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Palladium/Copper Catalysis**

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Carboallylation of Electron-Deficient Alkenes by Palladium/Copper Catalysis

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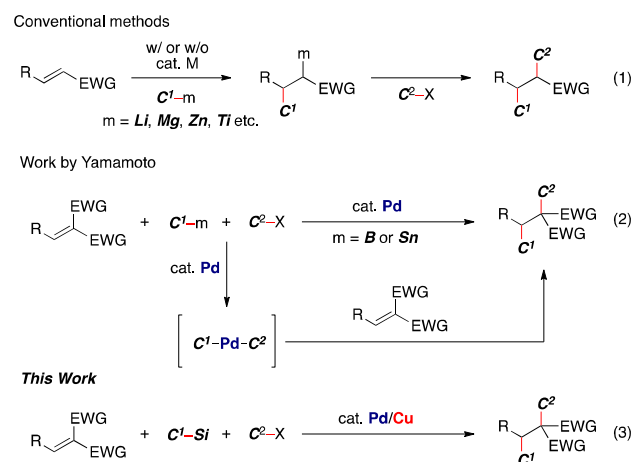
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A method for the carboallylation of electron-deficient alkenes with tetraorganosilicon reagents and allylic carbonates based on Pd/Cu catalysis has been developed. This method affords a wide range of structurally diverse carbon skeletons from readily available starting materials, and tolerates various functional groups.

The conjugate addition of organometallics across electron-deficient alkenes followed by reactions of the resulting alkylmetals with carbon-electrophiles is useful for the construction of carbon skeletons and has been applied to the preparation of bioactive molecules (eq 1).¹ However, such reactions typically consist of multi-step operations, and require moisture- and/or air-sensitive organometallic reagents such as organozinc, -aluminium, -copper, -titanium, or triorganoboron reagents.^{1,2} In contrast, methods based on catalytically generated alkyl complexes of transition-metals are more useful, as they require merely a single operation to construct two C–C bonds and they can use air- and moisture-stable organometallics such as organoboronic acid derivatives or organostannanes via the transmetalation of these stable organometallics and transition-metal catalysts. Yamamoto and co-workers have reported pioneering work on the Pd-catalyzed diallylation of electron-deficient alkenes using allylstannanes (eq 2).^{3a–c} Related transformations including allylbenzylations,^{3d} allylpropargylations,^{3e,f} allylcyanations,^{3g} and acetonation-allylations^{3h} have also been developed. However, the accessible combinations of carbon functionalities remain limited. Although an alternative method based on radical reactions have been developed, the reaction was limited to alkylallylation.⁴

During the course of our studies on synergistic cooperative metal catalysis,^{5,6} we anticipated that catalytic

organocupration of electron-deficient alkenes⁷ followed by Pd-catalyzed allylation⁸ could achieve higher compatibility of such dicarbofunctionalizations. In this scenario, the scope of carbon functionalities should be expanded compared to the known Pd systems, as the nucleophiles and electrophiles are activated independently by the Cu and Pd catalysts. Herein, we report the allylarylations, alkenylallylations, and alkylallylations of electron-deficient alkenes with air- and moisture-stable HOMSI[®] reagents⁹ by Pd/Cu catalysis (eq 3). Moreover, we report preliminary results on the asymmetric allylarylations of alkenes.



The allylarylation of benzalmalononitrile (**1a**) with phenyl HOMSI[®] (**2a**), which exhibits good stability toward air and moisture, and allyl methyl carbonate (**3a**) was carried out using various phosphine ligands and CuCl complexes of *N*-heterocyclic carbenes (NHCs). After screening various reaction parameters, the allylarylation of **1a** (0.30 mmol) with **2a** (0.30 mmol) and **3a** (0.30 mmol) proceeded efficiently in the presence of Pd(OAc)₂ (1.0 mol%), 1,3-bis(diphenylphosphino)propane (dppp, 1.0 mol%), (IMes)CuCl (5.0 mol%), and LiOt-Bu (20 mol%) to furnish **4a** in 96% yield without formation of allylbenzene (**5a**) (entry 1). The effects of

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the phosphine ligands are summarized in entries 2–7. PPh_3 , $\text{P}(n\text{-Pr})_3$, and PCy_3 afforded the corresponding allylarylation product **4a** in moderate to good yield, whereas $\text{P}(t\text{-Bu})_3$ resulted in poor yield (entries 2–5). Bidentate phosphines such as 1,2-bis(diphenylphosphino)ethane (dppe) and 1,1'-bis(diphenylphosphino)ferrocene (dppf) were also effective (entries 6 and 7). The effects of the (NHC)CuCl complexes are shown in entries 8–10. (SIMes)CuCl, i.e., a complex similar to (IMes)CuCl showed good reactivity (entry 8). Bulkier NHC-ligated copper complexes afforded **4a** in lower yields and **5a** in moderate yields (entries 9 and 10). The effects of varying the base are shown in entries 11–13. The yields of **4a** decreased using NaOt-Bu or KOt-Bu (entries 11 and 12). When K_2CO_3 was used, **4a** was obtained in 44% yield (entry 13). Under the optimized reaction conditions, the reaction did not proceed in the absence of $\text{Pd}(\text{OAc})_2$ or (IMes)CuCl (entries 14 and 15). These results clearly demonstrate that both Pd and Cu catalysts are indispensable for the present transformation.

Table 1. Allylarylation of benzalmalononitrile (**1a**) with phenyl HOMSi⁺ (**2a**) and allyl methyl carbonate (**3a**)

Reaction conditions: $\text{Pd}(\text{OAc})_2$ (1.0 mol%), dppp (1.0 mol%), (IMes)CuCl (5.0 mol%), LiOt-Bu (20 mol%), 1,4-dioxane, 100 °C, 6 h, standard conditions.

IMes: $\text{R}^1 = \text{R}^2 = \text{Me}$
IPr: $\text{R}^1 = i\text{-Pr}$, $\text{R}^2 = \text{H}$
SIMes: $\text{R}^1 = \text{R}^2 = \text{Me}$
SIPr: $\text{R}^1 = i\text{-Pr}$, $\text{R}^2 = \text{H}$

Entry	Deviation from the standard conditions	Yield of 4a (%) ^a	Yield of 5a (%) ^a
1	none	96	<5
2	PPh_3 instead of dppp	53	26
3	$\text{P}(n\text{-Pr})_3$ instead of dppp	84	<5
4	PCy_3 instead of dppp	82	<5
5	$\text{P}(t\text{-Bu})_3$ instead of dppp	14	<5
6	dppe instead of dppp	77	<5
7	dppf instead of dppp	59	<5
8	(SIMes)CuCl instead of (IMes)CuCl	74	<5
9	(IPr)CuCl instead of (IMes)CuCl	23	50
10	(SIPr)CuCl instead of (IMes)CuCl	18	34
11	NaOt-Bu instead of LiOt-Bu	70	<5
12	KOt-Bu instead of LiOt-Bu	50	<5
13	K_2CO_3 instead of LiOt-Bu	44	<5
14	w/o $\text{Pd}(\text{OAc})_2$	<5	<5
15	w/o (IMes)CuCl	<5	9

^a Yield determined by GC (internal standard: $n\text{-C}_{13}\text{H}_{28}$).

With optimized conditions in hand, the scope of organosilicon reagents was examined with **1a** and **3a** (Table 2). Electron-donating or -withdrawing substituents at the *para*-

position of the aryl group of the aryl silicon reagents **2a–d** were tolerated. Acetyl group, which would be difficult to be tolerated under the conditions based on the moisture-sensitive organometallics, was intact, although the yield was moderate due to the undesired cross-coupling between **2d** and **3a** to afford *p*-allylacetophenone. Moreover, it should be noted that alkenyl and alkyl silicon reagents were also viable substrates under the standard conditions. Alkenyl HOMSi⁺ reagents afforded the alkenylallylation products in good yields under retention of the stereochemistry of the double bond (**2f–i**). Methyl, *n*-alkyl, and cyclopropyl groups could thus be introduced (**2j–l**).

Table 2. Scope of organosilicon reagents **2**.

Reaction conditions: $\text{Pd}(\text{OAc})_2$ (1.0 mol%), dppp (1.0 mol%), (IMes)CuCl (5.0 mol%), LiOt-Bu (20 mol%), 1,4-dioxane, 100 °C, 6 h.

1a (1.0 mmol) + 2 (1.0 mmol) + 3a (1.0 mmol) → 4a-l

Ar = Ph (**2a**): 92%
 = *p*-OMeC₆H₄ (**2b**): 63%
 = *p*-CNC₆H₄ (**2c**): 40%^a
 = *p*-Ac (**2d**): 36%^{a,b}
 = *o*-MeC₆H₄ (**2e**): 72%^b

2f, 48%^a
2g, 67%^{a,b,c} (Z/E = 94:6)
2h, 80%
2i, 67%
2j, 55%
2k, 76%
2l, 69%

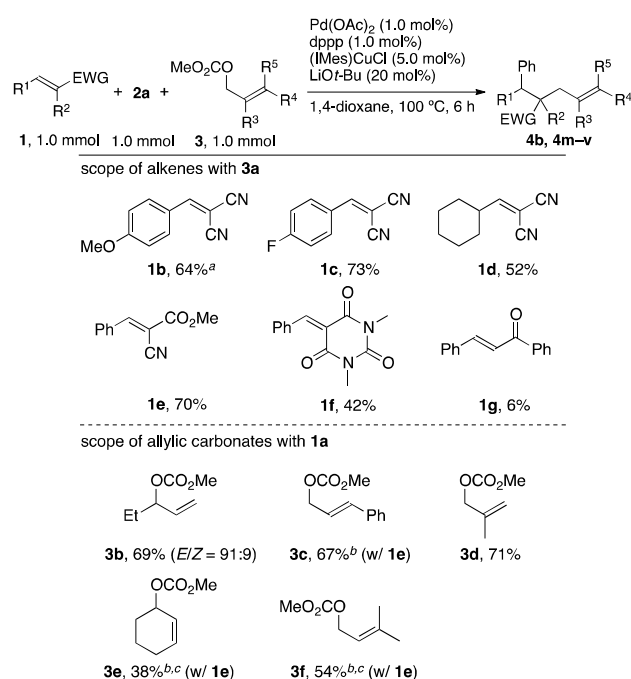
^a 0.50 mmol scale. ^b Dppe was used instead of dppp. ^c Z/E = 96:4.

The scope of alkenes **1** and allylic carbonates **3** was demonstrated in Table 3. 1,1-Dicyano-2-(4-methoxyphenyl)ethene (**1b**), 1,1-dicyano-2-(4-fluorophenyl)ethene (**1c**), and 1,1-dicyano-2-cyclohexylethene (**1d**) afforded the corresponding products in moderate to good yields. 1-Cyano-1-alkoxycarbonyl alkene **1e** afforded the corresponding allylarylation product, which represents useful intermediates en route to β -amino acid derivatives, in good yield, while barbituric acid derivative **1f** afforded the allylarylation product in moderate yield. Chalcone (**1g**) was not a viable substrate under the standard conditions probably due to low efficiency of the arylcupration across chalcone. A variety of allylic carbonates including acyclic and cyclic ones were examined. When branched allylic carbonate **3b** was employed, the corresponding linear product was obtained in good yield with high stereoselectivity. Under the applied reaction conditions, various functionalities including OTBS, amide, alkoxycarbonyl, and CN substituents remained intact.

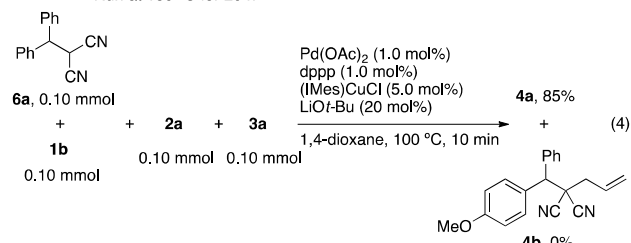
To gain insight into the underlying reaction mechanism, time-course of the allylarylation of **1a** with **2a** and **3a** was monitored (Figure S2). At the initial stage, hydroarylation

product **6a** was observed. This observation would support that the present allylarylation proceeds through Cu-catalyzed hydroarylation of **1a** followed by Pd-catalyzed allylation of **6a**.^{6k,l} In fact, allylarylation of **1b** in the presence of hydroarylation product **6a** preferentially afforded allylation product **4a** rather than allylarylation product **4b** (eq 4).

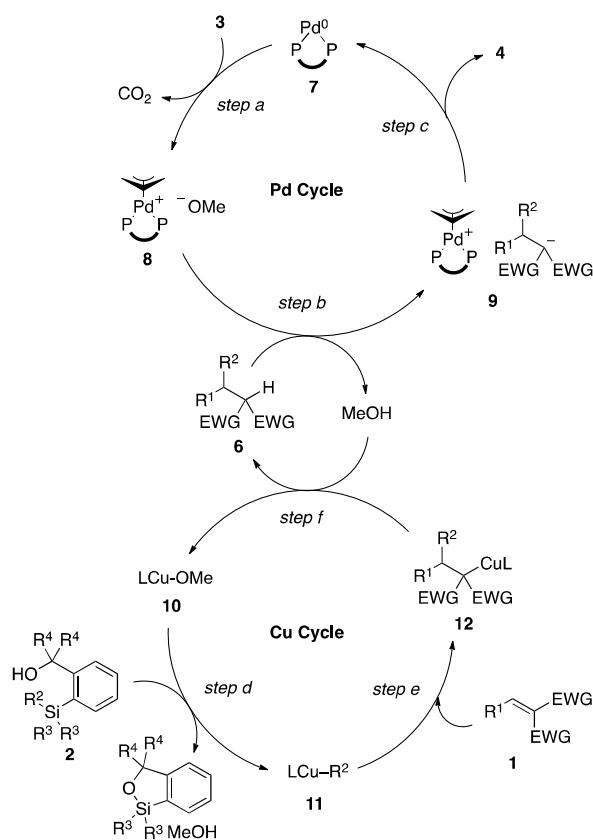
Table 3. Scope of alkenes **1** and allylic carbonates **3**.



^a 0.50 mmol scale. ^b Dppe was used instead of dppp. ^c Run at 130 °C for 20 h.

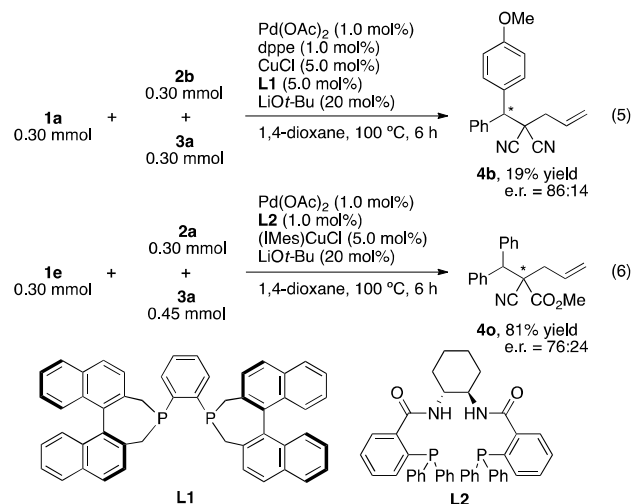


According to the mechanistic studies, a plausible reaction mechanism is depicted in Scheme 1. An organocopper complex **11** should be generated from copper alkoxide **10** and organosilicon reagent **2** (step d in the Cu cycle). An organocupration across electron-deficient alkenes followed by protonation with MeOH should afford hydroarylation product **6** and copper alkoxide **10** (steps e and f in the Cu cycle). The nucleophilic substitution of π -allylpalladium complex **8**, which should be generated from low-valent palladium complex **7** and allylic carbonates **3**, with carbon-nucleophiles generated from **6** should afford the allylarylation product **4** under concomitant regeneration of the low-valent palladium species **7** (steps a, b and c in the Pd cycle).



Scheme 1. A plausible mechanism.

To further demonstrate the synthetic utility of the present method, asymmetric allylarylations were explored. When chiral bidentate phosphine **L1**¹⁰ was employed, the allylarylation of **1a** afforded **4b** in 19% yield (e.r. = 86:14) (eq 5). Moreover, an asymmetric allylarylation of **1e** was achieved by using a chiral palladium catalyst containing **L2**,¹¹ which afforded **4o** in 81% yield (e.r. = 76:24) (eq 6).



Conclusions

In conclusion, we have developed carballylations of electron-deficient alkenes by Pd/Cu catalysis, in which two different organic functionalities such as aryl, alkenyl, alkyl, and allyl moieties are introduced simultaneously across the C=C bond of alkenes. Though preliminary, asymmetric allylarylations were accomplished using chiral-phosphine-ligated Pd and Cu catalysts. The present transformations should thus be powerful tools to construct complex carbon skeletons from readily available alkenes in high step-efficiency.

Conflicts of interest

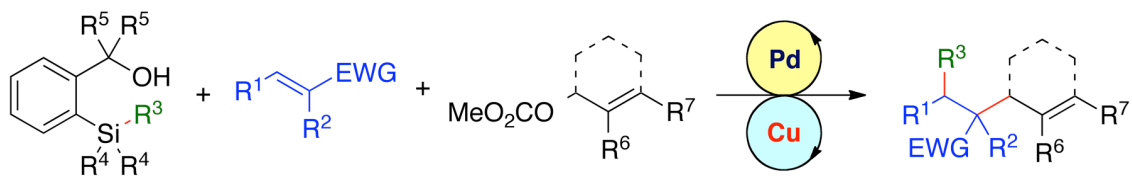
There are no conflicts to declare.

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R^3 = aryl, alkenyl, alkyl

The carboallylation of electron-deficient alkenes with tetraorganosilicon reagents and allylic carbonates has been developed by palladium/copper catalysis.