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COMMUNICATION

Nickel-catalyzed Negishi cross-couplings of 6-chloropurines with organozinc halides at room temperature†

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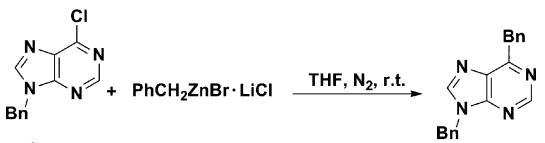
An efficient method for the synthesis of 6-alkyl or 6-aryl purines (nucleosides) was developed *via* nickel-catalyzed Negishi cross-couplings of 6-chloropurines and organozinc halides. The ligand-free process gave good to excellent isolated yields at room temperature.

Cross-coupling reactions of organometallic reagents, such as Suzuki–Miyaura, Kumada, Negishi, and Stille reactions, are one of the most direct methods for constructing carbon–carbon bonds in organic synthesis.[1] Among all the coupling reactions, the Negishi reaction has developed to be a powerful tool for the preparation of many chemical and pharmaceutically active compounds due to its compatibility with various functional groups, high chemoselectivity and the excellent stereoselectivity of organozinc reagents, and the easy preparation of a wide variety of organozinc halides (RZnX) and diorganozincs (R_2Zn).[1c,2] This reaction is usually catalyzed by nickel or palladium complexes, and ancillary ligands are usually needed to sufficiently enhance the reactivities of the palladium and nickel catalysts.[1b] Many kinds of Pd- or Ni-catalyzed Negishi cross-coupling reactions, involving aryl–aryl, aryl–alkenyl, aryl–alkyl and alkyl–alkyl, have been reported[3,2d] in the presence of some ancillary ligands. So studies have focused on the ancillary ligands[4,1b], and some special ligands have been designed to extend the scope of substrates.[5] In view of the high cost of the palladium precursors, inexpensive nickel has certainly received researcher's attention from the very beginning.

Azaarenes, the core unit existing in some natural products or drugs such as purine and pyrimidine derivatives and so on, have been extensively studied because they have a variety of biological activities. Studies on the synthesis and modification of azaarenes are very important and significant in research as well as in industry. Among these studies, cross-coupling reactions of organometallic reagents are applied incisively and prominently as a promising research direction of huge synthetic potential.[1,3,6,7] However, almost all the Negishi cross-coupling reactions for azaarenes–alkyl, such as purine, pyrimidine, pyridine and pyrazine compounds, were catalyzed by palladium with some ligands by employing heteroaryl bromide, iodide[8] and chloride[9] as starting material. Only Walters *et al.*[10] reported that the cross-coupling reaction of alkylzinc halides and chloropyrazine could be catalyzed by $NiCl_2$(dppp). In other words, there are almost no studies of Ni-catalyzed cross-coupling reactions of azaarenes. To fill this need, and during the ongoing course of our study on the modification of purine analogues,[11] we report herein the Negishi cross-coupling reactions of 6-chloropurines with organozinc halides catalyzed by $Ni(acac)_2$.

As a model reaction, the cross-coupling reaction of 9-benzyl-6-chloropurine (**1a**) and benzylzinc bromide (**2a**) was selected to screen the catalysts and optimize the reaction conditions. Different catalysts, including Pd or Ni catalysts, were initially studied at room temperature (Table 1, entries 1–7). The activity of the Ni-catalysts were higher than that of the Pd-catalysts, and nickel acetylacetonate ($Ni(acac)_2$) gave the best results, affording the cross-coupling product **3a** in 96% yield (entry 7). The further optimization of reaction conditions showed that the cross-coupling product **3a** was obtained in almost quantitative yields at lower benzylzinc bromide (1.5 eq) and $Ni(acac)_2$ loadings

Table 1 Optimization of the cross-coupling reaction conditions[a]



1a 2a 3a

Entry	Catalyst (mol%)	**2a** (equiv)	Time (h)	Yield (%)[b]
1	$Pd(PPh_3)_4$ (10%)	3	18	62
2	$PdCl_2$ dppf (10%)	3	18	40
3	$PdCl_2$ (10%)	3	18	66
4	$NiCl_2(PPh_3)_2$ (10%)	3	18	65
5	$NiCl_2$ dppp (10%)	3	12	84
6	$NiCl_2$ (10%)	3	18	69
7	$Ni(acac)_2$ (10%)	3	10	96
8	**$Ni(acac)_2$ (5%)**	**1.5**	**20**	**98**
9	$Ni(acac)_2$ (2%)	1.5	24	91
10	—	1.5	24	0

[a] Reaction conditions: **1a** (0.1 mmol), THF (1 mL). [b] Isolated yield based on **1a**.

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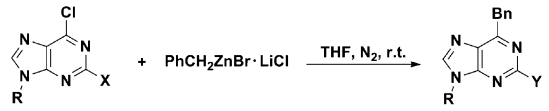
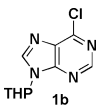
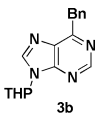
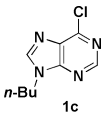
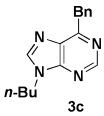
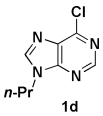
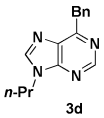
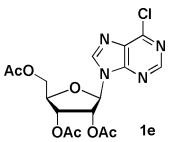
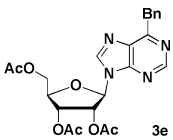
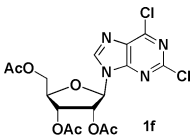
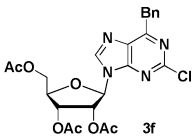
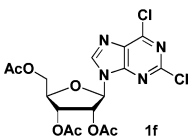
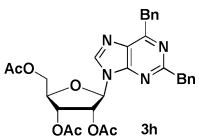
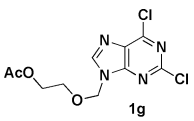
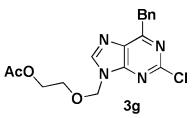
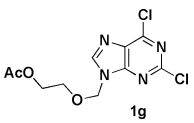
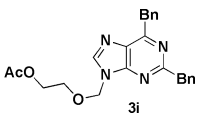
† Electronic supplementary information (ESI) available: Experimental procedures, compound characterizations, and the copies of ^{1}H NMR and ^{13}C NMR spectra. See DOI: 10.1039/c1ob06265d

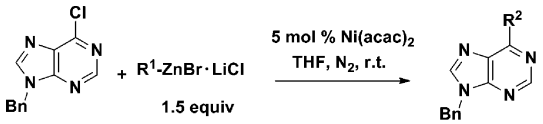
Table 2 The cross-coupling reaction of 6-chloropurines with benzylzinc bromide[a]

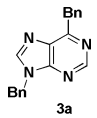
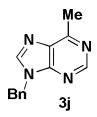
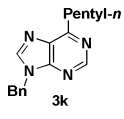
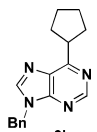
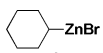
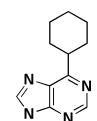
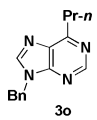


Entry	6-Chloropurines	Product	Yield (%)[b]
1	 1b	 3b	98
2	 1c	 3c	97
3	 1d	 3d	98
4	 1e	 3e	80
5	 1f	 3f	78
6[c]	 1f	 3h	50
7	 1g	 3g	75
8[c]	 1g	 3i	65

[a] Reaction conditions: **1b–g** (0.1 mmol), **2a** (0.15 mmol), $Ni(acac)_2$ (0.005 mmol), THF (1 mL). [b] Isolated yield based on **1**. [c] **2a** (0.3 mmol) was used.

Table 3 The cross-coupling reaction of 9-benzyl-6-chloro-purine with various alkylzinc halides[a]



Entry	R^1–ZnX	Product	Yield (%)[b]
1	Bn–ZnBr 2a	 3a	98
2	Me–ZnBr 2b	 3j	92
3	*n*-Pentyl–ZnBr 2c	 3k	80
4	 ZnBr 2d	 3l	71
5	 ZnBr 2e	 3m	76
6	*i*-Pr–ZnBr 2f	 3n	40
7	*i*-Pr–ZnBr 2f	 3o	37

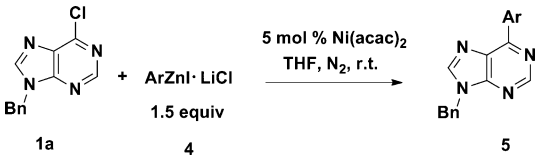
[a] Reaction conditions: **1a** (0.1 mmol), **2a–2f** (0.15 mmol), $Ni(acac)_2$ (0.005 mmol), THF (1 mL). [b] Isolated yield based on **1a**.

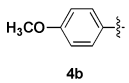
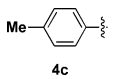
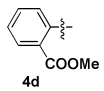
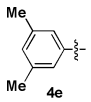
(5%) (entries 7–9). These encouraging results indicated that $Ni(acac)_2$ without any ancillary ligand was an effective catalyst for Negishi coupling reactions of 9-benzyl-6-chloropurine and benzylzinc bromide.

Next, to evaluate the generality of the reaction, a number of 6-chloropurines with various substituents at N9, including alkyl and sugar carbon substituents, were subjected to the optimized reaction conditions (Table 2). N9 alkyl or tetrahydropyranyl (THP) substituted purines proceeded smoothly in more than 97% yields (entries 1–3). And to our delight, 2′,3′,5′-triacyl-6-chloropurine nucleoside gave the corresponding product in 80% isolated yield (entry 4), providing a useful access for the preparation of purine nucleoside analogues. More meaningfully, the cross-coupling reactions employing acetyl protected 2,6-dichloropurine nucleoside were able to selectively produce 6-benzyl-2-chloropurine nucleoside **3f** and 2,6-dibenzylpurine nucleoside **3h** just by changing the quantity of benzylzinc bromide (entries 5–6).[12] Acyclovir side chain protected 2,6-dichloropurine **1g** gave the same results (entries 7–8).

Other alkylzinc halides were also subjected to the reaction under the optimized conditions (Table 3). As expected, primary alkylzinc halides, such as benzylzinc **2a**, methylzinc **2b**, and pentylzinc **2c**,

Table 4 The Negishi cross-coupling reaction of 9-benzyl-6-chloro-purine with arylzinc iodide[a]



Entry	Ar	Product	Yield (%)[b]
1	 4a	**5a**	83
2	 4b	**5b**	84
3	 4c	**5c**	82
4[c]	 4d	**5d**	89
5	 4e	**5e**	86

[a] Reaction conditions: **1a** (0.1 mmol), **4a–4e** (0.15 mmol), $Ni(acac)_2$ (0.005 mmol), THF (1 mL). [b] Isolated yield based on **1a**. [c] Catalyzed by 5 mol% of $Ni(acac)_2$ and 5 mol% of dppp.

produced the corresponding products in good to excellent yields (entries 1–3). Cyclic alkyl zinc bromides, involving cyclopentylzinc **2d** and cyclohexylzinc **2e**, also gave the desired products in satisfactory yields (entries 4, 5). However, isopropyl zinc bromide **2f** gave a mixture of **3n** and **3o**, a rearrangement product of **3n** (entries 6, 7).

In order to test if the arylzinc halides could be used as substrates for the reaction, we tried to synthesize a series of arylzinc halides. Because arylzinc bromides were obtained in very low yields, we at last chose arylzinc iodides as the substrates. As shown in Table 4, a series of 6-arylpurines were successfully synthesized from the corresponding arylzinc iodides in high yields (entries 1–5). Functional groups attached to the arylzinc iodides, such as CH_3, OMe, and COOMe, were well tolerated.

In summary, we have established that $Ni(acac)_2$ can efficiently catalyze Negishi cross-coupling reactions of 6-chloropurines with alkyl or aryl zinc halides under ligand-free conditions at room temperature. To the best of our knowledge, this is the first process that is conducted under *ligand-free* conditions among all the Ni- or Pd-catalyzed Negishi cross-couplings. This process provides a novel economically efficient approach to the modification of purine nucleoside compounds and enriches the methodology of Negishi cross-coupling reactions.

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