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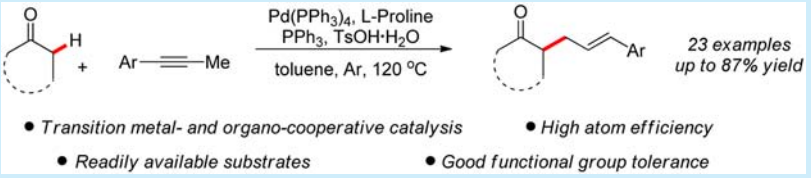
Cooperative Palladium/Proline-Catalyzed Direct α-Allylic Alkylation of Ketones with Alkynes

Chi Yang, Kaifan Zhang, Zijun Wu, Hequan Yao, and Aijun Lin*

State Key Laboratory of Natural Medicines (SKLNM) and Department of Medicinal Chemistry, School of Pharmacy, China Pharmaceutical University, Nanjing 210009, P. R. China

Supporting Information

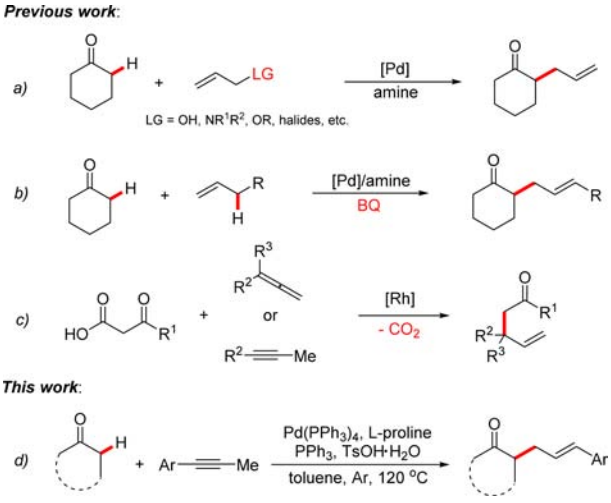


ABSTRACT: The cooperative palladium/L-proline-catalyzed direct α-allylic alkylation of ketones with alkynes is achieved. This reaction exhibits high atom economy since a leaving group is not liberated and a stoichiometric amount of extra oxidant is not needed. A broad range of functional groups are tolerated, and the reaction scope could be further expanded to aldehydes.

Unsaturated ketones, especially those bearing γ,δ-unsaturated C−C double bonds, are important building blocks existing in numerous biologically active compounds and natural products.[1] Moreover, they also serve as versatile synthetic intermediates in natural products synthesis.[2] Traditional methods toward the synthesis of these precious structures involve transition-metal-catalyzed C−C bond formation between in situ formed metal enolates and allyl agents,[3] while stoichiometric strong metallic bases were a prerequisite and corresponding stoichiometric metal salts were formed. In addition, some competitive side reactions were unavoidable (e.g., Cannizzaro reactions).

Recently, transition-metal and organo-cooperative catalyses[4] have been widely investigated for the α-alkylation,[5] α-alkenylation,[6] and α-arylation[7] of ketones and aldehydes. In 2006, Cordóva and Ibrahem first reported a palladium and L-proline co-catalyzed α-allylic alkylation of ketones with allylic acetate to access γ,δ-unsaturated ketones (Scheme 1a).[8a] Subsequently, various allylic compounds such as allylic alcohols,[8b,c] allylic amines,[8d] and allylic ethers[8e] containing leaving groups were validated to the construction of γ,δ-unsaturated ketones. In 2014, Lei, Luo, and co-workers developed a palladium/L-proline co-catalyzed oxidative coupling reaction of ketones with allylic hydrocarbons employing stoichiometric amount of *p*-benzoquinone (BQ) as oxidant (Scheme 1b).[8f] Dong, Breit, and co-workers reported a Rh-catalyzed decarboxylative reaction of β-keto acids and alkynes/allenes to provide γ,δ-unsaturated ketones independently (Scheme 1c).[9] Although many efforts have been devoted to α-allylic alkylation of ketones, a brief and atom-efficient strategy is still highly desirable. Combined with our previous work on the functionalization of alkynes,[10] herein we report a palladium/L-proline co-catalyzed cross-coupling reaction between ketones and internal methyl alkynes[11] to construct γ,δ-unsaturated ketones in a more succinct and highly efficient manner (Scheme 1d).

Scheme 1. Strategies toward the Synthesis of γ,δ-Unsaturated Ketones



We initiated our investigation with cyclohexanone **1a** and 1-phenyl-1-propyne **2a** as model substrates, $Pd(PPh_3)_4$ as the catalyst, and benzoic acid as an additive in toluene at 120 °C under argon atmosphere. Gratifyingly, preliminary attempts using pyrolidine (**A1**) as co-catalyst led to the allylic alkylated product **3aa** in 18% yield (Table 1, entry 1). Commercially available L-proline (**A2**) showed good reactivity and afforded **3aa** in 37% yield, while other amine catalysts such as diphenyl(pyrrolidin-2-yl)methanol (**A3**), methyl L-prolinate

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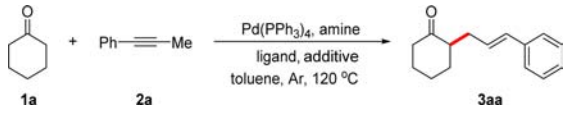
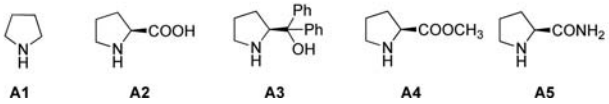
Table 1. Screening of Reaction Conditions[a]



1a 2a 3aa

entry	amine	ligand	additive	yield (%)[b]
1	**A1**		PhCOOH	18
2	**A2**		PhCOOH	37
3	**A3**		PhCOOH	13
4	**A4**		PhCOOH	<5
5	**A5**		PhCOOH	19
6	**A2**	dppf	PhCOOH	16
7	**A2**	(±)-binap	PhCOOH	27
8	**A2**	dppp	PhCOOH	24
9	**A2**	PPh_3	PhCOOH	44
10	**A2**	1, 10-phenanthroline	PhCOOH	9
11	**A2**	PPh_3	AcOH	14
12	**A2**	PPh_3	CF_3COOH	49
13	**A2**	PPh_3	PivOH	41
14	**A2**	PPh_3	TfOH	60
15	**A2**	**PPh_3**	**$TsOH·H_2O$**	**80**
16[c]	**A2**	PPh_3	$TsOH·H_2O$	42
17		PPh_3	$TsOH·H_2O$	nr
18[d]	**A2**	PPh_3	$TsOH·H_2O$	nr
19	**A2**	PPh_3		trace
20[e]	**A2**	PPh_3	$TsOH·H_2O$	17



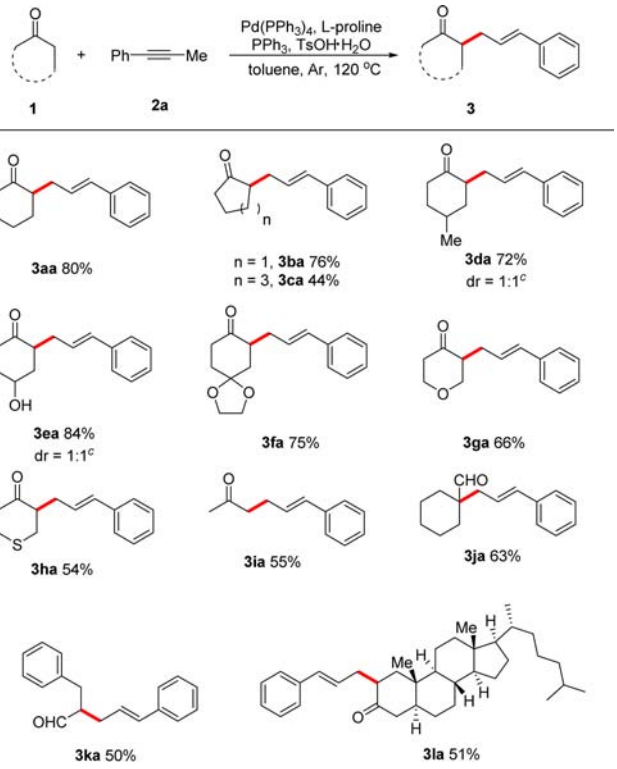
A1 A2 A3 A4 A5

[a]Reaction conditions: **1a** (0.25 mmol), **2a** (0.44 mmol), $Pd(PPh_3)_4$ (10 mol %), amines (30 mol %), additives (15 mol %), and ligands (20 mol %) in toluene (2 mL) at 120 °C for 24 h under argon atmosphere. [b]Isolated yields. [c]$Pd(PPh_3)_4$ (5 mol %), L-proline (15 mol %), and PPh_3 (10 mol %) was used. [d]$Pd(PPh_3)_4$ was removed. [e]80 °C, 39% ee.

(**A4**), and pyrrolidine-2-carboxamide (**A5**) exhibited inferior performance (Table 1, entries 2−5). In order to improve the reaction efficiency, both monodentate and bidentate phosphine ligands were tested, and PPh_3 could afford **3aa** in 44% yield (Table 1, entries 6−9). A brief examination of additives revealed that **3aa** could be isolated in 80% yield when $TsOH·H_2O$ was used (Table 1, entry 15), while other acids such as AcOH, CF_3COOH, PivOH, and TfOH delivered **3aa** in lower yields (Table 1, entries 11−14). Decreasing the loading amount of $Pd(PPh_3)_4$ and L-proline led to an obvious drop of yield (Table 1, entry 16). Control experiments showed that $Pd(PPh_3)_4$, L-proline, and $TsOH·H_2O$ were essential to this reaction (Table 1, entries 17−19). Although optically active L-proline was used, no ee value was detected under the standard conditions due to the high reaction temperature. Decreasing the temperature to 80 °C (Table 1, entry 20) led to a promising 39% enantioselectivity of **3aa**, while only 17% yield was obtained (see Table S1 for details).

With the optimized conditions in hand, we then explored the substrate scope of ketones, and the results are shown in Scheme 2. The size of simple cyclic ketones was tested, and the α-allylic alkylated cyclopentanone **3ba** and cycloheptanone **3ca** were obtained in 76% and 44% yields. Cyclohexanone with methyl or hydroxyl group at the C4-position reacted smoothly to afford **3da** and **3ea** in 72% and 84% yields. To our delight, the intermolecular potential hydroalkoxylation of **2a** was not

Scheme 2. Substrate Scope of Ketones[a,b]



[a]Reaction conditions: **1a** (0.25 mmol), **2a** (0.44 mmol), $Pd(PPh_3)_4$ (10 mol %), L-proline (30 mol %), $TsOH·H_2O$ (15 mol %), and PPh_3 (20 mol %) in toluene (2 mL) at 120 °C for 24 h under argon atmosphere. [b]Isolated yields. [c]Diastereoisomeric ratio (dr) was determined by ^1H NMR analysis.

detected,[12] which indicated that the nucleophilic hydroxyl group could be subjected to this reaction. It is noteworthy that the acid-sensitive group ketal could also survive under the standard conditions and provide **3fa** in 75% yield. Tetrahydropyran-4-one and tetrahydrothiopyran-4-one worked well and gave **3ga** in 66% yield and **3ha** in 54% yield. Acyclic ketone was also investigated, and acetone delivered **3ia** in 55% yield. Furthermore, in order to expand the substrate scope, cyclic and acyclic aldehydes were also examined, and **3ja** and **3ka** were obtained in 63% and 50% yield, respectively. These results revealed that both ketones and aldehydes could be activated efficiently with our catalyst system. Moreover, natural product 5α-cholestan-3-one **1l**, containing a six-membered cyclic ketone moiety, could also be alkylated at the less hindered site of the ketone in 51% yield.

Next, we turned our attention to exploring the substrate scope of alkynes, and the results are summarized in Scheme 3. The 1-aryl-1-propynes with electron-donating groups, such as methyl and methoxyl groups at the C4-position of the phenyl ring, afforded **3ab** and **3ac** in 75% and 79% yields. Electron-withdrawing groups on the C4-position showed slightly lower reactivity and furnished **3ad** and **3ae** in 47% and 59% yields. C3-Methyl- and C3,5-dimethyl-substituted 1-phenyl-1-propynes gave **3af** in 64% yield and **3ah** in 71% yield, while **3ag** with C2-methyl was obtained in 48% yield due to steric effects. In addition, substrates with aryl substituents, such as biphenyl, thienyl, and naphthyl groups, could also be compatible and provided **3ai**−**al** in 55−87% yields. Unfortunately, when but-1-

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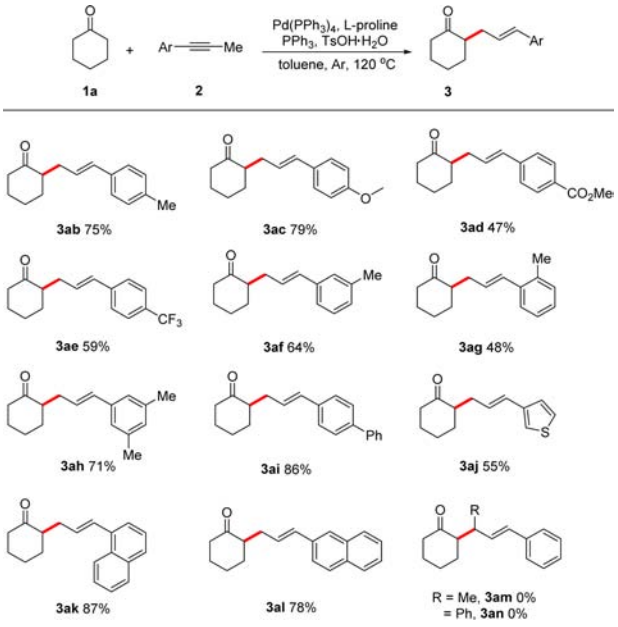
Scheme 3. Substrate Scope of Alkynes[a,b]

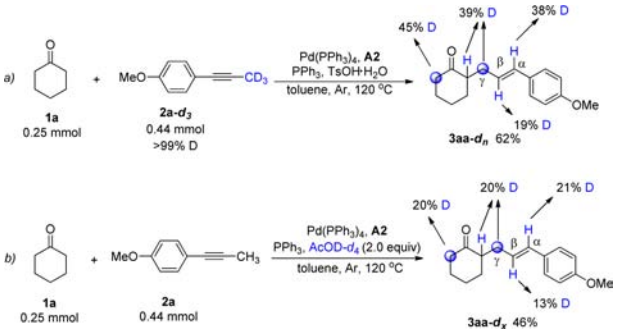


[a]Reaction conditions: **1a** (0.25 mmol), **2a** (0.44 mmol), $Pd(PPh_3)_4$ (10 mol %), L-proline (30 mol %), $TsOH·H_2O$ (15 mol %), and PPh_3 (20 mol %) in toluene (2 mL) at 120 °C for 24 h under argon atmosphere. [b]Isolated yields.

yn-1-ylbenzene **2m** and prop-1-yne-1,3-diyldibenzene **2n** were employed, no corresponding products were obtained.

To gain more insight into the mechanism of this reaction, deuterated-labeling experiments were conducted. Ketone **1a** reacted with **2a-d_3** under the standard conditions (Scheme 4a),

Scheme 4. Deuterated-Labeling Experiments[a]

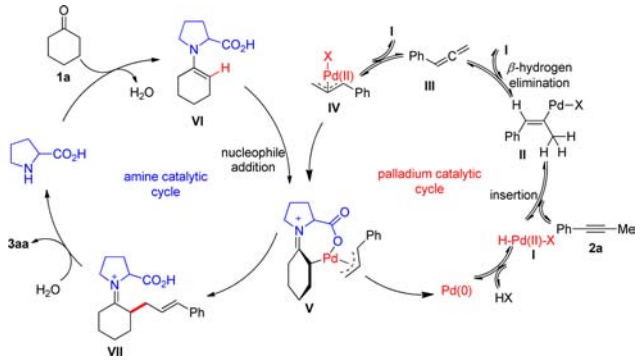


[a]The extent of deuterium incorporation was determined using ^1H NMR spectroscopy.

affording **3aa-d_n** in 62% yield. The incorporation of hydrogen at the γ-position of **3aa-d_n** suggested that the procedure for the insertion of the intermediate **I** to **2a-d_3** and β-hydrogen elimination of the intermediate **II** was reversible.[11g,h] When $TsOH·H_2O$ was replaced by 2.0 equiv of AcOD-d_4, the allylic alkylated product **3aa-d_x** was isolated in 46% yield (Scheme 4b). The incorporation of deuterium at the β-position of **3aa-d_x** in a 13% ratio suggested that the dissociation of the allene **III** from the palladium center of the intermediate **I** occurred to some extent after the β-hydrogen elimination.[13]

On the basis of previous work[11,14] and our deuterated-labeling experiments, a plausible catalytic cycle is proposed in Scheme 5. First, oxidative addition of Pd(0) with $TsOH·H_2O$

Scheme 5. Plausible Reaction Mechanism



generates a hydridopalladium species **I**. *Syn*-insertion of **I** into alkyne **2a** affords the intermediate **II**, which is followed by β-hydrogen elimination to afford phenyl allene **III**. Insertion of the intermediate **I** to phenyl allene **III** produces the π-allylpalladium species **IV**. Simultaneously, the L-proline reacts with the ketone **1a** to generate the enamine intermediate **VI**. It was reported that the formation of the intermediate **VI** could enhance the nucleophilicity of the α-positon of **1a**. According to the screening of reaction conditions (Table 1, entries 1−5), we suggest that the carboxylic acid of L-proline would be helpful to the formation of intermediate **V**.[8b] Reductive elimination of **V** delivers the iminium intermediate **VII** and regenerates the Pd(0) catalyst. Hydrolysis of **VII** produces the allylic alkylated product **3aa** with the regeneration of L-proline to the next catalytic cycle.

In conclusion, we have developed a cooperative palladium/L-proline-catalyzed direct α-allylic alkylation of ketones with alkynes. This reaction exhibits high atom economy since neither a leaving group is liberated nor is a stoichiometric amount of extra oxidant needed. A broad range of functional groups are tolerated, and the substrate scope could be further expanded to aldehydes. Further transformation of γ,δ-unsaturated ketones and asymmetric study are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b02649.

^1H and ^{13}C NMR spectra for all new compounds (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: ajlin@cpu.edu.cn.

Notes

The authors declare no competing financial interest.

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