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Highly Regioselective Three-Component Domino Heck−Negishi Coupling Reaction for the Functionalization of Purines at C6

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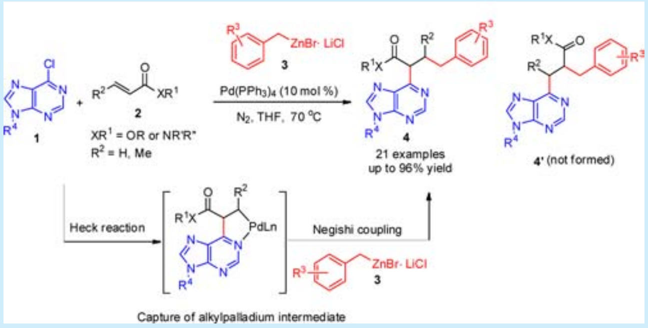
Supporting Information

ABSTRACT: A highly regioselective three-component domino Heck−Negishi coupling reaction has been developed. Organozinc reagents are used to trap an alkylpalladium intermediate of olefins for a first example in the domino Heck reaction. This reaction is applicable to acrylates (or acrylamides) and purine compounds, producing a series of novel purine compounds with carbon substituents at the C6 position in moderate to good yields.

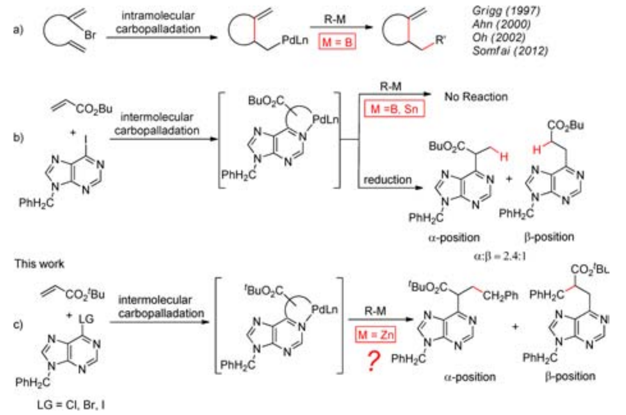


As a powerful method for constructing complex organic molecules, domino reactions with the formation of two or more bonds under identical reaction conditions in one efficient step have been extensively studied by synthetic chemists.[1] The well-known Heck coupling reaction, one of the most direct methods to form carbon−carbon bonds in organic synthesis, is also used as an initiation reaction for many domino reactions.[2] Recently, domino Heck reactions, such as Heck−C−H activation,[3] Heck−cyanation,[4] Heck−carbohalogenation[2b] and Heck−aza-Michael[5] et al. are becoming focuses for researchers.

Although a variety of organometals, such as organoborane, organoaluminum, organotin and organozinc compounds have widely been employed in domino carbopalladation−cross-coupling of alkynes, there are few successful examples of the carbopalladation−cross-coupling of olefins.[6] In 1997, the Grigg group reported Heck−Suzuki coupling reactions with alkylpalladation followed by trapping with organoborane reagents (Scheme 1a).[7a] Subsequently, great endeavors have been devoted to the one or two-component intramolecular Heck−Suzuki coupling reactions with a carbopalladium intermediate (Scheme 1a).[2a,7] However, the multicomponent domino Heck reaction has scarcely been reported up to now. Multicomponent domino reactions are more desirable and play an extremely important role in organic and medicinal chemistry, which can create structurally diverse or complex products from relatively simple starting materials.[8]

Purine bases and nucleosides, as the universal units in DNA and RNA, have found broad applications in biological and pharmaceutical chemistry. In particular, C6-alkylated purine analogues exhibit unique biological activities such as cytostatic,[9] antiviral, and antimicrobial activities[10] or receptor modulation.[11] The most direct and effective methods for the synthesis of purines bearing carbon substituent at C6 were transition-metal-catalyzed cross-coupling reactions such as Suzuki,[12] Negishi,[13,14] Stille,[15] and Sonogashira[16] cross-coupling reactions using 6-halopurines as starting material. Somewhat

Scheme 1. (a) Intramolecular Carbopalladation Followed by Trapping with Organoborane. (b) Intermolecular carbopalladation Followed by Reductive Elimination. (c) Intermolecular Carbopalladation Followed by Trapping with Organozinc Bromide



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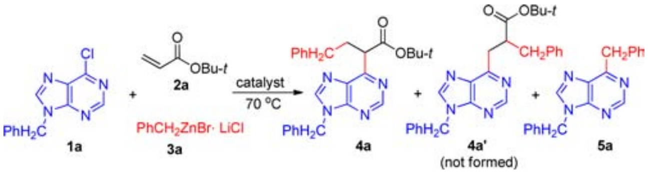
surprisingly, it is difficult to apply the Heck reaction in modifying purine derivatives.[17] Perhaps in this sequence the typical termination event of the Heck reaction, β-hydride elimination, is precluded because of the form of extremely stable alkylpalladium intermediate (Scheme 1b).

In 2004, the Dvořák group developed an intermolecular carbopalladation between 9-benzyl-6-iodopurine and butyl acrylate (Scheme 1b).[17] When phenylboronic acid or phenyltributyltin was used to trap the alkylpalladium intermediate, no reactions occurred. In this case, a formate anion was used to trap the alkylpalladium intermediate, and the reductive Heck reaction occurred, affording a mixture of both α- and β-products with low regioselectivity (Scheme 1b). In the context of ongoing projects in modifying of purine derivatives,[18] we encountered a requirement to trap the alkylpalladium intermediate by other organometal reagents. In the newly formed purine derivatives, the regioselectivity of α- and β-products was still a challenging problem (scheme 1c). Herein, we report the three-component domino Heck–Negishi reactions of 6-chloropurine derivatives, olefins, and organozinc bromides, affording the targeted purine derivatives with high regioselectivity.

Initially, 9-benzyl-6-chloropurine (**1a**), *tert*-butyl acrylate (**2a**), and benzylzinc bromide (**3a**) were selected as model substrates to optimize the reaction conditions (Table 1). When $Pd(PPh_3)_4$ was used as catalyst, the reaction proceeded well (entry 1). To our delight, the α-position product **4a** was detected as the major form (58% yield), along with the side product **5a** (18% yield) of Negishi coupling between **1a** and **3a**. It is worth mentioning that the Heck–Negishi reaction had high regioselectivity[19] and the β-position product **4a′** was not detected (entry 1). Subsequently, several kinds of Pd or Ni catalysts were examined, and no better results were observed, while the side product **5a** was exclusively formed with Ni catalyst (entries 1–5). Interestingly, the reaction was influenced greatly by the amount of THF, and the higher yield of **4a** was obtained with 1.0 mL of THF (entries 1 vs 6–8). Importantly, the yield of **4a** was highly dependent on the ratio of reactants (entries 9–15). When a small amount of benzylzinc bromide (**3a**) was employed, such as 1.5 equiv or 2.0 equiv, a trace amount of product **4a** was obtained (entries 12 and 13). Luckily, when the ratio of **1a**:**2a**:**3a** was 1:3:4, the highest yield of **4a** was obtained (77% yield), while the side-product **5a** could be avoided totally (entry 14). Thus, the optimized reaction conditions were as follows: 0.1 mmol of 9-benzyl-6-chloropurine (**1a**), 3.0 equiv of *tert*-butyl acrylate (**2a**), and 4.0 equiv of benzylzinc bromide (**3a**) were employed in 1.0 mL of THF (entry 14).

Table 1. Optimization of the Cross-Coupling Reaction Conditions[a]

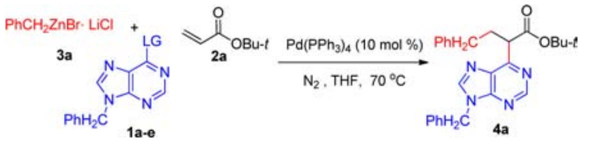


entry	catalyst (10 mol %)	**2a** (equiv)	**3a**[b] (equiv)	THF (mL)	yield[c] (%)	
					4a	**5a**
1	$Pd(PPh_3)_4$	5.0	3.0	1.0	58	18
2	$PdCl_2(dppf)$	5.0	3.0	1.0	26	40
3	$PdCl_2(PPh_3)_2$	5.0	3.0	1.0	25	42
4	$NiCl_2$ dppp	5.0	3.0	1.0	0	81
5	$Ni(acac)_2$	5.0	3.0	1.0	0	83
6	$Pd(PPh_3)_4$	5.0	3.0	0.5	30	50
7	$Pd(PPh_3)_4$	5.0	3.0	1.5	19	58
8	$Pd(PPh_3)_4$	5.0	3.0	2.0	18	60
9	$Pd(PPh_3)_4$	2.0	3.0	1.0	57	14
10	$Pd(PPh_3)_4$	3.0	3.0	1.0	66	trace
11	$Pd(PPh_3)_4$	7.0	3.0	1.0	58	19
12	$Pd(PPh_3)_4$	3.0	1.5	1.0	trace	72
13	$Pd(PPh_3)_4$	3.0	2.0	1.0	trace	73
14	**$Pd(PPh_3)_4$**	**3.0**	**4.0**	**1.0**	**77**	**0**
15	$Pd(PPh_3)_4$	3.0	5.0	1.0	72	trace

[a] Reaction conditions: **1a** (0.1 mmol), 70 °C, N_2, stirring overnight. [b] $PhCH_2ZnBr{\cdot}LiCl$ in THF (0.805 M). [c] Isolated yield based on **1a**.

Subsequently, different leaving groups at the C6 position of the purine component were examined (Table 2). When 6-bromo- (**1b**) or 6-iodopurine (**1c**) were used as purine components, the target products **4a** were obtained in 92% and 80% yields, respectively. However, no reactions occurred when OTs or OBt connected at C6 position of purine derivatives. Considering the low cost of purine component, 6-chloropurine derivatives (**1a**) was selected as the purine component for the following investigation.

Table 2. Effect of Different Leaving Groups at C6 Position of Purine Derivatives[a]



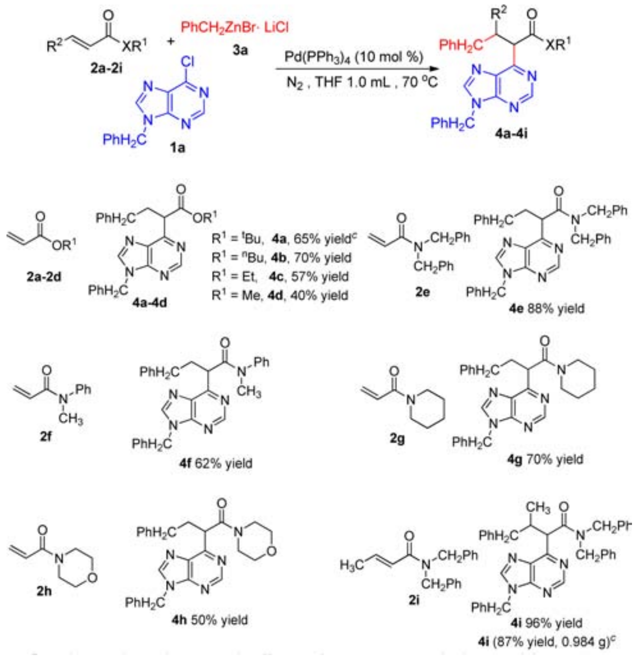
LG	Cl (**1a**)	Br (**1b**)	I (**1c**)	OTs (**1d**)	OBt (**1e**)
yield (%)[b]	77	92	80	0	0

[a] Reaction conditions: **1** (0.1 mmol), **2a** (3.0 equiv), **3a** (4.0 equiv, 0.5 mL of solution in THF), THF (1.0 mL), 70 °C, N_2, stirring overnight. [b] Isolated yield based on **1**.

Next, to evaluate the generality of the reaction, a series of α,β-unsaturated carboxylic acid esters and carboxamide derivatives were subjected to the optimized reaction conditions (Scheme 2). The domino reactions occurred smoothly when *tert*-butyl acrylate, *n*-butyl acrylate, ethyl acrylate, and methyl acrylate were tested, giving the 6-alkylpurine compounds in moderate to good yields (Scheme 2, **4a–d**). When α,β-unsaturated carboxamide derivatives were examined, the corresponding Heck–Negishi reactions proceeded well, affording **4e–h** with good yields (Scheme 2, **4e–h**). Moreover, when a methyl group was introduced at the β-position of α,β-unsaturated carboxamide (**2i**), the desired coupling product **4i** was obtained with excellent yield (Scheme 2, **4i**, 96% yield). In addition, when the reactions were performed on 2.0 mmol scale, good results could still be obtained (**4a**: 65% yield; **4i**: 87% yield, 0.984 g). In all cases, the Heck–Negishi reactions exhibited excellent levels of regioselectivity, and only α-position products were found.

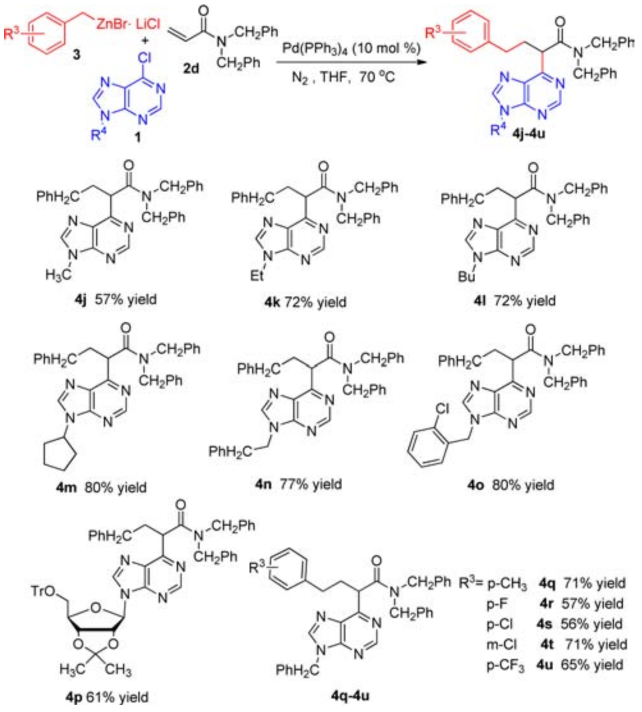
Then, a number of 6-chloropurine derivatives with various substituents at the N9 position, including alkyl and sugar carbon substituents, were investigated (Scheme 3). It was found that alkyl substituents at N9 position of purine had little effect on the yields of the target products, and N9-alkyl substituted

Scheme 2. Reaction of Various α,β-Unsaturated Carboxylic Acid Esters and Carboxamide Derivatives[a,b]



[a]Unless otherwise noted, all reactions were carried out with **1a** (0.1 mmol), **2** (3.0 equiv), **3a** (4.0 equiv, 0.5 mL of solution in THF), THF (1.0 mL), 70 °C, N_2, stirring overnight. [b]Isolated yield based on **1a**. [c]The reactions were performed on 2.0 mmol scale.

Scheme 3. Reaction of Various 6-Chloropurines and Benzylzinc Bromides[a,b]



[a]Reaction conditions: **1** (0.1 mmol), **2d** (3.0 equiv), **3** (4.0 equiv), 70 °C, N_2, stirring overnight. [b]Isolated yield based on **1**.

purines (**1f–k**) proceeded smoothly to give the corresponding products in 57–80% yields (Scheme 3, **4j–o**). Importantly, 6-chloropurine nucleoside could also afford the desired product **4p** in 61% yield (Scheme 3, **4p**), which provided a useful access for the preparation of purine nucleoside analogues. Indeed, it is the first time that purine nucleoside was modified via this domino Heck–Negishi strategy. Other heterocyclic compounds have also been investigated, including 2-chloropyridine, 2-chloropyrimidine, 2-chloropyrazine, and 8-bromoquinoline. Unfortunately, the competitive Negishi reactions worked well, and the domino Heck–Negishi reactions did not occur. Finally, a variety of organozinc halides were also subjected to the optimized conditions. When primary benzylzinc bromides including *p*-methylbenzylzinc bromide, *p*-fluorobenzylzinc bromide, *p*-chlorobenzylzinc bromide, *m*-chlorobenzylzinc bromide, or *p*-trifluoromethylbenzylzinc bromide were used as starting material, the corresponding products **4q–u** were obtained in good yields (Scheme 3, **4q–u**). The use of primary benzyl zinc bromide was necessary to ensure the occurrence of the domino Heck–Negishi reaction. When other alkyl- or arylzinc halides, such as methylzinc iodide, *n*-butylzinc iodide, isopropylzinc bromide, cyclopentylzinc bromide, (1-phenylethyl)zinc bromide as well as phenylzinc iodide were used, the side reactions of Negishi coupling proceeded well, while the Heck–Negishi coupling products could not be formed.

In summary, we have developed the first example of a three-component domino Heck–Negishi coupling reaction for the synthesis of novel purine compounds with carbon substituents at C6. It is the first time that organozinc reagents are used to trap an alkylpalladium intermediate of olefins in the domino Heck reaction. This three-component domino process can be applicable for a variety of olefins, purine compounds and organozinc halides. In all cases, this three-component domino Heck–Negishi reactions exhibited excellent levels of regioselectivity, and only α-position products were found.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedure, characterization data, and copies of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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