# A Pyridylsilyl Group Expands the Scope of Catalytic Intermolecular Pauson–Khand Reactions**

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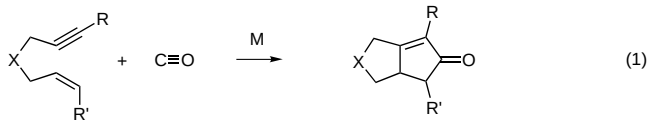
The [2+2+1] cycloaddition of alkyne, alkene, and carbon monoxide mediated or catalyzed by a transition metal M, which is known as the Pauson–Khand reaction (PKR),[1] has received particular attention in organic synthesis, since it allows the construction of biologically interesting five-membered carbocycles in a convergent manner. Although tremendous progress has been seen for the catalytic *intramolecular* PKR [Eq. (1)] and many reactions have been reported,[1] the

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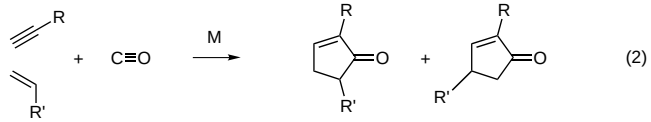
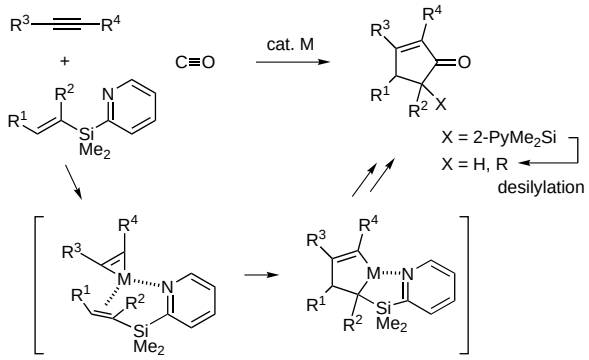



(2)

development of an efficient and general procedure for a catalytic *intermolecular* PKR [Eq. (2)] lags far behind.[1,2] In particular, the limitations imposed on the alkene counterpart are serious: 1) No catalytic intermolecular PKR has been reported yet for simple alkenes (the reactions are restricted to ethylene gas and strained alkenes),[2] and 2) in a stoichiometric PKR, simple alkenes exhibit low reactivity and regioselectivity.[1,3] This may be due to the low coordinating ability of alkenes in comparison with alkynes and carbon monoxide.

Although such problems might be overcome by incorporating a coordinating heteroatom tethered to the alkenes,[4,5] the removal of such a directing group after the PKR is strongly desirable from a synthetic point of view. Therefore, the utilization of a removable directing group[6] is expected to enhance the synthetic potential of the catalytic intermolecular PKR by eliminating the problems associated with reactivity and regioselectivity issues of the alkene.

Our recent demonstration that the dimethyl(2-pyridyl)silyl (2-PyMe$_2$Si) group serves as an excellent, removable directing group in a number of metal-catalyzed reactions[7,8] led us to investigate the possibility of alkenyldimethyl(2-pyridyl)silane as a substrate for a catalytic intermolecular PKR. The oxidative cyclization of alkyne, alkene, and metal can be regarded as a carbometalation of an (alkyne)metal complex across an alkene.[9] Therefore, we expected the facile and regioselective formation of a metallacyclopentene intermediate owing to the coordination effect of the pyridyl group on silicon (Scheme 1). We have already established the high




Scheme 1. The catalytic intermolecular Pauson–Khand reaction directed by a pyridylsilyl group.

reactivity of alkenyldimethyl(2-pyridyl)silanes in several carbometalation processes.[7b,f,10] Moreover, the resultant 2-PyMe$_2$Si-substituted cyclopentenone should be easily converted into the Si-free derivative by using various desilylation methods that we developed.[11]

We first screened for a catalyst for the intermolecular PKR using dimethyl(2-pyridyl)(vinyl)silane (**1a**). Among various metal complexes (Ti, Fe, Co, Mo, Ru, Rh, Pd, Ir, and Pt), [Ru$_3$(CO)$_{12}$] was found to catalyze this process.[12,13] The reaction of **1a** (1.0 equiv), phenylacetylene (**2a**, 1.5 equiv), and carbon monoxide (1 atm) at 100 °C in toluene in the presence of [Ru$_3$(CO)$_{12}$] (5 mol %) gave the desilylated cyclopentenone **3aa**, which was isolated in 55 % yield with virtually complete regioselectivity (Table 1, entry 1).[14] The trend in regioselectivity (the Ph group is in the position $\alpha$ to the carbonyl group) is in line with that observed in the stoichiometric PKR.[1] The realization of a catalytic intermolecular PKR without the need for a high pressure of carbon monoxide is particularly noteworthy. Under the identical conditions, no reaction occurred when dimethylphenyl(vinyl)silane was used in place of **1a**, which clearly implicates the strong directing effect of the pyridyl group. This is not only an example of the successful utilization of vinylsilane as an alkene counterpart in a catalytic intermolecular PKR,[15] but also a demonstration that **1a** could serve as a nongaseous ethylene equivalent in this reaction.[16]

When the alkyl-substituted alkyne **2b** was employed, a substantial decline in regioselectivity was observed (Table 1, entry 2). Symmetrical internal alkynes also participate in the catalytic intermolecular PKR with reasonable efficiency. When 1-phenylpropyne (**2e**) was used, cyclopentenone **3ae** was obtained with virtually complete regioselectivity (entry 5). However, when the chloro-substituted alkyne **2f** was allowed to react, there was a substantial decline in the regioselectivity (entry 6). Since **2e** and **2f** are sterically and

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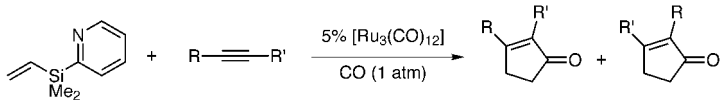
Table 1. Catalytic intermolecular PKR of **1a** and various alkynes **2**.[a]

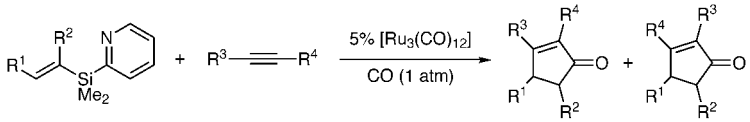



**1a** **2** **3** **4**

| Entry | **2** | Products | Yield [%] (**3**/**4**) |
|---|---|---|---|
| 1 | **2a** (R = H, R′ = Ph) | **3aa** | 55 (100/0)[b,c] |
| 2 | **2b** (R = H, R′ = $C_6H_{13}$) | **3ab** + **4ab** | 91 (59/41)[b] |
| 3 | **2c** (R = R′ = Ph) | **3ac** | 88[d] |
| 4 | **2d** (R = R′ = $C_3H_7$) | **3ad** | 59[d] |
| 5 | **2e** (R = $CH_3$, R′ = Ph) | **3ae** | 75 (100/0)[b,c] |
| 6 | **2f** (R = $(CH_2)_4Cl$, R′ = Ph) | **3af** + **4af** | 67 (87/13)[d] |

[a] Reaction conditions: **1a** (0.50 mmol), **2** (0.75 mmol), $[Ru_3(CO)_{12}]$ (0.025 mmol), CO (1 atm), solvent (1.5 mL). [b] Reaction at 100 °C in toluene. [c] Compound **4** was not detected by NMR spectroscopy and GC analysis. [d] Reaction at 120 °C in xylenes.

Table 2. Catalytic intermolecular PKR of substituted vinylsilanes **1** and alkynes **2**.[a]




**1** **2** **3** **4**

| **1** | **2** | Products | Yield [%] (**3**/**4**) |
|---|---|---|---|
| **1b** ($R^1 = C_4H_9$, $R^2$ = H) | **2a** ($R^3$ = H, $R^4$ = Ph) | **3ba** | 41 (100/0)[b,c] |
| **1b** ($R^1 = C_4H_9$, $R^2$ = H) | **2b** ($R^3$ = H, $R^4 = C_6H_{13}$) | **3bb** + **4bb** | 55 (89/11)[d] |
| **1b** ($R^1 = C_4H_9$, $R^2$ = H) | **2c** ($R^3 = R^4$ = Ph) | **3bc** | 44[b] |
| **1c** ($R^1 = (CH_2)_4OMe$, $R^2$ = H) | **2c** ($R^3 = R^4$ = Ph) | **3cc** | 48[b] |
| **1d** ($R^1$ = H, $R^2 = CH_3$) | **2b** ($R^3$ = H, $R^4 = C_6H_{13}$) | **3db** + **4db** | 40 (62/38)[e] |

[a] Reaction conditions: **1** (0.50 mmol), **2** (0.75 mmol), $[Ru_3(CO)_{12}]$ (0.025 mmol), CO (1 atm), solvent (1.5 mL). [b] Reaction at 140 °C in xylenes. [c] Compound **4** was not detected by NMR spectroscopy and GC analysis. [d] Reaction at 100 °C in toluene. [e] Reaction at 120 °C in xylenes.

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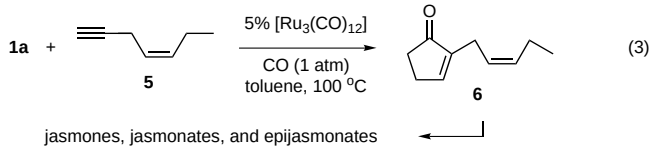
electronically similar, the observed differences in regioselectivity may be due to the directing effect of chloride, which has been occasionally observed in Ru and other metal complexes.[17]

We next turned our attention to the synthesis of more highly substituted cyclopentenones by employing substituted vinylsilanes (Table 2). The advantage of our system is that the use of $\alpha$- or $\beta$-substituted vinylsilanes (**1b–d**)[18] results in the regioselective production of substituted cyclopentenones with the substituent at the 5- or 4-position, respectively. In all cases, virtually complete regioselectivity with regard to the alkene subunit was observed. Thus, these substituted vinylsilanes not only serve as surrogates for terminal alkenes that cannot be applied in the previously reported catalytic PKR, but also enable the complete regioselective incorporation of the alkene subunit into the cyclopentenone skeleton. Although converting the 2-PyMe$_2$Si group into functional groups other than a hydrogen atom is not feasible at this stage, the present observations clearly demonstrate the power and usefulness of using the 2-PyMe$_2$Si group as a removable directing group in the catalytic intermolecular PKR.

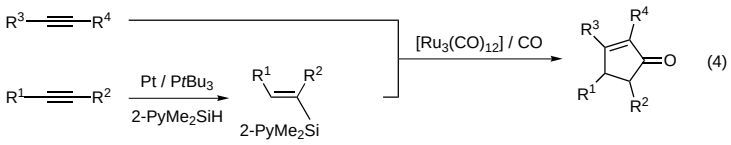
Our catalytic intermolecular PKR should be a straightforward approach toward the synthesis of natural and nonnatural cyclopentanoid products. For example, cyclopentenone **6**, which has emerged as an excellent precursor for the synthesis of jasmone,[19] methyl jasmonate,[19] and methyl epijasmonate,[19] can be prepared in a single chemical operation from **1a** and enyne **5** [Eq. (3); 60 % yield, 63 % regioselectivity].[20]




(3)

Moreover, the synthesis of rosaprostol,[21] tetrahydrodicranenone B,[21] equilenins,[22] or, more importantly, prostaglandins[23] should be also possible starting from a suitably substituted 2-cyclopentenone that can, in principle, be prepared by our catalytic intermolecular PKR methodology.

In conclusion, we have developed an efficient procedure for the catalytic, intermolecular, and regioselective PKR of unstrained alkenes by utilizing a 2-PyMe$_2$Si group as a removable directing group. Multisubstituted 2-cyclopentenones can now be analyzed retrosynthetically, as in Equation (4). The advantages of our strategy are that 1) it allows a




(4)

formal catalytic intermolecular PKR using simple alkenes, which was previously difficult to achieve; 2) it allows a complete regioselective incorporation of a substituent at the 4- or 5-position of the 2-cyclopentenone skeleton simply by choosing the position of the substituent in the starting alkenylsilane; 3) the position of the C=C bond can be strategically altered by simply changing the alkyne subunit to be hydrosilylated prior to the intermolecular PKR;[18] and 4) all the substituents arise from substituents on alkyne subunits which can be easily altered. Thus, this new strategy offers a general approach to a diverse range of cyclopentenoid structures and should find further applications in organic synthesis.

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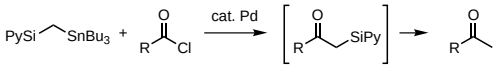

(5)

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