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Nickel-Catalysed Direct C2-Arylation of N-Heterocyclic Carbene[†]

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A highly efficient nickel catalysed method for the direct C2arylation of N-heterocyclic carbenes (NHCs) is reported. This protocol enables a facile access to C2-arylated imidazolium salts (NHC-Ar)X (X = Cl, Br, I or OTf). Experimental and theoretical studies suggest the viability of a Ni(I)/Ni(II) catalytic pathway in which the dinuclear Ni(I) species [(NHC)NiX]₂ plays a key role.

N-Heterocyclic carbenes (NHCs) (A, Scheme 1) are very versatile ligands in organometallic chemistry and catalysis,¹ which can be readily prepared by the deprotonation of 1,3-Imidazolium salts (I)² I are also known as a highly promising subclass of ionic liquids (ILs).³ Abnormal NHCs (aNHCs, B)⁴ feature the carbene atom at the imidazole-backbone (C4- or C5) instead of the C2-position. They are exceptionally strong σ donors⁵ and therefore have enormous potentials in synthesis and catalysis.⁶ The use of C2-arylated imidazolium salts (II) is the most reliable strategy for the synthesis of aNHCs^{4b} and metal-complexes.⁴ Moreover, II exhibit superior alkaline stability compared to I, rendering them attractive candidates for their applications in ILs⁷ and in high-performance hydroxide conducting membranes.⁸ Therefore, the significance of **II** prompted interests in the development of their facile synthetic methods.9

Transition metal catalysed direct C–H functionalization is a powerful strategy in organic synthesis.¹⁰ The C–H arylation of azole heterocycles has been well explored.¹¹ The C2-arylation of **A** or **I** is however considered difficult because of the stability of the C_{NHC}–M bond, making the reductive elimination at the metal atom challenging.^{5, 12} Cavell et al., reported the C2–H alkylation





of I with alkenes (Scheme 2, a).¹³ We recently devised a catalytic method for the direct C2-arylation of NHCs with $Pd_2(dba)_3$ (Scheme 2, c).^{9a} The C2–H arylation of I is also feasible with a copper catalyst (Scheme 2, b).^{9b} However, the scope of both Pd^{9a} and Cu^{9b} catalysis protocols is limited to aryl iodides. In comparison with palladium, nickel complexes exhibit higher reactivity towards $C_{(sp2)}$ –X (X = Cl or Br) bond and are considered as important candidates in sustainable synthesis.¹⁴ This encouraged us to reason that by employing a suitable nickel precatalyst the C2-arylation of NHCs (Scheme 2, d) should be conceivable.¹⁵ Herein we report the nickel catalysed direct C2-arylation of NHCs with aryl halides to C2-arylated imidazolium salts (Scheme 3).

We commenced our study with a standard reaction^{9a} of IPr (**1a**) and PhI with 5 mol% of Ni(cod)₂, which gave 65% (IPrPh)I(**2**)



Scheme 2 Catalytic synthesis of C2-alkylated (a), and C2-arylated (b, c, d) 1,3imidazolium salts. [Ni] = Ni(0) or Ni(1) precatalyst.

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Scheme 3 (a) Nickel catalysed C2-arylation of 1a with PhX. (b) C2-Arylated 1,3-imidazolium bromides: 3a-3j obtained by the arylation of 1a; 6a and 6b by SIPr (1b); and 7a-7c by Me₂-IPr (1c).

after 2h (Scheme 3, a). Encouraged by this outcome, we then employed aryl bromides as coupling partners. Interestingly, under similar experimental conditions PhBr underwent reaction with 1a to give (IPrPh)Br (3a) in 75% yield. Having optimized the procedure (see Table S1 of ESI), we examined the scope of this protocol to other aryl bromides and NHCs (Scheme 3, b). A variety of functional groups on aryl bromides were tolerated, including MeO- (3d, 3e), Me(O)C- (3f, 3g), and Me₂N- (3j), except that a small amount of (IPrH)Br salt was formed with aryl bromides featuring a carbonyl group (3f-3i). SIPr (1b) (SIPr = 1,3-bis(2,6-diisopropylphenyl)imidazolin-2vlidene) and Me₂-IPr (1c) (Me₂-IPr = 1,3-bis(2,6diisopropylphenyl)-4,5-dimethyl-imidazol-2-ylidene) carbenes underwent C2-arylation with aryl bromides to afford the corresponding imidazolium salts (6a, 6b, and 7a-7c) (Scheme 3, b).

Chlorobenzene reacted rather sluggishly and gave only 7% (IPrPh)Cl (4) after 4h (Scheme 3, a), whereas PhOTf furnished (IPrPh)OTf (5) in 16% yield. 4-Chloroanisol also gave the coupling product {IPr(4-anisyl)}Cl (8) on treatment with 1a (17% after 2h). Compounds 2, 3a-3j, 4, 5, 6a, 6b, 7a-7c, and 8 are air-stable solids and have been characterized by NMR spectroscopy and mass spectrometry (see Supporting Information). Molecular structures of 3a, 3b, and 3j (Figures S1-S3) were determined by single crystal X-ray diffraction studies.

However, no coupling of **1a** with 4-chlorotoluene was observed, instead Matsubara's¹⁶ T-shaped three-coordinated Ni(I) complex (IPr)₂NiCl **(9)** along with the homocoupling product 4,4'-bitolyl was formed via single electron transfer (SET) reaction (eq 1). Compound **9** exhibits an equilibrium¹⁷ with [(IPr)Ni(μ -Cl)]₂ **(10**-Cl) and IPr (eq 1) at 25 °C.

 $2 \operatorname{IPr} + \operatorname{Ni}(\operatorname{cod})_2 \xrightarrow{+ 4-\operatorname{Cl-toluene}}_{- 4,4'-\operatorname{bitolyl}} (\operatorname{IPr})_2 \operatorname{NiCl} \rightleftharpoons [(\operatorname{IPr})\operatorname{Ni}(\mu-\operatorname{Cl})]_2 + \operatorname{IPr} (1)$ (1a)
(19)
(10-Cl)

Compound **9** was found to be inactive and did not afford the expected product {IPr-(4-tolyl)}Cl on treatment of **1a** with

4-chlorotoluene. Interestingly, addition of one1 eq of PhBr in the same reaction mixture, containing **9** and **1a**, led to the

Table 1 Ni(I) mediated C2-arylation of IPr (1a	with ArX.	
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IDe	[Ni] 2.5	mol%					
1a	o-xylene,	140 °C	3a : Ar = Ph; 3h : Ar = 4-EtOOC-C ₆ H ₄)				
Entry	Ar	Х	[Ni]	Yield (h) ^a			
1	Ph	Br	[(IPr)Ni(μ-Cl)] ₂ (10 -Cl)	75 (3)			
2	Ph	Br	[(IPr)Ni(μ-Br)]₂ (10 -Br)	77 (2)			
3	Ph	Cl	[(IPr)Ni(μ-Cl)] ₂ (10 -Cl)	12 (3)			
4	Ph	Br	(IPr)2NiCl (9)	79 (2)			
5	$4-EtOOC-C_6H_4$	Br	[(IPr)Ni(µ-Br)] ₂ (10 -Br)	67 (3)			
^a yield, %; reaction time, h							

formation of (IPrPh)Br (**3a**) in 45% yield. This suggests the potential involvement of Ni(I) species in the catalytic C2-arylation of 1a.¹⁸

Therefore, we sought to probe the catalytic activity of welldefined Ni(I) complexes [(IPr)Ni(μ -Cl)]₂ (**10**-Cl),¹⁷ [(IPr)Ni(μ -Br)]₂ (**10**-Br),¹⁹ and ([IPr)₂NiCl (**9**).¹⁶ Indeed, all three were active and afforded **3a** in a high yield (Table 1, entries 1, 2, and 4) even with a lowered catalyst loading (2.5 mol% instead of 5 mol%). Moreover, the reaction of PhCl and **1a** (entry 3, Table 1) with 2.5 mol% of **10**-Cl appeared to be faster compared to that with 5 mol% of Ni(cod)₂, indicating higher activity of the former. Similarly, the coupling of **1a** and 4-EtOOCC₆H₄ with **10**-Cl (entry 5) gave a higher yield of **3h** in comparison with Ni(cod)₂.

Reaction of 1a and Ni(cod)₂ with ArCl gives stable dinuclear Ni(I) complexes {(IPr)Ni(μ -Cl)(μ -Ar)Ni(IPr)} (11-Cl) (Ar = 4- MeC_6H_4 or 4-MeOC₆H₄).²⁰ In order to shed more light on the mechanism of C2-arylation reactions of NHCs, we sought to prepare analogues bromo-derivatives {(IPr)Ni(µ-Br)(µ-Ar)-Ni(IPr)} (11-Br) by treatment of 1a and Ni(cod)₂ with PhBr or 4bromotoluene (Scheme 4). Under similar reaction conditions,²⁰ this however led to the formation of C2-arylated products $[2{IPr(4-R-C_6H_4)}]NiBr_4$ (14-R) (R = H or Me) as crystalline solids (see Supporting Information for further details), suggesting the anticipated compounds {(IPr)Ni(μ -Br)(μ -4-R-C₆H₄)Ni(IPr)} (11-Br) to be unstable. The formation of 14-R indicates the potential involvement of Ni(I) species 12-Br (the monomer of 10-Br) and 13-R.¹⁶⁻¹⁷ Compound 13-R (or its dimer) further undergoes reaction with ArBr to give 12-Br and biaryls via SET reactions.²⁰ Reaction of **10**-Br with ArBr and subsequent reductive elimination rationalize the formation of 14-R (see Figure 1). To confirm this, we also carried out a separate reaction of 10-Br with 4-bromotoluene, which readily gave 14-Me.

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Fig. 1 Calculated free energy profile (in kcal mol⁻¹ at 298.15 K) for the model Ni(I)/Ni(II) catalytic cycle for the C2-arylation of an NHC (1,3-dimethyl-imidazol-2-ylidene) with PhBr. Selected bond lengths are given in Å. All relative free energies were calculated at solution (*o*-xylene) with respect to the Ni(I) complex **15M**.

The findings listed in Table 1 and the outcome of reactions of 1a and Ni(cod)₂ with ArBr (Scheme 4) clearly emphasize the significance of Ni(I) species 10-Br in the catalytic C2-arylation of NHCs. We carried out quantum chemical calculations using density functional theory (DFT) for a model reaction NHC + PhBr \rightarrow (NHC-Ph)Br) (where NHC is 1,3- dimethylimidazol-2ylidene) to shed light on the potential reaction pathways (Figure 1). The dinuclear Ni(I) compound 15M (which mimics 10-Br, where M stands for model) was considered as the precursor complex. At this point, the approach of the PhBr to 15M gives 16M, only 2.3 kcal mol⁻¹ below the separated reactants. The formation of the $\eta^2\text{-complex}~\textbf{17M}$ occurs through the transition state TS16M-17M. The Ni(I)-Ni(I) bond length in 15M was found to be 3.20 Å. The developing of the η^2 -coordination between the PhBr and one of the Ni(I) atoms shortens the Ni(I)-Ni(I) distance to 2.55 Å in 17M. The second stage concerning the oxidative addition step is the breaking of

the C_{Ph}–Br bond and the formation of two new Br–Ni and C_{Ph}– Ni covalent bonds. The transition state **TS17M-18M** presents a relative free energy barrier of 19.4 kcal mol⁻¹, which is the rate-determining step (RDS) for the overall reaction. The formation of the four-membered intermediate **18M** was showed to be thermodynamically irreversible, with a relative energy calculated as -26.0 kcal mol⁻¹. The elongation of the Ni– Ni distance, going from 2.55 Å in **17M** to 3.55 Å in **18M**, probably means a break of the bimetallic coordination, thus facilitating the formation of Ni(II) complexes **19M** and **20M**, which are important to the next steps of the reaction.

The formation of two square-planar Ni(II) complexes **19M** and **20M** from **18M** is very exergonic (-80.6 kcal mol⁻¹). The last step is the reductive elimination from **20M** via the transition state **TS20-21M** to release (NHC-Ph)Br (**21M**). The NHC–Ph bond distance of 1.48 Å in **21M** is a typical value of a C–C covalent bond, confirming that the product is already formed.

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In conclusion, calculations corroborate experimental evidences on the existence of Ni(I)/Ni(II) catalytic cycle involving a dinuclear Ni(I) intermediate as the active species.

Moreover, the suitability of C2-arylated imidazolium salts in the synthesis of aNHC-complexes has been demonstrated with copper complexes **22** and **23** (Scheme 5). The molecular structure of **23** determined by X-ray diffraction studies is also



Scheme 5 Synthesis of aNHC-copper complexes 22 and 23. Solid-state molecular structure of 23.

shown in Scheme 5. The elongation of both N2–C3 (1.409(3) Å) and C2–C3 (1.371(3) Å) bond lengths and the decrease of the N2–C3–C2 (102.9^e) bond angle of **23** are fully consistent^{9a, 21} with the carbene nature of the C3 carbon atom.

In summary, we have demonstrated the direct C2-arylation of NHCs with different aryl electrophiles using nickel catalysis. Studies suggest that the dinuclear Ni(I) species [(NHC)Ni(μ -Br)]₂ react with aryl halides to form Ni(II) compounds, which undergo reductive elimination to deliver the coupling products. The suitability of C2-arylated imidazolium salts in the synthesis of aNHC complexes has been demonstrated with the copper complexes **22** and **23**. Building on the above-described findings, the preparation of C2-arylated imidazolium salts in biorenewable as unconventional reaction media (e.g. Deep Eutectic Solvents, DESs)²² as well as their employment as potential ILs for organic synthesis and organometallic transformations appear to be goals of worth pursuing.

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Notes and references

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- (a) F. E. Hahn and M. C. Jahnke, *Angew. Chem. Int. Ed.*, 2008, **47**, 3122–3172; (b) F. Lazreg, F. Nahra and C. S. J. Cazin, *Coord. Chem. Rev.*, 2015, **293–294**, 48–79; (c) M. N. Hopkinson, C. Richter, M. Schedler and F. Glorius, *Nature*, 2014, **510**, 485– 496; (d) S. Diez-Gonzalez, N. Marion and S. P. Nolan, *Chem. Rev.*, 2009, **109**, 3612–3676.
- (a) D. J. Nelson, *Eur. J. Inorg. Chem.*, 2015, 2012–2027; (b) L. Benhamou, E. Chardon, G. Lavigne, S. Bellemin-Laponnaz and V. Cesar, *Chem. Rev.*, 2011, **111**, 2705–2733.
- (a) T. Welton, Chem. Rev., 1999, 99, 2071–2084; (b) N. V. Plechkova and K. R. Seddon, Chem. Soc. Rev., 2008, 37, 123– 150; (c) R. Giernoth, Angew. Chem. Int. Ed., 2010, 49, 5608– 5609.

- (a) R. H. Crabtree, *Coord. Chem. Rev.*, 2013, **257**, 755–766; (b) E. Aldeco-Perez, A. J. Rosenthal, B. Donnadieu, P. Parameswaran, G. Frenking and G. Bertrand, *Science*, 2009, **326**, 556–559; (c) P. L. Arnold and S. Pearson, *Coord. Chem. Rev.*, 2007, **251**, 596–609.
- (a) T. Droge and F. Glorius, *Angew. Chem. Int. Ed.*, 2010, 49, 6940–6952;
 (b) D. J. Nelson and S. P. Nolan, *Chem. Soc. Rev.*, 2013. 42, 6723–6753.
- (a) S. Grundemann, A. Kovacevic, M. Albrecht, J. W. Faller and R. H. Crabtree, *Chem. Commun.*, 2001, 2274–2275; (b) O. Schuster, L. Yang, H. G. Raubenheimer and M. Albrecht, *Chem. Rev.*, 2009, **109**, 3445–3478; (c) M. Albrecht, *Chem. Commun.*, 2008, 3601–3610.
- K. Goossens, S. Wellens, K. Van Hecke, L. Van Meervelt, T. Cardinaels and K. Binnemans, *Chem. Eur. J.*, 2011, **17**, 4291– 4306.
- (a) A. G. Wright, T. Weissbach and S. Holdcroft, *Angew. Chem. Int. Ed.*, 2016, **55**, 4818–4821; (b) K. M. Hugar, H. A. Kostalik and G. W. Coates, *J. Am. Chem. Soc.*, 2015, **137**, 8730–8737.
- (a) R. S. Ghadwal, S. O. Reichmann and R. Herbst-Irmer, *Chem. Eur. J.*, 2015, **21**, 4247–4251; (b) S. Li, J. Tang, Y. Zhao, R. Jiang, T. Wang, G. Gao and J. You, *Chem. Commun.*, 2017, **53**, 3489–3492.
- (a) L. Ackermann, R. Vicente and A. R. Kapdi, *Angew. Chem. Int. Ed.*, 2009, **48**, 9792–9826; (b) J. Wencel-Delord and F. Glorius, *Nat. Chem.*, 2013, **5**, 369–375; (c) D. Alberico, M. E. Scott and M. Lautens, *Chem. Rev.*, 2007, **107**, 174–238.
- H.-Q. Do, R. M. K. Khan and O. Daugulis, J. Am. Chem. Soc., 2008, 130, 15185–15192.
- (a) A. Gomez-Suarez, D. J. Nelson and S. P. Nolan, *Chem. Commun.*, 2017, **53**, 2650–2660; (b) D. S. McGuinness, K. J. Cavell, B. W. Skelton and A. H. White, *Organometallics*, 1999, **18**, 1596–1605.
- N. D. Clement and K. J. Cavell, Angew. Chem. Int. Ed., 2004, 43, 3845–3847.
- (a) V. Ritleng, M. Henrion and M. J. Chetcuti, ACS Catal., 2016, 6, 890–906; (b) L.-J. Gu, C. Jin and H.-T. Zhang, Chem. Eur. J., 2015, 21, 8741–8744; (c) M. Henrion, V. Ritleng and M. J. Chetcuti, ACS Catal., 2015, 5, 1283–1302.
- (a) S. Z. Tasker, E. A. Standley and T. F. Jamison, *Nature*, 2014, 509, 299–309; (b) R. H. Crabtree, *Chem. Rev.*, 2015, 115, 127–150; (c) T. Zell, P. Fischer, D. Schmidt and U. Radius, *Organometallics*, 2012, 31, 5065–5073.
- S. Miyazaki, Y. Koga, T. Matsumoto and K. Matsubara, *Chem. Commun.*, 2010, 46, 1932–1934.
- B. R. Dible, M. S. Sigman and A. M. Arif, *Inorg. Chem.*, 2005, 44, 3774–3776.
- J. Wu, A. Nova, D. Balcells, G. W. Brudvig, W. Dai, L. M. Guard, N. Hazari, P. H. Lin, R. Pokhrel and M. K. Takase, *Chem. Eur. J.*, 2014, **20**, 5327–5337.
- C. A. Laskowski, D. J. Bungum, S. M. Baldwin, S. A. Del Ciello, V. M. Iluc and G. L. Hillhouse, *J. Am. Chem. Soc.*, 2013, **135**, 18272–18275.
- K. Matsubara, H. Yamamoto, S. Miyazaki, T. Inatomi, K. Nonaka, Y. Koga, Y. Yamada, L. F. Veiros and K. Kirchner, Organometallics, 2017, 36, 255–265.

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Journal Name

- (a) R. S. Ghadwal, J.-H. Lamm, D. Rottschafer, C. J. Schurmann and S. Demeshko, *Dalton Trans.*, 2017, **46**, 7664–7667; (b) D. Rottschäfer, C. J. Schürmann, J.-H. Lamm, A. N. Paesch, B. Neumann and R. S. Ghadwal, *Organometallics*, 2016, **35**, 3421– 3429; (c) R. S. Ghadwal, D. Rottschafer, D. M. Andrada, G. Frenking, C. J. Schurmann and H. G. Stammler, *Dalton Trans.*, 2017, **46**, 7791–7799; (d) R. S. Ghadwal, D. Rottschäfer and C. J. Schürmann, *Z. Anorg. Allg. Chem.*, 2016, **642**, 1236–1240.
- 22. J. García-Álvarez, E. Hevia and V. Capriati, *Eur. J. Org. Chem.*, 2015, **2015**, 6779–6799.

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Direct C2-arylation of NHCs with various aryl electrophiles to C2-arylated imidazolium salts is achieved using Ni-catalysis. The dinuclear Ni(I) species I undergoes oxidative addition with ArX *via* SET reaction to give the Ni(II) intermediate II. Reductive elimination delivers the arylation product (III) and regenerates the catalyst.

