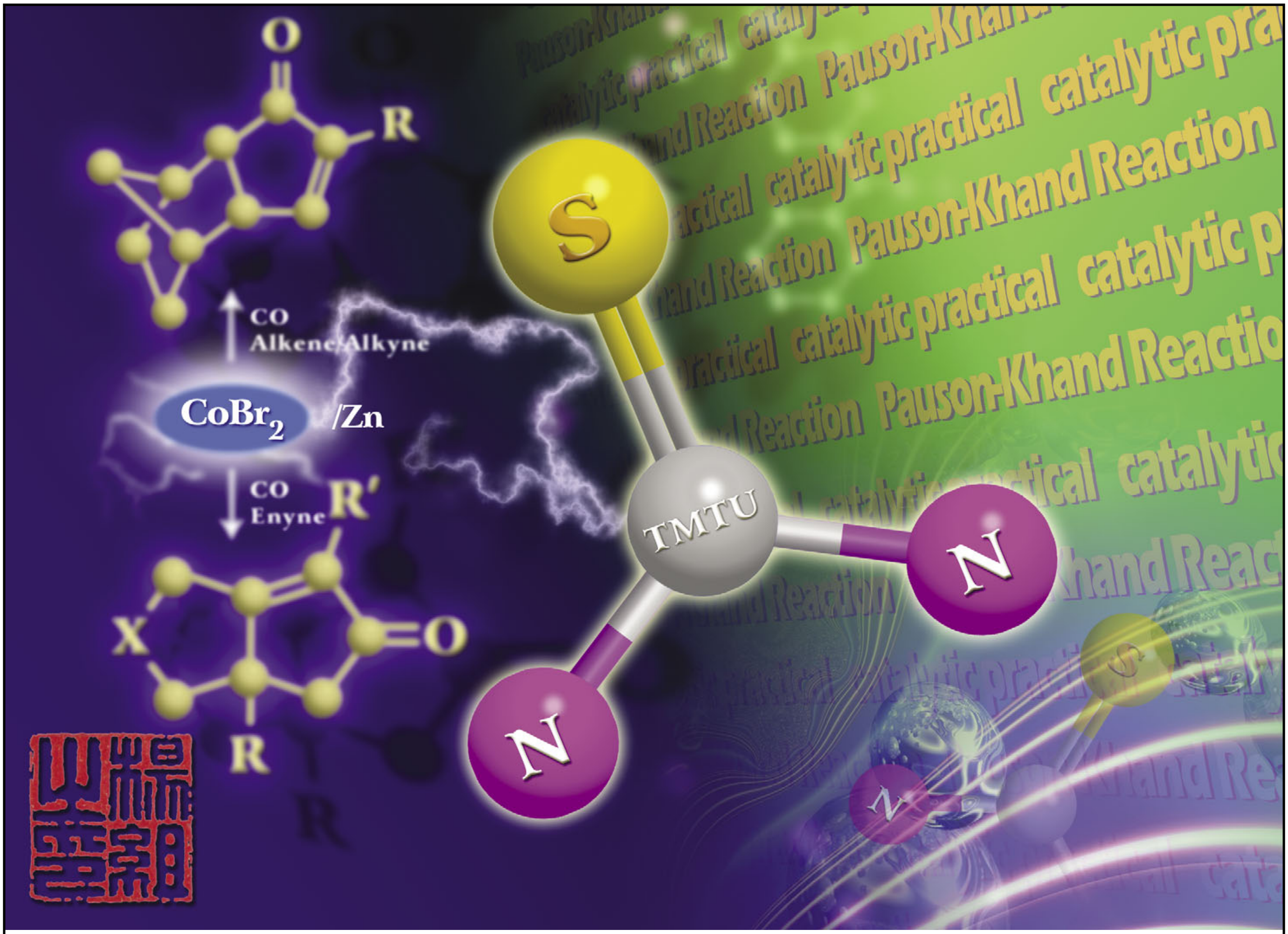

Showcasing research from the laboratory of Dr Zhen Yang at Peking University, Beijing, China.

$CoBr_2$–TMTU–zinc catalysed-Pauson–Khand reaction

A novel cobalt-TMTU complex, derived from the *in situ* reduction of $CoBr_2$ with Zn in the presence of TMTU can catalyze the Pauson–Khand reaction under a balloon pressure of CO, which enables the practical synthesis of cyclopentenones in terms of potential flexibility and atom economy.

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CoBr$_2$–TMTU–zinc catalysed-Pauson–Khand reaction†

Yuefan Wang,[a] Lingmin Xu,[a] Ruocheng Yu,[a] Jiahua Chen*[a] and Zhen Yang*[ab]

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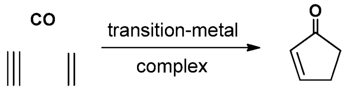
A cobalt–TMTU complex, derived from the *in situ* reduction of CoBr$_2$ with Zn in the presence of TMTU, can catalyze Pauson–Khand reaction at a balloon pressure of CO, which enables the synthesis of structurally diverse cyclopentenones. This catalytic system works efficiently for both intermolecular and intramolecular PK reactions.

The Pauson–Khand (PK) reaction,[1] a cobalt-mediated coupling of an alkene, an alkyne and CO that can produce a wide range of substituted cyclopentenones, is one of the most powerful reactions in organic synthesis (Scheme 1).



Scheme 1 The Pauson–Khand reaction.

In the past two decades, significant progress has been witnessed in the transition metal-catalyzed PK reactions[2] and the asymmetric PK reactions[3] for the formation of a variety of interesting cyclopentenones, which are not only useful building blocks for more elaborate structures,[4] but also the core structures existing in numerous important biologically active molecules.[5]

The Co-PK reaction has its downside though: it normally adopts Co$_2$(CO)$_8$ as a stoichiometric reagent, which is toxic, expensive as well as air and moisture sensitive; these factors thus hinder the Co$_2$(CO)$_8$-based PK reaction from being applied to large scale synthesis. In contrast with Co$_2$(CO)$_8$, CoBr$_2$ is a commercially available reagent with lower price, and is air and moisture stable. The *in situ* reduction of a stoichiometric amount of Co(II) with reducing agents (such as sodium-naphthalene and NaH-sodium *t*-amyloxide) has been proven to generate an active agent for the synthesis of cyclopentenones[6] *via* inter- and intramolecular PK reaction.[7] Yet, despite the efforts made in exploring the CoBr$_2$-mediated PK reaction by various improvements of reaction conditions,[8] a practical version of CoBr$_2$-catalyzed PK reaction has not been achieved. Herein, we would like to report our latest discovery of a practical and catalytic version of the PK reaction by employing a novel type of Co-complex system derived from the *in situ* reduction of CoBr$_2$ with Zn in the presence of tetramethyl thiourea (TMTU). Both CoBr$_2$ and TMTU are commercially available and inexpensive, thus making the reactions practically attractive.

We previously reported that substituted thioureas could serve as effective ligands in the transition metal catalyzed carbonylative reaction.[9] We further identified that TMTU was an effective ligand in Co$_2$(CO)$_8$- and PdCl$_2$-catalyzed PK reactions.[10] Motivated by these encouraging findings, we started to test the CoBr$_2$-catalyzed PK reaction in the presence of TMTU. After a number of experiments,[11] we found out that a Co-complex derived from the *in situ* reduction of CoBr$_2$ (10 mol%) with Zn (2 equiv.) in the presence of TMTU (60 mol%) could perform as an efficient catalyst in the intermolecular PK reactions. Resultantly, cyclopentenones **1c–8c** were obtained in good yields in the presence of molecular sieves[12] at a balloon pressure of CO at 70 °C (Table 1).

It is worthwhile to mention that TMTU plays a pivotal role in this PK reaction, because when the same annulation reactions were carried out with CoBr$_2$–TMTU in a ratio less than 1/3, no annulated products were obtained (see ESI† for details).

Considering the distinctive and beneficial role played by TMTU in the Co-catalyzed PK reaction, we were motivated to further test its beneficial effect on the intramolecular Co-catalyzed PK reaction.[13] To that end, 12 enynes (**9a–20a**) were selected as substrates to undertake the annulation under the optimized conditions. To our delight, the selected substrates could give their corresponding products in good to excellent yields (Table 2). It is worthwhile to mention that when zinc amount was reduced to 0.2 mmol, the annulation of substrate **10a** could still proceed smoothly in the presence of molecular sieves. However, upon further reduction of zinc amount to less than 0.1 mmol, only a trace amount of annulated product **10c** was obtained (see ESI† for details).

We draw the following observations from the above results: (1) both allylpropargyl malonates (entries 1–8) and allylpropargylamines (entries 9–11) are good substrates and the expected annulated product could be obtained in good to excellent yields; (2) terminal alkynes as well as alkyl- or phenyl substituted alkynes are good substrates that enable this PK reaction, which is similar to the results generated in the rhodium-catalyzed PK reaction,[2q] but in contrast to those observed in the titanium catalyzed PK reaction.[14] As a result, enynes, possessing both electron donating and electron withdrawing groups, could give

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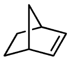
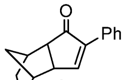
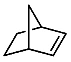
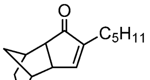
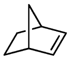
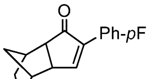
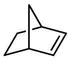
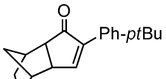
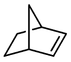
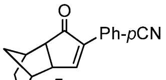
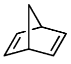
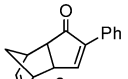
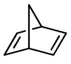
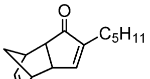
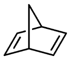
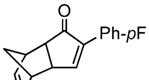
† Electronic supplementary information (ESI) available. See DOI: 10.1039/c2cc17971g

Table 1 Intermolecular PK reactions[a]

$$\text{TMTU/CoBr}_2\text{/Zn} \xrightarrow[\text{CO, toluene, 4 Å MS, 70 °C}]{\text{alkene, alkyne}} \text{cyclopentenone}$$

Entry	Alkene	Alkyne	Cyclopentenone	Time/h	Yield[b] (%)
1	 **1a**	PhC≡CH **1b**	 **1c**	24	85
2	 **1a**	n-$C_5H_{11}C{\equiv}CH$ **2b**	 **2c**	24	93
3	 **1a**	pF–PhC≡CH **3b**	 **3c**	15	86
4	 **1a**	ptBu–PhC≡CH **4b**	 **4c**	15	75
5	 **1a**	pCN–PhC≡CH **5b**	 **5c**	11	88[c]
6	 **2a**	PhC≡CH **1b**	 **6c**	24	76
7	 **2a**	n-$C_5H_{11}C{\equiv}CH$ **2b**	 **7c**	15	84
8	 **2a**	pF–PhC≡CH **3b**	 **8c**	15	67

[a] Reaction conditions: olefin (2.0 mmol), alkyne (1.0 mmol), $CoBr_2$ (0.10 mmol), TMTU (6.60 mmol), Zn (2.0 mmol) and molecular sieves in toluene at 70 °C under CO (balloon pressure). [b] Isolated yields. [c] ^1H NMR yield.

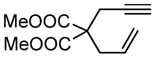
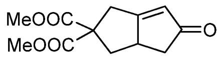
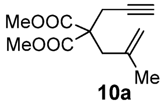
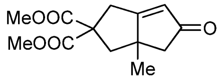
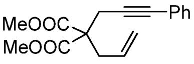
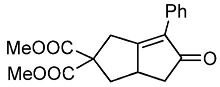
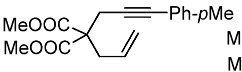
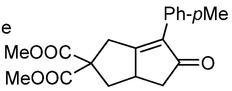
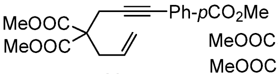
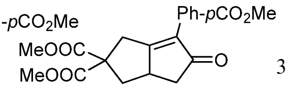
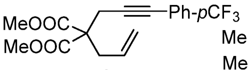
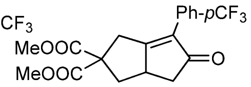
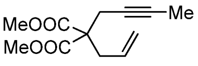
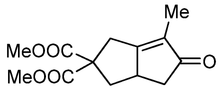
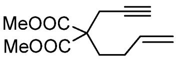
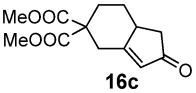
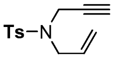
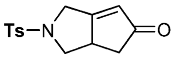
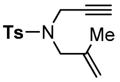
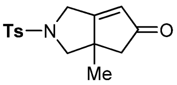
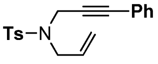
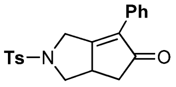
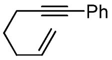
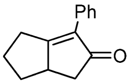
excellent yields of annulated products (entries 4–6); (3) different from previous results,[15] 1,1-disubstituted olefins could also be annulated to afford their corresponding products in good yields (entries 2 and10).

The reaction mechanism is not yet clear and the detailed role of TMTU in the reaction is to be determined in further studies. Understanding the mechanistic aspect of this reaction and applying this reaction to the total syntheses of natural products are the subjects which we are currently investigating.

In summary, we have developed a practical and catalytic PK reaction by employing $CoBr_2$–TMTU–Zn as a novel catalyst, which can accelerate the conversion of enynes into structurally diverse cyclopentenones. As $CoBr_2$–TMTU–Zn catalyzed PK reaction has proven to be a practical and robust reaction, thanks to the advantages of $CoBr_2$ and TMTU including their stability toward air and moisture, commercial availability and affordable prices, our reported catalytic PK reaction should be

Table 2 Intramolecular PK reactions with allylpropargyl malonates and allylpropargylamines[a]

$$\text{TMTU/CoBr}_2\text{/Zn} \xrightarrow[\text{CO, toluene, 4Å MS, 70 °C}]{\text{enyne}} \text{cyclopentenone}$$

Entry	Enyne	Cyclopentenone	Time/h	Yield[b] (%)
1	 **9a**	 **9c**	3	86
2	 **10a**	 **10c**	3	91
3	 **11a**	 **11c**	3	90
4	 **12a**	 **12c**	5	94
5	 **13a**	 **13c**	3	88
6	 **14a**	 **14c**	3	93
7	 **15a**	 **15c**	5	83
8	 **16a**	 **16c**	16	72[c]
9	 **17a**	 **17c**	3	89
10	 **18a**	 **18c**	3	73
11	 **19a**	 **19c**	3	93
12	 **20a**	 **20c**	22	62[c,d]

[a] Reaction conditions: enyne (0.5 mmol), $CoBr_2$ (0.05 mmol), TMTU (0.3 mmol), Zn (1.0 mmol) and molecular sieves in toluene at 70 °C under CO (balloon pressure). [b] Isolated yield. [c] 20 mol% $CoBr_2$ was used. [d] 90 °C.

useful in large scale synthesis of the cyclopentenones, and is believed to contribute additional value to this powerful reaction.

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