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Thioureas as Ligands in the Pd-Catalyzed Intramolecular Pauson–Khand Reaction

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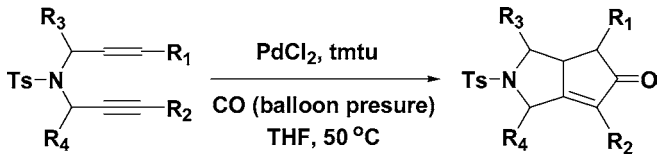
ABSTRACT



The thiourea–Pd complex was established as a novel type of catalyst in the PKR of allylpropargylamine, and the demonstrated chemistry may prove to be valuable for developing thiuorea as a ligand for the Pd-catalyzed Pauson–Khand reaction.

The Pauson−Khand reaction[1] (PKR) is utilized as an effective method to construct cyclopentenone frameworks in the synthesis of many complex molecules,[1b−d] such as (+)-epoxydictymene.[2] Catalytic PKRs with the use of Co,[3] Ti,[4] Ni,[5] Ru,[6] Rh,[7] and Ir[8] complexes have been reported in the past decade; however, no successful example of the Pd-catalyzed PKR is currently known.[9]

Recently we reported tetramethyl thiourea (tmtu) as an effective additive in the Co-catalyzed PKR.[10] In view of a lack of any precedents in the utilization of palladium as a catalyst in the PKR, we decided to apply thioureas in the Pd-catalyzed PKR. We now report herein our preliminary results on the Pd-catalyzed PKR using thioureas as effective ligands.

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We selected commercially available thiourea (**I**), dimethyl thiourea (**II**), and tmtu (**III**), as well as our synthesized thiourea (**IV**)[11] (Figure 1) as the ligands for studying the

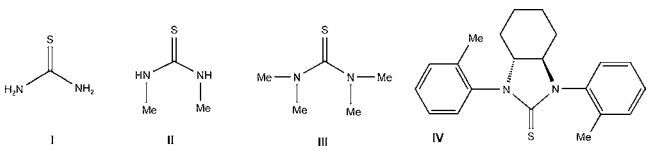
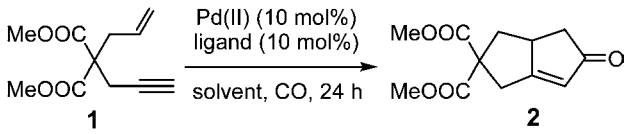


Figure 1. Selected thioureas for the Pd-catalyzed PKR.

Pd-catalyzed PKR. The Pd(II)−thiourea complexes were made by mixing Pd(II) with thioureas **I**−**IV** in ratios ranging from 1/1 to 1/4, and enyne **1** was selected as the substrate for the PKR. The screening reactions were run in parallel, and the results are summarized in Table 1.

Table 1. Pd-Catalyzed PKR[a]



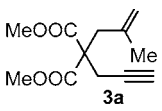
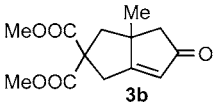
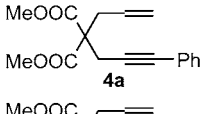
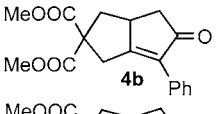
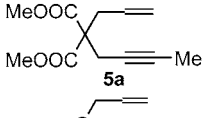
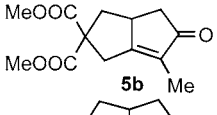
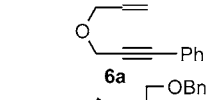
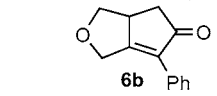
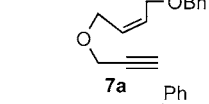
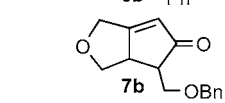
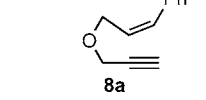
entry	Pd(II)	ligand	Pd(II): ligand ratio[b]	temp (°C)	solvent	yield (%)[c]
1	$PdCl_2$	none		50	THF	27
2	$PdCl_2$	tu (**I**)	1:1	50	THF	33
3	$PdCl_2$	dmtu (**II**)	1:1	50	THF	16
4	$PdCl_2$	tmtu (**III**)	1:1	50	THF	72
5	$PdCl_2$	**VI**	1:1	50	THF	56
6	$Pd(OAc)_2$	tmtu (**III**)	1:1	50	THF	0
7	$Pd(CN)_2Cl_2$	tmtu (**III**)	1:1	50	THF	0
8	$Pd(dba)_2$	tmtu (**III**)	1:1	50	THF	0
9	$PdCl_2$	tmtu (**III**)	1:1	50	CH_3CN	67
10	$PdCl_2$	tmtu (**III**)	1:1	50	DCE	70
11	$PdCl_2$	tmtu (**III**)	1:1	50	DME	50
12	$PdCl_2$	tmtu (**III**)	1:1	50	toluene	29
13	$PdCl_2$	tmtu (**III**)	1:1	25	THF	38
14	$PdCl_2$	tmtu (**III**)	1:1	80	THF	10

[a] Reagent and conditions: enyne **1** (0.5 mmol) in 10 mL of solvent, 50 °C under CO (balloon pressure). The rest of the data regarding the complexes derived from thioureas **I** and **II**, as well as the other ratios of the Pd-complexes made from thiourea **III** and **IV** are not included in this table because those reactions either gave low yields or did not promote the reaction at all. [c] Yield of isolated product.

According to the results, the complexes derived from thioureas **III** and **IV** with $PdCl_2$ in 1:1 ratio gave the desired product **2** in 72% and 56% yields, respectively (entries 4 and 5 in Table 1). The other Pd(II)−thiourea complexes gave either low yields (entries 2 and 3) or did not promote the reaction at all (entries 6−8). It became clear that the *N*,*N*-tetrasubstituted feature of thioureas, and the 1:1 ratio of $PdCl_2$ with thiourea represented the key elements in this PKR. Among the solvents used (entries 4 and 9−12), THF was the best choice. Reaction temperature is also important, and a better result is achieved when the reaction was carried out at 50 °C (entries 4, 5, 13, and 14). Interestingly, $PdCl_2$ without ligand can also catalyze the reaction; however, the palladium catalyst was completely precipitated after a few hours of the reaction and only 27% yield of product was obtained (entry 1 in Table 1).

Since the $PdCl_2$/tmtu-catalyzed reaction gave the best result, especially with consideration to commercial availability, tmtu (**III**) was then used as a ligand to perform the Pd-catalyzed PKRs with a broad range of substrates. To this end, allylpropargylmalonates **3a**−**5a** (entries 1−3 in Table 2), allylpropargyl ethers **6a**−**8a** (entries 4−6 in Table 2),

Table 2. Pd−tmtu-Catalyzed Intramolecular PKR[a]

entry	enyne	cyclopentenone	time/h	yield (%)[b]
1			48	NR
2			24	24 (81)
3			24	18 (50)
4			24	40 (93)
5			48	31
6		SM decompose		

[a] Reagent and conditions: enyne (0.05 mmol) in THF (10 mL), 50 °C under CO (balloon pressure). [b] Yield of isolated product. The yields in parentheses are those obtained based on recovery of starting materials.

and allylpropargylamines **9a**−**20a** (entries 1−12 in Table 3) were synthesized and evaluated.

First, we examined the reaction of allylpropargyl malonates **3a**−**5a**. Unlike the Co/thiourea-catalyzed PKR,[10] these substrates were found either to be not reactive or to suffer from low conversion under the conditions listed in Table 2. We then investigated the allylpropargyl ethers **6a**−**8a** in the PKR. A similar trend in reactivity was observed.

We finally evaluated the allylpropargylamines **9a**−**20a**. To our delight, all of the enynes possessing alkyl and phenyl substituents on the alkyne moiety gave the expected cyclopentenones and six of them afforded good to excellent yields (entries 2, 3, 5, and 8−10 in Table 3).

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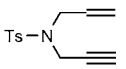
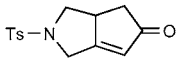
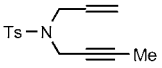
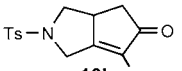
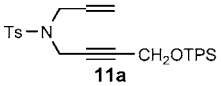
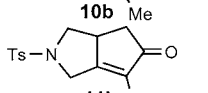
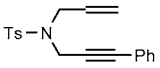
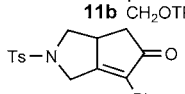
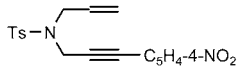
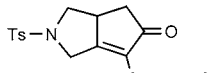
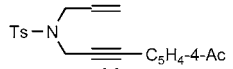
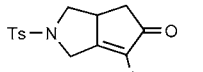
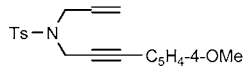
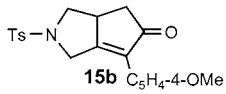
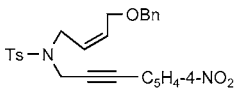
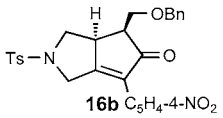
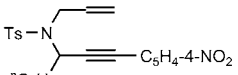
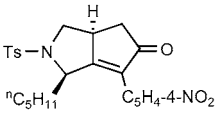
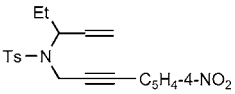
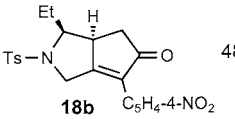
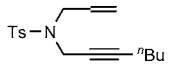
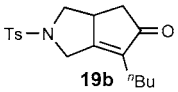
Table 3. Pd−tmtu-Catalyzed PKR of Allylpropargylamines[a]

entry	enyne	cyclopentenone	time/h	yield (%)[b]
1	 **9a**	 **9b**	24	63
2	 **10a**	 **10b**	36	92
3	 **11a**	 **11b**	36	89
4	 **12a**	 **12b**	48	58 (95)
5	 **13a**	 **13b**	48	90
6	 **14a**	 **14b**	48	64 (95)
7	 **15a**	 **15b**	48	43 (96)
8	 **16a**	 **16b**	48	80
9	 **17a**	 **17b**	36	96
10	 **18a**	 **18b**	48	70
11	 **19a**	 **19b**	48	58 (93)

[a] Reagent and conditions: Enyne (0.05 mmol) in THF (10 mL), 50 °C under CO (balloon pressure). [b] Yield of isolated product. The yields in parentheses are those obtained based on recovery of starting materials.

Although four of the substrates suffered from low conversion to their products (entries 4, 6, 7, and 11 in Table 3), because these substrates are fairly stable under the reaction conditions, the desired coupling yields could in fact be improved by increasing the reaction time.

Importantly, contrary to popular thought,[12] the alkynes attached with electron-deficient groups (entries 5, 6, and 8−10 in Table 3) gave better results than other members of the family. The results, to our knowledge, have not been reported so far.

Last, it is notable that when substrates **16a** and **17a** (entries 8 and 9 in Table 3) were employed in the cyclization, only one diastereoisomer was obtained, and the relative stereochemistry was determined by NOE analysis.

Although the thiourea−Pd complex can significantly speed up the PKR, its catalytic mechanism is unclear. Based on the available structural information for PtCl-tmtu,[13] we speculate that catalysis is taking place with the ligand bound to the metal center in consideration of the requirement of a 1:1 ratio of $PdCl_2$ with tmtu in this PKR. This hypothesis, once validated, could be useful for the design of chiral thiourea for the Pd-catalyzed asymmetric PKR.

In summary, we have established that a thiourea−Pd complex is a novel type of catalyst in the PKR of allylpropargylamine, and the demonstrated chemistry may prove to be valuable for developing thiuorea as a ligand for the Pd-catalyzed PKR. Further study regarding the reaction mechanism by joint efforts of experimental and computational chemistry is currently underway in our laboratory, and the results will be reported in due course.

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Supporting Information Available: Experimental procedure and NMR and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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