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Benchtop nickel-catalyzed reductive coupling of aldehydes with alkynes and ynamides†

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We demonstrate the potential of Ni(COD)(DQ), a bench-stable Ni⁰ complex, as a catalyst for the reductive coupling of aldehydes with alkynes and ynamides, providing silylated allyl alcohols with excellent yields and regioselectivities. Mass spectrometric identification of the intermediates and DFT studies supported the proposed mechanism.

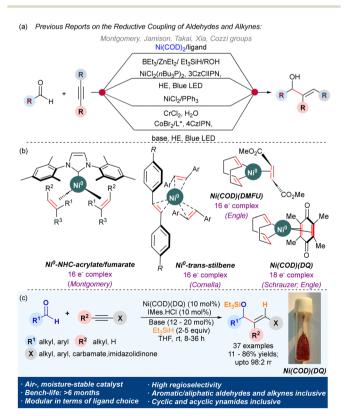
The reductive coupling of alkynes and aldehydes provides a ubiquitous stereoselective route to allyl alcohols (Scheme 1a).¹ Due to the wide applications of allyl alcohols as a potent synthetic intermediate and a prominent fragment in natural products, drugs, perfumes, etc.,2 much focus has been devoted to their stereoselective synthesis. Specifically, the nickelcatalyzed reductive coupling approach has gained popularity due to the high regio-/stereocontrol observed in the products and the use of inexpensive metal. 1d-f,3 Ni-complexes also exhibit a lower barrier for oxidative addition and reductive elimination compared to the platinum group metal complexes.⁴ However, this exceptional reactivity of Ni^o complexes makes them highly air and moisture sensitive. The major commercial Ni⁰ source, Ni(COD)₂, degrades within a few hours on the benchtop. The catalytic activity of other stable commercial sources like Ni(CO)₄, Ni(PPh₃)₄, Ni(COD)(DQ), etc., are underexplored.5

Various attempts to improve the benchtop stability and leverage the unique reactivity of Ni⁰ complexes have been reported.6 Montgomery uncovered the exceptional stability of Ni⁰-NHC 16e⁻ complexes ligated with electron-deficient olefins (EDOs) like fumarates and acrylates (Scheme 1b). Fumarate complexes demonstrated superior air stability than acrylates and exhibited remarkable catalytic activity in the alkyne/aldehyde reductive coupling and amination reaction of aryl chlorides. Then, Engle and coworkers reported a wide range of Ni⁰(COD)(EDO)

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complexes like Ni(COD)(DMFU) (16e⁻ complex),⁸ Ni(COD)(DQ) (18e complex), etc. that are exceptionally stable over the benchtop and catalyzed C-C and C-N bond forming reactions efficiently. 9,10 They used Ni(COD)(DQ)/SIPr.HCl system for the catalytic amination of aryl chlorides. 10a The Cornella group utilized para-substituted stilbenes as ligands to achieve Ni(stb)3 (16e- complexes) with excellent air stability and catalytic activity.11

Motivated by the efficiency of Montgomery's Ni(NHC)(EDO)₂ complexes in the reductive coupling of alkynes, we envisaged



Scheme 1 (a) Reductive coupling of alkynes and aldehydes; (b) benchstable Ni⁰ precatalysts; (c) present work.

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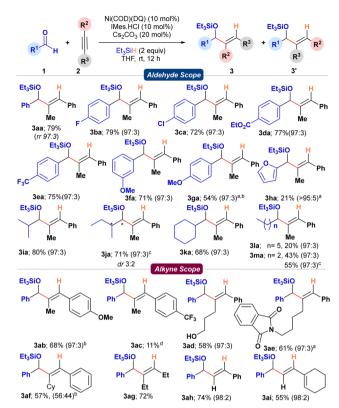
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the access to Ni(NHC)(EDO)₂ complexes in a modular fashion by reacting NHC salts with Ni(COD)(DQ) to catalyze alkyne/ aldehyde reductive coupling (Scheme 1c). The in situ generated Ni(NHC)(DQ) complexes could eliminate the requirement of a glovebox for this transformation.

We began our investigation by subjecting Ni(COD)(DQ) (10 mol%) with various monophosphines, bis-phosphines, and free-NHCs (10 mol%) for the reductive coupling of benzaldehyde 1a and 1-phenyl-1-propyne 2a in THF at 45 °C, with triethyl silane as the reducing agent. However, with phosphine ligands, the reaction failed to provide the desired coupled product 3aa. With free-IPr as a ligand, the reaction provided the silvlated allyl alcohol 3aa in 20% yield with poor regioselectivity. With IMes carbene, at 45 °C, the resulting active catalyst provided the desired silylated allyl alcohol 3aa in a 73% isolated yield and 97:3 rr. Other imidazolium salts like SIPr.HCl, ICy.HBF4 and IBn.HBF₄ failed to provide 3aa. Cs₂CO₃ was the suitable base for forming the active catalyst via deprotonation of the NHC salts. With Ni(COD)(DQ) (10 mol%), IMes.HCl (10 mol%), Cs₂CO₃ (20 mol%) in THF at rt using triethyl silane, the reaction provided the best yield of 3aa (82% NMR yield) entirely on the benchtop without relying on a glovebox (see ESI†). With 2 mol% loading, a diminished yield of 3aa (13%) was obtained.

With the optimized conditions, the substrate scope of the aldehydes was initially studied with 1-phenyl-1-propyne 2a. With benzaldehyde 1a, the reaction provided the corresponding silylated allyl alcohol 3aa in a 79% isolated yield with 97:3 regioselectivity (Scheme 2). Substrates bearing electronically diverse substituents like -F, -Cl, electron-withdrawing -CF₃, -CO₂Et, and -OMe were compatible under the reaction conditions giving the desired products 3ba-3fa with good yields (71-79%) and regioselectivity (97:3). Whereas, substrates bearing electrondonating groups in conjugation with the aldehyde functionality as in the case of 1g and 1h showed diminished reactivity. At 45 °C, 1g and 1h were successfully transformed to the desired allylic alcohols 3ga and 3ha in moderate yields (54 and 21%, respectively). Similarly, α-branched aliphatic aldehydes 1i-1k smoothly reacted under the standard conditions to provide the corresponding silvlated allyl alcohols 3ia-3ka in good to excellent yields (68-80%) and high regioselectivities. Contrarily, linear chain aliphatic aldehydes (11, m) provided diminished yields of 3l, m (20 and 43%, respectively) under standard conditions. To investigate if the competing base-mediated enolization of linear aliphatic aldehydes was responsible for the diminished yields, IMes carbene was employed directly instead of generating it in situ from the imidazolium salt using a base (Cs₂CO₃). To our delight, under base-free conditions, 1m provided the desired product 3ma in an enhanced yield (55%, Scheme 2).

Then, we studied the scope of alkynes with benzaldehyde 1a as the standard aldehyde partner. With 1-(p-anisyl)-1-propyne 1b, the reaction provided the desired silylated allylic alcohol 3ab in 68% yield and 97:3 dr (Scheme 2). However, with an electronwithdrawing -CF₃ group at the para-position, the reaction was sluggish to provide the silvlated allyl alcohol 3ac in poor yield (11%) even after 36 h. This contrast in reactivity could be attributed to the poor initial coordination of the electron-



Scheme 2 Substrate scope for the reductive coupling of aldehydes and alkynes; a performed at 45 °C for 24 h; b isolated as free alcohol; c with free IMes carbene; d stirred for 36 h.

deficient alkyne with the metal center. The reaction tolerated substrates bearing coordinating functionalities like -OH (2d) and phthalimides (2e), providing the desired functionalized allyl alcohol derivatives 3ad and 3ae in 58 and 61% yields, respectively, without compromising the regioselectivity. However, increasing the steric bulk on the aliphatic chain by introducing cyclohexyl moiety (2f) significantly affected the regioselectivity, providing the product 3af with 57% yield and 1:1 regioselectivity. Dialiphatic substituted (2g) and terminal alkynes (2h, i) smoothly delivered the corresponding products (3ag-3ai) in good yields (55-74%) and excellent regioselectivities. Terminal alkyne 2i was an enyne, and under standard conditions, the formation of the silylated dieneallylic alcohol 3ai is noteworthy (Scheme 2).

We then focused on studying the reductive coupling of ynamides using the bench-stable Ni(COD)(DQ) precatalyst (Scheme 3). The previous report by Sato and coworkers on the reductive coupling restricted to N-alkynyl oxazolidinones with aldehydes using Ni(COD)2/NHC catalyst is noteworthy. 12 A quick optimization of the reaction conditions for the reductive coupling of 1a and ynamide 4b with Ni(COD)(DQ) revealed KO^tBu (12 mol%) as the suitable base (see ESI†). Applying the above conditions to simple N-Boc-protected ynamide 4a with 1a as partner provided 5aa in good yield (52%; rr > 95:5). Due to the inherent electronic bias in ynamides and the coordinating ability of the Boc-group, the reductive coupling proceeded with excellent regiocontrol (>95:5). Under Sato's conditions, using Ni(COD)2/NHC catalyst, 4a provided the coupled product in

Ni(COD)(DQ) (10 mol%) Et₃SiC IMes.HCl (10 mol%) EtoSiH, THF, rt. 20 h Et₃SiO Et₃SiO 'nВu _nBu nB... EtO₂C 5bd, R = -CO₂Et, 86% 5bg, R = -OMe, 29% 'nВи _nBu 'nВu 64%; dr 85:15 Limitations: (Failed) Et₂SiO

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Scheme 3 Scope for the reductive coupling of aldehydes and ynamides. ^a8 h reaction time

comparable yield (61% NMR yield; rr > 95:5). The reaction tolerated -F, -Cl, and -CO₂Et functionalities on the aldehyde's aromatic ring, providing the corresponding enamide allyl alcohol derivatives 5ab-5ad in good yields (52-59%; rr > 95:5). Similarly, N-alkynyl oxazolidinone 4b smoothly reacted with a range of aryl, heteroaryl, and alkyl aldehydes to provide the corresponding silvlated allyl alcohols (5ba-5bk) in good to excellent yields (29-86%). At a 1.8 mmol scale, 1a and 4b efficiently converted to product 5ba in 78% yield under standard conditions. Chiral N-alkynyl oxazolidinone (4c) derived from L-alanine with 1a, under the standard conditions, provided 5ca in 64% yield and 85:15 dr. The scope of N-alkynyl substrates was further expanded to N-alkynyl imidazolidinone. To our delight, N-alkynyl imidazolidinone 4d reacted smoothly with 1a to provide the corresponding product 5da in 51% yield (rr > 95:5). Intrigued by this result, we attempted the doublereductive coupling of N,N'-dialkynyl imidazolidinone 4e with aldehyde 1a. Pleasingly, the reaction provided the double reductive coupling product 5ea in 33% yield and 1:1 dr. Other N-alkynyl substrates bearing an amide or Ts-group failed to provide the coupling products (Scheme 3).

Further, we performed control experiments to determine the precatalyst's benchtop stability and understand the mechanism of the reductive coupling. Engle and coworkers demonstrated the exceptional thermal stability (up to 200 °C) of Ni(COD)(DQ) and other related complexes.9 Here, we studied Ni(COD)(DQ) precatalyst's potential to catalyze the reductive coupling upon prolonged storage over the benchtop (>6 months). The reaction of 1a and 2a under standard reaction conditions, with freshly prepared precatalyst, provided 3aa in 81% yield and 97:3 rr (Scheme 2). The same batch of the precatalyst was stored on the benchtop under ambient conditions without any special precautions. The catalytic activity was tested at regular intervals for up to 200 days, and the

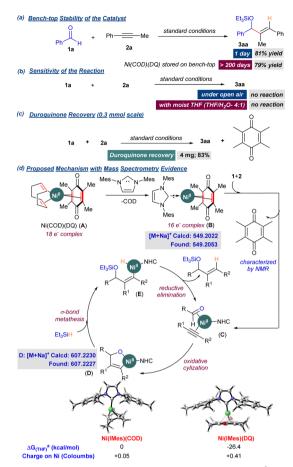
yields of 3aa were recorded (see ESI†). Even after 200 days, only minor changes in the catalytic activity (79% yield of 3aa) were observed. Intrigued by the stability of the precatalyst, we further explored if the coupling reaction was tolerant to ambient conditions in the presence of air and moisture. However, the starting materials 1a and 2a failed to react under ambient conditions. A similar outcome was observed when we performed the reaction using degassed moist THF as the solvent, excluding oxygen. These experiments suggested that the precatalyst under the reaction conditions first converted to a more reactive Ni^o species, which drives the catalytic cycle. The EDO ligand (DQ) that stabilized the Ni⁰ precatalyst could be decomplexing under the reaction conditions followed by subsequent coordination of the starting materials. TLC analysis of the reaction mixture indeed showed a spot corresponding to DQ immediately after adding the starting materials, and the spot remained until the end of the reaction (see ESI†). GCMS trace confirmed the presence of DQ at the end of the reaction. After the completion of the reaction, this spot was separated by column chromatography and characterized by ¹H NMR to be DQ (recovery: 83%).

We then attempted the characterization of intermediates by mass spectrometry (MS) analysis by drawing aliquots for analysis at specific stages of the experiment. Mass spectrometry analysis of the mixture prior to the addition of substrates 1a and 2a revealed the formation of [Ni⁰(NHC)(DQ)] (B, Scheme 4). The mixture was again analyzed by MS after adding the substrates 1a and 2a, followed by stirring at rt for 1 h. To our delight, the signal corresponding to the five-membered oxanickelacycle intermediate was observed, and notably, the DQ ligand was dislodged, supporting our previous observations. DFT supported the preferential decomplexation of COD over DQ from Ni(COD)(DQ), followed by the addition of IMes. The formation of B was thermodynamically more favorable compared to [Ni(IMes)(COD)] by 26 kcal mol⁻¹ (Scheme 4). Enhanced back-bonding into DQ in complex B was evident from the natural charges obtained from the NBO analysis.

Based on the above observations and the literature on the reductive coupling of aldehydes and alkynes, a plausible mechanism has been presented for the Ni(COD)(DQ)-mediated reductive coupling. Initially, the IMes.HCl salt in the presence of Cs₂CO₃ enables the formation of IMes carbene. The carbene on complexation with Ni(COD)(DQ) precatalyst provides B (16ecomplex). Our attempts to isolate complex B rendered unsuccessful due to extreme air sensitivity. Adding 1 and 2 triggers the decomplexation of DQ, enabling the substrate coordination resulting in complex C. C then undergoes oxidative cyclization to provide the oxanickelacycle D. The intermediate D further undergoes a σ-bond metathesis with Et₃SiH to provide the Ni-H intermediate E, which on reductive elimination provides the coupled product 3 and active catalyst is turned over (Scheme 4).

A series of downstream functionalizations of the aldehydeynamide coupled product 5ba was planned to demonstrate the synthetic utility of the products (Scheme 5). 13 First, the deprotection of the TES-group was successfully carried out on 5ba with TBAF to provide the enamidoalcohol 6 in 88% yield without disturbing the enamide group. 13a The structure of 6 was confirmed by X-ray

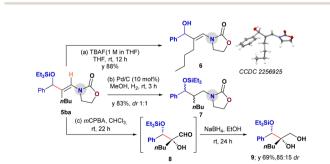
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Scheme 4 Control experiments and plausible mechanism. ^aGibbs free energies were calculated at M062X(SMD)/def2-TZVP (THF). Charges (NBO) at M062X/def2-TZVP

crystallography. Further, the reduction of 5ba with 10% Pd/C and H₂ provided the saturated oxazolidinone functionalized alcohol derivative 7 in 83% yield (dr 1:1).13b Finally, treating 5ba with mCPBA under standard epoxidation conditions^{13c} resulted in a cascade epoxidation/oxazolidinone-assisted ring-opening followed by hydrolysis to provide the aldehyde 8. In situ reduction of 8 with NaBH₄ delivered the silvlated triol **9** in 69% yield (dr 85:15; Scheme 5).

In conclusion, the study showed that the bench-stable Ni(COD)(DQ) can achieve reductive coupling with comparable efficiency to Ni(COD)2, reducing storage and handling costs.



Scheme 5 Synthetic utility of product 5ba.

The precatalyst successfully coupled various aromatic/aliphatic aldehydes with alkyne and ynamide partners, providing the products with high yields and regioselectivities. The methodology demonstrated a modular approach for in situ Ni(NHC)(EDO) complex generation, enabling faster ligand screening for enantioselective catalysis. The exceptional stability and catalytic activity of Ni(COD)(DQ) on the bench for over six months offer the potential for user-friendly Ni⁰ chemistry.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

- 1 (a) K. Takai, S. Sakamoto, T. Isshiki and T. Kokumai, Tetrahedron, 2006, **62**, 7534–7539; (b) Y.-L. Li, S.-Q. Zhang, J. Chen and J.-B. Xia, Am. Chem. Soc., 2021, 143, 7306-7313; (c) F. Calogero, G. Magagnano, S. Potenti, A. Gualandi, A. Fermi, P. Ceroni and P. Giorgio Cozzi, Adv. Synth. Catal., 2022, 364, 3410-3419; (d) K. M. Miller, W.-S. Huang and T. F. Jamison, J. Am. Chem. Soc., 2003, 125, 3442-3443; (e) G. M. Mahandru, G. Liu and J. Montgomery, J. Am. Chem. Soc., 2004, 126, 3698-3699; (f) Y.-L. Zheng and M. Ye, Chin. J. Chem., 2020, 38, 489-493.
- 2 (a) D. McTavish and E. M. Sorkin, Drugs, 1991, 42, 65-89; (b) R. M. Moslin and T. F. Jamison, J. Org. Chem., 2007, 72, 9736-9745; (c) K. S. Woodin and T. F. Jamison, J. Org. Chem., 2007, 72, 7451-7454.
- 3 (a) E. Oblinger and J. Montgomery, J. Am. Chem. Soc., 1997, 119, 9065-9066; (b) W.-S. Huang, J. Chan and T. F. Jamison, Org. Lett., 2000, 2, 4221-4223; (c) H. A. Malik, G. J. Sormunen and Montgomery, J. Am. Chem. Soc., 2010, 132, 6304-6305; (d) E. P. Jackson and J. Montgomery, J. Am. Chem. Soc., 2015, 137, 958-963; (e) H. Wang, G. Lu, G. J. Sormunen, H. A. Malik, P. Liu and J. Montgomery, J. Am. Chem. Soc., 2017, 139, 9317-9324.
- 4 V. P. Ananikov, ACS Catal., 2015, 5, 1964-1971.
- 5 (a) P. W. Jolly and G. Wilke, in The Organic Chemistry of Nickel, ed. P. W. Jolly and G. Wilke, Academic Press, 1974, pp. 244-328; (b) G. N. Schrauzer and H. Thyret, Z. Naturforsch. B, 1962, 17, 73–76.
- 6 (a) J. E. Dander, N. A. Weires and N. K. Garg, Org. Lett., 2016, 18, 3934-3936; (b) N. D. Clement, K. J. Cavell and L.-L. Ooi, Organometallics, 2006, 25, 4155-4165.
- 7 (a) A. J. Nett, S. Cañellas, Y. Higuchi, M. T. Robo, J. M. Kochkodan, M. T. Haynes, J. W. Kampf and J. Montgomery, ACS Catal., 2018, 8, 6606-6611; (b) M. T. Robo, A. R. Frank, E. Butler, A. J. Nett, S. Cañellas, P. M. Zimmerman and J. Montgomery, Organometallics, 2022, 41, 3293-3300.
- 8 N. Kim, V. T. Tran, O. Apolinar, S. R. Wisniewski, M. D. Eastgate and K. M. Engle, Synlett, 2021, 1570-1574.
- 9 V. T. Tran, N. Kim, C. Z. Rubel, X. Wu, T. Kang, T. C. Jankins, Z.-Q. Li, M. V. Joannou, S. Ayers, M. Gembicky, J. Bailey, E. J. Sturgell, B. B. Sanchez, J. S. Chen, S. Lin, M. D. Eastgate, S. R. Wisniewski and K. M. Engle, Angew. Chem., Int. Ed., 2023, 62, e202211794.
- 10 (a) V. T. Tran, Z.-Q. Li, O. Apolinar, J. Derosa, M. V. Joannou, S. R. Wisniewski, M. D. Eastgate and K. M. Engle, Angew. Chem., Int. Ed., 2020, 59, 7409-7413; (b) T. You and J. Li, Org. Lett., 2022, 24, 6642-6646.
- 11 (a) L. Nattmann and J. Cornella, Organometallics, 2020, 39, 3295-3300; (b) L. Nattmann, R. Saeb, N. Nöthling and J. Cornella, Nat. Catal., 2020, 3, 6-13.
- 12 (a) N. Saito, T. Katayama and Y. Sato, Org. Lett., 2008, 10, 3829-3832; (b) N. Saito, T. Katayama and Y. Sato, Heterocycles, 2011, 82, 1181-1187.
- (a) D. A. Evans, T. B. Dunn, L. Kværnø, A. Beauchemin, B. Raymer, E. J. Olhava, J. A. Mulder, M. Juhl, K. Kagechika and D. A. Favor, Angew. Chem., Int. Ed., 2007, 46, 4698-4703; (b) Q. Jiang, T. Yang, Q. Li, G.-M. Liang, Y. Liu, C.-Y. He, W.-D. Chu and Q.-Z. Liu, Org. Lett., 2023, 25, 3184-3189; (c) H. Xiong, R. P. Hsung, L. Shen and J. M. Hahn, Tetrahedron Lett., 2002, 43, 4449-4453.