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One Pot Preparation of Bicyclopentenones from Propargyl Malonates (and Propargylsulfonamides) and Allylic Acetates by a Tandem Action of Catalysts

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One of the most remarkable features in living organisms is the specific synthesis of numerous metabolites.[1] A number of enzymes are involved in the synthesis of a selected metabolite and every enzyme shows high substrate specificity among many structurally related intermediates. As a result, the whole sequence of transformation could be carried out in one pot with high efficiency. Mimicking of this feature with conventional chemical catalysts would be a great interest among organic chemists. The success of these manipulations would allow not only a conceptual advance in the design of new processes, but also economically useful processes, which will minimize the use of chemicals and the production of waste, and the processing time.

Some relevant reports such as a domino reaction of specially designed substrates with a single catalyst[2] have appeared in the literature. More closely related and interesting processes, for example, a preparation of branched polyolefins from ethylene as a sole feedstock with two catalysts[3] and an olefin metathesis followed by other transformations in one pot,[4,5] have been reported recently. Meantime, multienzymatic processes in vitro have also been accomplished.[6]

Given the understanding of the state of the art and the need, it is desirable to devise the one-pot multistep transformation, in which the first step catalyzed by one catalyst creates the products to be subjected to the second catalyst for the next step. And that in turn sets up the third reaction, and so on.

In this context we choose the following multiple C−C bond-forming transformations for a demonstration (Scheme 1). This transformation includes two reactions; the first allylation generates an enyne intermediate (**3**) via the Pd π-allyl complex[7] from the mixture of **1** and **2** and the following Pauson−Khand type reaction (PKR hereafter) of the resultant enyne **3** yields a bicyclopentenone (**4**).

Key to the success of this transformation would be the identification of the *right* combinations of catalysts which are compatible with each other because the first allylation reaction

Scheme 1. Two-Step One-Pot Preparation of Bicyclopentenones
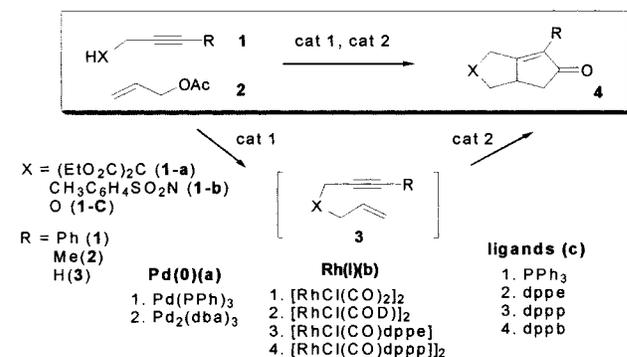
could be facilitated by the electron-rich Pd(0) catalyst and the second PKR needed a Lewis acidic catalyst.

Early attempts using various combinations of previously known catalysts[7,8] have failed. However, the progress of this study was fortunately expedited by two recently published works: one is Rh(I)-catalyzed PKR[9] and another is Pd(dppb)-catalyzed allylic substitution.[10] Since these reactions are reported to be done in *rather mild and neutral conditions,* they are expected to be compatible in one vessel.

Preliminary experiments with each catalyst looked promising. The allylation of a propargyl malonate (**1-a-1**) by palladium catalyst with a variety of ligands in the presence of bis-(trimethylsilyl)acetamide (BSA) proceeded nicely to give **3-a-1** in a variety of solvents such as CH_2Cl_2 or toluene (entries 1 and 5) as expected. No further reaction with the resultant enyne (**3-a-1**) was observed even under CO pressure in several hours.

On the other hand, rhodium(I) alone, however, did not induce an allylation or intermolecular PKR between **1-a-1** and allyl acetate (**2**) at all cases (entries 6−9). But if the reaction mixture was allowed to be under the same reaction condition for a prolonged period (>20 h), a multitude of side products began to appear.[11]

The tandem reaction was then examined with a mixture of catalysts.[12] It was observed that the efficiencies of the tandem reaction were sensitive to the catalyst combinations and the reaction conditions.

Since sodium propargyl malonate as a nucleophile in the allylation was not compatible with the catalysts, it was better to use **1-a-1** together with *N,O*-bis(trimethylsilyl)acetamide (BSA). The allylation was also substantially influenced by the nature of both ligands for the Pd(O) and Rh(I) counterparts. 1,4-Bis-(diphenylphosphino)butane (dppb) worked well in general (entry 5). The Lewis acidity of Rh(I) seems to influence substantially the allylation efficiency. While [RhCl(CO)₂]₂ (**b-1**) and [RhCl-(CO)dppe] (**b-3**) were not compatible with Pd(dba)₂/dppb so that even the first allylation reaction was blocked, [RhCl(CO)(dppp)]₂ (**b-4**) and [RhCl(CO)(dppb)]₂ (generated in situ by mixing of **b-2** and dppb)[13] were compatible with the presumed Pd(dppb).[14]

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(11) Refer to the gas-chromatogram in the Supporting Information for the multicatalytic process and for a reaction with the same mixture by Pd(0) and Rh(I), respectively.

(12) In typical experiments substrates **1-a-1** and **2** were added to a solution of the mixture of catalysts **a** and/or **b** at ambient temperature. The reaction mixture was evacuated and charged with CO (1 atm) and allowed to react at room temperature for a couple of hours first and then, if there was no change, heated at the appropriate temperature.

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Table 1. Trials to Optimize the Tandem Reactions

	Pd(0) catalysts		Rh(1) catalysts								
entry	Pd precursor (mol %)	external ligand	Rh precursor (mol %)	external ligand	solvent	base	additives	temp (°C)	time (h)	yield of **3**[a] (%)	yield of **4**[a] (%)
1	**a-2**(3)	**c-1**(6)			toluene	BSA		110	5	92	–
2	**a-2**(3)	**c-2**(6)			toluene	BSA		110	3	93	–
3	**a-2**(3)	**c-3**(6)			toluene	BSA		110	3	90	–
4	**a-2**(3)	**c-4**(6)			CH$_2$Cl$_2$	BSA		40	5	90	–
5	**a-2**(3)	**c-4**(6)			toluene	BSA		110	1	95	–
6			**b-1**(3)		CH$_2$Cl$_2$	BSA		40	8	–	–
7			**b-2**(3)	**c-1**(3)	toluene	BSA		90	8	–	–
8			**b-3**(3)		toluene	BSA		110	15	–	–
9			**b-4**(3)		toluene	BSA		110	10	–	–
10	**a-2**(3)	**c-2**(6)	**b-1**(5)		toluene	BSA		110	45	–	–
11	**a-2**(3)	**c-4**(6)	**b-1**(5)		toluene	BSA		110	45	*b*	23
12	**a-2**(3)	**c-4**(6)	**b-1**(5)	**c-4**(5)	toluene	BSA		110	35	15	–
13	**a-2**(3)	**c-4**(6)	**b-2**(5)	**c-3**(5)	toluene	BSA		110	30	92	–
14	**a-2**(3)	**c-4**(6)	**b-3**(5)		toluene	BSA		110	30	5	–
15	**a-2**(3)	**c-4**(6)	**b-3**(5)		toluene	BSA	AgOTf	110	30	10	–
16	**a-2**(3)	**c-4**(6)	**b-4**(5)		THF	BSA		80	30	85	–
17	**a-2**(3)	**c-4**(6)	**b-4**(3)		THF	BSA	AgOTf	110	30	50	–
18	**a-2**(3)	**c-4**(6)	**b-4**(5)		toluene	BSA		110	35	*b*	44
19	**a-2**(3)	**c-4**(6)	**b-4**(7)		toluene	BSA		110	35	*b*	60
20	**a-2**(3)	**c-4**(6)	**b-4**(10)		toluene	BSA		110	35	–	91
21	**a-2**(3)	**c-4**(6)	**b-2**(5)	**c-4**(6)	toluene	BSA		110	35	15	–
22	**a-2**(3)	**c-4**(6)	**b-2**(10)	**c-4**(10)	toluene	BSA		110	35	*b*	50

[a] Yields were obtained by Silics gel column chromatography. [b] Enzynes (**3**) were detected but their yields were not determined.

For PKR, a combination with monomeric Rh(I) catalysts bearing diphosphine ligands, such as **b-3,** was not sufficiently active enough under this condition (entries 11−15), but that with dimeric Rh(I) catalysts, e.g. **b-4** or a mixture of **b-2** and dppb, was effective (entries 18−20 and 22). Addition of silver triflate to activate **b-3** made the whole transformation even worse by interfering with the activity of Pd(0) and Rh(I) (entry 15).

After further screening, we found that a combination of **a-2** and **c-4** with **b-4** possessed the balanced reactivity. The reaction was monitored by gas chromatograpy to confirm that **3-a-1** was obtained completely in a couple of hours, and then was transformed into **4-a-1** in 20 h (entry 18−20). The ratio of Rh(I)/Pd seemed to be optimized by 2−3 to 1. Under this condition a combination of two catalysts worked synergistically to impede the formation of unwanted side products and to provide **4-a-1** as a sole product (*91% based on* **1-a-1**), even though the reaction usually lasted longer than 20 h.[11] This one-pot process is obviously better than the usual two separate operations, in which the overall yield can barely exceed 80% despite each step providing 90% yield, respectively.

The two-step one-pot operation was realized only in refluxing toluene (entries 16 and 20) in a reasonable period of time (6−25 h). On the basis of these and further optimization data, we set up our protocol with a lower dose of catalysts.[15]

We now turn our attention to determining the scope of the substrates in this transformation (Table 2). The reactions with propargyl malonates (**1-a**) proceed nicely when the acetylenes are substituted at both sides. For example, **1-a-1** gave an excellent yield (92%) of **4-a-1** and **1-a-2** reacted rather slowly and yielded **4-a-2** in 73% yield. But no **4-a-3** was obtained from a terminal propargyl malonate (**1-a-3**).

The reaction with the propargylsulfonamides (**1-b**) proceeded uneventfully regardless of the substitution pattern to give the corresponding **4-b**, for example, 90% yield for Ph, 91% for Me, and 92% for H, respectively. But this transformation was not effective with the propargyl alcohols (**1-c**), even though their pK_a values were similar to those of **1-b**. This might be attributed to

Table 2. Representative Examples of the Tandem Reaction[a]

entry	X	R	substrate	time (h)	yield of **4** (%)[b]
1	(EtO$_2$C)$_2$C	Ph	**1-a-1**	25	92
2		Me	**1-a-2**	25	73
3		H	**1-a-3**	25	0[c]
4	CH$_3$C$_6$H$_4$SO$_2$N	Ph	**1-b-1**	10	90
5		Me	**1-b-2**	10	91
6		H	**1-b-3**	6	92
7	O	Ph	**1-c-1**	17	0[c]
8		Me	**1-c-2**	17	0[c]

[a] A mixture of **1** (1.0 eq) and **2** (2.0 equiv) together with Pd$_2$(dba)$_3$(CHCl$_3$) (1.5 mol %), dppb (3.0 mol %), BSA (1.2 equiv), and [RhClCO (dppp)]$_2$ (7 mol %) in toluene was heated at 110 °C for an appropriate period. [b] Yields were obtained after Silica gel column chromatography. [c] A complex mixture was obtained.

the steric environment at a potential nucleophilic site, which could attack metals competitively.

In summary, we have successfully demonstrated the multiple C−C bond formation by a combination of the two catalysts. This transformation is easy to carry out because the reaction condition is normalized and quite efficient to give high chemical yield of the desired products with minimal use of solvents and reagents, and minimal production of waste. Further studies to extend this concept, to develop the general research tools including high throughput screening for the rapid identification of the right combination, and to elucidate the mechanistic insights will be the immediate research subjects in this group.

Supporting Information Available: Experimental procedures, ^{31}P NMR spectra of precatalysts and the mixture, and GC-chromatogram for the control experiments and a tandem reaction (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(14) This does not necessarily mean that two precatalysts remained unchanged in the mixture. In fact, ^{31}P NMR studies strongly suggested the interactions between precatalysts prior to the reaction. Refer to the Supporting Information.

(15) Refer to footnote *a* in Table 2.