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Tertiary amine self-catalyzed intramolecular C_{sp3}-H functionalization with *in situ* generated allenes for the formation of 3-alkenyl indolines

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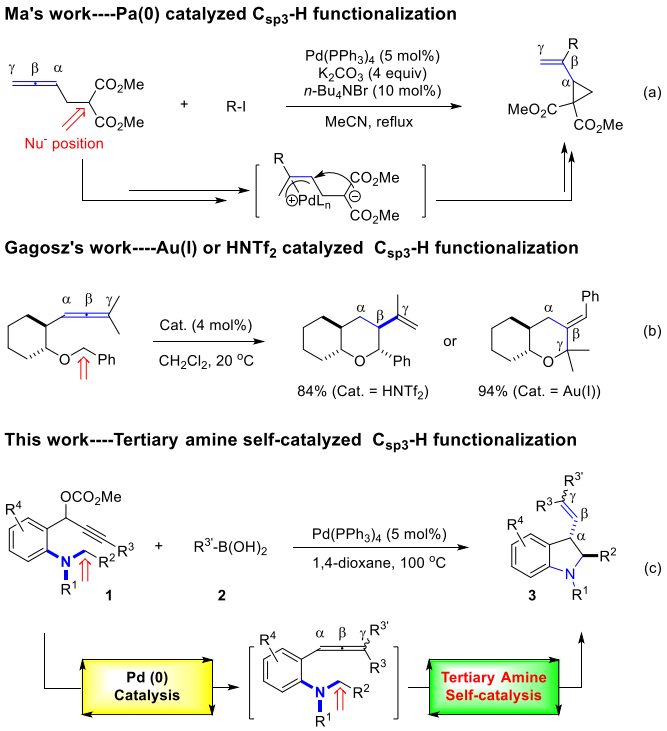
A novel methodology for the synthesis of 3-alkenyl indolines through the reaction of *in situ* generated allenes with *N*-benzylic C_{sp3}-H has been developed. The reaction was realized by Pd(0) catalyzed allenylation of propargyl carbonate with organoboron and subsequent tertiary amine self-catalyzed C_{sp3}-H functionalization in a one-pot process. Control reactions suggested that the substrate itself might also serve as a Lewis base for the *N*-benzylic C_{sp3}-H functionalization.

As is well known, the C-H bond functionalization strategy provides a direct, economical and efficient platform to construct target molecules.[1] In recent years, a rapid development of C-H bond functionalization for the formation of C-C and C-X (X = *O*, *N*, S, etc.) bonds was witnessed.[2] With high density of unsaturation and diverse reactivity, allene become a premium participator for C-H functionalization. Recently, C-H functionalization with allenes, including intramolecular[3] and intermolecular[4] processes, was well utilized to construct annulation structures. Along with the application of Rhodium,[4a-e] Cobalt,[4f] Indium,[3b,e] Gallium,[3b,e] Platinum,[3b,e,j,l] Gold,[3a,c,f,h,l,k] Mercury,[3d] and Bismuth[3g] catalysis, C_{sp2}-H functionalization with allenes shows powerful developmental prospect. However, with large dissociation energy and low proton acidity, the exquisitely selective functionalization of conventional C_{sp3}-H bonds with allenes for the formation of specific hetero- or carbocyclic structures is still a great challenge. In 2000, Ma and co-workers reported an excellent Pd(0)-catalyzed coupling-cyclization reaction to synthesize vinylic cyclopropane derivatives (Scheme 1, a).[5] This reaction underwent a intramolecular nucleophilic substitution of π-allyl palladium species with a geminal diester C_{sp3} site.[6] In 2010, Dixon and co-workers developed an elegant methodology to synthesize spirocyclic lactam compounds by Pd(0) catalyzed geminal dicarbonyl C_{sp3}-H functionalization with allenes.[7] In 2011, Gagosz and Bolte achieved a refreshing $HNTf_2$ or Au(I) catalyzed C_{sp3}-H functionalization via a pivotal process including a novel hydride shift of etheric C_{sp3}-H onto allene moiety (Scheme 1, b).[8a] In 2013, Alcaide, Almendros and co-workers reported a novel Au(I)-catalyzed intramolecular formal 5-exo hydroalkylation reaction of allenyl-tethered arenes to achieve C_{sp3}-H functionalization with allenes.[8b]



Scheme 1 Intramolecular C_{sp3}-H functionalization with allenes

Propargylic compounds are versatile building blocks in synthetic organic chemistry. Pd-catalyzed transformation of propargylic substrates affords a variety of useful compounds, such as allenes, alkynes, enynes, carbocyles and heterocycles.[9] During the course of our ongoing program on developing new methodology for the construction of carbo- and heterocyclic

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For ESI and crystallographic data in CIF or other electronic format See DOI: 10.1039/x0xx00000x

compounds,[10] we designed a substrate (**1**) bearing propargyl carbonate and tertiary amine moiety.[11] We planned to develop novel synthetic routs for the construction of six-, seven- or eight-membered rings through *N*-phenyl C_{sp2}-H functionalization with *in suit* generated allenes (Figure 1). However, even R^1 substituent was a *p*-methoxy group, no C_{sp2}-H functionalization product was observed. Interestingly, a *N*-benzylic C_{sp3}-H functionalized indoline product was obtained instead. Herein, we reported a sequential Pd(0) catalyzed allenylation and tertiary amine self-catalyzed C_{sp3}-H functionalization procedure to synthesize 3-alkenyl indolines (Scheme 1, c). To the best of our knowledge, this tertiary amine self-catalyzed *N*-benzylic C_{sp3}-H functionalization with allenes has yet been discovered.

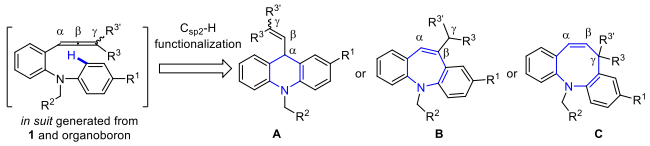
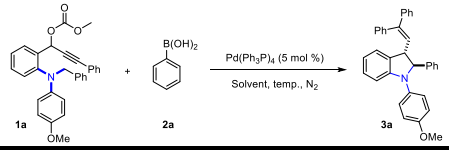


Figure 1 Strategy for heterocycles formation

Table 1 Optimization of the reaction conditions[a]



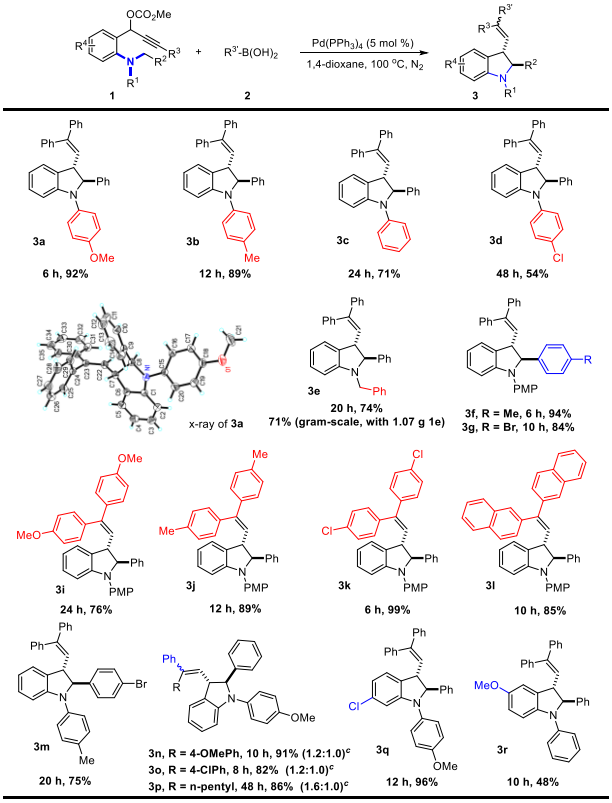
Entry	Solvent	Base (equiv)	Temp. (°C)	Time (h)	Yield of **3a** (%)[b]
1	MeCN	-	100	12	34
2	PhMe	-	100	12	76
3	MeOH	-	100	12	10[c]
4	THF	-	100	12	88
5	$(MeOCH_2)_2$	-	100	12	88
6	MTBE	-	100	12	79
7	1,4-Dioxane	-	100	12	90
8	1,4-Dioxane	-	80	12	80
9	1,4-Dioxane	-	100	12	65[d]
10	1,4-Dioxane	-	100	12	90[e]
11	1,4-Dioxane	Cs_2CO_3 (0.2)	100	12	89
12	1,4-Dioxane	Cs_2CO_3 (2.0)	100	12	88
13	1,4-Dioxane	-	100	2	69[f]
14	**1,4-Dioxane**	**-**	**100**	**6**	**92**
15	1,4-Dioxane	-	100	20	90

[a] Solvent (0.05 M), **1a** (0.2 mmol), **2a** (2.0 equiv) and $Pd(Ph_3P)_4$ (5 mol %) were added to a screw-capped tube or Schlenk tube under N_2. [b] Isolated yield. [c] See reference 12. [d] 1.5 Equiv of **2a** was used. [e] 2.5 Equiv of **2a** was used. [f] A mixture of **3a** (69%) and the allene intermediate (21%) with a ratio of 10:3 was obtianed.

Initially, our investigation began with the attempt of 1-(2-(benzyl(4-methoxyphenyl)amino)phenyl)-3-phenylprop-2-yn-1-yl methyl carbonate (**1a**) and phenylboronic acid (**2a**). Firstly, the reaction of **1a** with **2a** was carried out with 5 mol % of $Pd(Ph_3P)_4$ as the catalyst under N_2.[12] When acetonitrile was used as the solvent, only 34% yield of (2S,3S)-3-(2,2-diphenylvinyl)-1-(4-methoxyphenyl)-2-phenylindoline (**3a**) could be isolated (Table 1, entry 1). The structure of **3a** was confirmed by X-ray crystallography.[13] Subsequently, other solvents, such as toluene, methanol[14] and tetrahydrofuran (THF), were investigated (entries 2-4). Surprisingly, the yield of **3a** was increased to 88% with THF (entry 4). Encouraged by the nice result of THF, we further screened other ether solvents with higher boiling points (entries, 5-7). While 1,4-dioxane was used as solvent, a better yield of **3a** (90%) could be achieved (entry 7). Nevertheless, a lower yield of **3a** was observed when the reaction was carried out at 80 °C (entry 8, 80%).

Then, we tested the effects of the amount of **2a**. When 1.5 equiv of **2a** was used, the yield of **3a** was reduced to 65% (Table 1, entry 9). Increasing the amount of **2a** to 2.5 equiv only gave a same yield as that of 2.0 equiv (entry 10). With additional base, such as 0.2 or 2.0 equiv of Cs_2CO_3, similar yields as entry 7 were obtained (entries 11 and 12), suggesting the reaction does not need an external base. When the reaction was carried out within 2 h (entry 13), a mixture of **3a** with the allene intermediate was detected in a combined yield of 90% with a ratio of 10:3 (**3a**, 69% determined by ^1H NMR). Increasing the reaction time to 6 h provided the final product **3a** in 92% yield (entry 14). However, changing the reaction time to 20 h did not afford a better result (entry 15, 90%). It is worth noting that free propargylic alcohol **1** was not suitable substrates for this reaction, resulting in no desired product.

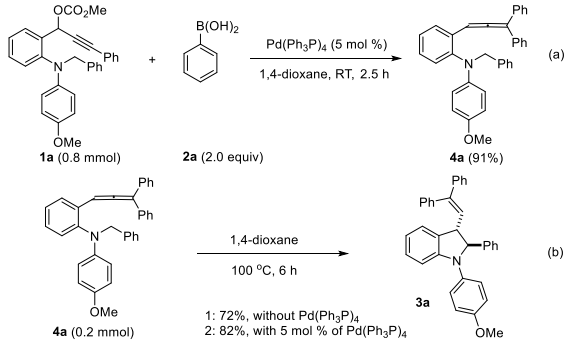
Table 2 The scope of the reaction[a]



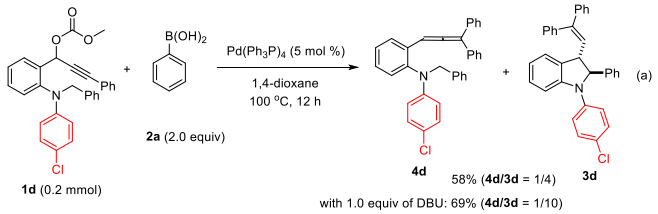
[a] The reactions were carried out under the optimized reaction conditions. PMP = *p*-MeOPh [b] Isolated yield. [c] Reacted with **2a** and the ratio was determined by ^1H NMR analysis.

With the optimized reaction conditions in hand (Table 1, entry 14), we next examined the substrate scope (Table 2). Firstly, we investigated the electronic effect of the substituent R^1 (**3a**-**3d**). Markedly, the substrates with electron-donating groups gave much better yields with shorter reaction times (**3a**,

6h, 92%; **3b**, 12 h, 89%) than that with electron-withdrawing substituents (**3d**, 48 h, 54%). When R^1 was alkyl substituent, such as benzyl group, the corresponding *N*-benzyl product **3e** was formed in 74% yield. Subsequently, R^2 substituent was explored (**3f**-**3h**). Substrates both with *p*-MePh and *p*-BrPh groups were well suitable for the reaction, offering the desired 3-alkenyl indolines in good to excellent yields (**3f**, 94%; **3g**, 84%). When R^2 = H, no desired product **3h** was isolated, suggesting the aromatic R^2 substituent was necessary for this reaction. Then, the effects of R^3 and $R^{3'}$ substituents were studied (**3i**-**3p**). When R^3 and $R^{3'}$ was the same, good to excellent yields of corresponding 3-alkenyl indolines could be obtained irrespective of the presence of electron-withdrawing or electron-donating groups on the aryl ring (**3i**-**3m**, 75-99%). With electron withdrawing substituents on the phenyl ring, such as R^3 = $R^{3'}$= *p*-ClPh, the desired indoline (**3k**) was generated quantitatively (99%). When R^3 was different from $R^{3'}$, good to excellent yields of target products (**3n**-**3p**, 82-91%) could be achieved with *cis* and *trans* isomers. Finally, we investigated the electronic effect of R^4. Substrates with electron-withdrawing group gave much better yield (**3q**, 96%) than that with electron-donating substituent (**3r**, 48%).

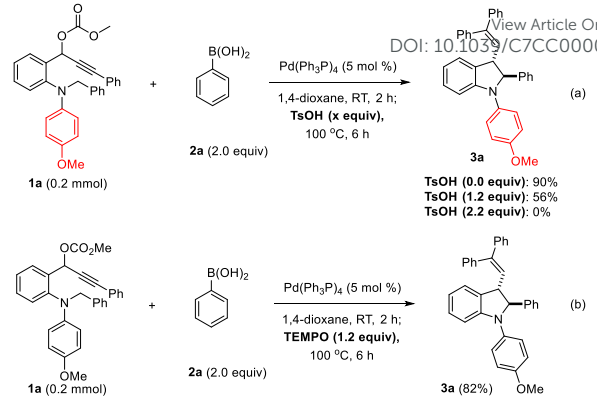


Scheme 2 Intermediate capture and transformation



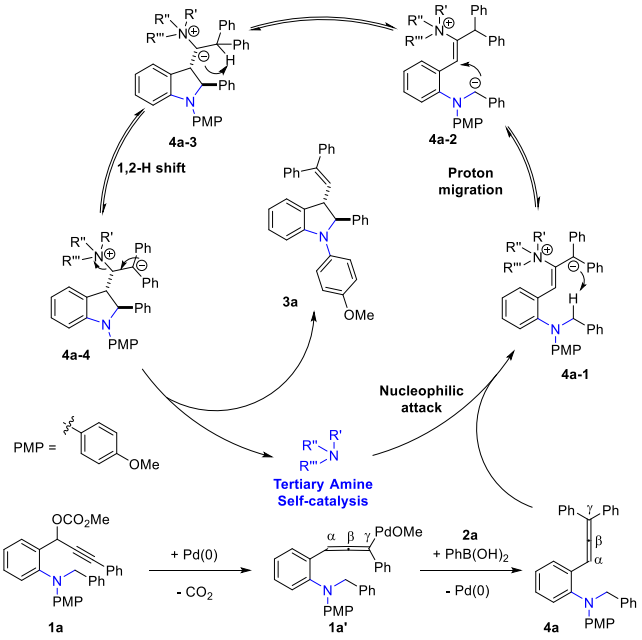
Scheme 3 Validation of base promotion hypothesis

To understand the reaction mechanism, several control experiments were conducted. In order to trap a possible intermediate, we carried out the reaction of **1a** with **2a** at room temperature. Luckily, the allenylation compound **4a** was isolated in 91% yield (Scheme 2, a). And **4a** could be transformed to **3a** with 72% yield in the absence of $Pd(Ph_3P)_4$ (Scheme 2, b-1). In the presence of $Pd(Ph_3P)_4$, **4a** was obtained with a higher yield of 82% (Scheme 2, b-2). These results implied that allenylation compound is a possible intermediate and $Pd(Ph_3P)_4$ was not indispensable for the subsequent cyclization.



Scheme 4 Further mechanistic investigations

Based on the results above (Scheme 2), we conjecture that the tertiary amine itself may serve as a base to catalyse the subsequent cyclization process. Treatment of **1d** and **2a** under the optimized reaction conditions, a mixture of **4d** and **3d** was obtained after 12 h in 58% overall yield with a ratio of 1/4 (Scheme 3). On the other hand, with the addition of 1.0 equiv of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), the total yield of **4d** and **3d** was increased to 69% (**4d**/**3d** = 1/10). These results suggested that organic base (DBU) could promote the reaction significantly.



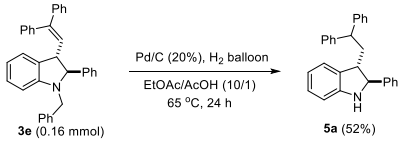
Scheme 5 Proposed reaction mechanism and catalytic cycle

To further clarify the reaction mechanism, we chose substrate **1a** for the acidic control experiments (Scheme 4, a). After the formation of allenylation intermediate (room temperature about 2 h), different amount of *p*-toluenesulfonic acid (TsOH) was added and the reaction mixture was kept at 100 °C for another 6 h. When 1.2 equiv of TsOH was used, **3a** was isolated in 56% yield. Increasing TsOH to 2.2 equiv, no desired product was detected. These results indicated that free tertiary amine was essential for the cyclization process. When the reaction was performed in the presence of a radical scavenger such as 2,2,6,6-tetramethylpiperidinooxy (TEMPO), the desired **3a** could still be formed in 82% yield (Scheme 4,

b).[15] The results implied that radical species might not be involved in the reaction process.

Based on the reported work[16] and our experimental results, a plausible mechanism is proposed with model substrates **1a** and **2a** as outlined in scheme 5. The reaction is initiated by S_N2' attack of Pd(0) on the propargylic carbonate **1a** to form allenyl-palladium intermediate **1a'**, that undergoes the transmetalation with phenylboronic acid (**2a**) and reductive elimination of Pd(II) to afford allenylation intermediate **4a**.[16a-d] Then, the nucleophilic attack of tertiary amine (the substrate molecule itself) to **4a** occurred to furnish **4a-1**.[16e-h] Subsequently, the proton migration (**4a-1** to **4a-2**), nucleophilic addition (**4a-2** to **4a-3**),[16g,h] 1,2-H shift (**4a-3** to **4a-4**) and elimination of tertiary amine (**4a-4** to **3a**) occurred successively to generate the final product **3a**. Moreover, an alternative path, that including direct hydrogen abstraction of *N*-benzylic C_{sp3}-H by tertiary amine followed by the attack of *N*-benzylic C_{sp3} anion to α-position of allenes, was also possible.

In order to achieve NH-free indoline, reaction of *N*-benzyl product **3e** with 20% Pd/C and H_2 balloon was carried out in EtOAc/AcOH (10/1) at 65 °C. Interestingly, **5a** was obtained in 52% yield (Scheme 6).



Scheme 6 Formation of NH-free indoline

In conclusion, we have developed a novel methodology for the synthesis of 3-alkenyl indolines. The process involves the sequential Pd(0) catalyzed allenylation and tertiary amine self-catalyzed C_{sp3}-H functionalization. Mechanistic investigations suggested that the substrate itself may also serve as a base catalyst for the *N*-benzylic C_{sp3}-H functionalization. This tertiary amine self-catalysis mode provided an attractive reference for the substrates design to improve E-factor[17] of chemicals manufacture.

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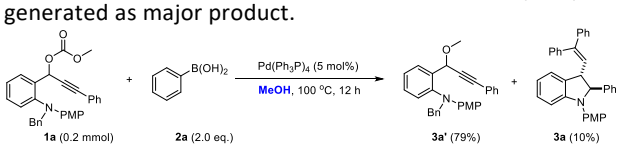
11. Detailed synthetic route of substrate **1**: see SI.
12. Screening of reaction conditions with other Pd catalysts, see SI, Table S1.
13. CCDC 1515762.
14. When methanol was used as the solvent, **3a'** (79%) was generated as major product.



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