

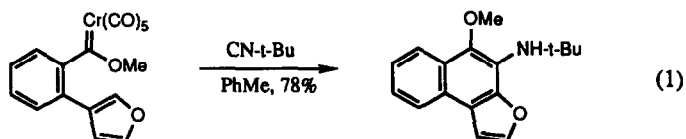
## Chemoselectivity in the Isonitrile Metathesis Route to Aromatic Amines

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**Abstract:** Chemoselectivity and structural effects in thermal benzannulation reactions employing chromium carbene complexes and isonitriles are reported. Alkyl, aryl, sterically hindered, electron deficient, and electron rich isonitriles all react efficiently with several chromium carbene complexes to provide aromatic amine products.

Simple Fischer carbene complexes<sup>1</sup> react with isonitriles to produce, initially, metal complexed ketenimines,<sup>2</sup> then a range of products including aminocarbene complexes, 2,3-bis(imino)azetidines, 1,2-bis(imino)cyclobutane complexes, 1,2-bis(imino)indane complexes,  $\delta$ -carbolinones, 2,3-dihydroazete complexes, imidazole complexes, indoles, nitrile complexes, and pyrroles depending on the structures of both the carbene complexes and the isonitriles as well as the reaction stoichiometry.<sup>3</sup> Recently, we reported new designed thermal benzannulation reactions of Fischer carbene complexes that employ isonitriles as coreactants (e.g. eq 1).<sup>4</sup> These results demonstrated that chromium dienylcarbene complexes efficiently react with isonitriles to produce aromatic amines in a mild thermal reaction. In addition, this process provides products regiocomplementary to those reported from photochemical reactions of chromium dienyl(amino)carbene complexes.<sup>5</sup>



Our proposed reaction mechanism invokes metathesis of an isonitrile with a dienylcarbene complex to generate a key chromium complexed dienylketenimine intermediate I (eq 2), subsequent electrocyclization of the ketenimine,<sup>6</sup> followed by tautomerization and demetallation complete the reaction pathway. This is a two stage thermal process, in which the metathesis typically occurs below room temperature while the subsequent electrocyclization requires elevated temperatures. The intermediate complexes I are not usually isolated, but analogous species have been characterized previously.<sup>2</sup> We report herein on how reactant structures affect isonitrile metathesis and on the reaction chemoselectivity.

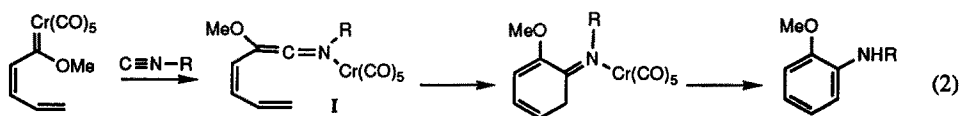
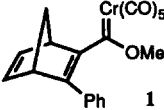
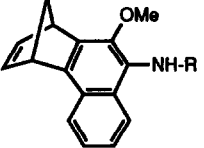
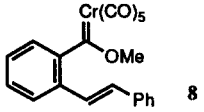
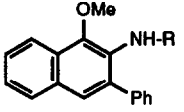
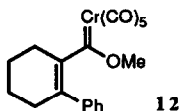
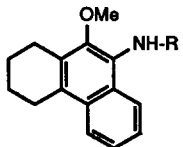
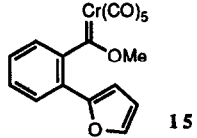
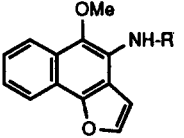


Table I summarizes the reactions between several chromium dienylcarbene complexes and a range of isonitriles which provide efficient benzannulation under mild conditions.<sup>7,8</sup> Structural effects (steric and electronic) on the reactions were most apparent from the conditions required to effect reaction. Steric effects play little role as evidenced by comparable results in entries 1, 2, 3 and, in particular, 5 which employs the sterically hindered 2,6-xylyl isonitrile reactant. Electronic factors, however, have a pronounced role in the initial metathesis step. Electron rich isonitriles such as those with benzyl, *n*-butyl, or *t*-butyl substituents readily react with the carbene complexes at 0°C. However, isonitriles containing electron withdrawing substituents such as *p*-toluenesulfonyl or carboethoxy have reduced nucleophilicity and are slow to react at 0°C. The subsequent electrocyclization step from the intermediate ketenimine complexes requires elevated temperatures of 30° to 110°C for reaction. The facility of this reaction step is mostly dependent on the structure of the formal dienylketenimine unit rather than the nitrogen substituent. For example, substrate 15, containing a biaryl unit, requires temperatures over 100°C for reaction, while complex 1, with a strained alkene, reacts at 30° to 60°C. However, electron withdrawing substituents (entries 14 vs 15) do activate the electrocyclization step.

Product 14 is extremely labile due to ejection of sulfinate by the amine substituent and no more than 30% of the product can be obtained from the standard reaction conditions. This problem was solved by reaction in the presence of zinc chloride which served to complex the nitrogen lone pair electrons and hence prevent sulfinate ejection. The zinc chloride also seemed to act as a Lewis acid catalyst, promoting a more rapid electrocyclization than in the absence of the additive.

Use of functionalized isonitriles illustrates the reaction chemoselectivity. In addition to simple alkyl and aryl isonitriles, alkene, ester, silyl and sulfone substituted isonitriles all provided the desired products in good yields. Alkenes with electron withdrawing substituents are known to react with simple chromium carbene complexes to provide cyclopropanation products<sup>1</sup> and alkenyl isonitriles are reported to react via the alkene substituent to yield 3-amino-2-acylpyrroles.<sup>9</sup> In contrast, dienylcarbene complexes reacted with propenyl isonitrile to yield the desired benzannulated products (entries 7 and 11). An unusual reactant is trimethylsilylcyanide which is in equilibrium with its isomeric form, trimethylsilylisocyanide.<sup>10</sup> Despite the small equilibrium constant, efficient trapping and metathesis by carbene complexes is observed in THF, but not toluene. The silylamine products are desilylated by silica gel column chromatography providing the aromatic amines 7 and 11 which are extremely labile with respect to oxidation. Therefore, the trimethylsilylcyanide reagent functions as a hydrogen isocyanide, HNC, synthon. Note that most applications of trimethylsilylcyanide, and related reagents, employ the reagent in a manner which results in cyanide,<sup>10,11</sup> rather than isocyanide,<sup>12</sup> transfer. In general, use of trimethylsilylcyanide was substrate dependent, so better results in the formation of primary amines were found using propenyl isocyanide. Metathesis with complexes 1 and 8 followed by cyclization at room temperature to refluxing solvent with subsequent hydrolysis by silica gel chromatography, led to 7 and 11 in good yields (entries 7 and 11).

Table I. Thermal Benzannulation Reactions of Carbene Complexes and Isonitriles

Entry	Carbene	Conditions	Products	Yield
	 1	$\xrightarrow{\text{CN-R}}$		
1	CN-t-Bu	Et <sub>2</sub> O 0°C 1h, ↑↓ 8 h	2 R = t-Bu	83%
2	CN-n-Bu	t-BuOMe 0°C 2h, ↑↓ 12 h	3 R = n-Bu	70%
3	CN-Bn	THF RT 21 h	4 R = Bn	85%
4	CN-CH <sub>2</sub> COOEt	THF RT 2h, ↑↓ 8 h	5 R = CH <sub>2</sub> COOEt	81%
5	CN-2,6-Me <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	CH <sub>2</sub> Cl <sub>2</sub> RT 1h, ↑↓ 8 h	6 R = 2,6-Me <sub>2</sub> C <sub>6</sub> H <sub>3</sub>	86%
6	NC-SiMe <sub>3</sub>	THF 0°C 1h, RT 2 h	7 R = H	56%
7	CN-CH=CHMe	THF RT 8h, ↑↓ 1 h	7 R = H	68%
	 8	$\xrightarrow{\text{CN-R}}$		
8	CN-t-Bu	t-BuOMe 0°C 1h, 32°C 12 h	9 R = t-Bu	89%
9	CN-CH <sub>2</sub> COOEt	THF RT 2h, ↑↓ 8 h	10 R = CH <sub>2</sub> COOEt	80%
10	NC-SiMe <sub>3</sub>	THF/PhMe RT 16h, ↑↓ 24 h	11 R = H	32%
11	CN-CH=CHMe	Et <sub>2</sub> O RT 2h, ↑↓ 2 h	11 R = H	76%
	 12	$\xrightarrow{\text{CN-R}}$		
12	CN-t-Bu	t-BuOMe 0°C 1h, ↑↓ 48 h	13 R = t-Bu	71%
13	CN-CH <sub>2</sub> -Ts	THF, ZnCl <sub>2</sub> RT 4h, ↑↓ 5 h	14 R = CH <sub>2</sub> -Ts	84%
	 15	$\xrightarrow{\text{CN-R}}$		
14	CN-t-Bu	PhMe 0°C 3h, ↑↓ 24 h	16 R = t-Bu	72%
15	CN-CH <sub>2</sub> COOEt	THF RT 4h, ↑↓ 12 h	17 R = CH <sub>2</sub> COOEt	64%

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7. In a typical reaction, the isonitrile (2 equiv) was added to a solution of the carbene complex cooled to 0°C. After consumption of the carbene complex as evidenced by a change in color, the reaction was brought to reflux and heated until complete as indicated by disappearance of a low R<sub>f</sub> spot corresponding to the amide resulting from hydrolysis of the intermediate ketenimine complex.
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