Published in final edited form as:

Synthesis (Stuttg). 2015 May ; 47(8): 1076–1084. doi:10.1055/s-0034-1380160.

Rhodium-Catalyzed Intermolecular [5+1] and [5+2] Cycloadditions Using 1,4-Enynes with an Electron-Donating Ester on the 3-Position

Casi M. Schienebeck^{a,†}, Wangze Song^{a,†}, Angela M. Smits^a, and Weiping Tang^{*,a,b}

^aSchool of Pharmacy, University of Wisconsin, Madison, WI 53706

^bDepartment of Chemistry, University of Wisconsin, Madison, WI 53705

Abstract

Various 3-acyloxy-1,4-enynes could be employed in rhodium-catalyzed intermolecular [5+1] and [5+2] cycloadditions with CO or alkynes, respectively. The rate of these cycloadditions could be accelerated significantly by using 1,4-enynes with an electron-donating ester on the 3-position. The scope of rhodium-catalyzed [5+1] and [5+2] cycloadditions were examined by using 1,4-enynes bearing an electron-donating ester.

Graphical abstract

Keywords

catalysis; cycloaddition; rhodium; rings; benzene

1. Introduction

Transition metal-catalyzed cycloadditions are one of the most important reactions in organic chemistry.¹ Mono- and polycyclic compounds can be constructed efficiently by forming at least two bonds in cycloaddition reactions. The even-carbon component in cycloadditions are often commercially available (e.g. many alkenes and alkynes) or can be easily prepared (e.g. dienes, trienes, etc.). The discovery of novel odd-carbon component is highly desirable and may lead to the realization of a series of new cycloadditions. We and others recently found that 3-acyloxy-1,4-enynes could be employed as novel five-carbon building blocks in rhodium-catalyzed [5+1]² and [5+2]³ cycloadditions (Scheme 1).⁴ This discovery has led to

Fax: +1 (608) 262-5345. wtang@pharmacy.wisc.edu.

[†]C.M.S. and W.S. contributed equally.

Supporting Information (¹H and ¹³C NMR spectra) for this article is available online.

the development of new methods for the preparation of highly substituted six- and seven-membered rings.

We recently examined the effect of different esters on the 3-position of the 1,4-enyne in Rh-catalyzed [5+2] cycloaddition.⁵ We found that electron-donating ester could significantly accelerate the rate of the [5+2] cycloaddition (Scheme 2a). DFT calculation suggested that the electron-donating ester could stabilize the positive charges on the carbonyl carbon and lower the energy of the transition state in the rate-determining step (RDS) as shown in Scheme 2b.⁶ The RDS involves a Rh-promoted 1,2-acyloxy migration and an oxidative cyclization to form a six-membered metallacycle. After the first step, insertion of alkyne followed by reductive elimination can afford the seven-membered ring product **1a**.

In this full paper, we explored the scope of the rhodium-catalyzed intermolecular [5+2] and [5+1] cycloadditions of 1,4-enynes bearing an electron-donating ester on the 3-position with alkynes and CO, respectively. Lower catalyst loading, higher yields, and mild conditions are some of the benefits we gained by using the electron-donating esters in these two cycloadditions.

2. Rh-catalyzed intermolecular [5+2] cycloaddition

Prior to our work,⁵ transition metal-catalyzed 1,2-acyloxy migration of propargylic esters have been extensively studied in various reactions.^{4,7} The effect of the ester on these reactions including ours, however, have not been systematically investigated. As shown in Scheme 1, pivalate or acetate were employed in most cases. By employing *p*-dimethylaminobenzoate **1d**, we are able to lower the loading of Wilkinson catalyst from 10 mol% to 0.5 mol% for many substrates in the intermolecular [5+2] cycloaddition of 3-acyloxy-1,4-enynes and alkynes. The amount of propargylic alcohol can also be lowered from 2.0 equivalent to 1.1 equivalent. The scope of Rh-catalyzed [5+2] cycloaddition is then examined under this new condition (Equation 1 and Table 1).

A variety of functionalized terminal alkynes proved to be excellent 2-carbon components for our newly improved [5+2] cycloaddition reaction (Table 1, Entries 1-6). These successful functional groups include a primary or tertiary alcohol, sulphonamide, ether, or nitrile. The conjugated enyne was not very efficient in this reaction and needed slightly higher catalyst loading (Entry 7). In our previous study we found that non-functionalized alkynes needed a separate catalyst and ligand, [Rh(COD)Cl]₂ with (4-CF₃C₆H₄)₃P, in order to obtain good yields.^{3a} However, with the *p*-dimethylaminobenzoate substituted ACE, simple Wilkinson's catalyst worked best, albeit at a higher catalyst loading (entry 8).

(3)

We also examined the [5+2] cycloaddition with internal alkynes (Equation 2 and Table 2). Functionalized internal alkyne **5a** efficiently participated in the reaction at the lower catalyst loading (Table 2, Entry 1). The sensitive ynoate **5b** was previously not successful in the [5+2] cycloaddition with pivalate substituted ACE.^{3a} However, with the new electron-rich 5-carbon component **1d**, we were able to obtain excellent yield of the desired cycloheptatriene at a higher catalyst loading (Entry 2). Unsymmetrical internal propargyl alcohol **5c** produced a mixture of the two seven-membered-ring isomers in a ratio of 5:1 at 2 mol% catalyst loading (Entry 3). Finally we were unable to successfully obtain the desired products using alkynes **5d** and **5e** (Entries 4 and 5).

Other alkyl group can also be tolerated on the R¹-position (**7a**, Equation 3). However, alkyl and aryl substitutions on the alkene shut down the reaction even at a higher catalyst loading (**7b** and **7c**).

The dimethylaminobenzoate ester also improved the reaction for secondary ACEs. The pivalate substituted secondary ACE only provided 16% yield of the [5+2] cycloaddition product; however, the electron-rich ACE had a dramatically improved yield, 53% (Equation 4). It is worth to mention that the addition of electron-deficient ligand is necessary in this case.

(4)

Other electron-rich esters, such as indolyl-substituted ester **11**, worked equally well and afforded product **12** in high yield (Equation 5).

(5)

We also examined other transition metal catalysts for the [5+2] cycloaddition of enyne **1d** and propargylic alcohol **3a** (Table 3). Of the catalysts tested, none provided the desired cycloaddition product.

3. Rh-catalyzed intermolecular [5+1] cycloaddition

Research groups of Fukuyama, Ryu, Fensterbank, and Malacria developed a [5+1] cycloaddition of ACEs with CO.^{2a} The ACEs they employed had either a pivalate or acetate. Since the electron-rich ester improved the [5+2] reaction so much, we decided to see what effect it had on the [5+1] reaction. The previously established conditions for [5+1] cycloaddition required 50-80 atm of CO and heating to 80 °C.^{2a} However, when we switched to the newly discovered electron-rich ACE **1d**, we were able to isolate the desired phenol **14a** in 69% yield using the same catalyst with only 1 atm of CO and at room temperature (Table 4, Entry 1).

We then examined the scope of this [5+1] cycloaddition. Benzoate and pivalate esters did not work at all under these mild conditions (Table 4, Entries 2 and 3). A number of secondary esters were also successful and they generally required heating to 50 °C. Both phenyl and naphthyl groups were tolerated for R² (entries 4 and 8). However, an alkyl substituent on this carbon of the alkene resulted in poor yields (Entry 5). Not surprisingly, pivalate versions of the ACEs resulted in no reaction under the optimized conditions (Entries 6 and 7). While an electron deficient aryl substituent shut down the reaction (Entry 9), electron-rich aryl substituents were tolerated on the terminal carbon of alkene of the ACE (Entries 10 and 11). Substituents on the inner carbon of the alkene also shut down the reaction (Entry 12).

In addition to dimethylaminobenzoate, electron-rich indolyl-substituted ACE **11** was an excellent substrate for the [5+1] reaction and afforded product **15** (Equation 8).

(8)

We also examined other transition metal catalysts for the [5+1] cycloaddition of enyne **1d** and CO (Table 5). Of the catalysts we tested, none provided the desired cycloaddition product.

4. Conclusion

In summary, when an electron-rich ester was introduced into the ACE for the [5+2] cycloaddition a dramatic rate acceleration was observed. A much lower catalyst loading could be utilized while retaining high yields of the cycloheptatriene products for a variety of alkynes and ACEs. This electron-rich ACE was also able to improve the utility of the [5+1] cycloaddition as well. The ester effect may have implications for other transformations involving 1,2-acyloxy migration of propargylic esters.

Unless otherwise noted, all reactions in non-aqueous media were conducted under dry argon in glassware that had been oven-dried prior to use. Anhydrous solutions of reaction mixtures were transferred via an oven-dried syringe or cannula. All solvents were dried prior to use. Thin layer chromatography was performed using precoated silica gel plates. Flash column chromatography was performed with silica gel (40-63 μ m). Infrared spectra (IR) were obtained as neat oil. ^1H and ^{13}C Nuclear Magnetic Resonance spectra (NMR) were obtained on a 400 MHz or 500 MHz spectrometer recorded in ppm (δ) downfield of TMS ($\delta = 0$) in CDCl_3 . Signal splitting patterns were described as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), pentet (p) or multiplet (m), with coupling constants (J) in hertz. High resolution mass spectra (HRMS) were performed by the Analytical Instrument Center at the School of Pharmacy or the Department of Chemistry on an Electron Spray Injection (ESI) mass spectrometer.

Note—Characterization data for substrates and products in Scheme 2, Table 1, Table 2, and Equation 4 were published in our previous communication.⁵

Representative procedure for the preparation of ester 7a—A solution of 1-octyn-3-ol (4 g, 31.7 mmol) in acetone (140 ml) was cooled to 0 °C and Jones reagent (4.754 g of chromium (VI) oxide in 12.8 ml of a 25% aqueous solution of H_2SO_4) was added dropwise and stirred for 1 h at room temperature. After the reaction was complete, as determined by TLC, the mixture was filtered over celite and the solvent evaporated. The residue was then extracted with ether and the organic layers were combined and dried over MgSO_4 . The crude residue was then purified by flash chromatography on silica gel to afford the corresponding ketone in nearly quantitative yield.

A solution of the above ketone (3.93 g, 31.7 mmol) in anhydrous THF (200 ml) was cooled to -78 °C and a 1.0 M solution of vinyl magnesium bromide (127 ml) was added dropwise. The solution was stirred for 1 h and quenched with ammonium chloride and filtered through a pad of celite. The solvent was evaporated and the aqueous layer washed with ether. The combined organic layers were then dried over MgSO_4 and then concentrated in vacuum. The crude residue was purified by flash chromatography on silica gel to afford the tertiary alcohol in 40% yield.

A solution of the above tertiary alcohol (1 g, 6.6 mmol) in THF (30 ml) was cooled to -78 °C and a 2.5 M solution of *n*BuLi (2.6 ml) was added dropwise. The mixture was stirred at room temperature for 1 h. The mixture was then cooled back down to -78 °C and 4-(dimethylamino)-benzoyl chloride (1.45 g, 7.9 mmol) was added. The reaction mixture was then stirred at room temperature overnight. The reaction was then quenched with ammonium chloride and filtered through a pad of celite. The solvent was evaporated and the aqueous layer was washed with ether. The combined organic layers were then dried over MgSO₄ and the concentrated in vacuum. The crude residue was purified by flash chromatography on silica gel to afford ester **7a** in 55% yield.

Representative procedure for the formation of 4a via Rh-catalyzed [5+2]

cycloaddition of 1d and alkyne—To a flask containing 1,4-enyne **1d** (1 equiv.) and alkyne (1.1 equiv) was added RhCl(PPh₃)₃ (0.5 mol %) and chloroform (0.4M). The flask was flushed with argon and allowed to stir at 50 °C. The reaction was monitored by TLC until **1d** was completely consumed (~24h). The solvent was evaporated under vacuum and the resulting residue was purified via flash chromatography on silica gel (hexanes / ethyl acetate) to yield product **4a** in 97% yield.

Representative procedure for the formation of 14a via Rh-catalyzed [5+1]

cycloaddition of 1d and CO—To a flask containing 1,4-enyne **1d** (1 equiv.) was added [Rh(CO)₂Cl]₂ (5 mol %) and dichloroethane (0.4M). The flask was flushed with CO and allowed to stir at room temperature under a CO balloon of 1 atm. The reaction was monitored by TLC until **1d** was completely consumed (24h). The solvent was evaporated under vacuum and the resulting residue was purified via flash chromatography on silica gel (hexanes / ethyl acetate) to yield product **14a** in 69% yield.

4-Dimethylamino-benzoic acid 1-ethynyl-1-vinyl-hexyl ester (7a)

Solid, m.p. = 56-59 °C. ¹H NMR (400Mz, CDCl₃) δ 7.93-7.84 (m, 2H), 6.68-6.59 (m, 2H), 5.99 (dd, *J* = 17.1, 10.4 Hz, 1H), 5.64 (dd, *J* = 17.1, 0.9 Hz, 1H), 5.30 (dd, *J* = 10.4, 0.9 Hz, 1H), 3.03 (s, 6H), 2.70 (s, 1H), 2.10 (ddd, *J* = 13.4, 11.6, 5.0 Hz, 1H), 1.93 (ddd, *J* = 13.4, 11.5, 5.0 Hz, 1H), 1.67-1.51 (m, 2H), 1.42-1.24 (m, 4H), 0.96-0.84 (m, 3H); ¹³C NMR (100Mz, CDCl₃) δ 165.1, 153.5, 138.5, 131.6, 117.6, 116.2, 110.9, 82.0, 77.6, 75.6, 41.5, 40.3, 31.9, 23.8, 22.8, 14.3. IR (film): 3306, 3257, 3091, 2954, 2930, 2868, 2360, 2341, 1709, 1605, 1526, 1367, 1275, 1181, 1088, 984, 924, 828, 768, 731, 697. cm⁻¹. HRMS (ESI) *m/z* calc. For C₁₉H₂₅NO₂ (M+H)⁺ 300.1958, found 300.1958.

4-Dimethylamino-benzoic acid 1-ethynyl-3-phenyl-allyl ester (7b)

Ester **7b** was prepared according to previously published procedures.^{3a}

Solid, m.p. = 100-105 °C. ¹H NMR (400Mz, CDCl₃) δ 7.92-7.80 (m, 2H), 7.37-7.27 (m, 2H), 7.27-7.05 (m, 3H), 6.84 (d, *J* = 15.5 Hz, 1H), 6.55-6.45 (m, 2H), 6.32-6.15 (m, 2H), 2.87 (s, 6H), 2.55 (dd, *J* = 2.2, 0.8 Hz, 1H); ¹³C NMR (100Mz, CDCl₃) δ 165.9, 153.8, 136.1, 134.5, 131.9, 128.9, 128.6, 127.2, 124.4, 116.3, 110.9, 80.3, 75.4, 63.9, 40.3. IR (film): 3295, 3058, 3028, 2918, 2867, 2820, 2360, 1701, 1604, 1527, 1370, 1264, 1180,

1087, 946, 828, 768, 735, 693 cm^{-1} . HRMS (ESI) m/z calc. For $\text{C}_{20}\text{H}_{19}\text{NO}_2$ ($\text{M}+\text{Na}$)⁺ 328.1308, found 328.1310.

4-Dimethylamino-benzoic acid 1-ethynyl-but-2-enyl ester (7c)

Ester 7c was prepared according to previously published procedures.^{3a}

Oil. ^1H NMR (400Mz, CDCl_3) δ 7.89-7.80 (m, 2H), 6.66-6.43 (m, 2H), 6.07-5.89 (m, 2H), 5.61 (ddq, J = 15.2, 6.5, 1.6 Hz, 1H), 2.97 (d, J = 1.2 Hz, 6H), 2.49 (dd, J = 2.2, 1.0 Hz, 1H), 1.80-1.59 (m, 3H); ^{13}C NMR (100Mz, CDCl_3) δ 165.9, 153.7, 131.8, 131.4, 126.5, 116.6, 110.9, 80.8, 74.5, 63.8, 40.3, 17.8. IR (film): 3291, 3038, 2917, 2856, 2819, 2360, 2341, 1699, 1606, 1526, 1369, 1316, 1262, 1179, 1087, 964, 944, 828, 767, 698, 669 cm^{-1} . HRMS (ESI) m/z calc. For $\text{C}_{15}\text{H}_{17}\text{NO}_2$ ($\text{M}+\text{Na}$)⁺ 266.1151, found 266.1151.

1H-Indole-2-carboxylic acid 1-ethynyl-1-methyl-allyl ester (11)

Ester 11 was prepared according to published procedures.⁵

Oil. ^1H NMR (500Mz, CDCl_3) δ 8.86 (s, 1H), 7.68 (d, J = 10.0 Hz, 1H), 7.43 (d, J = 10.0 Hz, 1H), 7.34-7.31 (m, 1H), 7.22 (s, 1H), 7.17-7.13 (m, 1H), 6.12 (dd, J = 20.0, 10.0 Hz, 1H), 5.70 (d, J = 15.0 Hz, 1H), 5.33 (d, J = 10.0 Hz, 1H), 2.78 (s, 1H), 1.92 (s, 3H); ^{13}C NMR (125Mz, CDCl_3) δ 160.4, 138.4, 137.2, 127.65, 127.61, 125.6, 122.8, 121.0, 116.3, 112.2, 109.2, 82.1, 75.7, 75.2, 28.9. IR (film): 3390, 2360, 1699, 1490, 1156, 1033, 942, 869 cm^{-1} . HRMS (ESI) m/z calc. For $\text{C}_{15}\text{H}_{13}\text{NO}_2$ ($\text{M}+\text{Na}$)⁺ 262.0840, found 262.0842.

Representative procedures for Rh-catalyzed [5+2] cycloaddition

To a flask containing 1,4-enyne substrate (1 equiv.) and alkyne (1.1 equiv) was added $\text{RhCl}(\text{PPh}_3)_3$ (0.5 mol%) and chloroform (0.4 M). The flask was flushed with argon and allowed to stir at 50 °C. The reaction was monitored by TLC until the 1,4-enyne was completely consumed (~24 h). The solvent was evaporated and the resulting residue was purified via flash chromatography on silica gel to yield product **8a** or **12**.

4-Dimethylamino-benzoic acid 4-hydroxymethyl-7-pentyl-cyclohepta-1,3,6-trienyl ester (8a)

Oil, 72% yield, 25.2 mg. ^1H NMR (400Mz, CDCl_3) δ 8.09-7.88 (m, 2H), 6.77-6.59 (m, 2H), 6.37 (d, J = 6.3 Hz, 1H), 6.10 (dt, J = 6.3, 1.5 Hz, 1H), 5.41-5.22 (m, 1H), 4.27 (t, J = 1.2 Hz, 2H), 3.06 (s, 6H), 2.50 (d, J = 7.3 Hz, 2H), 2.23-2.01 (m, 2H), 1.50-1.30 (m, 2H), 1.30-1.05 (m, 4H), 0.81 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100Mz, CDCl_3) δ 165.8, 153.9, 152.1, 137.6, 136.1, 132.0, 120.2, 120.1, 118.6, 116.3, 111.0, 66.3, 40.3, 32.3, 31.7, 29.2, 29.0, 22.6, 14.3. IR (film): 3405, 2955, 2928, 2859, 2360, 2341, 1706, 1604, 1529, 1445, 1370, 1274, 1181, 1122, 1063, 945, 908, 827, 765, 728, 696 cm^{-1} . HRMS (ESI) m/z calc. For $\text{C}_{22}\text{H}_{29}\text{NO}_3$ ($\text{M}+\text{Na}$)⁺ 378.2040, found 378.2042.

1H-Indole-2-carboxylic acid 4-hydroxymethyl-7-methyl-cyclohepta-1,3,6-trienyl ester (12)

Solid, m.p. = 119-123 °C, 85% yield, 33.2 mg. ^1H NMR (400Mz, CDCl_3) δ 9.10 (dd, J = 19.3, 8.3 Hz, 1H), 7.73 (d, J = 8.1 Hz, 1H), 7.48-7.31 (m, 3H), 7.18 (t, J = 7.5 Hz, 1H), 6.44 (d, J = 6.4 Hz, 1H), 6.17 (d, J = 6.4 Hz, 1H), 5.35 (t, J = 7.4 Hz, 1H), 4.29 (s, 2H), 2.52 (d, J = 7.3 Hz, 2H), 1.85 (s, 3H), 1.65-1.59 (m, 1H); ^{13}C NMR (100Mz, CDCl_3) δ 160.7, 151.5,

137.6, 137.5, 131.2, 127.7, 126.6, 126.0, 123.0, 121.3, 120.8, 120.1, 118.4, 112.3, 110.2, 66.2, 29.2, 18.0. IR (film): 3345, 3062, 2950, 2925, 2874, 2360, 2342, 1703, 1525, 1310, 1245, 1186, 1147, 1053, 908, 731 cm^{-1} . HRMS (ESI) m/z calc. For $\text{C}_{18}\text{H}_{17}\text{NO}_3$ ($\text{M}+\text{H}$)⁺ 296.1281, found 296.1281.

Esters 13a, 13b, 13c, and 13d were prepared according to published procedures.^{3a}

4-Dimethylamino-benzoic acid 1-ethynyl-3-naphthalen-2-yl-allyl ester (13a)

Oil. ^1H NMR (500Mz, CDCl_3) δ 7.97 (d, J = 10.0 Hz, 2H), 7.80-7.77 (m, 4H), 7.61 (d, J = 10.0 Hz, 1H), 7.46-7.43 (m, 2H), 7.10 (d, J = 15.0 Hz, 1H), 6.63 (d, J = 10.0 Hz, 2H), 6.47 (dd, J = 15.0, 5.0 Hz, 1H), 6.36-6.34 (m, 1H), 3.01 (s, 6H), 2.67 (s, 1H); ^{13}C NMR (100Mz, CDCl_3) δ 165.8, 153.7, 134.4, 133.6, 133.53, 133.51, 131.8, 128.5, 128.3, 127.8, 127.6, 126.5, 126.4, 124.6, 123.8, 116.3, 110.8, 80.2, 75.3, 63.8, 40.2. IR (film): 3294, 2046, 1662, 1449, 1416, 1114, 1023, 836 cm^{-1} . HRMS (ESI) m/z calc. For $\text{C}_{24}\text{H}_{21}\text{NO}_2$ ($\text{M}+\text{Na}$)⁺ 378.1464, found 378.1471.

4-Dimethylamino-benzoic acid 3-(4-chloro-phenyl)-1-ethynyl-allyl ester (13b)

Oil. ^1H NMR (500Mz, CDCl_3) δ 7.95 (d, J = 7.0 Hz, 2H), 7.34-7.25 (m, 4H), 6.90 (d, J = 15.5 Hz, 1H), 6.64 (d, J = 7.5 Hz, 2H), 6.35-6.28 (m, 2H), 3.03 (s, 6H), 2.64 (s, 1H); ^{13}C NMR (100Mz, CDCl_3) δ 165.8, 153.8, 134.5, 134.2, 133.1, 131.9, 129.0, 128.3, 125.0, 116.2, 110.9, 80.0, 75.4, 63.6, 40.3. IR (film): 3310, 2360, 1699, 1656, 1514, 1179, 1087, 944, 766 cm^{-1} . HRMS (ESI) m/z calc. For $\text{C}_{20}\text{H}_{18}\text{ClNO}_2$ ($\text{M}+\text{Na}$)⁺ 362.0919, found 362.0924.

4-Dimethylamino-benzoic acid 1-ethynyl-3-(4-methoxy-phenyl)-allyl ester (13c)

Oil. ^1H NMR (500Mz, CDCl_3) δ 7.95 (d, J = 10.0 Hz, 2H), 7.36 (d, J = 5.0 Hz, 2H), 6.90-6.85 (m, 3H), 6.63 (d, J = 5.0 Hz, 2H), 6.26-6.20 (m, 2H), 3.80 (s, 3H), 3.03 (s, 6H), 2.63 (s, 1H); ^{13}C NMR (100Mz, CDCl_3) δ 165.8, 160.0, 153.7, 134.0, 131.8, 128.7, 128.4, 122.0, 116.4, 114.2, 110.8, 80.4, 75.0, 64.0, 55.5, 40.2. IR (film): 3296, 2359, 1702, 1607, 1513, 1183, 1028, 947, 769 cm^{-1} . HRMS (ESI) m/z calc. For $\text{C}_{21}\text{H}_{21}\text{NO}_3$ ($\text{M}+\text{Na}$)⁺ 358.1413, found 358.1416.

4-Dimethylamino-benzoic acid 3-[4-(tert-butyl-dimethyl-silanyloxy)-3-methoxy-phenyl]-1-ethynyl-allyl ester (13d)

Oil. ^1H NMR (500Mz, CDCl_3) δ 7.79 (d, J = 7.5 Hz, 2H), 6.79-6.71 (m, 3H), 6.64 (d, J = 7.5 Hz, 1H), 6.47 (d, J = 9.0 Hz, 2H), 6.13-6.05 (m, 2H), 3.66 (s, 3H), 2.86 (s, 6H), 2.49 (s, 1H), 0.84 (s, 9H), 0.00 (s, 6H); ^{13}C NMR (125Mz, CDCl_3) δ 165.9, 153.7, 151.2, 145.7, 134.5, 131.8, 129.9, 122.3, 121.1, 120.5, 116.4, 110.8, 110.3, 80.4, 75.1, 63.9, 55.6, 40.2, 25.9, 18.7, -4.4. IR (film): 3298, 2361, 1707, 1545, 1454, 1281, 1033, 901, 676 cm^{-1} . HRMS (ESI) m/z calc. For $\text{C}_{27}\text{H}_{35}\text{NO}_4\text{Si}$ ($\text{M}+\text{Na}$)⁺ 488.2227, found 488.2237.

Representative procedures for Rh-catalyzed [5+1] cycloaddition

To a flask containing 1,4-enyne (1 equiv.) was added $[\text{Rh}(\text{CO})_2\text{Cl}]_2$ (5 mol%) and dichloroethane (0.4 M). The flask was flushed with CO and allowed to stir at room

temperature or 50 °C under a CO balloon of 1 atm. The reaction was monitored by TLC until the 1,4-enyne was completely consumed. The solvent was evaporated and the resulting residue was purified via flash chromatography on silica gel to yield [5+1] cycloaddition product.

4-Dimethylamino-benzoic acid 5-hydroxy-2-methyl-phenyl ester (14a)

Solid, m.p. = 193-195 °C, 69% yield, 16.1 mg. ^1H NMR (400Mz, CDCl_3) δ 8.07 (d, J = 8.6 Hz, 2H), 7.07 (d, J = 8.3 Hz, 1H), 6.70 (d, J = 8.7 Hz, 2H), 6.62 (d, J = 6.5 Hz, 2H), 5.34 (broad, 1H), 3.08 (s, 6H), 2.12 (s, 3H); ^{13}C NMR (100Mz, CDCl_3) δ 165.6, 154.8, 154.0, 150.4, 132.3, 131.6, 122.4, 115.9, 113.2, 111.0, 110.1, 40.3, 15.7. IR (film): 3346, 3030, 2925, 2858, 2360, 1679, 1602, 1506, 1376, 1284, 1183, 1150, 1105, 908, 825, 767, 733 cm^{-1} . HRMS (ESI) m/z calc. For $\text{C}_{16}\text{H}_{17}\text{NO}_3$ ($\text{M}+\text{H}$) $^+$ 272.1281, found 272.1281.

4-Dimethylamino-benzoic acid 2-hydroxy-biphenyl-4-yl ester (14b)

Solid, m.p. = 137-143 °C, 66% yield, 18 mg. ^1H NMR (400Mz, CDCl_3) δ 8.13-8.02 (m, 2H), 7.57-7.36 (m, 5H), 7.31-7.22 (m, 1H), 6.86 (d, J = 7.1 Hz, 2H), 6.77-6.65 (m, 2H), 5.54-5.21 (broad, 1H), 3.09 (s, 6H); ^{13}C NMR (100Mz, CDCl_3) δ 165.6, 154.0, 153.3, 152.1, 136.9, 132.3, 130.8, 129.5, 129.4, 128.1, 125.7, 116.1, 114.7, 111.0, 110.0, 40.3. IR (film): 3363, 3210, 3060, 3030, 2924, 2856, 2822, 2361, 2342, 1716, 1689, 1603, 1531, 1417, 1372, 1270, 1182, 1157, 1067, 909, 764, 731, 698 cm^{-1} . HRMS (ESI) m/z calc. For $\text{C}_{21}\text{H}_{19}\text{NO}_3$ ($\text{M}+\text{Na}$) $^+$ 356.1257, found 356.1259.

4-Dimethylamino-benzoic acid 3-hydroxy-4-methyl-phenyl ester (14c)

Solid, m.p. = 185-190 °C, 35% yield, 15.8 mg. ^1H NMR (500Mz, CDCl_3) δ 8.04 (d, J = 8.7 Hz, 2H), 7.11 (d, J = 8.1 Hz, 1H), 6.67 (dd, J = 17.2, 7.9 Hz, 4H), 5.24 (broad, 1H), 3.07 (s, 6H), 2.21 (s, 3H); ^{13}C NMR (125Mz, CDCl_3) δ 166.1, 154.6, 154.0, 150.3, 132.3, 131.4, 121.4, 116.2, 114.0, 111.0, 109.4, 40.3, 15.6. IR (film): 3367, 3283, 2926, 2857, 2824, 2360, 2341, 1674, 1603, 1528, 1376, 1291, 1272, 1182, 1149, 1109, 1079, 909, 828, 766, 734 cm^{-1} . HRMS (ESI) m/z calc. For $\text{C}_{16}\text{H}_{17}\text{NO}_3$ ($\text{M}+\text{H}$) $^+$ 272.1281, found 272.1286.

4-Dimethylamino-benzoic acid 3-hydroxy-4-naphthalen-2-yl-phenyl ester (14d)

Solid, m.p. = 187-188 °C, 54% yield. ^1H NMR (500Mz, CDCl_3) δ 8.07 (d, J = 5.0 Hz, 2H), 7.98-7.95 (m, 2H), 7.90-7.88 (m, 2H), 7.58 (d, J = 8.0 Hz, 1H), 7.55-7.53 (m, 2H), 7.36 (d, J = 8.5 Hz, 1H), 6.91-6.89 (m, 2H), 6.71 (d, J = 9.0 Hz, 2H), 5.37 (s, 1H), 3.09 (s, 6H); ^{13}C NMR (100Mz, CDCl_3) δ 165.7, 154.0, 153.5, 152.2, 134.3, 133.8, 132.9, 132.3, 131.0, 129.4, 128.2, 128.1, 128.0, 127.4, 126.8, 126.6, 125.6, 114.8, 111.0, 110.0, 40.3. IR (film): 3539, 2349, 1686, 1539, 1399, 1221, 764, 685 cm^{-1} . HRMS (ESI) m/z calc. For $\text{C}_{25}\text{H}_{21}\text{NO}_3$ ($\text{M}+\text{Na}$) $^+$ 406.1413, found 406.1415.

4-Dimethylamino-benzoic acid 2-hydroxy-4'-methoxy-biphenyl-4-yl ester (14e)

Solid, m.p. = 155-156 °C, 51% yield. ^1H NMR (500Mz, CDCl_3) δ 8.06 (d, J = 9.0 Hz, 2H), 7.39 (d, J = 8.5 Hz, 2H), 7.22 (d, J = 8.0 Hz, 1H), 7.02 (d, J = 8.5 Hz, 2H), 6.84-6.82 (m, 2H), 6.70 (d, J = 9.5 Hz, 2H), 5.25 (s, 1H), 3.86 (s, 3H), 3.08 (s, 6H); ^{13}C NMR (125Mz, CDCl_3) δ 165.7, 159.6, 153.9, 153.4, 151.8, 132.2, 130.7, 130.5, 128.9, 125.4, 116.1, 115.0,

114.6, 111.0, 109.8, 55.6, 40.3. IR (film): 3333, 2341, 1689, 1603, 1318, 1223, 828, 766 cm^{-1} . HRMS (ESI) m/z calc. For $\text{C}_{22}\text{H}_{21}\text{NO}_4$ ($\text{M}+\text{Na}$)⁺ 386.1362, found 386.1364.

4-Dimethylamino-benzoic acid 4'-(tert-butyl-dimethyl-silanyloxy)-2-hydroxy-3'-methoxy-biphenyl-4-yl ester (14f)

Oil, 64% yield. ^1H NMR (400Mz, CDCl_3) δ 8.06 (d, J = 9.2 Hz, 2H), 7.24 (d, J = 8.0 Hz, 1H), 6.94-6.91 (m, 3H), 6.85-6.81 (m, 2H), 6.70, (d, J = 9.2 Hz, 2H), 5.40 (s, 1H), 3.86 (s, 3H), 3.08 (s, 6H), 1.02 (s, 9H), 0.20 (s, 6H); ^{13}C NMR (125Mz, CDCl_3) δ 165.7, 154.0, 153.4, 151.9, 145.2, 132.2, 130.6, 129.9, 125.6, 121.8, 121.4, 116.1, 114.4, 113.2, 111.0, 109.7, 55.8, 40.3, 26.0, 18.7, -4.2. IR (film): 3368, 2361, 1683, 1472, 1283, 1032, 762, 692 cm^{-1} . HRMS (ESI) m/z calc. For $\text{C}_{28}\text{H}_{35}\text{NO}_5\text{Si}$ ($\text{M}+\text{Na}$)⁺ 516.2176, found 516.2182.

1H-Indole-2-carboxylic acid 5-hydroxy-2-methyl-phenyl ester (15)

Solid, m.p. = 191-192 °C, 73% yield. ^1H NMR (400Mz, $(\text{CD}_3)_2\text{CO}$) δ 8.33 (s, 1H), 7.62 (d, J = 8.4 Hz, 1H), 7.45 (d, J = 8.4 Hz, 1H), 7.30 (s, 1H), 7.21 (t, J = 7.2 Hz, 1H), 7.02 (q, J = 17.2, 7.2 Hz, 2H), 6.59-6.57 (m, 2H), 2.74 (s, 1H), 1.98 (s, 3H); ^{13}C NMR (100Mz, $(\text{CD}_3)_2\text{CO}$) δ 160.3, 157.1, 150.6, 138.9, 138.7, 132.181, 132.117, 126.2, 123.2, 121.5, 113.38, 113.33, 110.3, 110.25, 110.20, 15.4. IR (film): 3333, 1732, 1407, 1254, 1110, 904, 769 cm^{-1} . HRMS (ESI) m/z calc. For $\text{C}_{16}\text{H}_{13}\text{NO}_3$ ($\text{M}+\text{Na}$)⁺ 290.0787, found 290.0788.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank NIH (R01GM088285) and the University of Wisconsin for financial support.

References

1. For selected reviews, see: Lautens M, Klute W, Tam W. Chem Rev. 1996; 96:49. [PubMed: 11848744] Ojima I, Tzamarioudaki M, Li ZY, Donovan RJ. Chem Rev. 1996; 96:635. [PubMed: 11848768] Fruhauf HW. Chem Rev. 1997; 97:523. [PubMed: 11848882] Trost BM, Krische MJ. Synlett. 1998;1.Yet L. Chem Rev. 2000; 100:2963. [PubMed: 11749312] Aubert C, Buisine O, Malacria M. Chem Rev. 2002; 102:813. [PubMed: 11890758] Michelet V, Toullec PY, Genet JP. Angew Chem Int Ed. 2008; 47:4268.Yu ZX, Wang Y, Wang Y. Chem Asian J. 2010; 5:1072. [PubMed: 20432504] Inglesby PA, Evans PA. Chem Soc Rev. 2010; 39:2791. [PubMed: 20505862] Aubert C, Fensterbank L, Garcia P, Malacria M, Simonneau A. Chem Rev. 2011; 111:1954. [PubMed: 21391568]
2. a) Brancour C, Fukuyama T, Ohta Y, Ryu I, Dhimane AL, Fensterbank L, Malacria M. Chem Commun. 2010; 46:5470.b) Fukuyama T, Ohta Y, Brancour C, Miyagawa K, Ryu I, Dhimane AL, Fensterbank L, Malacria M. Chem Eur J. 2012; 18:7243. [PubMed: 22505021]
3. a) Shu XZ, Li X, Shu D, Huang S, Schienebeck CM, Zhou X, Robichaux PJ, Tang W. J Am Chem Soc. 2012; 134:5211. [PubMed: 22364320] b) Shu XZ, Huang S, Shu D, Guzei IA, Tang W. Angew Chem Int Ed. 2011; 50:8153.c) Shu XZ, Schienebeck CM, Song W, Guzei IA, Tang W. Angew Chem Int Ed. 2013; 52:13601.
4. For our recent reviews, see: Shu XZ, Shu D, Schienebeck CM, Tang W. Chem Soc Rev. 2012; 41:7698. [PubMed: 22895533] Schienebeck CM, Li X, Shu XZ, Tang W. Pure Appl Chem. 2014; 86:409. [PubMed: 24839310]
5. Schienebeck CM, Robichaux PJ, Li X, Chen L, Tang W. Chem Commun. 2013; 49:2616.

6. Xu X, Liu P, Shu XZ, Tang W, Houk KN. J Am Chem Soc. 2013; 135:9271. [PubMed: 23725341]
7. a) Marion N, Nolan SP. Angew Chem Int Ed. 2007; 46:2750. b) Marco-Contelles J, Soriano E. Chem Eur J. 2007; 13:1350. [PubMed: 17200921] c) Wang S, Zhang G, Zhang L. Synlett. 2010:692.

Biographies

Casi M. Schienebeck received her B.A. degree in chemistry from the University of Minnesota-Twin Cities in 2009. She began her undergraduate research at the University of Wisconsin-Madison under the supervision of Professor Richard Hsung and continued her graduate studies under the supervision of Professor Weiping Tang at the same institute.

Wangze Song received his B.S. degree in Chemistry from Nankai University in 2008 and his M.S. degree in Chemistry from Zhejiang University in 2011. He worked in Professor Chi Zhang's lab at Nankai University and Professor Yanguang Wang and Professor Ping Lv at Zhejiang University. He is currently pursuing his Ph.D. degree at the University of Wisconsin-Madison under the supervision of Professor Weiping Tang.

Angela M. Smits was born in Eau Claire, Wisconsin. She attended Chippewa Falls High School and is currently studying chemistry at the University of Wisconsin-Madison as an undergraduate student.

Weiping Tang graduated from Peking University with a BS degree in Chemistry. He received his M.S. degree from New York University and Ph.D. degree from Stanford University. He was a Howard Hughes Medical Institute postdoctoral fellow at Harvard University and Broad Institute. He is currently an associate professor in the School of Pharmacy and Department of Chemistry at the University of Wisconsin-Madison. His group is primarily interested in developing new transition metal-catalyzed reactions.

Scheme 1. Rhodium-catalyzed intermolecular [5+1] and [5+2] cycloadditions of 3-acyloxy-1,4-enyne with CO or alkyne

Scheme 2. Effect of ester in rhodium-catalyzed intermolecular [5+2] cycloaddition of 3-acyloxy-1,4-enyne with alkyne

Table 1
Rh-catalyzed [5+2] cycloaddition of 1d and terminal alkynes^a

<p>(Ar = <i>p</i>-Me₂NC₆H₄)</p>			
entry	alkyne	yield	ratio (4/4')
1	3a ,	4a , 97%	only 4a
2	3b ,	4b , 87%	only 4b
3	3c ,	4c , 89%	>20:1
4	3d ,	4d , 95%	only 4d
5	3e ,	4e , 96%	17:1
6	3f ,	4f , 74%	only 4f
^{7b}	3g ,	4g , 58%	>20:1
^{8c}	3h ,	4h , 77%	8:1

^a Conditions: [Rh(PPh₃)₃Cl] (0.5 mol %), alkyne 3 (1.1 equiv), CHCl₃ (0.4 M), 50 °C, 24h unless noted otherwise. Isomeric ratios were determined by ¹H NMR of crude products.

^b [Rh(PPh₃)₃Cl] (2 mol %)

^c [Rh(PPh₃)₃Cl] (10 mol %)

Table 2
Rh-catalyzed [5+2] cycloaddition of 1d and internal alkynes^a

<p>Reaction scheme: Enediyne 1d (Me-OCOAr-CH=CH-C≡C-) reacts with internal alkyne 5 (R-C≡C-R') in the presence of a Rh(I) catalyst to form a mixture of two isomeric cycloheptatriene derivatives, 6 and 6'. The aryl group Ar is defined as <i>p</i>-Me₂NC₆H₄. The products are labeled (2).</p>			
entry	alkyne	yield	ratio (4/4')
1	5a ,	6a , 82%	–
2 ^c	5b ,	6b , 89%	–
3 ^b	5c ,	6c , 77%	5:1
4	5d ,	a complex mixture	
5	5e ,	a complex mixture	

^a Conditions: [Rh(PPh₃)₃Cl] (0.5 mol %), alkyne **3** (1.1 equiv), CHCl₃ (0.4 M), 50 °C, 24h unless noted otherwise. Isomeric ratios were determined by ¹H NMR of crude products.

^b [Rh(PPh₃)₃Cl] (2 mol %)

^c [Rh(PPh₃)₃Cl] (10 mol %)

Table 3
Other transition metal catalysts for [5+2] cycloaddition^a

entry	conditions	yield ^b
1	[Au(PPh ₃)Cl] (0.5 mol %)	0%
2	[Au(PPh ₃)Cl] (0.5 mol %), AgBF ₄ (0.5 mol%)	0%
3	[PtCl ₂] (0.5 mol %)	0%
4	[Ir(COD)Cl] ₂ (0.5 mol %)	0%
5	[Pd(OAc) ₂] (0.5 mol %)	0%

^a Conditions: alkyne **3a** (1.1 equiv), CHCl₃ (0.4 M), 50 °C, 24h unless noted otherwise.

^b The yield was determined by ¹H NMR of crude product

Table 4
Scope of 3-acyloxy-1,4-enynes in Rh-catalyzed [5+1] cycloaddition with CO at ambient pressure (Ar = p-Me₂NC₆H₄)^a

<p style="text-align: right;">(7)</p>		
entry	3-acyloxy-1,4-enyne	yield
1	<p>1d, R¹ = Me</p>	14a , 69%
2	1b , R = Ph	no reaction
3	1c , R = <i>t</i> Bu	no reaction
	<p>7b, R² = Ph</p>	14b , 66%
4 ^b		
5 ^b	<p>7c, R² = Me</p>	14c , 35%
	<p>13a, R² = 1-Naph</p>	14d , 54%
6 ^b	7b , R ² = Ph	no reaction
7 ^b	7c , R ² = Me	no reaction
8 ^b	<p>13b, R² = 4-R^x-2-R^y-Ph</p>

entry	3-acyloxy-1,4-enyne	yield
9 ^b	13b , R ^x = Cl, R ^y = H	no reaction
10 ^b	13c , R ^x = MeO, R ^y = H	14e , 51%
11 ^b	13d , R ^x = TBSO, R ^y = MeO	14f , 64%
12	<p>13e,</p>	no reaction

^a Conditions: [Rh(CO)₂Cl]₂ (5 mol %), 3-acyloxy-1,4-enyne (1.0 equiv), CO (1 atm), ClCH₂CH₂Cl (0.4 M), rt, 24h unless noted otherwise;

^b The reaction was heated at 50 °C for 1h.

Table 5
Other transition metal catalysts examine for [5+1]

entry	conditions	yield
1	[Au(PPh ₃)Cl] (0.5 mol %)	0%
2	[Au(PPh ₃)Cl] (0.5 mol %), AgBF ₄ (0.5 mol%)	0%
3	[PtCl ₂] (0.5 mol %)	0%
4	[Ir(COD)Cl] ₂ (0.5 mol %)	0%
5	[Pd(OAc) ₂] (0.5 mol %)	0%

^a Conditions: CO (1 atm), ClCH₂CH₂Cl (0.4 M), rt, 24h unless noted otherwise.

^b The yield was determined by ¹H NMR of crude product