View Article Online View Journal

ChemComm

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: J. Tang, L. Lv, X. Dai, C. Li, Li and C. Li, *Chem. Commun.*, 2018, DOI: 10.1039/C7CC09290C.



This is an Accepted Manuscript, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this Accepted Manuscript with the edited and formatted Advance Article as soon as it is available.

You can find more information about Accepted Manuscripts in the **author guidelines**.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard <u>Terms & Conditions</u> and the ethical guidelines, outlined in our <u>author and reviewer resource centre</u>, still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this Accepted Manuscript or any consequences arising from the use of any information it contains.



rsc.li/chemcomm

Published on 22 January 2018. Downloaded by University of Reading on 22/01/2018 15:46:28.



COMMUNICATION

Nickel-Catalyzed Cross-Coupling of Aldehydes with Aryl Halides via Hydrazone Intermediates

Received 00th January 20xx, Accepted 00th January 20xx

Jianting Tang,^{ab} Leiyang Lv,^a Xi-Jie Dai,^a Chen-Chen Li,^a Lu Li,^a and Chao-Jun Li*^a

DOI: 10.1039/x0xx00000x

www.rsc.org/

Traditional cross-couplings require stoichiometric organometallic reagents. A novel nickel-catalyzed cross-coupling reaction between aldehdyes and aryl halides via hydrazone intermedaites has been developed, merging the Wolff-Kishner reduction and the classical cross-coupling reactions. Aromatic aldehydes, aryl iodides and aryl bromides are especially effective in the new crosscoupling chemistry.

The Wolff-Kishner reaction, discovered by Kishner in 1911¹ and Wolff in 1912,² is a synthetically effective method to reduce carbonyls into methylene derivatives through decomposition of the formed hydrazone intermediates.³ It is widely accepted that the reaction (Scheme 1a) begins with reversible formation of hydrazone and, then, the deprotonation gives an N-anionic intermediate.⁴ The subsequent transformation of this intermediate to carbanion is the rate-determining step, which is followed by rapid proton-transfer, evolution of nitrogen gas and protonation of the new carbanion to finally deliver the reduced product.⁴ However, Wolff's and Kishner's original protocols are inconvenient because the prepared hydrazones need to be mixed with hot solid KOH and porous platinized plate,¹ or heated within a sealed tube at 160–200 °C.² Thus, different modifications for this reaction were developed to replace these harsh conditions, of which a milestone was attained by Huang who operated the reaction by employing excessive safer and cheaper hydrazine hydrate (N_2H_4 · H_2O) as well as high-boiling-point solvents.⁵ This protocol is also problematic since a temperature of about 190 °C is required to achieve a satisfactory reaction rate.⁵ In this regard, Cram, Myers, Caglioti and Henbest further improved the reaction by lowering the temperature to room temperature, $^{4, 6}$ 66 $^{\circ}C^{7}$ and 100 °C,⁸ respectively. However, under such temperature, these methods necessitate intractable isolation of generally unstable hydrazones ahead of their reduction,^{4, 7} or suffer from low yield (≤ 60 %) of the target products,⁸ or need laborious preparation of 1,2-bis(tert-butyldimethylsilyl)-hydrazine.⁶ Therefore, continuing efforts to make the Wolff-Kishner reaction more practical by simultaneously lowering the reaction temperature, simplifying the operation procedure and achieving high yields is still highly desirable.

Besides the Wolff-Kishner reduction, another essential tool in modern synthetic chemistry is the various transition-metal catalyzed cross-coupling reactions (Scheme 1b) between different electrophiles,⁹ or between nucleophiles and electrophiles such as the Suzuki coupling, 10, 11 the Kumada coupling,¹⁰ the Stille coupling,^{10, 11} the Hiyama coupling,^{10, 11} the Negishi coupling,^{10, 11} the Sonogashira coupling¹¹ and decarboxylative coupling.¹² The "carbanion equivalents" are R– B(OH)₂,^{10, 11} –Si(OR)₃,^{10, 11} –MgBr,¹⁰ –ZnCl,^{10, 11} –Sn(Bu)₃,^{10, 11} or -COOH,¹² etc., while the electrophiles are generally Ar-I,^{10,11} -Br,^{10, 11} or –Cl.^{10, 11} We postulated that the hydrazones involved in the well-known Wolff-Kishner reaction might be intercepted as the carbanion equivalents in the classical transition-metal catalyzed cross-coupling reactions, thus providing the reduced products through the concurrent coupling with electrophiles. This new cross-coupling chemistry would bridge the classical Wolff-Kishner reduction and the transition-metal catalyzed cross-coupling reactions, and thus provide a new tool in organic syntheses.

However, such a hypothesis poses a tremendous challenge because there have been extensive research works on the cross-coupling between hydrazones and electrophiles, *but none of them accessed such cross-coupling products*.¹³⁻¹⁶ Specifically, Mauger reported a cross-coupling of hydrazone with aryl halides catalyzed by palladium to produce the Narylation products, azines, exclusively in 2005.¹³ Immediately afterwards, a palladium-catalyzed cross-coupling between N*tert*-butylhydrazone and bromobenzene was developed by Hartwig to synthesize aryl ketones.¹⁵ In addition, various Ntosylhydrazones have been adopted in cross-coupling

^{a.} Department of Chemistry and FQRNT Centre for Green Chemistry and Catalysis, McGill University, 801 Sherbrook Street West, Montreal, Quebec H3A 0B8, Canada. E-mail: cj.li@mcgill.ca

^b Key Laboratory of Theoretical Organic Chemistry and Functional Molecule for Ministry of Education, School of Chemistry and Chemical Engineering, Hunan University of Science and Technology, 2 Taoyuan Road, Xiangtan, Hunan 411201, China

[†] Electronic Supplementary Information (ESI) available. See DOI: 10.1039/x0xx00000x

Published on 22 January 2018. Downloaded by University of Reading on 22/01/2018 15:46:28.

DOI: 10.1039/C7CC09290C Journal Name

reactions to construct substituted olefins¹⁴ and cyclic compounds.¹⁶ Nevertheless, we felt confident that through elaborate choice of transition-metal catalyst, ligand, solvent and base, we might be able to tune the cross-coupling from N-selectivity to C-selectivity, thereby leading to the reductive C-cross-coupling products upon loosing of nitrogen (Scheme 1c).



To begin our study, the hydrazone generated in situ from benzaldehyde (1a) and iodobenzene (2a) were selected as the model substrates. Recently, we reported the rutheniumcatalyzed nucleophilic addition of aldehyde hydrazone to carbonyl compounds,^{17, 18} arylimines,¹⁹ or conjugated carbonyl compounds.²⁰ However, the ruthenium-catalyzed system does not work for the designated cross-coupling (ESI⁺, Table 1S, entries 1-10). Thus, other transition metal catalysts such palladium (ESI[†], Table 2S, entries 1–30), copper (ESI[†], Table 3S, entries 1-8), cobalt (ESI[†], Table 3S, entries 9-13) and iron (ESI[†], Table 3S, entries 14-22) complexes were tested due to their great success in the previous cross-coupling reactions.^{10,} ²¹ Unfortunately, the desired cross-coupling product 3aa was detected only in trace amounts for these catalysts, with azines and benzene as the major byproducts. Lastly, we resorted to nickel catalysts to further study the reaction. Interestingly, while NiCl₂, NiBr₂, NiF₂, Ni(acac)₂, Ni(PPh₃)₄ and Ni(CO)₂(PPh₃)₂ catalysts all only gave a trace of **3aa** (ESI[†], Table 4S, entries 1– 25), Ni(COD)₂ showed marked efficiency in catalyzing this cross-coupling reaction. Subsequently, we focused our optimization of the reaction on $\operatorname{Ni}(\operatorname{COD})_2$ catalyst under different conditions (Table 1).

Notably, this protocol was designed to conduct the reaction at 50 °C in such a way that the *in situ* formed hydrazones were used directly without isolation (See Supporting Information for experiment details). It was found that phosphine ligand, base and solvent are all key factors for the success of this reaction. It should be noted that no cross-coupling product **3aa** was detected without Ni(COD)₂ catalyst. Without the ligand, quite low yield (19%) of **3aa** was obtained (Table 1, entry 1). Employing phosphine ligands like PPh₃, PPh₂Me and PPhMe₂ (Table 1, entries 2–4) gave increased yields of 31%, 44% and

59%, respectively. Among the ligands examined, PMe₃ gave the highest yield (Table 1, entry 5). We tentatively attributed this high reactivity to both the electron-donating and the small size of methyl group in the ligand. Thus, a similarly electronrich ligands PEt₃ and PCy₃ (Table 1, entry 6 and 7) only gave a trace of 3aa, which could be ascribed to the increased steric effect of the ethyl and cyclohexyl groups, shielding the active sites of the nickel catalyst from attack by the substrates. It is noteworthy that a much lower yield of 20% was observed for the methyldiphosphine analogue, dmpe ligand (Table 1, entry 8). The poor reactivity is likely due to the strong chelating effect between dmpe and nickel catalyst, which slowed down its dissociation from the metal centre during the catalytic cycle. The base is indispensable to the cross-coupling chemistry since no 3aa product was obtained without base (Table 1, entry 9). DBU as base provided the optimal yield, while the use of inorganic bases such as KO^tBu, KOH or K₃PO₄ resulted in much lower yields (Table 1, entries 10-12). The solvent also plays a vital role as THF was found to be the choice compared with dioxane, ethyl acetate, toluene and acetonitrile (Table 1, entries 13-17).

 Table 1. Optimization of the Ni(COD)2-catalyzed cross-coupling of benzaldehyde

 hydrazone with iodobenzene

| СНО | N ₂ H ₄ ·H ₂ O solvent, 25 °C | N ^r NH ₂ Ni(COD ligand (base solvent, | 2a (0.1 mmol)) ₂ (10 mol%) 50 mol%) 50 °C, 36 h | 3aa |
|-------|---|--|--|---------|
| entry | ligand | base | solvent | 3aa (%) |
| 1 | | DBU | THF | 19 |
| 2 | PPh ₃ | DBU | THF | 31 |
| 3 | PPh ₂ Me | DBU | THF | 44 |
| 4 | PPhMe ₂ | DBU | THF | 59 |
| 5 | PMe ₃ | DBU | THF | 71 |
| 6 | PEt ₃ | DBU | THF | trace |
| 7 | PCy3 | DBU | THF | trace |
| 8 | dmpe ^a | DBU | THF | 20 |
| 9 | PMe ₃ | - | THF | 0 |
| 10 | PMe ₃ | KOʻBu | THF | 29 |
| 11 | PMe ₃ | кон | THF | trace |
| 12 | PMe ₃ | K ₃ PO ₄ | THF | trace |
| 13 | PMe ₃ | DBU | dioxane | 43 |
| 14 | PMe ₃ | DBU | ethyl acetate | 41 |
| 15 | PMe ₃ | DBU | toluene | 24 |
| 16 | PMe ₃ | DBU | acetonitrile | 15 |
| 17 | PMe ₂ | DBU | hexane | trace |

Reaction conditions: **1a** (0.4 mmol), N_2H_4 ·H₂O (0.48 mmol), **2a** (0.1 mmol), Ni(COD)₂ (0.01 mmol), ligand (0.05 mmol), DBU (0.2 mmol), THF (450 μ L), 50 °C, 36 h, under N₂. See supporting information for experimental details. Yields of **3aa** were determined by ¹H NMR of the crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard. Trace yields of **3aa** were detected by GC-MS. [a] The amount of dmpe (1,2-bis(dimethylphosphino)ethane) is 0.025 mmol.

With the optimized conditions in hand, we then investigated the substrate scope of this novel cross-coupling reaction. A broad scope of aromatic aldehydes were proven effective for such transformations (Table 2). Aromatic aldehydes with electron-withdrawing groups performed more efficiently than those with electron-donating ones. Specifically, the Me- and MeO-substituted aldehydes provided the corresponding products in 20-82% yields (Table 2, 3ba, 3ca, 3da, 3ea, 3fa, 3ga, 3ha and 3ia). Surprisingly, the target products were obtained in excellent yields for the 2-F and 2-Cl benzaldehydes (93% and 91% respectively) even with smaller loading of catalyst (5 mol%) within a shorter reaction time (24 h) (Table 2, 3ja and 3ka). Under the same conditions, 3-F and 3-Cl substituted benzaldehydes also gave excellent yields of 95% and 92%, respectively (Table 2, 3la and 3ma). Lower yields were obtained for the para-substituted aromatic aldehydes (Table 2, 3na and 3oa). However, only 20% yield was afforded for the 4-CF₃ aromatic aldehyde, which possesses a strong electron-withdrawing group (Table 2, 3pa). Similarly, increasing the number of -Cl group also resulted in lower yields of the corresponding target products (Table 2, 3qa and 3ra). To our delight, when 1-naphthaldehyde was used, 95% of the target product was achieved (Table 2, 3sa). A slightly decreased yield of 80% was obtained with 9phenanthrenecarboxaldehyde (Table 2, 3ta). This optimized protocol can also be applied to heterocyclic aldehydes and excellent to moderate yields were obtained for 2-furaldehyde (90%, Table 2, 3ua) and 3-thiophenecarboxaldehyde (62%, Table 2, 3va), respectively. The catalytic system, however, converts phenylacetaldehyde and propionaldehyde to the desired products in trace yields (Table 2, 3wa and 3xa). Encouragingly, 8% or 30% yields were obtained by using the longer chain 2-pentenal and cinnamaldehyde substrates, respectively (Table 2, 3ya and 3za).



Reaction conditions: **1** (0.4 mmol), N₂H₄·H₂O (0.48 mmol), **2a** (0.1 mmol), Ni(COD)₂ (0.01 mmol), PMe₃ (0.05 mmol), DBU (0.2 mmol), THF (450 μ L), 50 °C, 36 h, under N₂. See supporting information for experimental details. Yields of isolated product **3** are given unless otherwise noted. Trace yields of **3** were detected by GC-MS. [a] Yields were determined by GC-MS and ¹H NMR of the crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard because of difficult isolation of **3**.

This cross-coupling chemistry also demonstrated its sensitivity to the electronic properties of the substituted iodobenzene (2) (Table 3). Electron-donating groups such as 4-OMe, 4-Me, 2-Me, and 4-NH₂ on 2 mediated the reaction with yields up to 71%, but longer reaction time of 48-72 h is required (Table 3, 3ba (X = I), 3fa, 3ga and 3ab). In contrast to iodobenzene, chlorobenzene did not react with benzaldehyde hydrazone to produce 3aa under the optimized conditions (Table 3, 3aa, X = Cl). Thus, using 4-chloroiodobenzene as the substrate gave a 55% of the iodo-coupling product while keeping the chloro group intact (Table 3, 3oa). Furthermore, other substituted iodobenzenes bearing electron-withdrawing groups including 4-fluoro-iodobenzene, 2-fluoro-iodobenzene and 3-trifluoromethyl-iodobenzene were also investigated to afford yields of 46-60% within the reaction time of 24-36 h (Table 3, 3na, 3ja, 3ac). Moreover, the reaction was shown influenced by steric effect, as 2 with 2-F and 2-Me groups (Table 3, 3ja and 3ga) gave lower yields than those of 4-F and 4-Me counterparts (Table 3, 3na and 3fa), respectively. The cross-coupling reaction proceeded also well with 1iodonaphthalene (Table 3, 3sa), but inefficiently with 1iodobutane (Table 3, 3ad) as the target product yields of 57% and trace were obtained, respectively. Gratifyingly, the crosscoupling was applicable to iodo-substituted heterocycles such as 2-iodopyridine (Table 3, 3ae) and 2-iodothiophene (Table 3, 3af), which delivered yields (unoptimized) of 20% and 40%, respectively. It is particularly attractive that bromobenzene (Table 3, 3aa (X = Br)) and 4-methoxy bromobenzene (Table 3, **3ba** (X = Br)) also provided good yields of 73% and 71%, similar to their iodobenzene analogues. At last, 2-CF₃ (Table 3, 3ag) and 3-F (Table 3, 3la) substituted bromobenzene were investigated for this reaction, which gave yields of 18% and 60%, respectively, within reaction time of 60-72 h.

COMMUNICATION



Ni(COD)₂ (0.01 mmol), PMe₃ (0.05 mmol), DBU (0.2 mmol), THF (450 μ L), 50 °C, 24, 36, 48, 60, 72 or 120 h, under N₂. See supporting information for experimental details. Yields of isolated product **3** are given unless otherwise noted. Trace yields of **3** were detected by GC-MS. [a] Yields were determined by GC-MS and ¹H NMR of the crude reaction mixture using 1,3,5-trimethoxybenzene as internal standard because of difficult isolation of **3**.

To investigate the synthetic potential of this reaction, we applied the optimized protocol to synthesize 1,2,3-trimethoxy-5-(4-methoxybenzyl)benzene (Scheme 2, **3b**), an important antimitotic agent.²² With 3,4,5-trimethoxybenzaldehyde **1b** and 4-methoxyiodobenzene **2b** as substrates, 75% yield of **3b** was obtained, which is higher than the reported one (60%).²² The result extends the applicability of this cross-coupling reaction.



 $\begin{array}{l} \label{eq:scheme 2} \mbox{Scheme 2} \mbox{Synthesis of 1,2,3-trimethoxy5-(4-methoxybenzyl)benzene. Reaction conditions: $1b$ (0.4 mmol), N_2H_4-H_2O$ (0.48 mmol), $2b$ (0.1 mmol), $Ni(COD)_2$ (0.01 mmol), PMe_3 (0.05 mmol), DBU (0.2 mmol), THF (450 µL), 48h, under N_2. Yield of isolated product is given. } \end{array}$

Conclusions

Published on 22 January 2018. Downloaded by University of Reading on 22/01/2018 15:46:28

In summary, a novel nickel-catalyzed cross-coupling reaction between aldehydes and aryl halides has been developed via the Wolff-Kishner hydrazone intermediates. The method provides a simple and efficient strategy for cross-couplings using naturally abundant aldehydes and readily accessible hydrazine, complementary to the use of organometallic reagents in the classical cross-coupling reactions. It merges the two powerful synthetic methods in chemistry and opens up new routes in designing chemical synthesis. Further studies on This work was financially supported by the Canada Research Chair (Tier 1) foundation, FQRNT (CCVC), NSERC, CFI, and McGill University. We also thank CSC (China Scholarship Council) for the sponsorship of the visiting scholar fellowship (No. 201608430077, Dr. J. Tang), National Postdoctoral Program for Innovative Talents (No. BX201700110, Dr. L. Lv) and China Postdoctoral Science Foundation Funded Project (No. 2017M623270, Dr. L. Lv).

Conflicts of interest

The authors declare no competing financial interest.

Notes and references

1.

2.

3.

4.

5.

6.

7.

8.

9

10.

18.

- N. Kishner, J. Russ. Phys. Chem. Soc, 1911, 43, 582-595.
- L. Wolff, Justus Liebigs Ann. Chem., 1912, **394**, 86-108.
- J. T. Kuethe, K. G. Childers, Z. Peng, M. Journet, G. R. Humphrey, T. Vickery, D. Bachert and T. T. Lam, *Org. Process Res. Dev.*, 2009, **13**, 576-580.
- D. J. Cram and M. R. V. Sahyun, *J. Am. Chem. Soc.*, 1962, **84**, 1734-1735.
- M. Huang, J. Am. Chem. Soc., 1946, 68, 2487-2488.
- M. E. Furrow and A. G. Myers, J. Am. Chem. Soc., 2004, 126, 5436-5445.
- L. Caglioti and M. Magi, *Tetrahedron*, 1963, **19**, 1127-1131.
- M. F. Grundon, H. B. Henbest and M. D. Scott, *J. Chem.* Soc., 1963, **0**, 1855-1858.
- D. J. Weix, Acc. Chem. Res., 2015, 48, 1767-1775.
- R. Jana, T. P. Pathak and M. S. Sigman, *Chem. Rev.*, 2011, **111**, 1417-1492.
- 11. X.-F. Wu, H. Neumann and M. Beller, *Chem. Soc. Rev.*, 2011, **40**, 4986-5009.
 - N. Rodriguez and L. J. Goossen, Chem. Soc. Rev., 2011, 40, 5030-5048.
 - C. Mauger and G. Mignani, *Adv. Synth. Catal.*, 2005, **347**, 773-782.
 - Z. Shao and H. Zhang, Chem. Soc. Rev., 2012, 41, 560-572.
 - A. Takemiya and J. F. Hartwig, J. Am. Chem. Soc., 2006, 128, 14800-14801.
 - Y. Xia and J. Wang, Chem. Soc. Rev., 2017, **46**, 2306-2362.
 - H. Wang, X.-J. Dai and C.-J. Li, *Nat. Chem.*, 2017, **9**, 374-378
 - W. Wei, X.-J. Dai, H. Wang, C. Li, X. Yang and C.-J. Li, Chem. Sci., 2017, **8**, 8193-8197.
- N. Chen, X.-J. Dai, H. Wang and C.-J. Li, *Angew. Chem. Int.* Ed., 2017, 56, 6260-6263.
- 20. X.-J. Dai, H. Wang and C.-J. Li, *Angew. Chem. Int. Ed.*, 2017, **56**, 6302-6306.
- 21. G. Cahiez and A. Moyeux, *Chem. Rev.*, 2010, **110**, 1435-1462.
- 22. M. Cushman, D. Nagarathnam, D. Gopal, H. M. He, C. M. Lin and E. Hamel, *J. Med. Chem.*, 1992, **35**, 2293-2306.

DOI: 10.1039/C7CC09290C

Journal Name