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Palladium−NHC-Catalyzed Allylic Alkylation of Pronucleophiles with Alkynes

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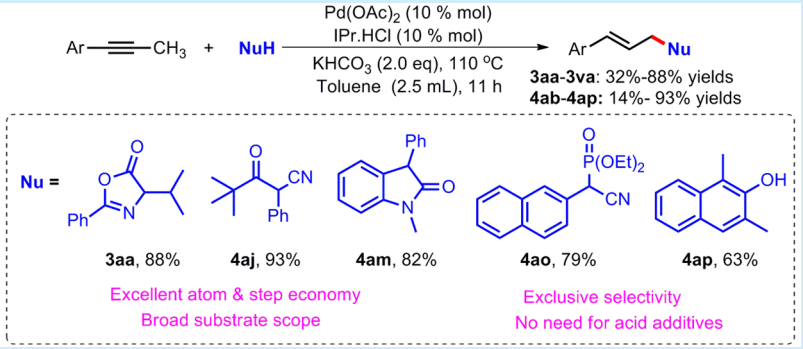
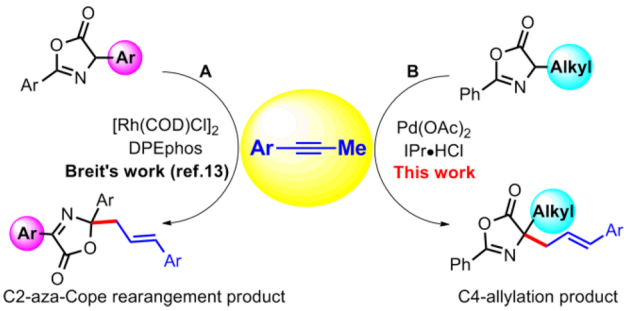
Supporting Information



ABSTRACT: The palladium−N-heterocyclic carbene (NHC)-catalyzed allylic alkylation of various pronucleophiles with alkynes has been accomplished under mild conditions. The protocol exhibits broad functional group compatibility and high atom economy. Moreover, the catalytic process avoids the use of external oxidants and acid as additives.

The allylic unit has always attracted the research interest of chemists because of its diverse range of transformations in synthetic chemistry. Consequently, a great deal of effort has been devoted to applying distinct strategies to introduce the allylic moiety into various molecules over the past decades.[1] Among these strategies, transition-metal-catalyzed allylic substitution reactions[2] and direct allyl C−H oxidation reactions[3] have evolved into effective synthetic tools that have been widely applied in organic synthesis. Although tremendous progress has been achieved, the efficiency of these strategies is still limited to prefunctionalization of substrates[1c,4] or the use of an external equivalent of oxidant is required.[3e,5] Therefore, the development of appropriate methodologies that avoid these limitations is particularly important. As an ideal electrophilic π-allyl precursor, alkynes have attracted the attention of chemists and they have been widely used for sp^3 C−X (X = C, N, O, etc.) coupling reactions. This is because of the high atom economy of the approach, and because the preinstallation of an allylic leaving group or the use of external equivalent oxidants is avoided.[6] In the past decade, substantial efforts have been made to develop highly selective allylic C−H functionalization of alkynes. To date, numerous excellent results have been achieved, including hydroamination,[7] oxygenation,[8] alkylation,[9] arylation,[10] dearomatization,[11] and others.[12] Among these, azlactone derivatives as one type of excellent nucleophile were employed in the allyl alkylation of alkynes by Breit's group in 2017.[13] In the reaction, rhodium-catalyzed regioselective addition of azlactones to internal alkynes and subsequent aza-Cope rearrangement for the construction of synthetically useful *N,O*-acetal derivatives are performed (Scheme 1, **A**); however, regrettably, azlactones

Scheme 1. Alkynes Involved in Allylation of Azlactones



that were substituted by an alkyl group at C-4 position did not work in the reaction. Herein, we report on the palladium−*N*-heterocyclic carbene (NHC)-catalyzed allylic alkylation of azlactone derivatives with alkynes to afford the C4-allyled products (Scheme 1, **B**). Our method provides a useful complement to the rhodium-catalyzed allylation, and the C-4 alkyl substituted azlactones exhibit favorable reaction activity. Moreover, the other pronucleophiles such as α-cyanoketone, oxindole, α-cyanophosphonate, and β-naphthol also suitable for this transformation. In particular, NHCs, as a type of

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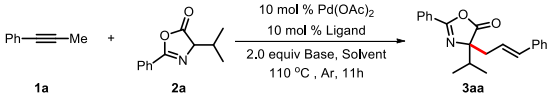
unique ligand, are used for the first time in the catalytic allyl alkylation of alkynes, wherein they exhibit exclusive activity and regioselectivity.

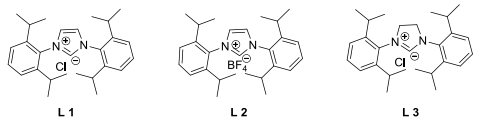
In the initial study, we selected prop-1-yn-1-ylbenzene (**1a**) and 4-isopropyl-2-phenyloxazol-5(4H)-one (**2a**) as model substrates to optimize the reaction conditions. In the presence of IPr·HCl, $KHCO_3$, and $PhCO_2H$ as the additive, a series of palladium catalysts were examined in toluene at 110 °C under argon for 11 h; the results revealed that $Pd(OAc)_2$ was the best catalyst, giving the allylic alkylated product **3aa** in 88% yield (see Table S1 for details). Control experiments indicated that the precatalyst, *N*-heterocyclic carbene ligand, and base were essential to this transformation; $PhCO_2H$ was not required (see Table S1 for details). Encouraged by these results, we further screened the reaction parameters including solvents, ligand, base, and others factors under an argon atmosphere extensively, in the absence of benzoic acid as the additive. Screening of bases showed that $KHCO_3$ proved to be most efficient, giving **3aa** in 88% yield (Table 1, entries 1−4; see Table S2 for details). A range of NHCs were then tested, and the results showed that **L1** was the best while indicating the importance of the electronic effect of the NHC ligands. We next screened the phosphine ligands and found that the use of PPh_3 could produce **3aa** in 62% yield, whereas both BINAP and DPPP exhibited inferior catalytic activity (Table 1, entries 7−9). Subsequently, other solvents such as chlorobenzene, dioxane, DME, and DCE were also examined, and toluene was established as the best choice (Table 1, entries 10−13). After screening the reaction time and catalyst loadings (Table 1 entries 14 and 15; see Table S2 for details), the optimized reaction conditions were established as $Pd(OAc)_2$ (10 mol %), IPr·HCl (10 mol %), and $KHCO_3$ (2.0 equiv) in toluene at 110 °C for 11 h.

Table 1. Optimization of Reaction Conditions[a,b]



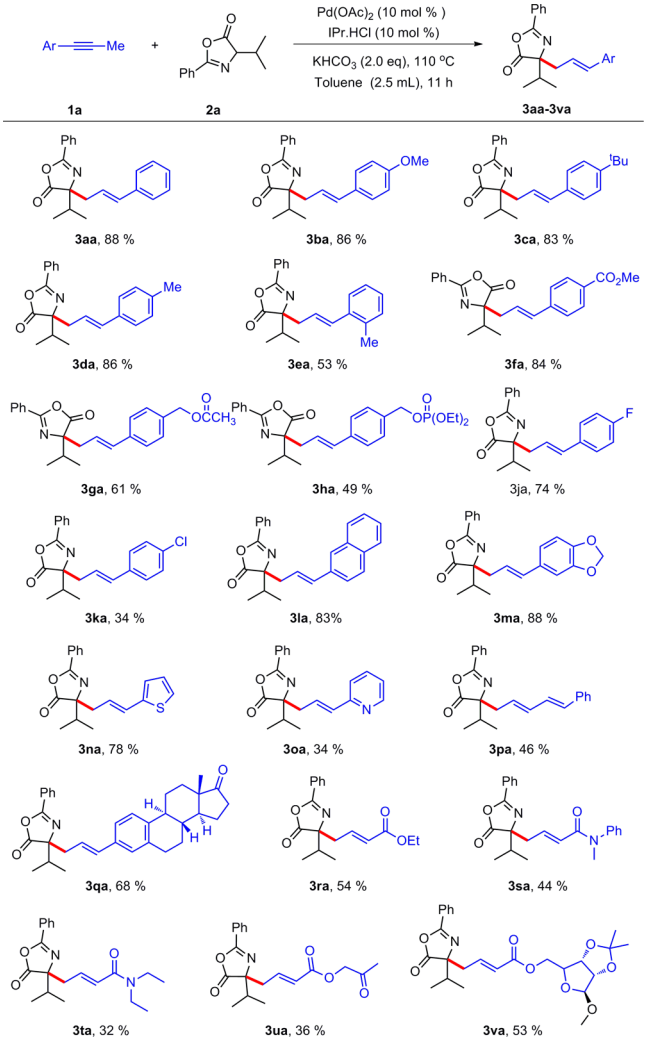
Entry	Ligand	Base	Solvent	Yield [%]
1	**L1**	K_2CO_3	Toluene	83
2	**L1**	Na_2CO_3	Toluene	55
3	**L1**	K_3PO_4	Toluene	50
4	**L1**	$KHCO_3$	Toluene	88
5	**L2**	$KHCO_3$	Toluene	83
6	**L3**	$KHCO_3$	Toluene	22
7	PPh_3	$KHCO_3$	Toluene	62
8	BINAP	$KHCO_3$	Toluene	trace
9	DPPP	$KHCO_3$	Toluene	19
10	**L1**	$KHCO_3$	Chlorobenzene	trace
11	**L1**	$KHCO_3$	Dioxane	86
12	**L1**	$KHCO_3$	DME	82
13	**L1**	$KHCO_3$	DCE	trace
14	**L1**	$KHCO_3$	Toluene	67[c]
15	**L1**	$KHCO_3$	Toluene	78[d]

[a]Reaction conditions: **1a** (0.4 mmol), **2a** (0.2 mmol), $Pd(OAc)_2$ (10 mol %), ligand (10 mol %), and base (2.0 equiv) in solvent (2.5 mL) at 110 °C under Ar for 11 h. [b]Isolated yield. [c]$Pd(OAc)_2$ (5 mol %), IPr·HCl (5 mol %). [d]6 h.



With the optimized conditions in hand, we then examined the substrate scope of the reaction with respect to the alkynes; the results are summarized in Scheme 2. Thus, alkynes bearing either electron-donating or electron-withdrawing substituents on the phenyl ring, such as methoxyl, *tert*-butyl, methyl, diethyl (methyl) phosphate, fluoro, chloro, and ester groups, were compatible with the catalytic system and proceeded smoothly to give the corresponding allylation products **3aa**−**ka** in good to excellent yields. When the phenyl group was displaced with a naphthalene moiety, the linear allylation product **3la** was also isolated in 83% yield. As another reaction partner, 5-(prop-1-yn-1-yl)benzo[*d*][1,3]dioxole could also be smoothly converted into the desired product **3ma** in 88% yield. Moreover, heteroaromatic alkynes such as 2-thiophene and 2-pyridine were well tolerated in this transformation. To our delight, skipped enynes and estrone-derived alkynes were also suitable substrates for the allylation under the optimized reaction

Scheme 2. Substrate Scope of of the Reaction with Respect to Alkynes[a,b]



[a]Reaction conditions: **1a** (0.4 mmol), **2a** (0.2 mmol), $Pd(OAc)_2$ (10 mol %), IPr·HCl (10 mol %), and $KHCO_3$ (2.0 equiv) in toluene (2.5 mL) at 110 °C under Ar for 11 h. [b]Isolated yields.

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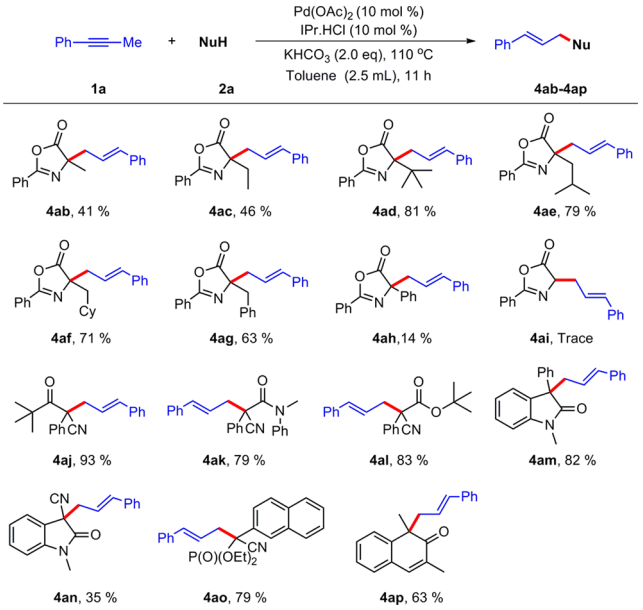
conditions, which afforded the desired products **3pa** and **3qa** in moderate yields. Notably, 2-butynoic acid derivatives were also well tolerated in the practical allylation reaction, affording the desired products **3ra**–**va** in moderate yields.

We then examined the generality of the reaction with pronucleophiles under the optimized reaction conditions; the results are shown in Scheme 3. The substrate scope of the

Scheme 3. Substrate Scope of the Reaction with Respect to Nucleophiles[a,b]

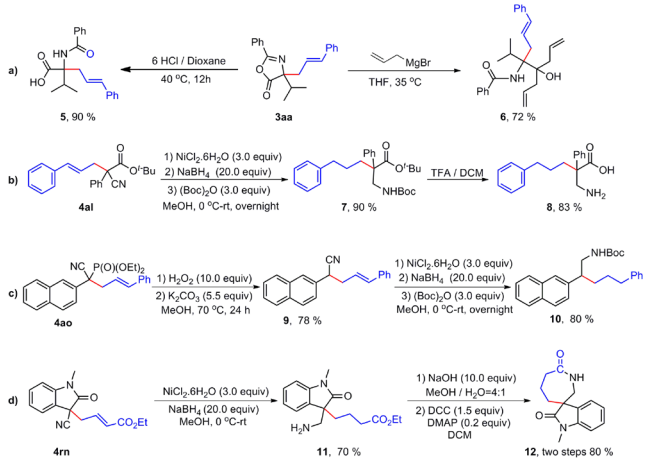


[a]Reaction conditions: **1a** (0.4 mmol), **2a** (0.2 mmol), $Pd(OAc)_2$ (10 mol %), IPr·HCl (10 mol %), and $KHCO_3$ (2.0 equiv) in toluene (2.5 mL) at 110 °C under Ar for 11 h. [b]Isolated yields.

reaction with various azlactones derived from amino acids with 1-phenyl-1-propyne (**1a**) under the optimal conditions was first examined. Specifically, azlactones containing methyl (**2b**), ethyl (**2c**), *tert*-butyl (**2d**), isobutyl (**2e**), cyclohexylmethyl (**2f**), or benzyl (**2g**) groups participated in this transformation, affording the corresponding allyl alkylation products **4ab**–**ag** in moderate to good yields. In contrast, 2,4-diphenyloxazol-5(4*H*)-one (**2h**) as a substrate only gave the expected product **4ah** in 14% yield, probably because of the electric effect imparted by the phenyl group. Meanwhile, substrates bearing a cyano group were also compatible with the reaction conditions and provided **4aj**–**al** in 79–93% yields. Furthermore, oxindole derivatives were also investigated and delivered the target products **4am** and **4an** in 82% and 35% yields, respectively. When diethyl (cyano(naphthalen-2-yl)methyl)phosphonate (**2o**) was used as the substrate, the reaction also proceeded smoothly to furnish the product **4ao** in 79% yield. To our delight, 1,3-dimethylnaphthalen-2-ol (**2p**) as the reaction partner under the optimal reaction conditions gave the dearomatization product **4ap** in 63% yield with excellent selectivity. Unfortunately, when but-1-yn-1-ylbenzene was applied in the reaction, the result showed that no product was obtained.

To demonstrate the utility of the reaction products, a range of transformations of the functionalized allylation products were carried out. First, the ring-opening hydrolysis of azlactone **3aa** by treatment with 6 N HCl in dioxane produced the corresponding *N*-protected amide **5** in 90% yield (Scheme 4a). Moreover, **3aa** was transformed into *N*-(5-allyl-5-hydroxy-4-

Scheme 4. Derivatization of Reaction Products



isopropyl-1-phenylocta-1,7-dien-4-yl)benzamide (**6**) through the addition of allylmagnesium bromide to azlactone (Scheme 4a). Next, *tert*-butyl 2-(((*tert*-butoxycarbonyl)amino)methyl)-2,5-diphenylpentanoate (**7**) could be obtained by performing the reduction reaction of **4al** at room temperature with $NiCl_2 \cdot 6H_2O/NaBH_4$ in methanol and then was efficiently converted into the all-carbon quaternary β-amino acid derivatives **8** upon treatment with TFA in DCM (Scheme 4b). On the other hand, with a basic solution of H_2O_2, the alkylation product **4ao** could be transformed into the α-monoallylation nitrile compound **9**, which is a very important intermediate[14] that could be further transformed into Boc-protected amine **10**, which included the exhaustive reduction of the olefinic and the cyano groups (Scheme 4c). The spirocyclic oxindole skeleton is widely found in pharmaceutical molecules and natural products, and it exhibits unique chemical characteristics.[15] Thus, when ethyl 2-but-ynoate (**1r**) was used as the substrate, the allylation reaction with 1-methyl-2-oxoindoline-3-carbonitrile (**2n**) could proceed smoothly and produce the corresponding product in relatively higher yield than **4an**. Meanwhile, reaction of the oxindole **4rn** with $NiCl_2 \cdot 6H_2O/NaBH_4$ furnished the amino oxindole **11** in 70% yield; subsequent hydrolysis of the ester and intramolecular condensation reaction of the carboxylic acid with the amine generated the spiro-fused compound **12**, which represents one of the spirocyclic indole frameworks as a versatile compound (Scheme 4d).

To illustrate the formation of allene intermediates, we further investigated the reaction of phenyl allene (**1x**) with 4-isopropyl-2-phenyloxazol-5(4*H*)-one (**2a**) under the optimized reaction conditions, and found that the target coupling product **3aa** was obtained in 78% yield (Scheme 5). This result implied that the phenyl allene intermediate may be involved in this transformation. Based on previous reports[9a,16] and on the experimental results, a plausible mechanism was proposed. Initially, the active palladium catalyst **A** is generated in situ through ligand exchange of $Pd(OAc)_2$ with free IPr·HCl in the presence of base. Subsequently, a hydridopalladium intermediates **B** is presumably generated in situ and *syn*-migratory insertion of **B** into alkyne **1a** furnished the intermediate **C**. Next, phenyl allene **D** is generated via β-hydrogen elimination

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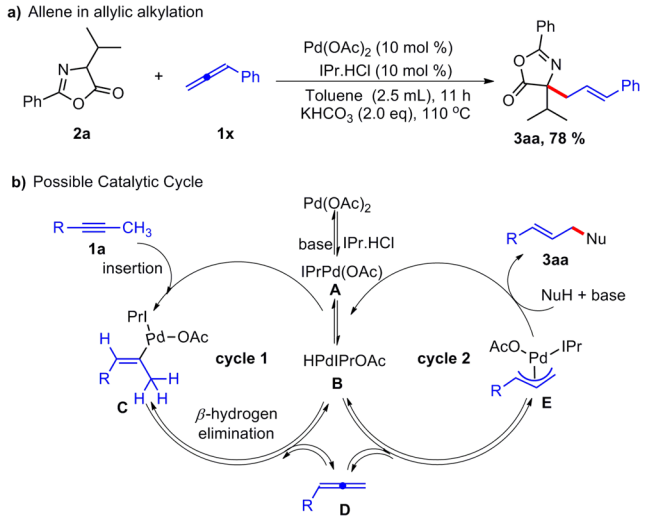
Scheme 5. Possible Catalytic Cycle



of **C** along with regeneration of the hydridopalladium intermediate **B**. Finally, migratory insertion of **B** into phenyl allene **D** furnished the highly active π-allylpalladium(II) electrophile **E**, which was attacked by pronucleophiles in the presence of base to give the target product **3aa** and the active palladium catalyst **A** is generated, completing the catalytic cycle.

In conclusion, palladium−NHC-catalyzed allylic alkylation of various pronucleophiles with alkynes under mild conditions has been achieved for the first time. This system is characterized by a broad substrate scope, wide functional group tolerance, and high atom economy. Importantly, 2-butynoic acid derivatives and skipped enynes were also tolerated, and dearomatization products could be obtained from the reaction of β-naphthol with alkyne under the optimized reaction conditions.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02937.

Experimental details and characterization data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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