Coupling of β-Cyanocarbene-Chromium Complexes with 2-Alkynylbenzoyl Derivatives: A [5+5]-Cycloaddition Approach to Phenanthridines

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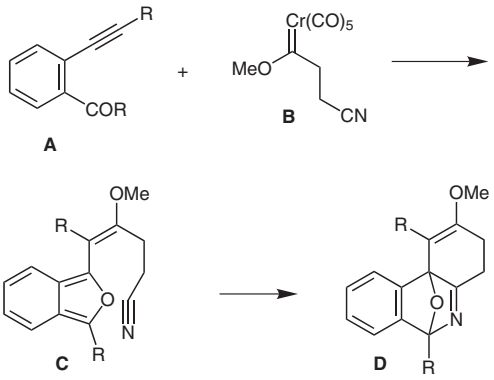
Dedictaed to Professor Martin F. Semmelhack on the occasion of his 65th birthday

Abstract: The coupling of β-cyanocarbene complexes and 2-alkynylbenzoyl derivatives has been examined. The reaction afforded phenanthridine derivatives in a complex tandem process involving carbene–alkyne coupling, isobenzofuran formation, intramolecular Diels–Alder reaction using a nitrile dienophile, and deoxygenation. The chemistry could not be reproduced in non-chromium-based systems.

Key words: carbene complexes, chromium, cycloadditions, alkynes, nitriles, Diels–Alder reactions

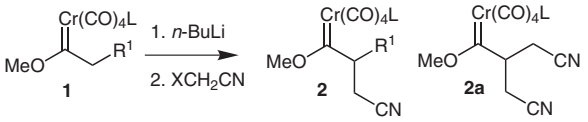
This manuscript reports on the scope, limit, and mechanistic considerations for the preparation of isoquinoline derivatives through coupling of β-cyanocarbene complexes and 2-alkynylbenzoyl systems.[1] In the original design of this reaction depicted in Scheme 1, coupling of the functionalized alkyne **A** and the β-cyanocarbene complex **B** will initially generate an isobenzofuran intermediate **C**,[2] which could potentially undergo an intramolecular Diels–Alder reaction with the nitrile dienophile, resulting in **D**. Only limited studies where nitriles serve as dienophiles in Diels–Alder reactions have appeared. Although Diels–Alder reactions of nitriles with simple dienes are known,[3] only one example of the Diels–Alder reaction between a nitrile and a furan/isobenzofuran has been reported.[4] The reverse reaction has ample precedent, and is a key step in the synthesis of furans from oxazoles and alkynes.[5] Isobenzofurans can be generated through expulsion of nitriles from simpler analogues of **D**, which occurs upon mild thermolysis.[6]

We are not aware of any precedent for β-cyano Fischer carbene complexes. Three methods were successfully developed for the synthesis of this class of compounds. The simplest method involves the alkylation of simple carbene complexes **1** (Equation 1, see Figure 1 for identity of R groups) with bromo- or iodoacetonitrile.[7] A problem with this method is that alkylation of the simple methylcarbene complexes **1a**,**b** produces only the dialkylation product **2a**. Only alkoxycarbene complexes could be prepared using this method. Aminocarbene complexes could not be alkylated using this procedure, possibly due to a competing proton transfer process.[8] An alternative method involves synthesis from β-cyano acid chlorides **3**

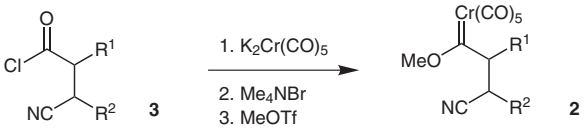


Scheme 1

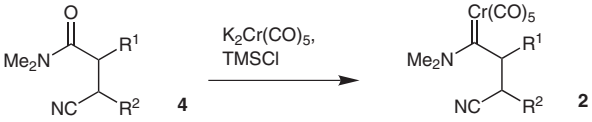
(Equation 2) using $Cr(CO)_5$ dianion.[9] A similar route was employed for the direct conversion of β-cyanoamides **4** to β-cyano aminocarbene complexes **7** (Equation 3).[10] These latter routes were used for the preparation of *o*-cyanophenylcarbene complexes **6**. Alkoxycarbene complexes **2a**,**c**,**d** and **6a** are unstable in comparison with analogous complexes lacking a cyano group. These carbene complexes are difficult to purify and rapidly acquire a greenish color in the air. Aminocarbene complexes **2e** and phosphine-substituted[11] complex **2b** were more stable than alkoxy pentacarbonylcarbene analogues. Alkynylbenzoyl starting materials were prepared through well-established methods.



Equation 1



Equation 2



Equation 3

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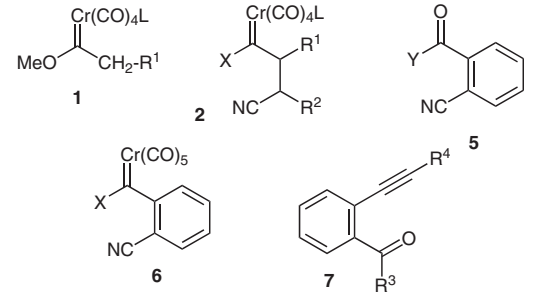


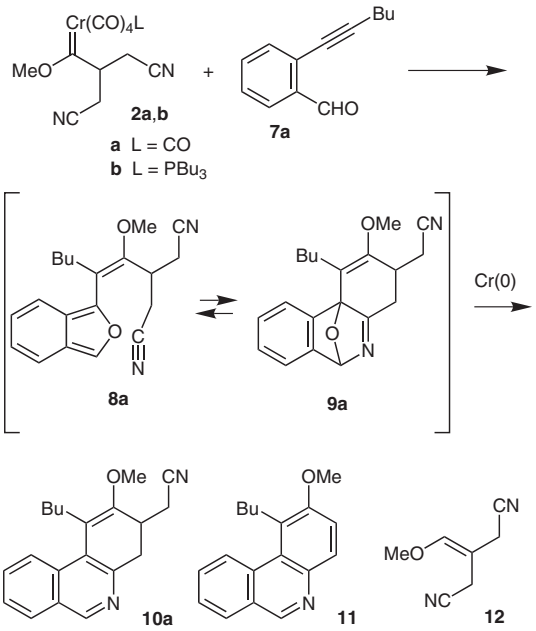
complexes **1**
a R^1 = H, L = CO
b R^1 = H, L = PBu_3
c R^1 = Pr, L = CO

compounds **2**
a R^1 = CH_2CN, R^2 = H, X = OMe, L = CO
b R^1 = CH_2CN, R^2 = H, X = OMe, L = PBu_3
c R^1 = *n*-Pr, R^2 = H, X = OMe, L = CO
d R^1,R^2 = -$(CH_2)_4$- (cis), X = OMe, L = CO
e R^1,R^2 = -$(CH_2)_4$- (cis), X = NMe_2, L = CO

complexes **6**
a X = OMe (from **5**, X = Cl)
b X = NMe_2

compounds **7**
a R^3 = H, R^4 = *n*-Bu
b R^3 = Me, R^4 = *n*-Bu
c R^3 = Ph, R^4 = *n*-Bu
d R^3, R^4 = H
e R^3 = NMe_2, R^4 = Bu
f R^3 = NMe_2, R^4 = TMS

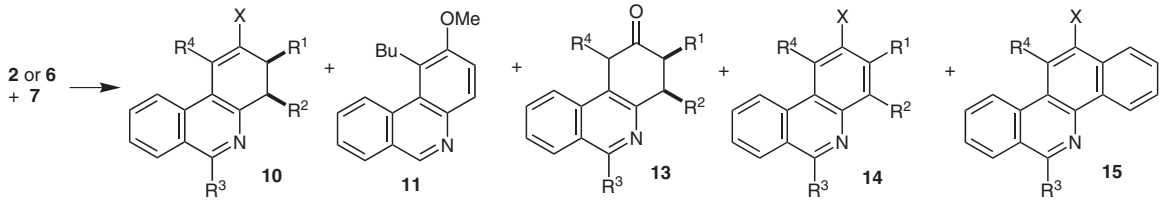
Figure 1 Legend for correlation of substituent identifiers with substituent patterns.



Scheme 2

Coupling of dicyanocarbene complex **2a** with alkyne aldehyde **7a** was examined initially (Scheme 2 and Table 1, entry A). This coupling reaction afforded enol ether **12** (0–20% yield) and the phenanthridine derivatives **10a** and **11**. Enol ether **12** results from a known decomposition reaction of Fischer carbene complexes.[12] Formation of compound **10a** likely involves generation of isobenzofuran **8a** followed by intramolecular Diels–Alder reaction to afford adduct **9a**, which is deoxygenated to afford compound **10a**.[13] The origin of acetonitrile loss product **11** is unclear.

Table 1 Coupling of β-Cyanocarbene Complexes with Alkynylbenzoyl Systems

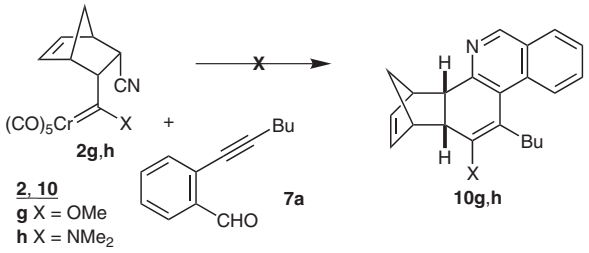


Entry[a]	Reactants	R^1	R^2	R^3	R^4	X	**10** (**13**)[b]	**11**	**14**	**15**
A[c]	**2a** + **7a**	CH_2CN	H	H	*n*-Bu	OMe	40%	36%	–	–
B[d]	**2b** + **7a**	CH_2CN	H	H	*n*-Bu	OMe	48%	19%	–	–
C	**2c** + **7a**	*n*-Pr	H	H	*n*-Bu	OMe	–	–	53%	–
D	**2d** + **7d**	-$(CH_2)_4$-		H	H	OMe	21%	–	–	–
E	**2e** + **7d**	-$(CH_2)_4$-		H	H	NMe_2	(42%)	–	–	–
F	**2d** + **7b**	-$(CH_2)_4$-		Me	*n*-Bu	OMe	39%	–	–	–
I[e]	**2c** + **7e**	*n*-Pr	H	NMe_2	*n*-Bu	OMe	–	–	37%	–
J	**6a** + **7a**	–	–	H	*n*-Bu	OMe	–	–	–	20%
K	**6b** + **7a**	–	–	H	*n*-Bu	NMe_2	–	–	–	40%
L	**6b** + **7c**	–	–	Ph	*n*-Bu	NMe_2	–	–	–	59%

[a] Table entry letters correspond to substituent identifiers in adducts.
[b] The yield in parentheses is the yield for ketone **13**
[c] Compound **12** was also formed in 0–20% yield.
[d] Adducts are denoted by substituent identifier **a**.
[e] See the negative result in Equation 4 for entries G and H.

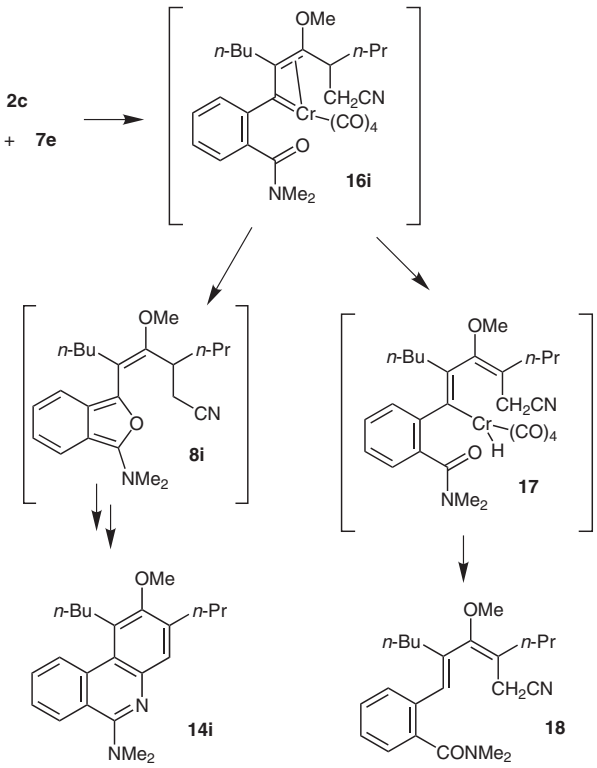
This compound does not arise from loss of acetonitrile from **10a** since formation of this compound does not depend on reaction time and since **10a** is not converted to **11** under the reaction conditions. Use of the phosphine analogue **2b** led to only **10a** and **11** (entry B), however the ratio was different. The added stability of complex **2b** relative to **2a** likely suppresses competing carbene complex decomposition.

Coupling of various β-cyanocarbene complexes with 2-alkynylbenzoyl derivatives has been examined (Table 1). Moderately efficient formation of the net dehydrogenation product **14c** was observed using the monocyanocarbene complex **2c** (entry C). The reaction was less efficient for formation of tetracyclic compound **10d** (entry D) however the reaction process was considerably more efficient using the more stable aminocarbene complex **2e** (entry E), which afforded the ketone **13e** after enamine hydrolysis. The analogous reaction using ketone **2b** was also more efficient (entry F), possibly due to the increased stability of the isobenzofuran intermediate.[14] Norbornene-carbene complexes **2g**,**h** (Equation 4) did not afford any identifiable products from coupling with alkyne **7a**, possibly due to the strain associated with this ring system. Alknylbenzamide **7e** couples with carbene complex **2c** (entry I and Scheme 3) to afford the expected compound **14i**, accompanied by a sizable amount of an uncyclized compound tentatively identified as the *E*/*Z* mixture of dienylnitrile amide **18**. Formation of **18** can occur through allylic CH activation from intermediate isobenzofuran **16i** to afford the dienylchromium species **17**, which then affords the product **18** after reductive elimination. Previous studies have also suggested that isobenzofuran formation is more difficult from amides versus ketones and aldehydes.[15] Arylcarbene complex analogues **6a**,**b** were also tested (entries J–L). Similar trends were noted in the formation of compound **15** in that higher yields were obtained using an aminocarbene complex (entry L) or if an isobenzofuran-stabilizing substituent (phenyl, entry K) is present.



Equation 4

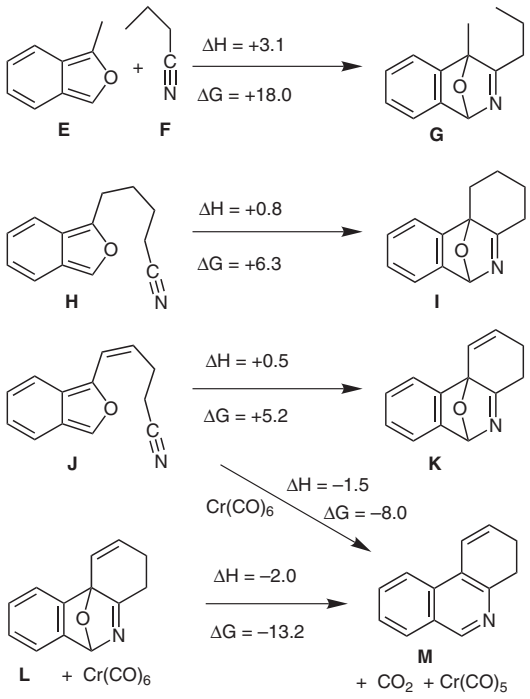
The key step for the novel annulation reactions in Table 1 is the Diels–Alder reaction between an isobenzofuran and a nitrile, which is not expected to be favorable.[5,6] The unique success of the nitrile-isobenzofuran Diels–Alder step in this reaction is likely due to either: (1) an unusually favorable six-membered-ring-forming Diels–Alder reaction, (2) equilibrium of isobenzofuran-nitriles and the respective Diels–Alder adducts (e.g. the interconversion of



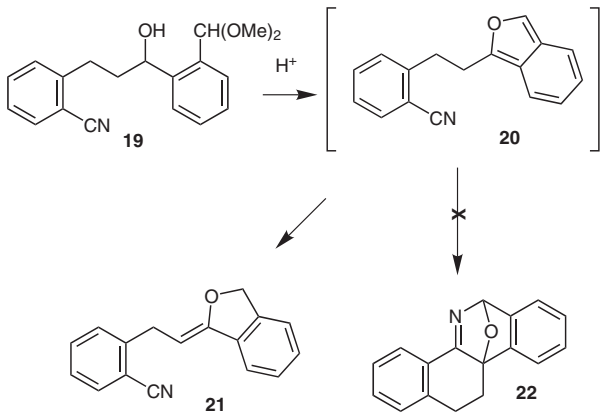
Scheme 3

8a and **9a** in Scheme 2) driven toward product formation through reductive removal of the oxygen bridge by chromium(0) byproducts, or (3) involvement of chromium-complexed intermediates. In order to better evaluate the feasibility of key Diels–Alder events, the thermodynamic parameters of select reactions were evaluated using DFT calculations (Scheme 4, all values are in kcal/mol). The isobenzofuran-nitrile Diels–Alder reaction is slightly endothermic in all examples depicted in Scheme 4, however the entropic effects are less detrimental to the free energy of the intramolecular reactions in intramolecular systems. If the deoxygenation process (conversion of **L** to **M**) is included in the overall thermodynamic cycle, the overall reaction becomes exothermic. Use of a carbonyl ligand of chromium hexacarbonyl as the hypothetical reducing agent results in a very favorable reaction process for the conversion of the Diels–Alder adduct to the isoquinoline. The overall conversion of isobenzofuran intermediate **J** to dihydrophenanthrene **M** is also now an energetically feasible process.

Experiments were designed that would determine the feasibility of intramolecular isobenzofuran-nitrile Diels–Alder reactions (Scheme 5). Compound **19** was prepared[16] and subjected to reaction with acid. These conditions are expected to generate isobenzofuran intermediate **20**.[17] The Diels–Alder adduct **22** was not observed under these reaction conditions. The only identifiable product from this reaction was tentatively assigned as alkylidenephthalan **21**. Alkylidenephthalans are often obtained from isobenzofurans through a 1,5-hydrogen shift process.[18]

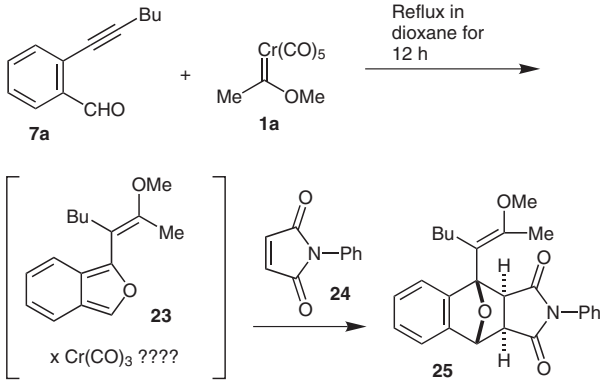


Scheme 4



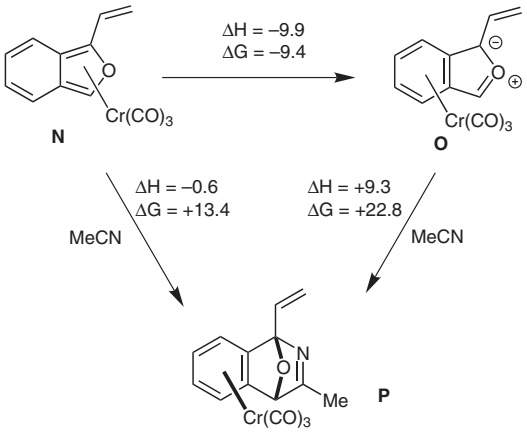
Scheme 5

Based on observations of related reaction processes,[2b] there is some degree of stabilization imparted to the isobenzofuran intermediate (see Scheme 6). In reference 2b it was noted that the three-component coupling of alkynylbenzaldehyde **7a**, carbene complex **1a**, and *N*-phenylmaleimide (**24**) actually produced an adduct **25** in moderate yield (52%) under the conditions noted in Scheme 6. Based on previous descriptions of isobenzofurans,[14] the free isobenzofuran intermediate **23** should not have a lifetime of more than a few seconds at 100 °C, and thus the reaction in Scheme 6 should not have yielded any Diels–Alder adducts. The successful use of these conditions suggest that isobenzofuran intermediates generated through chromium carbene–alkyne coupling reactions have substantially greater lifetimes than typical isobenzofurans, possibly due to stabilization by complexation to chromium.



Scheme 6

In consideration of the result depicted in Scheme 6, calculations using chromium complexed vinylisobenzofuran intermediates were examined (Scheme 7). Both the (η^5-furan)Cr(CO) complex **N** and the (η^6-arene)Cr(CO)$_3$ complex **O** were subjected to DFT energy minimization using the 6-31G* basis set. The arene complex **O** is more stable than the furan complex **N**, despite the fact that this imparts a carbonyl ylide structure to the furan ring system. Cycloaddition of acetonitrile to the furan complex **N**, leading to arene complexed adduct **P** is slightly exothermic. Initial formation of furan-complexed isobenzofurans followed by cycloaddition to form arene-complexed adducts could be exothermic and exergonic in an intramolecular reaction.



Scheme 7

Based on the studies in Schemes 6 and 7, the success of this nitrile-isobenzofuran Diels–Alder reaction could be attributed to either of two scenarios: (1) presence of a suitable reductant that can drive the unfavorable isobenzofuran/Diels–Alder adduct equilibrium toward cycloadduct formation through a deoxygenation–aromatization process, or (2) initial formation of furan-complexed isobenzofuran intermediate which undergoes a more energetically favorable Diels–Alder reaction to afford the arene-complexed Diels–Alder adduct.

In summary, nitrile-isobenzofuran Diels–Alder reactions, a previously undocumented reaction process, can be useful for phenanthridine synthesis.[19] Although the reaction produces the final phenanthridines in mediocre yield, the complex structure arises through the coupling of simple and readily available components in a single reaction process proceeding through several distinct mechanistic events. All of our efforts to understand the reaction computationally have led us to the conclusion that this reaction should have never worked at all. Considerable efforts to optimize the efficiency of this process have to date produced only mediocre yields, however given the thermodynamic unfavorability of the key step, the difficulty in optimization of this reaction is understandable.

^{1}H and ^{13}C NMR spectra were recorded on a Varian 200 MHz or a 400 MHz spectrometer. Chemical shifts are reported in parts per million (δ) downfield from the reference tetramethylsilane. Coupling constants (*J*) are reported in Hertz (Hz). A PerkinElmer 1720X spectrometer was used to record the IR spectra and band positions are reported in reciprocal centimeters (cm^{-1}). Only key diagnostic bands are reported, C–H stretching frequencies in the region 2800–3100 cm^{-1} are not reported. Mass spectra (EI) were obtained at the University of California at Riverside or at the University of Nebraska. Flash column chromatography was performed using thick walled glass columns and 'flash grade' silica gel. TLC was done using precoated 0.25 mm silica gel plates purchased from Sorbtech. The relative proportion of solvents in mixed chromatography solvents refers to the v/v ratio. All commercially available reagents were purchased in reagent grade and used without purification. Et_2O, THF and dioxane were distilled from sodium benzophenone ketyl. All reactions were performed in an inert atmosphere created by a slight positive pressure (ca. 0.1 psi) of N_2.

Carbene Complexes 2a–c; General Procedure 1

To a solution of carbene complex **1a–c** (1 mmol) in Et_2O (20 mL) was added *n*-BuLi (1 mmol) at –78 °C. After 0.5 h, this solution was added to a solution of haloacetonitrile (10 mmol) in THF (20 mL) at 0 °C by means of canula. The mixture was stirred for 2 h at 0 °C. The solvent was removed in a rotary evaporator. Flash column chromatography of the crude product over silica gel gave the product **2a–c**. Complexes **2a–c** were quite unstable and were used within a few hours after purification.

Carbene Complex 2a

General Procedure 1 was followed using carbene complex **1a** (0.400 g, 1.6 mmol), *n*-BuLi (2.9 mL of a 1.4 M hexane solution, 4.0 mmol) and bromoacetonitrile (0.28 mL, 4.0 mmol). Purification using flash chromatography (silica gel, hexane–EtOAc, 3:1) gave carbene complex **2a** (0.400 g, 46%) contaminated with 5–10% of bromoacetonitrile.

IR (neat): 2259, 2066, 1919, 1454 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 4.90 (s, 3 H), 4.50 (quintet, *J* = 6.6 Hz, 1 H), 2.65 (dd, *J* = 17.4, 6.6 Hz, 2 H), 2.58 (dd, *J* = 17.4, 6.6 Hz, 2 H).

^{13}C NMR ($CDCl_3$): δ = 353.9, 222.6, 215.8, 116.5, 69.0, 59.3, 19.3.

Carbene Complex 2b

General Procedure 1 was followed using carbene complex **1b** (0.30 g, 0.92 mmol),[11] *n*-BuLi (0.44 mL of a 1.6 M hexane solution, 0.70 mmol) and bromoacetonitrile (0.85 g, 0.71 mmol). Purification using flash chromatography (silica gel, hexane–EtOAc, 4:1) gave **2b** (0.14 g, 88%) and starting material **1b** (0.16 g).

IR (neat): 2235, 2008, 1883 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 4.70 (s, 3 H), 4.45 (m, 1 H), 2.45–2.78 (m, 4 H), 1.60–1.78 (m, 6 H), 1.25–1.55 (m, 12 H), 0.97 (br t, *J* = 6.8 Hz, 9 H).

^{13}C NMR ($CDCl_3$): δ = 338.6 (d), 222.2, 221.9, 116.8, 64.6, 58.3, 27.8 (d), 25.4, 24.3 (d), 18.8, 13.6.

Carbene Complex 2c

General Procedure 1 was followed using carbene complex **1c** (0.52 g, 1.78 mmol), *n*-BuLi (1.1 mL of a 1.6 M hexane solution, 1.76 mmol) and iodoacetonitrile (0.45 g, 2.67 mmol). Purification using flash chromatography (silica gel, hexane–EtOAc, 9:1) gave **2c** (0.507 g, 87%).

IR (neat): 2240, 2063, 1919 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 4.85 (s, 3 H), 4.22 (m, 1 H), 2.39 (t, *J* = 6.5 Hz, 1 H), 1.2–1.8 (m, 5 H), 0.95 (t, *J* = 6.5 Hz, 3 H).

Carbene Complexes 2d and 6a;[20] General Procedure 2

1. *Dipotassium Pentacarbonylchromate*: Graphite (64 equiv) was heated at 150–160 °C while being stirred under argon for 2 h. The graphite was cooled to r.t. and potassium (8 equiv) was added as tiny pieces under a positive flow of argon. The mixture was heated to 160 °C with stirring for 1 h. THF was added to the bronze colored material and cooled to –78 °C. $Cr(CO)_6$ (3.5 equiv) was then added under a positive flow of argon. The mixture was stirred for 30 min at –78 °C and placed in an ice-bath until a thick slurry of product was formed. This mixture was directly used in the next step.

2. *Tetramethylammonium Salt of the Chromium Carbene Complex*: To the solution of dipotassium pentacarbonylchromate in THF at –78 °C obtained from step 1, the acid chloride (1 equiv) in THF was added dropwise. The resulting mixture was stirred at –78 °C for 15 min, at 0 °C for 1.5 h, and at r.t. for 1 h. The solvent was removed under reduced pressure. Cold H_2O was added to the residue and filtered through Celite. To the filtrate was added a sat. aq solution of Me_4NBr, leading to immediate precipitation of the ammonium salt. The precipitate was removed by extracting the aqueous layer with CH_2Cl_2. The organic layer was then dried (Na_2SO_4) and the solvent removed on a rotary evaporator to give a pale yellow solid.

3. *Alkylation of Tetramethylammonium Acylate Salt*: To a solution of the ammonium salt (1 equiv) in CH_2Cl_2 obtained in step 2, was added methyl triflate (1.2 equiv) at 0 °C. The mixture was then stirred at 0 °C for 0.5 h and at r.t. for 1 h. The mixture was filtered through Celite, washed with sat. aq $NaHCO_3$ solution, H_2O, brine, and dried (Na_2SO_4). The solvent was removed on a rotary evaporator to yield the carbene complex. Purification was done by flash column chromatography using hexane–EtOAc (4:1) as the eluting solvent. Both of these complexes were highly unstable and used within a few hours after purification.

Carbene Complex 2d

General Procedure 2 was followed using dipotassium pentacarbonylchromate [prepared from graphite (2.34 g, 195 mmol), potassium metal (0.95 g, 24.3 mmol), and $Cr(CO)_6$ (2.42 g, 11.0 mmol)], *cis*-2-cyanocyclohexanecarbonyl chloride (0.55 g, 3.2 mmol),[21] and methyl triflate (0.63 g, 3.84 mmol). The crude product was purified by flash chromatography to give **2d** as a dark yellow solid (0.670 g, 61%).

IR (neat): 2264, 2063, 1919 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 4.90 (s, 3 H), 3.96 (m, 1 H), 3.08 (m, 1 H), 1.58–2.20 (m, 6 H), 1.25–2.20 (m, 6 H), 1.25–1.58 (m, 2 H).

^{13}C NMR ($CDCl_3$): δ = 358.3, 215.6, 214.2, 130.8, 69.6, 68.2, 30.6, 29.6, 25.6, 24.8, 22.0.

Carbene Complex 6a

General Procedure 2 was followed using dipotassium pentacarbonylchromate [prepared from graphite (2.34 g, 195 mmol), potassium metal (0.95 g, 24.3 mmol) and $Cr(CO)_6$ (2.42 g, 11.0 mmol)], acid chloride **5a** (0.53 g, 3.2 mmol), and methyl triflate (0.63 g, 3.84 mmol). The crude product was purified by passage through a short silica gel column to give **6a** (0.378 g, 35%) and was immediately used in the next step as it was unstable.

IR (KBr): 2068, 1930 cm^{-1}.

^1H NMR ($CDCl_3$): δ (poorly resolved) = 7.52–7.80 (m, 2 H), 7.30–7.50 (m, 2 H), 4.95 (s, 3 H).

Carbene Complexes 2e and 6b; General Procedure 3

To the solution of dipotassium pentacarbonylchromate (prepared using general procedure 2, step 1) in THF at –78 °C, the amide (1 equiv) in THF was added dropwise. The resultant mixture was stirred at –78 °C for 0.5 h, warmed to 0 °C for 1 h, and cooled to –78 °C. Chlorotrimethylsilane (3 equiv) was then added. After 0.5 h, the mixture was warmed to r.t. Neutral Al_2O_3 (2.5 g/1 mmol of amide) was added to absorb the product, and the solvent was removed under reduced pressure. The resulting dry powder was purified by flash chromatography on a silica gel column using hexane–CH_2Cl_2 (1:1) as eluent.

Carbene Complex 2e

General Procedure 3 was followed using dipotassium pentacarbonylchromate [prepared from graphite (1.78 g, 148 mmol), potassium metal (0.72 g, 18.5 mmol) and $Cr(CO)_6$ (2.42 g, 8.4 mmol)], *cis*-*N*,*N*-dimethyl-2-cyanocyclohexanecarboxamide (0.82 g, 4.55 mmol),[22] and chlorotrimethylsilane (1.50 g, 14.0 mmol). The crude product was purified by flash chromatography to give **2e** (0.650 g, 40%).

IR (neat): 2053, 1903 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 3.98 (s, 3 H), 3.93 (br s, 1), 3.55 (s, 3 H), 3.29 (br s, 1 H), 1.3–2.3 (m, 8 H).

^{13}C NMR ($CDCl_3$): δ = 280.0, 217.2, 213.8, 131.1, 62.0, 56.1, 46.7, 31.7, 31.3, 28.2, 26.2, 22.3.

Carbene Complex 6b

General Procedure 3 was followed using dipotassium pentacarbonylchromate [prepared from graphite (2.34 g, 195 mmol), potassium metal (0.95 g, 24.3 mmol) and $Cr(CO)_6$ (2.42 g, 11.0 mmol)], amide **5b**[23] (1.04 g, 6.0 mmol) and chlorotrimethylsilane (1.95 g, 18.0 mmol). The crude product was purified by flash chromatography to give **6b** (1.35 g, 64%).

IR (neat): 2057, 1918 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 7.55–7.78 (m, 2 H), 7.34 (d, *J* = 8 Hz, 1 H), 6.95 (d, *J* = 8 Hz, 1 H), 4.13 (s, 3 H), 3.19 (s, 3 H).

^{13}C NMR ($CDCl_3$): δ = 272.3, 216.1, 213.8, 154.7, 134.0, 133.0, 126.7, 121.4, 100.6, 51.4, 46.4.

Coupling of β-Cyanocarbene Complexes 2 or 6 with *o*-Alkynylbenzoyl Derivatives 7; General Procedure 4

To a refluxing solution of *o*-alkynylbenzoyl derivative **7** (1 equiv) in dioxane (10 mL) under argon was added dropwise a 0.05 M solution of carbene complex **2** or **6** (1.1 equiv) in dioxane over a 2 h period. After the addition was complete, the mixture was allowed to reflux for a period of 16–24 h. The mixture was cooled to r.t. and concentrated on a rotary evaporator. EtOAc (25 mL) was added and the residue was filtered through Celite. The solvent was removed on a rotary evaporator and the crude products were purified by flash column chromatography.

Coupling of Carbene Complex 2a with 2-hex-1-ynylbenzaldehyde (7a) (Table 1, Entry A)

General Procedure 4 was followed using carbene complex **2a** (100 mg, 0.30 mmol) and 2-hex-1-ynylbenzaldehyde (**7a**;[24] 60 mg, 0.32 mmol). The crude product was purified using flash chromatography on silica gel with hexane–EtOAc (1:1) as eluent to yield products **10a** (36 mg, 40%), **11** (29 mg, 36%), and a compound tentatively identified as enol ether **12** (5 mg, 13%, yield varies widely between experimental runs).

10a

IR (neat): 2239, 1615, 1551 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 8.99 (s, 1 H), 8.09 (d, *J* = 8.4 Hz, 1 H), 7.94 (d, *J* = 8.4 Hz, 1 H), 7.67 (t, *J* = 7.5 Hz, 1 H), 7.55 (t, *J* = 7.5 Hz, 1 H), 3.84 (s, 3 H), 3.45 (m, 1 H), 3.00–3.30 (m, 2 H), 2.65–3.00 (m, 2 H), 2.18–2.5 (m, 2 H), 1.10–1.50 (m, 4 H), 0.80 (t, *J* = 7 Hz, 3 H).

^{13}C NMR ($CDCl_3$): δ = 156.8, 148.4, 144.6, 133.0, 130.5, 128.8, 128.3, 126.7, 124.5, 118.4, 118.1, 58.1, 36.6, 31.0, 30.4, 28.2, 22.5, 18.8, 13.7.

MS: *m*/*z* (%) = 307 (M^+ + 1, 13), 306 (M^+, 55), 291 ($M^+ - CH_3$, 10), 266 (45), 210 (100), 180 (21), 167 (24).

HRMS: *m*/*z* calcd for $C_{20}H_{22}N_2O$: 306.17322; found: 306.17373.

11

IR (neat): 2957, 2871, 1616, 1495 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 9.10 (br s, 1 H), 8.69 (d, *J* = 8.4 Hz, 1 H), 8.12 (d, *J* = 9.0 Hz, 1 H), 8.04 (d, *J* = 7.7 Hz, 1 H), 7.84 (t, *J* = 7.3 Hz, 1 H), 7.71 (t, *J* = 7.3 Hz, 1 H), 7.44 (d, *J* = 9.0 Hz, 1 H), 4.01 (s, 3 H), 3.35 (t, *J* = 8.0 Hz, 2 H), 1.75–1.98 (m, 2 H), 1.50–1.75 (m, 2 H), 1.09 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR ($CDCl_3$): δ = 157.1, 150.8, 139.8, 133.2, 130.3, 129.2, 128.8, 127.3, 127.0, 126.6, 113.3, 56.4, 30.8, 28.2, 23.2, 13.9.

MS: *m*/*z* (%) = 267 (M^+ + 2, 6), 266 (M^+ + 1, 26), 265 (M^+, 54), 222 (100), 206 (5), 191 (7), 179 (29), 152 (7).

HRMS: *m*/*z* calcd for $C_{18}H_{19}NO$: 265.146664; found: 265.145879.

12[25]

IR (neat): 2248 (m), 1652 (s) cm^{-1}.

^1H NMR ($CDCl_3$): δ = 6.40 (br s, 1 H), 3.73 (s, 3 H), 3.28 (s, 2 H), 3.14 (s, 2 H).

Coupling of Carbene Complex 2b with 2-Hex-1-ynylbenzaldehyde (7a) (Entry B)

General Procedure 4 was followed using carbene complex **2b** (0.165 g, 0.33 mmol) and 2-hex-1-ynylbenzaldehyde (**7a**;[24] 0.056 g, 0.30 mmol). The crude product was purified using flash chromatography on silica gel with hexane–EtOAc (1:1) as eluent to yield products **10a** (0.044 g, 48%) and **11** (0.015 g, 19%).

Coupling of Carbene Complex 2c with 2-Hex-1-ynylbenzaldehyde (7a) (Entry C)

General Procedure 4 was followed using carbene complex **2c** (0.150 g, 0.45 mmol) and 2-hex-1-ynylbenzaldehyde (**7a**;[24] 0.075 g, 0.40 mmol). In this experiment Ph_3P (0.118 g, 0.45 mmol) was added and toluene was used as the solvent (in place of dioxane). The crude product was purified using flash chromatography on silica gel using hexane–EtOAc (4:1) as eluent to yield product **14c** (0.065 g, 53%).

IR (neat): 2958, 2871, 1591, 1446 cm^{-1}.

^1H NMR ($CDCl_3$): δ = 9.15 (s, 1 H), 8.71 (d, *J* = 8 Hz, 1 H), 8.04 (d, *J* = 8.0 Hz, 1 H), 7.96 (s, 1 H), 7.83 (t, *J* = 7.7 Hz, 1 H), 7.68 (t, *J* = 7.7 Hz, 1 H), 3.85 (s, 3 H), 3.43 (t, *J* = 8.0 Hz, 2 H), 2.87 (t, *J* = 7.7 Hz, 2 H), 1.70–1.93 (m, 4 H), 1.52–1.70 (m, 2 H), 1.05 (t, *J* = 7.3 Hz, 3 H), 1.03 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR ($CDCl_3$): δ = 156.8, 152.4, 142.8, 137.3, 133.3, 132.4, 130.3, 129.5, 129.3, 127.3, 126.5, 126.0, 122.4, 61.6, 32.4, 31.8, 28.7, 23.2 (2 C), 14.2, 13.9.

MS: *m*/*z* (%) = 309 (M^+ + 2, 3), 308 (M^+ + 1, 20), 307 (M^+, 59), 292 (M^+ – CH_3, 4), 264 (100), 234 (16), 222 (9), 204 (9), 192 (13), 165 (5).

HRMS: *m*/*z* calcd for $C_{21}H_{25}NO$: 307.193615; found: 307.194478.

Coupling of Carbene Complex 2c with 2-Ethynylbenzaldehyde (7d) (Entry D)

General Procedure 4 was followed using carbene complex **2c** (0.345 g, 1.0 mmol) and 2-ethynylbenzaldehyde (**7d**;[26] 0.117 g, 0.90 mmol). The crude product was purified using flash chromatography on silica gel with hexane–EtOAc (4:1) as eluent to yield product **10d** (0.050 g, 21%).

IR (neat): 2933, 1634 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 8.97 (s, 1 H), 8.01 (d, *J* = 8.0 Hz, 1 H), 7.92 (d, *J* = 8.0 Hz, 1 H), 7.68 (t, *J* = 7.5 Hz, 1 H), 7.53 (t, *J* = 7.5 Hz, 1 H), 6.08 (s, 1 H), 3.57 (s, 3 H), 3.45 (br s, 1 H, line width at half height = 15 Hz), 2.84 (m, 1 H, line width at half height = 12 Hz), 2.28 (m, 1 H), 1.35–1.90 (m, 7 H).

The *cis* stereochemistry was assigned based on the relatively narrow line widths for the ring junction protons at δ = 3.45 and 2.84. In the *trans*-isomer, these protons would be axial and would couple to two other axial protons, and should feature much wider and discernable patterns.

^{13}C NMR ($CDCl_3$): δ = 164.8, 146.1, 131.8, 130.3, 128.4, 127.3, 126.4, 124.5, 122.0, 89.1, 55.3, 41.8, 39.4, 26.4, 25.2, 24.1, 23.9.

MS: *m*/*z* (%) = 266 (M^+ + 1, 18), 265 (M^+, 99), 264 (27), 263 (M^+ – H_2, 100), 248 (40), 236 (27), 234 (27), 222 (35), 210 (99), 192 (36), 180 (16), 166 (29).

HRMS: *m*/*z* calcd for $C_{18}H_{19}NO$: 265.146664; found: 265.145504.

Coupling of Carbene Complex 2e with 2-Ethynylbenzaldehyde (7d) (Entry E)

General Procedure 4 was followed using carbene complex **2e** (0.355 g, 1.0 mmol) and 2-ethynylbenzaldehyde (**7d**;[26] 0.116 g, 0.89 mmol). In this experiment Ph_3P (0.262 g, 1.0 mmol) and toluene was used as the solvent (in place of dioxane). The crude product was purified using flash chromatography on silica gel with hexane–EtOAc (1:1) as eluent to yield product **13e** (0.095 g, 42%).

IR (neat): 2933, 1713, 1623 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 9.16 (s, 1 H), 7.10 (d, *J* = 7.7 Hz, 1 H), 7.70–7.85 (m, 2 H), 7.61 (m, 1 H), 4.02 (d, *J* = 21.8 Hz, 1 H), 3.76 (d, *J* = 21.8 Hz, 1 H), 3.49 (ddd, *J* = 10.7, 5.0, 3.8 Hz, 1 H), 3.06 (br s, 1 H, line width at half height = 10 Hz), 2.44 (m, 1 H), 2.07 (m, 1 H), 1.79 (m, 1 H), 1.40–1.70 (m, 4 H), 1.25 (m, 1 H).

The *cis* stereochemistry was assigned based on the appearance of the ring junction protons at δ = 3.49 (ddd, *J* = 10.7, 5.0, 3.8 Hz), and δ = 3.06 (br s, line width at half height = 10 Hz). In the *trans* isomer, these protons would be axial and would couple to two other axial protons, and should feature much wider and discernable patterns. The pattern at δ = 3.49 is consistent with an axial proton coupled to one other axial proton and two equatorial protons, as expected in the *cis* isomer. The pattern at δ = 3.06 is consistent with contribution from multiple small couplings, as expected for an equatorial proton.

^{13}C NMR ($CDCl_3$): δ = 209.4, 152.6, 151.4, 134.7, 131.0, 128.5, 127.1, 126.8, 121.8, 120.4, 48.1, 45.8, 38.7, 31.8, 26.0, 24.4, 22.0.

MS: *m*/*z* (%) = 252 (M^+ + 1, 23), 251 (M^+, 100), 234 (5), 222 (38), 208 (15), 196 (97), 180 (49), 167 (41), 152 (15), 115 (19).

HRMS: *m*/*z* calcd for $C_{17}H_{17}NO$: 251.131014; found: 251.130288.

Coupling of Carbene Complex 2d with 1-(2-Hex-1-ynylphenyl)ethanone (7b) (Entry F)

General Procedure 4 was followed using carbene complex **2d** (0.10 g, 0.29 mmol) and 1-(2-hex-1-ynylphenyl)ethanone (**7b**;[27] 0.052 g, 0.26 mmol). The crude product was purified using flash chromatography over silica gel with hexane–EtOAc (1:1) as eluent to yield product **10f** (0.035 g, 40%).

IR (neat): 2930, 1627 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 8.07 (d, *J* = 8.0 Hz, 2 H), 7.40–7.60 (m, 2 H), 3.75 (s, 3 H), 3.20 (m, 1 H), 2.93 (s, 3 H), 2.55–2.92 (m, 3 H), 1.10–1.60 (m, 12 H), 0.77 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$): δ = 159.4, 154.3, 149.6, 133.1, 128.6, 128.1, 126.3, 125.9, 125.2, 125.1, 116.5, 57.6, 41.8, 36.4, 31.0, 28.2, 26.3, 25.8, 24.8, 22.8, 22.7, 22.3, 13.8.

MS: *m*/*z* (%) = 337 (M^+ + 2, 2), 336 (M^+ + 1, 26), 335 (M^+, 100), 320 (M^+ – CH_3, 31), 306 (M^+ – C_2H_5, 9), 292 (35), 280 (22), 262 (10), 224 (10), 145 (15).

HRMS: *m*/*z* calcd for $C_{23}H_{29}NO$: 335.224.915; found: 335.225687.

Coupling of Carbene Complex 2c with Alkynylbenzamide 7e (Entry I)

General Procedure 4 was followed using carbene complex **1c** (0.485 g, 1.32 mmol) and alkynylbenzamide **7e**[28] (0.245 g, 1.00 mmol). The crude product was purified using hexane–EtOAc (4:1) as the eluent to yield the highly fluorescent product **14i** (0.135 g, 37%). Two additional nonfluorescent compounds were also isolated (total 0.160 g, 43%) and assigned as isomers of **18**; a small amount of the slowest-running compound was isomerically pure.

14i

IR (neat): 1579 (m) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 8.57 (d, *J* = 8.8 Hz, 1 H), 8.21 (dd, *J* = 8.8, 1.8 Hz, 1 H), 7.68 (td, *J* = 8.8, 1.8 Hz, 1 H), 7.63 (s, 1 H), 7.55 (td, *J* = 8.8, 1.8 Hz, 1 H), 3.80 (s, 3 H), 3.34 (t, *J* = 7.8 Hz, 2 H), 3.10 (s, 6 H), 2.78 (t, *J* = 7.6 Hz, 2 H), 1.77 (m, 4 H), 1.57 (m, 2 H), 1.03 (t, *J* = 7.4 Hz, 3 H), 1.01 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR ($CDCl_3$): δ = 159.7, 154.7, 141.8, 136.8, 135.8, 131.4, 128.9, 127.3, 127.1, 126.4, 125.5, 121.8, 120.7, 61.5, 42.5, 32.4, 31.7, 28.9, 23.6, 23.3, 14.3, 13.9.

MS: *m*/*z* (%) = 350 (M^+, 100), 335 (38), 321 (24).

HRMS: *m*/*z* calcd for $C_{23}H_{30}N_2O$: 350.23581; found: 350. 23678.

18

IR (neat): 2246 (m), 1640 (s) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 7.40–7.15 (m, 4 H), 6.42 (s, 1 H), 3.44 (s, 3 H), 3.21 (s, 2 H), 3.03 (s, 3 H), 2.81 (s, 3 H), 2.30–2.15 (m, 4 H), 1.55–1.20 (m, 6 H), 0.91 (t, *J* = 7.0 Hz, 3 H), 0.82 (t, *J* = 7.8 Hz, 3 H).

^{13}C NMR ($CDCl_3$): δ = 170.6, 154.6, 137.5, 136.7, 133.4, 130.7, 129.1, 128.5, 127.5, 126.1, 118.7, 111.6, 56.3, 38.5, 34.6, 32.9, 30.1, 29.5, 22.8, 21.6, 16.6, 14.1, 13.7.

Coupling of Carbene Complex 6a with 2-Hex-1-ynylbenzaldehyde (7a) (Entry J)

General Procedure 4 was followed using carbene complex **6a** (0.385 g, 1.10 mmol) and 2-hex-1-ynylbenzaldehyde (**7a**;[24] 0.186 g, 1.0 mmol). The crude product was purified using flash chromatography on silica gel with hexane–EtOAc (9:1) as eluent to yield product **15j** (0.130 g, 40%).

IR (neat): 1615 (m), 1590 (m), 1519 (m), 146 (m) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 9.61 (overlapping s and d, *J* = 8.0 Hz), 8.84 (d, *J* = 8.5 Hz, 1 H), 8.21 (t, *J* = 7.7 Hz, 2 H), 8.00 (t, *J* = 7.4 Hz, 1

H), 7.82 (m, 3 H), 4.00 (s, 3 H), 3.51 (t, *J* = 8.1, 2 H), 1.88 (m, 2 H), 1.62 (sextet, *J* = 7.3 Hz, 2 H), 1.03 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR ($CDCl_3$): δ = 154.7, 150.1, 133.7, 130.5, 129.3, 127.8, 127.6, 127.3, 126.8, 126.1, 125.3, 121.9, 61.8, 31.7, 28.7, 23.0, 13.7.

MS: *m*/*z* = 315 (M^+, 70), 272 ($M^+ - C_3H_7$, 100), 229 (29), 185 (19), 316 (21).

HRMS: *m*/*z* calcd for $C_{22}H_{21}NO$: 315.16232; found: 315.16012.

Coupling of Carbene Complex 6b with 2-Hex-1-ynylbenzaldehyde (7a) (Entry K)

General Procedure 4 was followed using carbene complex **6b** (0.385 g, 1.10 mmol) and 2-hex-1-ynylbenzaldehyde (**7a**;[24] 0.186 g, 1.0 mmol). The crude product was purified using flash chromatography on silica gel with hexane–EtOAc (9:1) as eluent to yield product **15k** (0.130 g, 40%).

IR (neat): 2915, 1940, 1615, 1379 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 9.44 (m, 1 H), 9.38 (s, 1 H), 8.79 (d, *J* = 8.4 Hz, 1 H), 8.03–8.20 (m, 2 H), 7.60–7.84 (m, 4 H), 3.53 (t, *J* = 7.8 Hz, 2 H), 3.19 (s, 6 H), 1.55–1.75 (m, 2 H), 1.25–1.50 (m, 2 H), 0.91 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR ($CDCl_3$): δ = 151.0, 147.9, 141.2, 135.1, 133.6, 132.5, 132.3, 129.4, 128.6, 127.7, 127.1, 126.4, 126.3, 125.9, 125.7, 124.3, 122.6, 44.3 (2 C), 32.1 (2 C), 23.1, 13.9.

MS: *m*/*z* (%) = 330 (M^+ + 2, 4), 329 (M^+ + 1, 26), 328 (M^+, 86), 313 ($M^+ - CH_3$, 8), 286 (22), 285 (100), 271 (85), 269 (53), 254 (10), 241 (16), 215 (6), 142 (13).

HRMS: *m*/*z* calcd for $C_{23}H_{24}N_2$: 328.193949; found: 328.193884.

Coupling of Carbene Complex 6b with (2-Hex-1-ynylphenyl)phenylmethanone (7c)[29] (Entry L)

General Procedure 4 was followed using carbene complex **6b** (0.088 g, 0.25 mmol) and (2-hex-1-ynylphenyl)phenylmethanone (**2c**; 0.055 g, 0.21 mmol). The crude product was purified using flash chromatography on silica gel with hexane–EtOAc (3:1) as eluent to yield product **15l** (0.051 g, 60%).

IR (neat): 2957, 1940, 1574, 1377 cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 9.50 (m, 1 H), 8.82 (d, *J* = 8.0 Hz, 1 H), 8.29 (d, *J* = 8.0 Hz, 1 H), 8.16 (m, 1 H), 8.02 (d, *J* = 8.0 Hz, 1 H), 7.50–7.85 (m, 8 H), 3.56 (t, *J* = 7.5 Hz, 2 H), 3.23 (s, 6 H), 1.55–1.80 (m, 2 H), 1.25–1.50 (m, 2 H), 0.93 (t, *J* = 7.3 Hz, 3 H).

^{13}C NMR ($CDCl_3$): δ = 157.9, 148.0, 140.2, 140.0, 134.8, 133.9, 132.6, 132.4, 130.4 (2 C), 128.6, 128.5, 128.2 (3 C), 127.0, 126.7, 126.0, 125.9, 125.8, 125.7, 124.3, 122.1, 44.4 (2 C), 32.4, 32.2, 23.2, 13.9.

MS: *m*/*z* = 406 (M^+ + 2, 3), 405 (M^+ + 1, 24), 404 (M^+, 80), 389 ($M^+ - CH_3$, 7), 361 (94), 347 (100), 331 (18), 316 (9), 172 (21).

HRMS: *m*/*z* calcd for $C_{29}H_{28}N_2$: 404.225249; found: 404.226090.

Computational Details

All compounds were built using the Gausview program. These structures were then subjected to geometry optimization followed by frequency calculation using the Gaussian03 program.[30] All calculations were performed at the B3LYP level using the 6-31G* basis set. A frequency calculation (also at the B3LYP level using the 6-31G* basis set) was performed on the geometry-optimized structures. All reaction energies refer to interconversion of energy minimum conformations.

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