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Synergistic palladium/enamine catalysis for asymmetric hydrocarbon functionalization of unactivated alkenes with ketones†

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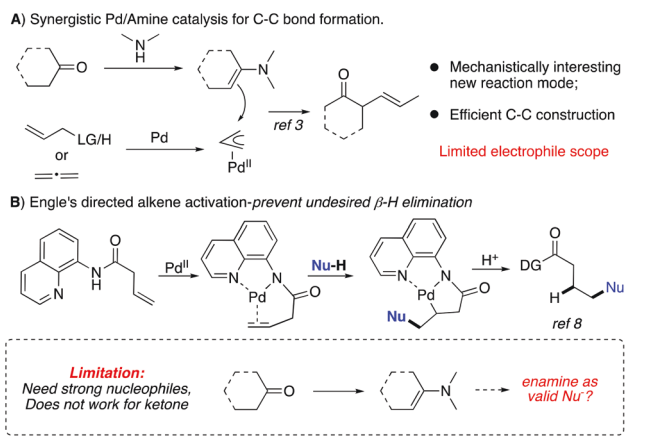
Synergistic palladium and enamine catalysis was explored to promote ketone addition to unactivated olefins. A secondary amine-based organocatalyst was identified as the optimal co-catalyst for the directed Pd-catalyzed alkene activation. Furthermore, asymmetric hydrocarbon functionalization of unactivated alkenes was also achieved with good to excellent yield (up to 96% yields) and stereoselectivity (up to 96% ee). This strategy presented an efficient approach to prepare α-branched ketone derivatives under mild conditions.

Introduction

Synergistic metal/organocatalysis has flourished over the past decade, enabling a combination of the orthogonal reactivity between transition metal chemistry and organocatalysis.[1] In particular, combining palladium and enamine chemistry offered a powerful toolbox for C–C bond construction.[2] A general reaction pattern is employing enamine as a nucleophile to react with a Pd-activated carbon electrophile. One type of this well-explored electrophile is the π-allyl complex, which is often generated *in situ via* Pd addition/oxidation toward allyl or allene moieties (Scheme 1A).[3] Although this protocol represents an efficient approach for a C–C bond construction, it suffers from several limitations, including limited substrate scope and lack of effective stereochemistry control.[4] This is mainly due to (A) the requirement of a pre-functionalized alkene to form a Pd π-allyl complex and (B) problematic reversible β-H elimination involved. Therefore, developing new reaction partners that can facilitate transformations in this dual-catalysis mode will not only offer practical synthetic utility but also foster mechanistic insight to further advance this intriguing reaction pattern.

The intrinsic reactivity of C–C double bonds allows alkenes to have a privileged position in organic synthesis.[5] Lewis acid catalyzed nucleophilic addition of alkenes has become a powerful synthetic approach for C–C and C–X bond construction.[6] However, palladium is considered as a weak π-acid towards alkene activation, and therefore, a strong nucleophile is required to attack the Pd-activated alkene.[7] Moreover, the resulting Pd–C intermediate could undergo fast β-H elimination, giving alkene products and other potential undesired side reactions. To overcome this problem, in 2016, Engle and coworkers first reported the application of the bidentate directing group (DG) strategy to enhance the reactivity of Pd, allowing un-activated alkene to be readily attacked by soft carbon nucleophiles.[8] More importantly, with a more sterically constrained Pd intermediate, the β-H elimination was successfully inhibited (Scheme 1B). This seminal work highlighted the advantage of applying the bidentate DGs to (A) improve the reactivity of the Pd(II) cation and (B) secure olefin hydrocarbofunctionalization through protodemetallation. Although a wide range of carbon nucleophiles, including 1,3-dicarbonyls, aryl carbonyls, and electron-rich arenes, have been successfully



Scheme 1 Combining organo and Pd catalysis for alkene functionalization.

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applied for this transformation, ketones and aldehydes remained problematic. Also, only a few examples have been reported for enantioselective addition to unactivated alkene using this strategy.[9] Inspired by these findings, we envisioned that the combination of Pd-catalyzed directed alkene activation with enamine addition could offer a valid strategy to further extend the reaction scope to ketone derivatives. More importantly, the adoption of chiral amine catalysts will provide an effective stereochemistry control to achieve asymmetric α-alkylation of a ketone.

It is important to note here that as we were working on this idea independently, a paper with a similar design from the Gong group was published, in which they reported the alkylation of substituted cyclic ketones through enamine activation.[10] The desired α-alkylation was obtained in good yields and ee. We herein report our efforts on this novel transformation with alternative reaction conditions. We are able to extend the substrate scope to various acetophenones, as well as β-keto-esters. It is our hope to offer another perspective on how we achieved this transformation using a different approach.

Results and discussion

Considering that the directing group is crucial for increasing the reactivity of the Pd catalyst, we first screened some commonly used directing groups (**1a–1e**) under Engle's conditions (HOAc, MeCN, 120 °C). The results are summarized in Table 1.

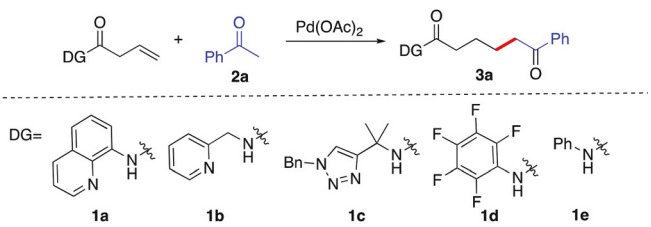
As expected, without the addition of amine, no desired product was observed in all the cases, which highlighted the challenge of applying acetophenone as a nucleophile toward Pd-activated alkene. Fortunately, when L-proline was applied as the co-catalyst with 8-aminoquinoline (AQ) as the directing group, the reaction successfully gave the desired addition product **3a** in 60% NMR yield. Interestingly, other directing groups could not promote this transformation even with the addition of proline, emphasizing the unique roles of AQ in this reaction. After screening a series of conditions, pyrrolidine was identified as the optimal co-catalyst with toluene as the solvent. The reaction proceeded smoothly at 80 °C with a nearly quantitative yield.

Inspired by this result, we then turned our attention to a more challenging asymmetric addition with the assistance of chiral amines. Representative conditions screened are summarized in Table 2.

As expected, treating **1a** with cyclohexanone **2b** under Pd/pyrrolidine conditions gave **4a** in 95% yield, as expected (entry 2). Various chiral amine catalysts were then tested for stereoselectivity. The Macmillan catalysts were ineffective in this system, which might be due to the lack of reactivity towards ketones.[11] L-Proline gave a decreased conversion and yield with 11% ee of **4a**. Clearly, a tight transition state with Pd and amine is crucial for good stereoselectivity. To avoid competitive OAc binding, $Pd(CH_3CN)_2Cl_2$ was then employed. An increased ee (15%) was obtained with L-proline as a co-catalyst (entry 5). Finally, with Jorgensen catalyst **A9**, product **4a** was obtained in 97% yield with 71% ee (entry 10). It is important to note that prolinol **A8** gave the product in 65% ee, while the OMe protected ligand **A7** gave almost no stereoselectivity (<5% ee). This result clearly suggested the importance of the hydroxyl group in promoting the stereoselectivity of the transformation. This is likely due to the coordination of OH with the Pd intermediate, which not only accelerates the overall reaction rate by rendering the enamine addition in an intramolecular manner but also provides a good stereochemistry control. One challenge that prevents further improvement of the enantioselectivity is the racemization of product **4a**. Extending the reaction time resulted in a decreased ee value under the reaction conditions (entry 11). To further fine-tune the reaction, we conducted the reaction at lower temperature (60 °C). Lower conversion (60%) and yield (55%) were observed, though higher ee was obtained (93%). To increase the reaction rate at a lower temperature, neat conditions were applied. The reaction gave 100% conversion and 95% isolated yield with 88% ee of **4a**. Notably, under Gong's conditions, only 60% ee was obtained, though with 93% yield. With these optimal conditions revealed, the reaction scope was evaluated. Substrates **3** from methyl-ketone are shown in Table 3.

In general, over 90% yields were obtained with almost all tested acetophenone derivatives. Both EDG (**3b–3d**) and EWG (**3e** and **3f**) modified ketones gave excellent yields. Slightly reduced yields were obtained with the *ortho*-substituted substrate (**3j** 89%, **3k**, 82%) due to steric hindrance. Interestingly, aryl halide substrates (**3g**, **3h**, and **3i**) worked very well for this transformation without the observation of Pd catalyzed oxidative addition of the C–X bond, revealing an orthogonal reactivity compared to typical Pd(0) involved coupling reactions. With 4′-iodoacetophenone **3j**, a modest yield was observed, due to the formation of the Heck type by-product in the presence of more active C–I bonds. Finally, the amino acid-modified derivative (**3o**) was also found to be suitable for this reaction, suggesting the potential application of this method in bio-compatible compound preparation. Internal alkene deriva-

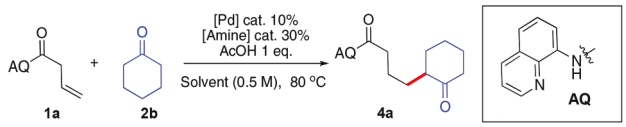
Table 1 Screening directing groups[a]



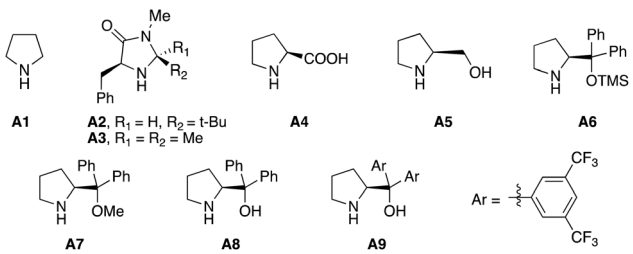
DGs	Conditions	Conv.[b]	Yield[b]
1a–1e	MeCN, 120 °C	<5%	<5%
1a	L-Proline 20%, MeCN, 120 °C	70%	60%
1b–1e	L-Proline 20%, MeCN, 120 °C	<10%	<10%
1a	Pyrrolidine 20%, Tol, 80 °C	100%	99% (94%[c])

[a] Reaction conditions: **1a** (1 eq.), **2a** (3 eq.), $Pd(OAc)_2$ (10 mol%), [amine] cat. (20 mol%), AcOH (1 eq.), solvent (0.5 M), 36 hours. [b] Conversion and yield were determined by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard. [c] Isolated yield.

Table 2 Optimization of amines for palladium/enamine catalysis[a]

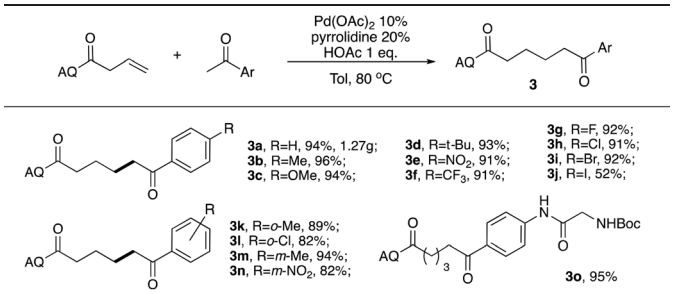


Entry	[Pd]	[Amine]	Sol.	Conv.[b]	Yield[b]	ee%[c]
1[d]	$Pd(OAc)_2$	n/a	MeCN	<5%	<5%	—
2	$Pd(OAc)_2$	**A1**	Tol	100%	95%	—
3	$Pd(OAc)_2$	**A2** or **A3**	Tol	<20%	<20%	0
4	$Pd(OAc)_2$	**A4**	Tol	62%	54%	11%
5	$Pd(CH_3CN)_2Cl_2$	**A4**	Tol	79%	77%	15%
6	$Pd(CH_3CN)_2Cl_2$	**A5**	Tol	100%	90%	33%
7	$Pd(CH_3CN)_2Cl_2$	**A6**	Tol	100%	91%	63%
8	$Pd(CH_3CN)_2Cl_2$	**A7**	Tol	100%	57%	<5%
9	$Pd(CH_3CN)_2Cl_2$	**A8**	Tol	100%	96%	65%
10	$Pd(CH_3CN)_2Cl_2$	**A9**	Tol	100%	97%	71%
11[e]	$Pd(CH_3CN)_2Cl_2$	**A9**	Tol	100%	97%	<5%
12[f]	$Pd(CH_3CN)_2Cl_2$	**A9**	Tol	60%	55%	93%
13[f]	$Pd(CH_3CN)_2Cl_2$	**A9**	neat	100%	99% (95%)[g]	88%



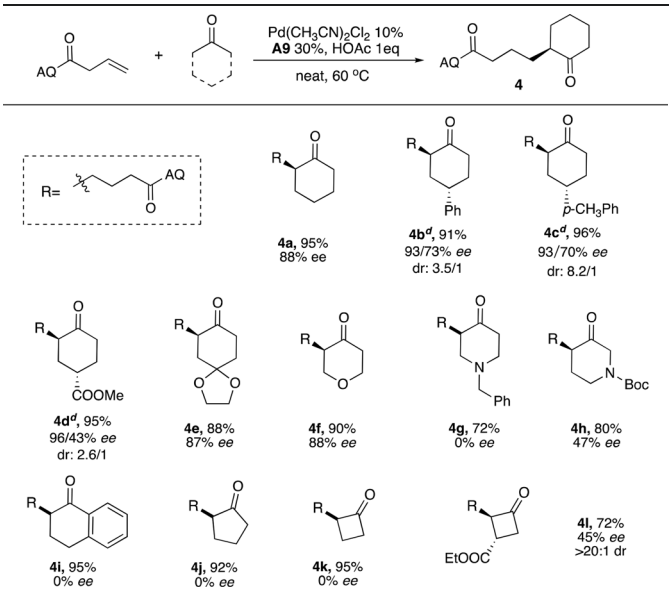
[a] Reaction conditions: [Pd] cat. (10 mol%), [amine] cat. (30 mol%), AcOH (1 eq.), solvent (0.5 M), at 80 °C, 24 hours. [b] Conversion and yield were determined by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard. [c] The ee value was determined by HPLC. [d] 120 °C, 36 hours. [e] 72 h. [f] 60 °C, 24 hours. [g] Isolated yield.

Table 3 Substrate scope of compound **3**[a,b]



[a] Reaction conditions: $Pd(OAc)_2$ (10 mol%), pyrrolidine (20 mol%), AcOH (1 eq.), solvent (0.5 M), 36 hours. [b] Isolated yield.

Table 4 Substrate scope for asymmetric ketone alkylation[a,b,c]



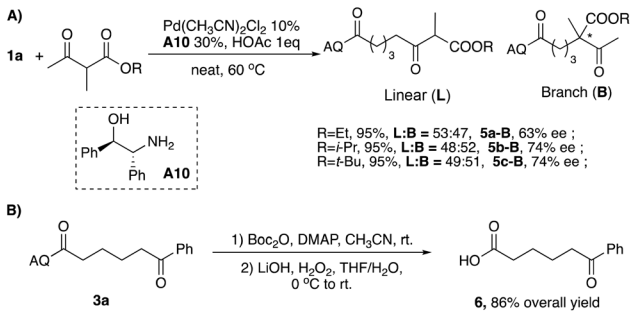
[a] Reaction conditions: $Pd(MeCN)_2Cl_2$. (10 mol%), **A9** (30 mol%), AcOH (1 eq.), 24 hours. [b] Isolated yield. [c] The dr and ee were determined by HPLC. [d] 80 °C.

tives, (*Z*) and (*E*)-*N*-(quinolin-8-yl)hex-3-enamide, were unreactive. Moreover, compound **3a** was synthesized on a gram scale, which indicated its practical synthetic value.

Exploration of asymmetric reaction performance with cyclic ketones was also performed and is summarized in Table 4. Compared to non-substituted cyclohexanone (**4a**), 4-substituted cyclohexanone derivatives (**4b–4d**) required a higher temperature (80 °C) to achieve the full conversion due to

increased hindrance. Interestingly, in these cases, problematic racemization was also inhibited, providing higher enantioselectivity. On the other hand, modest dr values were observed. The ketal derivative (**4e**) was also tolerated under this acidic condition without deprotection, excellent yield and ee were obtained. Next, both O and N containing cyclohexanones **4f–4h** were tested. 4-Oxotetrahydropyran (**4f**) provided 90% yield and 88% ee, while 4-oxopiperidine (**4g**) failed to observe any enantioselectivity possibly because of a quick epimerization. By switching to Boc protection, 3-oxopiperidine (**4h**) was achieved with modest ee, resulting from resonance of the amide group to lock the conformation. 1-Tetralone (**4i**) showed excellent yields with 0% ee due to the more acidic α-proton. Smaller cyclic ketones such as cyclopentanone (**4j**) and cyclobutanone (**4k**) gave excellent yields with no ee, which is likely due to the presence of more acidic α-protons, which caused quick racemization of the formed product. As a result, introduction of an ester into cyclobutanone (**4l**) to increase steric bulkiness not only resulted in moderate enantioselectivity (45% ee) but also delivered an excellent dr value (>20 : 1).

In addition to cyclic ketones, other carbonyl substrates were also explored (Scheme 2A). First, aldehyde was tested and proved not to be suitable for this transformation due to the undesired rapid aldol condensation side reaction. Other readily available ketone derivatives such as 1,3-diketones and β-keto-esters were also tested. In particular, we chose α-substituted 1,3-dicarbonyl compounds for further study because they could form products with a quaternary stereocenter to prevent racemization. After the extensive screening of catalysts (see the details in the ESI†), primary amine **A10** was identified as an effective catalyst in promoting condensation of β-keto-ester with AQ-modified olefin (Scheme 2A). Although all ketone esters (**5a**, **5b**, and **5c**) showed excellent yield (95%), a regioselectivity issue (linear *vs.* branch selectivity) was revealed as well, due to the formation of two possible enamine intermediates. All of these three substrates gave a similar regioselectivity ratio (from 53 : 47 to 48 : 52). With the increasing size of substituted group R, the enantioselectivity would be increased from 63% to 74% ee. We also demonstrated that the AQ directing group could be removed by a Boc protection-basic hydrolysis sequence, yielding the ε-keto acids **6** with 86% yield over two steps (Scheme 2B).[12]



Scheme 2 Substrate scope of compound **5** and the removal of AQ.

Conclusions

In summary, we reported a synergistic palladium/enamine catalyzed asymmetric addition of ketones to non-activated alkenes under mild conditions. Using this protocol, asymmetric α-alkylation of ketone derivatives was successfully achieved by combining the chiral enamine formation and directed Pd-catalyzed alkene activation, which offered an efficient and cooperative catalysis system. Furthermore, this study revealed a novel approach towards α-branched ketone derivatives, highlighting its valuable synthetic utility.

Experimental

General procedure to synthesize 3a–3o

An oven-dried vial was charged with $Pd(OAc)_2$ (10 mol%, 0.02 mmol), HOAc (1 equiv., 0.2 mmol), ketone (3 equiv., 0.6 mmol) and pyrrolidine (20 mol%, 0.04 mmol). The vial was placed under vacuum and charged with Ar. Alkene (**1a**) (1 equiv., 0.2 mmol) and toluene (1 M, 0.2 mL) were added into the vial sequentially under an Ar atmosphere. The reaction was run at 80 °C and monitored by TLC. Once the reaction completed, the solvent was removed under vacuum, and the resulting crude mixture was loaded on a silica gel column directly and purified by flash chromatography to give the desired product.

General procedure to synthesize 4a–4l

An oven-dried vial was charged with $Pd(MeCN)_2Cl_2$ (10 mol%, 0.02 mmol), HOAc (1 equiv., 0.2 mmol), ketone (4 equiv., 0.8 mmol) and **A9** (30 mol%, 0.06 mmol). The vial was placed under vacuum and charged with Ar. Alkene (**1a**) (1 equiv., 0.2 mmol) was added into the vial sequentially under an Ar atmosphere. The reaction was run at 60 °C and monitored by TLC. Once the reaction completed, the crude mixture was loaded on a silica gel column directly and purified by flash chromatography to give the desired product.

General procedure to synthesize 5a–5c

An oven-dried vial was charged with $Pd(MeCN)_2Cl_2$ (10 mol%, 0.02 mmol), HOAc (1 equiv., 0.2 mmol), ketone ester (3 equiv., 0.6 mmol) and **A10** (30 mol%, 0.6 mmol). The vial was placed under vacuum and charged with Ar. Alkene (**1a**) (1 equiv., 0.2 mmol) was added into the vial sequentially under an Ar atmosphere. The reaction was run at 60 °C and monitored by TLC. Once the reaction was completed, the crude mixture was loaded on a silica gel column directly and purified by flash chromatography to give the desired product.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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