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Nickel-catalyzed *N*-arylation of benzophenone hydrazone with bromoarenes†

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A nickel-catalyzed method for the cross-coupling of benzophenone hydrazone with aryl bromides is described. The use of a simple Ni(II)/NHC catalyst leads to the arylated hydrazones in good or acceptable yields. This protocol provides a simple, convenient alternative to the synthesis of arylhydrazines.

Arylhydrazines are a highly valuable class of "building blocks" in the synthesis of important nitrogen-containing heterocycle frameworks such as indazoles,[1] indoles (by the Fisher indole synthesis),[1,2] arylpyrazoles,[1,3] and arytriazoles.[1,4] Traditionally, arylhydrazines are prepared *via* the stoichiometric oxidation of anilines to the corresponding diazonium salts and subsequent reduction with tin(II) salts or sulfite ions.[5] The classical method suffers from harsh reaction conditions, limited functional group tolerability, generation of large amounts of wastes (tin wastes), and so on. Modern metal-catalyzed cross-coupling technology provides an attractive alternative to the synthesis of arylhydrazines, which has been applied over recent years.[6–11] In this regard, successful examples mainly include: (1) palladium-catalyzed reactions such as Pd-catalyzed arylations of benzophenone hydrazone[6] or protected hydrazides,[7] and Pd-catalyzed direct C–N coupling of hydrazine with aryl chloride/tosylates;[8] (2) Cu-catalyzed processes such as Cu-promoted arylation of Boc-protected hydrazine,[9] acylhydrazines,[10] phenylhydrazine,[11] and free hydrazine.[12] However, in the palladium catalysis, noble metal palladium and special ligands (usually more expensive than Pd reagents) are required, and for the Cu-catalyzed reactions, good outcomes depend substantially on the use of costly iodoarene electrophiles. On the other hand, cheap and practical nickel-based catalysts, a well-established partner of palladium systems in C–N coupling reactions,[13] have not yet been employed in catalytic cross-couplings of hydrazine-based nucleophilic substrates. Herein, we wish to present our initial findings on the nickel-catalyzed arylation of benzophenone hydrazone for arylhydrazine synthesis.

Benzophenone hydrazone is one of the most commonly employed hydrazine surrogates because it is readily available and conveniently used, and the resulting *N*-arylated benzophenone hydrazone are easily deprotected to afford the corresponding free arylhydrazines. Initially, the cross-coupling between *p*-bromotoluene (**1a**) and benzophenone hydrazone was selected as a model reaction to screen the optimal reaction conditions (Table 1). Since our previous work[14] has proven that a combination of [Ni]/*N*-heterocyclic carbene (NHC) was often an catalyst system more suitable for nickel-catalyzed aromatic aminations, the two model substrates was first subjected to the conditions of $Ni(PPh_3)_2Cl_2$/IPr·HCl/*t*-BuONa at room temperature in dioxane. Encouragingly, the coupling reaction was found to proceed with 54% yield of the product **2a** (entry 1). Furthermore, one advantage of the reaction is that a simple Ni^{II} complex rather than the hard-to-handle Ni^0 source (highly sensitive to air/moisture and toxic) was employed as precatalyst. In contrast, this cross-coupling did not occur in the absence of the nickel catalytic system whether at room temperature or elevated temperatures (entry 2), where only a decomposition of benzophenone hydrazone was observed. Our experiments showed that benzophenone hydrazone partially decomposes into free hydrazine and benzophenone under the basic conditions, and the decomposition exacerbates with elevating reaction temperatures (entry 2). Obviously, this decomposition side-reaction would hamper the achievement of the desired product in excellent yields because it competes against the desired coupling reaction. Further experimentation determined a balance point of reaction temperatures between maximizing the desired coupling reaction and minimizing the decomposition side-reaction, achieving a good yield of 73% (entry 3). A survey of other common nickel sources suggested that all the Ni^{II} precursors have a certain degree of efficacy in this transformation, affording the desired product in 50–60% yields

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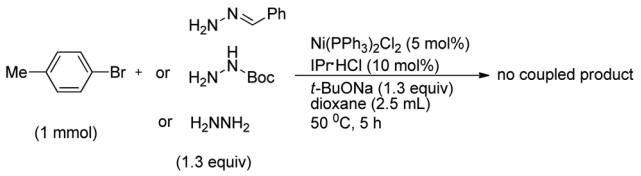
(entries 4–7). The nature of the bases used is crucial for this reaction. For example, strong base *t*-BuOK (entry 8) led to a substantial decomposition of benzophenone hydrazone and a complicated outcome; weaker bases such as Cs_2CO_3 (entry 9) and K_3PO_4 (entry 10) as well as a special base NaH (entry 11) did not work at all. As shown, the catalytic activity of the Ni catalyst was highly relevant to ancillary ligands since other types of ligands (entries 12–14) and even SIPr·HCl (entry 15) (a saturated counterpart of IPr·HCl) proved to be ineffective. For the solvents used, THF (entry 16) was far inferior but toluene (entry 17) comparable to dioxane. Additionally, our experiments showed that *p*-chlorotouene was intact and *p*-iodotoluene afforded a only slightly better yield (75%) under the optimized reaction conditions as established in entry 3 of Table 1.

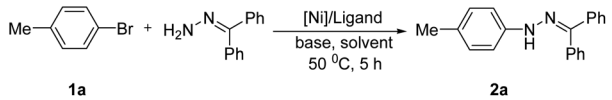
Several commonly-used hydrazine equivalents were also tested in the *N*-arylation reaction (Scheme 1). Consequently, it was found that these other hydrazine surrogates did not undergo the cross-coupling with *p*-bromotoluene under our optimal conditions. The outcomes cannot yet be clearly explained at present and further studies are needed.

Next, we examined *N*-arylation of benzophenone hydrazone with some representative bromoarenes under the optimized conditions (Table 2). Generally, the coupling reaction indeed took place with various aryl bromides but the yields were not very high in many cases. This may be likely because the complicated side-reactions always, to more or less degree, exist in the present reaction system. Taking unsubstituted, electron-neutral bromobenzene (**2d**) as the standard, the electronic nature of the substituents on aryl bromides does not seem to produce significant influence on the reaction (**2a**, **2e**, **2i**, **2j**, and **2m**). And quite different from usual metal-catalyzed coupling reactions, the adverse influence of electron-donating groups on the electrophilic partner is less than that of the electron-withdrawing ones (**2a**, **2e**, and **2m** *vs.* **2i** and **2j**). The reason is unclear at this time. On the other hand, the reaction is extremely sensitive to the steric effects of aryl bromides. Even when the substituents are at the *meta* position of bromoarenes,



Scheme 1

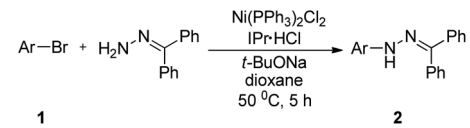
Table 1 Optimization of conditions for the nickel-catalyzed cross-coupling of *p*-bromotoluene with benzophenone hydrazone[a]

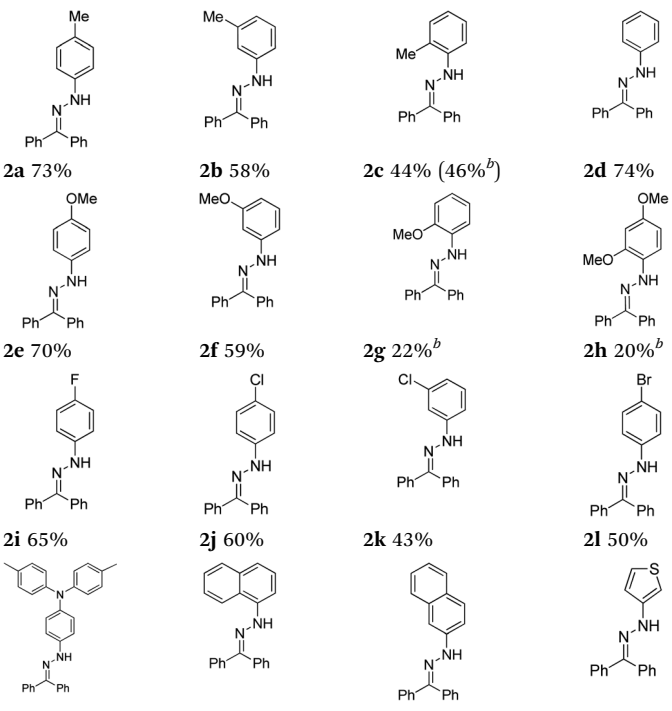


Entry	[Ni]	Ligand	Base	Solvent	Yield[b] (%)
1	$Ni(PPh_3)_2Cl_2$	IPr·HCl[c]	*t*-BuONa	Dioxane	54[d]
2	None	None	*t*-BuONa	Dioxane	0[e]
3	$Ni(PPh_3)_2Cl_2$	IPr·HCl	*t*-BuONa	Dioxane	73
4	$Ni(acac)_2$	IPr·HCl	*t*-BuONa	Dioxane	57
5	$NiCl_2·6H_2O$	IPr·HCl	*t*-BuONa	Dioxane	52
6	**C1**[f]	IPr·HCl	*t*-BuONa	Dioxane	59
7	**C2**[g]	IPr·HCl	*t*-BuONa	Dioxane	58
8	$Ni(PPh_3)_2Cl_2$	IPr·HCl	*t*-BuOK	Dioxane	ND[h]
9	$Ni(PPh_3)_2Cl_2$	IPr·HCl	$CsCO_3$	Dioxane	NR[i]
10	$Ni(PPh_3)_2Cl_2$	IPr·HCl	K_3PO_4	Dioxane	NR
11	$Ni(PPh_3)_2Cl_2$	IPr·HCl	NaH	Dioxane	NR
12	$Ni(PPh_3)_2Cl_2$	PCy_3[j]	*t*-BuONa	Dioxane	0
13	$Ni(PPh_3)_2Cl_2$	DPPF[k]	*t*-BuONa	Dioxane	0
14	$Ni(PPh_3)_2Cl_2$	Phena[l]	*t*-BuONa	Dioxane	0
15	$Ni(PPh_3)_2Cl_2$	SIPr·HCl[m]	*t*-BuONa	Dioxane	0
16	$Ni(PPh_3)_2Cl_2$	IPr·HCl	*t*-BuONa	THF	23
17	$Ni(PPh_3)_2Cl_2$	IPr·HCl	*t*-BuONa	Toluene	70

[a] *Reaction conditions*: *p*-bromotoluene (1.0 mmol), the hydrazone (1.3 mmol), [Ni] (0.05 mmol), ligand (0.1 mmol), base (1.3 mmol), solvent (2.5 mL), 50 °C, 5 h. [b] Isolated yield. [c] IPr·HCl: 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride. [d] A room-temperature reaction. [e] Reactions conducted at rt, 60 °C, and 100 °C, respectively. [f] **C1**: $Ni(PPh_3)_2$(1-naphthyl)Cl. [g] **C2**: $Ni(PPh_3)_2$(phenyl)Br. [h] Complicated products not determined. [i] No reaction. [j] PCy_3: tricyclohexylphosphine. [k] DPPF: 1,1′-bis(diphenylphosphino)ferrocene (0.05 mmol). [l] Phena: 1,10-phenanthroline (0.05 mmol). [m] SIPr·HCl: 1,3-bis(2,6-diisopropylphenyl)-4,5-dihydroimidazolium chloride (0.1 mmol).

Table 2 Nickel-catalyzed *N*-arylation of benzophenone hydrazine with aryl bromides[a]





[a] Conditions: bromoarene (1.0 mmol), hydrazone (1.3 mmol), Ni (0.05 mmol), IPr·HCl (0.1 mmol) *t*-BuONa (1.3 mmol), dioxane (2.5 mL), 50 °C, 5 h; isolated yield. [b] The reaction conducted at 100 °C.

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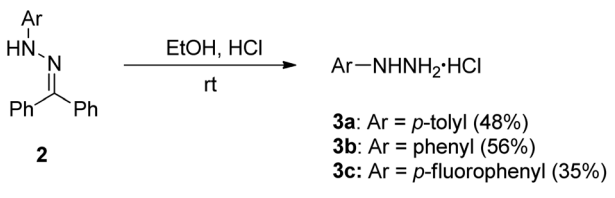
the yields diminished apparently (**2b**, **2f**, **2k**, and **2o**); the *ortho*-substituted aryl bromides (more sterically demanded) gave much lower yields of the coupled products (**2c**, **2g**, **2h**, and **2n**) with appreciable amounts of the starting material **1** recovered, and the elevated reaction temperature scarcely help the increase of yields (**2c**, **2g**, and **2h**). *p*-Dibromobenzene was smoothly *mono*-arylated in a moderate yield (**2l**), and heteroaryl bromide was also coupled with benzophenone hydrazone depite that the yield was not high (**2p**). It must be pointed out that the current conditions are intolerant of some functional groups such as cyano and ester, which were found to react with the free amino group of benzophenone hydrazone, and thus both bromo-benzonitrile and benzoate are not suitable substrates for the reaction.

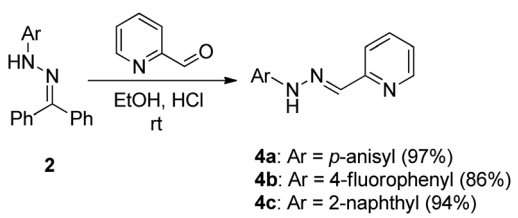
Aryl benzophenone hydrazones **2** may be regarded as a form of protected arylhydrazines and can be readily converted into the corresponding arylhydrazines by acidic hydrolysis. In the cases shown in Scheme 2, the hydrazone **2** was completely deprotected at room temperature in a mixture of concentrated hydrochloric acid and methanol (10 : 1 v/v), affording an arylhydrazine hydrochloride **3** simply by filtration and washing with CH_2Cl_2. Note that achieving only modest isolated yields results mainly from easy loss of the salt **3** in the purification process.

In the practical use, often it is not necessary to hydrolyzed aryl benzophenone hydrazones and isolate arylhydrazines beforehand. For example, a useful class of intermediate compounds **4** in the synthesis of *N*,*N*-diarylhydrazines[15] can be prepared easily from the exchanging reaction of aryl benzophenone hydrazones **2** with 2-pyridinealdehyde in excellent yields (Scheme 3); when the hydrazone **2** is treated with an enolizable ketone,[6c] the indole product **5** can be provided by the Fischer reaction in a one-pot mode (Scheme 4).

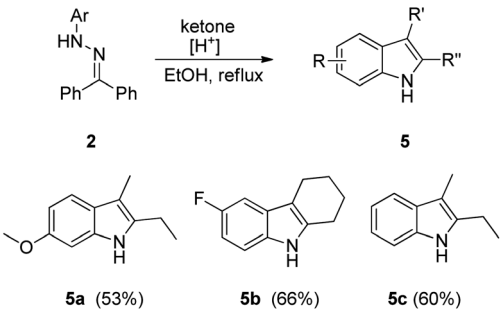
In conclusion, we have first demonstrated the feasibility for nickel-catalyzed cross-couplings of hydrazine-type substrates with haloarenes. Aryl benzophenone hydrazones can be prepared *via* nickel-catalyzed *N*-arylation of benzophenone hydrazone with bromoarenes under relatively mild conditions.



Scheme 2



Scheme 3



Scheme 4

This protocol provides a simple, convenient, and inexpensive route to arylhydrazines. Studies to improve the efficiency of Ni-based catalyst systems, expand the scope of electrophilic coupling partners, and understand the mechanistic details of reaction are under way, and the results will be reported in due course.

Experimental section

General procedure for nickel-catalyzed cross-couplings of benzophenone hydrazone with aryl bromines

An oven-dried 25 mL three-necked flask was charged with benzophenone hydrazone (1.3 mmol), $Ni(PPh_3)_2Cl_2$ (0.05 mmol), IPr·HCl (0.10 mmol), and *t*-BuONa (1.3 mmol). The flask was evacuated and backfilled with nitrogen, with the operation being repeated twice. A solution of the aryl bromine **1** (1.0 mmol) in dioxane (2.5 mL) was added *via* syringe, and stirred at an oil bath of 50 °C for 5 h. The reaction mixture was diluted with H_2O (20 mL) and ethyl acetate (30 mL). The organic layer was separated, washed sequentially with brine (40 mL) and water (40 mL), and dried over anhydrous Na_2SO_4. Concentration under vacuum gave the crude material which was purified by Al_2O_3 column chromatography (petroleum ether/EtOAc, 10 : 1) to give the desired product **2** with the yields as listed in Table 2.

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Notes and references

1 A. R. Katriazky and A. F. Pozharskij, *Handbook of Heterocyclic Chemistry*, Pergamon, Oxford, 2nd edn, 2000, p. 499.
2 G. R. Humphrey and J. T. Kuethe, *Chem Rev.*, 2006, **106**, 2875.
3 S. Fustero, M. Sánchez-Roselló, P. Barrio and A. Simón-Fuentes, *Chem. Rev.*, 2011, **111**, 6984.
4 K. T. Potts, *Chem. Rev.*, 1961, **61**, 87.
5 (*a*) R. H. Poirer and F. Benington, *J. Am. Chem. Soc.*, 1952, **74**, 3192; (*b*) A. S. S. Peter and W. K. Norman, *J. Org. Chem.*, 1958, **23**, 1599; (*c*) I. D. Entwistle, B. A. W. Johnstone and A. H. Wilby, *Tetrahedron*, 1982, **38**, 419.

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6 (*a*) J. F. Hartwig, *Angew. Chem., Int. Ed.*, 1998, **37**, 2090; (*b*) S. Wagaw, B. H. Yang and S. L. Buchwald, *J. Am. Chem. Soc.*, 1998, **120**, 6621; (*c*) S. Wagaw, B. H. Yang and S. L. Buchwald, *J. Am. Chem. Soc.*, 1999, **121**, 10251; (*d*) C. Mauger and G. Mignani, *Adv. Synth. Catal.*, 2005, **347**, 773; (*e*) A. Klapars, J. C. Antilla, X. Huang and S. L. Buchwald, *J. Am. Chem. Soc.*, 2001, **123**, 7727; (*f*) A. C. Ferretti, C. Brennan and D. G. Blackmond, *Inorg. Chim. Acta*, 2011, **369**, 292; (*g*) C. Mauger and G. Mignani, *Synth. Commun.*, 2006, **36**, 1123; (*h*) C. Mauger and G. Mignani, *US Pat.* 2007243999.

7 (*a*) Z. Wang, R.-T. Skerlj and G.-J. Bridger, *Tetrahedron Lett.*, 1999, **40**, 3543; (*b*) J. B. Arterburn, K. V. Rao, R. Ramdas and B. R. Dible, *Org. Lett.*, 2001, **3**, 1351; (*c*) Y.-K. Lim, K.-S. Lee and C.-G. Cho, *Org. Lett.*, 2003, **5**, 979; (*d*) N. Halland, M. Nazare, J. Alonso, O. R'kyek and A. Lindenschmidt, *Chem. Commun.*, 2011, **47**, 1042.

8 (*a*) R. J. Lundgren and M. Stradiotto, *Angew. Chem., Int. Ed.*, 2010, **49**, 8686; (*b*) A. DeAngelis, D.-H. Wang and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2013, **52**, 1.

9 (*a*) O. Loog, U. Mäeorg and U. Ragnarsson, *Synthesis*, 2000, 1591; (*b*) M. Wolter, A. Klapars and S. L. Buchwald, *Org. Lett.*, 2001, **3**, 3803; (*c*) K.-Y. Kim, J.-T. Shin, K.-S. Lee and C.-G. Cho, *Tetrahedron Lett.*, 2004, **45**, 117; (*d*) P. Starkov, I. Zemskov, R. Sillard, O. Tšubrik and U. Mäeorg, *Tetrahedron Lett.*, 2007, **48**, 1155; (*e*) M. S. Lam, H. W. Lee, A. S. C. Chan and F. Y. Kwong, *Tetrahedron Lett.*, 2008, **49**, 6192; (*f*) L. Jiang, X. Lu, H. Zhang, Y. Jiang and D. Ma, *J. Org. Chem.*, 2009, **74**, 4542.

10 (*a*) H. Suzuki and A. Yamamoto, *J. Chem. Res., Synop.*, 1992, 280; (*b*) X. D. Xiong, Y. W. Jiang and D. Ma, *Org. Lett.*, 2012, **14**, 2552.

11 H. Rao, Y. Jin, H. Fu, Y. Yang and Y. Zhao, *Chem.–Eur. J.*, 2006, **12**, 3636.

12 J. Chen, Y. Zhang, W. Hao, R. Zhang and F. Yi, *Tetrahedron Lett.*, 2013, **69**, 613.

13 B. M. Rosen, K. W. Quasdorf, D. A. Wilson, N. Zhang, A. M. Resmerita, N. K. Garg and V. Percec, *Chem. Rev.*, 2011, **111**, 1346.

14 (*a*) C. Chen and L.-M. Yang, *J. Org. Chem.*, 2007, **72**, 6324; (*b*) C.-Y. Gao and L.-M. Yang, *J. Org. Chem.*, 2008, **73**, 1624; (*c*) J.-H. Huang and L.-M. Yang, *Org. Lett.*, 2011, **13**, 3750; (*d*) X.-H. Fan, G. Li and L.-M. Yang, *J. Organomet. Chem.*, 2011, **696**, 2482.

15 W. Wu, X.-L. Li, X.-H. Fan and L.-M. Yang, *Eur. J. Org. Chem.*, 2013, 862.