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One-Pot Synthesis of Fused Tricyclic Heterocycles with Quaternary Carbon Stereocenter by Sequential Pauson–Khand Reaction and Formal [3+3] Cycloaddition

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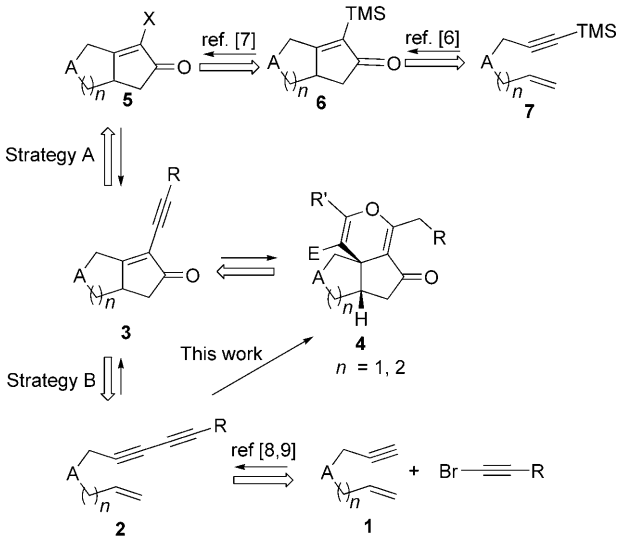
Dedicated to Professor Xiyan Lu on the occasion of his 80th birthday

Using transition-metal-catalyzed annulation reactions to construct complex polycyclic systems represents a powerful strategy for target-directed synthesis and is thus of continual interest to the synthetic community.[1] Among numerous methods which have been developed, the Pauson–Khand annulation reaction,[2] in which tethered enynes undergo a formal [2+2+1] cycloaddition reaction with carbon monoxide to afford bicyclic cyclopentenones, has been a powerful, reliable and routine transformation for the synthesis of complex polycyclic cyclopentane-containing molecules.[3]

Furthermore, in recent years, 2-(alkyn-1-yl)-2-enones have been shown to be very useful, reactive, and versatile building blocks to furnish not only highly substituted heterocycles such as furans[4,5a] and 4*H*-pyrans,[5b] but also polyfunctional electron-deficient 1,3-dienes and allenes.[5b] To study how fused rings affect the reactivity of 2-(alkyn-1-yl)-2-enones, we turned our attention to the efficient synthesis of fused bicyclic 2-(alkyn-1-yl)-2-enones. After retrosynthetic analysis, we envisaged two different strategies for the preparation of bicyclic 2-(alkyn-1-yl)-2-enones (Scheme 1).



Scheme 1. Retrosynthetic analysis of fused tricyclic 4*H*-pyrans **4**.

For strategy A, TMS-protected 1, 6- or 1,7-enyne **7** undergoes the Pauson–Khand reaction (PKR)[6] and subsequent halogenation[7] to give fused bicyclic 2-halide-2-enone **5** which undergoes cross-coupling with terminal alkynes to give bicyclic 2-(alkyn-1-yl)-2-enones. Strategy B, on the other hand, starts from the Sonogashira[8] or Cadiot–Chodkiewicz[9] cross-coupling reaction (CCR) of readily available terminal 1, 6-enynes and 1-alkynyl bromide to give 1-ene-6,8-diynes **2** (or 1-ene-7,9-diynes), followed by the Pauson–Khand type reaction of **2** to give the bicyclic adduct **3**. The ability to execute 'one-pot', sequential reactions, wherein the product of one reaction is the starting material for the next, is particularly significant. Strategy B has an obvious advantage over strategy A in its potential combination of the Pauson–Khand reaction and the subsequent transformation in a 'one-pot' reaction.[10] Herein, we report a novel [{$Rh(CO)_2Cl$}$_2$]-catalyzed Pauson–Khand-type reaction of **2** with CO to provide bicyclic 2-(alkyn-1-yl)-2-enones in mod-

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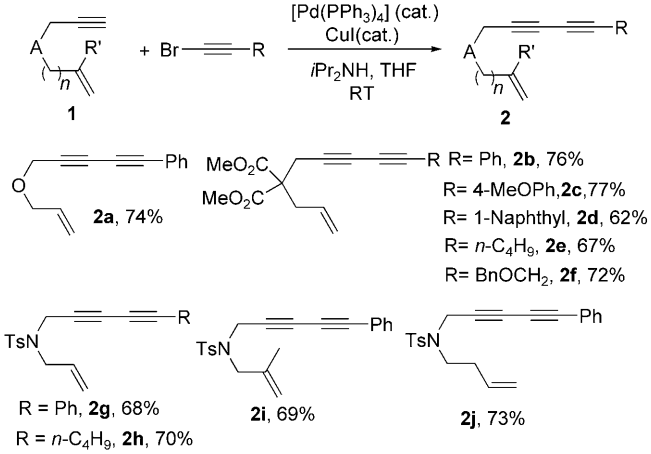
erate to excellent yields (using strategy B). Furthermore, this Pauson–Khand reaction can be combined with the K_2CO_3-catalyzed [3+3] cycloaddition of 2-(alkyn-1-yl)-enones with β-keto compounds to rapidly assemble tricyclic heterocycles[11] with a quaternary carbon stereocenter.

As expected, various substituted and tethered enediynes **2** could be prepared in good yields by the Sonogashira cross-coupling reaction of the corresponding readily available terminal 1, 6-enynes **1**[12] with 1-alkynyl bromide, catalyzed by $[Pd(PPh_3)_4]$ (5 mol%) and CuI (10 mol%) in the presence of base (Scheme 2).[8]

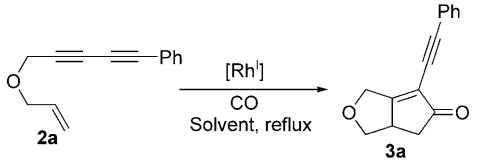


Scheme 2. Synthesis of 1-ene-6,8-diynes **2** by Sonogashira cross-coupling reaction of terminal 1, 6-enynes with 1-alkynyl bromide.

Following the successful synthesis of **2**, we screened the reaction conditions for the formal [2+2+1] cycloaddition reaction using enediyne **2a** as the standard substrate. The results are summarized in Table 1. The reaction proceeds smoothly under the catalysis of $[\{Rh(CO)_2Cl\}_2]$ (5 mol%) in the presence of CO in refluxing THF for 48 h, affording the desired fused bicyclic 2-(alkyn-1-yl) enone **3a** in 64% yield (Table 1, entry 4). Using other solvents such as toluene (an oft-used solvent in similar systems), 1,2-dichloroethane (DCE), and acetonitrile, or other catalysts, such as $[RhCl(PPh_3)_3]$, $[RhCl(CO)(PPh_3)_2]$, and $[\{RhCl(cod)\}_2]$ (with various phosphine ligands), led to lower yields. When using stoichiometric amounts of the classical cobalt complex $[Co_2(CO)_8]$ in the absence of CO[13] or catalytic amounts of $[Co_2(CO)_8]$ with tetramethyl thiourea in the presence of CO,[14] only an unidentified red complex was formed, in various solvent and at various temperatures, indicating that the reactivity of **2** is different with that of the corresponding 1,6-enynes.

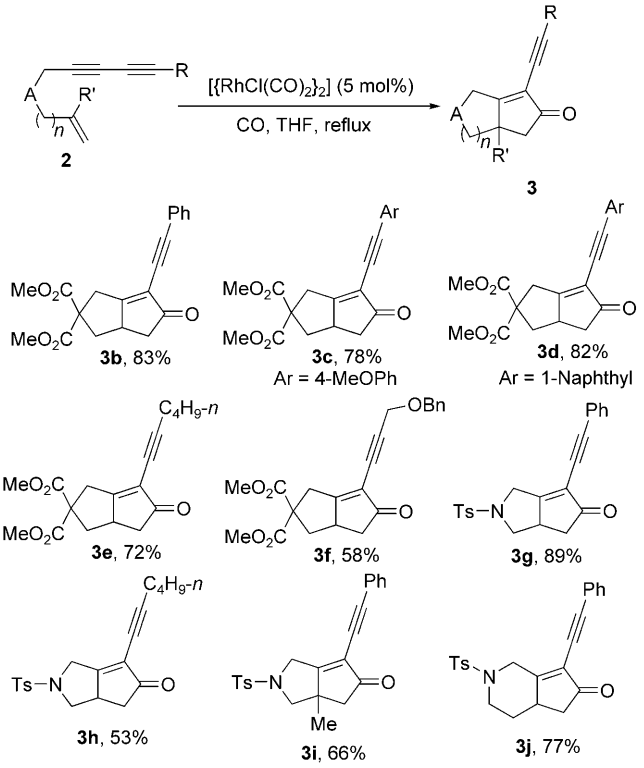
Various substituted enediynes were studied to determine the scope of this transformation. The results, summarized in Scheme 3, lead to several noteworthy conclusions: a) The tethered atom could be carbon (dimethyl malonate), nitrogen (N-tosylated amine) and as well as oxygen; b) not only substituted aromatic rings, but also alkyl groups can be introduced as the terminal R group in the enediyne to give bicyclic cycloadducts in moderate to excellent yields; c) a methyl group could be incorporated at the 2-position of 1-ene-6,8-diyne **2i** to afford the cycloadduct **3i** with a quaternary bridging carbon stereocenter; d) fused bicyclic [4.3.0]

Table 1. Screening conditions for the Pauson–Khand reaction of **2a**.[a]



Entry	Rh^I Catalyst	Ligand	Solvent	Yield [%][b]
1	$[\{Rh(CO)_2Cl\}_2]$	–	toluene	44
2	$[\{Rh(CO)_2Cl\}_2]$	–	CH_3CN	38
3	$[\{Rh(CO)_2Cl\}_2]$	–	DCE	37
4	$[\{Rh(CO)_2Cl\}_2]$	–	THF	64
5	$[RhCl(PPh_3)_3]$	–	THF	0
6	$[RhCl(CO)(PPh_3)_2]$	–	THF	0
7	$[\{RhCl(cod)\}_2]$	dppe	THF	14
8	$[\{RhCl(cod)\}_2]$	dppp	CH_3CN	26
9	$[\{RhCl(cod)\}_2]$	dppp	toluene	29
10	$[\{Rh(CO)_2Cl\}_2]$	dppp	toluene	43
11	$[\{Rh(CO)_2Cl\}_2]$	binap	toluene	32
12	$[\{Rh(CO)_2Cl\}_2]$	binap	THF	21

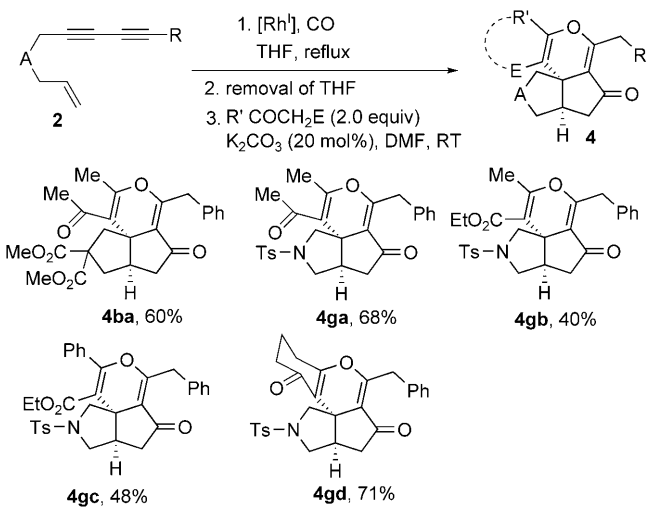
[a] Reagents and conditions used: **2a** (0.25 mmol), catalyst(5 mol%), ligand(6 mol%) in 10 mL of solvent for 24–48 h in the presence of CO (balloon). [b] Yield of isolated product. DCE = 1,2-dichloroethane; cod = 1,5-cyclooctadiene; dppe = 1,2-bis(diphenylphosphino)ethane; dppp = 1,3-bis(diphenylphosphino)propane; binap = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl.



Scheme 3. Rh^I-catalyzed formal [2+2+1] cycloaddition reaction of 1-ene-6,8-diynes in the presence of CO.

system **3j** could be prepared in 77% yield from the corresponding 1-ene-7,9-diyne **2j**.

To show the synthetic application of bicyclic 2-(alkyn-1-yl)-2-enones, we investigated a'one-pot' synthetic strategy to construct tricyclic 4*H*-pyrans from the corresponding acyclic 1-ene-6,8-diynes **2** by the combination of formal [2+2+1] cycloaddition with subsequent base-catalyzed formal [3+3] cycloaddition of the cycloadducts with β-keto compounds. After several attempts, we discovered that fused tricyclic 4*H*-pyrans **4** could be synthesized in 40–71% yields (two steps) with high diastereoselectivity (single diastereoisomer) by a simple sequential 'one-pot' operation, that is, Rh^I-catalyzed Pasuson–Khand reaction of 1-ene-6,8-diynes in refluxing THF, followed by removal of solvent and K_2CO_3-catalyzed formal [3+3] cycloaddition of the cycloadducts with β-keto compounds in DMF[15] at room temperature (Scheme 4). It is noteworthy that five bonds and three fused rings with one quaternary carbon sterocenter were formed during this simple 'one-pot' operation, and all atoms from the three components were incorporated into the product. The structure and relative stereochemistry of the product was established by single-crystal X-ray diffraction of fused tricyclic heterocycle **4ga** (Figure 1).[16]



Scheme 4. 'One-pot' synthesis of fused tricyclic heterocycles by sequential, [2+2+1] and [3+3] cycloadditions.

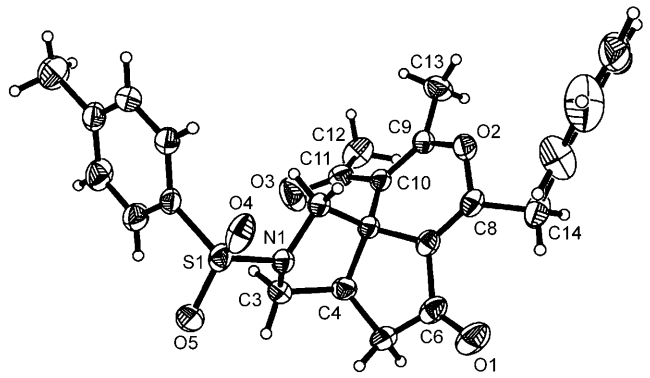


Figure 1. Molecular structure of racemic **4ga**, determined by X-ray diffraction . Thermal ellipsoids are set at 30% probability.

In summary, we have demonstrated a novel Rh^I-catalyzed formal [2+2+1] cycloaddition reaction of 1-ene-6,8-diynes leading to fused bicyclic 2-(alkyn-1-yl) enones in moderate to good yields. Furthermore, we have also developed an efficient, atom-economical, 'one-pot' sequential process to rapidly assemble fused tricyclic heterocycles with one quaternary carbon stereocenter, with high diastereoselectivity in reasonable yields. All three starting materials are readily available and the cycloadducts are readily converted into more complex ring systems with many convertible functional groups. The reaction scope, asymmetric catalysis, and synthetic applications in natural product synthesis are being studied in our group.

Experimental Section

Synthesis of 3g: A solution of enediyne **2g** (174.4 mg, 0.5 mmol), $[\{RhCl(CO)_2\}_2$ (9.8 mg, 5 mol%) in THF (10 mL) was refluxed under a positive pressure of CO (balloon). The reaction was complete in 24 h, as determined by thin-layer chromatography. After concentration, the residue was purified by column chromatography on silica gel (hexanes/ethyl acetate = 3:1) to afford **3g** (167.8 mg, yield: 89%).^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.76 (d, J = 8.0 Hz, 2H), 7.49 (d, J = 8.0 Hz, 2H), 7.37–7.27 (m, 5H), 4.46 (d, J = 17.0 Hz, 1H), 4.19 (d, J = 17.0 Hz, 1H), 4.07 (dd, J = 9.0, 8.0 Hz, 1H), 3.23–3.21 (m, 1H), 2.74 (dd, J = 18.0, 7.0 Hz, 1H), 2.66 (dd, J = 9.0, 1.0 Hz, 1H), 2.44 (s, 3H), 2.16 ppm (dd, J = 18.0 , 3.0 Hz, 1H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 203.05, 178.11, 144.25, 133.50,131.92, 130.08, 129.25,128.39, 127.47, 122.44, 121.85, 99.40, 77.91, 52.52, 48.02, 42.41, 39.60, 21.55 ppm; MS (EI): *m/z* (%): 377 [M^+](65.45), 195 [M+H−Ts−CH_2CO], 222 [M−Ts] (60.480); HRMS calcd for $C_{22}H_{19}NO_3S$: 377.1086, found: 377.1086.

'One-pot' synthesis of 4ga from enediyne 2g: After the cycloaddition reaction of enediyne **2g** (174.4 mg, 0.5 mmol) was complete (see above), the solvent was removed in vacuo and the residue was dissolved in DMF (5 mL). A solution of acetylacetone (100 mg, 1.0 mmol) in DMF (1 mL) and K_2CO_3 (13.8 mg, 20 mol%) were added to the reaction mixture, which was then stirred at room temperature until **3g** was consumed. Water (15 mL) was added and the mixture was extracted with diethyl ether (3×5 mL). The combined organic phase was washed successively with water (5 mL) and saturated brine (5 mL) and then dried over $MgSO_4$. Solvent was removed in vacuo and the residue was purified by column chromatography on silica gel(hexanes/ethyl acetate = 3:1) to give **4ga** (163.1 mg, overall yield, 68%) . ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.65 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 8.0 Hz, 2H), 7.32–7.20 (m, 5H), 4.15 (d, J = 14.0 Hz, 1H), 4.00 (d, J = 14.0 Hz, 1H), 3.38–3.33 (m, 1H), 3.22 (d, J = 10.0 Hz, 1H), 3.10 (d, J = 10.0 Hz, 1H), 3.04 (d, J = 10.0 Hz, 1H), 2.80–2.74 (m, 1H), 2.69 (dd, J = 19.0, 11.0 Hz, 1H), 2.44 (s, 3H), 2.29 (s, 3H), 2.23 (dd, J = 19.0,7.0 Hz, 1H), 2.02 ppm (s, 3H); ^{13}C NMR (125.8 MHz, $CDCl_3$): δ = 202.04, 200.79, 159.00, 153.24, 143.85, 136.04, 132.10, 129.68, 129.06, 128.59, 127.85, 126.92, 119.21, 115.23, 61.85, 55.35, 49.43, 44.91, 40.78, 34.85, 32.58, 21.56, 18.35 ppm; MS (EI): *m/z* (%): 477 [M^+] (1.14), 322 (100) [M−Ts]; HRMS calcd for $C_{27}H_{27}NO_5S$: 477.1610, found: 477.1610.

Acknowledgements

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Keywords: cycloaddition · diastereoselectivity · fused-ring systems · heterocycles · rhodium

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[15] The yield was lower if THF was not replaced by DMF for the second step. For example, **4ga** was obtained in only 48% yield.

[16] CCDC-669717 (**4ga**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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