

Rhodium-Catalyzed Dynamic Kinetic Asymmetric Transformations of Racemic Tertiary Allylic Trichloroacetimidates with Anilines

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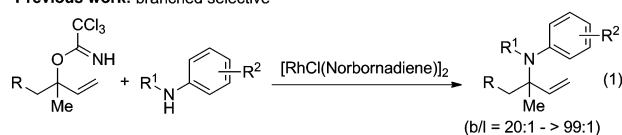
Supporting Information

ABSTRACT: The rhodium-catalyzed regio- and enantioselective amination of racemic tertiary allylic trichloroacetimidates with a variety of aniline nucleophiles is a direct and efficient route to chiral α,α -disubstituted allylic *N*-arylamines. We describe the first dynamic kinetic asymmetric transformations of racemic tertiary allylic electrophiles with anilines utilizing a chiral diene-ligated rhodium catalyst. The method allows for the formation of α,α -disubstituted allylic *N*-arylamines in moderate to good yields with good to excellent levels of regio- and enantioselectivity.

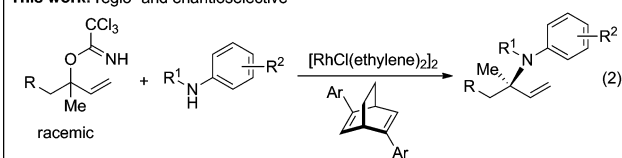
The prevalence of chiral amines in bioactive natural and non-natural products has stimulated numerous efforts toward their construction.¹ Although a variety of methods are available for the preparation of optically active amines,² the catalytic asymmetric synthesis of α,α -disubstituted amines remains relatively underdeveloped. A new approach to the asymmetric formation of α,α -disubstituted amines via palladium-catalyzed aza-Claisen rearrangements of linear allylic trihaloacetimidates has recently been reported.³ Although allylic amines are formed in good yield and enantioselectivity, full conversion necessitates high temperatures over a period of days.³ A more common approach to α,α -disubstituted amines involves the addition of organometallic reagents to ketimines.^{4–7} Several challenges could potentially emerge using this approach. First, the addition to ketimines containing an α -hydrogen is problematic because imines have a propensity to enolize.^{4b,7a} Second, stereoselectivity is often moderate with ketimines because they can exist as *E* and *Z* isomers, and differentiation of the enantiotopic faces is often limited.^{5b} Third, ketimines are significantly less reactive than aldimines and require activation by a Lewis acid.^{7a} In response to these challenges, Hayashi reported that rhodium–chiral diene complexes effectively catalyze the addition of sodium tetraarylborates to *N*-tosyl ketimines at 60–80 °C for 20 h.⁸

Transition-metal-catalyzed substitution of primary and racemic secondary allylic carbonates or acetates has been utilized for the regio- and enantioselective preparation of α -substituted *N*-arylamines.^{9,10} However, only the regioselective synthesis of α,α -disubstituted *N*-arylamines via substitution of primary and racemic tertiary allylic acetates and carbonates catalyzed by palladium,^{11a,b} iridium,^{10c} and iron complexes^{11c} has been described. We recently reported the rhodium-catalyzed regioselective amination of tertiary allylic imidates with aniline nucleophiles (eq 1).¹³ Our method is applicable to

Previous work: branched selective



This work: regio- and enantioselective



a wide range of substrates, affording the amination products in excellent yields and regioselectivity. Herein we disclose the first rhodium-catalyzed regio- and enantioselective amination of racemic tertiary allylic trichloroacetimidates with anilines to provide α,α -disubstituted allylic *N*-arylamines (eq 2).^{15,16}

During our previous regioselective studies,¹² control experiments with an enantiopure starting imide¹⁴ (98% ee) resulted in a nearly racemic branched amination product (<7% ee). On the basis of this result, we hypothesized that if isomerization of the diastereomeric π -allylrhodium intermediates¹⁷ occurs faster than attack by the aniline nucleophile (Figure 1), the dynamic

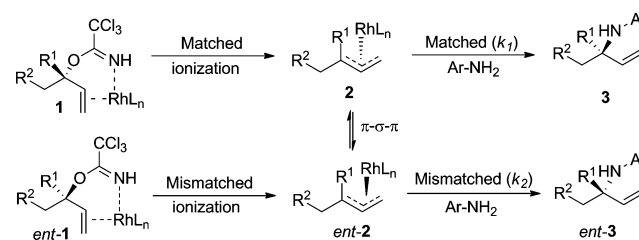


Figure 1. Strategy for DYKAT of tertiary allylic imidates.

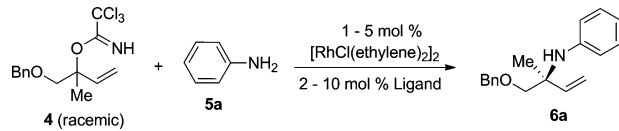
kinetic asymmetric transformation (DYKAT) of tertiary allylic trichloroacetimidates could be feasible.¹⁸ Ionization of the activated rhodium–alkene complexes **1** and *ent*-**1** (Figure 1)¹⁹ with the chiral rhodium catalyst would provide the corresponding diastereomeric π -allylrhodium complexes **2** and *ent*-**2**, respectively. We reasoned that an asymmetric environment about the rhodium center could decrease the rate of nucleophilic attack by anilines and increase the time allowed for rapid π – σ – π interconversion. An unfavorable interaction

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between one of the two π -allylrhodium intermediates would determine which enantiomer of the amination product **3** ($k_1 \gg k_2$) is preferentially formed.

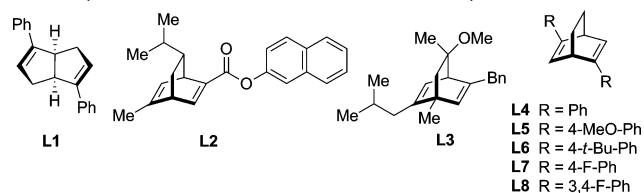
To test our hypothesis, we set out to explore the effects of the chiral diene ligands²⁰ **L1**–**L4** (Table 1) on the enantioselectivity

Table 1. Optimization Studies^a



entry	ligand	Rh loading (mol %)	aniline (equiv)	solvent	temp (°C)	time (h)	yield (%)	% ee
1	L1	5	3	THF	40	4	14	-2
2	L2	5	3	THF	40	1	59	-1
3	L3	5	3	THF	40	1	71	-26
4	L4	5	3	THF	40	1	72	73
5	L4	5	3	THF	25	1	77	84
6	L4	5	3	THF	0	1	77	83
7	L4	1	3	THF	25	4	41	77
8	L4	5	3	Et ₂ O	25	1	72	76
9	L4	5	3	Dioxane	25	1	73	78
10	L4	5	3	Toluene	25	1	71	82
11	L4	5	3	MTBE	25	1	78	86
12	L4	5	1.5	MTBE	25	1	69	89
13	L5	5	1.5	MTBE	25	1	60	71
14	L6	5	1.5	MTBE	25	1	64	84
15	L7	5	1.5	MTBE	25	1	85	94
16	L8	5	1.5	MTBE	25	1	74	90

^aAll of the reactions were conducted at 0.2 M with 1 equiv of **4**. Isolated yields are shown; ee's were determined by chiral HPLC.

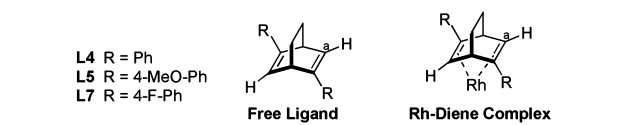


in the amination reaction of racemic tertiary allylic trichloroacetimidate **4** with aniline (**5a**) (Table 1). Lin ligand **L1**²¹ (entry 1) and Hayashi ligand **L2**²² (entry 2) afforded nearly racemic α,α -disubstituted *N*-arylamines **6a**. Use of Carreira ligand **L3**²³ (entry 3) provided a measurable enantioselectivity (26% ee) for the process. Hayashi ligand **L4**²⁴ (entry 4) was the most enantioselective at 40 °C, providing **6a** as a single regioisomer in 72% yield with 73% ee. Lowering the reaction temperature to 25 °C (entry 5) resulted in a significant enhancement of the enantioselectivity of **6a** (84% ee). Lowering the temperature further to 0 °C (entry 6) did not impact the results. Lowering the metal and ligand loadings to 1 mol % (entry 7) decreased both the yield and the enantioselectivity. A number of solvents (entries 8–11) were then investigated, and *tert*-butyl methyl ether (MTBE) induced the highest enantioselectivity, providing **6a** with 86% ee (entry 11). Further optimization by lowering the equivalents of **5a** resulted in a system that afforded 89% ee with a good yield (69%) and complete regioselectivity (entry 12).

Having established bicyclo[2.2.2]octadiene ligand **L4** as the optimal chiral ligand, we next examined the steric and electronic nature of the substituents on the phenyl ring (**L5**–**L8**, Table 1). While the use of electron-rich 4-methoxyphenyl-substituted diene **L5** resulted in a decrease in the enantioselectivity (71% ee; entry 13), changing the diene substituent to the electron-poor 4-fluorophenyl group (ligand **L7**, entry 15)

significantly improved both the yield (85%) and the enantioselectivity (94% ee).

To rationalize the improved enantioselectivity with an electron-withdrawing chiral diene ligand (**L7** vs **L5**, Table 1), the ligation of the diene ligands to rhodium was monitored by ¹³C NMR spectroscopy (Figure 2). It was determined that the



Ligand	¹³ C _a free δ (ppm)	¹³ C _a complex δ (ppm)	$\Delta\delta = (\delta_{\text{complex}} - \delta_{\text{free}})$	$J(^{103}\text{Rh}, ^{13}\text{C}_a)$ (Hz)
L4	129.7772	45.3250	-84.4522	10.8
L5	127.3815	44.0943	-83.2872	12.0
L7	129.5563	45.4043	-84.1520	10.6

Figure 2. Studies of the stabilities of Rh–diene complexes.

electron density of the diene ligand significantly influences the coordination shift ($\Delta\delta = \delta_{\text{complex}} - \delta_{\text{free}}$)^{20a,25} as a result of increasing back-donation from the rhodium metal center.²⁶ For example, electron-withdrawing ligand **L7** has a larger coordination shift than electron-donating diene ligand **L5**. This result suggests that the presence of the electron-withdrawing group on the chiral diene **L7** shifts the hybridization of the coordinated olefinic carbon from sp^2 toward more sp^3 character, making the diene bind more strongly to rhodium than electron-rich **L5**.²⁶ The magnitude of the ¹⁰³Rh–¹³C coupling constant of 10.6–12 Hz (Figure 2) suggests that there is considerable s character in the rhodium–chiral diene complexes.²⁷

Under these optimized conditions, the scope of the allylic amination reaction with respect to aniline nucleophiles **5b**–**i** (Table 2) was explored. Electron-rich and electron-deficient para-substituted anilines **5b**–**f** (entries 1–5) were found to be suitable nucleophiles, giving rise to α,α -disubstituted allylic *N*-arylamines **6b**–**f** in moderate to good yields (51–86%) with good to high enantioselectivity (85–96% ee). In addition, all of the reactions proceeded with excellent regioselectivity. The amination reactions of anilines **5c** (entry 2) and **5e** (entry 4) bearing the *p*-bromo and *p*-boronic acid ester substituents, respectively, are noteworthy because the corresponding allylic *N*-arylamines **6c** and **6e** could be amenable to subsequent cross-coupling reactions.²⁸ Aniline **5g** containing ester functionality at the meta position provided product **6g** (entry 6) as a single regioisomer in good yield (79%) with high levels of enantioselectivity (94% ee). This method also worked well with ortho-substituted anilines **5h** and **5i** (entries 7 and 8), and the allylic amines were isolated with high enantioselectivity (89–94% ee) and regioselectivity [branched/linear (b/l) ratio = 48:1–51:1]. This suggests that the system is tolerant of sterically demanding anilines. As a result, we sought to extend this catalytic method to the challenging acyclic secondary aniline **5j** (entry 9), which is known to provide amination products with poor regioselectivity.^{10a,c} The reaction proceeded smoothly under our optimal conditions, and *N*-arylamines **6j** was isolated in 70% yield with excellent selectivities (b/l = 30:1, 93% ee).

To establish the absolute stereochemistry of the amination products, allylic *N*-arylamines **6c** was converted to the trifluoroacetate (TFA) salt and shown by X-ray crystallographic analysis to be *S*-configured. The solid-state structure of the

Table 2. Survey of Aniline Nucleophiles^a

<div><div><div><div><div><div>CCl₃</div><div>O</div><div>C(=O)N</div></div></div><div><div><div>Me</div><div>C=C</div><div>BnOCH₂</div></div></div></div><div><div><div>4 (racemic)</div></div></div></div><div><div><div>5 mol %</div><div>[RhCl(ethylene)₂]₂</div><div>10 mol % L7, MTBE,</div><div>Aniline 5b-j, 25 °C, 1 h</div></div><div><div>branched (b)</div><div>linear (l)</div></div></div></div> <tr><th>entry</th><th>anilines</th><th>products</th><th>% yield</th><th>b/l ratio</th><th>% ee</th></tr> <tr><td>1</td><td><div><div><div><div><div></div><div>NH₂</div></div><div><div>F</div><div></div></div></div><div>5b</div></div></div><div><div><div><div><div></div><div>NH</div></div><div><div>Me</div><div></div></div><div><div>BnOCH₂</div><div></div></div></div><div>6b</div></div></div><td>82</td><td>>99:1</td><td>96</td></td></tr> 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9	<div><div><div><div><div></div><div>NH</div></div><div><div>MeO</div><div></div></div></div><div>5j</div></div></div> <div><div><div><div><div></div><div>N</div></div><div><div>Me</div><div></div></div><div><div>Me</div><div></div></div><div><div>BnOCH₂</div><div></div></div></div><div>6j</div></div></div> <td>70</td> <td>30:1</td> <td>93</td>	70	30:1	93																																																				

^aAll of the reactions were conducted with 1 equiv of **4** and 1.5 equiv of the aniline. Isolated yields are shown; ee's were determined by chiral HPLC and b/l ratios by GC.

amine–TFA salt shows that it exists as two independent cation–anion pairs through hydrogen bonding. The ammonium cations have the same configuration but different conformations.²⁹

In addition to tertiary allylic imide **4**, the functional-group tolerance of the present catalysis was evaluated with a number of branched imidates (Table 3). Both electron-rich and electron-deficient benzyl ether derivatives (**7** and **8**, entries 1 and 2) provided the amination products **16b** and **17b** with an enantioselectivity (~93% ee) comparable to that of benzyl ether **4** (96% ee; Table 2). The ester group, however, was not suitable for this system, and allylic amine **21b** (entry 6) was isolated with 59% ee. As the functional group became more bulky (entry 7), a significant reduction in enantioselectivity was also observed (76% ee). These results suggest that tertiary allylic imidates having

Table 3. Survey of Tertiary Allylic Imidates^a

entry	imidates	products	% yield	b/l ratio	% ee
1			76	>99:1	93
2			61	>99:1	92
3			84	>99:1	80
4			57	>99:1	86
5			62	>99:1	89
6			53	>99:1	59
7			92	90:1	76
8			70	5:1	56
9			68	7:1	52

^aAll of the reactions were conducted with 1 equiv of the allylic imide and 1.5 equiv of the aniline. Isolated yields are shown; ee's were determined by chiral HPLC and b/l ratios by GC.

benzyl, phenyl, and methyl ether groups at the β -position (entries 1–5) provide additional chelation control on the rhodium center,^{10a,30} whereas ester and silyl protecting groups (entries 6 and 7) reduce the ligation of the ether oxygen to the metal center. Reductions in regio- and enantioselectivity were also observed in the reactions of tertiary allylic imidates **14** and **15** lacking an oxygen substituent at the β -position (entries 8 and 9). We further examined the limitation of the current method with ethyl- and aryl-substituted imidates. Although we were able to prepare trichloroacetimidates having an aryl group at the α -position, these substrates rapidly underwent [3,3]-sigmatropic rearrangement.³¹ We were unable to prepare allylic imidates bearing an ethyl group at the α -position, presumably because their tertiary alcohol precursors were too sterically hindered to react with trichloroacetonitrile.

In summary, we have reported the first dynamic kinetic asymmetric transformation of racemic tertiary allylic acetimidates with aniline nucleophiles using a rhodium–diene ligand complex, providing α,α -disubstituted allylic *N*-arylamines in moderate to good yields with good to excellent regio- and enantioselectivity. Investigations into the full racemic tertiary allylic trichloroacetimidate scope and further transformations are ongoing and will be reported in due course.

■ ASSOCIATED CONTENT

■ Supporting Information

Complete experimental details and spectral data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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