Coupling of N-Heterocycle-Fused Enyne Aldehydes with γ,δ-Unsaturated Fischer Carbene Complexes

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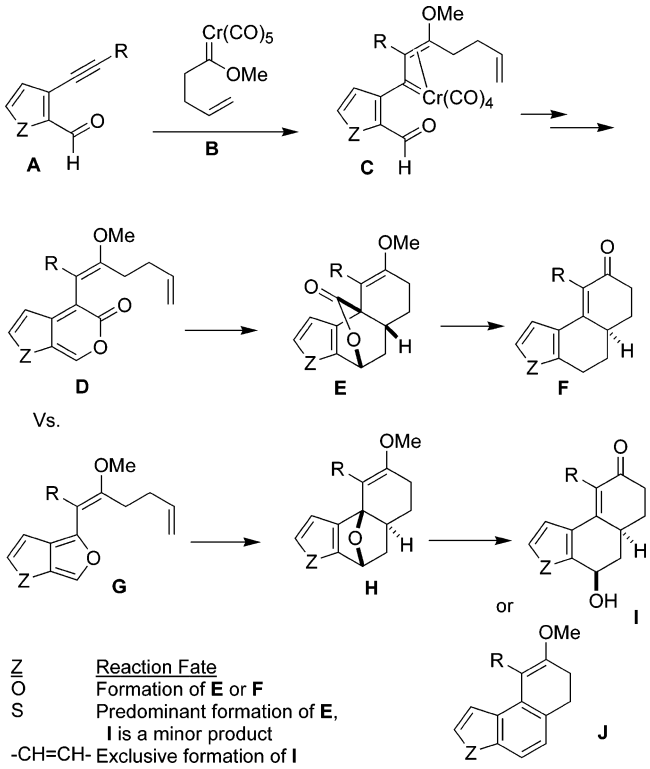
Received November 22, 2005

The coupling of γ,δ-unsaturated Fischer carbene complexes with enyne aldehyde derivatives fused to indole, imidazole, and pyrazole ring systems has been examined. The reaction leads to heterocycles fused to the hydronaphthalene ring system in a single step. The products of the reaction feature heterocycles fused either to benzene rings or to a cyclohexane ring. The product distribution correlates with the electronic richness of the heterocyclic ring. A moderate degree of diastereoselectivity was observed using heterocycles featuring chiral nitrogen substituents.

Introduction

Aromatic rings fused to five-membered-ring nitrogen heterocycles form the nucleus of numerous medicinally important compounds, including indoles, carbazoles, benzimidazoles, and unnatural compounds involving the pyrazole nucleus. Synthetic routes to these compounds typically involve the fusion of a nitrogen heterocycle onto a preexisting benzene ring or fusion of a benzene ring onto a preexisting nitrogen heterocycle.[1] Among the latter strategies, cycloaddition reactions involving nonaromatically fused furan rings (e.g. **G**, Z = N−R; Scheme 1) represent one of the more successful strategies for carbazole[2] and indole[3] synthesis. The use of pyrone analogues of these ring systems (e.g. **D**, Z = NR) has also been reported.[4] Analogues of **D** and **G** that feature an additional nitrogen in the ring (e.g. 1*H*-furo[3,4-*d*]imidazoles and 1*H*-furo[3,4-*c*]-pyrazole and pyrone analogues) are less well-known and are confined to a single manuscript[5] and patent applications.[6] The synthesis of *o*-quinonedimethane-like pyrazoles was recently reported.[7] These compounds could be equally useful for the preparation of benzimidazoles and benzopyrazoles.

Scheme 1



A novel method for the generation of analogous oxygen- and sulfur-fused heterocyclic pyrones (**D**) was recently reported.[8] This process employs the coupling of Fischer carbene complexes with furan or thiophene rings that contain aldehyde and alkynyl substituents in an ortho arrangement. The reaction employing γ,δ-unsaturated carbene complexes (e.g. **B**) led to either the bridged compound **E** or to the carbon dioxide extrusion product **F**, accompanied by minor amounts of the furan-derived alcohol **I**. Since electron-withdrawing groups on the initial heterocycle suppress the carbon dioxide extrusion process, a nonconcerted process proceeding through initial ionization of the C−O bond was proposed. The analogous reaction employing benzene ring

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(1) For a review of syntheses of compounds in this class, see: (a) Sundberg, R. J. In *Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Ed.; Elsevier: Amsterdam, 1996; Vol. 2, pp 119−206. (b) Joule, J. A. In *Science of Synthesis*; Thomas, E. J., Ed.; Thieme: Stuttgart, Germany, 2001; Vol. 10, pp 361−652. (c) Gallagher, P. T. In *Science of Synthesis*; Thomas, E. J. Ed.; Thieme: Stuttgart, Germany, 2001; Vol. 10, pp 693−744. (d) Elguero, J. In *Comprehensive Heterocyclic Chemistry II*; Shinkai, I., Ed.; Elsevier: Amsterdam, 1996; Vol. 3, pp 1−75. (e) Stanovnik, B.; Svete, J. In *Science of Synthesis*; Neier, R., Ed.; Thieme: Stuttgart, Germany, 2002; Vol. 12, pp 15−225. (f) Grimmett, M. R. In *Science of Synthesis*; Neier, R., Ed.; Thieme: Stuttgart, Germany, 2002; Vol. 12, pp 529−612.

(2) Gribble, G. W.; Silva, R. A.; Saulnier, M. G. *Synth. Commun.* **1999**, *29*, 729−747.

(3) Moskalev, N. V.; Gribble, G. W. *Tetrahedron Lett.* **2002**, *43*, 197−201.

(4) (a) Jackson, P. M.; Moody, C. J. *J. Chem. Soc., Perkin Trans. 1* **1990**, 2156−2158. (b) Pindur, U. *Heterocycles* **1990**, *31*, 1751−1761. (c) Moody, C. J. *Synlett* **1994**, 681−688.

(5) Korobitsyna, I. K.; Yur'ev, Yu. K.; Zhukova, I. G. *Z. Obshch. Khim.* **1957**, *27*, 1654−1658.

(6) Ishii, F. *Chem. Abstr.* **1995**, *124*, 274349.

(7) Konstantinidou, D.; Papageorgiou, M.; Stephanidou-Stephanatou, J.; Tsoleridis, C. A. *Tetrahedron Lett.* **2005**, *46*, 4843−4845.

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

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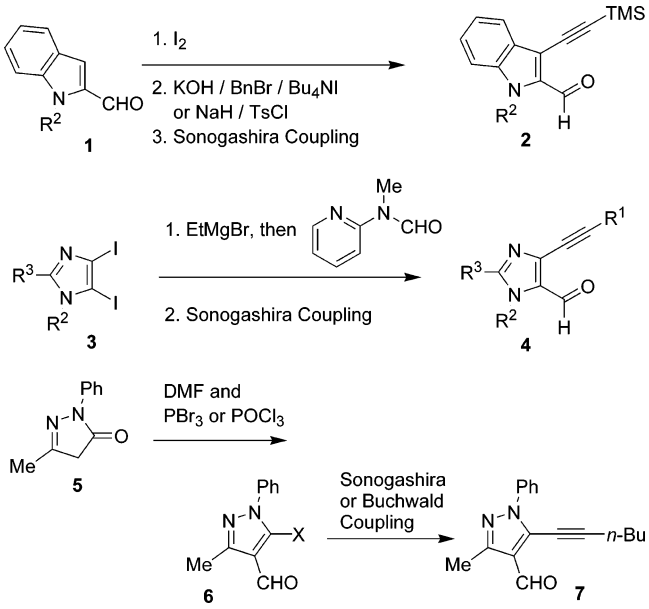
Publication on Web 02/01/2006

Scheme 2

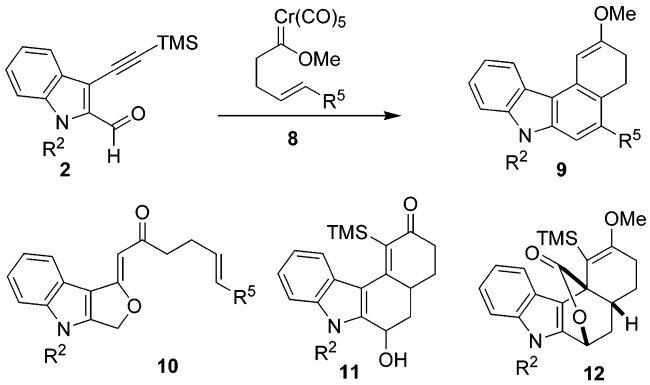


derivatives of **A** (Z = −CH═CH−) led to isobenzofuran-derived alcohols (**I**).[9] In some cases the conversion of benzooxanorbornenes to naphthalenes (**J**) (dehydration) was also observed.[10] The rationale for the product distribution is due to two factors. (1) Ring strain disfavors formation of the furan ring of **G**; thus, this pathway is most prevalent when the starting ring is a benzene ring (Z = −CH═CH−) than cases where it is a five-membered-ring heterocycle (Z = S, O). (2) Electron-rich aromatic rings disfavor the CO insertion process; hence, pyrone-derived products are more abundant when the starting aromatic ring is furan (Z = O) than when this ring is thiophene (Z = S). In this paper, extension of this reaction process to nitrogen heterocycles is reported. A critical issue in these studies is how the electron-donating potential of the heterocyclic ring will affect the distribution of pyrone-derived products and furan-derived products.

Results

Synthesis of Substrates. General synthetic routes to heterocyclic alkynes are depicted in Scheme 2**.** Indole alkyne aldehydes (**2**) were synthesized from the indole-2-carboxaldehyde **1** through a sequence involving iodination, followed by N protection, followed by Sonogashira coupling. Synthesis of the imidazole substrates **4** involved the sequential formylation and alkynylation of the *o*-diiodo heterocyclic compounds **3**. The regiochemistry of this process is determined by the order of the reaction processes; the halide adjacent to the non-π-bonded nitrogen atom is kinetically more activated for halogen−metal exchange processes.[11] Pyrazole substrates (**7**) were prepared through Villsmeyer formylation of pyrazolones (**5**)[12] followed by alkynylation. Initially this transformation was accomplished

Scheme 3

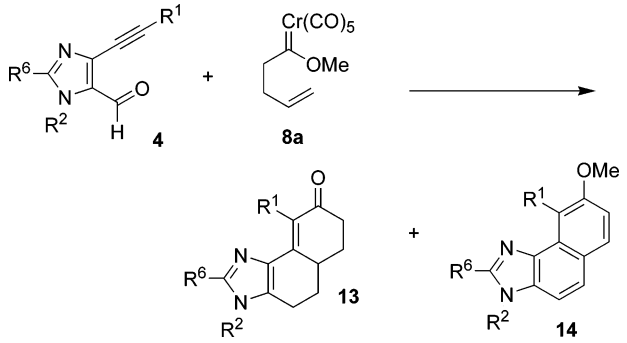


Identifier **2**
a R^2 = Bn
b R^2 = Ts

Identifier **8**
a R^5 = H
b R^5 = Me

Identifier **9-12**	R^2	R^5	**9**	**10**	**11**	**12**
a	Bn	H	73%	0%	0%	0%
b	Bn	Me	46%	34%	0%	0%
c	Ts	H	0%	0%	29%	11%

Scheme 4



through an inefficient bromoformylation followed by Sonogashira coupling. While this work was in progress, an efficient method for Sonogashira coupling using chlorides was reported, and this method was successful at converting the chloropyrazole **6** to the corresponding alkynylpyrazole.[13] A similar reaction sequence applied to oxindole was of limited success[14] for the preparation of 2-alkynyl-3-indolecarboxaldehydes.

Coupling of Carbene Complexes with Indoles. The coupling of both the *N*-benzylindole ynal **2a** and *N*-tosylindole ynal **2b** with Fischer carbene complexes **8a**,**b** was tested (Scheme 3). Predominantly the carbazole derivatives **9** were obtained from the reaction with the *N*-benzyl derivative. Only carbazole **9a** was obtained from the simple α,β-unsaturated carbene complex **8a**, but the reaction employing the 1,2-disubstituted alkene, complex **8b**, afforded the analogous carbazole **9b** and an alkylidenefuranone (**10b**) as a minor reaction component, presumably due to a more sluggish Diels−Alder reaction in this system. As noted in Scheme 1, carbazoles are derived from dehydration of the furan Diels−Alder adducts. The *N*-tosylindole derivative **2b** led to a low yield of the furan Diels−Alder derived indole derivative **11c**, accompanied by the pyrone Diels−Alder derived indole derivative **12c**.

Coupling of Carbene Complexes with Imidazoles. The coupling of imidazole ynals **4a**,**b** (Scheme 4 and Table 1, entries

(9) For the latest example, see: Li, R.; Zhang, L.; Camacho-Davila, A.; Herndon, J. W. *Tetrahedron Lett.* **2005**, *46*, 5117−5120.

(10) Ghorai, B. K.; Herndon, J. W. *Organometallics* **2003**, *22*, 3951−3957.

(11) (a) Carver, D. S.; Lindell, S. D.; Saville-Stones, E. A. *Tetrahedron* 1997, *53*, 14481−14496. (b) Iddon, B.; Khan, N. *J. Chem. Soc., Perkin Trans. 1* **1987**, 1445−1451. (c) Iddon, B. *Heterocycles* **1985**, *23*, 417−443.

(12) Barreiro, E. J.; Camara, C. A.; Verli, H.; Brazil-Mas, L.; Castro, N. G.; Cintra, W. M.; Aracava, Y.; Rodrigues, C. R.; Fraga, C. A. M. *J. Med. Chem.* **2003**, *46*, 1144−1152.

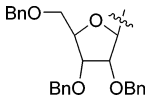
(13) Gelman, D.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2003**, *42*, 5993−5996.

(14) Several papers describe the bromoformylation of oxindole. In one of the publications, the yield for this process is reported as 28%. In our hands, this manuscript most accurately reflects our attempts at this reaction: Gilchrist, T. L.; Kemmitt, P. O.; Germain, A. L. *Tetrahedron* **1997**, *53*, 4447−4456.

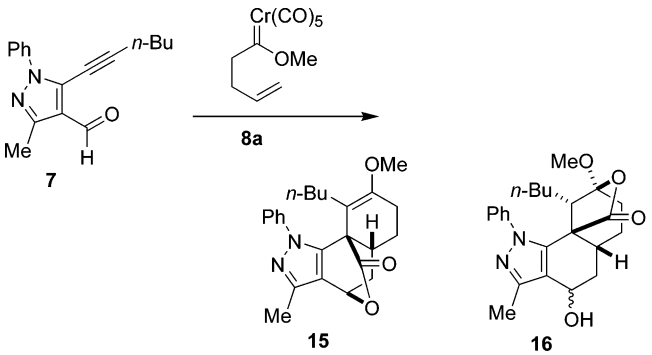
Table 1. Coupling of Carbene Complex 8a with Alkynylimidazolecarboxaldehydes 4

entry	identifier **4**, **13**, **14**	R^1	R^2	R^6	yield, % **13**	**14**
1	**a**	*n*-Bu	Bn	H	40	6
2[a]	**b**	TMS	Bn	H	45	0
3[a]	**c**	*n*-Bu	Bn	Ph	55	0
4	**d**	TMS	Bn	Ph	59	0
5	**e**	*n*-Bu	Bn	*t*-Bu	29	0
6	**f**	TMS	Bn	*t*-Bu	8	0
7	**g**	*n*-Bu	α-MeBn[b]	H	46 (3:1)	0−4
8	**h**	*n*-Bu	PRibosyl[c]	H	40% (5:1)	0%

[a] Triphenylphosphine added. [b] α-MeBn = −CH(CH$_3$)Ph. [c] PRibosyl =



Scheme 5



1 and 2) with carbene complex **8a** led to the pyrone Diels−Alder derived products **13a**,**b** in moderate yield, accompanied by a minor amount of an aromatized product (**14a**) in entry 1. Since competing ligation of the sp^2 nitrogen might be a factor in the reduced yields in these systems,[15] the reaction was tested in the presence of ligand additives (triphenylphosphine or tris(*o*-tolyl)phosphine). The optimized conditions are reported in the examples in Table 1. The highest yields were obtained using the 2-phenylimidazoles (entries 3 and 4). In entries 8 and 9, the sp^3 nitrogen of imidazole features a chiral substituent. Modest diastereoselectivity relative to the N substituent was observed in these reactions.[16] The reaction employing the α-methylbenzyl substituent afforded the expected adducts **13g** as a 3:1 mixture of diastereomers. The reaction employing the protected ribosyl substituent afforded the base-altered nucleoside derivative[17] **13h** as a 5:1 mixture of diastereomers.[18]

Coupling of Carbene Complexes with Pyrazoles. Coupling of the pyrazole derivative **7** (Scheme 5) with carbene complex **8a** led to a mixture of the bridged structure **15** and the alternatively bridged structure **16** as a 1:1 mixture of diastereomers. There are four likely diastereomers for structure **16**. The point of isomerism is most likely the hydroxy group, on the basis of the different appearance of H_A in the two diastereomers (δ 4.90, dt, J = 10.0, 6.4 Hz in one isomer and δ 4.88, dt, J = 4.8, 2.4 Hz in the other isomer). Compound **16** is a hydration/ring-isomerization product of compound **15**, and thus all of the reaction products are pyrone-derived products. The configuration of the *n*-butyl group cannot be reliably assigned, due to overlapping resonances; both configurations are of comparable stability, according to semiempirical calculations.

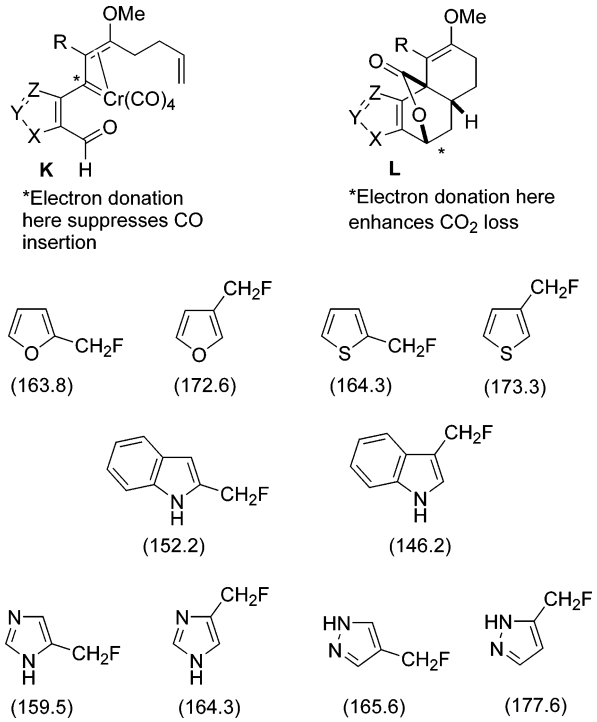


Figure 1. Calculated heterolytic bond dissociation energies for various heterocycle−CH_2F derivatives.[20] The numbers in parentheses reflect ΔE values (in kcal/mol) for ionization to a carbocation and fluoride ion.

Discussion

Furan vs Pyrone Intermediates. The coupling of five-membered-ring heterocycle ynals with γ,δ-unsaturated carbene complexes can potentially lead to furan- or pyrone-derived products according to previously reported studies.[8] For the indole case (Scheme 3), predominantly furan-derived products (**9**−**11**) were obtained; however, a minor amount of a pyrone-derived product (**12c**) could be isolated from the reaction employing the N-tosyl protecting group. It is also worth noting that previous studies of thiophene- and furan-templated alkyne aldehydes all afforded predominantly pyrone-derived products. These results likely reflect the relative electron-donating ability of the various heterocyclic rings and are consistent with numerous other carbene−alkene couplings, where the CO insertion is more likely to happen in electron-deficient systems (see intermediate **K** in Figure 1).[19]

Since a direct comparison of the electron-donating capabilities of the heterocyclic ring systems employed in this investigation

(15) Several examples of stable imidazole−Cr(CO)$_5$ complexes have been reported. (a) Daamen, H.; Oskam, A.; Stufkens, D. J.; Waaijers, H. W. *Inorg. Chim. Acta* **1979**, *34*, 253−260. (b) Beck, W.; Weis, J. C. *J. Organomet. Chem.* **1971**, *30*, 89−96. (c) Grotjahn, D. B.; Kroll, F. E. K.; Schaefer, T.; Harms, K.; Dötz, K. H. *Organometallics* **1992**, *11*, 298−310.

(16) For a review of relative asymmetric induction in carbene complex reactions, see: Wulff, W. D. *Organometallics* **1998**, *17*, 3116−3134.

(17) (a) For a review of this class of compounds see: Kool, E. T. *Acc. Chem. Res.* **2002**, *35*, 936−943. (b) Precursor compounds to **4h** were also employed for the synthesis of a class of base-altered nucleosides known as fleximers: Seley, K. L.; Zhang, L.; Hagos, A.; Quirk, S. *J. Org. Chem.* **2002**, *67*, 3365−3373.

(18) For a review of the use of carbene complexes in carbohydrate systems, see: Dotz, K. H.; Jakel, C.; Haase, W. C. *J. Organomet. Chem.* **2001**, *617*−*618*, 119−132.

(19) Results in the following papers illustrate this effect. (a) Hoye, T. R.; Rehberg, G. M. *Organometallics* **1989**, *8*, 2070−2071. (b) Korkowski, P. F.; Hoye, T. R.; Rydberg, D. B. *J. Am. Chem. Soc.* **1988**, *110*, 2676−2678. (c) Grotjahn, D. B.; Kroll, F. E. K.; Schäfer, T.; Harms, K.; Dötz, K. H. *Organometallics* **1992**, *11*, 298−310.

could not be located, ab initio calculations of the heterolytic bond dissociation energies of representative heterocycle−CH_2F derivatives were performed (see Figure 1). These calculations reveal that electron-donation ability (as inferred from the carbocation stabilizing ability) follows the order indole > imidazole > furan > thiophene > pyrazole and that in most cases the electron-donation ability is stronger when the atom contributing a lone pair to aromaticity is ortho to the electrophilic site (indole and pyrazole are exceptions). Apparently only the indole system is electron-rich enough to overcome ring strain issues and afford the furan-derived intermediates in the carbene−alkyne coupling reaction processes. Imidazole and pyrazole systems (Schemes 4 and 5) all afforded nearly exclusively pyrone-derived products (**13**, **15**, and **16**), consistent with the fact that these ring systems are less electron donating than the indole-derived systems. In the imidazole systems, loss of CO_2 after the Diels−Alder reaction was observed. Only CO_2-retained products were obtained for the pyrazole derivative. This observation can be rationalized on the basis of carbocation stabilizing ability at the asterisked carbon of Diels−Alder adduct **L**. Ionization at this position results in loss of CO_2,[8] and this is less likely to occur when the adjoining heterocyclic ring is pyrazole. The reaction pathway is nearly identical for imidazole- and furan-templated alkyne aldehydes.

Lower Yields with Imidazoles. Carbene−alkyne coupling products were obtained in lower yields using imidazole-templated alkyne aldehydes compared with yields for indole or pyrazole systems or yields in previous studies using furans and thiophenes. This can likely be attributed to either the ligand ability of imidazoles or their basicity. The ligand ability of imidazole might account for the higher yields in the presence of triphenylphosphine and for the higher yields using 2-phenylimidazole derivatives; however, the yields are actually lower for the 2-*tert*-butylimidazole analogues. Since carbene complex stabilized anions are thermally unstable,[21] the basicity of imidazole (pK_a of imidazole-H^+ is 7.0)[22] might be responsible for the reduced yields. This could also account for the greater success using 2-phenylimidazole derivatives, which should be less basic relative to the *tert*-butylimidazole analogue. Since pyrazoles are less basic than imidazoles,[23] this might also play a factor in the uniquely low yields in imidazole systems.

Diels−Alder Reaction. The Diels−Alder reaction was facile in every case involving monosubstituted alkenes, regardless of whether the reaction proceeds through a furan intermediate or a pyrone intermediate. In the one example involving a 1,2-disubstituted alkene, coupling of carbene complex **8b** with the indole derivative **2a**, the Diels−Alder step of the reaction was less efficient, leading to a mixture of the cycloaddition product **9a** and the alkylidenephthalan **10a**, which also results from successful carbene−alkyne coupling and indolofuran formation. If the substituent at nitrogen was chiral, some degree of relative asymmetric induction was observed in the Diels−Alder step, resulting in the diastereoselective formation of **13a**.

Conclusions

The coupling of γ,δ-unsaturated Fischer carbene complexes with enyne aldehyde derivatives fused to indole, imidazole, and pyrazole ring systems has been examined. In all cases, the reaction leads to heterocycles fused to the hydronaphthalene ring system in a single step. Reactions with indoles proceed through formation of a furoindole derivative followed by an intramolecular Diels−Alder reaction, followed by opening of the oxanorbornene ring system. Reactions with imidazoles and pyrazoles proceed through formation of a nonaromatically fused pyrone derivative followed by intramolecular Diels−Alder reaction, followed by loss of carbon dioxide in the imidazole cases. The furan vs pyrone product distribution correlates with the electronic richness of the heterocyclic ring. A moderate degree of diastereoselectivity was observed using heterocycles featuring chiral α-methylbenzyl groups or a benzyl-protected ribosyl group. The latter process results in the synthesis of a base-altered nucleoside analogue.

Experimental Section

General Procedure for the Coupling of Carbene Complexes with N-Heterocyclic Alkyne Aldehydes. A 0.02−0.06 M solution of carbene complex **8**[8] in dioxane was added dropwise to a 0.03−0.06 M solution of alkyne aldehyde at 100 °C, and refluxing was continued for 17 h until the reaction was complete. The resulting reaction mixture was concentrated on a rotary evaporator. The residue was purified by flash chromatography on silica gel using hexane/ethyl acetate mixtures as the eluent.

Coupling of *N*-Benzylindole 2a with Complex 8a. The general procedure was followed using butenylcarbene complex **8a** (80 mg, 0.28 mmol) and alkyne aldehyde **2a** (80 mg, 0.23 mmol). Prior to final purification by flash chromatography, the mixture was dissolved in chloroform (10 mL) and stirred in the air in the presence of silica gel for 10 h. After final purification by flash chromatography (hexane/ethyl acetate 6:1), a white solid identified as carbazole **9a** was obtained (85 mg, 73% yield).

Carbazole **9a**: ^{1}H NMR ($CDCl_3$) δ 8.23 (d, 1H, J = 8.0 Hz), 7.43−7.11 (m, 9H), 7.06 (d, 1H, J = 8.0 Hz), 6.54 (s, 1H), 5.47 (s, 2H), 3.92 (s, 3H), 3.03 (t, 2H, J = 7.4 Hz), 2.53 (t, 2H, J = 7.4 Hz); ^{13}C NMR ($CDCl_3$) δ 162.2, 141.0, 140.3, 137.3, 130.6, 128.6, 127.2, 126.3, 125.0, 124.8, 123.3, 122.9, 122.2, 118.9, 117.6, 108.5, 104.0, 94.0, 54.9, 46.4, 28.5, 27.9; IR (neat) 1635 (m), 1459 (m) cm^{-1}; MS (EI) *m*/*e* 339 (M^+, 100), 204 (39), 91 (94); HRMS calcd for $C_{24}H_{21}NO$ 339.1623, found 339.1619.

Coupling of *N*-Benzylindole 2a with Carbene Complex 8b. The general procedure was followed using pentenylcarbene complex **8b** (85 mg, 0.28 mmol) and alkyne aldehyde **2a** (80 mg, 0.23 mmol). Prior to final purification by flash chromatography, the mixture was dissolved in chloroform (10 mL) stirred in the air in the presence of silica gel for 10 h. After final purification by flash chromatography (hexane/ethyl acetate 6:1), a white solid identified as carbazole **9b** was obtained (37 mg, 46% yield). A second fraction tentatively identified as alkylidenefuran **10b** (mixture of isomers) was isolated.

Compound **9b**: ^{1}H NMR ($CDCl_3$) δ 8.20 (d, 1H, J = 7.7 Hz), 7.34−7.09 (m, 8H), 6.90 (s, 1H), 6.53 (s, 1H), 5.45 (s, 2H), 3.93

(20) The calculations were performed using Gaussian 03 (Hartree−Fock, 6-31G*): Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Montgomery, J. A., Jr.; Vreven, T.; Kudin, K. N.; Burant, J. C.; Millam, J. M.; Iyengar, S. S.; Tomasi, J.; Barone, V.; Mennucci, B.; Cossi, M.; Scalmani, G.; Rega, N.; Petersson, G. A.; Nakatsuji, H.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Klene, M.; Li, X.; Knox, J. E.; Hratchian, H. P.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Ayala, P. Y.; Morokuma, K.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Zakrzewski, V. G.; Dapprich, S.; Daniels, A. D.; Strain, M. C.; Farkas, O.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Ortiz, J. V.; Cui, Q.; Baboul, A. G.; Clifford, S.; Cioslowski, J.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Gonzalez, C.; Pople, J. A. *Gaussian 03*, revision C.02; Gaussian, Inc.: Wallingford, CT, 2004.

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(22) Storey, B. T.; Sullivan, W. W.; Moyer, C. L. *J. Org. Chem.* **1964**, *29*, 3118−3120.

(23) Taft, R. W.; Anvia, F.; Taagapera, M.; Catalán, J.; Elguero, J. *J. Am. Chem. Soc.* **1986**, *108*, 3237−3239.

(s, 3H), 2.96 (t, 2H, $J = 8.7$ Hz), 2.53 (t, 2H, $J = 8.7$ Hz), 2.40 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 161.4, 140.7, 140.0, 137.3, 133.0, 130.5, 128.6, 127.1, 126.2, 124.3, 123.4, 121.8, 121.4, 118.7, 116.0, 108.4, 105.9, 94.1, 54.9, 46.1, 27.4, 24.6, 20.9; IR (neat) 1642 (m), 1459 (m) cm^{-1}; MS (EI) *m/e* 353 (M^+, 9), 290 (100), 201 (52); HRMS calcd for $C_{25}H_{23}NO$ 353.1779, found 353.1772.

Compound **10b** (rapidly darkens in air): ^{1}H NMR ($CDCl_3$) δ 8.30 (m, 1H), 7.50−7.10 (m, 8H), 7.89 (two s, 1H), 5.58−5.39 (m, 6H), 3.05−2.85 (m, 2H), 2.25 (m, 2H), 1.65 (m, 3H).

Coupling of *N*-Tosylindole 2b with Carbene Complex 8a. The general procedure was followed using butenylcarbene complex **8a** (70 mg, 0.24 mmol) and alkyne aldehyde **2b** (79 mg, 0.20 mmol), using THF as the solvent; the reaction was conducted at reflux. Final purification by flash chromatography (hexane/ethyl acetate 6:1) yielded two fractions. The product in the first fraction was a white solid identified as cyclic ester **12c** (12 mg, 11% yield). The second fraction was a yellow solid identified as alcohol **11c** (29 mg, 29% yield); this compound was observed to darken rapidly in the air.

Compound **12c**: ^{1}H NMR ($CDCl_3$) δ 8.08 (d, 1H, $J = 8.8$ Hz), 7.70−7.55 (m, 3H), 7.40−7.05 (m, 4H), 6.33 (d, 1H, $J = 3.7$ Hz), 3.61 (s, 3H), 2.77 (ddd, 1H, $J = 13.2$, 8.8, 4.4 Hz), 2.40−2.00 (m, 2H), 2.25 (s, 3H), 2.06 (m, 1H), 1.65 (m, 1H), 1.16 (ddd, 1H, $J = 13.2$, 4.8, 1.1 Hz), 0.85 (m, 1H), 0.05 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 174.4, 163.6, 145.2, 137.8, 136.4, 133.7, 129.6, 129.1, 126.4, 124.9, 124.0, 123.4, 119.9, 115.4, 109.5, 72.0, 54.8, 52.3, 35.4, 26.5, 25.8, 21.4, 0.6; IR (neat) 1760 (s), 1615 (m) cm^{-1}. MS (EI) *m/e* 477 ($M - CO_2$, 23), 322 ($M - CO_2$, Ts, 74), 73 (100); MS (CI) *m/e* 522 ($M + 1$, 2.6), 507 (3.0), 478 (100).

Compound **11c**: ^{1}H NMR ($CDCl_3$) δ 7.97 (d, 1H, $J = 7.4$ Hz), 7.75 (d, 2H, $J = 8.8$ Hz), 7.59 (d, 1H, $J = 7.4$ Hz), 7.45−7.10 (m, 4H), 5.50 (t, 1H, $J = 8.1$ Hz), 4.44 (br s, 1H), 2.75−2.05 (m, 4H), 2.33 (s, 3H), 1.88−1.50 (m, 3H), −0.06 (m, 9H); ^{13}C NMR ($CDCl_3$) δ 202.3, 161.2, 145.4, 140.5, 138.1, 136.2, 135.0, 129.9, 127.8, 126.4, 125.8, 123.8, 123.5, 121.0, 114.4, 63.7, 41.6, 41.1, 36.1, 25.7, 21.5, 0.5; IR (neat) 3568 (br, m), 1651 (m) cm^{-1}.

Coupling of Imidazole Derivative 4a with Carbene Complex 8a. The general procedure was followed using carbene complex **8a** (300 mg, 1.01 mmol) and alkyne aldehyde **4a** (91 mg, 0.34 mmol) at 95 °C. Final purification by flash chromatography (hexane/ethyl acetate 6:1) yielded two fractions. The major fraction was identified as ketone **13a** (45 mg, 40% yield). The minor fraction was tentatively identified as naphthindole **14a** (7 mg, 6% yield).

Compound **13a**: ^{1}H NMR ($CDCl_3$) δ 7.54 (s, 1H), 7.37−7.35 (m, 3H), 7.11−7.06 (m, 2H), 5.08 (d, 1H, $J = 16.0$ Hz), 5.01 (d, 1H, $J = 16.0$ Hz), 3.19 (m, 1H), 2.98 (m, 1H), 2.60−2.37 (m, 4H), 1.98 (m, 2H), 1.87−1.55 (m, 3H), 1.36 (m, 4H), 0.89 (t, 3H, $J = 7.2$ Hz); ^{13}C NMR ($CDCl_3$) δ 199.2, 145.8, 137.4, 136.5, 135.3, 134.0, 132.1, 129.0, 128.2, 126.8, 48.6, 37.9, 37.6, 31.7, 31.4, 29.6, 25.2, 22.9, 21.0, 14.1; IR (neat) 1646 (s), 1590 (s) cm^{-1}; MS (EI) *m/e* 334 (35), 305 (13), 243 (86), 91 (100); HRMS calcd for $C_{22}H_{26}N_2O$ 334.2045, found 334.2040.

Compound **14a**: ^{1}H NMR 7.98 (s, 1H), 7.75 (d, 1H, $J = 8.8$ Hz), 7.58 (d, 1H, $J = 8.8$ Hz), 7.33−7.18 (m, 7H), 5.44 (s, 2H), 3.96 (s, 3H), 3.83 (t, 2H, $J = 7.4$ Hz), 1.66 (m, 4H), 1.26 (m, 2H), 0.97 (t, 3H, $J = 3.3$ Hz).

Coupling of Imidazole Derivative 4b with γ,δ-Unsaturated Carbene Complex 8a. The general procedure was followed using carbene complex **8a** (570 mg, 1.93 mmol) and alkyne aldehyde **4b** (114 mg, 0.40 mmol) at 62 °C. In this experiment triphenylphosphine (93 mg, 0.354 mmol) was added to the solution of aldehyde **4b** prior to the addition of the carbene complex. Final purification by flash chromatography (hexane/ethyl acetate 6:1) yielded ketone **13b** (56 mg, 45% yield).

Compound **13b**: ^{1}H NMR ($CDCl_3$) δ 7.49 (s, 1H), 7.35 (m, 3H), 7.10 (d, 2H, $J = 7.2$ Hz), 5.08 (d, 1H, $J = 15.6$ Hz), 5.01 (d, 1H, $J = 15.6$ Hz), 2.62−2.28 (m, 5H), 2.06 (m, 1H), 1.94 (m, 1H), 1.79−1.61 (m, 2H), 0.28 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 202.8, 161.2, 137.49, 137.46, 135.6, 134.5, 131.5, 129.3, 128.5, 127.1, 48.9, 38.6, 37.9, 31.3, 28.6, 21.2, 2.0; IR (neat) 1635 (s), 1572 (s) cm^{-1}; MS (CI) *m/e* 351 (15), 335 (100), 279 (18), 91 (39); HRMS calcd for $C_{21}H_{27}N_2OSi$ 351.1893, found 351.1901.

Coupling of Imidazole 4c with Carbene Complex 8a. The general procedure was followed using carbene complex **8a** (360 mg, 1.17 mmol) and alkyne aldehyde **4c** (100 mg, 0.29 mmol) at 62 °C. In this experiment, triphenylphosphine (76 mg, 0.29 mmol) was added to the solution of aldehyde **4c** prior to the addition of the carbene complex at 62 °C. Final purification by flash chromatography (hexane/ethyl acetate 6:1) yielded ketone **13c** (66 mg, 55% yield).

Ketone **13c**: ^{1}H NMR ($CDCl_3$) δ 7.58−7.56 (m, 2H), 7.39−7.30 (m, 6H), 7.05 (d, 2H, $J = 8$ Hz), 5.26 (d, 1H, $J = 15.5$ Hz), 5.19 (d, 1H, $J = 15.5$ Hz), 3.25 (dt, 1H, $J = 11.0$, 4.8 Hz), 3.09 (dt, 1H, $J = 10.0$, 4.8 Hz), 2.70−2.52 (m, 4H), 2.46 (dt, 1H, $J = 14.8$, 4.8 Hz), 2.03 (m, 2H), 1.75 (m, 2H), 1.62−1.39 (m, 4H), 0.94 (t, 3H, $J = 7.2$ Hz); ^{13}C NMR ($CDCl_3$) δ 199.7, 148.6, 146.4, 136.5, 136.4, 136.2, 132.3, 130.7, 129.4, 129.1, 128.8, 128.7, 128.1, 125.9, 48.3, 38.3, 38.0, 32.0, 31.7, 30.0, 25.7, 23.4, 21.8, 14.4; IR (neat) 1651 (s), 1590 (s) cm^{-1}; MS (EI) *m/e* 410 (M, 47), 381 (7), 319 (100), 91 (75); HRMS calcd for $C_{28}H_{30}N_2O$ 410.2358, found 410.2351.

Coupling of Imidazole 4d with Carbene Complex 8a. The general procedure was followed using carbene complex **8a** (365 mg, 1.23 mmol) and alkyne aldehyde **4d** (125 mg, 0.35 mmol) at 65 °C. Final purification by flash chromatography (hexane/ethyl acetate 6:1) yielded ketone **13d** (70 mg, 59% yield).

Ketone **13d**: ^{1}H NMR ($CDCl_3$) δ 7.58−7.55 (m, 2H), 7.38−7.30 (m, 6H), 7.02 (d, 2H, $J = 6.8$ Hz), 5.28 (d, 1H, $J = 17.2$ Hz), 5.19 (d, 1H, $J = 17.2$ Hz), 2.60 (dd, 2H, $J = 8.8$, 3.2 Hz), 2.54−2.44 (m, 2H), 2.31 (ddd, 1H, $J = 17.6$, 14.8, 5.2 Hz), 2.09 (m, 1H), 1.97 (m, 1H), 1.85−1.64 (m, 2H), 0.32 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 202.8, 161.1, 148.4, 136.7, 136.4, 136.3, 131.7, 130.6, 129.4, 129.1, 128.8, 128.6, 128.1, 125.9, 48.4, 38.7, 38.1, 31.3, 28.7, 21.7, 2.2; IR (neat) 1637 (s), 1575 (s) cm^{-1}; MS (EI) *m/e* 424 (22), 352 (40), 91 (100); HRMS calcd for $C_{27}H_{28}N_2OSi$ 424.1971, found 424.1955.

Reaction of Imidazole 4e with Carbene Complex 8a. The general procedure was followed using carbene complex **8a** (310 mg, 1.05 mmol) and alkyne aldehyde **4e** (100 mg, 0.31 mmol) at 65 °C. Final purification by flash chromatography (hexane/ethyl acetate 6:1) yielded ketone **13e** (35 mg, 29% yield).

Compound **13e**: ^{1}H NMR ($CDCl_3$) δ 7.33−7.29 (m, 3H), 6.92 (d, 2H, $J = 7.2$ Hz), 5.34 (d, 1H, $J = 17.2$ Hz), 5.24 (d, 1H, $J = 17.2$ Hz), 3.16 (dt, 1H, $J = 11.2$, 4.4 Hz), 3.03 (dt, 1H, $J = 11.2$, 4.4 Hz), 2.62−2.47 (m, 2H), 2.46−2.32 (m, 5H), 2.04−1.85 (m, 2H), 1.85−1.18 (m, 4 H) overlapping with 1.40 (s, 9H), 0.92 (t, 3H, $J = 7.2$ Hz); ^{13}C NMR ($CDCl_3$) δ 199.8, 155.3, 146.9, 136.8, 136.7, 136.7, 131.4, 129.2, 127.8, 125.6, 48.6, 38.3, 37.9, 34.0, 32.1, 31.8, 30.2, 30.0, 26.0, 23.7, 21.7, 14.6; IR (neat) 1646 (s), 1591 (s) cm^{-1}; MS (EI) *m/e* 390 (56), 361 (27), 299 (96), 91 (100); HRMS calcd for $C_{26}H_{34}N_2O$ 390.2671, found 390.2679.

Reaction of Imidazole 4f with Carbene Complex 8a. The general procedure was followed using carbene complex **8a** (400 mg, 1.35 mmol) and alkyne aldehyde **4f** (110 mg, 0.32 mmol) at 65 °C. Final purification by flash chromatography (hexane/ethyl acetate 6:1) yielded ketone **13f** (10 mg, 8% yield).

Compound **13f**: ^{1}H NMR ($CDCl_3$) δ 7.34−7.26 (m, 3H), 6.90 (d, 2H, $J = 6.8$ Hz), 5.35 (d, 1H, $J = 17.2$ Hz), 5.23 (d, 1H, $J = 17.2$ Hz), 2.50−2.36 (m, 3H), 2.26 (ddd, 1H, $J = 17.2$, 14.8, 3.2 Hz), 2.01 (m, 1H), 1.91 (m, 1H), 1.80−1.20 (m, 3H) overlapping with 1.38 (s, 9H), 0.29 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 202.76, 161.8, 155.2, 136.7, 136.6, 134.4, 130.7, 129.2, 127.9, 125.6, 48.7, 38.7, 38.0, 34.2, 31.4, 30.3, 28.6, 21.6, 2.0; IR (neat) 1636 (s), 1577 (s)

cm^{-1}; MS (EI) *m*/*e* 406 (4), 391 (43), 358 (15), 272 (8), 91 (100), 73 (13); HRMS calcd for $C_{25}H_{34}N_2OSi$ 406.2440, found 406.2442.

Coupling of Imidazole 4g with Carbene Complex 8a. The general procedure was followed using carbene complex **8a** (246 mg, 0.83 mmol) and alkyne aldehyde **4g** (71 mg, 0.25 mmol) at 75 °C. Final purification by flash chromatography (hexane/ethyl acetate 6:1) yielded three fractions. The product in the first fraction was tentatively identified as naphthimidazole **14g** (4 mg, 4% yield). The product in the second fraction was identified as the minor diastereomer of ketone **13g** (10 mg, 11% yield). The product in the third fraction was identified as the major diastereomer of ketone **13g** (31 mg, 35% yield).

Compound **14g**: ^{1}H NMR ($CDCl_3$) δ 8.14 (s, 1H), 7.73 (d, 1H, J = 9.0 Hz), 7.52 (d, 1H, J = 9.0 Hz), 7.32−7.13 (m, 7H), 5.70 (q, 1H, J = 6.6 Hz), 3.96 (s, 3H), 3.83 (m, 2H), 2.03 (d, 3H, J = 6.6 Hz), 1.69 (m, 2H), 1.54 (m, 2H), 0.96 (t, 3H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 156.1, 140.9, 136.9, 131.0, 129.1, 128.2, 127.7, 126.7, 125.9, 125.8, 111.4, 108.4, 56.5, 55.7, 32.5, 26.0, 22.8, 21.8, 14.3; MS (EI) *m*/*e* 358 (15), 225 (29), 211 (57), 181 (34), 105 (100), 79 (28); HRMS calcd for $C_{24}H_{26}N_2O$ 358.2045, found 358.2055.

Compound **13g** (minor): ^{1}H NMR ($CDCl_3$) δ 7.87 (s, 1H), 7.35 (m, 3H), 7.07 (dd, 2H, J = 7.7, 2.2 Hz), 5.24 (q, 1H, J = 7.3 Hz), 3.21 (m, 1H), 2.96 (m, 1H), 2.67−2.15 (m, 5H), 2.20−1.67 (m, 4H) overlapping with 1.89 (d, 3H, J = 7.3 Hz), 1.40 (m, 4H), 0.90 (t, 3H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 199.1, 145.0, 140.6, 135.4, 135.1, 134.2, 132.5, 129.1, 128.2, 125.7, 55.6, 37.9, 37.6, 31.8, 31.3, 29.5, 25.2, 23.0, 21.8, 21.6, 14.2; IR (neat) 1651 (s), 1588 (s) cm^{-1}; MS (EI) *m*/*e* 348 (64), 243 (100), 105 (69.81), 181 (34), 105 (100), 79 (28); HRMS calcd for $C_{23}H_{28}N_2O$ 348.2202, found 348.2213.

Compound **13g** (major): ^{1}H NMR ($CDCl_3$) δ 7.73 (s, 1H), 7.32 (m, 3H), 7.09 (m, 2H), 5.24 (q, 1H, J = 7 Hz), 3.30−2.89 (m, 2H), 2.75−2.25 (m, 4H), 2.20−1.50 (m, 5H) overlapping with 1.86 (d, 3H, J = 7.0 Hz), 1.42 (m, 4H), 0.90 (t, 3H, J = 6.8 Hz); ^{13}C NMR ($CDCl_3$) 199.4, 145.3, 140.4, 135.4, 134.4 132.7, 129.3, 128.5, 126.0, 55.7, 38.1, 37.8, 31.9, 31.4, 29.8, 25.5, 23.2, 22.1, 21.4, 14.4; IR (neat) 1651 (s), 1588 (s) cm^{-1}; MS (EI) *m*/*e* 348 (23), 243 (92), 105 (100); HRMS calcd for $C_{23}H_{28}N_2O$ 348.2202, found 348.2213.

Coupling of *N*-Ribosylimidazole 4h with Carbene Complex 8a. The general procedure was followed using carbene complex **8a** (201 mg, 0.68 mmol) and alkyne aldehyde **4h** (90 mg, 0.242 mmol) at 65 °C. Final purification by flash chromatography (hexane/ethyl acetate 5:1) yielded a single fraction identified as an inseparable 5:1 diastereomeric mixture of ketones **13h** (40 mg, 40% yield).

Compound **13h**: ^{1}H NMR ($CDCl_3$) δ 7.66 (s, 1H), 7.34−7.11 (m, 15H), 5.69 (d, 1H, J = 6.6 Hz), 4.66 (d, 1H, J = 12.0 Hz), 4.61 (d, 1H, J = 12.0 Hz), 4.56 (d, 1H, J = 11.8 Hz), 4.55 (d, 1H, J = 11.8 Hz), 4.45 (d, 1H, J = 11.8 Hz), 4.39 (d, 1H, J = 11.8 Hz), 4.31 (ddd, 1H, J = 3.2, 3.2, 2.4 Hz), 4.18 (dd, 1H, J = 6.6, 5.0 Hz), 4.08 (dd, 1H, J = 5.0, 2.4 Hz), 4.62 (dd, 1H, J = 10.4, 3.2 Hz), 3.50 (dd, 1H, J = 10.4, 3.2 Hz), 3.20 (m, 1H), 2.974 (m, 1H), 2.75 (dd, 1H, J = 17.2, 4.4 Hz), 2.52 (m, 2H), 2.41 (ddd, 1H, J = 15.6, 15.6, 4.8 Hz), 2.03 (m, 1H), 1.91 (br d, 1H, J = 12.4 Hz), 1.80−1.51 (m, 3H), 1.40 (m, 4H), 0.923 (t, 3H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 199.8, 146.5, 137.56, 137.53, 137.1, 136.8, 135.7, 134.1, 132.3, 128.78, 128.76, 128.41, 128.35, 128.33, 128.20, 127.99, 87.4, 82.7, 81.0, 76.6, 73.8, 72.9, 72.6, 70.0, 38.2, 38.0, 32.0, 31.7, 29.9, 25.5, 23.3, 21.5, 14.5; IR (neat) 1646 (s), 1590 (s) cm^{-1}; MS (FAB) *m*/*e* 648 (M + 2H, 20), 647 (M + H, 40), 460 (4), 329 (16), 307 (39), 289 (12), 243 (7), 176 (31), 154 (100), 137 (65); HRMS calcd for $C_{41}H_{47}N_2O_5$ 647.3485, found 647.3472. The following peaks are indicative of the minor diastereomer: ^{1}H NMR δ 7.72 (s, 1H), 5.67 (d, 1H, J = 6.8 Hz), 4.70−4.50 (numerous additional baseline peaks), 2.66 (m, 1H); ^{13}C NMR peaks at δ 137.1, 135.7, 87.4, and 81.0 all feature a "companion" resonance at about 20% of their intensity.

Coupling of Pyrazole 7 with Carbene Complex 8a. The general procedure was followed using carbene complex **8a** (364 mg, 1.23 mmol) and alkyne aldehyde **7** (110 mg, 0.41 mmol) at 65 °C. Final purification by flash chromatography (hexane/ethyl acetate 6:1) yielded three fractions. The product in the first fraction was identified as the major diastereomer of **16** (50 mg, 30% yield). The product in the second fraction was identified as the minor diastereomer of **16** (38 mg, 22% yield, the major diastereomer is a ca. 20% impurity). The product on the third fraction was identified as lactone **15** (45 mg, 28% yield).

Compound **16** (major): ^{1}H NMR ($CDCl_3$) δ 7.45−7.38 (m, 5H), 4.90 (dt, 1H, J = 10.0, 6.4 Hz), 2.95 (s, 3H, OMe), 2.44 (s, 3H, Me), 2.30−2.05 (m, 4H), 2.00−1.83 (m, 2H), 1.76 (m, 1H), 1.43 (m, 3H), 1.25 (m, 5H), 0.84 (t, 3H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) 175.7, 147.0, 140.2, 136.3, 129.4, 128.3, 122.4, 111.9, 65.2, 52.0, 49.9, 45.6, 41.2, 34.0, 30.0, 26.4, 25.6, 23.7, 23.2, 14.1, 13.5; IR (neat) 3400−3200 (br), 1771 (s) cm^{-1}; MS (CI) *m*/*e* 411 (73), 393 (6), 351 (4), 309 (100); HRMS calcd for $C_{24}H_{31}N_2O_4$ 411.2284, found 411.2292.

Compound **16** (minor): ^{1}H NMR δ 7.45−7.41 (m, 5H), 4.88 (dt, 1H, J = 4.8, 2.4 Hz), 2.96 (s, 3H, OMe), 2.67 (m, 1H), 2.38 (s, 3H), 2.30−2.18 (m, 2H), 2.00−1.68 (m, 5H), 1.28−1.10 (m, 6H), 0.83 (t, 3H, J = 7.2 Hz); IR (neat) 3400−3200 (br), 1771 (s) cm^{-1}; MS (CI) *m*/*e* 411 (M, 100), 393 (12), 347 (8), 309 (12).

Compound **15**: ^{1}H NMR ($CDCl_3$) δ 7.41−7.34 (m, 3H), 7.20 (d, 2H, J = 7.6 Hz), 5.58 (d, 1H, J = 4.8 Hz), 3.46 (s, 3H, OMe), 2.78 (ddd, 1H, J = 13.2, 9.2, 4.6 Hz), 2.50−2.16 (m, 4H) overlapping with 2.34 (s, 3H, Me), 1.92 (ddd, 1H, J = 10.8, 4.0, 2.4 Hz), 1.72 (m, 1H), 1.42−1.22 (m, 3H), 1.16−0.82 (m, 3H), 0.74 (t, 3H, J = 7.2 Hz); ^{13}C NMR 172.2, 152.5, 141.8, 140.9, 139.3, 128.9, 128.5, 127.4, 119.9, 112.5, 71.2, 54.8, 36.0, 35.1, 30.8, 30.6, 27.5, 25.1, 23.8, 13.9, 11.8; IR (neat) 1755 (s) cm^{-1}; MS (EI) *m*/*e* 392 (5), 348 (100), 333 (39), 305 (18), 291 (36), 259 (13), 221 (8), 83 (12); HRMS calcd for $C_{24}H_{28}N_2O_3$ 392.2100, found 392.2101.

Acknowledgment. This research was supported by the SCORE program of the NIH and the donors of the Petroleum Research Fund, administered by the American Chemical Society. Mass spectral data were acquired at the Nebraska Center for Mass Spectrometry or at the University of California—Riverside.

Supporting Information Available: Text giving general experimental procedures and complete experimental procedures for the preparation of compounds **2a**,**b**, **4a**−**h**, and **7** from commercially available chemicals and figures giving proton and ^{13}C NMR spectra for compounds **2a**,**b**, **4a**−**h**, **7**, **9a**,**b**, **11c**, **12c**, **13a**−**h**, **15**, and **16** (major diastereomer). This material is available free of charge via the Internet at http://pubs.acs.org.

OM051008Q