Synthetic Methods

International Edition: DOI: 10.1002/anie.201606955
German Edition: DOI: 10.1002/ange.201606955

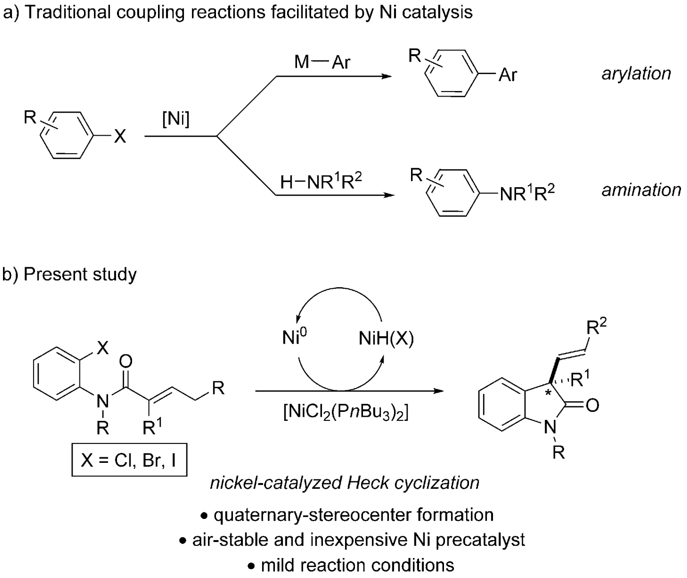
Construction of Quaternary Stereocenters by Nickel-Catalyzed Heck Cyclization Reactions

Jean-Nicolas Desrosiers, Liana Hie, Soumik Biswas, Olga V. Zatolochnaya, Sonia Rodriguez, Heewon Lee, Nelu Grinberg, Nizar Haddad, Nathan K. Yee, Neil K. Garg, and Chris H. Senanayake*

Abstract: *A nickel-catalyzed Heck cyclization for the construction of quaternary stereocenters is reported. This transformation is demonstrated in the synthesis of 3,3-disubstituted oxindoles, which are prevalent motifs seen in numerous biologically active molecules. The method shows broad scope, proceeds in synthetically useful yields, and provides a rare means to construct stereochemically complex frameworks by nonprecious-metal catalysis.*

In recent years, there has been tremendous interest in the development of cross-coupling reactions facilitated by nonprecious-metal catalysis.[1] Reactions catalyzed by nickel, in particular, have been highly sought after. In comparison to palladium, the metal most frequently used in cross-coupling reactions, nickel is significantly more abundant, much less expensive, and also possesses a lower CO_2 footprint.[1] Contributions in the field of nickel-catalyzed cross-coupling include arylation and amination reactions (Scheme 1 a), and coupling reactions that allow for the introduction of sp^3-hybridized carbon atoms.[1a]

As a part of our efforts to incorporate the use of nonprecious-metal catalysis in the preparation of active pharmaceutical ingredients, we became interested in the use of nickel catalysis to forge new rings and install quaternary stereocenters. We targeted the Heck cyclization for this task, given the success of the palladium-catalyzed variant.[2,3] Examples of nickel-catalyzed Heck cyclization reactions have been reported;[4] however, no methodological studies focused on building quaternary stereocenters have been described.[5] In fact, we are only aware of a single example of a nickel-catalyzed Heck cyclization to build a quaternary stereocenter, which proceeded in modest yield.[6] Encouraged by the growing demonstrated versatility of nickel,[1] as well as the arylcyanation methodologies described by Watson and Jacobsen[7a] and Nakao et al.[7b] for the construction of quaternary centers, we sought to develop the first nickel-catalyzed Heck cyclization methodology to construct quaternary stereocenters. We report the success of these efforts, as demonstrated in the synthesis of medicinally privileged 3,3-disubstituted oxindole frameworks[8] (Scheme 1 b). The reaction possesses wide scope in terms of suitable substrates, proceeds in synthetically useful yields, and provides a rare means to construct stereocomplex frameworks by nonprecious-metal catalysis.



Scheme 1. a) Common nickel-catalyzed coupling reactions and b) present study of nickel-catalyzed Heck cyclization for quaternary-stereocenter formation.

Although analogous to the palladium-catalyzed Heck cyclization, the nickel-catalyzed variant bears less precedent and is complicated by several challenges. First, catalyst regeneration from the nickel(II) hydride species back to Ni^0 is more arduous than in the corresponding palladium-catalyzed system.[9] The nickel(II) hydride resting-state species can induce undesired side reactions, such as over-reduction or isomerization.[10] Second, Guo and co-workers demonstrated by DFT calculations that the energy barrier of the β-hydride elimination step for Ni systems is higher than for Pd systems by 8.7 $kcal\,mol^{-1}$.[9] The organonickel intermediate could then potentially undergo other transformations, such as protonolysis or dimerization, instead of the productive β-H elimination.[10] In addition to the aforementioned challenges, the nickel-catalyzed Heck reaction for

---

[*] Dr. J.-N. Desrosiers, Dr. S. Biswas, Dr. O. V. Zatolochnaya, Dr. S. Rodriguez, Dr. H. Lee, Dr. N. Grinberg, Dr. N. Haddad, Dr. N. K. Yee, Dr. C. H. Senanayake
Department of Chemical Development US
Boehringer-Ingelheim Pharmaceuticals, Inc.
900 Ridgebury Road, Ridgefield, CT 06877 (USA)
E-mail: nick.desrosiers@boehringer-ingelheim.com

L. Hie, Prof. N. K. Garg
Department of Chemistry and Biochemistry
University of California, Los Angeles (USA)
Homepage: http://garg.chem.ucla.edu

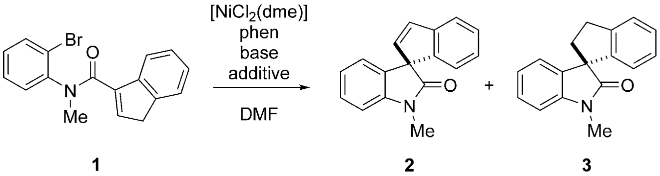
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under http://dx.doi.org/10.1002/anie.201606955.

quaternary-center formation is presumably difficult, given that only a single example of such a process has been reported previously.[6]

We selected **1** as a substrate for initial testing of the nickel-catalyzed intramolecular Heck reaction[11] for quaternary-stereocenter construction and surveyed various bases and reducing agents in the presence of phenanthroline (phen), [$NiCl_2$(dme)], and DBU (Table 1). Preliminary results indicated the base-sensitivity of the starting material (Table 1, entries 1–3). In these examples, decomposition was observed. The use of carbonate bases, such as K_2CO_3, afforded the desired spiroxindole **2** and reduced product **3** (Table 1, entry 4). Also, slight variations in the nickel/phenanthroline ratio gave nonreproducible results. To facilitate catalyst activation/regeneration and to ensure the reproducibility of reaction yields, we tested several external reducing agents.[12] In the presence of these reducing agents, varying amounts of the reduced product **3** were observed. Among the reductants explored (Table 1, entry 5–11), manganese gave the highest yields of **2**. The combination of manganese and a lower temperature was found to be optimal (Table 1, entries 12 and 13).[13]

We carried out an extensive survey of ligands to improve the reaction profile and yield (Figure 1). Most phenanthroline derivatives provided no higher yield than 52% (**L1**–**L7**). The use of the N-heterocyclic carbenes IPr and SIPr gave poor yields. The desired cyclized product could be obtained in higher yields when bis(phosphines) were employed; the best result was observed with dppe (59% yield of **2**). The use of monophosphine ligands (PPh_3, PCy_3, P*t*Bu_3, P*n*Bu_3, PEt_3) demonstrated that electron-rich nonhindered ligands, such as P*n*Bu_3, led to a striking improvement in the yield of **2**, which was formed in the presence of P*n*Bu_3 in 90% yield according to a ^{1}H NMR assay and isolated in 85% yield. Furthermore, it was discovered that the air-stable precatalyst [$NiCl_2$(P*n*Bu_3)$_2$] could be used in place of [$NiCl_2$(dme)] and the ligand to give **2** in comparable yield.[14]

Table 1: Optimization of the reaction conditions.[a]



Entry	Base	Additive	*T* [°C]	Yield **2** [%][b]	Yield **3** [%][b]
1	DBU	none	120	3	0
2	Et_3N	none	120	0	0
3	KOAc	none	120	0	0
4	K_2CO_3	none	120	10–57	0–15
5	K_2CO_3	Ph−B(OH)$_2$	80	0	0
6	K_2CO_3	Ph−B(pin)	80	0	0
7	K_2CO_3	$PhSiH_3$	80	0	0
8	K_2CO_3	Et_3SiH	80	36	64
9	K_2CO_3	Cr	80	14	0
10	K_2CO_3	Zn	80	53	47
11	K_2CO_3	Mn	80	77	23
12	K_2CO_3	Mn	60	79	12
13	Na_2CO_3	Mn	60	81	6

[a] Reaction conditions: [$NiCl_2$(dme)] (10 mol%), phen (10 mol%), additive (3.0 equiv), base (3.0 equiv), DMF (0.3 M). [b] The yield was determined by HPLC peak integration. DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene, dme = dimethoxyethane, DMF = *N*,*N*-dimethylformamide.

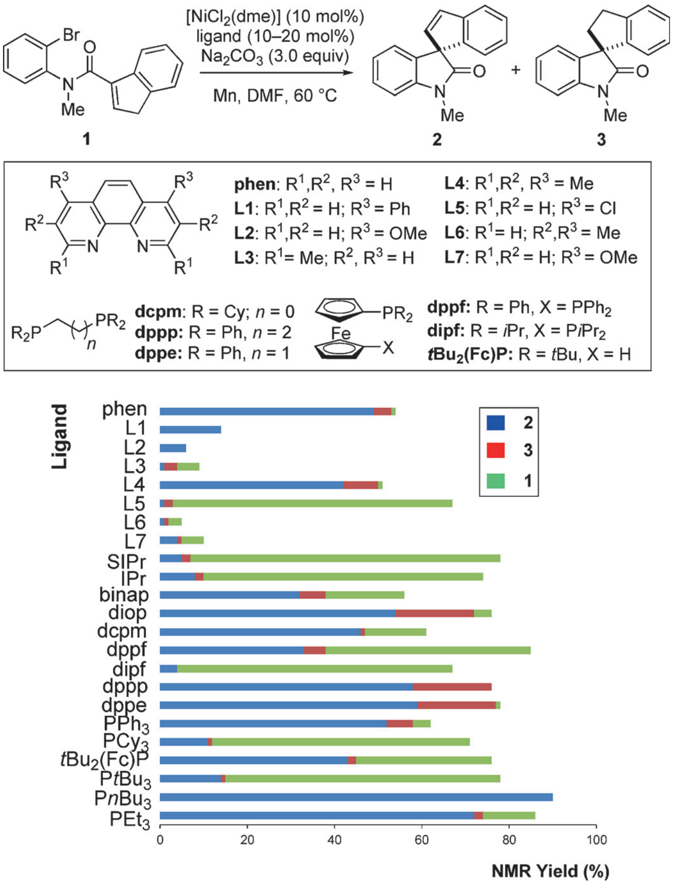
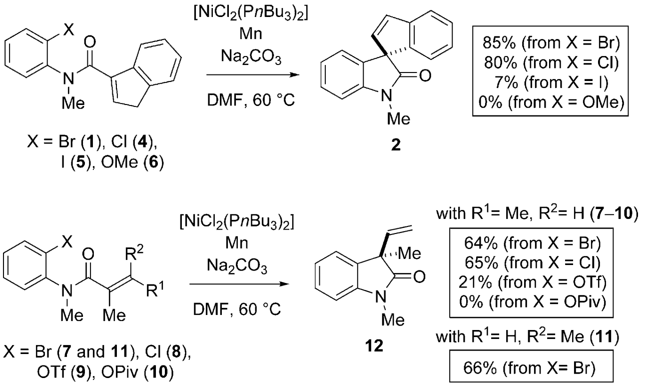


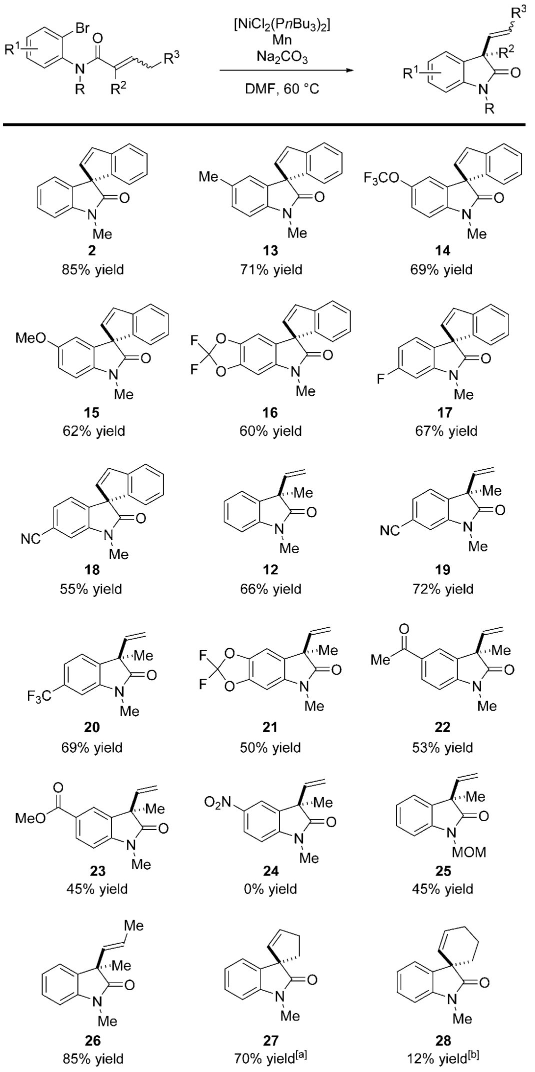
Figure 1. Survey of ligands. Yields were determined by ^{1}H NMR spectroscopy with dimethyl fumarate as an external standard. SIPr = 1,3-bis(2,6-diisopropylphenyl)imidazolidin-2-ylidene, IPr = 1,3-bis(2,6-diisopropylphenyl)-1,3-dihydro-2*H*-imidazol-2-ylidene, binap = (2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl, diop = 2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis-(diphenylphosphanyl)butane.

Having optimized the reaction conditions,[15] we explored the effects of the electrophile with substrates derived from indene carboxylic acid (substrates **1** and **4**–**6**), tiglic acid (substrates **7**–**10**), and angelic acid (substrate **11**; Scheme 2). Both the aryl bromide **1** and chloride **4** are competent electrophiles and afforded spirooxindole **2** in good yield. However, the cyclization proceeded in lower yield or provided no oxindole when iodide **5** or methoxide **6** was used as the electrophile. With substrates **7**–**10**, similar behavior was observed, and the bromide **7** and chloride **8** afforded oxindole **12** in the highest yields. Lower conversion was observed for the triflate derivative **9**, and the pivalate substrate **10** did not give oxindole **12**. The effect of the alkene configuration on the formation of the quaternary center was then studied. *E* and *Z* alkenes **7** and **11** afforded oxindole **12** in similar yields of 64 and 66%, respectively.

The compatibility of the transformation with various functional groups (alcohols, nitriles, esters, ketones, and



Scheme 2. Influence of the source of the electrophile and the alkene geometry. Piv = pivaloyl.



Scheme 3. Scope of the nickel-catalyzed Heck cyclization. Reaction conditions: substrate (100.0 mg), [NiCl$_2$(P*n*Bu$_3$)$_2$] (10 mol%), Mn (3.0 equiv), Na$_2$CO$_3$ (3.0 equiv), DMF (0.3 M), 60 °C, 12 h. [a] Product obtained from the corresponding aryl iodide. [b] The yield was determined by using ^{1}H NMR analysis with dimethyl fumarate as an external standard.

amides) was first evaluated in a robustness screening.[16] The observations were then confirmed by subjecting a wide array of substrates to the optimal reaction conditions (Scheme 3). The reaction tolerates a variety of aryl substituents, such as ether (products **14** and **15**), nitrile (products **18** and **19**), ketal (products **16** and **21**), fluoro (product **17**), keto (product **22**), ester (product **23**), trifluoromethyl, (product **20**) and methyl groups (product **13**). A MOM-protected aniline, which can be readily deprotected under acidic conditions, gave rise to the desired cyclized product **25**. An attempt to generate **24** containing a nitro substituent was not successful.

The alkene substitution pattern of the substrate was then examined. A high yield was observed for the cyclization of a substrate containing a propene side chain, which gave oxindole **26** with exclusive formation of the *E* alkene. A cyclopentene-derived substrate was also evaluated; intriguingly, in this case the iodo-substituted arene was required for the generation of the desired product **27** in 70% yield.[17] In contrast, the corresponding cyclohexyl-based substrate was converted into **28** in only 12% yield. Notably, there are only few examples of nickel-catalyzed Heck cyclization reactions in the presence of basic nitrogen atoms.[4i,11b,18]

An asymmetric version of the nickel-catalyzed Heck cyclization was then examined. When substrate **1** was treated with the ligand catASium KtB, oxindole **2** was obtained in enantiomerically enriched form in 37% yield with e.r. 70:30.[19] This result suggests that ligated nickel is involved in the enantiodetermining migratory-insertion step. Despite the modest yield, this preliminary result is promising for a future comprehensive study on the enantioselective nickel-catalyzed Heck cyclization.

With the objective to provide additional insight into the mechanism of this transformation, we conducted control experiments.[19] The presence of a cyclopropyl substituent as a radical clock on the alkene did not provide a significant amount of the cyclized product with ring opening. A radical-induced cyclization is then not likely to be the major mechanistic pathway. In the absence of Na$_2$CO$_3$, the reaction gave oxindole **2** and **3** in 53 and 18% yield, respectively. This result demonstrates the importance of combining manganese and a base to attain high yields. When the reaction was initiated with a catalytic amount of [Ni(cod)(P*n*Bu$_3$)$_2$] (cod = 1,5-cyclooctadiene), the presence of 3 equivalents of manganese were still required for high yields to be attained.[20] A stoichiometric amount of [Ni(cod)(P*n*Bu$_3$)$_2$] produced **2** with 73% yield in the absence of manganese.[21]

In conclusion, we have reported a methodological study on the first nickel-catalyzed intramolecular Heck reaction for the synthesis of quaternary stereocenters. The transformation was studied in the context of the synthesis of 3,3-disubstituted oxindoles and gives products in synthetically useful yields while tolerating various functional groups. The use of an air-stable nickel precatalyst provides additional cost-efficiency and makes the methodology experimentally convenient. This method demonstrates the potential of Ni catalysis for the construction of stereochemically complex polycyclic frameworks. Optimization of the enantioselective version of this transformation by the use of chiral ligands will be the subject of future investigations.

Acknowledgements

We thank the Boehringer-Ingelheim-Pfizer-Glaxo-Smith-Kline-Abbvie Non-Precious Metal Catalysis Consortium for general discussions in this area. We are grateful to Bristol-Myers Squibb (L.H.), the ACS Division of Organic Chemistry (L.H.), the Foote and Majeti-Alapati families (L.H.), and UCLA for fellowship support.

Keywords: cyclization · Heck reaction · heterocycles · homogeneous catalysis · nickel

How to cite: *Angew. Chem. Int. Ed.* **2016**, *55*, 11921–11924
Angew. Chem. **2016**, *128*, 12100–12103

---

[1] a) S. Z. Tasker, E. A. Standley, T. F. Jamison, *Nature* **2014**, *509*, 299–309; b) T. Mesganaw, N. K. Garg, *Org. Process Res. Dev.* **2013**, *17*, 29–39; c) D.-G. Yu, B.-J. Li, Z.-J. Shi, *Acc. Chem. Res.* **2010**, *43*, 1486–1495; d) B. M. Rosen, K. W. Quasdorf, D. A. Wilson, N. Zhang, A.-M. Resmerita, N. K. Garg, V. Percec, *Chem. Rev.* **2011**, *111*, 1346–1416; e) B.-J. Li, D.-G. Yu, C.-L. Sun, Z.-J. Shi, *Chem. Eur. J.* **2011**, *17*, 1728–1759.

[2] a) M. Mori, I. Oda, Y. Ban, *Tetrahedron Lett.* **1982**, *23*, 5315–5318; b) M. O. Terpko, R. F. Heck, *J. Am. Chem. Soc.* **1979**, *101*, 5281–5283; c) M. M. Abelman, T. Oh, L. E. Overman, *J. Org. Chem.* **1987**, *52*, 4130–4133; d) W. G. Earley, T. Oh, L. E. Overman, *Tetrahedron Lett.* **1988**, *29*, 3785–3788; e) A. Ashimori, L. E. Overman, *J. Org. Chem.* **1992**, *57*, 4571–4572; f) A. Madin, L. E. Overman, *Tetrahedron Lett.* **1992**, *33*, 4859–4862; g) R. Amengual, E. Genin, V. Michelet, M. Savignac, J.-P. Genêt, *Adv. Synth. Catal.* **2002**, *344*, 393–398; h) D. Kiely, P. J. Guiry, *J. Organomet. Chem.* **2003**, *687*, 545–561; i) C. A. Busacca, D. Grossbach, S. J. Campbell, Y. Dong, M. C. Eriksson, R. E. Harris, P.-J. Jones, J.-Y. Kim, J. C. Lorenz, K. B. McKellop, E. M. O'Brien, F. Qiu, R. D. Simpson, L. Smith, R. C. So, E. M. Spinelli, J. Vitous, C. Zavattaro, *J. Org. Chem.* **2004**, *69*, 5187–5195; j) C. A. Busacca, D. Grossbach, R. C. So, E. M. O'Brien, E. M. Spinelli, *Org. Lett.* **2003**, *5*, 595–598.

[3] For selected reviews on palladium-catalyzed Heck cyclization, see: a) I. P. Beletskaya, A. V. Cheprakov, *Chem. Rev.* **2000**, *100*, 3009–3066; b) G. Zeni, R. C. Larock, *Chem. Rev.* **2006**, *106*, 4644–4680; c) K. C. Nicolaou, P. G. Bulger, D. Sarlah, *Angew. Chem. Int. Ed.* **2005**, *44*, 4442–4489; *Angew. Chem.* **2005**, *117*, 4516–4563; d) A. B. Dounay, L. E. Overman, *Chem. Rev.* **2003**, *103*, 2945–2963; e) S. Cacchi, G. Fabrizi, *Chem. Rev.* **2005**, *105*, 2873–2920.

[4] a) G. P. Boldrini, D. Savoia, E. Tagliavini, C. Trombinni, A. Umani Ronchi, *J. Organomet. Chem.* **1986**, *301*, C62–64; b) S. A. Lebedev, V. S. Lopatina, E. S. Petrow, L. P. Beletskaya, *J. Organomet. Chem.* **1988**, *344*, 253–259; c) A. R. Ehle, Q. Zhou, M. P. Watson, *Org. Lett.* **2012**, *14*, 1202–1205; d) K. Inamoto, J.-I. Kuroda, K. Hiroya, Y. Noda, M. Watanabe, T. Sakamoto, *Organometallics* **2006**, *25*, 3095–3098; e) L. Sun, W. Pei, C. Shen, *J. Chem. Res.* **2006**, 388–389; f) A. A. Kelkar, T. Hanaoka, Y. Kubotam, Y. Sugi, *Catal. Lett.* **1994**, *29*, 69–75; g) T. M. Gøgsig, J. Kleimark, S. O. Nilsson Lill, S. Korsager, A. T. Lindhardt, P.-O. Norrby, T. F. Srydstrup, *J. Am. Chem. Soc.* **2012**, *134*, 443–452; h) S. Z. Tasker, A. C. Gutierrez, T. F. Jamison, *Angew. Chem. Int. Ed.* **2014**, *53*, 1858–1861; *Angew. Chem.* **2014**, *126*, 1889–1892; i) S. Iyer, C. Ramesh, A. Ramani, *Tetrahedron Lett.* **1997**, *38*, 8533–8536; j) P.-S. Lin, M. Jeganmohan, C.-H. Cheng, *Chem. Asian J.* **2007**, *2*, 1409–1416; k) Z.-X. Wang, Z.-C. Chai, *Eur. J. Inorg. Chem.* **2007**, 4492–4499; l) S. Ma, H. Wang, K. Gao, F. Zhao, *J. Mol. Catal. A* **2006**, *248*, 17–20; m) B. M. Bhanage, F. Zhao, M. Shirai, M. Arai, *Catal. Lett.* **1998**, *54*, 195–198.

[5] Few nickel-catalyzed methods to build quaternary stereocenters are available; examples include arylcyanation, C−O bond cleavage, Friedel–Crafts alkylation, and Michael addition. For selected examples, see Ref. [7] and the following: a) D. J. Spielvogel, S. L. Buchwald, *J. Am. Chem. Soc.* **2002**, *124*, 3500–3501; b) A. Zhang, T. V. Rajanbabu, *J. Am. Chem. Soc.* **2006**, *128*, 5620–5621; c) S. L. Zultanski, G. C. Fu, *J. Am. Chem. Soc.* **2013**, *135*, 624–627; d) Y. C. Hong, P. Gandeepan, S. Mannathan, W. T. Lee, C. H. Cheng, *Org. Lett.* **2014**, *16*, 806–809; e) J.-R. Gao, H. Wu, B. Xiang, W.-B. Yu, L. Han, *J. Am. Chem. Soc.* **2013**, *135*, 2983–2986; f) J. Cornella, E. P. Jackson, R. Martin, *Angew. Chem. Int. Ed.* **2015**, *54*, 4075–4078; *Angew. Chem.* **2015**, *127*, 4147–4150; g) J. Clariana, N. Gálvez, C. Marchi, M. Moreno-Mañas, A. Vallribera, E. Molins, *Tetrahedron* **1999**, *55*, 7331–7344.

[6] R. Lhermet, M. Durandetti, J. Maddaluno, *Beilstein J. Org. Chem.* **2013**, *9*, 710–716.

[7] a) M. P. Watson, E. N. Jacobsen, *J. Am. Chem. Soc.* **2008**, *130*, 12594–12595; b) Y. Nakao, S. Ebata, A. Yada, T. Hiyama, M. Ikawa, S. Ogoshi, *J. Am. Chem. Soc.* **2008**, *130*, 12874–12875.

[8] a) B. Bin Yu, D. Q. Yu, H. M. Liu, *Eur. J. Med. Chem.* **2015**, *97*, 673–698; b) D. Cheng, Y. Ishihara, B. Tan, C. F. Barbas III, *ACS Catal.* **2014**, *4*, 743–762; c) G. M. Ziarani, N. Lashgari, *Arkivoc* **2012**, 277–320; d) F. Zhou, Y.-L. Liu, J. Zhou, *Adv. Synth. Catal.* **2010**, *352*, 1381–1407.

[9] B.-L. Lin, L. Liu, Y. Fu, S.-W. Luo, Q. Chen, Q.-X. Guo, *Organometallics* **2004**, *23*, 2114–2123.

[10] a) S. Chakraborty, J. Zhang, J. A. Krause, H. Guan, *J. Am. Chem. Soc.* **2010**, *132*, 8872–8873; b) S. Lin, M. W. Day, T. Agapie, *J. Am. Chem. Soc.* **2011**, *133*, 3828–3831; c) B. L. Tran, M. Pink, D. J. Mindiola, *Organometallics* **2009**, *28*, 2234–2243; d) C. A. Tolman, *J. Am. Chem. Soc.* **1972**, *94*, 2994–2999.

[11] a) D. Solé, Y. Cancho, A. Llebaria, M. Josep, J. M. Moreto, A. Delgado, *J. Org. Chem.* **1996**, *61*, 5895–5904; b) H. Kim, C. Lee, *Org. Lett.* **2011**, *13*, 2050–2053.

[12] For examples of the use of external reductants for nickel-catalyzed systems, see: a) L. Hie, S. D. Ramgren, T. Mesganaw, N. K. Garg, *Org. Lett.* **2012**, *14*, 4182–4185; b) I. Colon, D. R. Kelsey, *J. Org. Chem.* **1986**, *51*, 2627–2637.

[13] When the amount of manganese was decreased to 1.0 equivalent, only a slight decrease in the yield (71%) was observed. With 0.5 equivalents, the yield of the reaction decreased significantly to 13%.

[14] This reaction could be set up outside of a glovebox and gave similar yields to those observed when a glovebox was used.

[15] Lowering of the nickel-catalyst loading to 5 mol% led to a decrease in the yield of **2** to 42%.

[16] For the concept of robustness screening, see: K. D. Collins, F. Glorius, *Nat. Chem.* **2013**, *5*, 597–601. See the Supporting Information for screening results.

[17] The corresponding bromide substrate provided oxindole **27** in 20% yield at 60 °C and 27% yield at 80 °C.

[18] a) D. Solé, Y. Cancho, A. Llebaria, J. M. Moretó, A. Delgado, *J. Org. Chem.* **1996**, *61*, 5895–5904; b) S. Z. Tasker, T. F. Jamison, *J. Am. Chem. Soc.* **2015**, *137*, 9531–9534.

[19] See the Supporting Information for experimental details.

[20] A working hypothesis to explain this result is that manganese not only reduces $[NiCl_2(PnBu_3)_2]$, but is also involved in the catalytic cycle.

[21] On the basis of this result, a Ni^0/Ni^{II} catalytic cycle could hypothetically be responsible for the oxindole products obtained.

Received: July 18, 2016