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# Palladium-catalyzed [3+2] annulation of allenyl carbinol acetates with C,N-cyclic azomethine imines†

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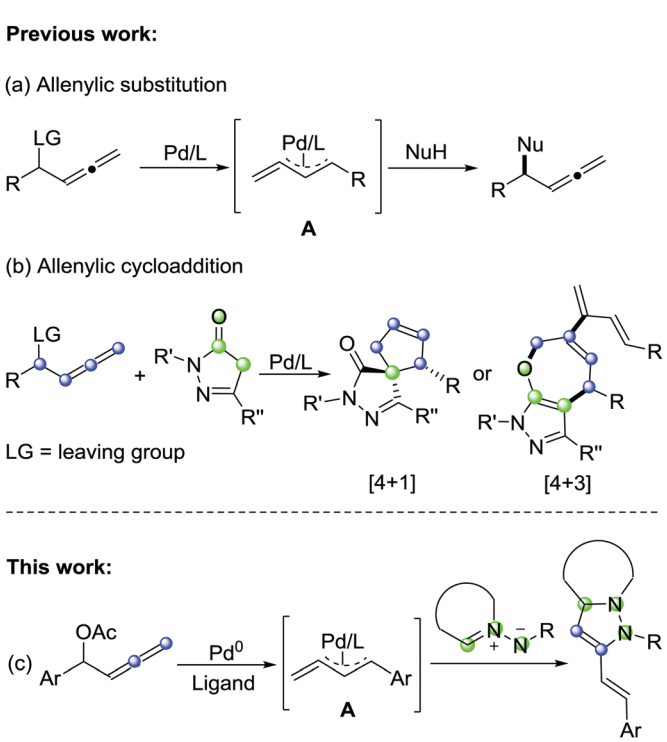
**In this paper, a palladium-catalyzed [3+2] annulation of allenyl carbinol acetates with azomethine imines has successfully been developed under mild reaction conditions, affording biologically interesting tetrahydropyrazoloisoquinoline derivatives in high to excellent yields and with excellent stereoselectivity. The reaction follows a tandem [3+2] cycloaddition/allylation/elimination of AcOH pathway. Allenyl carbinol acetates also reacted well with *in situ* generated azomethine imine under cocatalysis of Ag(I)/Pd(0) catalysts in a similar reaction pathway.**

Transition metal-catalyzed cycloadditions are extremely powerful tools for the convergent synthesis of diverse carbo- and heterocyclic compounds.[1] Readily accessible and versatile allenes are often employed as key reaction partners for the development of various cycloaddition reactions.[2] Among all types of allene compounds, allenyl carbinol esters demonstrated distinctive capability in palladium catalysis and thus have attracted considerable attention in recent years.[2] In general, under palladium catalysis conditions, allenyl carbinol esters generate palladium-butadienyl species **A** having diverse reactivities. Plenty of reports dealt with allenylic substitution reactions of allenyl carbinol esters through reaction of intermediate **A** with a variety of nucleophiles to construct novel allene molecules (Scheme 1a).[3] In comparison, the cycloaddition reaction *via* palladium-butadienyl intermediates was rarely studied.[2] Most recently, utilizing the palladium-butadienyl species from allenyl carbinol esters as four-membered synthons, Shao and coworkers developed Pd-catalyzed asymmetric [4+1] cycloaddition and [4+3] cycloaddition/cross coupling reaction to construct valuable spiro- and bicyclic compounds (Scheme 1b).[4] To the best of our knowledge, allenyl carbinol acetates serving as two-carbon synthons for palladium-catalyzed [3+2] annulation have never been reported. As part of our previous work on the Pd-catalyzed cycloaddition reaction of methylene-TMM[5] and our continuing efforts on cycloaddition reactions,[6] herein, we present the first palladium-catalyzed [3+2] annulation of allenyl carbinol acetates with azomethine imines to furnish biologically interesting functionalized dihydropyrazolo[5,1-*a*]isoquinoline derivatives[7] (Scheme 1c).

We commenced our exploration with allenyl carbinol acetate (**1a**) and C,N-cyclic azomethine imine (**2a**) as model substrates (Table 1). Employing $Pd(dba)_2$ (5 mol%)/$PPh_3$ (11 mol%) as the catalyst, the allenyl carbinol acetate **1a** was reacted with azomethine




Scheme 1 Pd-Catalyzed allenylic substitutions and cycloaddition reactions of allenic esters.

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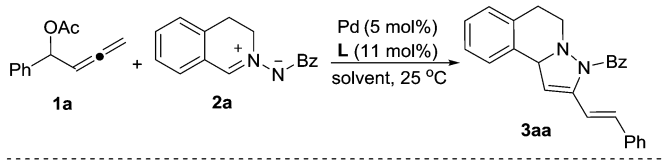
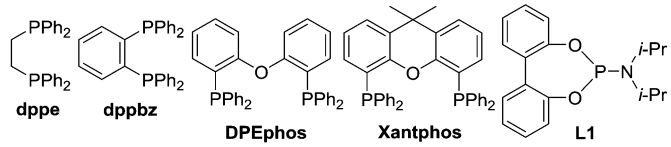
Table 1 Screening of the reaction conditions[a]

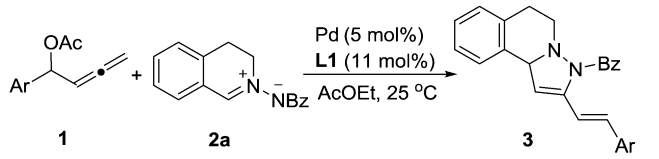



| Entry | L | Solvent | *t*/h | Yield[b] (%) |
|---|---|---|---|---|
| 1 | $PPh_3$ | DCE | 12 | 88 |
| 2 | dppe | DCE | 16 | 89 |
| 3 | dppbz | DCE | 16 | 52 |
| 4 | DPEphos | DCE | 16 | 79 |
| 5 | Xantphos | DCE | 16 | 90 |
| 6 | **L1** | DCE | 12 | 91 |
| 7 | **L1** | DCM | 12 | 90 |
| 8 | **L1** | THF | 24 | 77 |
| 9 | **L1** | $CH_3CN$ | 12 | 76 |
| 10 | **L1** | Toluene | 24 | 87 |
| 11 | **L1** | AcOEt | 12 | 94 |
| 12[c] | **L1** | AcOEt | 12 | 99 |

[a] Unless otherwise indicated, all the reactions were carried out with **1a** (0.20 mmol) and **2a** (0.10 mmol) in 1 mL of solvent at rt using $Pd(dba)_2$ (5 mol%)/**L** (11 mol%) as the catalyst under argon. [b] Isolated yield. [c] 2 mL of solvent was used.

Table 2 Scope of allenyl carbinol acetates **1**[a]




| Entry | Ar | *t*/h | 3 | Yield[b] (%) |
|---|---|---|---|---|
| 1 | Ph (**1a**) | 12 | **3aa** | 99 |
| 2 | 2-$FC_6H_4$ (**1b**) | 16 | **3ba** | 94 |
| 3 | 3-$FC_6H_4$ (**1c**) | 18 | **3ca** | 98 |
| 4 | 4-$FC_6H_4$ (**1d**) | 14 | **3da** | 99 |
| 5 | 2-$ClC_6H_4$ (**1e**) | 16 | **3ea** | 98 |
| 6 | 3-$ClC_6H_4$ (**1f**) | 16 | **3fa** | 99 |
| 7 | 4-$ClC_6H_4$ (**1g**) | 14 | **3ga** | 99 |
| 8 | 2,4-$Cl_2C_6H_3$ (**1h**) | 16 | **3ha** | 93 |
| 9 | 3,4-$Cl_2C_6H_3$ (**1i**) | 19 | **3ia** | 99 |
| 10 | 3,5-$Cl_2C_6H_3$ (**1j**) | 19 | **3ja** | 97 |
| 11 | 2-$BrC_6H_4$ (**1k**) | 18 | **3ka** | 82 |
| 12 | 3-$BrC_6H_4$ (**1l**) | 18 | **3la** | 99 |
| 13 | 4-$BrC_6H_4$ (**1m**) | 18 | **3ma** | 92 |
| 14 | 2-$MeC_6H_4$ (**1n**) | 18 | **3na** | 99 |
| 15 | 3-$MeC_6H_4$ (**1o**) | 17 | **3oa** | 98 |
| 16 | 4-$MeC_6H_4$ (**1p**) | 17 | **3pa** | 99 |
| 17 | 2-$MeOC_6H_4$ (**1q**) | 12 | **3qa** | 91 |
| 18 | 3-$MeOC_6H_4$ (**1r**) | 18 | **3ra** | 97 |
| 19 | 4-$MeOC_6H_4$ (**1s**) | 14 | **3sa** | 85 |
| 20 | 2-Naphthyl (**1t**) | 16 | **3ta** | 98 |

[a] All the reactions were performed with **1** (0.20 mmol), **2a** (0.1 mmol), $Pd(dba)_2$ (0.005 mmol) and **L1** (0.011 mmol) in ethyl acetate (2 mL) at 25 °C under argon. [b] Isolated yield.

imine **2a** in 1,2-dichloroethane (DCE) at 25 °C (entry 1). The reaction completed in 12 h to give the [3+2] cycloadduct in 88% yield. According to this initial result, we next evaluated several diphosphine ligands and a phosphoramidite ligand (**L1**) (entries 2–6). Most ligands resulted in high yields (entries 2 and 4–6), except for dppbz (entry 3). Ligand **L1** proved to be a promising ligand, yielding the 2,3-dihydropyrazole derivative **3aa** in 91% yield (entry 6). Using the **L1** ligand, we then screened several solvents such as dichloromethane (DCM), THF, $CH_3CN$, toluene, and ethyl acetate (AcOEt) (entries 7–11). The results revealed that ethyl acetate was the optimal solvent, leading to a 94% yield (entry 11). Additionally, when 2 mL of ethyl acetate was used to increase the solubility of **2a** under otherwise identical conditions, the yield was increased to 99% yield (entry 12). Consequently, we established the optimized reaction conditions as follows: using $Pd(dba)_2$ (5 mol%) and phosphoramidite **L1** (11 mol%) as the catalyst in 2 mL of ethyl acetate at 25 °C.

Subsequently, under the best reaction conditions, we applied this [3+2] annulation reaction to a variety of substituted allenyl carbinol acetates **1** for construction of 2,3-dihydropyrazole derivatives (Table 2). In general, this protocol can be implemented for a series of allenyl carbinol acetates **1** and the corresponding products were obtained in good to excellent yields (82–99%) (entries 1–20). The halides including fluorine, chlorine, and bromine as well as electron-donating groups such as methyl and methoxyl and their substitution position on the benzene ring had no significant impact on reaction efficiency (entries 1–19). In addition, naphthyl-substituted allenyl carbinol acetate **1t** executed the reaction to give 98% yield of product **3ta** (entry 20). The products' structures were resolved using X-ray crystallographic data of product **3aa**.[8] Only *E*-isomers were produced in all the cases (entries 1–20).

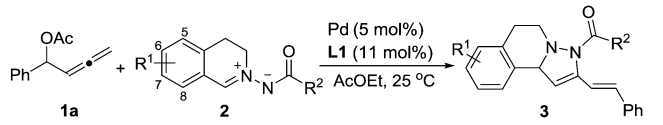
Next, diversified azomethine imines were synthesized and evaluated in this [3+2] annulation (Table 3). Several halogenated and methyl-substituted azomethine imines furnished the corresponding products in high to excellent yields (entries 1–8). A special tricyclic azomethine imine (**2j**) acted efficiently, producing 99% yield of the product (entry 9). Azomethine imines with different benzoyl protecting groups performed the reaction well (entries 10–16). The substrate bearing an acetyl protecting group also worked, delivering the corresponding product in 65% yield (entry 17).

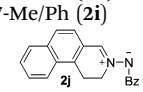
In particular, allenyl carbinol acetate also reacted well with *in situ* generated azomethine imine (Scheme 2). In the presence of AgOTf, hydrazide **2s** could easily be transformed into azomethine imine *in situ*, which then reacted with allenyl carbinol acetate **1a** under catalysis of $Pd(PPh_3)_4$ in one-pot to produce the desired product **3as** in 72% yield.

An asymmetric version of the reaction was also investigated (Table 4). Several axially chiral phosphoramidite ligands were tried (entries 1–4). Using **S3** as a chiral ligand, a moderate 51% ee was obtained (entry 3). A screening of several solvents such as DCM, THF, $CH_3CN$, toluene, $Et_2O$ and $CF_3Ph$ (entries 5–10) revealed that the reaction in toluene led to 87% yield and 80% ee (entry 8). However, a further attempt to improve enantioselectivity failed.

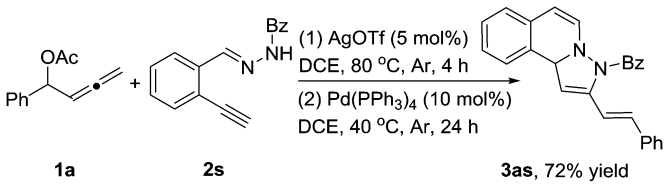
 

Table 3 Scope of the C,N-cyclic azomethine imines **2**[a]




| Entry | $R^1/R^2$ | $t$/h | 3 | Yield[b] (%) |
|---|---|---|---|---|
| 1 | 7-F/Ph (**2b**) | 26 | **3ab** | 70 |
| 2 | 5-Cl/Ph (**2c**) | 26 | **3ac** | 76 |
| 3 | 6-Cl/Ph (**2d**) | 23 | **3ad** | 95 |
| 4 | 5-Br/Ph (**2e**) | 26 | **3ae** | 80 |
| 5 | 6-Br/Ph (**2f**) | 20 | **3af** | 91 |
| 6 | 7-Br/Ph (**2g**) | 24 | **3ag** | 75 |
| 7 | 5-Me/Ph (**2h**) | 17 | **3ah** | 85 |
| 8 | 7-Me/Ph (**2i**) | 17 | **3ai** | 92 |
| 9 |  | 24 | **3aj** | 99 |
| 10 | H/4-$FC_6H_4$ (**2k**) | 16 | **3ak** | 90 |
| 11 | H/4-$ClC_6H_4$ (**2l**) | 12 | **3al** | 99 |
| 12 | H/4-$BrC_6H_4$ (**2m**) | 12 | **3am** | 99 |
| 13 | H/4-$MeC_6H_4$ (**2n**) | 12 | **3an** | 92 |
| 14 | H/4-$MeOC_6H_4$ (**2o**) | 16 | **3ao** | 78 |
| 15 | H/4-$CF_3C_6H_4$ (**2p**) | 16 | **3ap** | 98 |
| 16 | H/4-$NO_2C_6H_4$ (**2q**) | 19 | **3aq** | 88 |
| 17 | H/Me (**2r**) | 16 | **3ar** | 65 |

[a] All the reactions were performed with **1a** (0.20 mmol), **2** (0.1 mmol), $Pd(dba)_2$ (0.005 mmol) and **L1** (0.011 mmol) in ethyl acetate (2 mL) at 25 °C under argon. [b] Isolated yield.



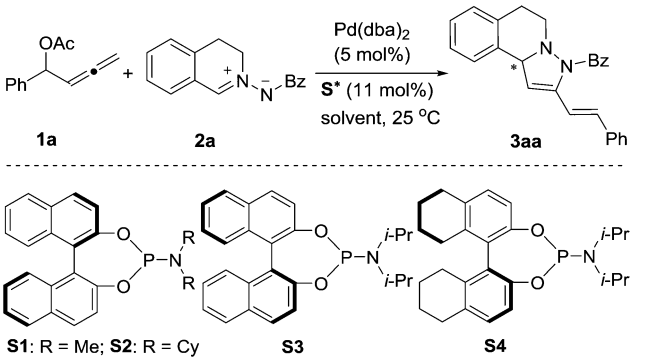

Scheme 2 Ag(I)/Pd(0)-Catalyzed one-pot intramolecular cyclization/[3+2] cycloaddition reaction.

As shown in Scheme 3, Pd-catalyzed [3+2] annulation operated successfully on a 2 mmol scale (0.5 g) and completed in 12 h under the standard reaction conditions to produce product **3aa** in 97% yield. Product **3aa** was subjected to hydrogenation promoted by Pd/C, giving products **4a** and **4b** in 54% and 15% yield, respectively. $SmI_2$-Mediated ring-opening led to tetrahydroisoquinoline **5** in 58% yield.

To investigate the mechanism of this reaction, control experiments were designed and performed (Scheme 4). Without the use of palladium catalyst and ligand **L1**, no annulation product **3aa** was observed. When only phosphine ligand **L1** was employed under similar standard conditions without $Pd(dba)_2$, the desired product **3aa** could also not be observed. These results suggest that the palladium catalyst formed from $Pd(dba)_2$ and **L1** did catalyze this reaction and phosphine could not work as an organocatalyst to promote this reaction. In fact, the successful asymmetric reaction in Table 4 has proved that the palladium complex formed from $Pd(dba)_2$ and phosphine worked as the catalyst in this reaction.

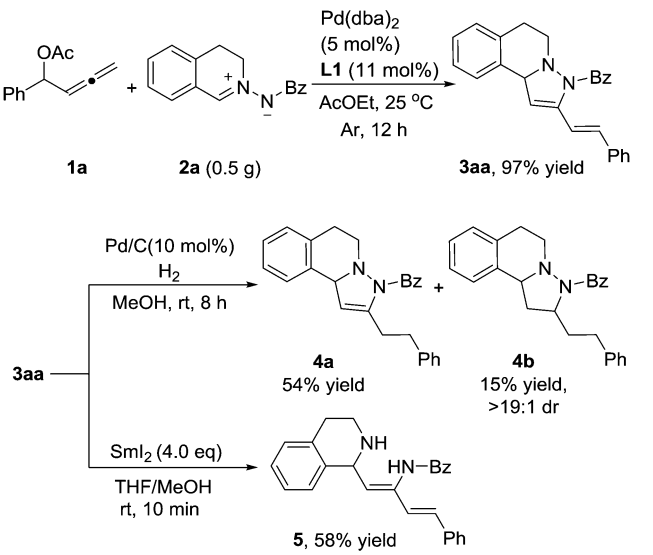
According to our previous work,[5] some related reports[2,4] and the results in Scheme 4, we described a logical mechanism in Scheme 5. Pd-Butadienyl intermediate **I** from allenyl carbinol

Table 4 Investigation on asymmetric variants[a]



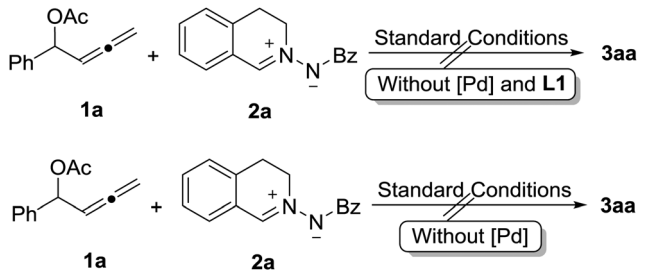

| Entry | S*x* | Solvent | $t$/h | Yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|---|
| 1 | **S1** | DCE | 24 | 90 | −7 |
| 2 | **S2** | DCE | 48 | 70 | −40 |
| 3 | **S3** | DCE | 12 | 91 | 51 |
| 4 | **S4** | DCE | 36 | 80 | 41 |
| 5 | **S3** | DCM | 12 | 90 | 61 |
| 6 | **S3** | THF | 20 | 77 | 67 |
| 7 | **S3** | $CH_3CN$ | 10 | 76 | 47 |
| 8 | **S3** | Toluene | 20 | 87 | 80 |
| 9 | **S3** | $Et_2O$ | 12 | 86 | 79 |
| 10 | **S3** | $CF_3Ph$ | 12 | 87 | 77 |

[a] Unless otherwise indicated, all the reactions were performed with **1a** (0.20 mmol) and **2a** (0.10 mmol) in the presence of $Pd(dba)_2$ (5 mol%) and a chiral ligand (11 mol%) in 1 mL of solvent. [b] Isolated yield. [c] Determined by HPLC analysis using a chiral stationary phase.

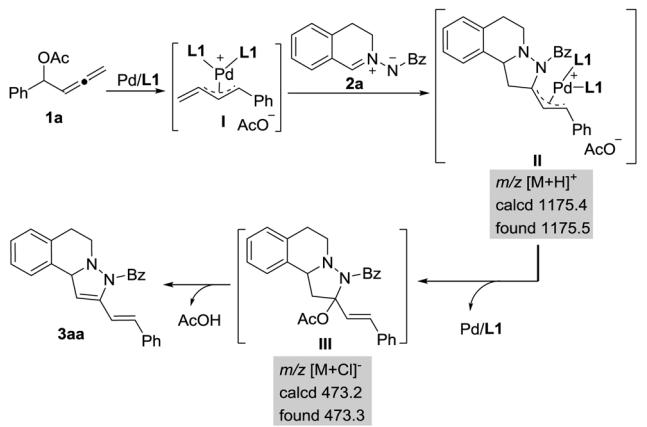



Scheme 3 Scale-up reaction and further transformations of the cycloadduct.

acetate **1a** undergoes [3+2] cycloaddition with azomethine imine **2a**, affording intermediate **II**. Subsequent allylation of the acetyloxy anion gave intermediate **III** and regenerated the Pd catalyst. Further elimination of acetic acid generated product **3aa**. Furthermore, we conducted a mass spectrometry analysis study on the reaction mixture. As illustrated in Scheme 5, the key species **II** and **III** have been successfully detected, further elucidating the rationalization of the proposed pathway.




Scheme 4 Control experiments.




Scheme 5 A proposed mechanism.

In conclusion, palladium-catalyzed [3+2] annulation has been accomplished under mild reaction conditions to give the functionalized tetrahydropyrazoloisoquinoline derivatives in good to excellent yields. The reaction follows a tandem [3+2] cycloaddition/allylation/elimination of AcOH pathway. This is the first example of allenyl carbinol acetates acting as C2 synthons for annulation reactions.

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## Conflicts of interest

There are no conflicts to declare.

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8 Crystallographic data for **3aa** have been deposited with the Cambridge Crystallographic Data Centre as deposition number CCDC 1923209†.

 