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Direct Enantioselective α-Allylation of Unfunctionalized Cyclic Ketones with Alkynes via Pd-Amine Cooperative Catalysis

Jin Tu Danence Lee and Yu Zhao*

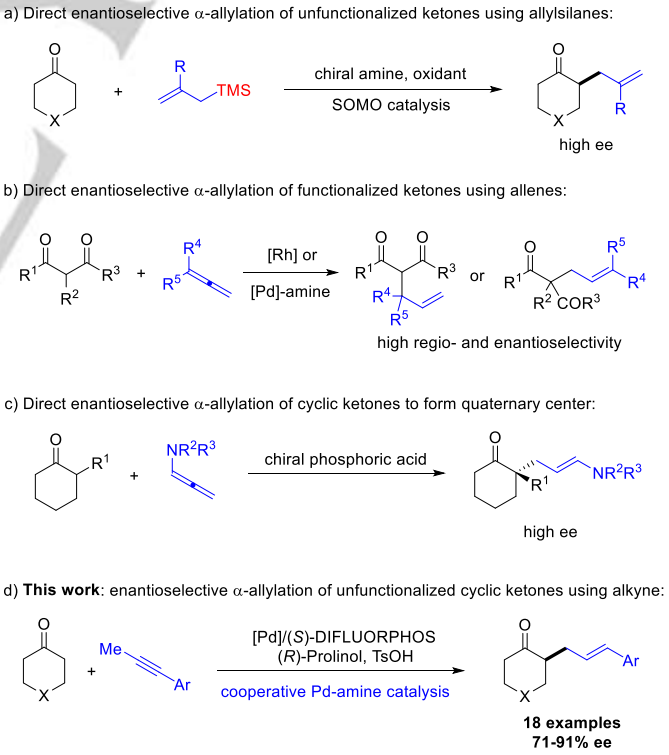
Abstract: *We present herein the first direct enantioselective α-allylation of unfunctionalized cyclic ketones using alkynes as an economical choice of reagent. This transformation uses a simple procedure with commercially available palladium, chiral bisphosphine ligand and chiral amine catalysts, and affords valuable ketones with a α-tertiary stereocenter in good to high enantiopurity. In this transformation, a chiral palladium complex containing the (S)-DIFLUORPHOS ligand catalyzes the isomerization of alkynes into an electrophilic allylpalladium species, which is attacked by the enamine generated in situ from the condensation of (R)-prolinol with the ketone substrate.*

The functionalization of carbonyl groups at the α-position for carbon-carbon bond formation is one of the most important and fundamental transformations in organic synthesis. In this respect, the direct catalytic enantioselective α-alkylation of carbonyls has become a subject of fervent interest.[1] In particular, dual catalysis[2] involving the use of chiral amines as one of the cooperating catalysts, has achieved notable success in the direct enantioselective α-alkylation of aldehydes.[3] Likewise, there has also been significant progress in recent years on the direct catalytic enantioselective α-alkylation of carboxylates.[4] In stark contrast, the direct catalytic enantioselective α-alkylation of ketones has remained largely under-developed.[5] Successful examples of the direct catalytic enantioselective α-alkylation of ketones have mainly been restricted to functionalized ketones such as 1,3-diketones,[6] β-ketoesters[7] and others[8]. For unfunctionalized ketones, there remains a continued reliance on indirect methods such as the use of chiral auxiliaries[9] and/or pre-formed enolates[10] for effective enantioselective α-alkylation. The development of a direct and more economical method for the enantioselective α-alkylation of unfunctionalized ketones would thus be highly desirable.

A significant advancement in this challenging endeavour was reported by the MacMillan group, who applied the concept of SOMO catalysis to direct enantioselective α-allylation of unfunctionalized cyclic ketones (Scheme 1a).[11] In this transformation, allylsilanes were employed as the reagent. In addition, the Melchiorre group also successfully developed an enantioselective α-alkylation of unfunctionalized cyclic ketones using electron-deficient benzyl bromides or α-bromo ketones under photo-organocatalysis.[12] While these are successful examples of direct enantioselective α-alkylation of unfunctionalized ketones, it is necessary to pre-install leaving groups such as silanes and bromides on the reagents nonetheless.

Recently, there has been an emerging area of research on the use of alkynes or allenes as electrophilic allylmetal precursors.[13] In this context, a transition-metal catalyzes the hydrofunctionalization of alkynes or allenes to form an electrophilic allylmetal species, which can undergo carbon-carbon bond formation with a nucleophile without the generation of any stoichiometric by-product. Compared to the more classical allylic substitution methods that require the use of pre-installed leaving group, this strategy of using alkynes/allenes is advantageous for economy in chemical synthesis. In fact, several research groups have successfully applied this strategy to the direct enantioselective α-allylation of ketones. While the Breit group and the Luo group achieved the enantioselective α-allylation of 1,3-dicarbonyls using allenes under Rh- or Pd-amine catalysis (Scheme 1b),[14] the Toste group reported a chiral phosphoric acid-catalyzed α-allylation of substituted cyclic ketones using allenamides to deliver the products in high enantioselectivity (Scheme 1c).[15] All these methods, however, focused on the establishment of quaternary centers from functionalized ketones.

Herein, we disclose the first direct catalytic enantioselective α-allylation of unfunctionalized cyclic ketones with internal alkynes as the atom-economical allylmetal precursor (Scheme 1d). This single-step transformation proceeds via Pd-amine cooperative catalysis using commercially available ligand/catalyst, and generates valuable ketones bearing a α-tertiary stereogenic center with good to excellent enantioselectivity. It is worth noting that the Lin group also adopted a similar strategy for the α-allylation of unfunctionalized ketones. In their recent elegant report, however, racemic products were obtained despite the use of chiral L-proline and Pd catalyst.[16]



Scheme 1. Emerging strategies for direct enantioselective α-allylation of ketones.

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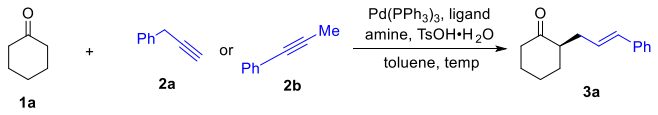
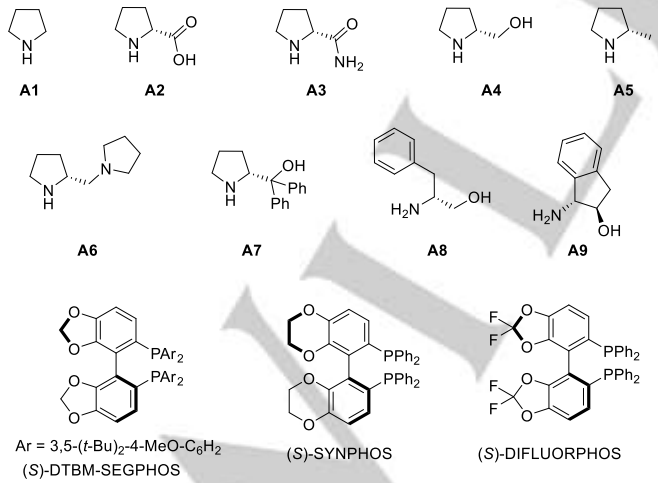
Table 1. Optimization of **3a** formation via Pd-amine cooperative catalysis[a]



entry	alkyne	ligand	amine	T °C (Time)	yield of **3a** (%)[b]	ee (%)
1	**2a**	(*S*)-BINAP	**A1**	80 (24 h)	40	24
2	**2a**	(*S*)-BINAP	**A2**	80 (24 h)	19	29
3	**2a**	(*S*)-BINAP	**A3**	80 (24 h)	19	55
4	**2a**	(*S*)-BINAP	**A4**	80 (24 h)	32	72
5	**2a**	(*S*)-BINAP	**A5**	80 (24 h)	<5	-
6	**2a**	(*S*)-BINAP	**A6**	80 (24 h)	<5	-
7	**2a**	(*S*)-BINAP	**A7**	80 (24 h)	<5	-
8	**2a**	(*S*)-BINAP	**A8**	80 (24 h)	28	2
9	**2a**	(*S*)-BINAP	**A9**	80 (24 h)	23	2
10	**2b**	(*S*)-BINAP	**A4**	80 (24 h)	40	72
11[c]	**2b**	(*S*)-BINAP	**A4**	80 (24 h)	80	70
12[c]	**2b**	(*S*)-Tol-BINAP	**A4**	80 (24 h)	87	66
13[c]	**2b**	(*S*)-DTBM-SEGPHOS	**A4**	80 (24 h)	85	62
14[c]	**2b**	(*S*)-SEGPHOS	**A4**	80 (24 h)	99	60
15[c]	**2b**	(*S*)-SEGPHOS	**A4**	55 (120 h)	34	77
16[d]	**2b**	(*S*)-SEGPHOS	**A4**	55 (120 h)	78	77
17[d]	**2b**	(*S*)-SYNPHOS	**A4**	55 (120 h)	25	69
18[d]	**2b**	(*S*)-DIFLUORPHOS	**A4**	55 (120 h)	75	79
19[d]	**2b**	(*S*)-DIFLUORPHOS	**A4**	60 (72 h)	33	78
20[e]	**2b**	**(*S*)-DIFLUORPHOS**	**A4**	**55 (120 h)**	**80**	**80**
21[e]	**2b**	(*S*)-BINAP	**A4**	55 (120 h)	59	75
22[e]	**2b**	(*R*)-DIFLUORPHOS	**A4**	55 (120 h)	64	63

[a] Reaction conditions: **1a** (0.125 mmol), **2a** or **2b** (0.22 mmol), 5 mol% $Pd(PPh_3)_4$, 5 mol% ligand, 30 mol% amine, 15 mol% $TsOH{\cdot}H_2O$ in toluene (1 mL) under N_2 atmosphere. [b] Determined by 1H NMR spectroscopy using 1,3,5-trimethoxybenzene as internal standard. [c] Ratio **1a**: **2b** (0.875 mmol, 7 equiv: 0.125 mmol, 1 equiv), [d] Ratio **1a**: **2b** (1.5 mmol, 12 equiv: 0.125 mmol, 1 equiv) [e] Ratio **1a**: **2b** (1.88 mmol, 15 equiv: 0.125 mmol, 1 equiv).



We began our investigation using cyclohexanone **1a**, and terminal alkyne **2a** as the reagent[17] and BINAP as the chiral ligand for Pd catalyst. When an achiral amine **A1** was used, a noticeable ee of 24% was obtained for the desired product **3a** (entry 1, Table 1). We then went on to screen other commercially available chiral amines (entries 2-9) in a bid to find a suitably matched chiral amine pair for (*S*)-BINAP. Among these co-catalysts, we were delighted to get a crucial breakthrough in terms of enantioselectivity when (*R*)-prolinol, **A4**, provided a big improvement in *ee* to 72%, albeit with a low yield of 32% (entry 4). The hydroxy moiety, which could be involved in interaction with the palladium catalyst, proved to be important for the reaction. When chiral amine **A5** with a methyl substituent was used instead, no conversion was observed for the reaction at all (entry 5). When internal alkyne **2b** was examined under our conditions, a slight increase in the yield of **3a** was observed (40% vs 32%, entry 10). When an excess of **1a** was used, a vast improvement in yield to 80% was obtained (entry 11). This set of conditions was then adopted for further optimization.

Additional chiral ligands bearing similar binaphthyl backbone as (*S*)-BINAP were screened next (entries 12-14). Although all these ligands gave reduced enantioselectivities, we were drawn to the results of (*S*)-SEGPHOS as it gave a full quantitative yield of **3a** (Table 1, entry 14). We wondered if we could exploit the higher reactivity afforded by (*S*)-SEGPHOS to perform the reaction at a lower temperature. Indeed, by lowering the temperature to 55 °C and extending the reaction time to 120 h, an improved *ee* of 77% was obtained for **3a** (entry 15). The use of a larger excess of **1a** again led to a vast improvement in yield from 34% to 78% without affecting the *ee* (entry 16). To further improve the yield and *ee,* more analogues of (*S*)-SEGPHOS were screened (entries 17-18) with electron-deficient (*S*)-DIFLUORPHOS[18] providing an improved result of 75% yield and 79% *ee*. Performing the reaction with shorter reaction time and slightly elevated temperature, however, reduced the yield significantly to 33% (entry 19). Finally, the best yield (80%) and *ee* (80%) for this challenging transformation were obtained when 15 equivalents of the cheap and commercially available **1a** was used (entry 20). (*S*)-DIFLUORPHOS proved superior to (*S*)-BINAP under the optimized reaction conditions (entry 21) with (*R*)-DIFLUORPHOS being less compatible with (*R*)-prolinol than (*S*)-DIFLUORPHOS in inducing enantioselectivity (entry 22). Further time-based studies were performed to to probe the possibility of product racemization under the optimized reaction conditions. The results showed that the *ee* of **3a** remained unchanged throughout the duration of the experiment, eliminating the possiblity of product racemization.

With the optimized reaction conditions in hand, the scope of the transformation was investigated. As shown in Scheme 2, substrates containing electron-neutral (**3b**) and electron-wthdrawing groups at *para*- (**3c-3e**), *meta*- (**3f-3g**) or *ortho*- (**3h-3i**) positions of the aryl ring were well tolerated giving reasonable yields and good enantioselectivities for the products. In particular, by lowering the reaction temperature to 50 °C, excellent enantioselectivity of up to 91% was obtained for substates with an electron-withdrawing methanoate group at the *ortho*-postion of the aryl ring (**3h-3i**)). Electron-donating groups at *para*- (**3j**) and *meta*- (**3k**) or *ortho*- (**3l**) positions of the aryl ring gave equally good enantioselectivities and comparable yields. Gratifyingly, other bulky aryl groups such as napthalene (**3m**) and phenanthrene (**3n**) as well as heterocycles such as pyridine (**3o**) and thiophene (**3p**) were also well tolerated for our system.

Whilst tolerant of a broad range of alkynes, this catalytic system works best only for 6-membered cyclic ketones like cyclohexanone, tetrahydropyranone (**3q**) and cyclohexanedione acetal (**3r**). Cyclic ketones of other ring-size and acyclic ketones were also tested but they generally gave dismal enantioselectivities and/or yield. This represents the limitation of the current catalytic system.

The structure and absolute configuration of the alkylated product **3b** and **3c** were unambiguously assigned by single crystal X-ray analysis. The structures of the others were assigned by analogy.

Based on the important precedents on transition metal-amine dual catalysis,[13k, 14b, 16] we propose a similar cooperative catalytic cycle in Scheme 3.

For the amine catalytic cycle, condensation of ketone **1** and (*R*)-prolinol catalyst generates the enamine nucleophile **I** *in situ***.** For the palladium catalytic cycle, a chiral palladium (0) complex

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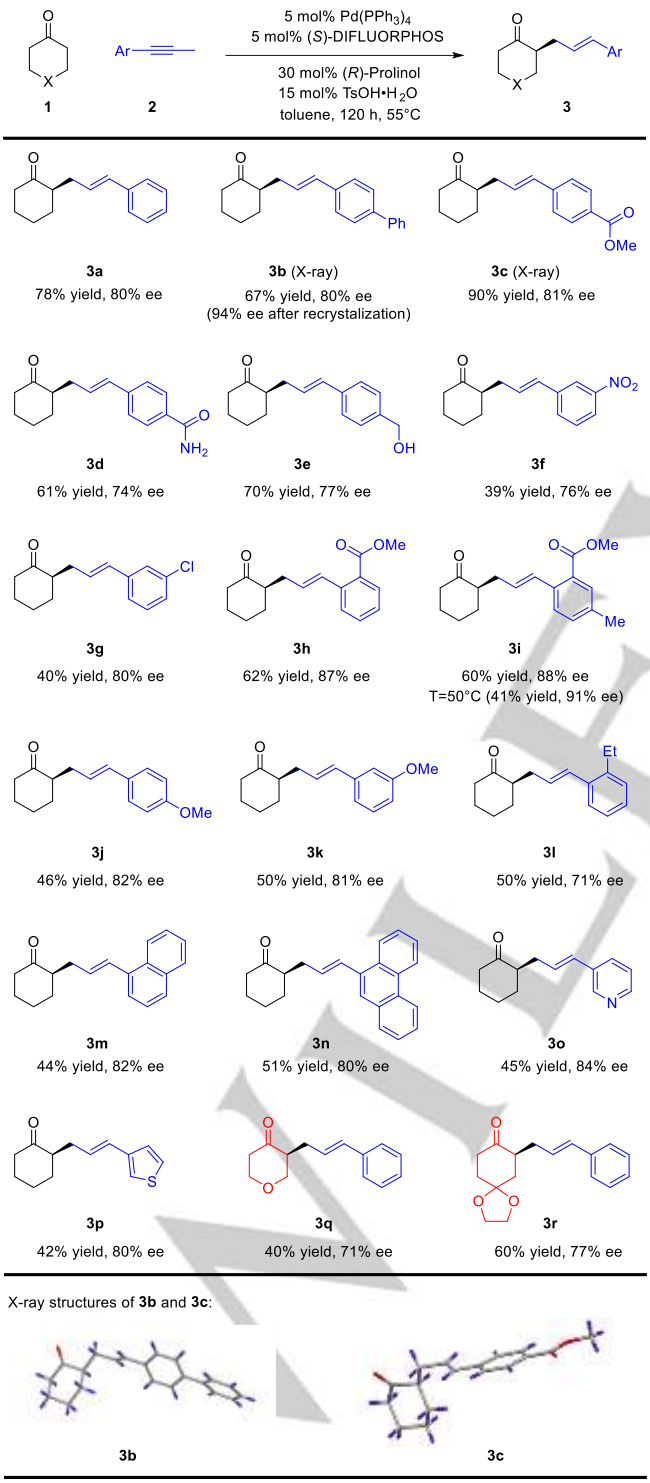
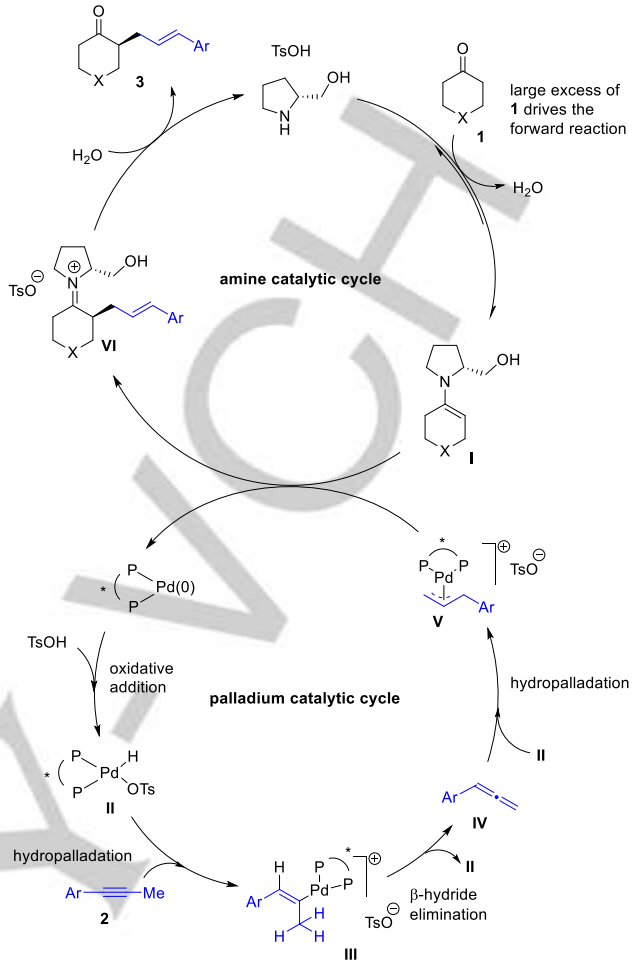
forms a Pd-hydride species **II** through oxidative addition onto TsOH. The Pd-hydride species then catalyzes the isomerization of alkynes into allenes **IV** through the hydropalladation of **2** to form intermediate **III** followed by a β-hydride elimination. The allene **IV** then undergoes hydropalladation with **II** to generate Pd-π-allyl species **V.** The chiral enamine nucleophile **I** then selectively adds to the electrophilic π-allyl **V** at the terminal position. It is noteworthy that no internal addition product was observed in our studies at all. This step regenerates Pd(0) and produces iminium species **VI**, which readily hydrolyses to form enantio-enriched desired product **3** and regenerates amine and TsOH catalysts.



Scheme 2. Scope of direct enantioselective α-allylation of ketones



Scheme 3. The proposed mechanism.

Some requirements of this catalytic system merit further discussion. Firstly, the use of a relatively less sterically hindered prolinol catalyst **A4** proved to be beneficial compared with other chiral amine catalysts (see Table 1 for results). The comparision of **A4** and **A5** suggests that the hydroxy moiety may be involved in some secondary interaction with intermediate **V** (e.g., interaction with the Pd center) leading to enhanced reactivity. The use of a tertiary amino alcohol **A7** resulted in no reactivity possibly due to steric demands.

Secondly, our optimization studies illustrated that the use of a large excess of the ketone substrate was key to providing a reasonable yield of **3.** We believe that the large excess **1** works in two ways: 1) It compensates for the lack of reactivity of unfunctionalized ketones by driving the equilibrium of the amine-ketone condensation step forward to form a sizeable amount of enamine nucleophiles**;** 2) It minimises any undesirable acid-base quenching reactions between the Pd and amine catalyst by keeping the amine catalyst within its catalytic cycle.

In summary, we report the first direct enantioselective α-allylation of unfunctionalized cyclic ketones with alkynes as the reagent under Pd-amine cooperative catalysis. This catalytic system uses a simple procedure with commercially available palladium and chiral secondary amine catalysts. Synthetically useful, enantioenriched, *γ*,*δ*-unsaturated ketones bearing tertiary stereogenic centres could be obtained in a single-step without recourse to chiral auxiliaries, pre-formed enolates or activated, functionalized ketones. The development of efficient catalytic procedures to perfom α-alkylation of a broader range of unfunctionalized ketone substrates is under investigation.

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Keywords: α-allylation of ketone • cooperative catalysis • palladium pi-allyl • enamine catalysis • tertiary stereocenter

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COMMUNICATION

*Jin Tu Danence Lee and Yu Zhao**

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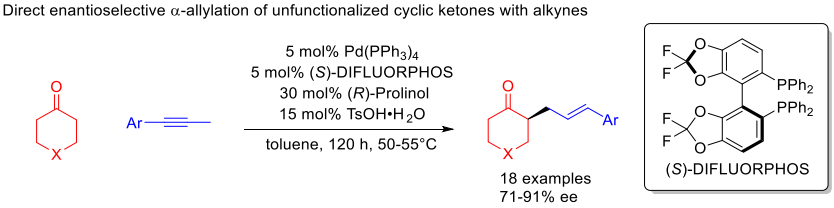
Direct Enantioselective α-Allylation of Unfunctionalized Cyclic Ketones with Alkynes via Pd-Amine Cooperative Catalysis

Direct enantioselective α-allylation of unfunctionalized cyclic ketones with alkynes



- First direct enantioselective α-allylation of unfunctionalized ketones with alkynes
- Commercially available catalysts and easily accessible internal alkyne reagents

We present herein the first direct enantioselective α-allylation of unfunctionalized cyclic ketones using alkynes as an economical choice of reagent. This transformation uses a simple procedure with commercially available palladium, chiral bisphosphine ligand and chiral amine catalysts, and affords valuable ketones with a α-tertiary stereocenter in good to high enantiopurity. In this transformation, a chiral palladium complex containing the (S)-DIFLUORPHOS ligand catalyzes the isomerization of alkynes into an electrophilic allylpalladium species, which is attacked by the enamine generated in situ from the condensation of (R)-prolinol with the ketone substrate.