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Palladium-catalyzed highly atom-economic allylation of oxindoles with vinyl cyclopropanes[†]

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A highly atom-economic allylation of oxindoles with vinyl cyclopropanes catalyzed by Pd(PPh₃)₄ has been developed, which set up a practical venue for the installation of an all-carbon quaternary center at the 3-position in oxindoles under mild reaction conditions. Importantly, the reaction proceeded well without any additives and no waste produced, affording linear products with high regioselectivities (> 20:1). Enantioselective allylic alkylation has also been realized to provide the desired products in good yields and 35% ee.

The 3,3-disubstituted oxindoles are ubiquitous in alkaloid natural products and pharmaceutical compounds.[1] Many of these compounds, such asmollenine,[2] physostigmine,[3] and flustramine B,[4] contain an allyl chain at the C3 position of oxindole skeletons. This structural motif could be constructed in an effective fashion utilizing Trost allylic alkylation methodology (Scheme 1, **a**).[5] Traditionally, such kind of transformation took place employing activated allylic alcohol derivatives as precursor of π-allyl transition metal intermediate **T** that inevitably generates stoichiometric amount of waste.[6] And in most cases the addition of a large amount of base for the formation of the nucleophilic enolates is necessary. From the standpoint of green chemistry, more atom-/step-economic and sustainable approach towards these synthetic purposes is still increasingly in demand.[7] In our previous work,[8] through the direct use of allylic alcohol instead of its derivatives in the allylation of oxindoles under Pd catalysis with 5 mol% PhCO₂H as co-catalyst, the degree of atom economy was enormously improved due to only water is formed as by-product (Scheme 1, **b**).[8a] On the basis of these achievements, we wondered whether vinyl cyclopropanes
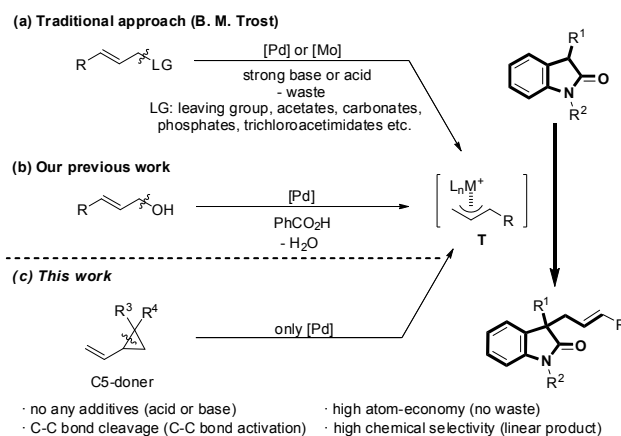
Scheme 1 Construction of 3,3-disubstituted oxindoles via palladium-catalyzed allylic alkylation.

(VCPs)[9] could be used as simple reactant for the synthesis of biological important oxindoles bearing an all-carbon quaternary center at the C3 position via palladium-catalyzed allylic alkylation pathway.

VCPs recently emerged as a family of useful organic synthons, which can be transformed easily into allyl metal complex **T** through β-carbon elimination (C-C bond activation) in the presence of low-valent transition metals. However, most investigations into the reactivity of these allyl metal complexes have centered on the [3+2] cycloaddition[10] with olefins or other dipolarphiles, while nuleophilic addition to afford linear or branched ring-opened products is far less established. In 2009, Fürstner group reported an example of the addition of vinyl cyclopropanes with Grignard reagents by iron catalysis, affording the linear products with moderate selectivity.[11] Later, Plietker and co-workers showed that the reaction between vinyl cyclopropanes and soft carbon nucleophiles could occur with Bu₄N[Fe(CO)₃(NO)] as catalyst.[12] Szabó et al,[13a-b] Hyland et al,[14] and Guo et al[15] independently developed palladium catalyzed ring-opening process of vinyl cyclopropanes with boronates, boronic acids, and purines serving as another

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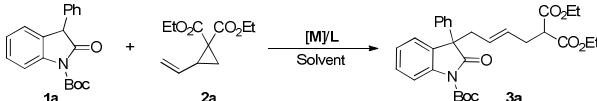[c.] University of Chinese Academy of Sciences, Beijing 100049, P. R. China
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reaction partners, respectively. Up to date, allylic alkylation between vinyl cyclopropanes and carbon nucleophiles by palladium catalysis has scarcely been reported.[16] In this article, we presentthe preliminary results on the direct allylic alkylation reaction of oxindoles with vinyl cyclopropanes in place of allylic alcohol and their derivatives under mild reaction conditions. Importantly, the reaction proceeded well catalyzed by Pd[0] without additives (base or acid), and no any waste produced, affording the linear products with superior selectivity over the branched products, which offers an highly atom-/step-economic route for the synthesis of 3,3-disubstitued oxindoles (Scheme 1, **c**).

Table 1 Optimization of the reaction conditions for the allylation of oxindole **1a** with vinyl cyclopropane **2a**[a]

| Entry	Cat. [mol%]	L [mol%]	Solvent	Yield[b]	L/B[c]
1	Fe(acac)$_3$ [5]	PPh$_3$ [10]	Toluene	-	-
2	Cu(OAc)$_2$ [5]	-	Toluene	-	-
3	Ni(AcAc)$_2$ [5]	-	Toluene	-	-
4	Sc(OTf)$_3$ [5]	PPh$_3$[10]	Toluene	-	
5	Mn(OAc)$_2$ [5]	PPh$_3$[10]	Toluene	-	-
6	Pd(PPh$_3$)$_4$[10]	-	Toluene	99%	> 20:1
7	Pd(PPh$_3$)$_4$[10]	-	THF	99%	> 20:1
8	Pd(PPh$_3$)$_4$[10]	-	Dioxane	91%	> 20:1
9	Pd(PPh$_3$)$_4$[10]	-	Hexane	-	-
10	Pd(PPh$_3$)$_4$[10]	-	PhNO$_2$	-	-
11	Pd(PPh$_3$)$_4$[10]	-	PhCl	-	-
12	Pd(PPh$_3$)$_4$[5]	-	THF	99%	> 20:1
13	Pd(PPh$_3$)$_4$[2]	-	THF	97%[d]	> 20:1
14	Pd(PPh$_3$)$_4$[1]	-	THF	80%	> 20:1

[a] Reaction conditions: oxindole **1a** (0.1mmol), vinyl cyclopropane **2a** (0.12mmol, 1.2 equiv.), catalyst and ligand in 1 mL of solvent at 25 °C for 3 h under nitrogen atmosphere. [b] Yield was determined by NMR analysis. [c] The L/B ratio was determined by ^{1}H NMR analysis. [d] Isolated yield.

Initially, the studies were carried out to examine the catalytic activities of many different metals to the model reaction of oxindole **1a** with vinyl cyclopropane **2a** in toluene at room temperature. The desired product was not detected under catalysis of 5 mol% of Fe(acac)$_3$ with PPh$_3$ as the ligand (Table 1, entry 1). Other metal salts including Cu(OAc)$_2$, Ni(AcAc)$_2$, Sc(OTf)$_3$, Mn(OAc)$_2$, and Pd(PPh$_3$)$_4$ were then screened, and excitingly a conversion of up to 99% with a linear/branched (L/B) ratio of > 20:1 for **3a** was achieved when 10 mol% Pd(PPh$_3$)$_4$ was utilized as catalyst (entries 2-6). Toluene and THF were proved to be equally superior reaction media than other solvents (entries 6-11). The amount of catalyst Pd(PPh$_3$)$_4$ can be reduced to 2 mol% while maintaining the best outcomes, **3a** was isolated in 97% yield (entries 12-13). Further reducing of the catalyst loading to 1 mol% is detrimental to the reaction results (entry 14).

Having established the optimized reaction conditions, we investigated the generality of this alkylation by variation of

oxindoles with vinyl cyclopropane **2a** as another reaction partner and the results were showed in scheme 2.

**Scheme 2** Oxindole scope with vinyl cyclopropane **2a** as the nucleophile[a]
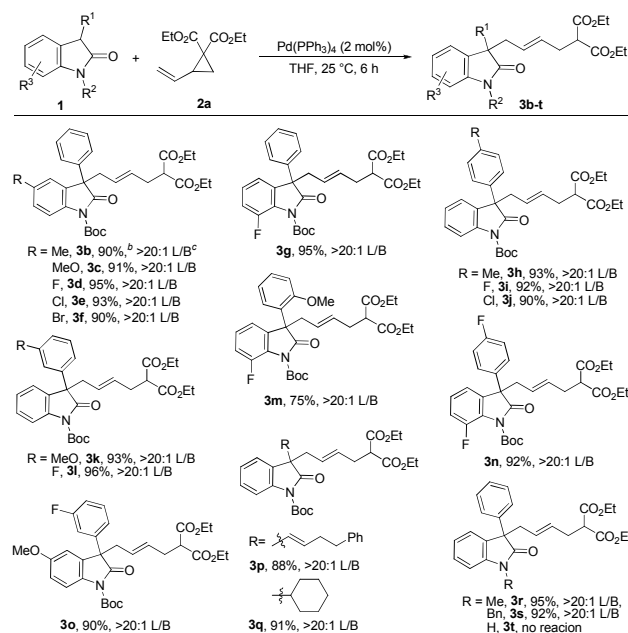
[a] Reaction conditions: oxindole **1** (0.3 mmol), vinyl cyclopropane **2a** (0.36 mmol, 1.2 equiv.), Pd(PPh$_3$)$_4$ (2 mol%) in 2 mL of THF at 25 °C for 6 h under nitrogen atmosphere. [b] Isolated yields. [c] The L/B ratio was determined by ^{1}H NMR analysis.

Oxindoles possessing a substituent such as methyl, methoxyl or halogen at the 5-position are applicable to this process, and the reaction proceeded smoothly to give the desired products **3b-f** in excellent yields and regioselectivities (>90% yields, >20:1 L/B ratios). Meanwhile, the introduction of fluorine element at the C7 position had no any obvious influence on the reaction outcomes and **3g** was obtained with more than 20:1 L/B ratio as well. To our delight, the same outstanding results were achieved for a variety of 3-aryl substituted oxindoles (**1h-1l**), regardless of the electronic property of substituent in the aromatic ring at the C3 or C4 position. Crucially, substrates can be extend to multi-substituted oxindoles, allylated products **3m-3o** can be isolated readily in high yields and excellent L/B ratios. We were pleasant to find that vinyl group did not hamper the reactivity of the oxindoles, 88% yield and perfect L/B ratio of >20:1 was acquired for product **3p** from this transformation. Significantly, dialkylated **3q** can be composed in 91% yield with more than 20:1 L/B ratio when 3-cyclohexane oxindole **1q** was utilized as reaction reactant. The allylic alkylation also worked well with the existence of other *N*-protecting groups, namely methyl (**3r**) and benzyl (**3s**). Unfortunately, *N*-protection-free oxindole **1t** is inactive to the transformation.

Next, a series of esters were tested under the optimal reaction conditions and the results were outlined in scheme 3. The diethyl ester can be converted to dimethyl and ditrifluoethyl ester, and generated the corresponding products **3u** and **3v** in high yields with more than 20:1 L/B ratio,

respectively. Gratifyingly, cyano was successfully employed in this reaction as well, affording exclusively **3w** in almost

Scheme 3 Screening of various ester in vinyl cyclopropane **2**[a]

R = CO₂Me, **3u**, 91%,[b] > 20:1 L/B[c]
CO₂CH₂CF₃, **3v**, 87%, > 20:1 L/B

3w, 96%, > 20:1 L/B

3x, 83%, >20:1 L/B
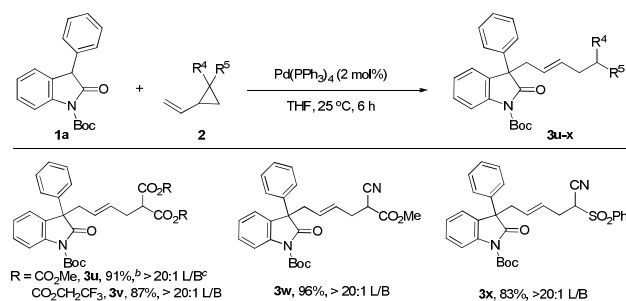
[a] Reaction conditions: 3-substituted oxindole **1a** (0.3 mmol), vinyl cyclopropane **2** (0.36 mmol, 1.2 equiv.), Pd(PPh₃)₄ (2 mol%) in 2 mL of THF for 6 h under nitrogen atmosphere. [b] Isolated yields. [c] The L/B ratio was determined by ¹H NMR analysis.

quantitative yield. Furthermore, a satisfied result in terms of both yield and regioselectivity was achieved for reactant containing sulfone and cyno functionalities which offer ample opportunities for further derivatization of the molecular **3x**.

Finally, we poured much attention into an attempt for the asymmetric allylic alkylation of **1a** and **2a** by Pd₂(dba)₃ catalysis with chiral P-containing ligands (Scheme 4). The reaction didn't occur with the use of typical phosphine ligands **P-1** and **P-2**

Scheme 4 Preliminary attempt for the asymmetric allylation reaction[a]
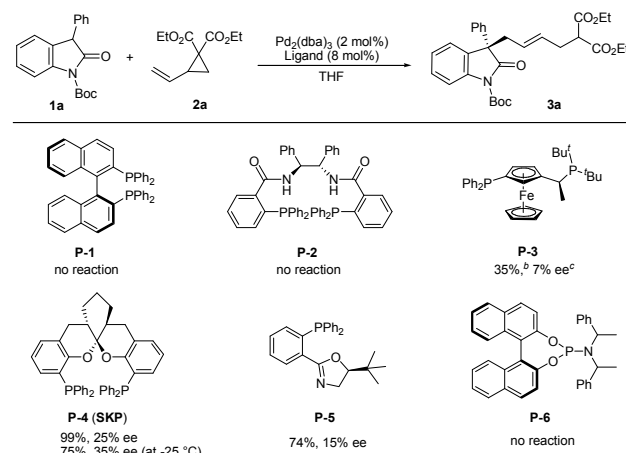
[a] Reaction conditions: oxindole **1a** (0.1 mmol), **2a** (0.12 mmol), Pd₂(dba)₃ (2 mol%) and Ligand (8 mol%) in 1mL of THF for 6 h under nitrogen atmosphere. [b] Isolated yields. [c] The ee values was determined by chiral HPLC analysis.

(entries 1 and 2). Ferrocene-diphosphine ligand **P-3** led to **3a** in 35% yield with 7% ee (entry 3). Remarkably, the unique SKP ligand **P-4**[17] demonstrated highly efficient reactivity, resulting in full conversion and 25% ee, lowering the temperature to -25°C improved enantioselectivity to 35% with the decrease of yield (entry 4). Finally, other typical monophosphine ligands **P-5** and **P-6** were tested for this transformation and no acceptable result was acquired (entries 5 and 6).

In summary, we have demonstrated that vinyl cyclopropanes can be utilized as very effective reactant in the

Pd⁰-catalyzed allylic alkylation for quickly assembling an all-carbon quaternary allylic center at the 3-position of oxindole in good yields with excellent regioselectivites. Importantly, this special strategy provided a very high atom-economic protocol for the synthesis of 3,3-disubstituted oxindoles, that the addition of additives is no longer indispensable and no any waste produced. Moreover, this transformation tolerates a wide scope of functional groups in both substrates. The enantioselective allylic alkylation has also been realized to afford the desired product in high yield and 35% ee. Further efforts will be devoted to the improvement of the ee values of the enantioselective reactionfor the preparation of optical purity oxindoles in our laboratory.

Acknowledgements

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