Coupling of Fischer Carbene Complexes with *o*-Alkynylbenzamides

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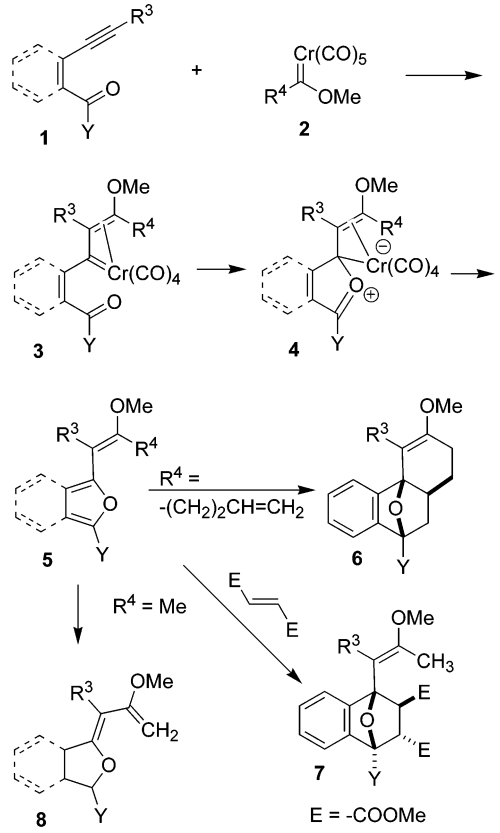
Received May 27, 2003

The coupling of 2-alkynylbenzamide derivatives with carbene complexes has been examined for systems that contain remote alkene functionality tethered either to the starting carbene complex or to the nitrogen of the amide. In most cases the reaction proceeds via alkyne insertion, followed by isobenzofuran formation, followed by intramolecular Diels−Alder reaction, followed by dehydration to afford aminonaphthalene derivatives. In examples using carbene complex tethered alkenes, intramolecular cyclopropanation is a competing reaction process.

Introduction

In a recent series of papers, the generation of furans[1] and isobenzofurans[2] from the coupling of Fischer carbene complexes with enyne-aldehydes or enyne-ketones was demonstrated (Scheme 1). Non-benzo analogues of **1** afford stable furan derivatives (e.g., **5**, no benzo fusion). Benzo analogues of **1** afford isobenzofurans (e.g., **5**, benzo fusion), which are unstable but readily undergo inter- and intramolecular Diels−Alder reactions when suitable dienophiles are present.[2] In the absence of a dienophile, a net 1,7-hydrogen shift process occurs to afford the alkylidenephthalan derivatives (e.g., **8**). Numerous examples of these processes featuring both terminal and internal alkynes have been demonstrated. Analogues that differ in the carbonyl group functionality (i.e., Y ≠ H, alkyl, or aryl) have been considerably less well studied. In an earlier publication,[1] failure of an ester analogue (Y = OMe) to form an alkoxyfuran was noted. Similar attempts to generate isobenzofurans from 2-alkynyl benzoates have also failed. Other examples in the literature note that new C−O bonds do not from in the reaction of Fischer carbene complexes and γ,δ-alkyne-esters.[3] In the formation of carbonyl ylides from rhodium carbenoids, a lower degree of success was noted for ester derivatives.[4] This affect can likely be attributed to the lesser nucleophilicity of the ester carbonyl group relative to a ketone/aldehyde carbonyl group,[5] or to an equilibrium process favoring the more stable ester carbonyl group over the isobenzofuran.[6]

Scheme 1



On the basis of these observations, the isobenzofuran-forming process is more likely to be successful if more nucleophilic carbonyl derivatives are employed. The work in this article focuses on the tandem coupling of 2-alkynylbenzamide derivatives (**1**, Y = NR_2, or **11**, Scheme 2) and carbene complexes followed by intramolecular Diels−Alder reaction. Amide carbonyls will afford aminoisobenzofurans, which can then undergo intramolecular Diels−Alder reactions with appended dienophiles.[7]

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(1) Herndon, J. W.; Wang, H. *J. Org. Chem.* **1998**, *63*, 4564−4565.

(2) (a) Ghorai, B. K.; Menon, S.; Johnson, D. L.; Herndon, J. W. *Org. Lett.* **2002**, *4*, 2121−2124. (b) Ghorai, B. K.; Herndon, J. W. *Org. Lett.* **2001**, *3*, 3535−3538. (c) Jiang, D.; Herndon, J. W. *Org. Lett.* **2000**, *2*, 1267−1269.

(3) (a) Wulff, W. D.; McCallum, J. S.; Kunng, F. A. *J. Am. Chem. Soc.* **1988**, *110*, 7419−7434. (b) Anderson, J. C.; Cran, J. W.; King, N. P. *Tetrahedron Lett.* **2002**, *43*, 3849−3852.

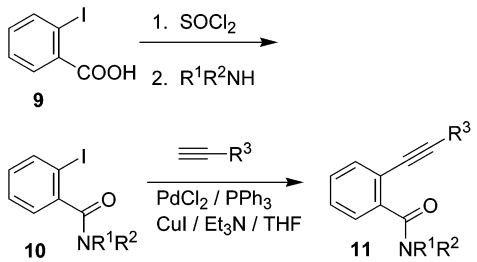
(4) There are numerous examples of successful formation of carbonyl ylides from diazo compounds that contain pendant esters; however formation of a carbonyl ylide from a pendant ketone is easier than from an ester. Padwa, A.; Hornbuckle, S. F.; Fryxell, G. E.; Stull, P. D. *J. Org. Chem.* **1989**, *54*, 817−824.

(5) Gal, J. F.; Elegant, L.; Azzaro, M. *Bull. Soc. Chim. Fr.* **1974**, 411−414.

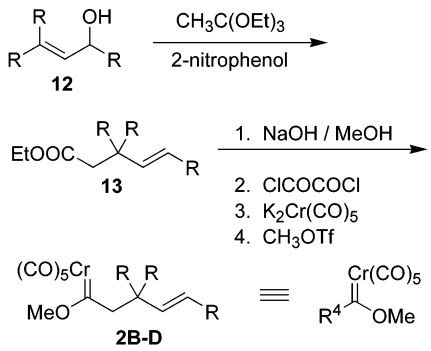
(6) For a review of isobenzofurans, see: Friedrichsen, W. *Adv. Heterocycl. Chem.* **1999**, *73*, 1−96.

10.1021/om030383k CCC: $25.00
Publication on Web 08/14/2003

Scheme 2



Scheme 3



Results and Discussion

The general synthetic route to 2-alkynylbenzamide derivatives (**11**) is depicted in Scheme 2. This process involves conversion of commercially available 2-iodobenzoic acid (**9**) to the acid chloride, followed by reaction with a secondary amine to afford the amide, and then Sonogashira coupling[8] to afford the desired 2-alkynylbenzamide. The γ,δ-unsaturated carbene complexes employed in this study were prepared from allylic alcohols using the sequence depicted in Scheme 3. Ortho ester Claisen rearrangement, followed by hydrolysis of the ester and conversion to the acid chloride, followed by treatment with dipotassium pentacarboylchromate[9] affords the carbene complexes.

In the first phase of the studies, tandem carbene coupling−intramolecular Diels−Alder reactions were examined for systems where the dienophile is tethered to the carbene complex. Coupling of carbene complex **2B** with alkyne **11A** led to a mixture of the aminonaphthalene derivative **14A** and cyclopropane derivative **16A** (Scheme 4). This reaction pathway was general (Table 2), and in all cases this type of coupling led to mixtures of isobenzofuran-Diels−Alder adducts (naphthalene **14** or diketone **15**) and cyclopropane derivatives **16**. In the case of 1,2-disubstituted alkene **2D** the major Diels−Alder product was diketone **15C**. The reaction was also attempted in the presence of dirhodium tetraacetate to determine if alterations in the cyclopropane−aminonaphthalene ratio could be effected;[10] however the only effect was a slight yield increase. The optimal solvent for the reaction in Scheme 4 was toluene, which leads to the formation of (toluene)Cr(CO)$_3$ as a byproduct. To simplify purification, all of the crude reaction mixtures were treated with aqueous hydrochloric acid, and amine-containing products were separated out by acid extraction techniques.

Scheme 4

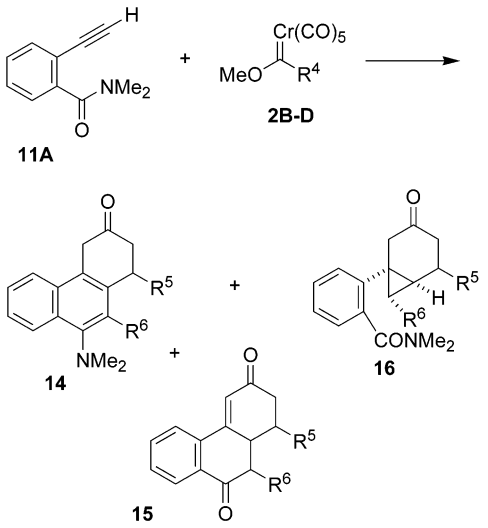


Table 1. Correlation between Substituent Letters and Substituents for Alkyne-amides 11 and Carbene Complexes 2

amides **11**	carbene complexes **2**
A R^1, R^2 = Me, R^3 = H	**A** R^4 = Me
B R^1 = Bn, R^2 = $-(CH_2)_2CH{=}CH_2$, R^3 = H	**B** R^4 = $-(CH_2)_2CH{=}CH_2$
C R^1 = Bn, R^2 = $-(CH_2)_2CH{=}CH_2$, R^3 = Bu	**C** R^4 = $-CH_2CH(Ph)CH{=}CH_2$
D R^1 = Bn, R^2 = $-(CH_2)_3CH{=}CH_2$, R^3 = H	**D** R^4 = $-(CH_2)_2CH{=}CHCH_3$
E R^1 = Bn, R^2 = $-(CH_2)_3CH{=}CH_2$, R^3 = Bu	**E** R^4 = $-CH_2C(CH_3)_2CH{=}CH_2$

Formation of the products in Scheme 4 most likely occurs via the reaction pathway in Scheme 5. Initial coupling affords the vinylcarbene complex **17**, which undergoes either ylide formation to afford the isobenzofuran intermediate **19** or intramolecular cyclopropanation to afford the cyclopropane. Formation of bicyclo[4.1.0]heptane derivatives from γ,δ-unsaturated carbene complexes and simple alkynes is a known process.[11] The formation of cyclopropane derivatives appears to be relatively independent of the alkene substitution pattern.[12] The Diels−Alder reaction should initially provide

(7) (a) Bernab, P.; Castedo, L.; Dominguez, D. *Tetrahedron Lett.* **1998**, *39*, 9785−9788. (b) Peters, O.; Debaerdemaeker, T.; Friedrichsen, W. *J. Chem. Soc., Perkin Trans. 1* **1999**, 59−70. (c) Kappe, C. O.; Cochran, J. E.; Padwa, A. *Tetrahedron Lett.* **1995**, *36*, 9285−9288. (d) Beak, P.; Chen, C. W. *Tetrahedron Lett.* **1983**, *24*, 2945−2948. (e) Sarkar, T. K.; Basak, S.; Panda, N. *Tetrahedron Lett.* **2002**, *43*, 1341−1344. (f) Sarkar, T. K.; Ghosh, S. K.; Chow, T. J. *J. Org. Chem.* **2000**, *65*, 3111−3115. (g) Sarkar, T. K.; Basak, S.; Ghosh, S. K. *Tetrahedron Lett.* **2000**, *41*, 759−762.

(8) Thorand, S.; Krause, N. *J. Org. Chem.* **1998**, *63*, 8551−8553.

(9) For pioneering work in the development of this approach to carbene complex synthesis, see: (a) Semmelhack, M. F.; Lee, G. R. *Organometallics* **1987**, *6*, 1839−44. (b) Schwindt, M. A.; Lejon, T.; Hegedus, L. S. *Organometallics* **1990**, *9*, 2814−2819.

(10) This idea was inspired by recent successes in transferring the carbene unit of Fischer carbene complexes to other metals. (a) Sierra, M. A.; del Amo, J. C.; Mancheño, M. J.; Gómez-Gallego, M. *J. Am. Chem. Soc.* **2001**, *123*, 851−861. (b) Sierra, M. A.; del Amo, J. C.; Mancheno, M. J.; Gomez-Gallego, M.; Torres, M. R. *Chem. Commun.* **2002**, 1842−1843. (c) Goettker-Schnetmann, I.; Aumann, R.; Bergander, K. *Organometallics* **2001**, *20*, 3574−3581. (d) Goettker-Schnetmann, I.; Aumann, R. *Organometallics* **2001**, *20*, 346−354. (e) Barluenga, J.; Lopez, L. A.; Lober, O.; Tomas, M.; Garcia-Granda, S.; Alvarez-Rua, C.; Borge, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 3392−3394.

(11) Hoye, T. R.; Vyvyan, J. R. *J. Org. Chem.* **1995**, *60*, 4184−4195.

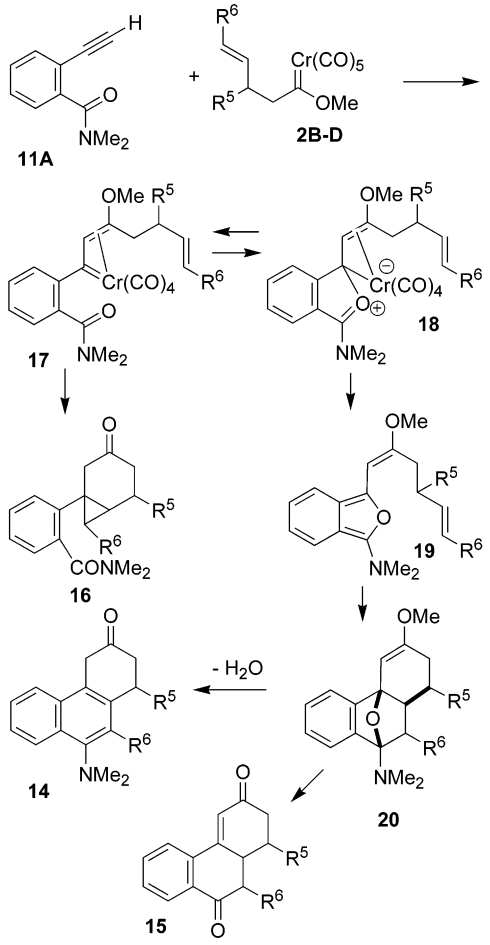
(12) We are not aware of an exhaustive study of the relative reactivity; however in a study of intramolecular cyclopropanation by chromium carbene complexes, all alkene substitution patterns appear to be tolerated. Soderberg, B. C.; Hegedus, L. S. *Organometallics* **1990**, *9*, 3113−3121.

Table 2. Coupling of 2-Alkynylbenzamide 11A with γ,δ-Unsaturated Carbene Complexes 2B−D

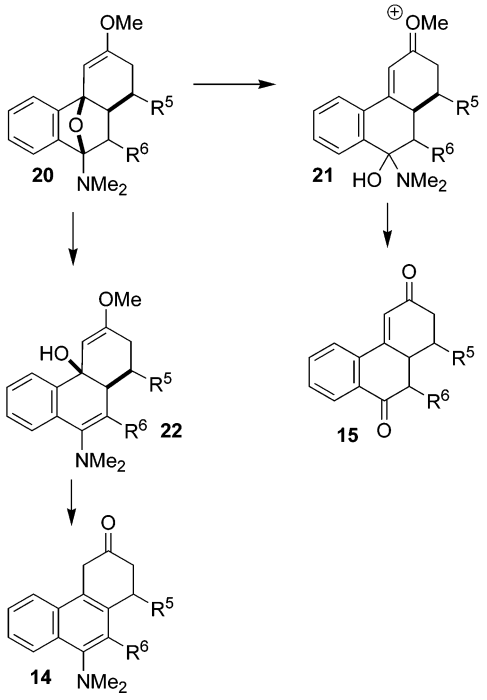
entry[a]	carbene complex	R_5	R_6	conditions[b]	aminonaphthalene **14**	diketone **15**	cyclopropane**16**
A	**2B**	H	H	I	20		10
A′	**2B**	H	H	II	29		10
B	**2C**	Ph	H	I	20		10[c]
B′	**2C**	Ph	H	II	32		7[c]
C	**2D**	H	Me	I	2	40	8
C′	**2D**	H	Me	II	6	42	8

[a] There is a correlation between Table 2 entry letters and substituent letters for compounds **14**−**22**. [b] Conditions I: toluene, 110° C, 40 h, then HCl (1:2); conditions II: $Rh_2(OAc)_4$ (5 mol %), toluene, 110° C, 40 h, then HCl (1:2). [c] A single diastereomer (unassigned) was obtained.

Scheme 5



Scheme 6



the bridged structure **20**;[13] however in all of the examples tested this intermediate rapidly undergoes dehydration to afford the aminonaphthalene ring system **14** or diketone **15**. Even in the absence of the acid workup, no products featuring an intact oxygen bridge were observed. Formation of diketone **15** is unique to the case where $R^6 \neq H$.

Formation of **14** versus **15** might be related to the timing of events in the cleavage of the oxygen bridge (Scheme 6). The diketone is reminiscent of the products obtained from aldehyde/ketone analogues of amide **11A**[2a,b] and might result from initial C−O cleavage at the allylic position followed by hydrolysis of the resulting oxonium salt **21**, as was proposed for those cases. Formation of the aminonaphthalene may involve cleavage adjacent to nitrogen, and aminonaphthalene formation would thus occur through enamine **22**.[14] Conformational preferences may account for the preferential formation of **15** from derivatives where $R^6 \neq H$. Overlap of the nitrogen lone pair with the oxaborbornene C−O bond is difficult due to steric interaction between R^6 and the nitrogen methyls, which forces the oxanorbornene ring to initially cleave at the allylic position rather than adjacent to nitrogen.

The competing cyclopropanation process was not observed to any extent in the coupling of γ,δ-unsaturated carbene complexes with aldehyde/ketone analogues of **11**,[2a,b] and the total yield of Diels−Alder adducts was universally higher in those cases. Three scenarios can likely explain this reactivity difference: (1) aldehyde/ketone carbonyl groups are more reactive in the isobenzofuran-forming step than the amide carbonyl groups, (2) nucleophilic addition of the amide carbonyl to the carbene complex is reversible and equilibrium favors the free amide (e.g., **17**) over the carbonyl ylide (e.g., **18**),[15] or (3) nucleophilic addition of the amide carbonyl to the

(13) The exo Diels−Alder adduct has been depicted and is anticipated on the basis of literature precedent. (a) Meegalla, S. K.; Rodrigo, R. *Synthesis* **1989**, 942−944. (b) Yamaguchi, Y.; Yamada, H.; Hayakawa, K.; Kanematsu, K. *J. Org. Chem.* **1987**, *52*, 2040−2046. (c) Tobia, D.; Rickborn, B. *J. Org. Chem.* **1987**, *52*, 2611−2615.

(14) Related Diels−Alder reactions have produced mixtures of **22** and **14**. (a) Chen, C. W.; Beak, P. *J. Org. Chem.* **1986**, *51*, 3325−3334. (b) Peters, O.; Friedrichsen, W. *Tetrahedron Lett.* **1995**, *36*, 8581−8582.

(15) The amide carbonyl group is more stable than the aldehyde or ketone carbonyl group. Wiberg, K. B.; Hadad, C. M.; Rablen, P. R.; Cioslowski, J. *J. Am. Chem. Soc.* **1992**, *114*, 8644−8654.

Scheme 7

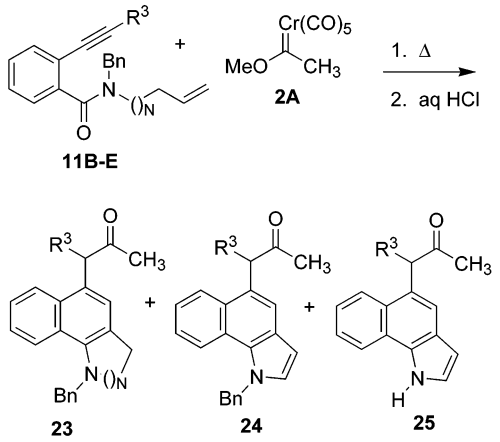


Table 3. Coupling of Nitrogen-Tethered Amide/ Alkenes 11B−E with Methylcarbene Complex 2A

entry[a,b]	*N*	R^3	yield **23**	yield **24**	yield **25**
A	1	H	46	9	
B	1	*n*-Bu		45	22
C	2	H	20		
D	2	*n*-Bu	55		

[a] There is a correlation between Table 2 entry letters and substituent letters for compounds **23**−**25**. [b] All yields are isolated yields.

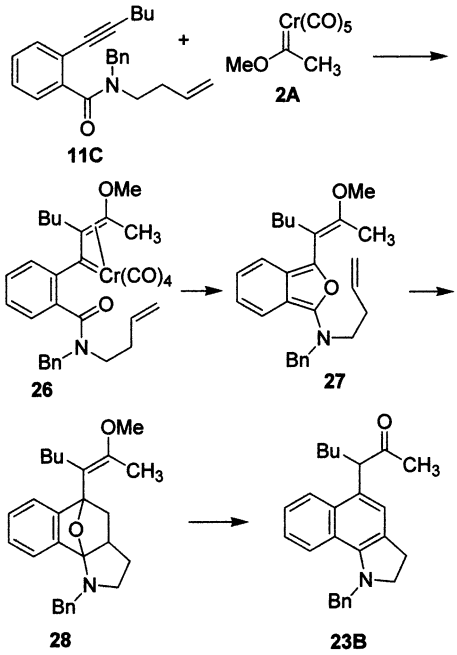
carbene complex is reversible and the Diels−Alder step is less efficient for aminoisobenzofurans. Since amide carbonyl groups are more basic than ketone carbonyl groups,[16] scenario 1 is less likely.

Analogous studies where the dienophile is tethered to the carbonyl group through the amide nitrogen were also undertaken (Scheme 7 and Table 3). This reaction process was found to be general and afforded either the indole or quinoline derivatives. In cases where $N = 1$, the initially formed dihydroindole derivatives **23** underwent air oxidation to the indole derivatives **24** and **25**.[17] The pathway for formation of initial product **23** is depicted in Scheme 8. Intramolecular cyclopropanation does not compete in these cases since it could occur only through a macrocyclic ring forming process.

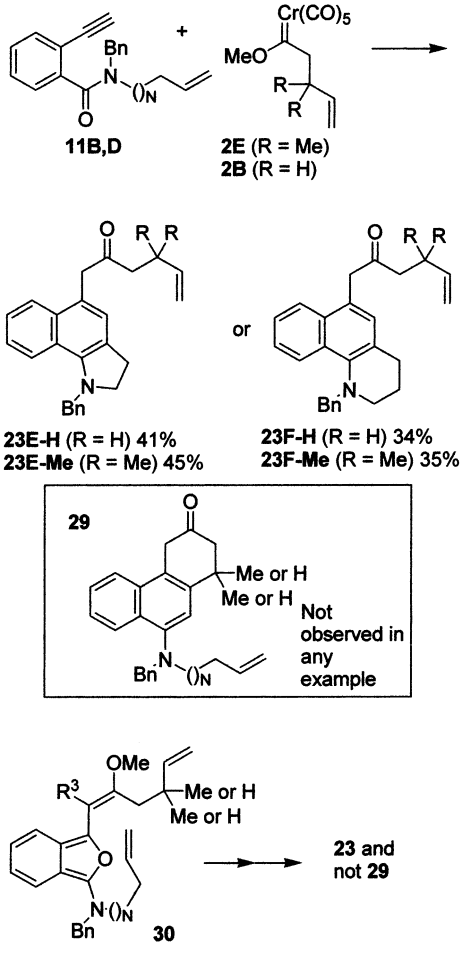
The final phase of these studies involves a competing Diels−Alder process where a dienophile is tethered both to the carbene complex and to the carbonyl group (Scheme 9). In these studies, the product from Diels−Alder onto the carbonyl tether (e.g., **23**) was obtained exclusively, regardless of the tether length. In the coupling of simple butenylcarbene complex **2B** with **11B** or **11D**, unanticipated isomerization of the remote alkene functionality of **23E**,**F** was also observed; all possible isomers could be identified to some extent in the crude proton NMR spectrum. A pure product was obtained from the gem dimethyl-containing carbene complex **2E**, in which case the isomerization process is blocked.

The alternative Diels−Alder adduct **29** was not observed in any of the reactions in Scheme 9. The analogous intramolecular cyclopropanation products **16** were not observed in these reactions as well. Since

Scheme 8



Scheme 9



cyclopropanation must precede isobenzofuran formation, the pendant alkene appears to have some role in preventing the cyclopropanation pathway and perhaps accelerates the formation of the carbonyl ylide intermediate **18**. The origin of the high Diels−Alder selectivity for the reactions in Scheme 9 likely reflects confor-

(16) Fratiello, A.; Schuster, R. E. *Inorg. Chem.* **1969**, *8*, 480−484.
(17) For debenzylation of *N*-benzyl indoles under protic conditions, see: Murphy, W. S.; Bertrand, M. *J. Chem. Soc., Perkin Trans. 1* **1998**, 4115−4120.

mational preferences of the isobenzofuran intermediate **30**. Simple MM2 calculations for isobenzofuran intermediate **30** predict that the enol ether alkene is conjugated, while the N-substituents are orthogonal to the isobenzofuran ring. This places the N-tethered pendant alkene in a more appropriate orientation for the Diels–Alder reaction. The effect is obviously quite powerful since the Thorpe–Ingold effect is irrelevant in determining the more favorable reaction pathway. Note that compound **29** does not form in the coupling of **11D** with either **2B** or **2E**.

Conclusion

In summary, the suitability of 2-alkynylbenzamide derivatives for the previously reported tandem isobenzofuran formation/intramolecular Diels–Alder reaction process has been demonstrated for amide derivatives. The overall tandem process appears to be less favorable than for ketone/aldehyde analogues, possibly due to the greater stability of the amide carbonyl group.

Experimental Section

Starting Amides and Carbene Complexes. Carbene complexes **2A**,[18] **2B**,**C**,[19] and **2D**[2a] have been previously reported. Preparation of amides **11A**–**D** and carbene complex **2E** is in the Supporting Information.

General Procedure for Coupling of Carbene Complexes 2 with *o*-Alkynyl Benzamides 11. To a refluxing solution of *o*-alkynyl benzamide **11** (1 equiv) [and in some cases $Rh_2(OAc)_4$ (0.05 equiv)] in toluene (5 mL) under argon was added dropwise a solution of carbene complex **2** (1.4 equiv) in toluene (50 mL/mmol) over a period of 1 h. After the addition was complete, the mixture was allowed to reflux for a period of 40 h. The reaction mixture was cooled to room temperature and concentrated in vacuo. Ethyl acetate (25 mL) was added, and the residue was filtered through Celite. The solvent was removed on a rotary evaporator, and the crude products were dissolved in ether. To this solution of crude product in ether (25 mL) was added 10% aqueous HCl (10 mL/mmol), and the mixture was stirred for 6 h at room temperature. (i) *Ether Layer*: The organic layer was separated and washed with water and brine and dried over anhydrous Na_2SO_4. Evaporation of solvent and purification by flash column chromatography gave pure products. (ii) *Aqueous Layer*: The combined aqueous layers were neutralized with dilute aqueous NaOH solution and extracted with dichloromethane. The combined dichloromethane layers were washed with brine and dried (Na_2SO_4). The solvent was removed on a rotary evaporator, and the crude product was purified by flash column chromatography on silica gel.

Coupling of Carbene Complex 2B with 2-Ethynyl-*N*,*N*-dimethylbenzamide (11A) (Table 2, entry A). The general procedure was followed using carbene complex **2B** (0.24 g, 0.83 mmol) and 2-ethynyl-*N*,*N*-dimethylbenzamide (0.10 g, 0.58 mmol). The crude product from acid/base extraction was purified using flash chromatography (silica gel/hexanes–ethyl acetate, 4:1) to yield the product **14A** (0.028 g, 20%), and the crude product from ether extraction was purified using flash chromatography (silica gel/hexanes–ethyl acetate, 4:6) to yield the product **16A** (0.015 g, 10%). **Compound 14A**: ^{1}H NMR ($CDCl_3$) δ 8.28 (m, 1 H), 7.80 (m, 1 H), 7.60–7.42 (m, 2 H), 6.91 (s, 1 H), 3.88 (s, 2 H), 3.23 (t, 2 H, J = 7.0 Hz), 2.90 (s, 6 H), 2.74 (t, 2 H, J = 7.0 Hz); ^{13}C NMR ($CDCl_3$) δ 210.30, 150.11, 133.16, 132.85, 128.02, 126.53, 124.91, 124.77, 122.74 (2C), 114.81, 45.31 (2C), 40.23, 39.06, 30.11; IR (cm^{-1}) 1714, 1595; MS (*m*/*e*) 240 (M^+ + 1, 21), 239 (M^+, 99), 210 (100), 182 (20), 165 (36), 152 (21), 141 (14), 115 (16); HRMS calcd for $C_{16}H_{17}NO$ 239.131014, found 239.130046. **Compound 16A**: ^{1}H NMR ($CDCl_3$) δ 7.48–7.08 (m, 4 H), 3.15 (s, 3 H), 2.86 (s, 3 H) overlapping with 2.84 (m, 1 H), 2.48–2.30 (m, 2 H), 2.21–1.95 (m, 3 H), 1.15 (m, 1 H), 0.93 (dd, 1 H, J = 8.8, 5.8 Hz), 0.80 (t, 1 H, J = 5.8 Hz); ^{13}C NMR ($CDCl_3$) δ 210.93, 171.15, 142.45, 137.01, 130.92, 129.26, 126.72, 126.45, 46.90, 39.08, 35.07 (2C), 34.69, 24.29, 21.02, 13.74; IR (cm^{-1}) 1705, 1629; MS (*m*/*e*) 258 (M^++1, 4), 257 (M^+, 5), 170 (100), 141 (5), 128 (13), 115 (9); HRMS calcd for $C_{16}H_{19}NO_2$ 257.141579, found 257.140776.

Coupling of Carbene Complex 2B with 2-Ethynyl-*N*,*N*-dimethylbenzamide (11A) (Table 2, entry A′). The general procedure was followed using carbene complex **2B** (0.24 g, 0.83 mmol), $Rh_2(OAc)_4$ (0.018 g, 0.04 mmol), and 2-ethynyl-*N*,*N*-dimethylbenzamide (**11A**) (0.10 g, 0.58 mmol). The crude product from acid/base extraction was purified using column chromatography (silica gel/hexanes–ethyl acetate, 4:1) to yield the product **14A** (0.040 g, 29%), and the crude product from ether extraction was purified using column chromatography (silica gel/hexanes–ethyl acetate, 4:6) to yield the product **16A** (0.015 g, 10%).

Coupling of Carbene Complex 2C with 2-Ethynyl-*N*,*N*-dimethylbenzamide (11A) (Table 2, entry B). The general procedure was followed using carbene complex **2C** (0.30 g, 0.82 mmol) and 2-ethynyl-*N*,*N*-dimethylbenzamide (0.10 g, 0.58 mmol). The crude product from acid/base extraction was purified using column chromatography (silica gel/hexanes–ethyl acetate, 4:1) to yield the product **14B** (0.036 g, 20%), and the crude product from ether extraction was purified using column chromatography (silica gel/hexanes–ethyl acetate, 4:6) to yield the product **16B** (0.019 g, 10%). **Compound 14B**: ^{1}H NMR ($CDCl_3$) δ 8.30 (m, 1 H), 7.89 (m, 1 H), 7.65–7.50 (m, 2 H), 7.40–7.15 (m, 3 H), 7.07 (d, 2 H, J = 6.3 Hz), 6.81 (s, 1 H), 4.67 (t, 1 H, J = 5.5 Hz), 4.05 (d, 1 H, J = 21.2 Hz), 3.85 (d, 1 H, J = 21.2 Hz), 3.15 (dd, 1 H, J = 14.5, 5.5 Hz), 2.98 (dd, 1 H, J = 14.5, 5.5 Hz), 2.83 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 208.82, 150.22, 142.94, 135.22, 132.81, 128.75 (2C), 128.18, 127.69 (2C), 126.82, 126.57, 125.08, 124.90, 123.18, 123.04, 115.23, 47.29, 46.97, 45.11 (2C), 40.38; IR (cm^{-1}) 1718, 1595; MS: (*m*/*e*) 316 (M^++1, 20), 315 (M^+, 100), 287 (48), 272 (5), 242 (8), 228 (21), 215 (14), 182 (21), 165 (25), 115 (19); HRMS calcd for $C_{22}H_{21}NO$ 315.162314, found 315.163007. **Compound 16B**: ^{1}H NMR ($CDCl_3$) δ 7.50–7.00 (m, 9 H), 3.30–2.80 (m, 4 H) overlapping with 3.05 (s, 3 H), 2.78 (s, 3 H), 2.50 (dd, 1 H, J = 16.1, 5.2 Hz), 1.60 (m, 1 H), 0.86 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 211.19, 170.88, 144.63, 142.57, 136.90, 130.91, 129.26, 128.84 (2C), 126.99 (2C), 126.77 (2C), 126.65, 47.14, 43.35 (2C), 43.13, 39.02, 34.54, 25.91, 21.65; IR (cm^{-1}) 1709, 1634; MS (*m*/*e*) 333 (M^+, 7), 201 (5), 174 (100), 144 (8), 129 (20), 117 (35), 115 (16); HRMS calcd for $C_{22}H_{23}NO_2$ 333.172879, found 333.173041.

Coupling of Carbene Complex 2C with 2-Ethynyl-*N*,*N*-dimethylbenzamide (11A) (Table 2, entry B′). The general procedure was followed using carbene complex **2C** (0.24 g, 0.83 mmol), $Rh_2(OAc)_4$ (0.018 g, 0.04 mmol), and 2-ethynyl-*N*,*N*-dimethylbenzamide (**11A**) (0.10 g, 0.58 mmol). The crude product from acid/base extraction was purified using column chromatography (silica gel/hexanes–ethyl acetate, 4:1) to yield the product **14B** (0.058 g, 32%), and the crude product from ether extraction was purified using column chromatography (silica gel/hexanes–ethyl acetate, 4:6) to yield the product **16B** (0.014 g, 7%).

Coupling of Carbene Complex 2D with 2-Ethynyl-*N*,*N*-dimethylbenzamide (11A) (Table 2, entry C). The general procedure was followed using carbene complex **2D** (0.25 g, 0.82 mmol) and 2-ethynyl-*N*,*N*-dimethylbenzamide (**11A**) (0.10 g, 0.58 mmol). A trace amount of a compound consistent with **14C** was found in the crude product of acid/base extraction. The crude product from ether extraction was purified using

(18) Hegedus, L. S.; McGuire, M. A.; Schultze, L. M. *Org. Synth.* **1987**, *65*, 140–145.

(19) Zhang, Y.; Herndon, J. W. *J. Org. Chem.* **2002**, *67*, 4177–4185.

column chromatography (silica gel/hexanes−ethyl acetate, 2:1) to yield the products **15C** (0.052 g, 40%) and **16C** (0.012 g, 8%). **Compound 14C**: ^{1}H NMR ($CDCl_3$) δ 8.20 (m, 1 H), 7.80 (m, 1 H), 7.55−7.40 (m, 2 H), 4.92 (s, 2 H), 3.22 (t, 2 H, J = 7.5 Hz), 3.02 (s, 6 H), 2.72 (t, 2 H, J = 7.5 Hz), 2.40 (s, 1 H); IR (cm^{-1}) 1715. **Compound 15C**: ^{1}H NMR ($CDCl_3$) δ 8.09 (dd, 1 H, J = 8.0, 1.2 Hz), 7.79 (d, 1 H, J = 8.0 Hz), 7.64 (td, 1 H, J = 8.0, 1.2 Hz), 7.56 (td, 1 H, J = 8.0, 1.2 Hz), 6.78 (d, 1 H, J = 2.4 Hz), 2.82 (dddd, 1 H, J = 13.6, 9.2, 4.6, 2.4 Hz), 2.68−2.38 (m, 4 H), 1.89 (m, 1 H), 1.38 (d, 3 H, J = 6.8 Hz); irradiation at δ 6.78, δ 2.82 (ddd, 1 H, J = 13.6, 9.2, 3.2 Hz); irradiation at δ 1.38, 2.59 (d, 1 H, J = 12.0 Hz); ^{13}C NMR ($CDCl_3$) δ 198.77, 197.69, 154.32, 136.69, 133.86, 132.35, 131.18, 127.62, 125.18, 123.86, 47.75, 41.74, 36.43, 27.58, 11.83; IR (cm^{-1}) 2917, 1680, 1664, 1587; MS (*m*/*e*) 227 (M^+ + 1, 8), 226 (M^+, 46), 198 (M^+ − CO, 21), 183 (11), 170 (M^+ − 2CO, 100), 155 (11), 141 (35), 128 (9), 115 (22); HRMS calcd for $C_{15}H_{14}O_2$ 226.099380, found 226.098648. **Compound 16C**: ^{1}H NMR ($CDCl_3$) δ 7.45−7.10 (m, 4 H), 3.15−2.62 (m, 4 H) overlapping with 3.14 (s, 3 H) and 2.88 (s, 3 H), 2.39 (m, 1 H), 2.14 (m, 1 H), 1.55 (m, 1 H), 0.92 (m, 1 H), 0.85 (d, 3 H, J = 5.4 Hz); ^{13}C NMR ($CDCl_3$) δ 211.86, 171.38, 139.33, 137.52, 131.83, 128.97, 126.84, 126.47, 48.56, 39.04, 35.49, 34.67, 29.70, 28.88, 25.19, 20.64, 16.34; IR (cm^{-1}) 2927, 1711, 1634; MS (*m*/*e*) 272 (M^+ + 1, 2), 271 (M^+, 5), 174 (100), 141 (8), 128 (14), 115 (8); HRMS calcd for $C_{17}H_{21}NO_2$ 271.157229, found 271.157275.

Coupling of Carbene Complex 2D with 2-Ethynyl-*N*,*N*-dimethylbenzamide (11A) (Table 2, entry C′). The general procedure was followed using carbene complex **2D** (0.27 g, 0.89 mmol), $Rh_2(OAc)_4$ (0.018 g, 0.04 mmol), and 2-ethynyl-*N*,*N*-dimethylbenzamide (**11A**) (0.11 g, 0.64 mmol). The crude product from acid/base extraction was purified using column chromatography (silica gel/hexanes−ethyl acetate, 4:1) to yield the product **14C** (0.010 g, 6%), and the crude products from ether extraction were purified using column chromatography (silica gel/hexanes−ethyl acetate, 2:1) to yield the products **15C** (0.060 g, 42%) and **16C** (0.015 g, 8%).

Coupling of Carbene Complex 2A with *o*-Alkynylbenzamide Derivative 11B (Table 3, entry A). The general procedure was followed using carbene complex **2A** (0.16 g, 0.64 mmol) and *o*-alkynylbenzamide derivative **11B** (0.12 g, 0.42 mmol). The crude product from acid/base extraction was purified using column chromatography (silica gel/hexanes−ethyl acetate, 4:1) to yield the product **23A** (0.060 g, 46%), and the crude product from ether extraction was purified using column chromatography (silica gel/hexanes−ethyl acetate, 4:1) to yield the product **24A** (0.012 g, 9%). **Compound 23A**: ^{1}H NMR ($CDCl_3$) δ 7.98 (d, 1 H, J = 8.0 Hz), 7.82 (d, 1 H, J = 8.0 Hz), 7.55−7.26 (m, 7 H), 7.25 (s, 1 H), 4.59 (s, 2 H), 4.03 (s, 2 H), 3.62 (t, 2 H, J = 8.8 Hz), 3.15 (t, 2 H, J = 8.8 Hz), 2.12 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 207.56, 148.53, 139.68, 132.78, 128.53 (2C), 127.46 (2C), 127.10, 126.60, 125.67, 125.45, 124.84, 124.66, 123.46, 123.27 (2C), 59.41, 55.06, 49.23, 29.75, 28.75; IR (cm^{-1}) 2922, 1708, 1570; MS (*m*/*e*) 316 (M^+ + 1, 3), 315 (M^+, 12), 272 (M^+ − COMe, 74), 180 (18), 152 (5), 91 (100); HRMS calcd for $C_{22}H_{21}NO$ 315.162314, found 315.162322. **Compound 24A**: ^{1}H NMR ($CDCl_3$) δ 8.10 (br d, 1 H, J = 8.0 Hz), 7.90 (br d, 1 H, J = 8.0 Hz), 7.69 (s, 1 H), 7.45−7.22 (m, 5 H), 7.17 (d, 1 H, J = 3.0 Hz), 7.08 (br d, 2 H, J = 8.0 Hz), 6.70 (d, 1 H, J = 3.0 Hz), 5.81 (s, 2 H), 4.11 (s, 2 H), 2.10 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 208.09, 137.64, 130.03, 129.66, 129.38, 129.01 (2C), 127.60, 126.11 (2C), 125.71, 125.30, 125.10, 123.86, 123.75, 123.71, 123.29, 121.54, 102.99, 53.73, 50.17, 28.69; IR (cm^{-1}) 2924, 1711, 1634; MS (*m*/*e*) 314 (M^+ + 1, 4), 313 (M^+, 18), 270 (M^+ − COMe, 73), 179 (10), 91 (100); HRMS calcd for $C_{22}H_{19}NO$ 313.146664, found 313.146821.

Coupling of Carbene Complex 2A with *o*-Alkynylbenzamide Derivative 11C (Table 3, entry B). The general procedure was followed using carbene complex **2A** (0.16 g, 0.64 mmol) and *o*-alkynylbenzamide derivative **11C** (0.12 g, 0.42 mmol). The crude products from combined acid/base extraction and ether extraction were purified using column chromatography (silica gel/hexanes−ethyl acetate, 4:1) to yield the products **24B** (0.058 g, 45%) and **25B** (0.021 g, 22%). **Compound 24B**: ^{1}H NMR ($CDCl_3$) δ 8.20 (br d, 2 H, J = 8.0 Hz), 7.70 (s, 1 H), 7.60−7.30 (m, 5 H), 7.22 (d, 1 H, J = 2.7 Hz), 7.16 (br d, 2 H, J = 8.0 Hz), 6.75 (d, 1 H, J = 2.7 Hz), 5.86 (s, 2 H), 4.35 (t, 1 H, J = 6.4 Hz), 2.31 (m, 1 H), 2.06 (s, 3 H), 1.97 (m, 1 H), 1.55−1.20 (m, 4 H), 0.92 (t, 3 H, J = 6.4 Hz); ^{13}C NMR ($CDCl_3$) δ 209.60, 137.63, 129.71, 129.48, 129.37, 129.00 (2C), 128.02, 127.59, 126.13 (2C), 125.70, 125.08, 124.41, 123.75, 123.55, 121.71, 121.11, 103.10, 56.12, 53.72, 31.53, 30.26, 28.41, 22.79, 13.91; IR (cm^{-1}) 2929, 1710, 1505; MS (*m*/*e*) 370 (M^+ + 1, 4), 369 (M^+, 14), 326 (M^+ − COMe, 71), 270 (33), 192 (9), 91 (100); HRMS Calcd for $C_{26}H_{27}NO$ 369.209265, found 369.208142. **Compound 25B**: ^{1}H NMR ($CDCl_3$) δ 8.95 (br s, 1 H), 8.13 (d, 1 H, J = 8.0 Hz), 8.05 (d, 1 H, J = 8.0 Hz), 7.59 (s, 1 H), 7.52 (br t, 1 H, J = 8.0 Hz), 7.47 (br t, 1 H, J = 8.0 Hz), 7.27 (t, 1 H, J = 2.6 Hz), 6.66 (t, 1 H, J = 2.6 Hz), 4.28 (t, 1 H, J = 6.8 Hz), 2.23 (m, 1 H), 1.98 (s, 3 H), 1.89 (m, 1 H), 1.45−1.10 (m, 4 H), 0.83 (t, 3 H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 209.74, 130.22, 128.89, 127.89, 125.38, 124.55, 124.35, 123.44, 122.58, 122.51, 120.74, 120.25, 104.37, 56.06, 31.57, 30.19, 28.41, 22.79, 13.90; IR (cm^{-1}) 3359, 2929, 1698, 1378; MS (*m*/*e*) 280 (M^+ + 1, 3), 279 (M^+, 16), 236 (M^+ − COMe, 65), 192 (16), 180 (100); HRMS calcd for $C_{19}H_{21}NO$ 279.162314, found 279.161813.

Coupling of Carbene Complex 2A with *o*-Alkynylbenzamide Derivative 11D (Table 3, entry C). The general procedure was followed using carbene complex **2A** (0.20 g, 0.80 mmol) and *o*-alkynylbenzamide derivative **11D** (0.18 g, 0.59 mmol). The crude product from acid/base extraction was purified using column chromatography (silica gel/hexanes−ethyl acetate, 4:1) to yield the product **23C** (0.040 g, 20%). **Compound 23C**: ^{1}H NMR ($CDCl_3$) δ 8.26 (d, 1 H, J = 8.0 Hz), 7.82 (d, 1 H, J = 8.0 Hz), 7.68 (d, 2 H, J = 8.0 Hz), 7.60−7360 (m, 5 H), 7.13 (s, 1 H), 4.38 (s, 2 H), 4.07 (s, 2 H), 3.21 (br t, 2 H, J = 4.6 Hz), 2.99 (t, 2 H, J = 6.7 Hz), 2.19 (s, 3 H), 1.85−2.20 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 207.34, 144.20, 139.62, 132.06, 130.53, 129.35, 128.64 (2C), 127.37 (2C), 127.01, 125.58, 125.27, 124.96, 124.81, 124.29, 123.65, 59.24, 48.85, 46.98, 28.88, 27.80, 16.55; IR (cm^{-1}) 2917, 1705, 1570; MS (*m*/*e*) 330 (M^+ + 1, 9), 329 (M^+, 39), 286 (M^+ − COMe, 100), 196 (32), 152 (5), 91 (99); HRMS calcd for $C_{22}H_{23}NO$ 329.177965, found 329.177784.

Coupling of Carbene Complex 2A with *o*-Alkynylbenzamide Derivative 11E (Table 3, entry D). The general procedure was followed using carbene complex **2A** (0.16 g, 0.64 mmol) and *o*-alkynylbenzamide derivative **11E** (0.16 g, 0.44 mmol). The crude product from acid/base extraction was purified using column chromatography (silica gel/hexanes−ethyl acetate, 4:1) to yield the product **23D** (0.095 g, 55%). **Compound 23D**: ^{1}H NMR ($CDCl_3$) δ 8.25 (d, 1 H, J = 8.0 Hz), 8.04 (d, 1 H, J = 8.0 Hz), 7.63 (d, 2 H, J = 8.0 Hz), 7.55−7.30 (m, 5 H), 7.03 (s, 1 H), 4.35 (s, 2 H), 4.27 (t, 1 H, J = 7.2 Hz), 3.28−3.12 (m, 2 H), 2.93 (t, 2 H, J = 6.6 Hz), 2.22 (m, 1 H), 2.04 (s, 3 H), 2.00−1.70 (m, 3 H), 1.48−1.10 (m, 4 H), 0.89 (t, 3 H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$) δ 209.05, 143.84, 139.59, 131.79, 129.52, 129.26, 128.62 (2C), 127.75, 127.31 (2C), 126.99, 125.49, 125.10 (2C), 123.83, 123.53, 59.20, 55.00, 46.97, 31.56, 30.17, 28.69, 27.84, 22.75, 16.57, 13.89; IR (cm^{-1}) 2930, 1713, 1454; MS (*m*/*e*) 386 (M^+ + 1, 6), 385 (M^+, 19), 342 (M^+ − COMe, 100), 252 (6), 208 (10), 129 (19), 91 (65); HRMS calcd for $C_{27}H_{31}NO$ 385.240565, found 385.241114. Comb. Anal. Calcd for $C_{27}H_{31}NO$: C 84.03, H 8.04, N 3.63. Found: C 83.86, H 7.64, N 3.63.

Coupling of Carbene Complex 2E with *o*-Alkynylbenzamide Derivative 11B (Scheme 9). The general procedure was followed using carbene complex **2E** (0.18 g, 0.57 mmol) and *o*-alkynylbenzamide derivative **11B** (0.12 g, 0.41 mmol) with the exception that in this experiment after thermolysis

crude product was purified using column chromatography (silica gel/hexanes−ethyl acetate, 9:1) to yield the products, which were subsequently hydrolyzed by using 5% HCl aqueous in methanol at 0 °C for 5 h. After neutralization with 10% $NaHCO_3$ solution, the mixture was extracted with dichloromethane. The crude product was purified using column chromatography (silica gel/hexanes−ethyl acetate, 9:1) to yield the product **23E-Me** (0.072 g, 45%). **Compound 23E-Me**: ^{1}H NMR ($CDCl_3$) δ 7.93 (d, 1 H, J = 8.0 Hz), 7.75 (d, 1 H, J = 8.0 Hz), 7.48 (d, 2 H, J = 7.2 Hz), 7.42−7.27 (m, 5 H), 7.15 (s, 1 H), 5.90 (dd, 1 H, J = 17.6, 10.3 Hz), 4.92 (d, 1 H, J = 17.6 Hz), 4.92 (d, 1 H, J = 10.3 Hz), 4.55 (s, 2 H), 3.96 (s, 2 H), 3.58 (t, 2 H, J = 8.6 Hz), 3.11 (t, 2 H, J = 8.6 Hz), 2.43 (s, 2 H), 1.07 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 208.22, 148.34, 147.24, 139.66, 132.75, 128.55 (2C), 127.49 (2C), 127.02, 126.63, 125.64, 125.23, 125.01, 124.56, 123.48, 123.21, 123.11, 110.81, 59.43, 54.96, 52.38, 50.09, 36.44, 29.75, 26.97 (2C); IR (cm^{-1}) 2919, 1713, 1455; MS (*m*/*e*) 383 (M^+, 7), 381 ($M^+ - 2$, 21), 286 (21), 270 (100), 179 (10), 91 (97); HRMS calcd for $C_{27}H_{29}NO$ 383.224915, found 383.225485.

Coupling of Carbene Complex 2E with *o*-Alkynylbenzamide Derivative 11D (Scheme 9). The general procedure was followed using carbene complex **2E** (0.25 g, 0.78 mmol) and *o*-alkynylbenzamide derivative **11D** (0.17 g, 0.56 mmol) with the exception that in this experiment after thermolysis the crude product was purified using column chromatography (silica gel/hexanes−ethyl acetate, 9:1) to yield the products, which were subsequently hydrolyzed by using 5% HCl aqueous in methanol at 0 °C for 5 h. After neutralization with 10% $NaHCO_3$ solution, the mixture was extracted with dichloromethane. The crude product was purified using column chromatography (silica gel/hexanes−ethyl acetate, 9:1) to yield the product **23F-Me** (0.078 g, 35%). **Compound 23F-Me**: ^{1}H NMR ($CDCl_3$) δ 8.23 (d, 1 H, J = 8.0 Hz), 7.75 (d, 1 H, J = 8.0 Hz), 7.63 (d, 2 H, J = 7.0 Hz), 7.55−7.30 (m, 5 H), 7.02 (s, 1 H), 5.95 (dd, 1 H, J = 17.6, 10.6 Hz), 4.97 (d, 1 H, J = 17.6 Hz), 4.96 (d, 1 H, J = 10.6 Hz), 4.33 (s, 2 H), 3.99 (s, 2 H), 3.12 (m, 2 H), 2.94 (t, 2 H, J = 6.8 Hz), 2.50 (s, 2 H), 1.86 (m, 2 H), 1.13 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 207.94, 147.27, 144.00, 139.66, 132.11, 130.50, 129.27, 128.63 (2C), 127.35 (2C), 126.98, 125.41, 125.19, 124.89, 124.77, 124.47, 123.51, 110.83, 59.16, 52.64, 49.67, 46.88, 36.46, 27.77, 27.01 (2C), 16.45; IR (cm^{-1}) 2959, 1714, 1574; MS (*m*/*e*) 398 ($M^+ + 1$, 10), 397 (M^+, 24), 286 (100), 194 (17), 91 (79); HRMS calcd for $C_{28}H_{31}NO$ 397.240565, found 397.240906.

Acknowledgment. We thank the National Institutes of Health (SCORE program) for financial support of this research project. We thank Ke Wang and Dr. Suryesh Iyer for experimental assistance. We thank the UC-Riverside mass spectral facility for acquisition of mass spectral data.

Supporting Information Available: General experimental procedures and synthesis and characterization of amides **11B**−**D** and carbene complex **2E**. Attempted characterization of complex mixtures that result from the coupling of carbene complex **2B** with amides **11B** and **11D**. This material is available free of charge via the Internet at http://pubs.acs.org.

OM030383K