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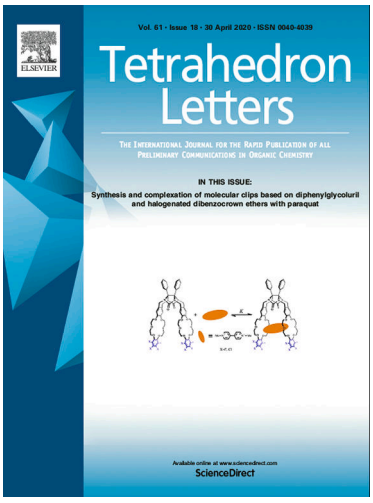

Carbamate as an accelerating group in intermolecular Pauson-Khand reaction

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Carbamate as an accelerating group in intermolecular Pauson-Khand reaction

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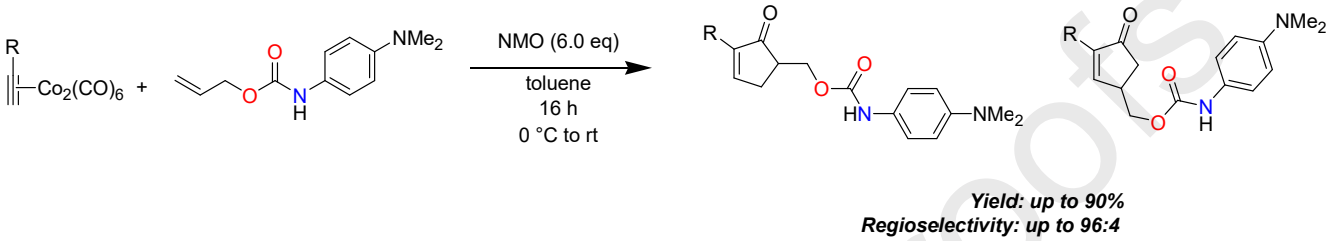
Shota Asano[a], Kaori Itto-Nakama[a] and Hirokazu Arimoto[a]



Yield: up to 90%
Regioselectivity: up to 96:4

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Carbamate as an accelerating group in intermolecular Pauson-Khand reaction

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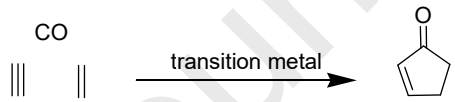
ABSTRACT

The Pauson-Khand reaction (PKR) is a powerful means for the construction of cyclopentenones. However, its applications have been limited to the intramolecular version of this reaction because poor yield and regioselectivity are often the major problems in intermolecular PKR. Here we describe that a carbamate moiety in alkene substrate accelerates this intermolecular PKR. The reaction of *N*-4-dimethylaminophenyl *O*-allyl carbamate with alkyne-cobalt complex gave cyclopentenones in high yield (up to 90%) and regioselectivity (>9:1).

Introduction

The Pauson-Khand reaction (PKR)[1] is a [2+2+1] cycloaddition of a set of an alkyne, alkene, and carbon monoxide meditated by transition metal to provide five-membered carbocycles (Scheme 1). The intermolecular PKR has been frequently used in total synthesis of natural products,[2] but examples of intermolecular PKR have been limited to highly-reactive alkene substrates,[3] such as norbornene,[4] cyclopropene,[5] allene,[6] and heterocycles.[7]

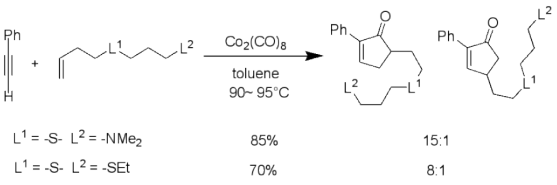


Scheme 1. The Pauson-Khand Reaction

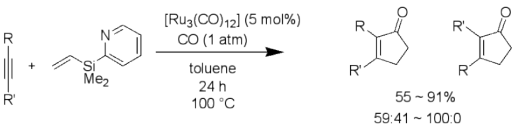
To address this limitation of intermolecular PKR, Krafft and co-workers investigated neighboring effects of heteroatomes[8] and found that sulfur and nitrogen atoms in alkene substrates improved both yield and regioselectivity of cyclopentenone products[9] (Scheme 2). In a ruthenium-catalyzed variant of intermolecular PKR, Yoshida and co-workers[10] used dimethyl (2-pyridyl)-silyl group as a directing group (Scheme 3). The yields were not always satisfactory. Carretero and co-workers reported[11] that 2-(*N,N*-diethylamino)-phenyl vinyl sulfoxide afforded good diasteroselectivities and yields (Scheme 4).

In this report, we explore new directing groups in intermolecular PKR. We found that alkene substrates with a carbamate moiety afforded cyclopentenones in good to excellent yields and regioselectivities (Scheme 5).

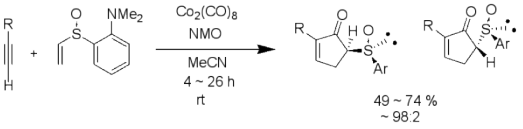
Scheme 2. Krafft et al.[9]



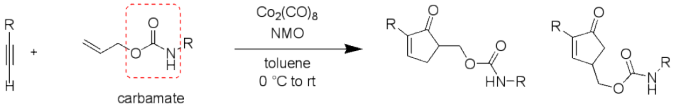
Scheme 3. Yoshida et al.[10]



Scheme 4. Carretero et al.[11]



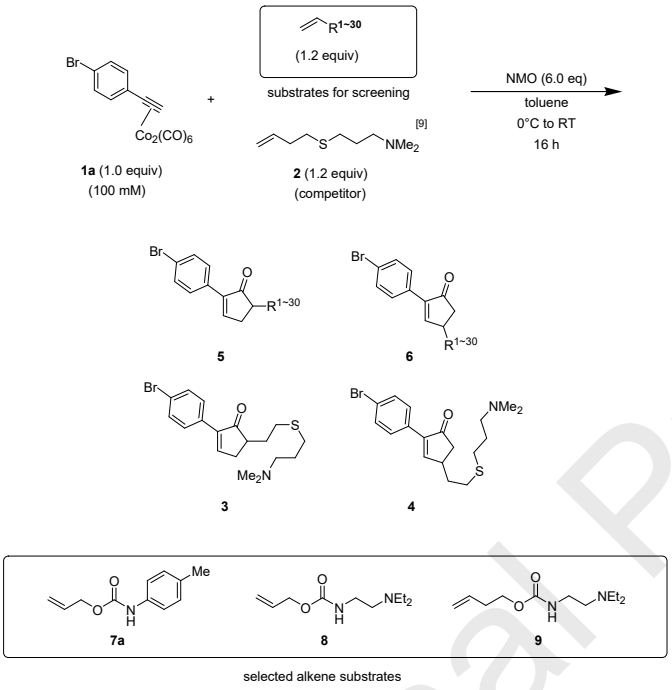
Scheme 5. This work



Re

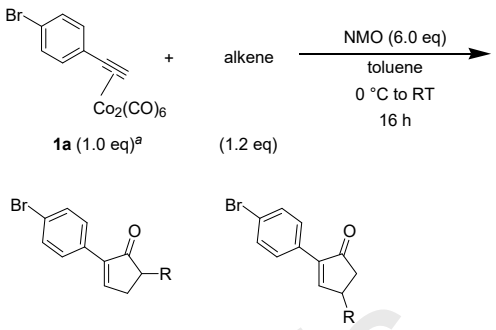
We initiated our study by screening of a series of alkenes with a potentially coordinating functionality for the intermolecular PKR with 100 mM alkyne cobalt complex (**1a**) and several groups of alkenes (Table S1) in the presence of NMO[12] (Scheme 6). The Krafft's alkene **2**[9] with a sulfide moiety was used in each experiment as a competitive substrate. Most of the alkenes (>30 compounds, Supplementary Table S.1) were less reactive than the Krafft's alkene **2**, and **3** and **4** were the predominant products. However, alkenes (**7a**, **8** and **9**) with a carbamate moiety were able to complete with **2** to exhibit signals of their corresponding cyclopenetenones in LC/MS.

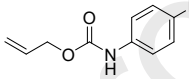
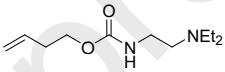
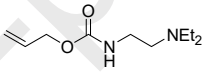
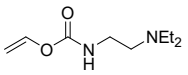
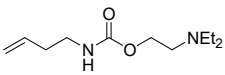
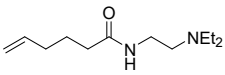
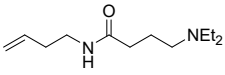
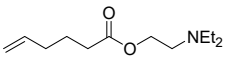
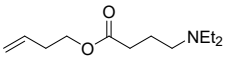
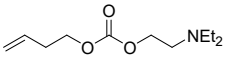
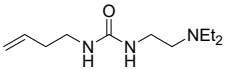
Scheme 6
Screening for alkene substrates with a potentially coordinating functionality.



To further examine the effect carbamates on intermolecular PKR, alkene substrates, we performed the intermolecular PKRs in the absence of alkene **2**. Homoallyl alcohol without a carbamate moiety gave the corresponding cyclopentenones in 18% yield (Table 1, entry 1). On the other hand, substrates **7a**, **8** and **9** including a carbamate moiety gave PKR adducts in 46-62% yields (entries 2-4). Then, we modified a homoallyl moiety and a carbamate moiety of substrate **8**. Vinyl carbamate **10** afforded only a trace amount of PKR adducts (entry 5). Carbamate **11**, a regioisomer of alkene **8**, provided with a decreased yield (entry 6). We also examined amides (**12** and **13**), esters (**14** and **15)**, carbonate **16**, and urea **17**. These substrates afforded the corresponding cyclopentenones in low to modest yields (entries 7-12), and *O*-allyl carbamate among various carbonyl functionalities was concluded to be an excellent substrate in intermolecular PKRs. The importance of a diethylamino group on the intermolecular PKR was then investigated (Supplementary Table S.2) and these attempts suggested the amine functionality was not crucial.

Intermolecular PKRs with selected alkene substrates and examination of various carbonyl functionalities.



entry	alkene		yield [%][b]	5:6[c]
1			18[d]	85:15
2		**7a**	46[d]	93:7
3		**8**	53[e]	72:28
4		**9**	62[e]	77:23
5		**10**	trace[f]	—
6		**11**	30[e]	80:20
7		**12**	46[e]	77:23
8		**13**	trace[f]	—
9		**14**	35[e]	75:25
10		**15**	32[e]	75:25
11		**16**	44[e]	76:24
12		**17**	23[e]	78:22

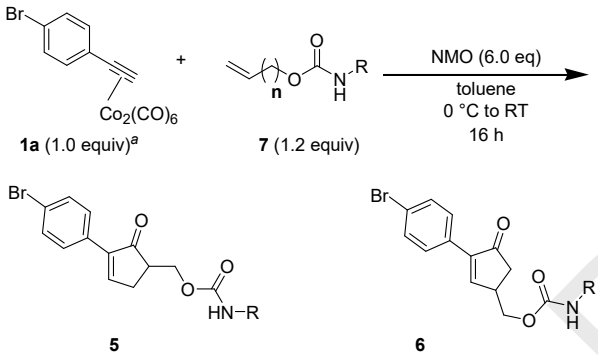
[a]100 mM. [b]Yields are the sum of 5 and 6. [c]Regioselectivity was determined by ^{1}H NMR. [d]Isolated yield. [e]Yields are estimated from 1H NMR of the mixture of alkene and cyclopentenone **5** and **6**. [f]The corresponding cyclopentenone was detected in a LC/MS analysis..

We modified the *N*-aryl moiety of alkene substrates **7a** (Table 2). The reaction with phenyl carbamate **7b** afforded the corresponding cyclopentenones in 51% yields (entry 1).

Con ith aryl ring (**7c**, **7d**, **7e** and **7f**) gave decreased yields (entries 2-5). Electron-donating substitutes such as *tert*-butyl, methoxy and *i*-propoxy (**7g**, **7h** and **7i**) also decreased the yields of the intermolecular PKR. These results may indicate that the electron density of aryl ring is not the key determinant of this reaction.

Interestingly, however, the substrate with a *p*-dimethylamino substituent (entry 9) significantly improved the yield of cyclopentenones up to 81%. NMO was indispensable in the reaction (entry 10). By increasing the amount of substrate **7j** to 2.0 equiv, the yield and regioselectivity were improved further (entry 11) and the PKR adducts were obtained in satisfactory yield in a shorter reaction period (4 hours, entry 12). With a substrate derived from homoallyl alcohol (entry 13), yield of the cyclopentenones was 32% that was lower than that with related substrate 7j (81%, Table 2, entry 9). These results suggest the importance of the distance of two coordinating moieties, urethane and alkene, in a substrate. We also examined additive- and solvent-effects with the substrate **7j**, but the efforts did not improve the reaction (Supplementary Table S.3 and S.4).

Table 2
Intermolecular PKRs with various *N*-aryl carbamates.



entry		7	yield [%][b,c]	5:6[d]
1	**7b (n=1)**	(R = Ph)	51	92:8
2	**7c (n=1)**	(R = 4-Pyridyl)	0	—
3[e]	**7d (n=1)**	(R = 4-NCC_6H_4)	0	—
4	**7e (n=1)**	(R = 4-FC_6H_4)	38	89:11
5	**7f (n=1)**	(R = 4-$NO_2C_6H_4$)	<38	88:12
6	**7g (n=1)**	(R = 4-*t*BuC_6H_4)	37	90:10
7	**7h (n=1)**	(R = 4-$MeOC_6H_4$)	21	72:28
8	**7i (n=1)**	(R = 4-*i*$PrOC_6H_4$)	46	94:6
9	**7j (n=1)**	(R = 4-$Me_2NC_6H_4$)	81	92:8
10[f]	**7j**		<2	85:15
11[g]	**7j**		87	96:4
12[g,h]	**7j**		78	92:8
13	**7k (n=2)**	(R = 4-$Me_2NC_6H_4$)	32	76:24

[a]100 mM. [b]Yields are the sum of **5** and **6**. [c]Isolated yield. [d]Regioselectivity was determined by ^{1}H NMR. [e]*p*-Aminobenzonitlire was obtained in 74 %. [f]The reaction was performed for 48 h without NMO. [g]alkene = 2.0 equiv. [h]The reaction was performed for 4 h.

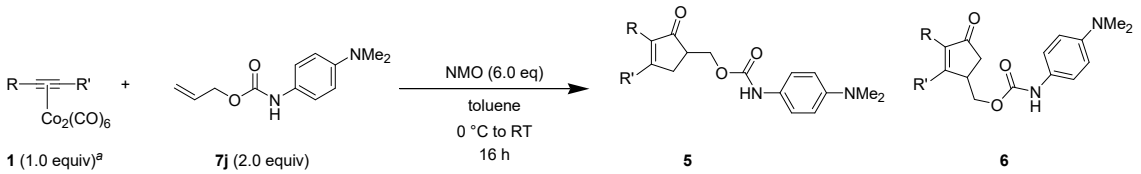
Having optimized the alkene substrate **7j**, we turned our attention to the scope of alkyne-cobalt complex (Table 3). We had used cobalt-complex **1a** throughout this study, but phenyl (**1b**) and 4-methoxyphenyl derivatives (**1c**) were also shown to be good substrates for the reaction with alkene **7j** (entries 1 and 2). However, aliphatic and silyl substituents in alkyne-cobalt complex **1d**, **1e**, and **1f** with alkene **7j** decreased the yield and regioselectivity of intermolecular PKR (entries 3~5). internal alkynes (entries 6 and 7).

To support our hypothesis of a carbamate as a ligand of cobalt in intermolecular PKR, we performed the reaction of cobalt complex **1a** and alkene **7j** in the presence of carbamate **7j'** (Scheme 7). Because **7j'** lacks alkene, it cannot be the substrate of PKR. The reaction conditions were otherwise the same with those of entry 11 in Table 2. We found that the presence of **7j'** not only decreased the yield by ca. 40% but also altered the selectivity between two cyclopentenone products. We believe that both of the carbamate moieties of **7j** and **7j'** competitively coordinate to a cobalt intermediate of PKR and thus reduced the efficiency of the reaction. Moreover, **7j'** may have affected the regioselectivity of the PKR products by coordinating a reaction intermediate.[13]

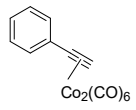
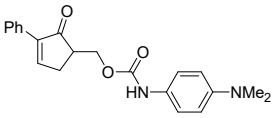
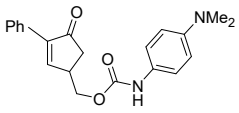
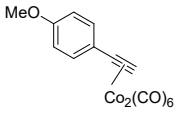
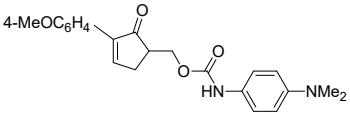
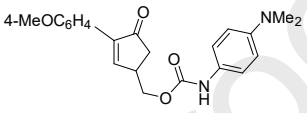
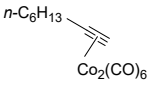
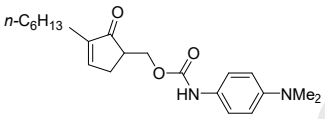
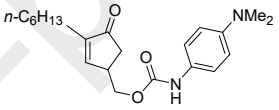
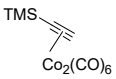
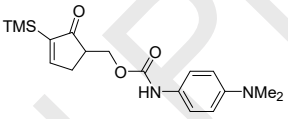
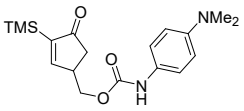
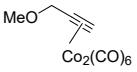
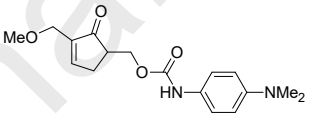
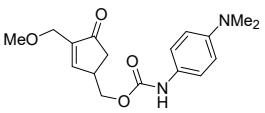
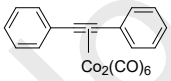
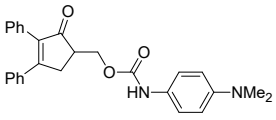
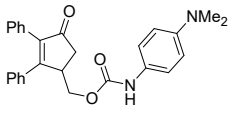
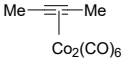
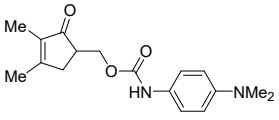
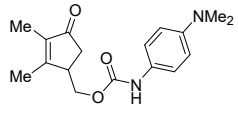
In summary, carbamate functionality is a good accelerating group in the intermolecular PKR. Further efforts towards the use of this finding to total synthesis of natural products are now in progress and will be reported in due course.

Ta

Intermolecular PKRs with various alkyne and alkene **7j**.

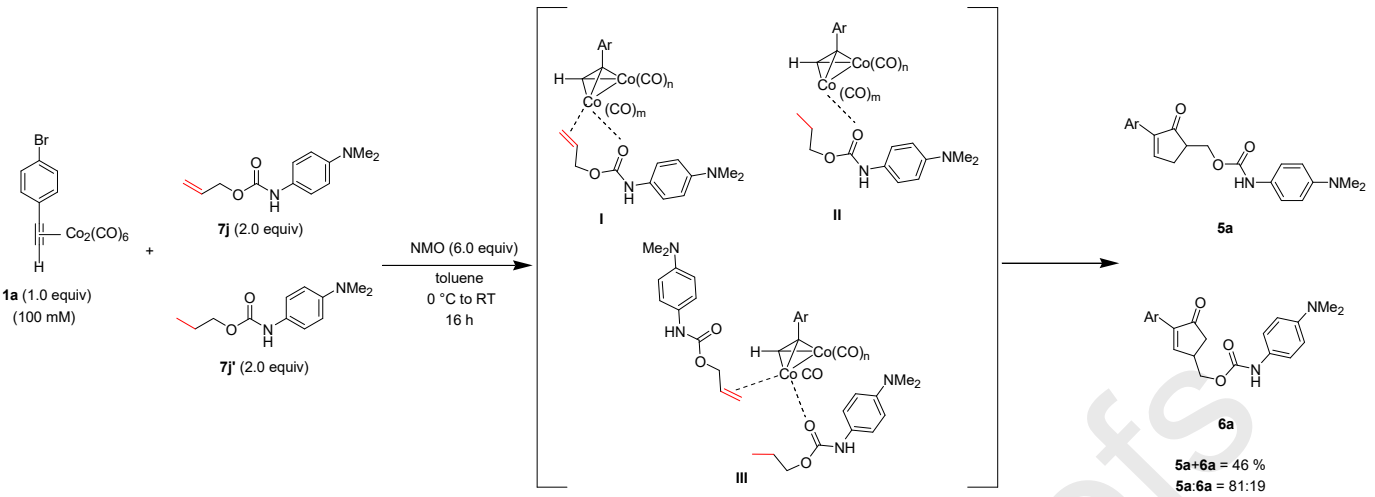


1 (1.0 equiv)[a] **7j** (2.0 equiv) **5** **6**

entry	**1**	products	yield [%][b,c]	**5:6**[d]
1	 **1b**	 **5b**	 **6b**	90	91:9
2	 **1c**	 **5c**	 **6c**	81	92:8
3	 **1d**	 **5d**	 **6d**	33	85:15
4	 **1e**	 **5e**	 **6e**	44	71:29
5	 **1f**	 **5f**	 **5f**	52	87:13
6	 **1g**	 **5g**	 **6g**	0	—
7	 **1h**	 **5h**	 **6h**	trace[e]	—

[a]100 mM. [b]Yields are the sum of **5** and **6**. [c]Isolated yield. [d]Regioselectivity was determined by ^{1}H NMR. [e]Corresponding cycloppentenone was detected in a LC/MS analysis..

Sch
Competitive reaction



Acknowledgement

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Appendix A. Supplementary data

Supplementary data to this article can be found online.

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Declaration of interests

■ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Graphical Abstract

Highlights

- Examples of intermolecular Pauson-Khand reaction (PKR) have been limited to reactive alkene substrates.

Carbamate as an accelerating group in intermolecular Pauson-Khand reaction

Shota Asano[a], Kaori Itto-Nakama[a] and Hirokazu Arimoto[a]

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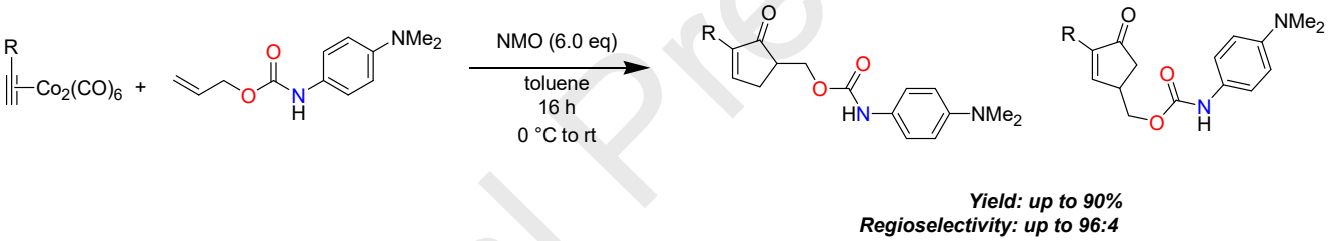

Yield: up to 90%
Regioselectivity: up to 96:4

- Carbamate in alkene substrates was demonstrated to facilitate intermolecular PKRs.
- Arylalkynes are the suitable substrates of this reaction.