Ni(COD)(DMFU): A Heteroleptic 16-Electron Precatalyst for 1,2-Diarylation of Alkenes

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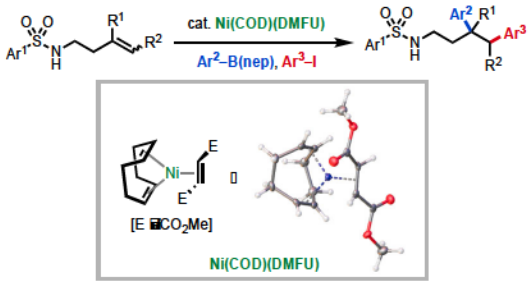

• well-defined, all-in-one precatalyst • operationally simple synthesis
• head-to-head comparisons with [Ni(COD)$_2$ + DMFU]
(10 examples, up to 20% yield improvement)

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Abstract Electron-deficient olefin (EDO) ligands are known to promote a variety of nickel-catalyzed cross-coupling reactions, presumably by accelerating the reductive elimination step and preventing undesired β-hydride elimination. While there is a growing body of experimental and computational evidence elucidating the beneficial effects of EDO ligands, significant gaps remain in our understanding of the underlying coordination chemistry of the Ni–EDO species involved. In particular, most procedures rely on in situ assembly of the active catalyst, and there is a paucity of pre-ligated Ni-EDO precatalysts. Herein, we investigate the 16-electron, heteroleptic nickel complex, Ni(COD)(DMFU), and examine the performance of this complex as a precatalyst in 1,2-diarylation of alkenes.

Key words nickel, precatalysts, homogeneous catalysis, electron-deficient olefin ligand

Homogenous nickel catalysis has advanced rapidly over past two decades.[1] Consequently, interest in the synthesis, coordination chemistry, and catalytic reactivity of organonickel complexes continues to grow. In particular, nickel–olefin complexes have played a central role in developing fundamental organometallic understanding of nickel chemistry and in catalytic reaction discovery.[2–7] Both homoleptic- and heteroleptic 16- and 18-electron nickel-olefin complexes are known and have been applied as homogeneous catalysts in a variety of transformations. In most catalytic applications, the olefin ligand is conveniently displaced in situ by a stronger σ-donor ligand, most commonly a phosphine-, N-heterocyclic carbene-, or nitrogen-based ligand (Figure 1).

In some cases, however, olefins are intimately involved as ligands in key intermediates and/or transition states in the catalytic cycle. For example, electron-deficient olefins (EDOs) have appeared in a variety of cross-coupling reactions as a unique class that is proposed to promote reductive elimination and prevent β-hydride elimination.[2] In the context of Ni-catalysis in particular, a number of transformations are uniquely promoted by EDO ligands,[5,6] and while recent studies have shed light on some mechanistic aspects of this chemistry,[5f,g,6a,b] a refined understanding of the structure and behavior of Ni–EDO complexes is lacking.

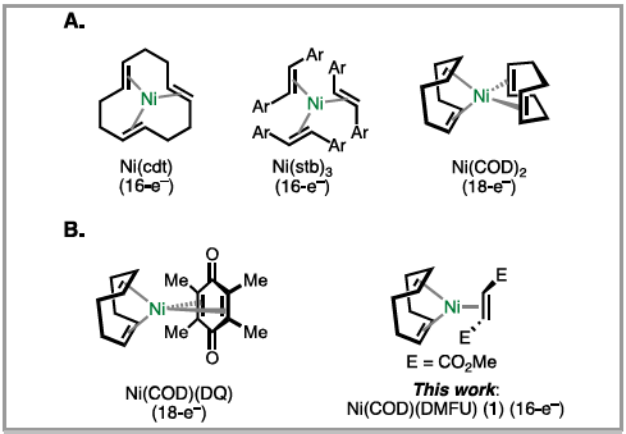
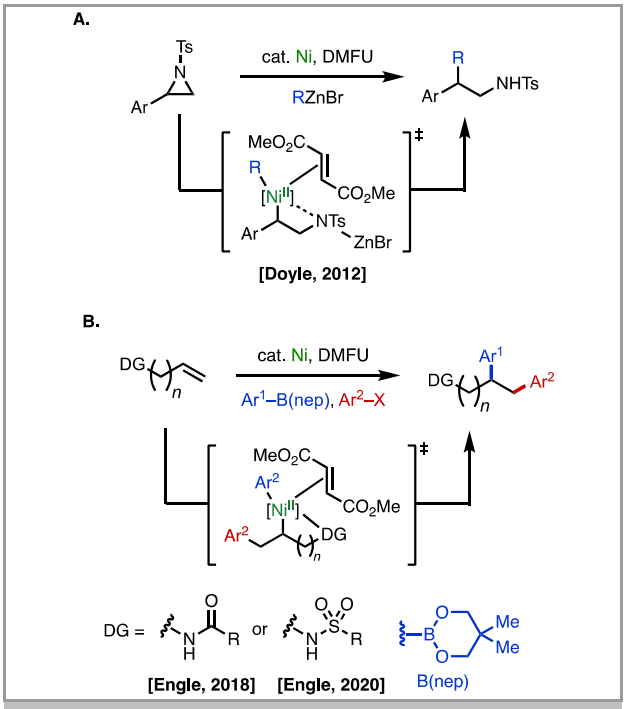


Figure 1 (A) Homoleptic and (B) heteroleptic 16- and 18-electron Ni(0)–olefin complexes. (Abbreviations: cdt = all-*trans*-1,5,9-cyclododecatriene, stb = *trans*-stilbene, COD = 1,5-cyclooctadiene, DQ = duroquinone, DMFU = dimethyl fumarate).

In 2012 the Doyle group described the use of dimethyl fumarate (DMFU) as the optimal ligand for promoting C–C reductive elimination step in the Negishi alkylation of styrenyl aziridines. In particular, it was demonstrated that reductive elimination from an independently prepared dialkylorganonickel intermediate complex only occurs in the presence of DMFU ligand (Scheme 1, A).[6a] Subsequently, using a novel sultam-derived EDO ligand, Fro-DO (Fro-DO = (*E*)-1,4-bis(2,2-dioxido-3,3a,4,8b-tetrahydro-*1H*-indeno[1,2-c]isothiazol-1-yl)but-2-ene-1,4-dione), they prepared a catalytically competent Ni(COD)(Fro-DO) complex and examined the beneficial effect of EDO ligands.[5f,g] In line with these findings, our lab discovered that EDO ligands enhance reactivity in Ni-catalyzed alkene

dicarbofunctionalization reactions, and DFT calculations revealed significantly lowered activation energy for the key C–C reductive elimination step (Scheme 1, B).[6b, 8]



Scheme 1 Ni-catalyzed reactions using dimethyl fumarate as optimum ligand. (A) DMFU accelerates reductive elimination in Negishi alkylation of styrenyl aziridines (B) DMFU lowers activation energy for C–C reductive elimination step in alkene 1,2-diarylation.

During the course of an investigation into the catalytic reactivity of Ni(COD)(DQ), a previously reported air-stable, 18-electron Ni(0)–olefin complex,[4c] we noted that Ni(COD)(olefin) complexes could be prepared by displacing a single COD ligand from $Ni(COD)_2$, in line with a previous report.[9] In contrast to Ni(COD)(DQ), however, EDO-coordinated 16-electron Ni(0) complexes decomposed immediately upon exposure to the air, implying that susceptibility to oxidation stems from an open coordination site. This observation, along with the unique contribution of EDO ligands to various realms of Ni-catalysis, motivated us to investigate the fundamental coordination chemistry of this 16-electron Ni–EDO complexes and their potential uses as practical precatalysts for challenging C–C couplings.[4, 10] In particular, based on the catalytic importance of DMFU as a ligand, we focused our attention on Ni(COD)(DMFU) (**1**; COD = 1,5-cyclooctadiene, DMFU = dimethyl fumarate). The synthesis of this complex was originally reported by Binger in 1984, yet structure and reactivity data for this complex have not been described.[9] In this communication, we report the single-crystal X-ray structure of Ni(COD)(DMFU) complex, computational analysis based on the solid-state structure, and practical advantages in catalytic reactivity when using the pre-ligated complex in one of our recent Ni-catalysis system.

We initiated our study by first attempting to prepare and isolate Ni(COD)(DMFU). To this end, by following the modified procedure from the literature,[9] we treated $Ni(COD)_2$ with an equimolar amount of DMFU in a solution of benzene under inert atmosphere (Figure 2). An immediate change of the heterogeneous mixture to a red, homogeneous solution indicated the formation of the desired complex. In an attempt to isolate the complex, the crude reaction mixture was triturated with copious amounts of hexanes to yield an air-sensitive bright red solid following vacuum filtration. ^{1}H NMR spectra of the isolated material confirmed the successful formation of Ni(COD)(DMFU), indicated by the distinctive patterns of alkenyl and allylic protons of COD ligands upon DMFU coordination.

Red, needle-like crystals of Ni(COD)(DMFU) were obtained by cooling a benzene/hexane solution of **1** at –33 °C. Single-crystal X-ray diffraction (XRD) confirmed the atomic connectivity, showing formation of a three-coordinate 16-electron complex, rather than the potential four-coordinate 18-electron complex bearing two DMFU ligands. Unlike homoleptic $Ni(stb)_3$ complexes,[4d,e] which adopt a distorted trigonal planar geometry with the torsion angles of the propellers averaging 30.3°, the pair of olefin moieties in COD are approximately orthogonal (98.9 °) with respect to DMFU in the solid state.[11] With respect to the DMFU fragment, the C=C bond length (1.417(5) Å) is significantly elongated in comparison to free DMFU (1.318 Å). Moreover, disruption of planarity/conjugation was evident from the dihedral angle between two carbonyl groups of 13.1° compared to 0.0 for the free molecule, showing significant back donation from the *d*-orbitals of nickel to the π*(C=C) orbital.

In terms of stability, complex **1** seems to be indefinitely (at least 3 months) stable when stored at low temperature (–33 °C) under inert atmosphere, as the physical appearance and the ^{1}H NMR of complex **1** remain unchanged. However, complex **1** decomposes within a few seconds upon exposure to air, as evidenced by a color change from red to black.

Additional information regarding the structure and bonding was obtained from density functional theory calculations (see Supporting Information for details). Natural population analysis revealed a +0.28814 charge on nickel assigned in complex **1**, supporting a formal oxidation state of Ni(0).[12] Second-order perturbation analysis of the Fock Matrix shows remarkable stabilization from nickel's lone-pair orbital to the π* orbital of $(C=C)_{dmfu}$ (66.12 kcal/mol), which is nearly 60 % of the overall stabilization from back donation (110.52 kcal/mol).[13] Accordingly, deletion analysis of the Fock Matrix for the corresponding back-bonding interactions reveals around 0.4 electrons are delocalized from Ni to DMFU.

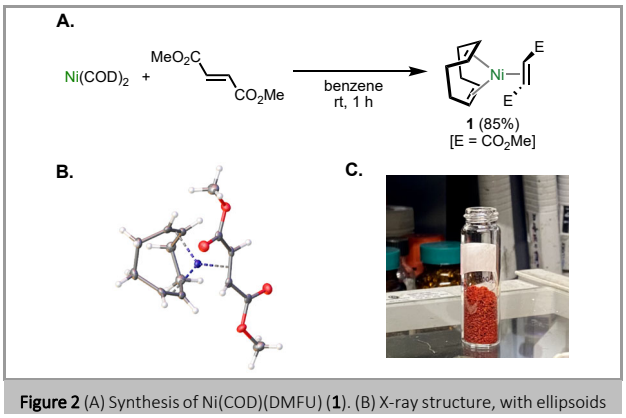
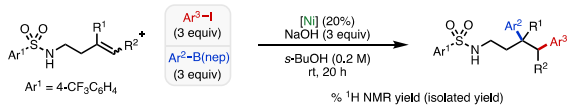


Figure 2 (A) Synthesis of Ni(COD)(DMFU) (**1**). (B) X-ray structure, with ellipsoids

represent 50% probability. (C) Isolated amorphous solid **1** under inert atmosphere.

Having characterized complex **1**, we next studied its performance as a precatalyst, using the sulfonamide-directed alkene 1,2-diarylation as a model system (Table 1).[6c] Specifically, we benchmarked performance against substrate/coupling partner combinations that were low to moderate yielding under standard conditions involving in situ DMFU coordination. Yields were compared under two different reaction conditions run in parallel: Conditions A involved a combination of equimolar amount of DMFU to $Ni(COD)_2$ (20 mol%) for *in situ* generation of **1**,[14] and Conditions B involved precatalyst **1**.[15] The use of preligated complex **1** resulted at least equal yield, and in some cases, it led to considerably improved catalytic activity. The positive change in yield was especially prominent for 1,1-disubstituted substrates (entry 1–5), which proceed via a particularly challenging 3°-C(sp^3)–Ar reductive elimination step. In these cases, up to 20% increases in yields were found. In contrast, the effect was inconsequential for 1,2-disubstituted alkenes (entry 6–8). Unfortunately, but not surprisingly, preligation was not advantageous for unreactive substrates under standard conditions. Overall, pregenerated complex **1** proved to be compatible for use in place of $Ni(COD)_2$/DMFU. Beyond the operational simplicity associated with its use, preligated **1** offers benefits in terms of catalytic activity with some challenging substrates. Though the origins of this effect remain unclear at this time, potential explanations include: 1) the highly soluble nature of **1** in the reaction solvent (*s*-BuOH), which allows it to dissolve faster, resulting in a higher initial concentration of nickel in solution at the beginning of the reaction; 2) by controlling the initial speciation, a higher fraction of the nickel is in an active on-cycle form early in the time course of the reaction, and 3) absence of extra COD which can potentially interfere with the alkene substrate and/or DMFU ligand binding to the metal center. To probe this last possibility, we performed a control experiment in which we added 20 mol % COD (1 equiv. relative to **1**) under conditions otherwise identical to entry 2, condition B. We found no appreciable decrease in yield,[16] indicating that additional COD does not affect the final yield, though it does not rule out possible role that it impacts the kinetics.

Table 1 Sulfonamide-directed Ni-catalyzed 1,2-diarylation using different substrates, nucleophiles, and electrophiles.

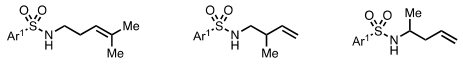


% ^{1}H NMR yield (isolated yield)

Entry	R	Ar	*Conditions A*: $Ni(COD)_2$ (20%), DMFU (20%)	*Conditions B*: Ni(COD)(DMFU) (20%)
1	R^1 = Me, R^2 = H	Ar^2 = 4-$PhOC_6H_4$, Ar^3 = Ph	(50)[a]	(70)
2		Ar^2 = 4-$MeOC_6H_4$, Ar^3 = Ph	49	67 (70)
3	R^1 = Et, R^2 = H	Ar^2 = 4-$MeOC_6H_4$, Ar^3 = Ph	23	31 (28)
4		Ar^2 = 4-$PhOC_6H_4$, Ar^3 = Ph	25	32 (29)
5	R^1 = Ph, R^2 = H	Ar^2 = 4-$MeOC_6H_4$, Ar^3 = Ph	39	52 (49)
6		Ar^2 = 4-Tol, Ar^3 = 4-CF_3Ph	56	72 (66)
7	R^1 = H, R^2 = (*Z*)-Me	Ar^2 = 4-Tol, Ar^3 = Ph	> 95	> 95
8	R^1 = H, R^2 = (*Z*)-Et	Ar^2 = 4-Tol, Ar^3 = Ph	75	75
9	R^1 = H, R^2 = (*E*)-Et	Ar^2 = 4-Tol, Ar^3 = Ph	75	74
10	R^1 = Me, R^2 = (*E*)-Me	Ar^2 = 4-Tol, Ar^3 = Ph	46	45

Reaction performed on 0.1 mmol scale. Percentage yield by ^{1}H NMR using 4,4′-di-*tert*-butylbiphenyl as the internal standardard in reaction. Isolated yields in parentheses. Conditions A and B for each entry were run in parallel. [a] Reported value using 20% $Ni(COD)_2$, 15% DMFU.

unreactive substrates



In summary, we have synthesized, characterized, and tested catalytic reactivity of the 16-electron, heteroleptic Ni(0) complex, Ni(COD)(DMFU) (**1**). This air-sensitive Ni(0) complex is sufficiently stable for growing crystals suitable for structural analysis, as well as for NMR characterization at ambient temperature, to confirm the 16-electron, 3-coordinate structure. Solid state structure-based calculations suggest the oxidation state of the nickel center to be close to 0, rather than 1, and shows notable back bonding interaction between the metal center and EDO ligand. Its practical utility was tested with sulfonamide-directed alkene 1,2-diarylation reaction as the model system, showing equal to improved reactivity in terms of yield.

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Supporting Information

YES

Primary Data

YES (XRD.cif)

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(8) The transition state for reductive elimination with dimethyl fumarate (DMFU) displays significantly lower activation energy than transition states with ethylene- or solvent-bound nickel ($\Delta G^{\ddagger}$ = 2.6 kcal/mol compared to $\Delta G^{\ddagger}$ = 14.6 kcal/mol or $\Delta G^{\ddagger}$ = 37.4 kcal/mol, respectively; see reference 6b for detail)

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(12) For comparison, values for related complexes are as follows: +0.21065 for Ni(COD)(DQ) and +0.09120 for $Ni(COD)_2$. (see Ref. 4c).

(13) The sum of second order perturbations from Ni(LP) to p*(C=C) of both DMFU and COD is much greater than the corresponding value for Ni(COD)(DQ), which was 82.62 kcal/mol.

(14) In the standard procedure in Ref. 6c, 20 mol% Ni(COD)2 and 15 mol% DMFU are used. In order to make a more direct comparison to Ni(COD)(DMFU) Condition A uses 20 mol% DMFU under otherwise identical conditions to Ref. 6c. Empirically, we have found that 15–20 mol% DMFU leads to similar yields (±5%) in the in situ coordination protocol.

(15) Representative example of 1,2-diarylation of alkenes (entry 2): To a 1-dram (4 mL) vial equipped with a Teflon-coated magnetic stir bar were added the alkene substrate (0.1 mmol) and the appropriate aryl boronic acid neopentylglycol ester (0.3 mmol). The vial was then equipped with a septum cap and brought into the glovebox. In the glovebox, anhydrous NaOH (0.3 mmol), the appropriate aryl iodide electrophile (0.3 mmol), a stock solution of 4,4′-di-tert-butylbiphenyl (internal standard; 0.2 mL of 0.25 mM solution in sec-butanol), and anhydrous sec-butanol (0.3 mL) were added. For conditions A, DMFU (20 mol%) and $Ni(COD)_2$ (20 mol%) was added, and for conditions B, Ni(COD)(DMFU) (20 mol%) was added, respectively. The vial was sealed with a screw-top cap, removed from the glovebox, and left to stir at room temperature for 16 h. After this time, the reaction mixture was quenched with sat. aq. $NaHCO_3$ (1 mL), diluted with diethyl ether (2 mL), and stirred vigorously for 20 min. Next, the organic and aqueous phases were separated, and the aqueous phase was further extracted with diethyl ether (3 × 2 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under vacuum. The resulting crude mixture was analyzed by ^{1}H NMR in $CDCl_3$, displaying 49% formation of **S21** from Conditions A, and 67% from Conditions B. ^{1}H NMR yields for diarylation were determined by integrating the ^{1}H resonances for the products relative to the resonances of internal standard (0.50 mmol; 18 H integrated to 0.90) at δ 1.37 ppm in $CDCl_3$. Purification by preparative thin-layer chromatography (PTLC; 20% acetone in hexanes) afforded **S21** as a colorless oil, which solidifies upon standing or cooling (33 mg, 70%; Conditions B). ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.85 (d, *J* = 7.9 Hz, 2H), 7.73 (d, *J* = 8.4 Hz, 2H), 7.12 (dpd, *J* = 14.1, 7.9, 3.3 Hz, 3H), 7.07–7.01 (m, 2H), 6.85–6.78 (m, 2H), 6.75–6.68 (m, 2H), 4.29 (d, *J* = 6.0 Hz, 1H), 3.81 (s, 3H), 2.97–2.83 (m, 2H), 2.77 – 2.65 (m, 2H), 2.10 (ddd, J = 15.2, 10.2, 5.3 Hz, 1H), 1.72 (ddd, J = 13.0, 10.3, 5.5 Hz, 1H), 1.18 (s, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 158.03, 143.73, 137.68, 137.32, 134.43 (q, *J* = 33.1 Hz), 130.66, 127.76, 127.70, 127.67, 123.12 (q, *J* = 273.50 Hz), 113.80, 55.40, 51.22, 42.06, 40.65, 39.93, 23.44. ^{19}F NMR (376 MHz, $CDCl_3$) δ –65.74. HRMS (ESI-TOF) Calc'd for $C_{25}H_{25}F_3NO_2S$ $[M-H]^-$ 476.1607, found 476.1506.

(16) 20 mol% COD (1 equiv. to [Ni]) was added into a trial run under condition B in order to reproduce the overall [COD] in condition A. This experiment resulted in 65% NMR yield, which is within 5% of the result without additional COD.