Rhodium-catalyzed tandem nucleophilic addition/bicyclization of diyne-enones with alcohols: a modular entry to 2,3-fused bicyclic furans[†]

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A novel, efficient and atom-economic Rh-catalyzed stereoselective tandem nucleophilic addition/bicyclization for the synthesis of 2,3-fused bicyclic furans from readily available acyclic diyne-enones and alcohols has been developed.

Rhodium-catalyzed reactions are powerful tools for the construction of organic compounds and have played an important role in modern organic synthesis.¹ Among the numerous methods for this endeavour, cyclization and nucleophilic addition catalyzed by rhodium are receiving much attention because of their high efficiency in the formation of carbon-carbon and carbon-heteroatom bonds.¹⁻³ In the past decade, the rhodium-catalyzed tandem addition/cyclization has been extensively investigated.⁴ However, most of the nucleophiles employed in the addition are organometallic reagents which transmetalate with the rhodium catalyst to produce organorhodium species acting as effective nucleophiles of alkynes and electron-deficient olefins.^{3,4} Moreover, because of the significant role of highly substituted furan not only in many natural products and important pharmaceuticals as a key structure, but also in synthetic chemistry as a useful building blocks, the development of new tandem reactions for constructing highly functionalized substituted furan from easily available acyclic starting materials has been stimulated by their appearance in many bioactive natural products and important pharmaceuticals.^{5,6} Herein we now report our discovery of novel rhodium-catalyzed tandem nucleophilic addition/bicyclization of acyclic diyne-enones with alcohols to construct 2,3-fused bicyclic furans with 100% atom-economy.7

Previous studies in our group aimed at the synthesis of multi-functionalized polysubstituted furan have proved that 2-(1-alknyl)-2-alken-1-ones^{8,9} is a highly efficient precursor of furan derivatives. As a continuation of the development of constructing polycyclic furan scaffold, we envisaged that diyne-enone might undergo a cascade reaction with nucelophiles in the presence of catalytic rhodium species to afford fused bicyclic furan derivatives.

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 Table 1 Optimization of the rhodium-catalyzed tandem nucleophilic cyclization^a



Entry	Conditions	Yield (%) of 2aa ^b
1	[RhCl(CO) ₂] ₂ , DCE, 20 h	27
2	RhCl(PPh ₃) ₃ /AgOTf(10%), DCE, 3 h	0
3	[RhCl(cod) ₂]/AgOTf(10%), DCE, 20 h	8
4	[RhCl(CO) ₂] ₂ , THF, 24 h	0
5	[RhCl(CO) ₂] ₂ , 1,4-Dioxane, 24 h	0
6 ^{<i>c</i>}	[RhCl(CO) ₂] ₂ , CO(0.2 atm), DCE, 3.5 h	35
7	[RhCl(CO) ₂] ₂ , CO(1.0 atm), DCE, 4 h	41
8	[RhCl(cod)] ₂ , CO(1.0 atm), DCE, 3 h	28
9	[RhCl(cod)] ₂ , CO(1.0 atm), MeOH, 4.5 h	16
10^{d}	[RhCl(cod)] ₂ , CO(1.0 atm), DCE, 1.5 h,	59
$11^{d,e}$	[RhCl(cod)] ₂ , CO(1.0 atm), TCE, 1.5 h	64
12	$[RhCl(cod)]_2$, CO(1.0 atm),	63
	DCE/MeOH(10/1), 1.5 h	
13	$[RhCl(CO)_2]_2$, CO(0.2 atm),	35
	DCE/MeOH(10/1), 2.5 h	
14	$[RhCl(cod)]_2$, CO(1.0 atm),	75
	TCE/MeOH(10/1), 2 h	
15	[RhCl(cod)] ₂ , CO(0.2 atm),	83
	TCE/MeOH (10/1), 3 h	

^{*a*} Conditions (unless other noted): **1a** (0.2 mmol, 0.05 M), methanol (2.0 equiv.), rhodium (5.0 mol%), 60 °C. ^{*b*} Isolated yield. ^{*c*} 0.2 atm. CO = 1 atm. CO/N₂ (CO/N₂ = 1/4). ^{*d*} Methanol (10.0 equiv.) was used. ^{*e*} TCE = 1,1,2,2-tetrachloroethane.

The starting point for our study was the rhodium-catalyzed conversion of substrates 1a, which was easily prepared by Sonogashira cross coupling of 2-bromo-1,3-diphenyl-prop-2en-1-one and terminal 1,6-diynes (Table 1). To our delight, the domino nucleophilic cyclization indeed occurred in 1,2-dichloroethane (DCE) under the catalysis of 5 mol% of [RhCl(CO)₂]₂, and afforded the bicyclic furan 2aa in 27% yield after 20 h at 60 °C (Table 1, entry 1). To further identify optimal reaction conditions, various rhodium complexes and different organic solvents were screened. Notably, [RhCl(cod)₂]/AgOTf species were proved to have poor efficiency and no catalytic activity was observed for RhCl(PPh₃)₃/AgOTf and [RhCl(CO)]₂ in THF or 1,4-dioxane at 60 °C (entries 2–5). Gratifyingly, there was a moderate improvement in the yield under a carbon monoxide atmosphere with a catalytic amount of [RhCl(CO)]₂ or [RhCl(cod)]₂

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Table 2 Screen the reaction scope via variation of nucleophile component^{*a*}



		- /	
1	i-PrOH	3	79 (2ab)
2	BnOH	3	51 (2ac)
3	t-BuOH	10	_ `
4	H ₂ O	4	45 (2ad)
5	Cyclopropylmethanol	5	60 (2ae)
6	Cyclohexanol	5	63 (2af)

^{*a*} Conditions: [RhCl(cod)]₂ (5%), TCE (0.05 M), TCE/ROH = 10/1, 60 °C, CO/N₂ (1/4, 1 atm).

(entries 6–8).¹⁰ Higher yields and faster reaction rates were achieved when 10 equivalents of methanol were used (entries 10–11). However, the yield decreases sharply when MeOH was used as a solvent (entry 9). Finally, the mixed solvent system (TCE/MeOH = 10/1, v/v) was found to be the best and the reaction furnished **2aa** in 83% isolated yield under a mixed CO/N₂ (1/4) atmosphere, while a relatively lower yield (75%) was obtained when the reaction was run under the CO atmosphere (entry 14 *vs.* 15).

With the optimal conditions in hand, we started to examine the scope of this domino process via variation of nucleophile component and the results are depicted in Table 2. The reaction of 1a with both primary and secondary alcohol proceeded smoothly to give the desired products in moderate to good yields (Table 2, entries 1-2). The bulkyl tertiary alcohol failed to produce the corresponding product (entry 3). Interestingly, water can also act as a nucleophile to afford 45% yield of 2ad with a hydroxy group which is ready for further functional transformation (entry 4). Finally, cyclopropyl methanol and cyclohexanol provided the corresponding bicyclic furans in reasonable yields (entries 5-6). However, the N-based nucleophile failed to react with 1a under the conditions which was likely due to the strong interaction between the amine and the rhodium catalyst leading to catalyst poisoning.

We next investigated the scope of the reaction by testing various divne-enones (Table 3). The results indicated that this cyclization is tolerant of different substitutions on the alkene, akyne and carbonyl moieties. Alkyl substitution on the carbonyl position (\mathbb{R}^1) was less effective than the aryl group (entries 1 vs. 2). The reaction of substrate 1c and 1d, tethered with a terminal alkyne ($R^3 = H$) proceeded smoothly to afford 2ca and 2da in good yields (entries 3-4). Fortunately, substrate **1f-h** tethered with an internal alkyne (\mathbb{R}^3 = butyl, aryl) could also allow for the efficient formation of bicyclic furans (entries 5-8). Interestingly, the electron-withdrawing group on \mathbf{R}^3 gave the corresponding product in higher yield than the electron-donating substituent one (entries 7 vs. 8). The alkyl substituent (\mathbf{R}^2) on the alkene moiety also produced the desired product 2ia (entry 9). The structure and the stereochemistry of the products were established by the X-ray

 Table 3 Synthesis of fused bicyclic furan 3 via variation of diyne-enone component 1



Entry	Diyne-enone 1 $X/R^1/R^2/R^3$	Time/h	Isolated Yield(%) ^a
1	C(CO ₂ Me) ₂ /Ph/Ph/H (1a)	3	83 (2aa)
2	$C(CO_2Me)_2/Me/Ph/H$ (1b)	1.5	62 (2ba)
3	$C(CO_2Me)_2/4$ - $ClC_6H_4/Ph/H$ (1c)	3	73 (2ca)
4	$C(CO_2Me)_2/Ph/4-ClC_6H_4/H$ (1d)	2	70 (2da)
5	$C(CO_2Me)_2/Ph/Ph/n-Bu$ (1e)	3	62 (2ea)
6	$C(CO_2Me)_2/Ph/Ph/Ph$ (1f)	3	81 (2fa)
7	$C(CO_2Me)_2/Ph/Ph/4-OMeC_6H_4$ (1g)	3	98 (2ga)
8	$C(CO_2Me)_2/Ph/Ph/4-NO_2C_6H_4$ (1h)	3	69 (2ha)
9	$C(CO_2Me)_2/Me/n-C_4H_9/H$ (1i)	1	60 (2ia)
10	NTs/Ph/Ph/H (1j)	3	61 (2ja)
11	NTs/Ph/Ph/Ph (1k)	3	75 (2ka)
12	O/Me/Ph/H (11)	3	0

crystallographic analysis of compound **2ha**.¹¹ It is noteworthy that the reactions of **1j** and **1k** with a TsN tether, together with a terminal alkyne ($\mathbb{R}^3 = \mathbb{H}$) or an internal alkyne ($\mathbb{R}^3 = \mathbb{H}$) also proved to be efficient cyclization precursors (entries 10–11). However, oxygen-tethered substrate was decomposed under the reaction conditions and could not give the corresponding product (entry 12).

To elucidate the mechanism, CD_3OD was employed as a nucleophile for this transformation. The rhodium nucleophilic tandem cyclization of **1a** with CD_3OD furnished the bicyclic furan product (*Z*)-**D-2a** in 72% yield under the optimized conditions, 96% of deuterium could be incorporated into the product and located *syn* to the furan ring (eqn (1)).



Consequently, a plausible mechanism that accounts for the formation of fused bicyclic furan 2 is outlined in Scheme 1. Two plausible catalytic cycles are proposed. In cycle A, the coordination of the rhodium complex to the double alkyne moieties of 1 would give intermediate A, which would in turn undergo tandem cyclizations to give a carbocation intermediate B with sp²C–Rh species. The introduction of a strong π -acid CO to the system would cause the electron density of the metal lower and thus help the rapid conversion of intermediate A into B. The carbocation of intermediate B could be rapidly trapped by the nucleophile to produce the intermediate C. Subsequent protonation of the sp²C–Rh bond would afford the bicyclic furan product 2 and regenerate the rhodium catalyst. While in cycle B, nucleophilic addition of nucleophile to the C–C double bond of intermediate A and subsequent



Scheme 1 Plausible mechanism for the rhodium-catalyzed nucleophilic tandem cyclization.

cyclization would give a furanyl rhodium complex \mathbf{D} .^{8*a*,9,12} The *syn*-addition of the sp²C–Rh to the alkyne moiety would also furnish the intermediate \mathbf{C} , which would in turn produce the final product and regenerate the catalyst as cycle A.

In summary, we have demonstrated a novel rhodiumcatalyzed stereoselective tandem nucleophilic addition/ bicyclization of various alcohols with diyne-enones, which provides an efficient, atom-economic route to multifunctionalized 2,3-fused bicyclic furans. Diyne-enones are easily prepared by the palladium-catalyzed cross-coupling reactions of α -bromo(iodo)-enones with 1,6-diynes, which will make this method more practical and useful. Further studies including the mechanism, expanding the scope of the nucleophile and the development of an asymmetric version are underway.

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