 h. [f] Hydroacylation carried out with 10 mol % [Rh(cod)(dppb)]BF<sub>4</sub> for 24 h. [g] Hydroacylation conducted with 5 mol % [Rh(cod)(dppb)]BF<sub>4</sub> at 105 °C for 24 h. Bn = benzyl, TBS = *tert*-butyldimethylsilyl.

isomer was obtained with 11 % *ee*. Additionally, no competing  $\beta$ -hydride elimination product was observed in this reaction.

As a further demonstration of the robust nature and operational simplicity of the sequential catalytic events, the enantioselective amination of tertiary allylic trichloroacetimidate **6k** (Scheme 3) was attempted. The reaction pro-



**Scheme 3.** Studies with tertiary allylic trichloroacetimidate substrate.

ceeded slowly under standard conditions to generate **7n**, which contains a nitrogen-substituted quaternary center, in poor yield. Increasing the catalyst loading (5  $\rightarrow$  7.5 mol %) and reaction temperature (25  $\rightarrow$  40 °C) provided amine **7n** in 54 % yield and 96 % *ee*.<sup>[26]</sup> Subsequent cyclization of alkenal **7n** with 10 mol % [Rh(cod)(dppb)]BF<sub>4</sub> at 105 °C for 12 h afforded nitrogen-containing heterocycle **9n** in 94 % yield without observable racemization (95 % *ee*).

In summary, a new strategy for the enantioselective synthesis of seven-membered-ring aza ketones has been developed. Construction of the enantioenriched nitrogen-containing heterocycles was carried out by a rhodium-catalyzed DYKAT of allylic trichloroacetimidates with 2-amino aryl aldehydes (C–N bond) followed by intramolecular hydroacylation (C–C bond) of the alkenal products. This two-step process proceeds under mild conditions, and exhibits broad substrate scope and functional-group tolerance. The corresponding seven-membered aza heterocycles are formed in high yields and with excellent levels of selectivity without any observable racemization of the enantioenriched allylic *N*-arylamines containing an *ortho*-aldehyde functionality. As the enantioselective synthesis of medium-sized-ring heterocycles continues to develop, we anticipate that this sequential reaction will have an impact on the strategies used for the preparation of biologically active natural products and potential pharmaceutical agents.

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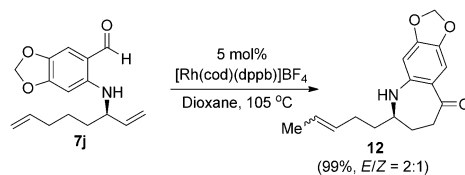
**Keywords:** allylic amination · asymmetric catalysis · intramolecular hydroacylation · nitrogen heterocycles · rhodium

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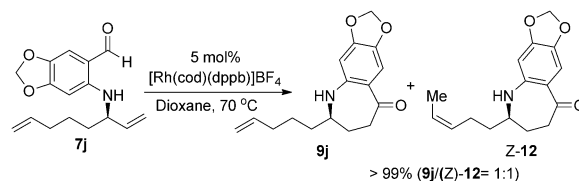
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- [25] At 70 °C, a 1:1 mixture of the desired nitrogen-containing heterocycle **9j** and *Z* isomer **12** was obtained in the reaction.



- [26] In previous studies, we observed that tertiary allylic imidates lacking an oxygen substituent at the β-position provided the α,α-disubstituted allylic arylamines in low selectivity (see Ref. [11a]). As a result, we did not explore this type of acetimidate in the rhodium-catalyzed sequential reactions.