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Catalytic annulation of 1-substituted-3-en-1-yn-5-als with cycloalkanones using acid–base dual catalysts

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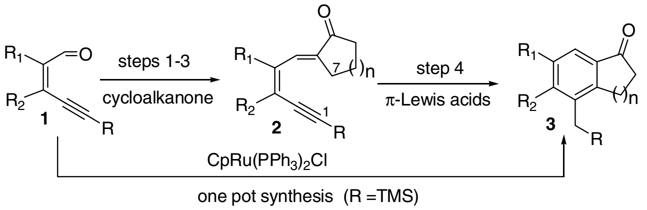
Abstract—$CpRu(PPh_3)_2Cl$ and DBU dual catalysts in combination enable a one-pot annulation of 1-R-3-en-1-yn-5-als (R = aryl, alkenyl, alkyl) and cycloalkanones to give highly substituted benzene products. This catalytic reaction consists of a tandem aldol condensation, dehydration and aromatization through a 1,7-hydrogen shift; the resulting 1-indanones and α-tetralones are obtained in moderate to good yields.

The replacement of a multi-step chemical synthesis with a one-pot tandem reaction has a significant impact on organic synthesis because complex organic molecules are prepared more economically through shorter routes.[1,2] Previously, we reported a cyclization of 3,5-dien-1-ynes **2** catalyzed by π-Lewis acids[3,4] to form substituted benzene derivatives **3** via a [1,7]-hydrogen shift.[5] In this reaction sequence, as depicted in Scheme 1, starting 3,5-dien-1-ynes **2** were prepared from 3-en-1-yn-5-als **1** and cycloalkanones in three steps via silyl enol ether formation, Mukaiyama aldol[6] condensation and dehydration. To achieve an atom economy, we have recently accomplished a direct annulation of 1-silyl-3-en-1-yn-5-als **1** and cycloalkanones to form indanones and α-tetralones **3** in a one-pot operation, as depicted in Scheme 1. In this tandem catalysis, $CpRu(PPh_3)_2Cl$ was much more efficient than $PtCl_2$, $AuCl_3$ and $RuCl_3$ because of its superior activity in aldol condensation; this ruthenium catalyst also enhanced the aromatization of 3,5-dien-1-yne intermediates **2**. This catalysis works efficiently for 3,5-dien-1-ynes bearing a C(1)-trimethylsilyl group (R = TMS), and became sluggish for the phenyl or alkyl analogues (R = Ph, alkyl). The suitability of this catalysis for silylalkyne substrates is closely related to the better yields in thermal cyclization than their phenyl and alkyl analogues (Scheme 2). Herein we report our additional findings that a combination of $CpRu(PPh_3)_2Cl$ and organic base DBU improved the efficiency of this tandem aldol condensation/aromatization sequence, which is extensible to for 3-en-1-yn-5-als **1** bearing a C(1)-phenyl, alkenyl or alkyl substituent.



Scheme 1.

In the preceding aromatization, the C(7)–H acidity of 3,5-dien-1-yne **2** is crucial for the cyclization efficiency because the mechanism, as depicted in Scheme 2, has been elucidated to involve a proton transfer process. We envisage that a suitable base accelerates the cyclization via a deprotonation and reprotonation pathway. Heating compound **5a** alone in hot xylene (140 °C, 48 h) afforded 2-indanone **6a** in 25% yield. The yields of desired indanone **6a** were increased to 55%, 37% and 41%, respectively, in the presence of $CpRu(PPh_3)_2Cl$, 2,6-lutidine, and DBU alone (5%). With Ru/2,6-lutidine and Ru/DBU catalysts in combination, each at 5% loading, the yield of desired **6a** was further increased to 70% and 83%, respectively (entries 5 and 6).

With this new finding, we further studied a direct formation of indanone **6a** through a tandem aldol condensation/aromatization reaction of 3-en-1-yn-5-al **4a** with cyclopentanone, which is also the starting building blocks for 3,5-dien-1-yne **5a**. Entries 1–3 (Table 1) show

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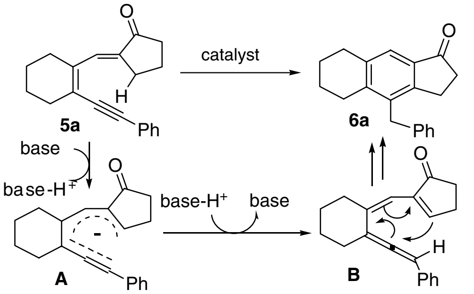


entry	catalyst	additive	**6a** (yields)^a
1	——	——	25 %
2	5% CpRu(PPh$_3$)$_2$Cl	——	55 %
3	——	5% 2,6-lutidine	37 %
4	——	5%DBU	41 %
5	5% CpRu(PPh$_3$)$_2$Cl	5% 2,6-lutidine	70 %
65	5% CpRu(PPh$_3$)$_2$Cl	%DBU	83 %

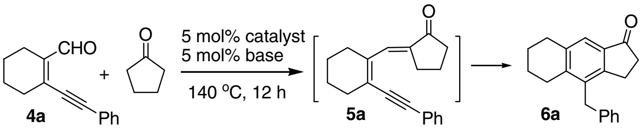
[a] For entries 1-6, starting 3,5-dien-1-yne **5a** was consumed completely.

Scheme 2.

the effects of various organic bases including 2,6-lutidine, DBU, and TMP (5 mol %); the resulting 2-indanone **6a** was obtained in low yields (13–18%). In the presence of CpRu(PPh$_3$)$_2$Cl (5 mol %), the yield of desired **6a** was only 20% although this catalyst was efficient for the silylalkyne analogues. The cyclization efficiencies were significantly improved using CpRu(PPh$_3$)$_2$Cl and suitable organic bases (entries 5–7) in combination with the DBU base giving the best yield (65%). Although CpRu(COD)Cl and 2PPh$_3$ are commonly used to generate CpRu(PPh$_3$)$_2$Cl, a mixture of these species and DBU gave cyclized 1-indanone **6a** in 35% yield. We also examined the effects of phosphine ligands for the CpRuL$_2$Cl catalyst; both electron-rich and electron-deficient phosphines failed to enhance in the cyclization efficiency (entries 9–11).

We examined the generality of this tandem catalysis using various 3-en-1-yn-5-als **4a**–**4i** and cyclic ketones (5 equiv). The cyclizations are performed with CpRu(PPh$_3$)$_2$Cl and DBU at 5% loading each; the results are depicted in Table 2.[7] Cyclization of **4a** with two cyclohexanones (Y = CH$_2$, CHMe) gave α-tetralones **6b** and **6c** in 58% and 41% yields, respectively (entries 1 and 2). Entries 3 and 4 show the suitability of this cyclization for alternation of the aldehyde X-substituents (X = CHMe, CMe$_2$); the corresponding 1-indanone **6d**–**6e** were obtained in 51–52% yields. In entries 5–7, the cyclization proceeded better with aldehyde **4d** bearing electron-deficient p-FC$_6$H$_4$ than with analogues **4e**,**f** bearing electron-rich p-CH$_3$C$_6$H$_4$ and p-MeOC$_6$H$_4$. This observation conforms to our expectation as the electron-deficient benzene is expected to increase the C(7)–H acidity of the 3,5-dien-1-yne intermediate. This tandem aldol condensation/aromatization sequence works with 3-en-1-yn-5-als bearing 2- and 3-thiophene functionalities (entries 8 and 9); notably, 3-thiophene product **6i** was obtained in a better yield (66%) than with 2-thiophene **6j** (45%). The cyclization of acyclic aldehyde **4i** with cyclopentanone and cyclohexanone gave the resulting 1-indanone **6k** and α-tetralone **6l** in 52% and 45% yields, respectively (entries 10 and 11).

Table 1. Cyclization of 2-(phenylethynyl)cyclohex-1-enecarbaldehyde by ruthenium catalyst[a]



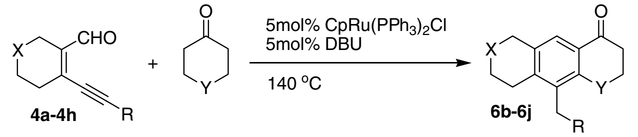
Entry	Catalyst	Base	**6a** (yields %)
1	—	2,6-Lutidine	14
2	—	DBU	18
3	—	TMP	13
4	CpRu(PPh$_3$)$_2$Cl	—	20
5	CpRu(PPh$_3$)$_2$Cl	2,6-Lutidine	54
6[b]	CpRu(PPh$_3$)$_2$Cl	DBU	65
7	CpRu(PPh$_3$)$_2$Cl	TMP	52
8	CpRu(COD)Cl + 2PPh$_3$	DBU	35
9	CpRu[P(p-CH$_3$OC$_6$H$_4$)$_3$]$_2$Cl	DBU	60
10	CpRu[P(p-FC$_6$H$_4$)$_3$]$_2$Cl	DBU	57
11[c]	CpRu[P(OCH$_3$)$_3$]$_2$Cl	DBU	62

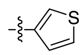
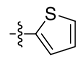
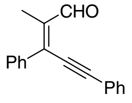
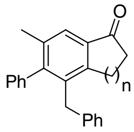
[a] Conditions: aldehyde (1.0 equiv), cyclopentanone (5.0 equiv), neat.

[b] Yield after reaction for 15 h.

[c] Yield is the same after reaction for 48 h.

Table 2. Ruthenium-catalyzed cyclization of 3-en-1-yn-5-als with cyclic ketones[a]

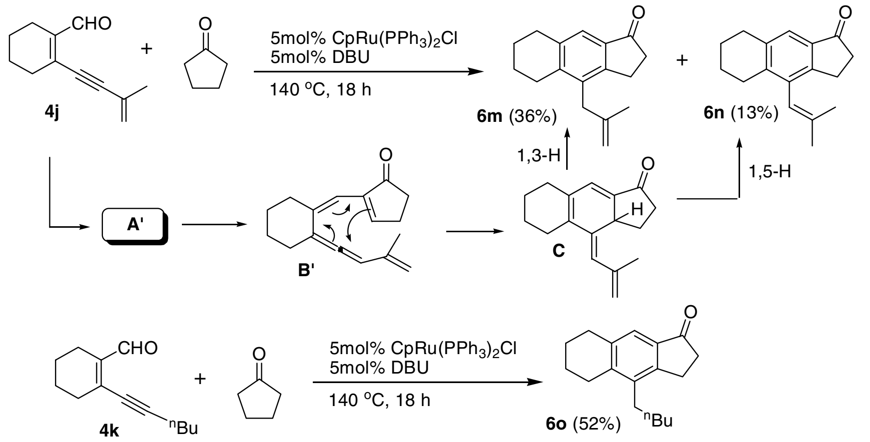


Entry	Aldehyde	Ketone	Products (yields %)[b]
1	(**4a**)	Y = CH$_2$	**6b** (58)
2[c]	(**4a**)	Y = CHMe	**6c** (41)
3	X = CHMe, R = Ph (**4b**)	Y = (CH$_2$)$_0$	**6d** (52)
4	X = CMe$_2$, R = Ph (**4c**)	Y = (CH$_2$)$_0$	**6e** (51)
5	X = CH$_2$, R = p-FC$_6$H$_4$ (**4d**)	Y = (CH$_2$)$_0$	**6f** (72)
6	X = CH$_2$, R = p-CH$_3$C$_6$H$_4$ (**4e**)	Y = (CH$_2$)$_0$	**6g** (61)
7	X = CH$_2$, R = p-OCH$_3$C$_6$H$_4$ (**4f**)	Y = (CH$_2$)$_0$	**6h** (35)
8	X = CH$_2$, R =  (**4g**)	Y = (CH$_2$)$_0$	**6i** (66)
9	X = CH$_2$, R =  (**4h**)	Y = (CH$_2$)$_0$	**6j** (45)
			
10	(**4i**)	Y = (CH$_2$)$_0$	**6k** $n = 1$ (52)
11	(**4i**)	Y = (CH$_2$)$_1$	**6l** $n = 2$ (45)

[a] Conditions: aldehyde (1 equiv), ketone (5 equiv), neat, 12 h.

[b] Yields are given after separation from silica column.

[c] Yield after reaction for 16 h.



Scheme 3.

Scheme 3 shows an extension of this tandem catalysis to 3-en-1-yn-5-al **4j** bearing an alkene group for which its cyclization with cyclopentanone gave 1-indanones **6m** and **6n** in 36% and 16% yields, respectively. Formation of these two products appears to arise from a 1,3 and 1,5-hydrogen shift of a hypothetic intermediate **C**. For 3-en-1-yn-5-al **4k** bearing an *n*-butyl group, the Ru/DBU combined catalyst also effected this tandem catalysis, giving desired product **6o** in 52% yield.

In conclusion, we have successfully improved the cyclization efficiency in the tandem aldol condensation/aromatization of 3-en-1-yn-5-als with cycloalkanones utilizing CpRu(PPh$_3$)$_2$Cl and DBU as dual catalysts.[8–10] This tandem reaction works for aldehyde substrates bearing not only an alkynyl C(1)-aryl substituent, but also a C(1)-alkenyl or alkyl substituent. The effects of the aryl substituents on annulation efficiency supports that the aromatization efficiency of 3,5-dien-1-yne intermediate is enhanced by its C(7)-hydrogen acidity.

Acknowledgment

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2. For recent examples, see: (a) Boxer, M. B.; Yamamoto, H. *J. Am. Chem. Soc.* **2007**, *129*, 2762; (b) Motokura, K.; Fujita, N.; Mori, K.; Mizugaki, T.; Ebitani, K.; Kaneda, K. *J. Am. Chem. Soc.* **2005**, *127*, 9674; (c) Nishibayashi, Y.; Yoshikawa, M.; Inada, Y.; Milton, M. D.; Hidai, M.; Uemura, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 2681.
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6. For the catalytic Mukaiyama aldol-dehydration sequence, see selected examples: (a) Yanagisawa, A.; Coudu, R.; Arai, T. *Org. Lett.* **2004**, *6*, 4281; (b) Ishihara, K.; Kurihara, H.; Yamamoto, H. S. *Synlett* **1997**, 597.
7. *General procedure of the tandem aldol condensation/dehydration and aromatization*: To cyclopentanone (200 mg, 2.38 mmol) were added CpRu(PPh$_3$)$_2$Cl (17.3 mg, 0.024 mmol), DBU (3.62 mg, 0.024 mmol) and 3-en-1-yn-al **4a** (100 mg, 0.48 mmol), and the mixture was heated at 140 °C for 12 h. The resulting solution was filtered through a celite bed, and eluted through a silica gel column (ethyl acetate/hexane = 1/10) to give 1-indanone **6a** (86.2 mg, 0.31 mmol) in 65% yield. ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.44 (s, 1H), 7.24 (t, $J = 6.8$ Hz, 2H), 7.17 (t, $J = 6.8$ Hz, 1H), 7.00 (d, $J = 6.8$ Hz, 2H), 4.06 (s, 2H), 2.94 (t, $J = 5.6$ Hz, 2H), 2.87–2.82 (m, 2H), 2.69–2.61 (m, 4H), 1.81–1.72 (m, 4H); ^{13}C NMR (CDCl$_3$, 100 MHz): δ 207.9, 152.0, 143.7, 138.8, 137.6, 135.8, 134.4, 128.5, 127.8, 126.0, 122.3, 36.3, 34.1, 30.3, 27.2, 24.6, 22.9, 22.4; HMRS calcd for C$_{20}$H$_{20}$O: 276.1514; found, 276.1519.
8. Formation of an enolate requires a base, whereas an acid favors dehydration of the aldol products. For the acid/base combined systems for aldol condensation and dehydration sequence, see: Refs. 2a,b and references cited therein.
9. The Ru/DBU mixture is not suitable for 1-silyl-3-en-1-yn-5-al **1** in this tandem catalysis due to the occurrence of desilylation, which gave desilylated benzene **3** in 23% yield.
10. The role of this dual catalyst in this tandem catalysis is shown by the data in Scheme 2 (entries 5 and 6) and Table 2 (entries 5–7), which reveal that this catalyst combination not only enhanced aldol condensation, but also the subsequent aromatization reaction.