One-Pot Sequential Reactions

Novel Ruthenium- and Platinum-Catalyzed Sequential Reactions: Synthesis of Tri- and Tetrasubstituted Furans and Pyrroles from Propargylic Alcohols and Ketones**

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Studies on multiple catalysts within the same medium to obtain desired products from simple starting materials are one of the current and important topics in synthetic chemistry.[1] The action of multiple catalysts lessens the reaction time and the yield loss by avoiding the isolation and purification of intermediates in multiple step sequences. Some interesting results in which multiple and different transition metal catalysts work in the same medium were reported,[2] but in most cases the reaction conditions, such as reaction temperature and reaction atmosphere, need to be changed on the way, or the successive addition of catalysts is necessary according to the reaction steps.[3]

Quite recently, we reported the ruthenium-catalyzed efficient propargylic substitution reactions of propargylic alcohols with various heteroatom- and carbon-centered nucleophiles to give the corresponding functionalized propargylic products in high yields with complete regioselectivities.[4] Noteworthy, the reactions are catalyzed only by thiolate-bridged diruthenium complexes[5] such as $[Cp^*RuCl(\mu_2\text{-}SR)_2RuCp^*Cl]$ ($Cp^* = \eta^5\text{-}C_5Me_5$; R = Me (**1a**), *i*Pr (**1b**), *n*Pr (**1c**)). The result prompted us to investigate the transition metal-catalyzed sequential reaction of functionalized propargylic products, which have a terminal alkyne, because organic compounds with a terminal alkyne are known to be converted into more valuable compounds by various transition metal catalysts.[6,7] We have now found a novel sequential reaction system by using heterobimetallic

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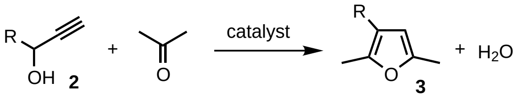
catalysts to give the corresponding tri- and tetra-substituted furans and pyrroles in moderate to high yields with complete regioselectivity from the reaction of propargylic alcohols with ketones in the presence of a catalytic amount of both **1a** and $PtCl_2$. In this reaction system, two different catalysts simultaneously promote their catalytic cycles in the same medium. Preliminary results are described herein.

Table 1: Reaction of propargylic alcohol (**2**) with acetone in the presence of [Cp*RuCl(μ-SMe)$_2$RuCp*Cl] (**1a**) and $PtCl_2$.[a]

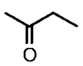
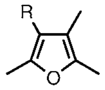
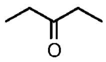
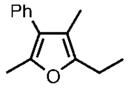
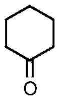
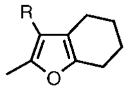
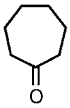
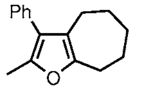
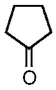
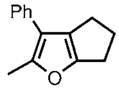


Entry	R	Cat (mol %)	*t* [h]	Yield of **3** [%][b]
1	Ph (**2a**)	**1a** (10) and $PtCl_2$ (20)	36	**3a**, 64 (75)[c]
2	Ph (**2a**)	**1a** (10) and $PtCl_2$ (20)	72	**3a**, 69
3	Ph (**2a**)	**1a** (10) and $PtCl_2$ (10)	100	**3a**, (83)[c]
4	Ph (**2a**)	**1a** (5) and $PtCl_2$ (10)	110	**3a**, (74)[c]
5	Ph (**2a**)	**1a** (10) and $AuCl_3$ (20)	36	**3a**, (36)[c,d]
6	*p*-MeC_6H_4 (**2b**)	**1a** (10) and $PtCl_2$ (20)	72	**3b**, 65
7	*p*-$MeOC_6H_4$ (**2c**)	**1a** (10) and $PtCl_2$ (20)	36	**3c**, 52
8	*p*-FC_6H_4 (**2d**)	**1a** (10) and $PtCl_2$ (20)	72	**3d**, 57
9	*p*-ClC_6H_4 (**2e**)	**1a** (10) and $PtCl_2$ (20)	72	**3e**, 74
10	*p*-$CF_3C_6H_4$ (**2f**)	**1a** (10) and $PtCl_2$ (20)	36	**3f**, 54
11	2-naphthyl (**2g**)	**1a** (10) and $PtCl_2$ (20)	72	**3g**, 64
12	Ph_2C=CH- (**2h**)	**1a** (10) and $PtCl_2$ (20)	36	**3h**, 29
13	cyclohexyl (**2i**)	**1a** (10) and $PtCl_2$ (20)	36	**3i**, 0

[a] All the reactions of **2** (0.60 mmol) with acetone (30 mL) were carried out in the presence of catalysts and NH_4BF_4 (20 mol%) at reflux temperature. [b] Yield of isolated compound. [c] Yield obtained by GLC. [d] 3-Phenyl-2,5-hexanedione was also formed with 27% yield obtained by GLC.

Treatment of 1-phenyl-2-propyn-1-ol (**2a**) in acetone in the presence of **1a** (10 mol%), NH_4BF_4 (20 mol%), and $PtCl_2$ (20 mol%) at reflux temperature for 36 h afforded 2,5-dimethyl-3-phenylfuran (**3a**) in 75% yield as measured by GLC (64% yield of the isolated product; Table 1, entry 1). A prolonged reaction time improved the yield of **3a** (Table 1, entries 2 and 3). The reaction proceeded even in the presence of smaller quantities of **1a** (5 mol%) and $PtCl_2$ (10 mol%; Table 1, entry 4). Noteworthy, the bimetallic system of **1a** and $PtCl_2$ is essential to promote the catalytic formation of **3a** effectively. Other transition-metal complexes, such as $Pd(OAc)_2$, [$PdCl_2(MeCN)_2$] and $PdCl_2$ were ineffectual, while $AuCl_3$[8] worked effectively but an intermediate diketone was also formed (see below; Table 1, entry 5). The use of various propargylic alcohols resulted in the formation of the corresponding 3-aryl and 3-alkenyl substituted 2,5-dimethylfurans (**3b**–**3h**) in moderate to high yields with a complete regioselectivity (Table 1, entries 6–12). Unfortunately, the reaction of 1-cyclohexyl-2-propyn-1-ol did not proceed at all (Table 1, entry 13).

Table 2: Reaction of propargylic alcohol (**2**) with ketone in the presence of [Cp*RuCl(μ-SMe)$_2$RuCp*Cl] (**1a**) and $PtCl_2$.[a]

Entry	**2**	Ketone	Furan (**3**)	Yield of **3**, %[b]
1 2 3	R = Ph (**2a**) R = *p*-MeC_6H_4 (**2b**) R = *p*-FC_6H_4 (**2d**)			R = Ph, 72 (**3j**) R = *p*-MeC_6H_4, 78 (**3k**) R = *p*-FC_6H_4, 65 (**3l**)
4[c]	R = Ph (**2a**)			85 (**3m**)
5 6 7	R = Ph (**2a**) R = *p*-FC_6H_4 (**2d**) R = *p*-ClC_6H_4 (**2e**)			R = Ph, 75 (**3n**) R = *p*-FC_6H_4, 75 (**3o**) R = *p*-ClC_6H_4, 69 (**3p**)
8	R = Ph (**2a**)			66 (**3q**)
9	R = Ph (**2a**)			0 (**3r**)

[a] All the reactions of **2** (0.60 mmol) with ketone (30 mL) were carried out in the presence of **1a** (0.06 mmol), $PtCl_2$ (0.12 mmol) and NH_4BF_4 (0.12 mmol) at reflux temperature for 36 h. [b] Isolated yield. [c] For 72 h.

Reactions of propargylic alcohols with other ketones were similarly carried out. Typical results are shown in Table 2. Formation of the corresponding 3-aryl-2,4,5-trimethylfurans (**3j**–**3l**) was observed in the reactions of propargylic alcohols (**2a**, **2b**, **2d**) with 2-butanone (Table 2; entries 1–3). The reaction of **2a** with 3-pentanone under the same reaction conditions gave 2-ethyl-3,5-dimethyl-4-phenylfuran (**3m**) in 85% yield (Table 2, entry 4). Noteworthy, the formation of other regioisomers of furans was not observed in all cases. The reactions of various propargylic alcohols with cyclohexanone gave the expected 3-aryl-2-methyl-4,5,6,7-tetrahydrobenzofurans (**3n**–**3p**) in high yields (Table 2, entries 5–7). From **2a** and cycloheptanone, 2-methyl-3-phenyl-5,6,7,8-tetrahydro-4*H*-cyclohepta[*b*]furan (**3q**) was obtained in 66% yield, but no reaction occurred with cyclopentanone (Table 2, entries 8 and 9, respectively).

To obtain some information of the reaction mechanism, the relationship between the product yields and the reaction time was investigated in the reaction between **2a** and acetone in the presence of **1a** and $PtCl_2$ (Figure 1). This time profile indicates the following: At first, **2a** is transformed rapidly into γ-ketoalkyne (**4a**) by the catalysis of **1a** (Scheme 1, step a).[4b] Then, hydration of the alkyne moiety in **4a** by the produced H_2O slowly gives the 1,4-diketone, **5a**, by the catalysis of $PtCl_2$ (Scheme 1, step b).[9] Intramolecular cyclization of the produced diketone then follows, which results in the formation of the furan, **3a**, also by the catalysis of $PtCl_2$ (Scheme 1, step c).[9b] This result clearly indicates that two different

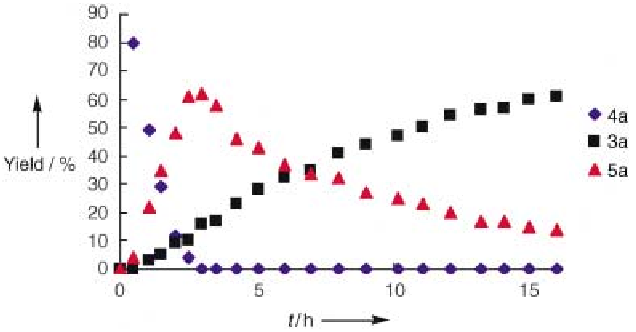
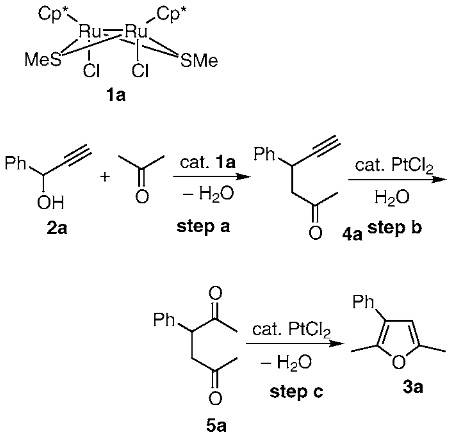
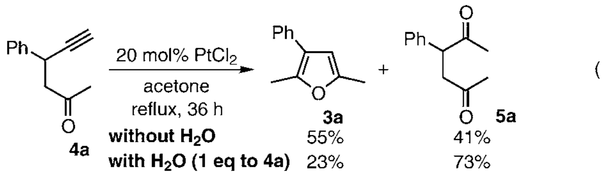


Figure 1. Time profile of the reaction of propargylic alcohol (**2a**) with acetone in the presence of [Cp*RuCl(μ-SMe)$_2$RuCp*Cl] (**1a**; 10 mol%) and $PtCl_2$ (20 mol%).

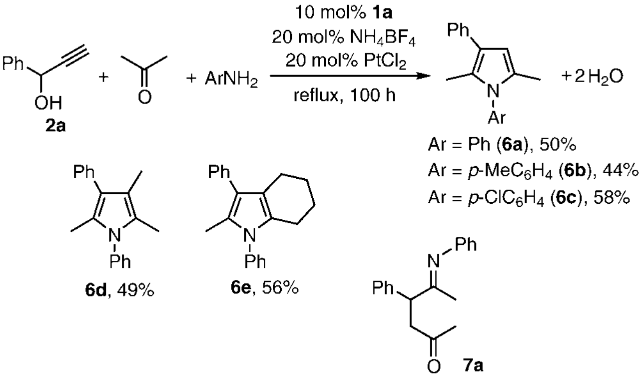


Scheme 1. Reaction of 1-phenyl-2-propyn-1-ol with acetone in the presence of [Cp*RuCl(μ-SMe)$_2$RuCp*Cl] and $PtCl_2$.

catalysts, such as **1a** and $PtCl_2$, can promote their catalytic cycles in the same medium. Separately, the transformation of **4a** into **3a** and **5a** was confirmed in the presence of $PtCl_2$ [Eq. (1)]. However, even upon adding stoichiometric

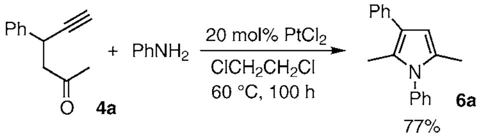
 (1)

amounts of water to **4a**, its conversion into **3a** via **5a** was slower than that in the present reaction system, thus showing that the coexistence of **1a** and $PtCl_2$ promotes this conversion more smoothly.



Scheme 2. Reactions of 1-phenyl-2-propyn-1-ol with ketones and anilines in the presence of [Cp*RuCl(μ-SMe)$_2$RuCp*Cl] and $PtCl_2$.

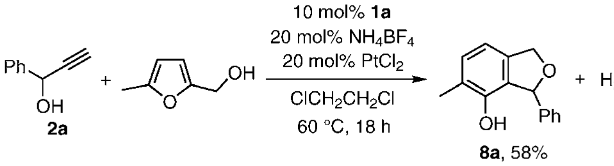
When the above new catalytic reactions were carried out in the presence of aniline derivatives (5 equiv relative to **2a**), the corresponding tri- and tetra-substituted pyrroles (**6**) were produced in moderate isolated yields with complete regioselectivity (Scheme 2).[10] No formation of the corresponding furans and other regioisomers of **6** was observed in all cases. Nucleophilic attack of anilines on the carbon-carbon triple bond in **4a** catalyzed by $PtCl_2$ may give the corresponding imines (**7a**).[11] Cyclization of **7a** catalyzed by $PtCl_2$ may produce the substituted pyrrole (**6a**). It was confirmed that the reaction of **4a** with aniline in the presence of $PtCl_2$ afforded **6a** in 77% isolated yield [Eq. (2)]. This result

 (2)

indicates that sequential three-component coupling reaction by the catalysis of **1a** and $PtCl_2$ occurs in the same medium.

The bimetallic system of **1a** and $PtCl_2$ can be applied to other sequential catalytic reactions. A typical example is shown in Scheme 3. The reaction of propargylic alcohol (**2a**) with 5-methyl-2-furylmethanol in the presence of a catalytic amount of both **1a** and $PtCl_2$ in 1,2-dichloroethane at 60 °C for 18 h afforded the corresponding phenol derivative **8a** in 58% yield.[12] Propargylation of the furylmethanol with **2a** was promoted by **1a** to give the corresponding furylmethyl propargylic ether,[4a] which was subsequently transformed into the corresponding phenol derivative by the so far known catalysis of $PtCl_2$.[13]

In summary, we have found novel ruthenium- and platinum-catalyzed sequential reactions to afford the corresponding tri- and tetra-substituted furans or pyrroles[14] from propargylic alcohols with ketones, or with ketones and anilines, respectively, in moderate to good yields with high regioselectivities. Two different kinds of catalysts **1a** and $PtCl_2$ sequentially promote each catalytic cycle in the same medium. Some phenol derivatives can also be prepared from propargylic alcohols and furylmethanol by this bimetallic



Scheme 3. Reaction of 1-phenyl-2-propyn-1-ol with 5-methyl-2-furylmethanol in the presence of [Cp*RuCl(μ-SMe)$_2$RuCp*Cl] and $PtCl_2$.

system. Further investigations involving the elucidation of the detailed reaction mechanism and broadening the scope of this sequential catalytic systems are currently in progress.

Experimental Section

A typical experimental procedure for the reaction of 1-phenyl-2-propyn-1-ol (**2a**) with acetone catalyzed by [Cp*RuCl(μ_2-SMe)$_2$-RuCp*Cl] (**1a**) and $PtCl_2$ is described below. Complex **1a** (38 mg, 0.06 mmol), NH_4BF_4 (12 mg, 0.12 mmol), and $PtCl_2$ (31 mg, 0.12 mmol) were placed in a 50 mL flask under N_2. Anhydrous acetone (30 mL) was added, and then the mixture was magnetically stirred at room temperature. After the addition of **2a** (79 mg, 0.60 mmol), the reaction flask was kept at reflux temperature for 36 h. The solvent was concentrated under reduced pressure by an aspirator, and then the residue was purified by TLC (SiO_2) with EtOAc-hexane (1/9) to give 2,5-dimethyl-3-phenylfuran[15] (**3a**) as a colorless oil (66.5 mg, 0.38 mmol, 64 % yield); ^{1}H NMR (270 MHz, $CDCl_3$): $\delta =$ 2.28 (s, 3H), 2.40 (s, 3H), 6.10 (s, 1H), 7.21–7.37 ppm (m, 5H); ^{13}C NMR (67.5 Hz, $CDCl_3$): $\delta = 12.9$, 13.4, 106.9, 121.4, 126.0, 127.3, 128.5, 134.5, 145.8, 149.7 ppm.

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[12] The molecular structure of **8a** was unambiguously determined by X-ray analysis. CCDC 203160 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).

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