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Nickel-catalyzed *N*-arylation of amines with arylboronic acids under open air

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Introduction

N-Alkyl and N-aryl aniline derivatives are highly important chemicals in pharmaceutical, agrochemical, and materials sciences. The classic copper-mediated arylation of amines with arylhalides is known as the Ullmann-Goldberg coupling, which is normally utilized for the preparation of these chemicals [1]. The development of palladium-catalyzed coupling between arylhalides and amines is recognized as Buchwald-Hartwig coupling [2], which has resulted in reports of numerous transitional-metal catalyzed couplings to form C-N bonds [3]. Currently, Pd, Ni, and Cu are commonly used as catalysts for Buchwald-Hartwig coupling (Fig. 1) [4]. As an alternative, Chan-Lam coupling between amines and arylboronic acids under aerobic conditions has been effective in the presence of copper [5]. Compatibility with a wide range of functional groups and the unique chemoselectivity of Chan-Lam coupling has attracted a number of chemists and resulted in expanded applications to form C--C, C--S, C--O, and C--X (X = Cl, Br, and I) bonds [6]. The original conditions reported in 1998 used excess stoichiometric amounts of copper [5a,b]; therefore, reactions using catalytic amounts of copper have been extensively studied [7]. For example, Schaper and co-workers recently found that copper(II) pyridyliminoarylsulfonate complexes can catalyze *N*-arylations with a loading of 2.5 mol% [8]. For the same transformation, nickel has also proven to be a useful

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ABSTRACT

In this study, a well-defined, novel NHC-Ni complex was developed and used to catalyze the *N*-arylation of alkyl- and arylamines with arylboronic acids in a rare version of Chan-Lam coupling. Although the same coupling using copper catalysts has been widely studied, the nickel-catalyzed version is rare and normally requires 10–20 mol% catalyst loading. This novel NHC-Ni complex in combination with 4,4'-dimethyl-2,2'-bipyridine, however, proved to be an effective catalyst that lowered the required catalyst loading to only 2.0 mol%.

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catalyst, but fewer investigations have used Ni catalysts compared with those using Cu catalysis [9]. In particular, Ni-catalyzed versions require high catalyst loading, and the development of a novel catalytic system would be an important development towards addressing this problem. Herein, we report an effective NHC-nickel catalyzed arylation of amines *via* Chan-Lam coupling. In this study, we found that 2.0 mol% of a novel NHC-Ni complex **C1** and 4,4'dimethyl-2,2'-bipyridine (dmbpy) co-ligands effectively catalyzes this reaction. To the best of our knowledge, this is the first example of an NHC-Ni complex catalyzed Chan-Lam coupling reaction.

Over the past decade, NHC-Ni complexes have shown unique reactivities in the coupling of amides [10] and the coupling and reduction of aryl ethers [11]. NHC-supported Ni catalysts are generally prepared in situ using air-sensitive Ni(COD)₂ as a nickel source and are used directly without further purification [12]. Well-defined classes of NHC-Ni precatalysts have been developed, but these are not as frequently mentioned as their d¹⁰ counterpart palladium catalysts. In this highly sought-after area, [(NHC)NiCpCl] half-sandwich complexes are good examples that can be accessed via simple heating of the NHC precursors in the presence of nickelocene [13]. This family is applied to catalytic reactions such as Suzuki-Miyaura coupling [14], Buchwald-Hartwig amination [15], and Kumada-Tamao-coupling [16] via activation by organometallic reagents, alkoxide, or arylboronic acids. Our group recently developed original NHCs equipped with a bicyclic architecture on the non-carbenic carbons, which we referred to as DHASI, and one of these DHASI ligands was successfully applied to Ni half-sandwich complexes. The developed [Ni(DHASIiPr)CpCl] complex showed high activity and a wide scope of substrates during Suzuki-Miyaura

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S. Ando et al. / Tetrahedron Letters xxx (xxxx) xxx

N-arylation with arylhalides

Extensively studied High efficiency (Low catalyst loading)



R = Alkyl or Ar X = I, Br, or Cl

N-arylation with arylboronic acid (or boronate)

Copper catalysts are widely studied.

Ni catalysts are rare and not effective (10-20 mol% of Ni).



R = Alkyl or Ar





Fig. 1. N-arylations of amines through representative coupling reactions and an overview of this study.

coupling [17]. During the investigation, we found that [Ni(DHA-SliPr)CpCl] catalyzed the homo-coupling of phenylboronic acids under air, where the TON (turn-over number) was more than 100. Motivated by this promising catalytic activity, we envisioned a DHASI-supported Ni half-sandwich complex that could be useful as an effective precatalyst in a Ni-catalyzed Chan-Lam coupling.

Results and discussion

We began our study by fine-tuning the reaction conditions with [Ni(DHASICy)CpCl] complex C1, which was newly synthesized for this work (see Table 1, and the ESI for a full list of the conditions tested). In the reports of previous work, DBU [9a,b,d] and 1,1,3,3tetramethylguanidine [9c] worked better than inorganic bases; in contrast, K₂CO₃ and K₃PO₄ were the only bases that worked for the coupling of morpholine and phenylboronic acid with our NHC-Ni complex C1 (see also Table S1). Boroxine and other boronate derivatives did not suit the coupling using NHC-Ni catalysis (Table S8). The use of co-ligands significantly improved the conversion, and dmbpy L2 proved to be the best among all the co-ligands tested (Entries 1-5, and Table S3). The use of an excess amount of phenylboronic acid was preferable to an excess amount of amine partners (Entry 3 vs. 7), and an additional aprotic polar co-solvent (see also Table S6), especially DMF, helped to afford the product in a better yield (Entries 9-11). The reaction at a higher temperature resulted in a decreased yield (Entry 12). The use of [Ni(DHASIiPr)CpCl] C2 [17], which is a robust precatalyst for Suzuki-Miyaura coupling, was fruitless (Entry 8), and the Ni half-sandwich complex C3 supported by SIPr [15a], which is one of the most widely used NHCs, was inferior to C1

Table 1

Optimization of the reaction conditions of Ni-catalyzed arylation of amines.





Entry	Х	Y	Co-Ligand	Yield 3 ^a (%)
1	2	1	none	6
2	2	1	L1	32
3	2	1	L2	37
4	2	1	L3	36
5	2	1	L4	30
6 ^b	2	1	L2	2
7 ^c	1	2.5	L2	44
8 ^{c,d}	1	2.5	L2	0
9 ^{c,e}	1	2.5	L1	43
10 ^{с,е}	1	2.5	L2	60
11 ^{с,е}	1	2.5	L3	56
12 ^{c,e,f}	1	2.5	L2	27
13 ^{c,e,g}	1	2.5	L2	32
14 ^{c,e,h}	1	2.5	L2	6
15 ^{c,e,i}	1	2.5	L2	0

 $^{\rm a}\,$ The yield was calculated using $^1{\rm H}\,{\rm NMR}$ with 2-aceton aphthalene as an internal standard.

^b Under an Ar atmosphere.

^c The reaction was performed for 8 h.

^d Complex **C2** was used instead of **C1**.

e A mixture of toluene/DMF (19/1) was used as a solvent.

^f The reaction was performed at 90 °C.

^g Complex C3 was used instead of C1.

^h NiCl₂·6H₂O was used instead of complex **C1**.

ⁱ The reaction was performed without the addition of a Ni source.

(Entry 13). Nickel(II) chloride hexahydrate also provided the coupled product, albeit with lower activity than that of NHC-Ni complexes (Entry 14). Obviously, aerobic conditions and a Ni catalyst are crucial elements for this transformation (Entries 6 and 15). We chose the conditions shown in entry 10 as optimal for the nickel-catalyzed arylation of amines.

With the optimal reaction conditions in hand, we tested the substrate scope for the *N*-phenylation of amines using [Ni(DHASICy) CpCl] **C1** and dmbpy (Figs. 2 and 3). Aliphatic amines coupled with phenylbononic acid in a moderate to good yield, with the noted exception of piperidine (**3a**–**3e**). It should be noted that benzylamine and its coupled product **3e** was not oxidized during the coupling. Acetamide and *tert*-butylcarbamate were also amenable to this coupling and resulted in a moderate yield, while the more acidic cyclic carbamate and *p*-toluenesulfonamide gave significantly lower yields (**3h**–**3i**). On average, the coupling using aniline

2

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ARTICLE IN PRESS

S. Ando et al./Tetrahedron Letters xxx (xxxx) xxx



Fig. 2. Substrate scope for the N-phenylation of aliphatic-, aromatic-, and heteroaromatic-amines.



Fig. 3. Substrate scope for arylation using a variety of arylboronic acids.

derivatives was more effective than when using aliphatic amines, and electron-rich and electron-deficient anilines were coupled with phenylboronic acid to give good yields (**3j**-**3p**). On the other hand, sterically hindered substrates were somewhat problematic, and their use resulted in moderate to poor yields (**3q**-**3t**). The *N*-arylation of indole did not effectively proceed (**3w**, see Fig. S3 for a list of incompatible substrates), but 4-amino- and 2-amino-pyridines reacted smoothly to give the arylated products (**3u** and **3v**).

We subsequently tested the effect of arylboronic acids on this coupling reaction (Fig. 3). Although the *o*-substituted arylboronic acids were influenced by steric repulsion (**4a–4c**), *p*-substituted arylboronic acids were amenable to this coupling (**4d–4h**).

Finally, we checked whether the racemization of an amine at a benzylic position would occur using (*S*)-1-phenylethylamine (>98% *ee*) as a substrate (Eq. (1)). The coupling with phenylboronic acid

was conducted under the optimal conditions, and the coupled product was obtained in a 53% yield which retained an optical purity of >98%*ee*. The racemization of 1-phenylethylamine is known to be catalyzed by some metals including Ni nanoparticles [18], but this was not the case for this reaction.



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4

S. Ando et al. / Tetrahedron Letters xxx (xxxx) xxx

Conclusion

An effective catalytic Chan-Lam coupling was developed using an original NHC-Ni complex in combination with a dmbpy coligand. Although the structure of the active catalyst remains unclear at this point, this catalytic system catalyzed the arylations of alkyl- and aryl-amines with arylboronic acids using only 2.0 mol % catalyst loading. The robustness of NHC complexes toward oxidative conditions and the high level of the σ -donating ability of NHC ligands could be the reason for catalysis that was more highly efficient than what has been reported to date for Ni catalysts. Further investigations to widen the substrate scope and to identify the structure of the active species are under way in our laboratory.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tetlet.2019.04.004.

References

- [1] (a) J. Lindley, Tetrahedron Report Number 163, Tetrahedron 40 (1984) 1433-1456:
- (b) F. Monnier, M. Taillefer, Angew. Chem. Int. Ed. 48 (2009) 6954-6971.
- [2] (a) A.S. Guram, S.L. Buchwald, J. Am. Chem. Soc. 116 (1994) 7901-7902;
- (b) F. Paul, J. Patt, J.F. Hartwig, J. Am. Chem. Soc. 116 (1994) 5969-5970.
- [3] (a) J.F. Hartwig, Nature 455 (2008) 314-322; (b) P. Ruiz-Castillo, S.L. Buchwald, Chem. Rev. 116 (2016) 12564-12649.
- [4] J. Bariwal, E. Van der Eycken, Chem. Soc. Rev. 42 (2013) 9283–9303.
- [5] (a) D.M.T. Chan, R. Wang, M.P. Winters, Tetrahedron Lett. 39 (1998) 2933-2936

(b) P.Y.S. Lam, C.G. Clarkt, S. Saubernt, J. Adamst, M.P. Winters, D.M.T. Chan, A. Combst, Tetrahedron Lett. 39 (1998) 2941-2944;

- (c) D.A. Evans, J.L. Katz, T.R. West, Tetrahedron Lett. 39 (1998) 2937-2940. [6] (a) J.X. Qiao, P.Y.S. Lam, Synthesis 6 (2011) 829-856;
 - (b) S.V. Ley, A.W. Thomas, Angew. Chem. Int. Ed. 42 (2003) 5400–5449; (c) S. Bhunia, G.G. Pawar, S.V. Kumar, Y. Jiang, D. Ma, Angew. Chem. Int. Ed. 56 (2017) 16136-16179:
 - (d) I. Munir, A.F. Zahoor, N. Rasool, S.A.R. Naqvi, K.M. Zia, R. Ahmad, Mol. Divers. (2018), https://doi.org/10.1007/s11030-018-9870-z.

 [7] (a) L.M. Huffman, S.S. Stahl, J. Am. Chem. Soc. 130 (2008) 9196–9197;
(b) A.E. King, T.C. Brunold, S.S. Stahl, J. Am. Chem. Soc. 131 (2009) 5044–5045; (c) A.E. King, B.L. Ryland, T.C. Brunold, S.S. Stahl, Organometallics 31 (2012) 7948-7957:

(d) J.C. Vantourout, R.P. Law, A. Isidro-Llobet, S.J. Atkinson, A.J.B. Watson, J. Org. Chem. 81 (2016) 3942-3950;

(e) J.C. Vantourout, H.N. Miras, A. Isidro-Llobet, S. Sproules, A.J.B. Watson, J. Am. Chem. Soc. 139 (2017) 4769-4779.

- V. Hardouin Duparc, G.L. Bano, F. Schaper, ACS Catal. 8 (8) (2018) 7308-7325.
- [9] (a) D.S. Raghuvanshi, A.K. Gupta, K.N. Singh, Org. Lett. 14 (2012) 4326-4329; (b) J. Shi, F.L. Li, H.X. Li, F. Wang, H. Yu, Z.G. Ren, W.H. Zhang, J.P. Lang, Inorg. Chem. Commun. 46 (2014) 159-162;
 - (c) S. Keesara, Tetrahedron Lett. 56 (2015) 6685-6688;
 - (d) K.A. Kumar, P. Kannaboina, R.D. Nageswar, P. Das, Org. Biomol. Chem. 14 (2016) 8989-8997.
- [10] (a) L. Hie, N.F. Fine Nathel, T.K. Shah, E.L. Baker, X. Hong, Y.F. Yang, P. Liu, K.N. Houk, N.K. Garg, Nature 524 (2015) 79-83;
 - (b) N.A. Weires, E.L. Baker, N.K. Garg, 2016, 8, 75-79.;
 - (c) B.J. Simmons, N.A. Weires, J.E. Dander, N.K. Garg, ACS Catal. 6 (2016) 3176-3179
 - (d) J.E. Dander, N.K. Garg, ACS Catal. 7 (2017) 1413-1423;
 - (e) N.A. Weires, D.D. Caspi, N.K. Garg, ACS Catal. 7 (2017) 4381-4385;
 - (f) J.M. Medina, J. Moreno, S. Racine, S. Du, N.K. Garg, Angew. Chem. Int. Ed. 56
- (2017) 6567-6571 [11] (a) M. Tobisu, A. Yasutome, H. Kinuta, K. Nakamura, N. Chatani, Org. Lett. 16 (2014) 5572-5575;
 - (b) M. Tobisu, N. Chatani, Acc. Chem. Res. 48 (2015) 1717-1726;
 - A.G. Sergeev, J.F. Hartwig, Science 332 (2011) 439-443;
 - (d) T. Igarashi, A. Haito, N. Chatani, M. Tobisu, ACS Catal. 8 (2018) 7475-7483;
 - (e) T.H. Wang, R. Ambre, Q. Wang, W.C. Lee, P.C. Wang, Y. Liu, L. Zhao, T.G. Ong, ACS Catal. 8 (2018) 11368-11376.
- [12] (a) M. Henrion, V. Ritleng, M.J. Chetcuti, ACS Catal. 5 (2015) 1283-1302; (b) V. Ritleng, M. Henrion, M.J. Chetcuti, ACS Catal. 6 (2016) 890-906.
- [13] C.D. Abernethy, A.H. Cowley, R.A. Jones, J. Organomet. Chem. 596 (2000) 3-5.
- [14] (a) V. Ritleng, A.M. Oertel, M.J. Chetcuti, Dalton Trans. 39 (2010) 8153-8160; (b) A.M. Oertel, V. Ritleng, M.J. Chetcuti, Organometallics 31 (2012) 2829-2840:

(c) J. Yau, K.E. Hunt, L. McDougall, A.R. Kennedy, D.J. Nelson, Beilstein J. Org. Chem. 11 (2015) 2171-2178;

(d) Y. Wei, A. Petronilho, H. Mueller-Bunz, M. Albrecht, Organometallics 33 (2014) 5834-5844.

- [15] (a) R.A. Kelly, N.M. Scott, S. Di, E.D. Stevens, S.P. Nolan, Organometallics 24 (2005) 3442-3447;
 - (b) A.R. Martin, Y. Makida, S. Meiries, A.M.Z. Slawin, S.P. Nolan, Organometallics 32 (2013) 6265–6270.
- [16] T.K. Macklin, V. Snieckus, Org. Lett. 7 (2005) 2519-2522.
- [17] S. Ando, H. Matsunaga, T. Ishizuka, J. Org. Chem. 82 (2017) 1266-1272.
- [18] (a) Y.K. Choi, M.J. Kim, Y. Ahn, M.J. Kim, Org. Lett. 3 (2001) 4099-4101; (b) A. Parvulescu, D. De Vos, P. Jacobs, Chem. Commun. (2005) 5307–5309; (c) A.J. Blacker, M.J. Stirling, M.I. Page, Org. Process Res. Dev. 11 (2007) 642-648:
 - (d) L.K. Thalén, J.E. Bäckvall, Beilstein J. Org. Chem. 6 (2010) 823-829;

(e) I. Geukens, E. Plessers, J.W. Seo, D.E. De Vos, Eur. J. Inorg. Chem. (2013) 2623-2628.