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Nickel-Catalyzed Intramolecular Arylcyanation for the Synthesis of 3,3-Disubstituted Oxindoles

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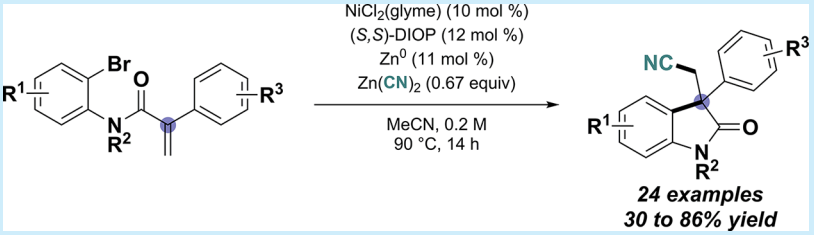
Supporting Information



ABSTRACT: A nickel-catalyzed arylcyanation reaction for the synthesis of 3,3-disubstituted oxindoles has been developed. This method features a bench-stable precatalyst system and serves as an economical alternative to the existing palladium-catalyzed arylcyanations described to date. A wide scope of oxindole products were accessible in moderate to good yields, and the rich chemistry of the newly installed nitrile functional group was demonstrated in the synthesis of various oxindole derivatives.

Nickel catalysis is playing an increasingly important role in modern organic synthesis.[1] The high cost of noble metals that dominate the landscape of catalytic C−C bond formation has led synthetic chemists to seek out viable alternatives. Accordingly, adopting the use of nonprecious and earth-abundant base metals is attractive for reasons of cost and sustainability. The widely practiced Heck reaction,[2] which traditionally employs palladium as the catalyst of choice, is one such transformation that stands to benefit tremendously from a switch to nickel.[3]

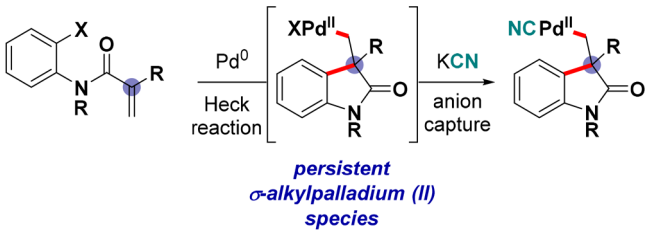
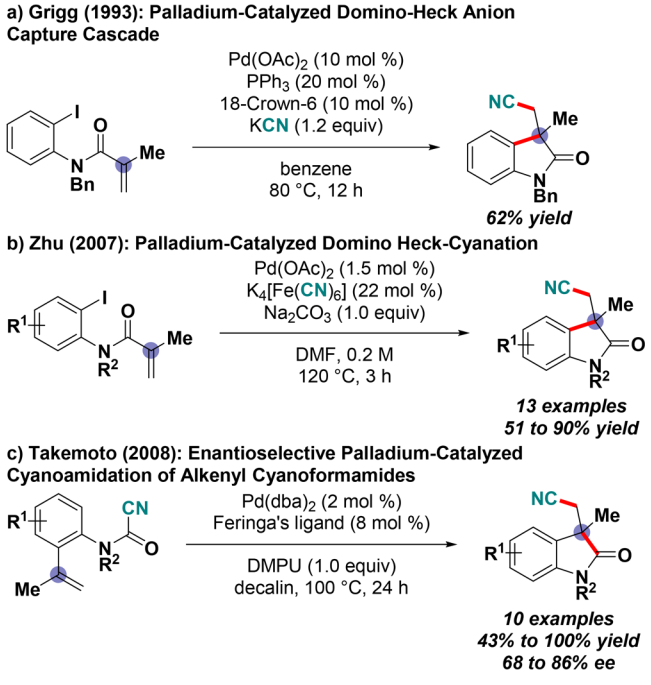


Figure 1. Domino Heck-cyanide capture cascade.

The domino Heck-anion capture cascade is a variation of the classic Heck reaction wherein a persistent σ-alkylpalladium(II) species is generated from an intramolecular Heck cyclization before undergoing successive halide-for-nucleophile exchange then reductive elimination to deliver the products of alkene vicinal difunctionalization (Figure 1).[4] This reaction is exemplified by the palladium-catalyzed alkene arylcyanation that was first disclosed by Grigg[5] (Scheme 1a), and it remains a topic of contemporary interest in our group.[6] Inspired by the recent reports of Garg,[7] Kong,[8] Zhou[9] and others[10] on nickel-catalyzed Heck methods and in continuation of our work on this reaction, we became interested in the pursuit of an analogous nickel-catalyzed alkene arylcyanation.[11]

Scheme 1. Palladium-Catalyzed Methods for Accessing 3-Cyanomethyl Oxindoles



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We observed that a particular emphasis had been placed on accessing the 3,3-disubstituted oxindole motif,[12] which is a privileged pharmacophore.[12a,13] In fact, an examination of the literature revealed a preponderance of palladium catalysis in the synthesis of 3,3-disubstituted oxindoles via Heck cyclization of acetanilides, and to a lesser extent, enolate α-arylation.[14] Although benzylic all-carbon quaternary centers[15] could be forged in many instances, the α-substituent that serves to block β-hydride elimination in the domino Heck reaction is often relegated to a methyl group for ease of method development. This lack of functional group content and subsequent anion capture with a carbon nucleophile, that is itself typically devoid of functionality, limits further elaboration at the 3-position. Due to the rich chemistry of the nitrile functional group,[16] we envisioned that installation of a cyanomethyl group at the 3-position via an alkene arylcyanation would address this limitation.[17]

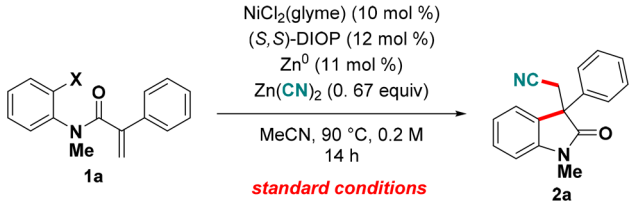
In addition to Grigg's seminal work, direct precedence in this area comes from Zhu's report on the palladium-catalyzed synthesis of 3,3-disubstituted cyanomethyl oxindoles using $K_4[Fe(CN_6)]$ as the cyanide source (Scheme 1b).[18] Modest enantioselectivities for select examples were also disclosed. Takemoto had also previously disclosed the enantioselective synthesis of 3,3-disubstituted oxindoles via a palladium-catalyzed intramolecular cyanoamidation of styrene derivatives employing Feringa's phosphoramidite[19] as the chiral ligand (Scheme 1c).[20] The related nickel-catalyzed, Lewis acid-assisted carbocyanations[21] that involve C−CN bond activation from the groups of Jacobsen[22] and Hiyama[23] also help to establish feasibility for the desired carbonickelation and reductive elimination steps. Recent contributions from Liu[24] and Beller[25] serve to complete the background literature for our proposed transformation by demonstrating the use of the less toxic $Zn(CN)_2$[26] as a cyanide source in a nickel-catalyzed process. Herein, we report a practical alternative to the existing palladium-based methods for the synthesis of 3,3-disubstituted oxindoles via a nickel-catalyzed arylcyanation.

An alternative to the air-sensitive $Ni(cod)_2$ would be ideal, as it would allow a user-friendly setup. Remarkable advances in reductive nickel catalysis have demonstrated the practicality of a Ni/Zn redox couple.[27] Indeed, on heating model substrate **1a** with a combination of $NiCl_2$(glyme) (10 mol %), DPPF (12 mol %), activated zinc dust (20 mol %) and $Zn(CN)_2$ (1.0 equiv), the desired oxindole **2a** was isolated in 68% yield along with minor amounts of the 6-*endo* cyclization product (Table 1, entry 2).[28] The zinc reductant was necessary, as no reaction occurred in its absence (Table 1, entry 4). Interestingly, metallic manganese powder was ineffective at serving as the reductant, and this may point to an additional role for the generated zinc salts that cannot be fulfilled by manganese salts (Table 1, entry 5).

Preliminary optimization experiments focused on **1a-Cl** (Table 1, entry 8) as the model substrate in the hopes of using the less costly aryl chloride derivatives. However, a greater tendency toward the 6-*endo* mode of cyclization as well as inferior overall yields deterred further study of these substrates.[28] The aryl triflate derivative **1a-OTf** (Table 1, entry 10) was also tested to access a cationic Heck pathway,[2a,29] although low yields were similarly observed.

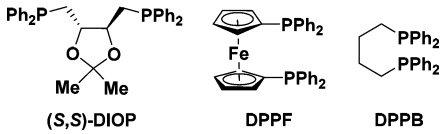
We sought to make the nickel-catalyzed arylcyanation enantioselective by screening various members of privileged ligand families. Unfortunately, our screening revealed that previously successful ligands utilized in asymmetric nickel catalysis gave poor to moderate yields of the racemic product.[30] This observation may stem in part from stringent structural and electronic requirements for the challenging C−CN reductive elimination, for which electron-rich chiral bisphosphines are poorly suited.[31]

Table 1. Effect of Deviations from the Standard Conditions[a]



entry	deviation from the *standard conditions*	yield (%) **2a**[b]
1	none (X = Br, **1a**)	85[c]
2	DPPF	68
3	DPPB	39
4	no reductant	0
5	Mn^0 as reductant	0
6	1 h 30 min instead of 14 h	61
7	80 °C	81
8	**1a-Cl** (X = Cl) instead of **1a**	13
9	**1a-I** (X = I) instead of **1a**	64
10	**1a-OTf** (X = OTf) instead of **1a**	11

[a]Reactions were conducted on a 0.2 mmol scale. [b]Determined by ^{1}H NMR analysis of the crude reaction mixture unless otherwise stated. [c]Isolated yield representing an average of 2 runs.



Substitution on the aryl halide was shown to be generally well-tolerated. Electron-rich aryl bromides such as **1b−d**, **1g**, and **1j** were excellent substrates for the arylcyanation reaction, affording the corresponding oxindoles **2b−d**, **2g**, and **2j** in moderate to good yields. The methylated substrate **1i** required a higher loading of $Zn(CN)_2$ (1.05 equiv) to achieve a moderate yield of **2i**.

Fluorinated and chlorinated aryl bromides such as **1e**, **1f**, **1h**, **1k**, and **1l** were also tolerated. Drastic differences in reactivity were observed when the *para*-substituents on the acrylamide aryl moiety were electronically varied, as exemplified by **2m** and **2n**. An electron-donating *p*-OMe substituent is expected to reverse the normal polarity of the acrylamide moiety in **1m**, thereby favoring the desired 5-*exo* mode of cyclization. In contrast, substrate **1n**, bearing the *p*-CF_3 substituent, should see

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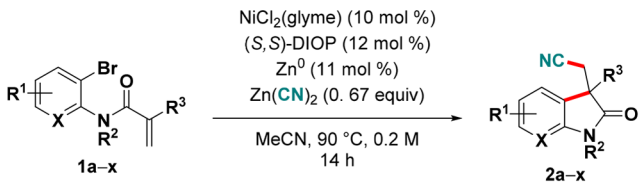
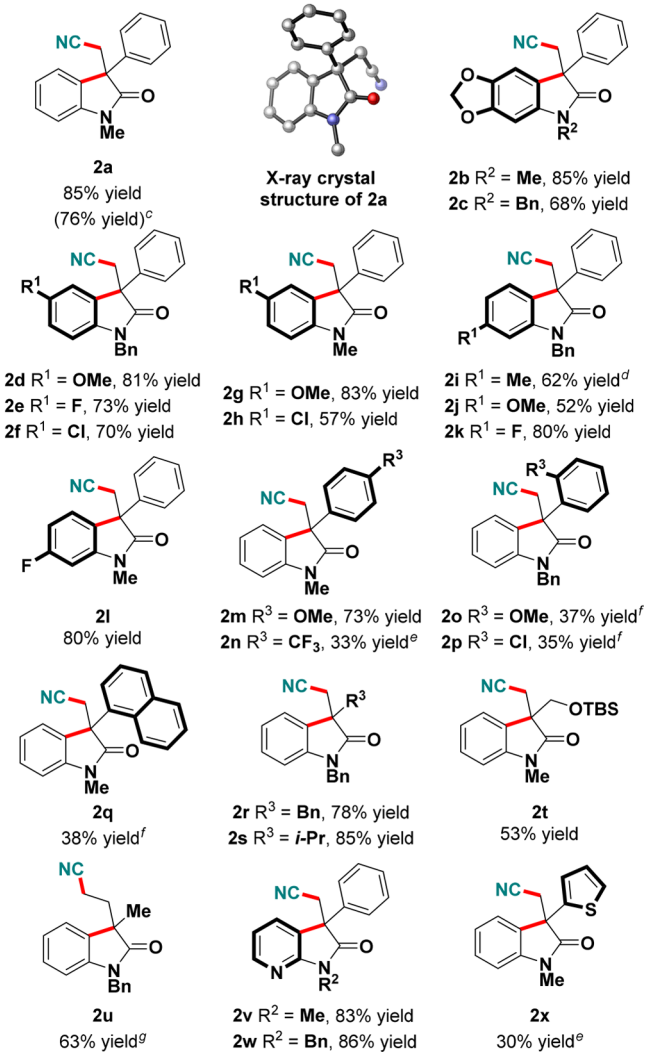
Scheme 2. Scope of the Nickel-Catalyzed Intramolecular Arylcyanation[a,b]





[a]Reactions were conducted on a 0.2 mmol scale unless otherwise stated. [b]All yields shown are isolated yields. [c]Reaction was conducted on a 1.0 mmol scale. [d]1.05 equiv of $Zn(CN)_2$ was used. [e]Remaining mass balance consists of unreacted substrate. [f]Remaining mass balance consists of unidentified side products. [g]See Figure 2 for the structure of **1u** or refer to the Supporting Information.

the normal polarity of the alkene reinforced, disfavoring the 5-*exo* migratory insertion.

Ortho substitution also proved to be limiting, as oxindoles **2o** and **2p** were isolated in diminished yields. Notably, the *o*-OMe group in **1o** is expected to polarize the alkene in analogy to **1m**; however, this did not promote efficient product formation. Combined with the observation that **1p** bearing an *o*-Cl substituent (which should also favor 5-*exo* migratory insertion) led to low yields of **2p**, this suggests that steric effects dominate the insertion step. A similar argument may be invoked for oxindole **2q** being isolated in a comparably low yield, although a disfavored conjugation-breaking migratory insertion with the naphthyl group emerges as an equally likely contributor to this outcome.

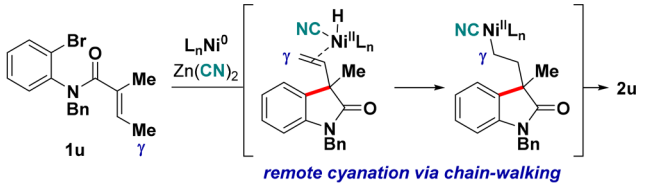
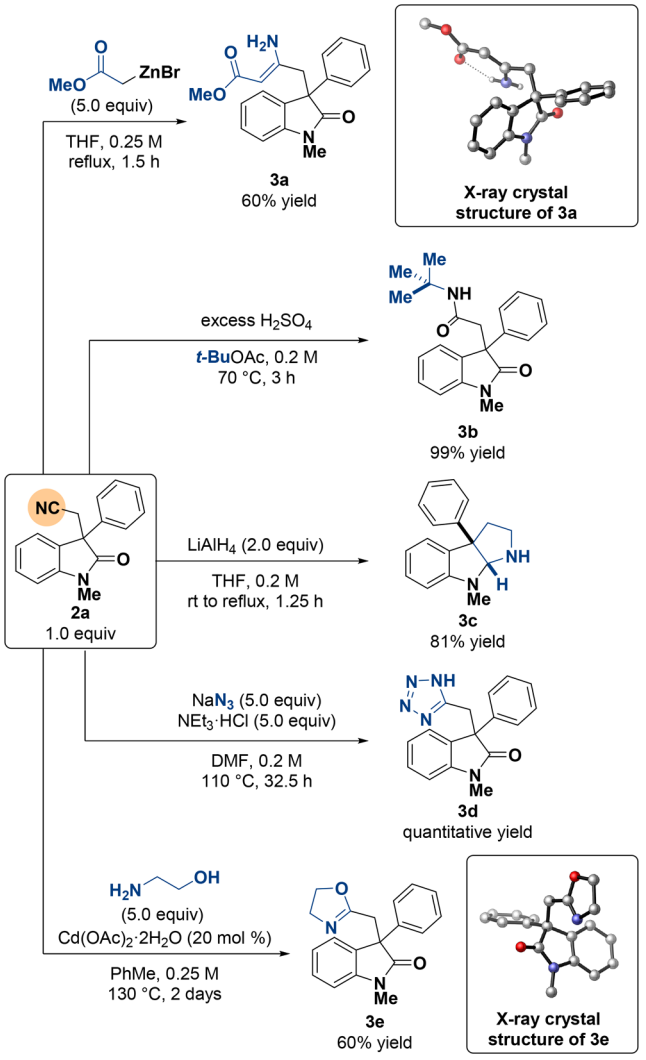


Figure 2. Observation of remote cyanation for substrate **1u**.

Alkyl groups at the benzylic position were well-tolerated, as was demonstrated by examples **2r** through **2t**. An interesting observation arises when preparing **2u**. The corresponding *o*-bromoanilide **1u**, derived from tiglic acid, bears a second methyl group toward which β-hydride elimination can occur to initiate chain-walking.[34] The putative hydridonickel(II) cyanide com-

Scheme 3. Derivatization Studies of 2a[a,b]



[a]Reactions were conducted on a 0.2 mmol scale. [b]All yields shown are isolated yields. *t*-BuOAc = *tert*-butyl acetate; THF = tetrahydrofuran; DMF = *N*,*N*-dimethylformamide; PhMe = toluene.

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plex can undergo reinsertion followed by reductive elimination to effect remote C−H cyanation at the γ position as was previously observed by Hiyama (Figure 2).[35]

Examples **2v** and **2w** demonstrate that heteroarylcyanations were also possible. To the best of our knowledge, these are the first examples under nickel catalysis. However, the 2-thiophene moiety in **1x** provided low yields of **2x**.

To demonstrate the value of the nitrile functional group, we set out to diversify **2a**. The anticipated versatility of the cyanomethyl functional handle was fully displayed in a series of successful derivatization experiments (Scheme 3).

An excess of the Reformatsky enolate[36] derived from methyl bromoacetate (5.0 equiv) was used in the Blaise reaction[37] to synthesize β-enamino ester **3a** in moderate yield. Notably, the possibility of further C−C bond construction starting from **3a** is appealing. A modified Ritter reaction[38] led to the formation of *N-tert*-butylated acetamide **3b** in essentially quantitative yield. Reductive cyclization by treating **2a** with $LiAlH_4$[18b,23b] followed by a brief period of reflux afforded tricyclic pyrroloindoline **3c**, presumably through the cyclization of a transient metal-loimine.[39] A [3 + 2] azide-nitrile cycloaddition furnished tetrazole **3d** in quantitative yield.[40] An interesting fusion of heterocycles was realized through a modification of the Witte-Seeliger oxazoline synthesis,[41] affording **3e** in 60% yield. The straightforward synthesis of **3a**−**3e** from easily accessible **2a** thus demonstrates the ease with which diverse oxindole derivatives can be accessed.

In conclusion, a nickel-catalyzed arylcyanation for the synthesis of 3,3-disubstituted oxindoles has been developed. Operational simplicity is achieved by employing a low-cost, air-stable precatalyst and bench-stable reagents with accessible starting materials. In addition, an assortment of novel heterocycles can be readily synthesized from the cyanomethyl functional handle, thereby demonstrating its exceptional synthetic versatility. Further studies to identify an appropriate chiral ligand to render this transformation asymmetric are underway in our laboratories.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b01772.

Optimization tables, experimental procedures, analytical data, copies of the ^{1}H, ^{13}C, and ^{19}F NMR spectra for all new compounds (**1o**, **1p**, **1q**, **1s**−**1u**, **1a-Cl**, **2a**−**2x**, and **3a**−**3e**), and X-ray crystallographic data for **2a**, **3a**, and **3e** (PDF)

Accession Codes

CCDC 1845445−1845447 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For recent reviews, see: (a) Tasker, S. Z.; Standley, E. A.; Jamison, T. F. *Nature* **2014**, *509*, 299−309. (b) Rosen, B. M.; Quasdorf, K. W.; Wilson, D. A.; Zhang, N.; Resmerita, A. M.; Garg, N. K.; Percec, V. *Chem. Rev.* **2011**, *111*, 1346−1416.

(2) For leading references, see: (a) Shibasaki, M.; Vogl, E. M.; Ohshima, T. *Adv. Synth. Catal.* **2004**, *346*, 1533−1552. (b) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945−2963. (c) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009−3066.

(3) (a) Wang, S.-S.; Yang, G.-Y. *Catal. Sci. Technol.* **2016**, *6*, 2862−2876. (b) Lin, B. L.; Liu, L.; Fu, Y.; Luo, S. W.; Chen, Q.; Guo, Q. X. *Organometallics* **2004**, *23*, 2114−2123.

(4) For a recent review, see: Giri, R.; KC, S. *J. Org. Chem.* **2018**, *83*, 3013−3022.

(5) (a) Grigg, R.; Sridharan, V. *J. Organomet. Chem.* **1999**, *576*, 65−87. Also see: (b) Grigg, R.; Santhakumar, V.; Sridharan, V. *Tetrahedron Lett.* **1993**, *34*, 3163−3164.

(6) We have recently developed alkene arylcyanation reactions for the synthesis of heterocycles: (a) Petrone, D. A.; Yen, A.; Zeidan, N.; Lautens, M. *Org. Lett.* **2015**, *17*, 4838−4841. (b) Yoon, H.; Petrone, D. A.; Lautens, M. *Org. Lett.* **2014**, *16*, 6420−6423.

(7) (a) Desrosiers, J. N.; Wen, J.; Tcyrulnikov, S.; Biswas, S.; Qu, B.; Hie, L.; Kurouski, D.; Wu, L.; Grinberg, N.; Haddad, N.; Busacca, C. A.; Yee, N. K.; Song, J. J.; Garg, N. K.; Zhang, X.; Kozlowski, M. C.; Senanayake, C. H. *Org. Lett.* **2017**, *19*, 3338−3341. (b) Desrosiers, J. N.; Hie, L.; Biswas, S.; Zatolochnaya, O. V.; Rodriguez, S.; Lee, H.; Grinberg, N.; Haddad, N.; Yee, N. K.; Garg, N. K.; Senanayake, C. H. *Angew. Chem., Int. Ed.* **2016**, *55*, 11921−11924.

(8) Li, Y.; Wang, K.; Ping, Y.; Wang, Y.; Kong, W. *Org. Lett.* **2018**, *20*, 921−924.

(9) Qin, X.; Lee, M. W. Y.; Zhou, J. S. *Angew. Chem., Int. Ed.* **2017**, *56*, 12723−12726.

(10) For selected examples, see: (a) Tasker, S. Z.; Gutierrez, A. C.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2014**, *53*, 1858−1861. (b) Gøgsig, T. M.; Kleimark, J.; Nilsson Lill, S. O.; Korsager, S.; Lindhardt, A. T.; Norrby, P. O.; Skrydstrup, T. *J. Am. Chem. Soc.* **2012**, *134*, 443−452.

(11) Work had previously been done in this area employing catalytic $Ni(cod)_2$. See: (a) Hinojosa, S.; Delgado, A.; Llebaria, A. *Tetrahedron Lett.* **1999**, *40*, 1057−1060. With stoichiometric $Ni(cod)_2$: (b) Cancho, Y.; Martín, J. M.; Martínez, M.; Llebaria, A.; Moretó, J. M.; Delgado, A. *Tetrahedron* **1998**, *54*, 1221−1232. (c) Solé, D.; Cancho, Y.; Llebaria, A.; Moretó, J. M.; Delgado, A. *J. Org. Chem.* **1996**, *61*, 5895−5904. (d) Solé, D.; Cancho, Y.; Llebaria, A.; Moretó, J. M.; Delgado, A. *J. Am. Chem. Soc.* **1994**, *116*, 12133−12134.

(12) For examples, see: (a) Cao, Z.; Zhou, F.; Zhou, J. *Acc. Chem. Res.* **2018**, *51*, 1443−1454. (b) Dalpozzo, R. *Adv. Synth. Catal.* **2017**, *359*, 1772−1810. (c) Trost, B. M.; Brennan, M. K. *Synthesis* **2009**, *2009*, 3003−3025.

DOI: 10.1021/acs.orglett.8b01772
Org. Lett. XXXX, XXX, XXX−XXX

(13) The nitrile functional group is also a known pharmacophore. See: (a) Fleming, F. F.; Yao, L.; Ravikumar, P. C.; Funk, L.; Shook, B. C. *J. Med. Chem.* **2010**, *53*, 7902−7917. (b) Fleming, F. F.; Fleming, F. F. *Nat. Prod. Rep.* **1999**, *16*, 597−606.
(14) For a review, see: Klein, J. E. M. N.; Taylor, R. J. K. *Eur. J. Org. Chem.* **2011**, *34*, 6821−6841.
(15) Quasdorf, K. W.; Overman, L. E. *Nature* **2014**, *516*, 181−191.
(16) For examples of nitrile group transformations, see: (a) Pearson-Long, M. S. M.; Boeda, F.; Bertus, P. *Adv. Synth. Catal.* **2017**, *359*, 179−201. and references therein. (b) Wang, M. X. *Acc. Chem. Res.* **2015**, *48*, 602−611.
(17) Direct arylation has also been achieved. See: (a) Sharma, U. K.; Sharma, N.; Kumar, Y.; Singh, B. K.; Van der Eycken, E. V. *Chem. - Eur. J.* **2016**, *22*, 481−485. A similar strategy has been achieved via a domino Heck-borylation. See: (b) Vachhani, D. D.; Butani, H. H.; Sharma, N.; Bhoya, U. C.; Shah, A. K.; Van der Eycken, E. V. *Chem. Commun.* **2015**, *51*, 14862−14865. Synthesis of nitrile-bearing indolinones via palladium-catalyzed oxidative arylalkylation: (c) Wu, T.; Mu, X.; Liu, G. *Angew. Chem., Int. Ed.* **2011**, *50*, 12578−12581. Direct arylation: (d) René, O.; Lapointe, D.; Fagnou, K. *Org. Lett.* **2009**, *11*, 4560−4563.
(18) (a) Jaegli, S.; Vors, J. P.; Neuville, L.; Zhu, J. *Synlett* **2009**, *4*, 2997−2999. Also see: (b) Pinto, A.; Jia, Y.; Neuville, L.; Zhu, J. *Chem. - Eur. J.* **2007**, *13*, 961−967.
(19) (a) Teichert, J. F.; Feringa, B. L. *Angew. Chem., Int. Ed.* **2010**, *49*, 2486−2528. (b) Arnold, L. A.; Imbos, R.; Mandoli, A.; De Vries, A. H. M.; Naasz, R.; Feringa, B. L. *Tetrahedron* **2000**, *56*, 2865−2878. (c) Feringa, B. L. *Acc. Chem. Res.* **2000**, *33*, 346−353.
(20) (a) Yasui, Y.; Kamisaki, H.; Ishida, T.; Takemoto, Y. *Tetrahedron* **2010**, *66*, 1980−1989. (b) Yasui, Y.; Kamisaki, H.; Takemoto, Y. *Org. Lett.* **2008**, *10*, 3303−3306.
(21) Nakao, Y.; Hiyama, T. *Pure Appl. Chem.* **2008**, *80*, 1097−1107.
(22) Watson, M. P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2008**, *130*, 12594−12595.
(23) (a) Hsieh, J.-C.; Ebata, S.; Nakao, Y.; Hiyama, T. *Synlett* **2010**, *2010*, 1709−1711. Also see: (b) Nakao, Y.; Ebata, S.; Yada, A.; Hiyama, T.; Ikawa, M.; Ogoshi, S. *J. Am. Chem. Soc.* **2008**, *130*, 12874−12875.
(24) Zhang, X.; Xia, A.; Chen, H.; Liu, Y. *Org. Lett.* **2017**, *19*, 2118−2121.
(25) Beattie, D. D.; Schareina, T.; Beller, M. *Org. Biomol. Chem.* **2017**, *15*, 4291−4294.
(26) For an example, see: (a) Cohen, D. T.; Buchwald, S. L. *Org. Lett.* **2015**, *17*, 202−205. $Zn(CN)_2$ in palladium-catalyzed cyanations: (b) Anbarasan, P.; Schareina, T.; Beller, M. *Chem. Soc. Rev.* **2011**, *40*, 5049. Akali metal cyanide salts have previously been employed. See: (c) Sakakibara, Y.; Sasaki, K.; Okuda, F.; Hokimoto, A.; Ueda, T.; Sakai, M.; Takagi, K. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 1013−1019.
(27) For a review, see: Richmond, E.; Moran, J. *Synthesis* **2018**, *50*, 499−513.
(28) See Supporting Information for details.
(29) The cationic Heck pathway is known to give better enantioselectivities in the palladium-catalyzed intramolecular Heck reaction. See: Cabri, W.; Candiani, I. *Acc. Chem. Res.* **1995**, *28*, 2−7.
(30) See Supporting Information for a full listing of chiral ligands attempted.
(31) Electron-deficient phosphites have traditionally been the ligands of choice in nickel-catalyzed hydrocyanation of alkenes. See: (a) Goertz, W.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Vogt, D. *Chem. Commun.* **1997**, 1521−1522. (b) Casalnuovo, A. L.; RajanBabu, T. V.; Ayers, T. A.; Warren, T. H. *J. Am. Chem. Soc.* **1994**, *116*, 9869−9882.
(32) The success of (*S*,*S*)-DIOP may be attributed to its wider bite angle. For pertinent reviews, see: (a) Birkholz, M.-N.; Freixa, Z.; van Leeuwen, P. W. N. M. *Chem. Soc. Rev.* **2009**, *38*, 1099. (b) van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Reek, J. N. H.; Dierkes, P. *Chem. Rev.* **2000**, *100*, 2741−2769. (c) van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Reek, J. N. H. *Pure Appl. Chem.* **1999**, *71*, 1443−1452. Also see: (d) Kagan, H. B.; Dang, T.-P. *J. Am. Chem. Soc.* **1972**, *94*, 6429−6433.
(33) 8% ee was observed. (*S*,*S*)-DIOP has experienced only modest success in the field of asymmetric hydrogenation; for attempts at improving the performance of (*S*,*S*)-DIOP, see: (a) Liu, D.; Li, W.; Zhang, X. *Tetrahedron: Asymmetry* **2004**, *15*, 2181−2184. Also see: (b) Zhu, G.; Cao, P.; Jiang, Q.; Zhang, X. *J. Am. Chem. Soc.* **1997**, *119*, 1799−1800.
(34) For a recent review on "chain-walking", see: Sommer, H.; Juliá-Hernández, F.; Martin, R.; Marek, I. *ACS Cent. Sci.* **2018**, *4*, 153−165.
(35) Yamada, Y.; Ebata, S.; Hiyama, T.; Nakao, Y. *Tetrahedron* **2015**, *71*, 4413−4417.
(36) For recent advances in Reformatsky chemistry, see: Ocampo, R.; Dolbier, W. R. *Tetrahedron* **2004**, *60*, 9325−9374.
(37) Hannick, S. M.; Kishi, Y. *J. Org. Chem.* **1983**, *48*, 3833−3835.
(38) Reddy, K. L. *Tetrahedron Lett.* **2003**, *44*, 1453−1455.
(39) For a review on metalloimine reactivity, see: Cainelli, G.; Panunzio, M.; Andreoli, P.; Martelli, G.; Spunta, G.; Giacomini, D.; Bandini, E. *Pure Appl. Chem.* **1990**, *62*, 605−612.
(40) Yoneyama, H.; Usami, Y.; Komeda, S.; Harusawa, S. *Synthesis* **2013**, *45*, 1051−1059.
(41) Witte, H.; Seeliger, W. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 287−288.
(42) The 3D X-ray crystal structure representations of **2a**, **3a**, and **3e** were prepared from the corresponding crystallographic data using CYLview. See: Legault, C. Y. *CYLview*, version 1.0b; Université de Sherbrooke: Sherbrooke, QC, Canada, 2009. http://www.cylview.org.

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