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Piano-Stool Rhodium Enalcarbenoids: Application to Catalyst Controlled Metal-Templated Annulations of Diazoenals and 1,3-Dicarbonyls

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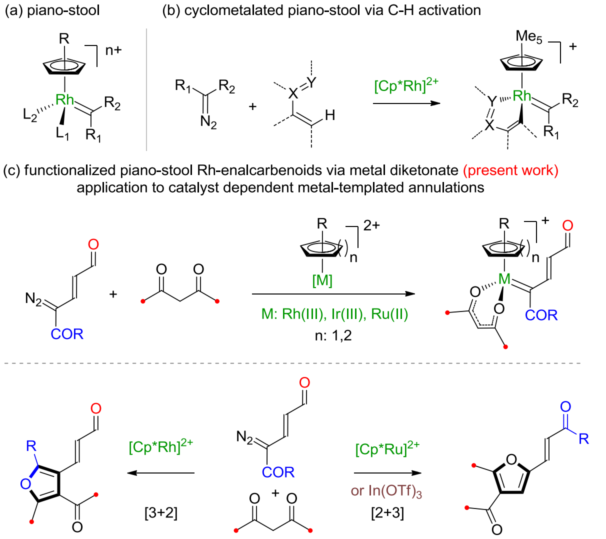
ABSTRACT: An electrophilic piano-stool rhodium(III)-enalcarbenoid resulted from the reaction of diazoenal with the cationic Cp*Rh(III) in the presence of a 1,3-diketone. The synthetic utility of these transient carbenoids has been demonstrated in the metal-templated [3+2] annulation of diazoenals and 1,3-dicarbonyls, thus leading to the enal-functionalized tetrasubstituted furans. The significance of the piano-stool enalcarbenoids has been further exemplified by the mechanistically distinct, complementary Lewis acid-templated [2+3] annulation of diazoenals and 1,3-dicarbonyls, resulting in the trisubstituted furanyl-enones and acrylates. Mechanistic investigations revealed that these annulations proceed through catalyst dependent chemoselective activation of diazoenal by the in situ formed metal diketonates. These methodologies gave access to core structures of indeno[1,2-b]furans, tetracyclic OLED, and a pan-AKT inhibitor.

KEYWORDS: piano-stool enalcarbenoid, diazoenal, furan, [2+3] annulation, [3+2] annulation

Rhodium carbenoids derived from diazo compounds are highly versatile reactive intermediates with broad synthetic applications.[1-6] Among the various rhodium catalysts, the dinuclear paddle-wheel rhodium carboxylates have proven to be exceptionally efficient catalysts for the carbenoid generation. The paddle-wheel Rh-carbenoid is central to a wide range of transformations such as cycloadditions (including cyclopropanations), σ-bond insertions (C-H, C-X, and X-H; X=heteroatom), and ylide reactions.[4-6] Recently, the half-sandwich Cp*Rh(III) complexes have emerged as valuable catalysts to access structurally divergent piano-stool carbenoids.[7-11] Remarkably, the piano-stool carbene complexes, due to their easily accessible coordination sites (Scheme 1a, L1 and L2), could offer distinct metal-templated reactions that are not possible by the rigid paddle-wheel carbenoid motif. Indeed, in the pioneering directed C-H functionalization approaches with diazo compounds, the transient cationic cyclometalated piano-stool carbenoid is key intermediate for the C-C bond forming carbene-migratory insertion (Scheme 1b).[9-10] However, despite the great synthetic potential, the metal-templated reactions of Rh(III) piano-stool carbenoids remained unexplored beyond the aforementioned directed C-H functionalization.[7]

Herein, we report the design of a new class of functionalized piano-stool Rh(III)-enalcarbenoids and their first application to the metal templated [3+2] annulation reaction of diazoenals and 1,3-dicarbonyls leading to the novel tetrasubstituted enal-functionalized furans (Scheme 1c).



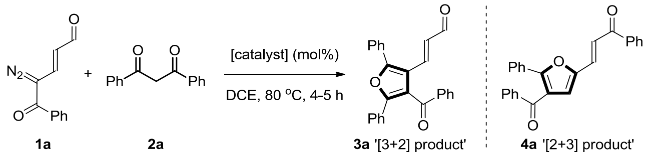
Scheme 1. Piano-stool rhodium-carbene complexes derived from diazo compounds.

The significance of piano-stool enalcarbenoids has been further exemplified by the contrasting Lewis acid-templated [2+3] annulation rendering trisubstituted furanyl-enones and acrylates (Scheme 1c). Tri- and tetrasubstituted furans are present in diverse biologically important natural products with intriguing structural complexity.[12] Despite many elegant approaches available for the substituted furans,[12,13] the new catalyst dependent approaches reported herein provides direct access to various tri and tetrasubstituted functionalized furans from the easily accessible same starting materials.[13-15]

1,3-Dicarbonyl compounds are versatile bidentate chelating ligands for various metal-diketonates.[16] In particular, the half-sandwich transition-metal complexes have been used to access a well-defined piano-stool diketonates.[17] In continuation of ongoing studies on the synthetic applications of a new class of diazoenals,[18,19] we envisioned that the cationic 16-electron Cp*Rh(III) piano-stool diketonates with a vacant coordination site could serve as a precursor to the novel piano-stool enalcarbenoid. Gratifyingly, control experiments showed that the reaction of 1,3-diketone **2a** with the diazoenal **1a** in the presence of 1 mol % $[Cp^*RhCl_2]_2$ and 10 mol % AgOTf, at the elevated temperature, delivers a new tetrasubstituted enal-functionalized furan **3a** (Table 1). The furan formation was proposed to involve a new class of metal-templated [3+2] annulation of the in situ generated Rh(III)-diketonate piano-stool enalcarbenoid. To the best of our knowledge, this is the first report on the construction of heterocycles by metal-templated reactions of piano-stool carbenoids distinct from the directed C-H functionalization approaches. So far, the only known reactions of 1,3-dicarbonyls with diazo compounds are Au-catalyzed C-H insertion[20] and the Ag-catalyzed C-C insertion reactions.[21] It is also noteworthy that, although annulation reactions of diazo compounds with various π-nucleophiles have been reported,[4] our study constitutes the first report on the annulation with 1,3-dicarbonyls via the π-rich metal diketonates.

A detailed study of the [3+2] annulation, using half sandwich metal catalysts Cp*M(III) (M: Rh, Co, Ir, Ru), and (arene)Ru(II), revealed that Cp*Rh(III) is exceptionally efficient, delivering exclusively the tetrasubstituted furan product **3a** in 82% yield (Table 1, entry 1). The Cp*Co(III) was inefficient toward [3+2] annulation, instead produced a trisubstituted furanyl-enone **4a** in 28% yield (entry 2). Formation of **4a** could be rationalized by the Lewis acidic metal-templated formal [2+3] annulation due to the preferential coordination of aldehyde motif over the carbenoid formation. Interestingly, the Cp*Ir(III) catalyst showed a slight preference toward [2+3] annulation (entry 3) and produced both **3a** (22%) and **4a** (30%). A dramatic difference in chemoselectivity was observed among the half-sandwich Ru(III) and Ru(II) catalysts (entries 4-7). The hard electron deficient Cp*Ru(III) gave furan **4a** in 64% yield through the carbonyl selective [2+3] annulation (entry 4). On the other hand, the relatively soft (benzene)Ru(II) and (p-cymene)Ru(II) catalysts exclusively produced furan **3a** through the carbenoid selective [3+2] annulation in 49% and 52% yield respectively (entries 5, 6). Surprisingly, the $[Cp^*Ru(MeCN)_3]PF_6$ was inactive towards the annulations (entry 7). Subsequently, the role of various Ag-salts was evaluated toward the annulation (entries 8-10). The $AgNTf_2$ and $AgSbF_6$ were less effective than AgOTf, whereas $AgBF_4$ was incompatible with the reaction. Increased catalyst loading led to reduced yield due to faster decomposition of diazoenal (entry 11). The yield of furan was increased with the increasing reaction temperature in high boiling chlorinated solvents and toluene (entries 12-13, see the SI for detailed optimization study). Dirhodium carboxylate catalysts, incapable of forming the metal-diketonate, resulted in the decomposition of the diazoenal and furan was not obtained (entries 14-15).

Table 1. Optimization of the [3+2] and [2+3] annulations.[a,b]



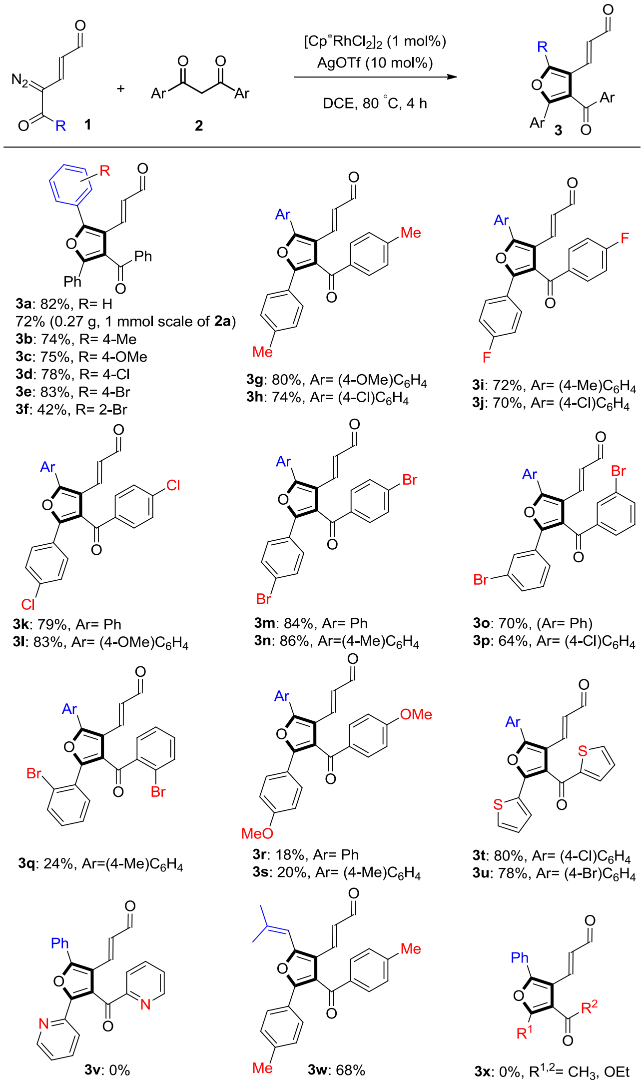
entry	[catalyst]	**3a** [%]	**4a** [%]
1	**$[Cp^*RhCl_2]_2$ (1) + AgOTf (10)**	**82**	-
2	$[Cp^*Co(CO)I_2]$ (**1**) + AgOTf (10)	<5	28
3	$[Cp^*IrCl_2]_2$ (**1**) + AgOTf (10)	22	30
4	$[Cp^*RuCl_2]_n$ (**1**) + AgOTf (10)	<5	64
5	$[(benzene)RuCl_2]_2$ + AgOTf (10)	49	-
6	$[(p\text{-cymene})RuCl_2]_2$ (**1**) + AgOTf (10)	52	-
7[c]	$[Cp^*Ru(MeCN)_3]PF_6$	-	-
8	$[Cp^*RhCl_2]_2$ (1) + $AgNTf_2$ (10)	60	-
9	$[Cp^*RhCl_2]_2$ (1) + $AgSbF_6$ (10)	43	-
10[c]	$[Cp^*RhCl_2]_2$ (1) + $AgBF_4$ (10)	-	-
11	$[Cp^*RhCl_2]_2$ (2) + AgOTf (10)	55	-
12[d]	$[Cp^*RhCl_2]_2$ (1) + AgOTf (10)	-	-
13[e]	$[Cp^*RhCl_2]_2$ (1) + AgOTf (10)	54	-
14[c,d]	$Rh_2(OAc)_4$ (5)	-	-
15[c,d]	$Rh_2(esp)_2$ (2)	-	-
16	RuCl3 (1) + AgOTf (10)	-	42
17[c]	RuCl3 (1)	-	-
18[c]	AgOTf (10)	-	-
19	CuOTf toluene complex (5)	-	42
20	$Cu(OTf)_2$ (5)	-	60
21	$Zn(OTf)_2$ (5)	-	30
22	$Sn(OTf)_2$ (5)	-	38
23	$Yb(OTf)_3$ (5)	-	35
24	$Sc(OTf)_3$ (5)	-	60
25	**$In(OTf)_3$ (5)**	-	**78**
26	$Nd(OTf)_3$ (5)	-	40
27[c]	$InCl_3$ (5)	-	-
28	$InCl_3$ (5) + AgOTf (15)	-	43

[a] A solution of **1a** (0.14 mmol in 2 mL) was added over 3 h to a solution of **2a** (0.13 mmol in 1 mL), catalyst, and continued the reaction for another 1-2 h. [b] Yield of isolated product. [c] **1a** was decomposed. [d] Reaction was carried out at 25 °C. [e] Reaction was carried out at 65 °C

The significance of the trisubstituted furans[12] prompted us to further investigate the mechanistically intriguing [2+3] annulation reaction of diazo enal **1a** and 1,3-dicarbonyl **2a**. Studies showed that in addition to the in situ formed transition-metal triflates (M: Co, Ir, and Ru; Table 1, entries 2-4, 16), a variety of other Lewis acid metal triflates based on Cu, Zn, Sn, Yb, Sc, In, and Nd, also catalyze the reaction at the elevated temperatures (entries 18-26, see the SI for complete optimization study). Although InCl3 was ineffective, the addition of AgOTf favored the annulation reaction (entries 27-28). Finally, the optimized conditions involving 5 mol % In(OTf)3 in dichloroethane at 80 °C delivered the trisubstituted furanyl-enone **4a** in 78% yield (entry 25).

The scope of [3+2] annulation reaction was examined (Table 2) using the optimized conditions. A variety of keto-diazoenals **1** with electron-rich and electron-deficient aryl substituents smoothly participated in the annulation and gave a high yield of enal-functionalized tetrasubstituted 2,5-diaryl-furans, e.g., **3a-e** (74-82%).[22,23] The sterically hindered 2-bromoaryl diazoenal gave furan **3f** in 42% yield. Notably, the alkenyl diazoenal also exclusively produced the multifunctionalized furan **3w** in 68% yield despite the potential C-H insertion and cyclopropanation side reactions. Annulation reaction with ester-diazoenals was unsuccessful. The reaction could be easily scaled up to obtain furanyl-enals in high yield (**3a**, 72% on a 1 mmol scale of **2a**).

Table 2. Substrate scope of the [3+2] annulation.[a]

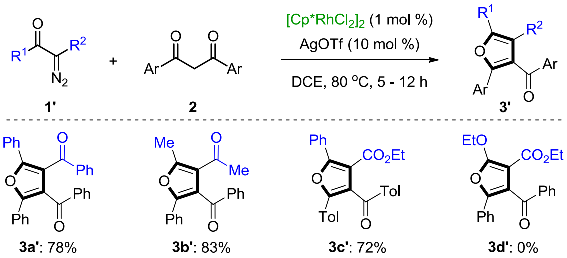


3a: 82%, R= H
72% (0.27 g, 1 mmol scale of **2a**)
3b: 74%, R= 4-Me
3c: 75%, R= 4-OMe
3d: 78%, R= 4-Cl
3e: 83%, R= 4-Br
3f: 42%, R= 2-Br
3g: 80%, Ar= $(4\text{-OMe})C_6H_4$
3h: 74%, Ar= $(4\text{-Cl})C_6H_4$
3i: 72%, Ar= $(4\text{-Me})C_6H_4$
3j: 70%, Ar= $(4\text{-Cl})C_6H_4$
3k: 79%, Ar= Ph
3l: 83%, Ar= $(4\text{-OMe})C_6H_4$
3m: 84%, Ar= Ph
3n: 86%, Ar=$(4\text{-Me})C_6H_4$
3o: 70%, (Ar= Ph)
3p: 64%, Ar= $(4\text{-Cl})C_6H_4$
3q: 24%, Ar=$(4\text{-Me})C_6H_4$
3r: 18%, Ar= Ph
3s: 20%, Ar= $(4\text{-Me})C_6H_4$
3t: 80%, Ar= $(4\text{-Cl})C_6H_4$
3u: 78%, Ar= $(4\text{-Br})C_6H_4$
3v: 0%
3w: 68%
3x: 0%, $R^{1,2}$= CH_3, OEt

[a] Reactions were performed using optimized conditions of Table 1.

Among the aryl diketones **2**, the alkyl and halo-substituted aryl groups were well tolerated (**3g-q**). A variety of F, Cl, and Br- aryl furans **3i-p** have been obtained in high yields (70-86%) except the sterically hindered 2-bromoaryl substituent severely hampered the annulation to give furan **3q** in 24% yield. The functionalized haloaryl furans could serve as valuable substrates for further diversification through cross-coupling reactions. Interestingly, the electron-rich 4-methoxy aryl substituent severely hampered the annulation reaction (**3r-s**, 18-20%).[24] Among the heteroaryl 1,3-diketones, the thienyl group was well tolerated to give furans **3t-u** in high yields (78-80%) whereas the 2-pyridyl group was not compatible, presumably due to the catalyst deactivation by the competing N-chelation (**3v**, 0%). Aliphatic 1,3-diones, malonates, and β-keto esters are not suitable substrates for the [3+2] annulation (**3x**, 0%).[24]

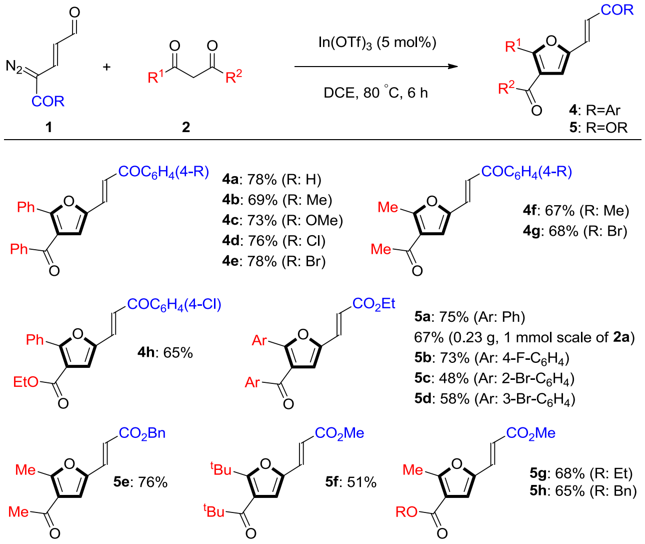
Table 3. [3+2] Annulation with other diazo compounds.



The [3+2] annulation reaction was also investigated with other diazo ketones (Table 3). Aromatic and aliphatic 2-diazo-1,3-diketones reacted smoothly to give tetrasubstituted furan **3a'** (78%) and **3b'** (83%) respectively. The sluggish reactivity of β-keto ester derived diazo compound led to longer reaction time to deliver furan **3c'** in good yield (72% after 12 h of reaction). In contrast, 2-diazomalonates are not suitable to the annulation reaction (**3d'**, 0%).

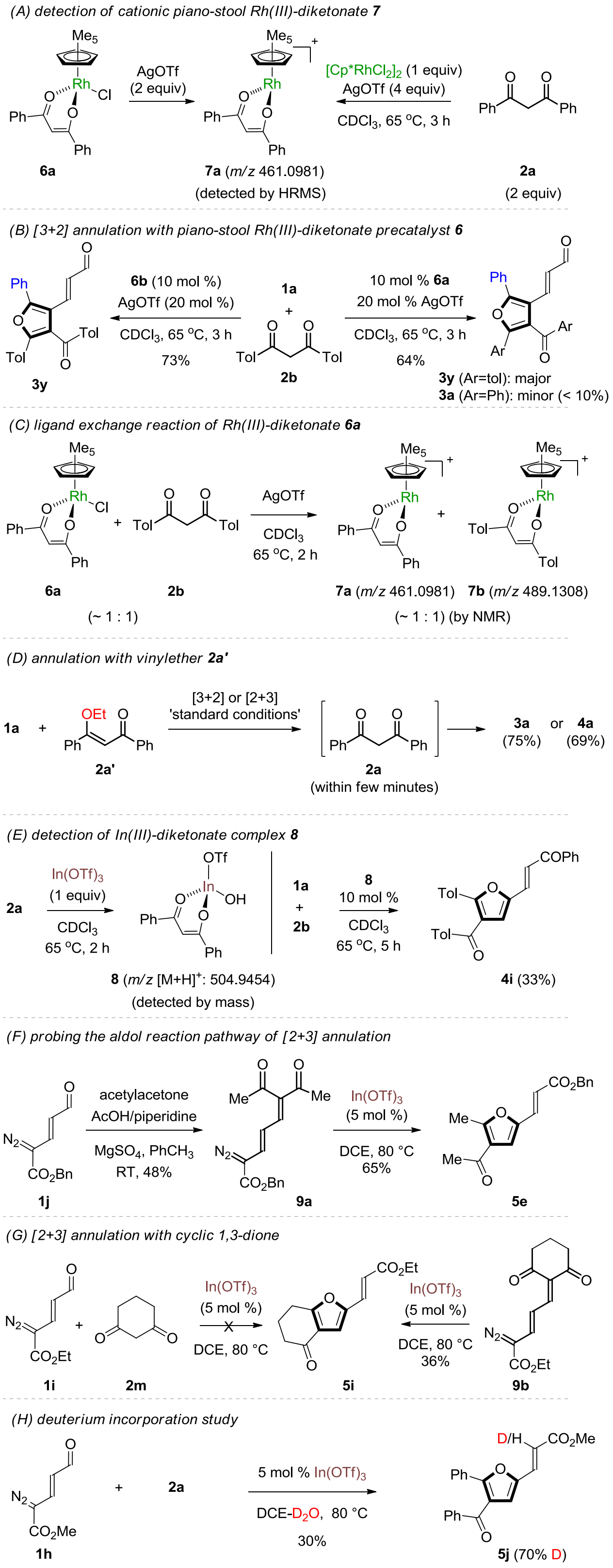
Subsequently, with the optimized conditions (table 1, entry 25) the scope of [2+3] annulation reaction was also examined (Table 4). Gratifyingly, both keto and ester-diazoenals **1** (R: Ar, OR) reacted with a variety of 1,3-dicarbonyls **2** resulting in the furanyl-enones **4** and furanyl-acrylates **5** respectively. The electronically distinct 4-substituted aryl keto-diazoenals reacted efficiently with the aryl 1,3-diketones to give high yields of furanyl-enones **4a-e** (69-78%). Notably, in contrast to the [3+2] annulation, the aliphatic 1,3-diketones, as well as β-keto esters also participated in the [2+3] annulation to give furanyl-enones **4f-h** in good yields (65-68%). The ester diazoenals also reacted with aryl and alkyl 1,3-diketones, as well as β-keto esters to give furanyl-acrylates **5a-b**, **5e**, and **5g-h** in good to high yield (65-76%).[22] The reaction was sensitive to the sterically hindered 1,3-dicarbonyls as the 2-bromophenyl diketone was less reactive (**5c**, 48%) than the 3-bromo isomer (**5d**, 58%) and moreover, the bulky t-butyl diketone also hampered the annulation (**5f**, 51%). Interestingly, the β-keto amides are not compatible with the annulation. The [2+3] annulation reaction was successfully carried out on a 1 mmol scale of **2a** to produce furan **5a** in good yield (0.23 g, 67%).

Table 4. Substrate scope of the [2+3] annulation.[a]



[a] Reactions were performed using optimized conditions of Table 1.

To gain insight into the mechanism of the [3+2] and [2+3] annulations, control experiments were carried out (Scheme 2, see SI for complete details). When the piano-stool Cp*Rh(III)Cl-diketonate **6a** was treated with 2 equiv of AgOTf, the cationic piano-stool [Cp*Rh(III)]-diketonate **7a** was detected by HRMS (m/z 461.0981, Scheme 2A). Moreover, the reaction between diketone **2a** and stoichiometric $[Cp^*RhCl_2]_2$ in the presence of AgOTf also resulted in **7a**. Gratifyingly, the [3+2] annulation of **1a** and **2b** in presence of 10 mol % piano-stool Cp*Rh(III)Cl-diketonate **6a** and 20 mol % AgOTf, furnished furanyl-enal **3y** (Ar= tol) along with the minor amount of furan **3a** (Ar= Ph, derived from **6a**) in 64% yield (Scheme 2B). On the other hand, annulation using diketonte **6b** (derived from tolyl diketone) gave furan **3y** as a single product in 73% yield. A facile ligand exchange was observed when a 1:1 mixture of Rh(III)-diketonate **6a,** and 1,3-diketone **2b** was treated with 2 equiv of AgOTf in $CDCl_3$ at 65°C resulting in an ~1:1 equilibrium mixture of cationic Rh(III)-diketonates **7a** and **7b** (Scheme 2C). Interestingly, under the annulation conditions, the vinylether **2a'** rapidly hydrolyzed to 1,3-diketone **2a** and subsequently reacted to give furan product in high yields (Scheme 2D, see SI). These studies support that the furan **3** formation proceeds via metal-templated [3+2] annulation of piano-stool Rh(III)-enalcarbenoid.

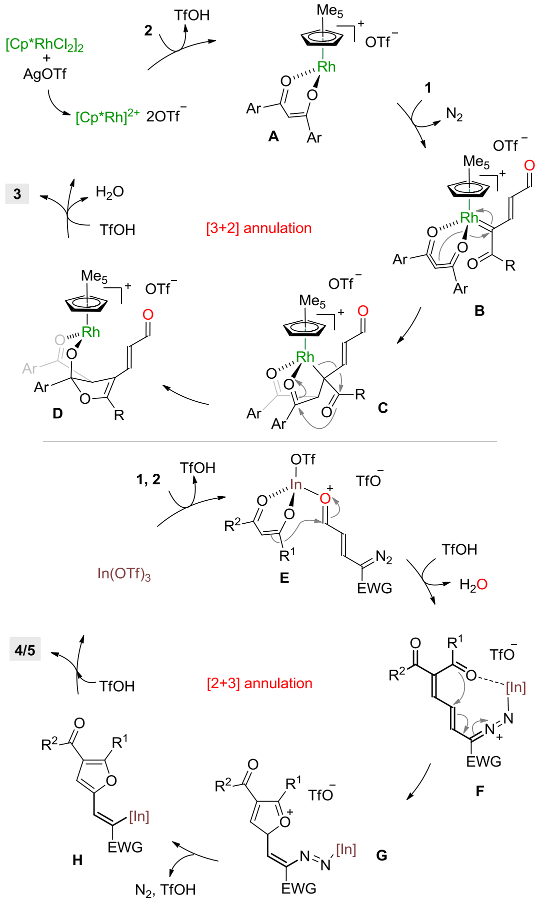


Scheme 2. Mechanistic studies.

In the In(OTf)3 catalyzed [2+3] annulation, the In(III)-diketonate **8** (Scheme 2E) was detected by the HRMS, m/z $(M+H)^+$: 504.9454. The annulation reaction of **1a** and

2b with 10 mol % **8** gave furan **4i** in 33% unoptimized yield (Scheme 2E). When the aldol condensation product **9a** was subjected to 5 mol % In(OTf)$_3$, the trisubstituted furanyl-acrylate **5e** was obtained in 65% yield (Scheme 2F). Importantly, the [2+3] annulation with the cyclic 1,3-diketone **2m** was unsuccessful due to the inability to form metal-diketonate (Scheme 2G). Whereas, in the presence of In(OTf)3, the aldol condensation product **9b** gave fused furan **5i** in 36% yield. These experiments confirm the metal-templated pathway of the [2+3] annulation. Further, performing the [2+3] annulation in the presence of D$_2$O gave 70% D incorporated furan **5j** (Scheme 2H).

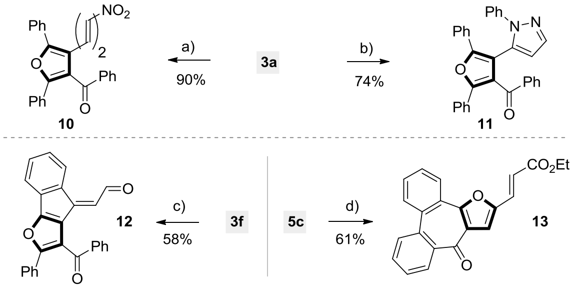
Based on the above studies, plausible mechanisms for the [3+2] and [2+3] annulations are proposed in Scheme 3. Initially, the nascent cationic half-sandwich [Cp*Rh(III)]-catalyst reacts with the 1,3-diketone **2** to give cationic piano-stool diketonate **A**. Reaction of **A** with diazoenal **1** results in the highly electrophilic piano-stool Rh(III)-enalcarbenoid **B**. Rapid metal-templated nucleophilic addition of diketonate to the carbenoid in **B** leads to the caged piano-stool **C** via C-C bond formation. Subsequent 5-exo-trig hetero-cyclization of 1,4-dicarbonyl in **C** leads to the pendant metal-chelated dihydrofuran **D**. Protodemetalation and dehydration of **D** completes the [3+2] annulation to give the enal-functionalized tetrasubstituted furan **3**.



Scheme 3. Plausible mechanisms of annulations.

In the case of In(OTf)$_3$ catalyzed [2+3] annulation (Scheme 3), the metal-diketonate **E** obtained from 1,3-dicarbonyl **2** and diazoenal **1** by selective coordination of the aldehyde motif triggers the metal-templated aldol condensation reaction, leading to the diazo-dienone **F**. Subsequent, [In]-catalyzed 5-exo-trig hetero-cyclization of **F** gives the furanyl (Z)-vinylindium **H** via **G**. Finally, protodemetallation of **H** provide the trisubstituted furanyl (E)-enone/acrylate **4**/**5**.

The synthetic importance of functionalized furans was demonstrated by a series of rapid structural diversifications (Scheme 4). Chemoselective π-extension of the furanyl-enal **3a** by Henry reaction gave synthetically important nitrodiene **10** in 90% yield.[25] A one-pot oxidative[3+2] cyclization of enal **3a** and phenyl hydrazine furnished the furanyl-pyrazole motif **11** (74%) present in the pan-Akt inhibitor GSK2141795.[26] Intramolecular Heck-coupling of 2-bromoaryl furanyl-enal **3f** gave the tricyclic indeno[1,2-b]furan **12** (58%), a core structure of biologically important natural products.[27] Pd-catalyzed cross-coupling of the 2-bromophenyl furanyl-acrylate **5c** furnished the tetracyclic furan **13** (61%), a core structure of the OLED material.[28]



Scheme 4. Synthetic applications of furan products. Conditions: a) CH_3NO_2, NH_4OAc, MeOH, 60 °C; b) i. $PhNHNH_2$, Et_2O; ii. Oxone, TFA, rt; c) 5 mol % $PdCl_2$, 10 mol % PPh_3, K_2CO_3, DCE, 80 °C; d) 5 mol % $PdCl_2(PPh_3)_2$, 10 mol % dppp, K_2CO_3, DMF, 150 °C.

In summary, we have designed a new class of piano-stool rhodium(III)-enalcarbenoid involving the cationic half-sandwich Cp*Rh(III) catalyzed reaction of 1,3-dicarbonyls and diazoenals. The transient electrophilic piano-stool Rh(III)-diketonate enalcarbenoid rapidly undergoes a novel metal-templated [3+2] annulation reaction resulting in the synthetically important enal-functionalized tetrasubstituted furans. In contrast, the complementary Lewis acid In(OTf)$_3$ catalyzed reaction of diazoenal and 1,3-dicarbonyl proceeds via the carbonyl-selective metal-templated [2+3] annulation and provides distinct trisubstituted furanyl-enones and acrylates. The functionalized furan products were further elaborated to core structures of indeno[1,2-b]furan natural products, pan-Akt inhibitor, and a tetracyclic OLED. Further studies on the synthetic applications of the new class of piano-stool enalcarbenoids, annulation reactions and their mechanistic aspects are underway.

ASSOCIATED CONTENT

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Notes

The authors declare no competing financial interest.

Supporting Information. Experimental procedures, analytical data and NMR spectra of compounds, and X-ray crystallographic data of **3a** and **5g** (CIF files).

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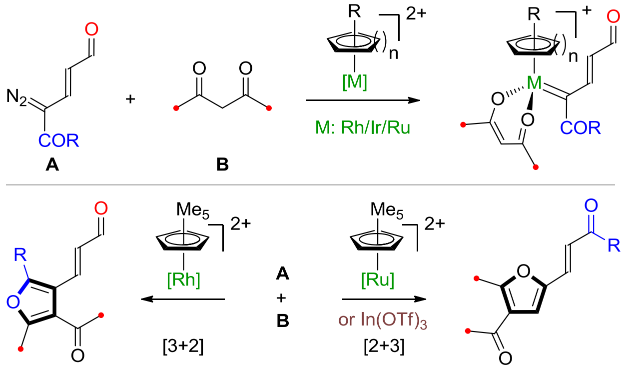

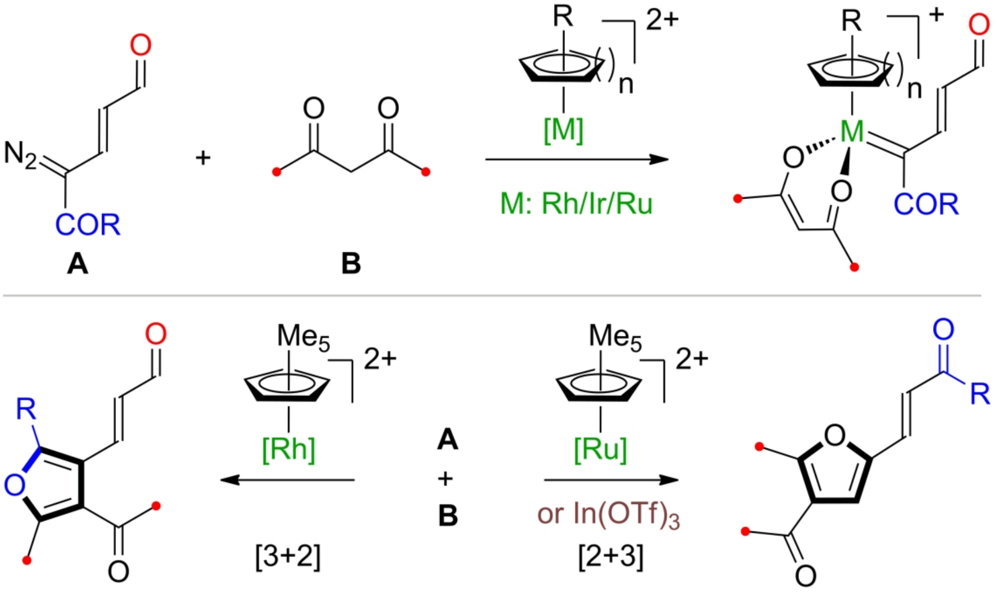

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