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Aust. J. Chem. **2012**, *65*, 1687–1690
http://dx.doi.org/10.1071/CH12350

Communication

Cu(OAc)$_2$-Mediated Cross-Coupling Reaction of Benzophenone *N,N,N*-Trimethylhydrazonium Salts and Aryl Boronic Acids

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Cu(OAc)$_2$-mediated coupling of benzophenone *N,N,N*-trimethylhydrazonium salts and aryl boronic acids proceeded to afford *N*-aryl imines.

Manuscript received: 24 July 2012.
Manuscript accepted: 11 September 2012.

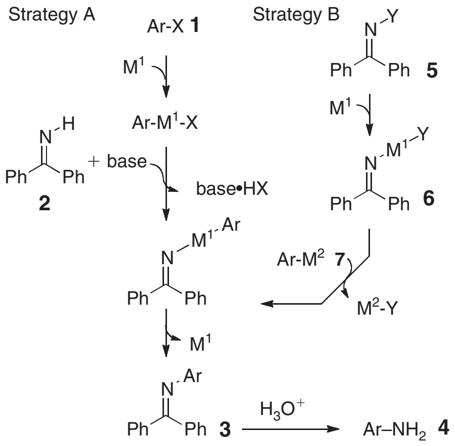
Recent progress on the synthesis of aryl amines based on the metal-catalyzed C-N bond formation reaction is remarkable.[1] In general, aryl halides and nucleophilic amino compounds are used in the C-N bond formation reaction. For the synthesis of protected primary aryl amines, *N*-H imine (C = NH, such as **2**) is an efficient nitrogen donor because the coupling product, *N*-aryl imine **3**, is stable under various conditions and is easily transformed to the corresponding primary amine **4** under mild acidic conditions (Scheme 1, strategy A).[2,3] The metal-catalyzed cross-coupling of imines having a leaving group at the imino-nitrogen (e.g. **5**: C = N-Y, where Y is a leaving group) and an aryl metal species **7** is an alternative method for the synthesis of *N*-aryl imine **3** (strategy B); however, this strategy has not been well examined partly because of few studies on the oxidative addition of **5** to the metal complex ($\mathbf{5} + \mathrm{M}^1 \rightarrow \mathbf{6}$).[4] Recently, the Cu-catalyzed coupling of benzophenone oxime **5** (Y = $\mathrm{OCOC_6F_5}$ or OAc) and aryl boronic acid **7** ($\mathrm{M}^2 = \mathrm{B(OH)_2}$) was reported.[5,6] This reaction proposed the intermediacy of alkylidene aminocuprate **6** formed by the oxidative addition of oximes to a copper complex.[4,6]

Previously, we reported the amino-Heck reaction (Narasaka-Heck reaction)[4c,7] of γ,δ-unsaturated ketone *N,N,N*-trimethylhydrazonium salts to give pyrroles.[8] This reaction is proposed to be initiated by oxidative addition of a *N,N,N*-trimethylhydrazonium salt to a palladium(0) complex, resulting in the formation of an alkylideneaminopalladium(II) species. This result suggested that the *N,N,N*-trimethylhydrazonium salt could be used as an imino donor **5** similar to the oxime for the synthesis of *N*-aryl imine **3** by strategy B as shown in Scheme 1. Thus, we decided to examine the metal-mediated coupling of *N,N,N*-trimethylhydrazonium with aryl boronic acid. In this letter, we describe the outcome of this investigation.[9]

Benzophenone *N,N,N*-trimethylhydrazonium iodide derivatives **10** were prepared from corresponding ketones **8** in two steps, using a modification to Smith's procedure[9] (Table 1). Benzophenone (**8a**) and several methoxy-substituted benzophenones **8b**–**d** were transformed to *N,N*-dimethylhydrazones **9** in moderate to high yields ($\mathrm{Me_2N\text{-}NH_2}$, cat AcOH, in a sealed tube at 140°C) (Runs 1–4). Interestingly, 2,5-dimethoxy benzophenone **8e** was not converted to the corresponding hydrazone **9e** under the reaction conditions (Run 5). Successively, hydrazones **9a**–**c** were converted to *N,N,N*-trimethylhydrazonium iodide **10a**–**c** by reacting with MeI in a sealed tube (Runs 1–3).[9] Benzophenone *N,N,N*-trimethylhydrazonium hexafluorophosphate (**11**) was prepared from iodide **10a** by treating with $\mathrm{NH_4PF_6}$ [$\mathrm{NH_4PF_6}$ (1.5 equiv), $\mathrm{CH_2Cl_2}$, $\mathrm{H_2O}$, rt, 10 h, 98 %].

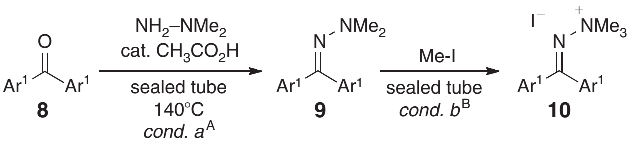
Next, the metal-mediated coupling of diaryl ketone *N,N,N*-trimethylhydrazonium salts and aryl boronic acids was examined (Table 2). The reaction products were determined after evaporation of the reaction mixture and separation by silica gel column chromatography.

Initially, we attempted to couple benzophenone *N,N,N*-trimethylhydrazonium iodide (**10a**) and *p*-tolylboronic acid (**12a**) in the presence of a metal catalyst in 1,4-dioxane at 70°C (Table 2, Runs 1–13). Although no coupling product was formed by the treatment of either Pd(0) or Pd(II) metal catalyst [$\mathrm{Pd(PPh_3)_4}$, $\mathrm{Pd_2(dba)_3}$ + [1,1′-bis(diphenylphosphino) ferrocene] (dppf), $\mathrm{Pd_2(dba)_3}$ + [1,3-Bis(diphenylphosphino) propane] (dppp), or $\mathrm{Pd(OAc)_2}$], the desired imine **14a** was obtained in 29 % when 10 mol-% $\mathrm{Pd(PPh_3)_4}$ and 1.2 equiv of $\mathrm{Cu(OAc)_2}$ were used (Run 1). By adding dppp or dppf as a ligand in the catalyst system of Pd(0)-$\mathrm{Cu(OAc)_2}$, the yield of imine **14a** increased to 44 and 54 %, respectively (Runs 3 and 4). By treating either with Cu(II) or Cu(I) salts such as $\mathrm{Cu(OAc)_2}$ or Cu(OAc), *N*-aryl imine **14a** was obtained in 44 and 40 % yield, respectively, which suggested that the same active copper species formed from both $\mathrm{Cu(OAc)_2}$ and Cu(OAc) in the coupling reaction conditions (Runs 4 and 5, respectively).[10] By the combined use of $\mathrm{Cu(OAc)_2}$ and Cu, *N*-aryl imine **14a** formed in 38 % yield (Run 6). Cu(I) thiophene-2-carboxylate



Scheme 1. Metal-catalyzed synthesis of *N*-Aryl imines **3**.

Table 1. Preparation of benzophenone *N,N,N*-trimethylhydrazonium salts 10



Run	Ar^1	$Cond^A$	Yield of **9** [%]^C	$Cond^B$	Yield of **10** [%]^C
1	**a**: C_6H_5	15 h	91	100°C, 10 min	71
2	**b**: 4-$MeOC_6H_4$	15 h	90	60°C, 10 min	61
3	**c**: 3,4-$(MeO)_2C_6H_3$	18 h	38	40°C, 10 min	50
4	**d**: 2,4-$(MeO)_2C_6H_3$	13 h	54	100°C, 20 min	0
5	**e**: 2,5-$(MeO)_2C_6H_3$	96 h	0	–	

^{A}Molar ratio: **8**/NH_2-NMe_2/CH_3CO_2H = 1/3/0.1.
^{B}Molar ratio: **9**/MeI = 1/3.
^{C}Isolated yields.

(CuTC) showed almost the same reactivity to Cu(OAc) and $Cu(OAc)_2$ (Run 7).[11] As shown in Run 8, the use of a catalytic amount of Cu reagent was ineffective in forming **14a**. The counter anion of the Cu reagent was found to be important for the coupling. Copper halides were ineffective in forming imine **14a** regardless of the use of Cu(II) or Cu(I) (Runs 9–11). Addition of dppf was also effective in the coupling reaction with $Cu(OAc)_2$, and afforded imine **14a** in 60 % yield (Run 13).

Next, various *p*-tolylboronic acid derivatives were examined under $Cu(OAc)_2$-mediated reaction conditions. The coupling reaction of boronic acid esters (*p*-tolylboronic acid ester of propylene glycol, 2,2-dimethylpropylene glycol, pinacol, and catechol) did not proceed at all. The coupling of potassium *p*-tolyltrifluoroborate (**13**) proceeded, but the yield of **14a** was lower than that obtained by the reaction with boronic acid **12a** (Table 2, 13 versus 14).

In the Pd(0)-catalyzed amino-Heck reaction of *N,N,N*-trimethylhydrazonium salt, a poorly nucleophilic anion such as BF_4^- and PF_6^- was found to be suitable as the counter anion of the salts.[8] However, in the $Cu(OAc)_2$-mediated coupling reaction, hexafluorophosphate **11** was not suitable as shown in Run 15.

A series of arylboronic acids were then subjected to the optimized conditions (Run 13) with benzophenone *N,N,N*-trimethylhydrazonium iodide **10a** (Runs 16–19). When *o*-tolylboronic acid was used, the coupling product **14b** was obtained in 54 % yield (Run 16). The reaction with phenylboronic acid having an electron-deficient group such as a cyano group did proceed, giving coupling product **14c**; however, the yield was 10 % and benzophenone (**8a**) was formed in 40 % yield (Run 17). In the reaction of *o*- or *p*-methoxyphenylboronic acid, the coupling product was obtained in 35 and 24 % yield, respectively (Runs 18 and 19).

The reaction of methoxy-substituted benzophenone hydrazonium salts with *p*-tolylboronic acid (**12a**) was also examined (Runs 20 and 21). Hydrazonium salt **10b** (Ar^1 = 4-$MeOC_6H_4$) reacted smoothly to give the corresponding imine **14f** in 60 % yield (Run 20). In the reaction of tetramethoxy hydrazonium salt **10c** (Ar^1 = 3,4-$(MeO)_2C_6H_3$), ketone **8c** was formed as a major product and the coupling product **14 g** was obtained in 36 % yield (Run 21).

In the $Cu(OAc)_2$-mediated coupling of diaryl ketone *N,N,N*-trimethylhydrazonium salts **10** and aryl boronic acids **12**, the formation of diaryl ketone **8**, hydrazone **9**, and aryl amine **15** was observed in some case. Ketone **8** could be formed by the hydrolysis of the coupling product **14,** hydrazonium salt **10**, or imino metal species such as **6** as depicted in Scheme 1, although the actual reaction mechanism is unclear. Hydrazone **9** presumably formed by demethylation as a result of attack of nucleophilic materials such as I^- in the reaction mixture. Aryl amine **15** was supposedly formed by the hydrolysis of the coupling product **14**.

In conclusion, we have developed a copper-mediated coupling of *N,N,N*-trimethylhydrazonium salts and aryl boronic acids to give *N*-aryl imines. The formation of *N*-aryl imine **14** suggested that $N(sp^2)$–$N(sp^3)$ bond cleavage had occurred by the aid of a copper complex, and thus, formed an alkylidene amino copper species such as **6** coupled with aryl boronic compounds. We could demonstrate the N-N bond cleavage and its application in the synthesis of nitrogen-containing compounds.[12] *N,N*-Dialkylhydrazones and *N,N,N*-trialkylhydrazonium salts are often used as the corresponding carbonyl compounds;[13] we showed that *N,N,N*-trimethylhydrazonium salt could be used as the nitrogen donor (ammonia equivalent) and expand the chemistry of hydhydrazonium salt. Further studies on the scope and the mechanism of the reaction are currently in progress.

Experimental

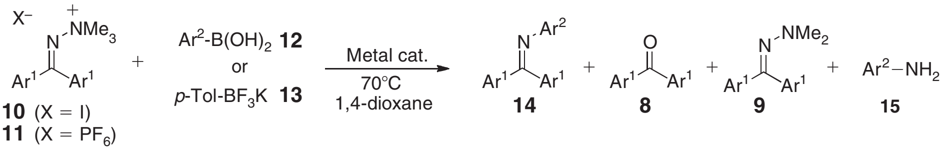
Typical Procedure for the Synthesis Diarylketone N,N,N-*Trimethylhydrazonium Salts Table 1, Run 1)*

A mixture of benzophenone *N,N*-dimethylhydrazone **9a** (1.0 g, 4.5 mmol) and iodomethane (1.9 g, 13 mmol) in ethanol in a sealed tube was stirred for 10 min at 100°C. After the reaction mixture was cooled to room temperature, volatile materials were removed under vacuum and the crude materials were purified by recrystallization (hexane, ethanol) to afford pure benzophenone *N,N,N*-trimethylhydrazonium iodide **10a** in 71 % yield.

Typical Procedure for the $Cu(OAc)_2$-Catalyzed Coupling Reaction of Benzophenone N,N,N-*Trimethylhydrazonium Salts and Aryl Boronic Acids (Table 2, Run 13)*

A mixture of benzophenone *N,N,N*-trimethylhydrazonium iodide (**10a**, 0.5 mmol), *p*-tolylboronic acid (**12a**, 0.60 mmol), $Cu(OAc)_2$ (0.6 mmol), and dppf (0.05 mmol) in dry 1,4-dioxane under a nitrogen atmosphere was stirred for 1 h at 70°C. After

Table 2. Metal-catalyzed coupling of benzophenone *N,N,N*-trimethylhydrzonium salts and aryl boronic acid derivatives[A]



Run	Ar^1	**10** or **11**	Ar^2	**12** or **13**	Metal cat. (equiv)	Time [h]		Yield [%][B]		
1	Ph	**10a**	*p*-Tol	**12a**	$Pd(PPh_3)_4$ (0.01), $Cu(OAc)_2$ (1.2)	1.5	**14a** 29	**8a** 65	**9a** 2	
2	Ph	**10a**	*p*-Tol	**12a**	$Pd_2(dba)_3$ (0.005), $Cu(OAc)_2$ (1.2), dppp (0.02)	3	**14a** 44	**8a** 32	**9a** 5	
3	Ph	**10a**	*p*-Tol	**12a**	$Pd_2(dba)_3$ (0.005), $Cu(OAc)_2$ (1.2), dppf (0.02)	3	**14a** 54	**8a** 40	**9a** 5	
4	Ph	**10a**	*p*-Tol	**12a**	$Cu(OAc)_2$ (1.2)	1	**14a** 44	**8a** 23	**9a** 2	**15a** 2
5	Ph	**10a**	*p*-Tol	**12a**	Cu(OAc) (1.2)	1	**14a** 40	**8a** 36	**9a** 1	
6	Ph	**10a**	*p*-Tol	**12a**	Cu(OAc) (0.6), Cu (0.6)	1	**14a** 38	**8a** 22		
7	Ph	**10a**	*p*-Tol	**12a**	CuTC (1.2)	3	**14a** 36	**8a** 56	**9a** 7	**15a** 1
8	Ph	**10a**	*p*-Tol	**12a**	$Cu(OAc)_2$ (0.1)	4	**14a** trace	**8a** 15		
9	Ph	**10a**	*p*-Tol	**12a**	CuI (1.2)	4		**8a** 9		
10	Ph	**10a**	*p*-Tol	**12a**	CuCl (1.2)	4		**8a** 57		
11	Ph	**10a**	*p*-Tol	**12a**	$CuCl_2$ (1.2)	4		**8a** 13		
12	Ph	**10a**	*p*-Tol	**12a**	$Cu(OAc)_2$ (1.2), PPh_3 (0.2)	1	**14a** 49	**8a** 11	**9a** 7	
13	Ph	**10a**	*p*-Tol	**12a**	$Cu(OAc)_2$ (1.2), dppf (0.1)	1	**14a** 60	**8a** 28	**9a**8	
14	Ph	**10a**	*p*-Tol	**13**	$Cu(OAc)_2$ (1.2), dppf (0.1)	2	**14a** 29	**8a** 15	**9a** 8	**15a** 13
15	Ph	**11**	*p*-Tol	**12a**	$Cu(OAc)_2$ (1.2)	1	**14a** trace	**8a** 12		
16	Ph	**10a**	*o*-Tol	**12b**	$Cu(OAc)_2$ (1.2), dppf (0.1)	1	**14b** 54		**9a** 28	
17	Ph	**10a**	*p*-$(CN)C_6H_4$	**12c**	$Cu(OAc)_2$ (1.2), dppf (0.1)	1	**14c** 10	**8a** 40	**9a** 19	
18	Ph	**10a**	*o*-$(MeO)C_6H_4$	**12d**	$Cu(OAc)_2$ (1.2), dppf (0.1)	1	**14d** 35	**8a** 23	**9a** 27	
19	Ph	**10a**	*p*-$(MeO)C_6H_4$	**12e**	$Cu(OAc)_2$ (1.2), dppf (0.1)	1	**14e** 24	**8a** 20	**9a** 15	
20	4-$MeOC_6H_4$	**10b**	*p*-Tol	**12a**	$Cu(OAc)_2$ (1.2), dppf (0.1)	2	**14f** 60	**8b** 17		
21	3,4-$(MeO)_2C_6H_3$	**10c**	*p*-Tol	**12a**	$Cu(OAc)_2$ (1.2), dppf (0.1)	2	**14g** 36	**8c** 50		

[A] The reaction was conducted with **10** or **11** (0.5 mmol), aryl boronic acid derivative (**12** or **13**, 1.2 equiv), and metal catalyst in 1,4-dioxane (1 mL) at 70°C.
[B] Isolated yields.

the reaction mixture was cooled to room temperature, volatile materials were removed under vacuum and the crude materials were purified by flash column chromatography (SiO_2, hexane/ethyl acetate = 20/1) to give *N*-diphenylmethylen-4-methylphenylamine **14a** (60 %), benzophenone (**8a**, 28 %), and hydrazone **9a** (8 %).

Supplementary Material

General experimental details and physical data including $^1H/^{13}C$ NMR charts for benzophenone *N,N,N*-trimethylhydrazonium iodide **10a**–**10c** and selected coupling products **14a, 14f, 14g** are available on the Journal's website.

Acknowledgements

This research was partially supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports and Culture, Japan.

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