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Transition-Metal-Free Dehydrogenative N–N Coupling of Secondary Amines with KI/KIO$_4$

Dehang Yin,[a] and Jian Jin*[a]

Abstract: A transition-metal-free method for the dehydrogenative N–N coupling of secondary amines has been accomplished. This oxidative KI-KIO$_4$ protocol is mild and operationally simple. A diverse range of diphenylamines, carbazoles and *N*-alkylanilines readily undergo N–N homo-coupling effectively. Notably, the N–N cross-coupling of two different arylamines is also demonstrated, which provides a straight-forward approach to the complex N–N structures.

Introduction

The N–N bonds are widely found in natural products,[1] pharmaceutical agents[2] and organocatalysts.[3] Compared to the C–C and C–N bonds which have received numerous elegant methods to enable their chemical synthesis, the N–N bond formation is less explored. Although simple substrates containing an N–N bond can be prepared from hydrazine, this is a non-viable option for complex molecules due to the overall inefficiency of multiple functionalization steps. Moreover, most hydrazine building blocks are highly carcinogenic and need extra safety precaution. Dehydrogenative coupling is drawing much attention because of high efficiency, atom economy and minimal environmental impact.[4] However, the traditional methods for direct N–N bond formation featured stoichiometric transition-metal oxidants, such as KMnO$_4$ which was still used frequently nowadays (Figure 1, path A).[5] Cu-catalyzed aerobic oxidation approach represented a major advance in this field. Several protocols were developed since Tsuji's seminal work (Figure 1, path B).[6] Very recently, an Fe-catalyzed version had also been reported (Figure 1, path C).[7] Remarkably, electrochemistry has experienced a renaissance in the field of organic synthesis,[8] which leads to the successful application in N–N bond construction (Figure 1, path D).[9] Herein we describe an operationally simple, transition-metal-free method for the dehydrogenative N–N coupling of secondary amines with KI/KIO$_4$ (Figure 1, path E).

Results and Discussion

We began our investigation into this dehydrogenative N–N coupling by subjecting bis(4-bromophenyl)amine to different transition-metal-free oxidants in MeCN at room temperature (Table 1). Like other oxidants we tried, KIO$_4$ failed to render any reaction alone (entry 1). Delightfully, after the additive screening, a dramatic and positive effect was observed. It afforded a quantitative yield of the dimeric product **1** when catalytic amount of KI or KI$_3$ was added into the reaction (entries 2–6). We chose KI as the additive for the following experiments with different oxidants (entries 7–14). NaClO indeed worked for the oxidation although with a moderate yield of 61% (entry 13). The expensive PhIO and PhI(OAc)$_2$ also performed well with high yields (entries 13 and 14). This oxidative N–N coupling reaction could be carried out in a variety of solvents (See Supporting Information), such as CH$_2$Cl$_2$ and MeOH among others (entries 15 and 16). While a nitrogen radical–radical coupling mechanism is preferred, we could not exclude other pathways at this stage.

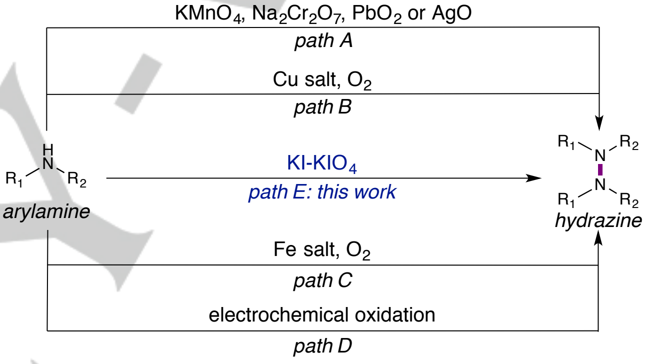

Figure 1. Dehydrogenative N–N coupling reactions.

With the optimal conditions in hand, we sought to evaluate the generality of the dehydrogenative N–N coupling protocol. Firstly, good to high yields of tetraphenylhydrazines could be obtained from diphenylamines bearing both electron-withdrawing and electron-donating groups (Scheme 1). The reaction of diphenylamines was typically clean with almost no C–N coupling byproduct observed, thus the N–N coupling products could be separated easily.

Application of this oxidative N–N coupling method to carbazoles at 80 ºC furnished bicarbazoles effectively (Scheme 2). Similar to the previous reports,[6e,9a] carbazoles lacking substitution at one or both of the 3- and 6-positions suffered from C–N coupling side reactions to some extent. It is of note that the halide substituents on aryl rings are useful for the further transformation. Recently, several natural products with the bicarbazole core structure were isolated.[10] Therefore, this N–N coupling method provides a practical approach to the total synthesis of these bioactive natural products.

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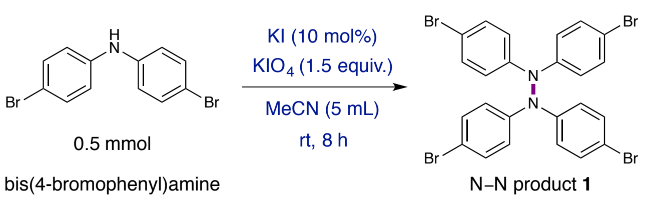
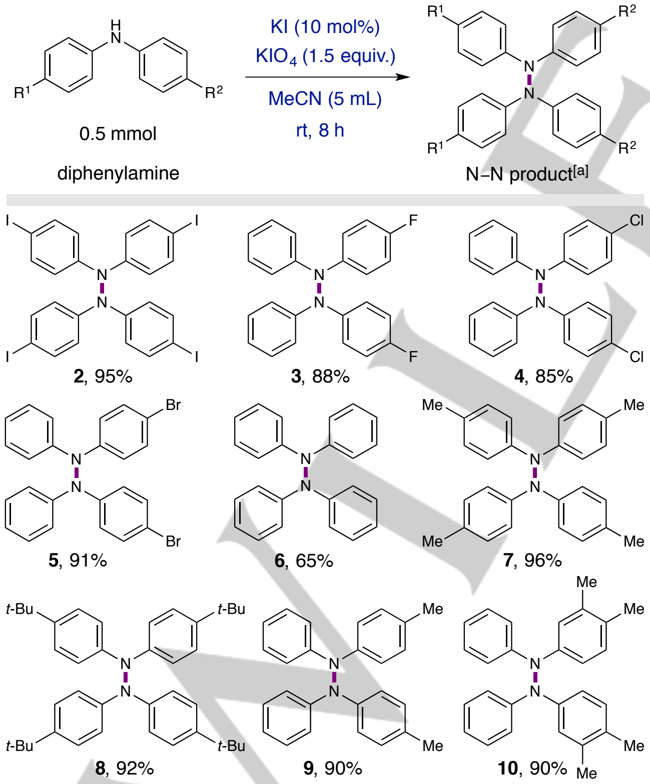
Table 1. Optimization of the Reaction Conditions.

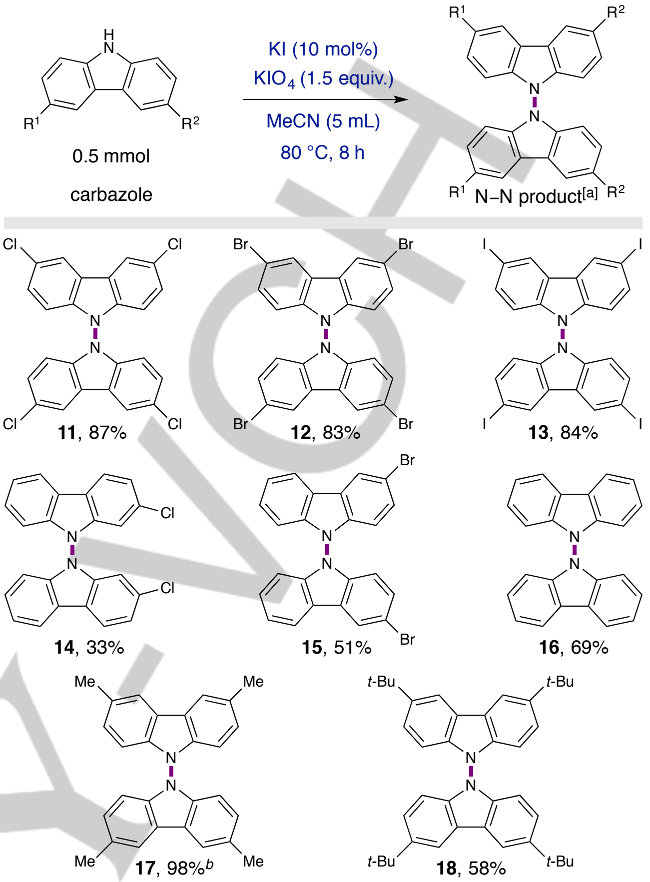


Entry	Additive	Oxidant	Conversion (%)	Yield (%)[a]
1	–	KIO_4	0	0
2	KI	KIO_4	100	99
3	KBr	KIO_4	0	0
4	KCl	KIO_4	0	0
5	I_2	KIO_4	0	0
6	KI_3	KIO_4	100	99
7	KI	KIO_3	0	0
8	KI	$NaBrO_3$	0	0
9	KI	$NaClO_4$	0	0
10	KI	$NaClO_3$	0	0
11	KI	$NaClO_2$	0	0
12	KI	NaClO	100	61
13	KI	$PhI(OAc)_2$	100	96
14	KI	PhIO	100	96
15[b]	KI	KIO_4	100	99
16[c]	KI	KIO_4	64	64

[a] Yields determined by H NMR using 1,3-benzodioxole as the internal standard. [b] CH_2Cl_2 used as the solvent. [c] MeOH used as the solvent.



Scheme 1. Oxidative Coupling of Diphenylamines. [a] Isolated yields. See Supporting Information for experimental details.

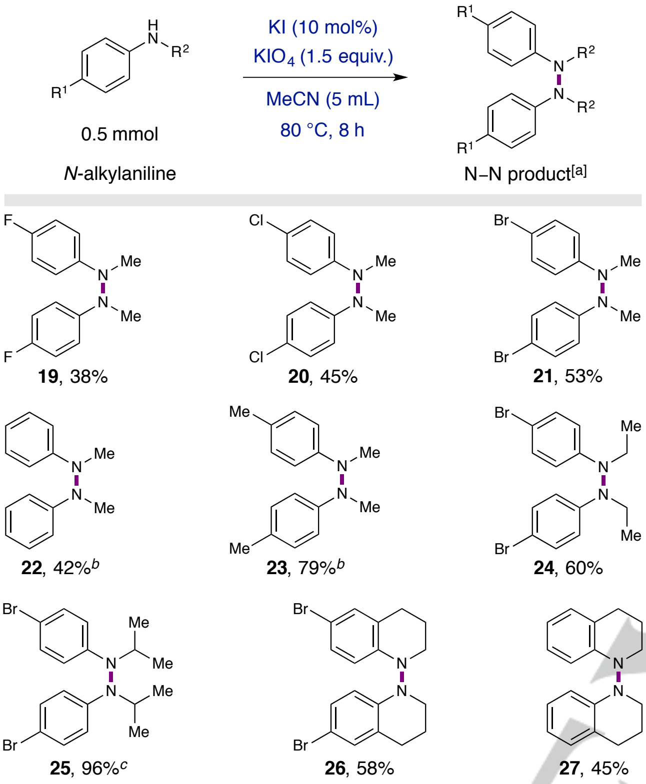


Scheme 2. Oxidative Coupling of Carbazoles. [a] Isolated yields. See Supporting Information for experimental details. [b] Reaction performed at room temperature for 12 h.

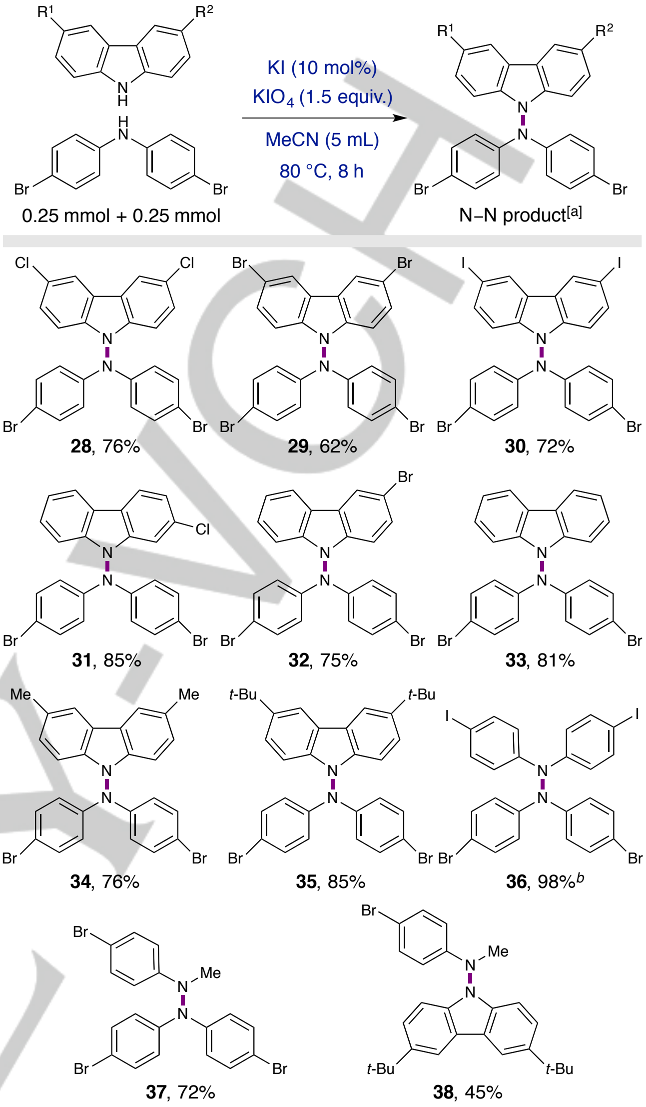
Oxidative dimerization of *N*-alkylanilines was also feasible under the dehydrogenative conditions (Scheme 3). *N*-Methyl, ethyl, isopropyl and cyclic anilines afforded the corresponding N–N coupling products in moderate to high yields. In general, the electron-richer substrates which are more prone to be oxidized exhibit the higher reactivity.

Finally, the N–N cross-coupling of two different arylamines were explored (Scheme 4). When bis(4-bromophenyl)amine and a carbazole substrate with a 1:1 ratio were subjected to the oxidative conditions, a high-level cross-coupling occurred while almost no homo-coupling product was observed. The cross-coupled products of up to 85% yields showed significantly greater-than-statistical selectivity (50% statistical yield for the 1:1 substrate ratio). Remarkably, a quantitative yield of the cross-coupled product **36** was obtained from 1:1 ratio of bis(4-bromophenyl)amine and bis(4-iodophenyl)amine. Moreover, the 1:1 mixture of bis(4-bromophenyl)amine and 4-bromo-*N*-methylaniline afforded a 72% yield of the cross-coupled product **37**. The final example showed that 3,6-di-*tert*-butyl-9*H*-carbazole could also cross-couple with 4-bromo-*N*-methylaniline. The origin of the cross-coupling outcome might be the quite weak N–N bond of tetraphenylhydrazines (e.g., BDE = 23.5 kcal/mol for $Ph_2N–NPh_2$).[6e,11] The dimerization of bis(4-bromophenyl)amine should be reversible, which eventually shifts the equilibrium to the more stable cross-coupled products. The above hypothesis was supported well by the experiment shown in Scheme 5.

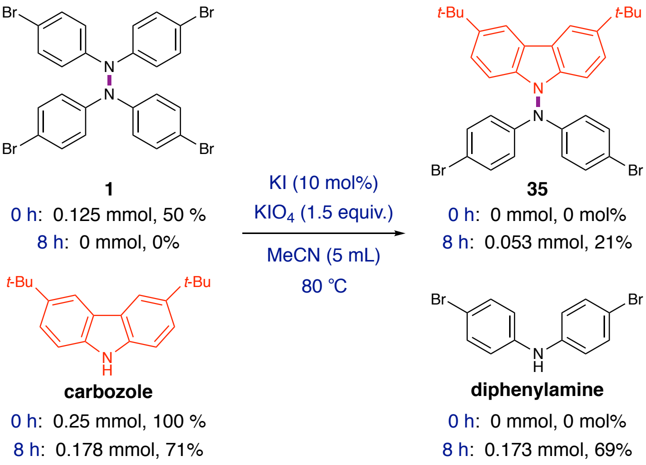
When an 1:2 mixture of the homo-coupling product **1** and 3,6-di-*tert*-butyl-9*H*-carbazole was subjected to the reaction conditions for 8 hours, it furnished the cross-coupling product **35** in 21% yield along with a 69% yield of bis(4-bromophenyl)amine.



Scheme 3. Oxidative Coupling of *N*-Alkylanilines. [a] Isolated yields. See Supporting Information for experimental details. [b] Reaction performed at room temperature for 8 h. [c] Reaction performed at 40 °C for 4 h.



Scheme 4. Selective N–N Cross-Coupling. [a] Isolated yields. See Supporting Information for experimental details. [b] Reaction performed at room temperature for 8 h.



Scheme 5. The possible origin of the cross-coupling.

Conclusion

In summary, we have developed a transition-metal-free method for the dehydrogenative N–N coupling of secondary amines with KI/KIO_4. The substrate scope includes but not limited to various diphenylamines, carbazoles and *N*-alkylanilines, furnishing homo-coupled tetraphenylhydrazines, bicarbazoles and dialkyl-diphenylhydrazines effectively. Moreover, the N–N cross-coupling of two different arylamines has also been demonstrated. This reaction is mild and operationally simple, which we anticipate would find broad applications in N–N bond formation. Further studies on the mechanism and extension of the KI/KIO_4 system are currently undergoing in our lab.

Experimental Section

General Procedure for the N–N cross-coupling: To an 8 mL vial equipped with a Teflon septum and a magnetic stir bar was charged KI (8.3 mg, 0.05 mmol, 0.1 equiv.), KIO_4 (172.5 mg, 0.75 mmol, 1.5 equiv.), secondary amine (0.50 mmol, 1.0 equiv.), and 5 mL of MeCN. The reaction mixture was degassed by sparging with nitrogen for 10 min with an outlet needle, and then reacted at room temperature or 80 ºC. Upon reaction completion as judged by TLC and LCMS (4-12 hours), the reaction mixture was concentrated *in vacuo*. Purification of the crude product by flash chromatography on silica gel or aluminium oxide neutral using petroleum ether afforded the desired product.

Acknowledgements

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Keywords: metal-free • N–N coupling • diphenylamine • carbazole • *N*-alkylaniline

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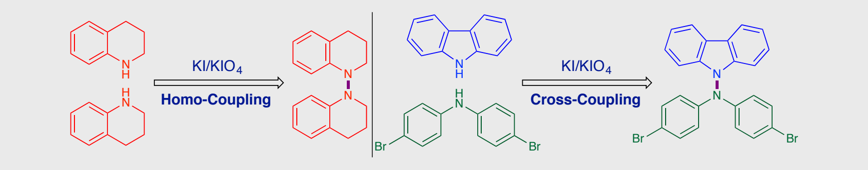

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Transition-Metal-Free Dehydrogenative N–N Coupling of Secondary Amines with KI/KIO$_4$

Iodine brother do it together: With the recipe of KI/KIO$_4$, a transition-metal-free method for the dehydrogenative N–N coupling of secondary amines has been accomplished. A diverse range of diphenylamines, carbazoles and *N*-alkylanilines readily undergo N–N homo-coupling effectively. Notably, the N–N cross-coupling of two different arylamines is also demonstrated, which provides a straight-forward approach to the complex N–N structures.

Key Topic: N–N coupling