

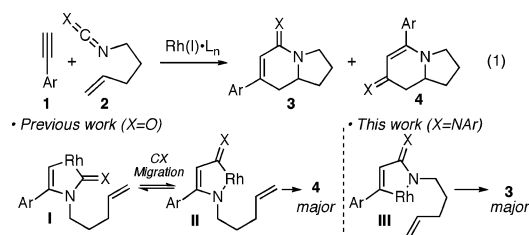
# Asymmetric Synthesis of Bicyclic Amidines via Rhodium-Catalyzed [2+2+2] Cycloaddition of Carbodiimides

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Recent advances in the field of transition metal-catalyzed cycloadditions have made them among the most efficient methods to assemble polycyclic carbocycles and heterocycles.<sup>1</sup> Cycloadditions employing carbodiimides are surprisingly scarce in the literature.<sup>2</sup> An intramolecular Pauson–Khand-type reaction of alkynyl carbodiimides has recently been described,<sup>3</sup> while [2+2+2] cycloadditions of diynes and carbodiimides have been documented to provide mostly inseparable mixtures.<sup>4,5</sup> To the best of our knowledge, there have been no reports of successful enantioselective [m+n+o]-type cycloadditions involving carbodiimides as a 2π component.



We previously described an unusual cycloaddition between phenyl acetylene **1a** and isocyanate **2** ( $X = O$ , eq 1), where the major pathway proceeds via metalacycles **I** and **II**, involving a CO migration process.<sup>6</sup> The resulting cycloaddition affords product **4** ( $X = O$ ) in good efficiency, while cycloadduct **3** can only be formed as the minor component (**3:4** = 1:7,  $Ar = Ph$ ). In an effort to selectively access products of type **3**, we envisioned that a cycloaddition employing carbodiimides (**2**,  $X = NAr$ ) should favor the formation of metalacycle **III** by placing the bulky imido moiety farther away from the rhodium center (**I** vs **III**). Herein, we report the successful application of this strategy, providing a selectivity complementary to that of the cycloaddition previously described using isocyanates.<sup>7</sup> Further, this reaction offers a novel entry into the asymmetric synthesis of bicyclic amidines (**3**,  $X = NAr$ ).<sup>8</sup>

Our investigations began with the cycloaddition of phenyl acetylene **1a** and the phenyl-substituted pentenyl carbodiimide **2a**, employing our previously developed reaction conditions (entries 1, 2, Table 1).<sup>6b</sup> These conditions afford the desired bicyclic amidine **3** in moderate yields, with the ligand **L2** providing the highest enantioselectivity. The *p*-tol-TADDOL-derived ligand **L3** provides a very efficient reaction with half the catalyst loading and shorter reaction times (entry 3). Further optimization led to the identification of *m*-xylyl-TADDOL derivative **L4** as the best ligand, affording the bicyclic amidine with good chemical yield and excellent enantioselectivity (entry 4). The amino group on the ligand proves to have a significant effect on the reaction; replacing the pyrrolidinyl moiety with the piperidine can further improve the product selectivity for **3**, although the enantioselectivity decreases (entry 5). It is significant to note that the type **4** product resulting from a rare isocyanide (CNR) migration<sup>9</sup> can be observed in the reaction mixture as the minor component.

Table 2 summarizes the scope of the enantioselective [2+2+2] cycloaddition of phenyl acetylene **1a** and a variety of aryl-

Table 1. Ligand Screen

entry	[Rh(C <sub>2</sub> H <sub>4</sub> ) <sub>2</sub> Cl] <sub>2</sub>	L* (mol %)	time (h)	<b>3</b> : <b>4</b> <sup>b</sup>	yield (%) of <b>3aa</b> <sup>c</sup>	ee (%) of <b>3aa</b> <sup>d</sup>
1	5%	<b>L1</b> (10)	12	2.4 : 1	40	84
2	5%	<b>L2</b> (10)	12	2.8 : 1	57	94
3	3%	<b>L3</b> (6)	3	3.4 : 1	64	95
4	3%	<b>L4</b> (6)	3	3.4 : 1	70	97
5	3%	<b>L5</b> (6)	3	4.8 : 1	78	89

Chemical structures of ligands **L1** through **L5** are shown below the table.

<sup>a</sup> Conditions: **1** (2 equiv), **2** (0.16 mmol), Rh catalyst, **L** in PhMe at 110 °C. <sup>b</sup> Product selectivity (**3:4**) is determined by <sup>1</sup>H NMR of the unpurified reaction mixture. <sup>c</sup> Isolated yield. <sup>d</sup> Determined by HPLC analysis using a chiral stationary phase.

Table 2. Carbodiimide Scope

entry	R	<b>3</b> : <b>4</b> <sup>b</sup>	yield (%) of <b>3</b> <sup>c</sup>	ee (%) of <b>3</b> <sup>d</sup>
1	<i>p</i> -OMe, <b>2b</b>	3.6 : 1	70	94
2	<i>o</i> -OMe, <b>2c</b>	3.8 : 1	68 (62) <sup>e</sup>	98 (96) <sup>e</sup>
3	<i>m</i> -Cl, <b>2d</b>	3.4 : 1	67	97
4	<i>o</i> -CF <sub>3</sub> , <b>2e</b>	9.4 : 1	82	97
5 <sup>f</sup>	<i>p</i> -CN, <b>2f</b>	9.5 : 1	55	92

<sup>a-d</sup> See Table 1. <sup>e</sup> 0.8 mmol scale of **2c**, 1 mol % Rh catalyst, and 2 mol % **L4**. <sup>f</sup> 5 mol % Rh catalyst and 10 mol % **L4**.

substituted carbodiimides. The reaction tolerates both electron-rich and electron-poor substituents at various positions to afford bicyclic amidines **3** in good yields and excellent enantioselectivity (entries 1–5). Aryl carbodiimides with strong electron-withdrawing groups provide much greater product selectivity (entries 4, 5). For larger scale reactions, the catalyst loading may be reduced to 1 mol % [Rh(C<sub>2</sub>H<sub>4</sub>)<sub>2</sub>Cl]<sub>2</sub> with virtually identical yield and enantioselectivity.

For further substrate development, we chose *o*-anisidine-derived carbodiimide as the standard cycloaddition partner. This selection was based on the optimal enantioselectivity obtained and the potential role of this functionality as an oxidatively cleavable protecting group of the resulting cycloadducts.<sup>10</sup>

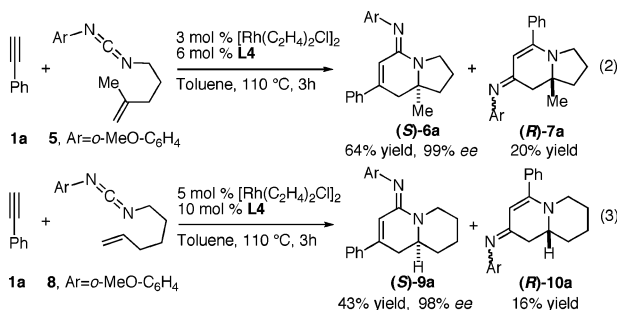
The asymmetric synthesis of amidine **6a**, possessing a nitrogen-substituted quaternary center, can be achieved in high efficiency from the corresponding disubstituted alkenyl carbodiimide (eq 2).<sup>6c</sup> Although a much more sluggish reaction, cycloaddition of carbo-

**Table 3.** Terminal Alkyne Scope

entry	R	carbodiimide	3 : 4 or 6 : 7 <sup>b</sup>	yield (%) of 3 or 6 <sup>c</sup>	ee (%) of 3 or 6 <sup>d,e</sup>
1	<i>p</i> -Br-C <sub>6</sub> H <sub>4</sub> , <b>1b</b>	<b>2c</b>	16 : 1	75	98
2	<i>m</i> -F-C <sub>6</sub> H <sub>4</sub> , <b>1c</b>	<b>2c</b>	> 19 : 1	77	99
3	3,5-F <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> , <b>1d</b>	<b>2c</b>	> 19 : 1	66	99
4	<i>p</i> -Ac-C <sub>6</sub> H <sub>4</sub> , <b>1e</b>	<b>2c</b>	> 19 : 1	78	99
5	<i>p</i> -CF <sub>3</sub> -C <sub>6</sub> H <sub>4</sub> , <b>1f</b>	<b>2c</b>	> 19 : 1	68	96
6	<i>m</i> -CN-C <sub>6</sub> H <sub>4</sub> , <b>1g</b>	<b>2c</b>	> 19 : 1	62	94
7	<i>m</i> -OMe-C <sub>6</sub> H <sub>4</sub> , <b>1h</b>	<b>2c</b>	6.3 : 1	69	99
8	<i>m</i> -Me-C <sub>6</sub> H <sub>4</sub> , <b>1i</b>	<b>2c</b>	3.4 : 1	61	98
9	"	<b>2e</b>	8.3 : 1	74	98
10	2-thienyl, <b>1j</b>	<b>2c</b>	3.2 : 1	58	98
11	"	<b>2e</b>	7.2 : 1	79	97
12	<i>p</i> -OMe-C <sub>6</sub> H <sub>4</sub> , <b>1k</b>	<b>2c</b>	1 : 2.8	20 (52) <sup>g</sup>	99
13	"	<b>2e</b>	1 : 1	37 (36) <sup>g</sup>	96
14	3,5-F <sub>2</sub> -C <sub>6</sub> H <sub>3</sub> , <b>1d</b>	<b>5</b>	> 19 : 1	79	98
15	<i>p</i> -Ac-C <sub>6</sub> H <sub>4</sub> , <b>1e</b>	<b>5</b>	16 : 1	74	99
16	<i>m</i> -OMe-C <sub>6</sub> H <sub>4</sub> , <b>1h</b>	<b>5</b>	4.5 : 1	66	96
17 <sup>f</sup>	<i>n</i> -Hex, <b>1l</b>	<b>2c</b>	> 19 : 1	74	91
18 <sup>f</sup>	(CH <sub>2</sub> ) <sub>4</sub> CO <sub>2</sub> Me, <b>1m</b>	<b>2c</b>	> 19 : 1	68	92
19 <sup>f</sup>	CH <sub>2</sub> CH <sub>2</sub> OTBS, <b>1n</b>	<b>2c</b>	> 19 : 1	76	96
20 <sup>f</sup>	(CH <sub>2</sub> ) <sub>2</sub> CH <sub>2</sub> OTBS, <b>1o</b>	<b>2c</b>	> 19 : 1	73	94
21 <sup>f</sup>	(CH <sub>2</sub> ) <sub>3</sub> CH <sub>2</sub> Cl, <b>1p</b>	<b>2c</b>	> 19 : 1	60	88
22 <sup>f</sup>	CH <sub>2</sub> CH <sub>2</sub> Ph, <b>1q</b>	<b>2c</b>	> 19 : 1	70	92

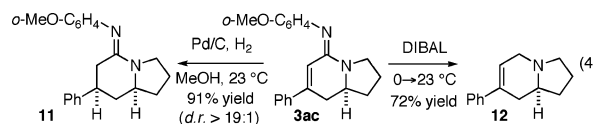
<sup>a-d</sup> See Table 1. <sup>e</sup> Absolute configuration assigned by analogy to (S)-**3bc** (established by X-ray analysis). <sup>f</sup> 5 mol % Rh catalyst and 10 mol % L4. <sup>g</sup> Isolated yield of **4** (a 2:1 mixture of imine isomers).

diimide **8** to construct the desired [4.4.0] bicyclic amidine **9a** proceeds in a moderate yield with excellent enantiocontrol (eq 3).



The cycloadditions of a variety of terminal alkynes and carbodiimides **2c** and **5** were examined (Table 3). The electronic and steric effects of alkynyl partners play important roles in the reaction outcomes. Aryl acetylenes substituted with various electron-poor groups participate in the cycloaddition readily to furnish almost exclusively the bicyclic amidine **3** or **6** with good yields and excellent enantioselectivity (entries 1–6, 14, 15).<sup>11</sup> The reactions of alkyne **1h**, which possesses a moderate *o*-withdrawing group, proceed with the same efficiency to afford the desired amidines in good product ratio (entries 7, 16). *m*-Tolyl acetylene **1i**, which is slightly more electron-rich than **1a**, and ethynyl thiophene **1j**, which is sterically smaller than **1a**, undergo the cycloaddition to provide the corresponding amidines in high enantiomeric excess with product ratios similar to those obtained with **1a** (entries 8, 10). The moderate product ratio can be greatly improved while maintaining the excellent enantiocontrol by using the *o*-CF<sub>3</sub>-phenyl carbodiimide **2e** (entries 9, 11). On the other hand, the reaction of electron-rich aryl acetylene **1k** proceeds with an opposite product selectivity (entries 12, 13), a trend that is consistent with our previous study.<sup>6b</sup> Cycloadditions with alkyl acetylenes require a slightly higher catalyst loading to ensure complete conversion (entries 17–22) but generate bicyclic amidines **3** with high efficiency (88–96% ee).

The resulting bicyclic amidines **3** are potentially useful chiral building blocks. Under appropriate conditions, the olefin and the amidine moiety can each be selectively reduced while leaving the other functionality untouched for further transformation (eq 4).



In summary, we have developed the first enantioselective [2+2+2] cycloaddition utilizing carbodiimides to give bicyclic amidines with excellent enantiocontrol. Observation of the isocyanide migration process during the cycloaddition is notable. Studies to explore the synthetic utility of bicyclic amidines **3** are ongoing.

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**Supporting Information Available:** Experimental procedures, characterization, <sup>1</sup>H and <sup>13</sup>C NMR spectra; CIF file for **3bc**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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