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Rhodium-catalyzed 1,3-acyloxy migration and subsequent intramolecular [4 + 2] cycloaddition of vinylallene and unactivated alkyne†

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Abstract

A Rh-catalyzed 1,3-acyloxy migration of propargyl ester followed by intramolecular [4 + 2] cycloaddition of vinylallene and unactivated alkyne was developed. This tandem reaction provides access to bicyclic compounds containing a highly functionalized isotoluene or cyclohexenone structural motif, while only aromatic compounds were observed in related transition metal-catalyzed cycloadditions.

The Diels–Alder cycloaddition is arguably the most powerful reaction for the construction of substituted six-membered rings from various 2π and 4π reactants.[1] However, unactivated 2π and 4π systems either require very harsh conditions or fail to undergo cycloadditions. In many cases, transition metal catalysts facilitated chemical transformations that were inaccessible under thermal conditions and they have proven to be of great value in cycloaddition reactions.[2] Vinylallenes are unique 4π-components that have been used in [4 + 2] cycloadditions with activated alkenes and alkynes under thermal conditions.[3,4] The cycloaddition of vinylallenes with unactivated alkynes required transition metal catalysts such as platinum[5] or rhodium complexes.[6] In both cases, polysubstituted benzene derivatives were obtained.

We recently found that $[Rh(CO)_2Cl]_2$ could catalyze 1,3-acyloxy migration of propargyl ester **1** to form allene **3**,[7] which was previously realized mainly by π-acidic metal-based catalysts such as silver, copper, platinum, and gold in various tandem transformations.[8,9] We envisioned that the combination of this novel reactivity of Rh(I) catalyst and its ability to promote cycloadditions might allow the tandem transformation from enyne **4** to product **6**: a net 1,3-acyloxy migration of propargyl ester **4**, a subsequent [4 + 2] cycloaddition of the resulting vinylallene with a tethered alkyne, and a final isomerization of isotoluene **5** to polysubstituted aromatic compound **6**.[10] In a related report, Liang and co-workers developed a $PtCl_2$-catalyzed tandem 1,3-acyloxy migration followed by [4 + 2] cycloaddition of vinylallene and alkyne to form similar aromatic products.[5] The unactivated 2π alkyne

†Electronic supplementary information (ESI) available: ^1H NMR, ^{13}C NMR, HRMS, and IR data and copies of NMR spectra for all starting materials and products. CCDC 846678. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2cc17406e

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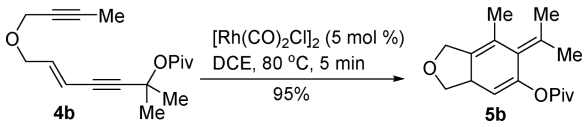
partners, however, were limited to terminal alkynes in the $PtCl_2$-catalyzed reaction. We thought that the scope of this tandem process could be expanded to include internal alkynes using rhodium catalyst *via* a different mechanism. Surprisingly, isotoluene derivative **5** was observed as the major product from rhodium-catalyzed isomerization of enyne **4**. A stable bicyclic compound **7** containing a cyclohexenone substructure was isolated upon hydrolysis (Scheme 1).

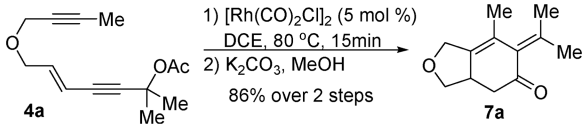
When we treated compound **4a**[11] with a catalytic amount of $[Rh(CO)_2Cl]_2$, an isotoluene derivative **5a** was isolated in 88% yield (Table 1, entry 1). The expected aromatic compound was not detected at all. When the reaction time was extended to approximately 1 h, compound **5** was almost completely decomposed into unidentified byproducts. Other Rh(I) catalysts did not promote the tandem acyloxy migration and cycloaddition process (entries 2–4), suggesting that the electron-withdrawing CO ligand was critical. Certain gold and platinum catalysts facilitated the 1,3-acyloxy migration;[9] no cycloaddition product, however, was observed in any case (entries 5–10).

The reaction worked equally well when the acetate was changed to pivolate (eqn (1)). Product **5b** could be isolated in high yield when the reaction was run for 5min. Isotoluene derivatives **5a** and **5b** were stable enough to be isolated and characterized by NMR. We tried to expand the scope of this tandem reaction, yet we found that most of the isotoluene derivatives could not be stored for long time. Many of them were decomposed into unidentified byproducts after a few days of storage.



(1)

We then decided to convert the isotoluene derivative into a more stable compound. The enol ester in product **5a** is essentially a masked ketone. The crude product from the cycloaddition reaction was treated with a basic solution of potassium carbonate in methanol (eqn (2)).[11] Cyclohexenone **7a** was obtained in 86% yield after two steps.



(2)

With the above two-step protocol in hand, we then examined the scope of the 1,3-acyloxy migration and [4 + 2] cycloaddition cascade. Terminal and various internal alkynes could participate in the [4 + 2] cycloaddition as 2π components (Table 2, entries 1–4). The X-ray structure of **7f** (CCDC 846678) further confirmed our structural assignment.[11] A substrate with a methyl substituent on the olefin led to the formation of product **7g** with an angular methyl group in the bicyclic system (entry 5). Both 5–6 and 6–6 fused carbocycles could be prepared efficiently (entries 6–8). The *gem*-dimethyl group of the propargyl ester could be replaced by a cyclohexane ring (entry 9).

A stereoselectivity issue arose for the exo-cyclic olefins when secondary propargyl esters were employed (entries 10–12). Although a high *Z*/*E* selectivity was observed for substrate **4l** with a *tert*-butyl group (entry 10), moderate selectivities were obtained for other substrates (entries 11 and 12). Phenol **7l′** derived from hydrolysis after isomerization was isolated in 30% yield. The (*Z*)-isomers of products **7m** and **7n** were obtained in over 50%yields. Small amounts of phenol products were also observed in these two cases. In addition, the rate of reaction dropped significantly for all secondary esters. Nonetheless, the addition of phosphite ligand $[(CF_3)_2CHO)]_3P$ improved both the rate and the yield.

To further probe the mechanism, we decided to try the [4 + 2] cycloaddition of independently prepared vinylallene with alkyne. When we treated ester **4b** with $AgSbF_6$ catalyst,[8] an inseparable mixture of vinylallene **8b** and enyne **4b** was obtained after 1 h (Scheme 2). Desired product **5b** was isolated in 78% yield from the above mixture in the presence of $[Rh(CO)_2Cl]_2$ catalyst, suggesting that the acyloxy substituted vinylallene was a plausible intermediate for the tandem reaction. No desired product was observed when this mixture was heated for 2 h in the absence of any catalyst.

We proposed that η^4-vinylallene complex **9** could be generated from enyne **4** *via* a Rh-catalyzed net 1,3-acyloxy migration of propargyl ester (Scheme 3). An oxidative cyclization of intermediate **9** would then yield alkylidene metallacyclopentene **10**.[12] Insertion of a tethered alkyne into metallacycle **10** followed by reductive elimination of metallacycloheptatriene **11** would then produce product **5** with a isotoluene motif, which might be stabilized by the acyloxy substituent because the isomerized aromatic products were obtained in previous transition metal catalyzed [4 + 2] cycloadditions of vinylallenes and unactivated alkynes.[5,6]

In conclusion, we have developed a Rh-catalyzed tandem 1,3-acyloxy migration and subsequent intramolecular [4 + 2] cycloaddition of vinylallenes and unactivated alkynes. The resulting product with an isotoluene substructure could be isolated and characterized. Upon hydrolysis, more stable cyclohexenones formed. The acyloxy group in the propargyl ester starting material eased the preparation of reactive allene functionality, stabilized the isotoluene moiety, and also differentiated the three olefins in the product for further functionalization. The Rh(I) catalyst in the reaction first served as a π-acid to promote the net 1,3-acyloxy migration of propargyl esters. The same catalyst then underwent oxidative addition, migratory insertion, and reductive elimination to afford the [4 + 2] cycloaddition product. The combination of these properties may provide myriad opportunities for the design of new reactions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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11. See ESI† for details.

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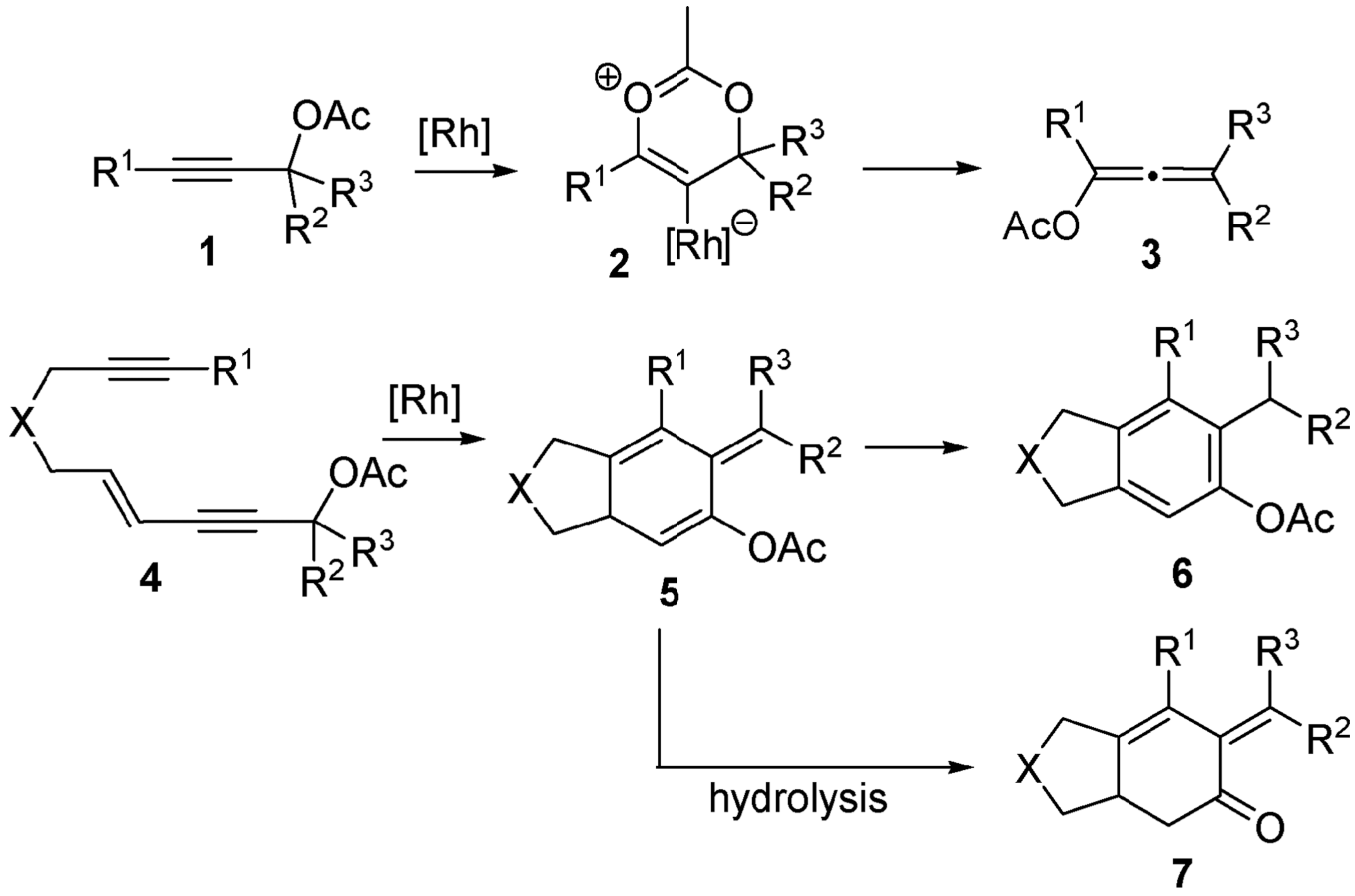
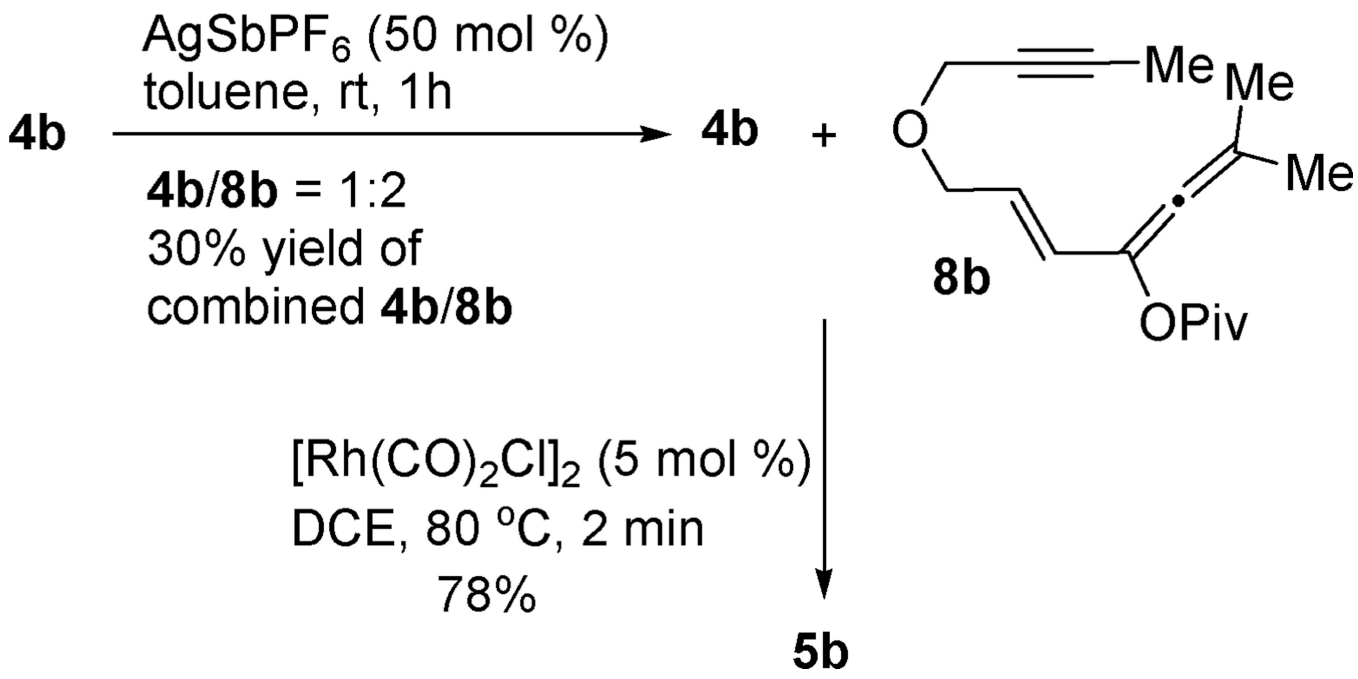
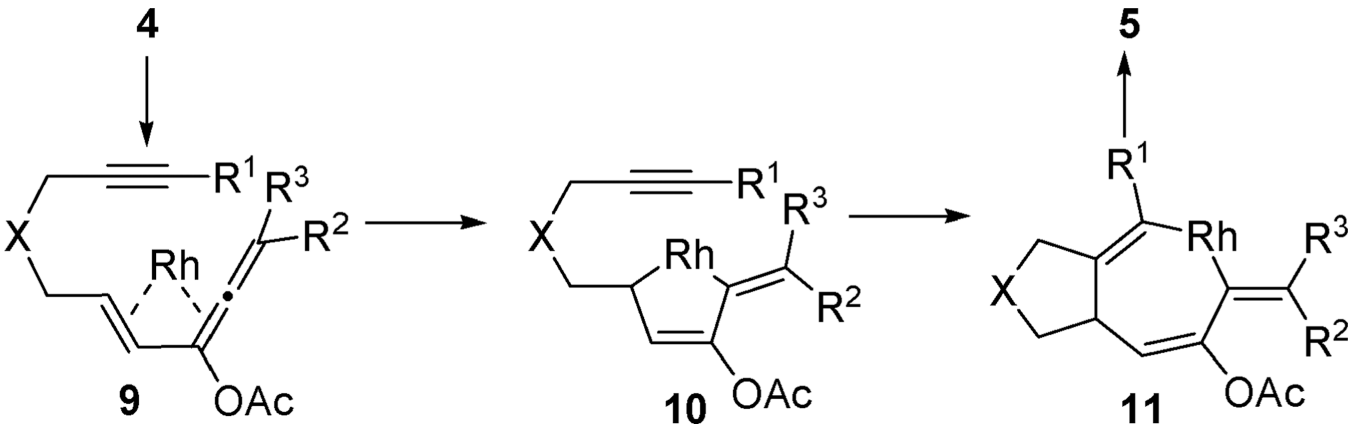
†Electronic supplementary information (ESI) available: ^{1}H NMR, ^{13}C NMR, HRMS, and IR data and copies of NMR spectra for all starting materials and products. CCDC 846678. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2cc17406e



Scheme 1.
1,3-Acyloxy migration and [4 + 2] cycloaddition of vinylallene and alkyne.



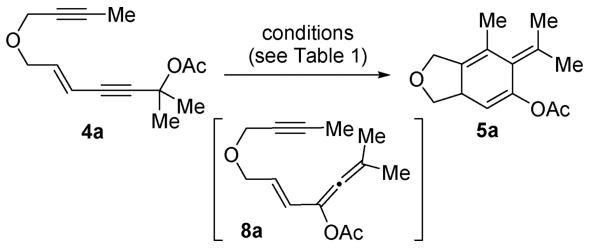
Scheme 2.
Preparation of vinylallene and its involvement in [4 + 2] cycloaddition.



Scheme 3.
Proposed mechanism for the tandem 1,3-acyloxy migration and subsequent [4 + 2] cycloaddition.

Table 1

Screening of catalysts and conditions for 1,3-acyloxy migration followed by [4 + 2] cycloaddition



Entry	Conditions	Results
1	$[Rh(CO)_2Cl]_2$ (5 mol%), DCE, 80 °C, 15 min	88%[a]
2	$[Rh(COD)Cl]_2$ (5 mol%), DCE, 80 °C, 15 min	NR
3	$Rh(PPh_3)_3Cl$ (5 mol%), DCE, 80 °C, 15 min	NR
4	$[Rh(COD)]BF_4$ (5mol%), DCE, 80 °C, 15min	Complex mixture
5	AuCl (5 mol%), DCE, 80 °C, 15 min	Complex mixture
6	$AuCl_3$ (5 mol%), DCE, 80 °C, 15 min	Complex mixture
7	$Au(PPh_3)Cl$ (5 mol%), DCE, 80 °C, 15 min	**4a/8a** = 2 : 1[b]
8	$Au(PPh_3)Cl$ (5 mol%), AgOTf (5 mol%), DCE, 80 °C, 10 min	Complex mixture
9	$PtCl_2$ (5 mol%), DCE, 80 °C, 15 min	**4a/8a** = 6 : 1[b]
10	$PtCl_2$ (10 mol%), CO (1 atm), DCE, 80 °C, 24 h	Complex mixture

[a] Isolated yield.

[b] No cycloaddition product was observed. The ratio was determined by ^{1}H NMR of the crude product.

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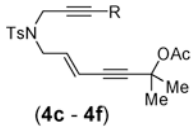
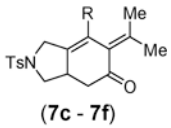
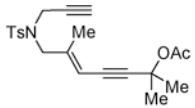
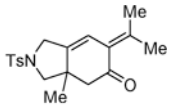
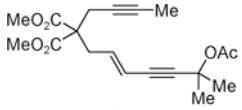
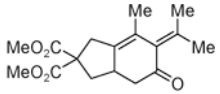
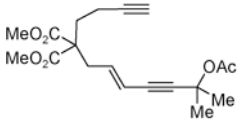
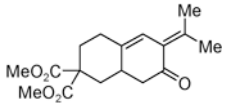
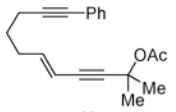
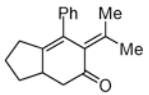
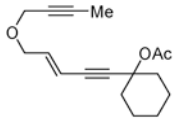
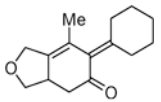
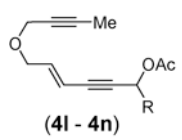
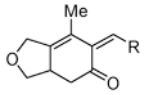
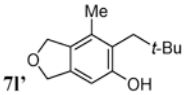
Table 2

Synthesis of cyclohexenone derivatives *via* Rh-catalyzed 1,3-acyloxy migration, [4 + 2] cycloaddition, and hydrolysis[a]

Entry	Substrate	Product	Yield
	 **(4c - 4f)**	 **(7c - 7f)**	
1	R = H, **4c**	**7c**	95%
2	R = Me, **4d**	**7d**	95%
3	R = Ph, **4e**	**7e**	92%
4	R = 4-BrC_6H_4, **4f**	**7f**	87%
5	 **4g**	 **7g**	90%
6	 **4h**	 **7h**	86%
7	 **4i**	 **7i**	95%
8	 **4j**	 **7j**	91%
9	 **4k**	 **7k**	86%

Entry	Substrate	Product	Yield
	 (**4l** - **4n**)	 (**7l** - **7n**) **7l**	
10[b,d]	R = *t*-Bu, **4l**	 **7l'**	(*Z*/*E* > 20 : 1)[c] *Z*-**7l** 61% **7l′**: 30%
11[b]	R = *i*-Pr, **4m**	**7m**	(*Z*/*E* = 3.7 : 1)[c] *Z*-**7m** 58%
12[b]	R = CH_2OTBS, **4n**	**7n**	(*Z*/*E* = 3 : 1)[c] *Z*-**7n** 52%

[a] Condition A: (1) $[Rh(CO)_2Cl]_2$ (5 mol%), DCE, 80 °C, 5–20 min; (2) K_2CO_3, MeOH.

[b] Condition B: (1) $[Rh(CO)_2Cl]_2$ (5 mol%), $[(CF_3)_2CHO]_3P$ (20 mol%), DCE, 80 °C, 15–20 min; (2) K_2CO_3, MeOH.

[c] The ratio was determined by ^1H NMR of the crude product.

[d] The substrate was heated at 80 °C for 45 min under condition B.