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

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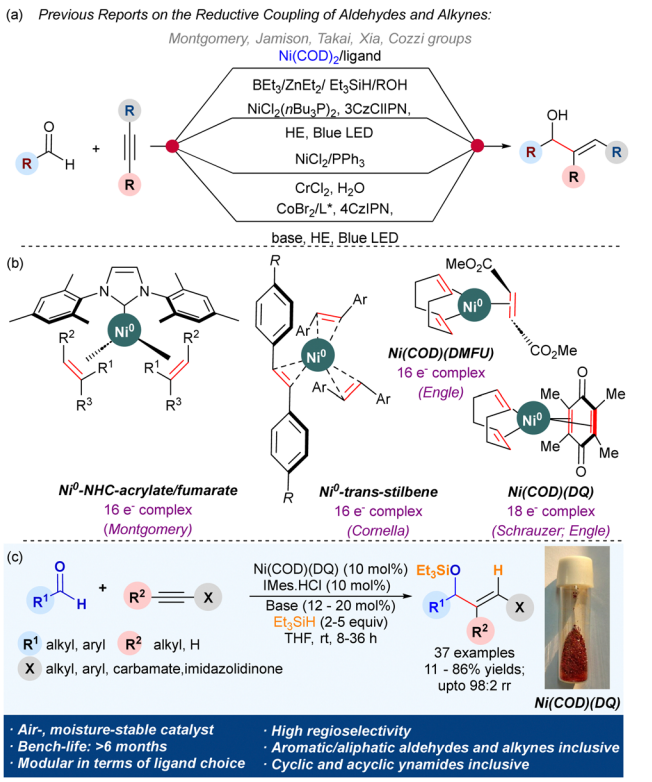
We demonstrate the potential of Ni(COD)(DQ), a bench-stable Ni^0 complex, as a catalyst for the reductive coupling of aldehydes with alkynes and ynamides, providing silylated allyl alcohols with excellent yields and regioselectivities. Mass spectrometric identification of the intermediates and DFT studies 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 nickel-catalyzed 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^0 complexes makes them highly air and moisture sensitive. The major commercial Ni^0 source, $Ni(COD)_2$, degrades within a few hours on the benchtop. The catalytic activity of other stable commercial sources like $Ni(CO)_4$, $Ni(PPh_3)_4$, Ni(COD)(DQ), *etc.*, are under-explored.[5]

Various attempts to improve the benchtop stability and leverage the unique reactivity of Ni^0 complexes have been reported.[6] Montgomery uncovered the exceptional stability of Ni^0–NHC 16e$^-$ complexes ligated with electron-deficient olefins (EDOs) like fumarates and acrylates (Scheme 1b).[7] 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 Ni^0(COD)(EDO) complexes like Ni(COD)(DMFU) (16e$^-$ complex),[8] Ni(COD)(DQ) (18e$^-$ complex), *etc.*[9] 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) bench-stable Ni^0 precatalysts; (c) present work.

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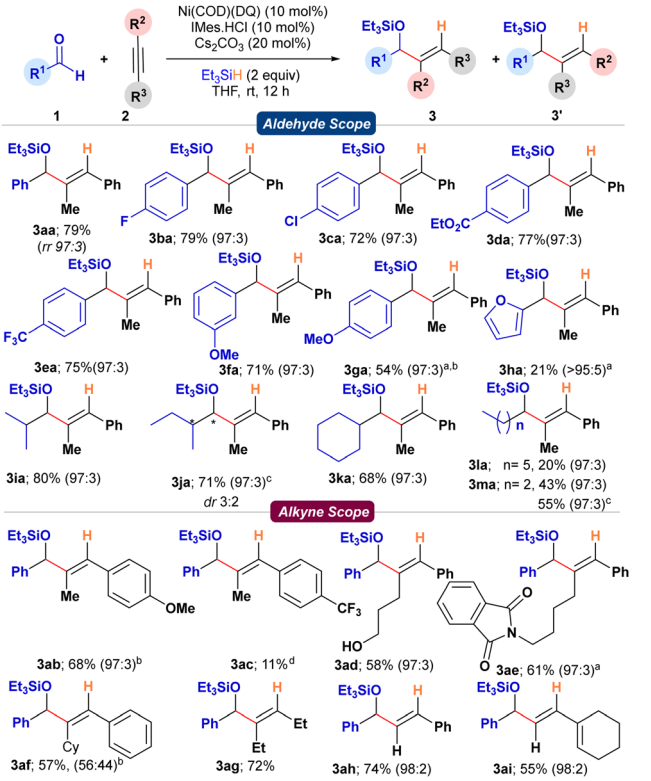
the access to Ni(NHC)(EDO)$_2$ complexes in a modular fashion by reacting NHC salts with Ni(COD)(DQ) to catalyze alkyne/aldehyde reductive coupling (Scheme 1c). The *in situ* generated Ni(NHC)(DQ) complexes could eliminate the requirement of a glovebox for this transformation.

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 silylated 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.HBF$_4$ and IBn.HBF$_4$ failed to provide **3aa**. Cs_2CO_3 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%), Cs_2CO_3 (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 –CF_3, –CO_2Et, 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 electron-donating 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 silylated allyl alcohols **3ia–3ka** in good to excellent yields (68–80%) and high regioselectivities. Contrarily, linear chain aliphatic aldehydes (**1l**, **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 (Cs_2CO_3). 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 electron-withdrawing –CF_3 group at the *para*-position, the reaction was sluggish to provide the silylated 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-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 diene-allylic alcohol **3ai** is noteworthy (Scheme 2).



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.

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^{t}Bu (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

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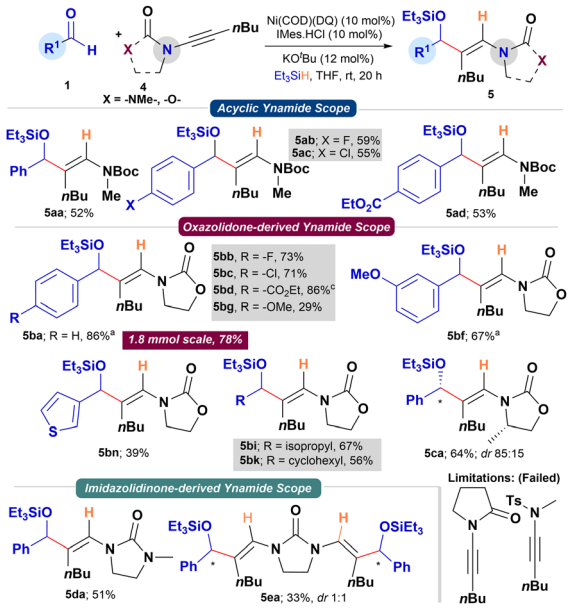

Scheme 3 Scope for the reductive coupling of aldehydes and ynamides. [a] 8 h reaction time.

comparable yield (61% NMR yield; rr > 95 : 5). The reaction tolerated –F, –Cl, and –CO_2Et 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 silylated 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 double-reductive 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^0 species, which drives the catalytic cycle. The EDO ligand (DQ) that stabilized the Ni^0 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 ^{1}H 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 [Ni^0(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 Cs_2CO_3 enables the formation of IMes carbene. The carbene on complexation with Ni(COD)(DQ) precatalyst provides **B** (16e$^-$ complex). 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 Et_3SiH 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 aldehyde–ynamide 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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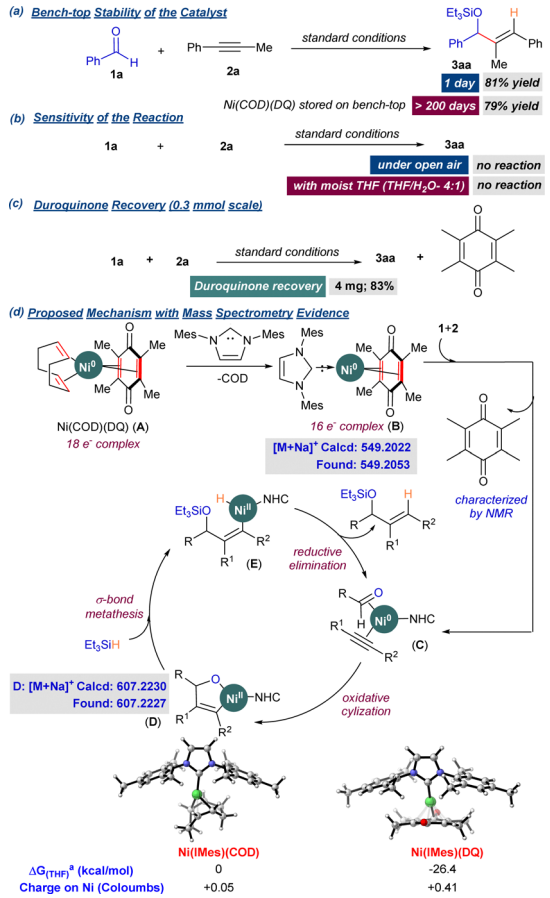
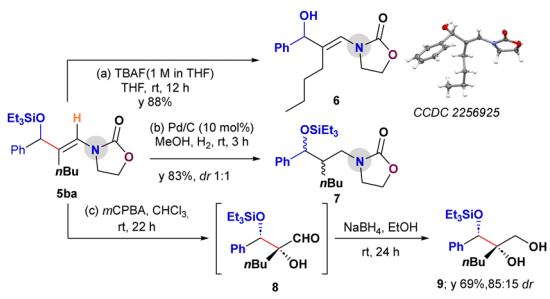


Scheme 4 Control experiments and plausible mechanism. [a]Gibbs free energies were calculated at M062X(SMD)/def2-TZVP (THF). Charges (NBO) at M062X/def2-TZVP.

crystallography. Further, the reduction of **5ba** with 10% Pd/C and H_2 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 $NaBH_4$ delivered the silylated 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 Ni^0 chemistry.

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Conflicts of interest

There are no conflicts to declare.

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