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Highly Regioselective Indoline Synthesis under Nickel/Photoredox Dual Catalysis

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Abstract

Nickel/photoredox catalysis is used to synthesize indolines in one step from iodoacetanilides and alkenes. Very high regioselectivity for 3-substituted indoline products is obtained for both aliphatic and styrenyl olefins. Mechanistic investigations indicate that oxidation to Ni(III) is necessary to perform the difficult C–N bond-forming reductive elimination, producing a Ni(I) complex which in turn is reduced to Ni(0). This process serves to further demonstrate the utility of photoredox catalysts as controlled single electron transfer agents in multi-oxidation state nickel catalysis.

Among the many advantages of using nickel in the development of new synthetic methods[1] is the availability of various oxidation states for catalysis, including Ni(0/I/II/III) and even a recently reported well-defined Ni(IV) species.[2] Nickel-catalyzed methods have generally fallen into either those proposed to proceed via a Ni(0/II) pathway (e.g., aryl cross-coupling,[3] reductive coupling[4]) or those proposed to proceed via a Ni(I/III) pathway (e.g., Csp^3 cross-coupling[5]). However, controlled access to additional oxidation states in a single catalytic cycle can lead to novel and interesting chemistry (Scheme 1). For example, Weix and coworkers recently reported a cross-electrophile coupling with a concurrent polar Ni(0/II) oxidative addition of an aryl halide and radical Ni(III/I/II) oxidative addition/reductive elimination of an alkyl electrophile.[6] The simultaneous recent reports from the research groups of Molander[7] and MacMillan and Doyle[8] also describe aryl–alkyl cross-coupling by using visible light photoredox catalysis[9] to generate alkyl carbon radicals which can be trapped by Ni(II) intermediates.[10] Then, after reductive elimination, the subsequent Ni(I) species is reduced by the same photoredox catalyst to Ni(0) to complete the catalytic cycle. This field continues to grow rapidly, giving access to novel reaction manifolds.[11] Herein, we report a nickel-catalyzed synthesis of indolines, likely enabled by a mechanistically distinct direct oxidation and reduction of nickel intermediates.

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Note

The authors declare no competing financial interests.

Supporting Information

Experimental procedures and spectral data for all unknown compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

Our development of nickel-catalyzed Mizoroki–Heck reactions of aliphatic olefins[12] prompted us to consider whether an appropriately positioned nitrogen-based functional group could intercept the Ni–alkyl migratory insertion intermediate and participate in a direct Csp^3–N reductive elimination, thus providing indoline products (Scheme 2a). Such reductive eliminations are known to be accelerated by oxidation to Ni(III) in stoichiometric reactions,[13] so we reasoned that this reaction might be appropriate for multi-oxidation state nickel catalysis. This approach would also be analogous to the Larock indole synthesis (Scheme 2a).[14]

However, in contrast to indoles, where convergent annulation strategies are common, most methods to synthesize indolines, a common motif in natural products and pharmaceutically active compounds, involve multiple steps.[15] Generally, either the Csp^3–N bond or the Csp^2–Csp^3 bond is formed first, followed by a cyclization to form the five-membered ring. Perhaps surprisingly, given the ubiquity of the Larock indole synthesis, a general indoline synthesis of 2-haloaniline derivatives with alkenes has not been reported, although a few alkene annulation methods have been developed (Scheme 2b). This approach presents two main challenges: C–N bond reductive elimination must outcompete β-hydride elimination (forming Heck-type products), and Csp^3–N reductive elimination is inherently challenging.[16] These two issues were first addressed by Larock and coworkers, who reported indoline formation using 1,3-dienes, which cannot undergo β-H elimination.[17] C–N bond formation also presumably proceeds via external nucleophilic attack on a π-allyl intermediate. Other intermolecular annulation approaches involve the use of alkenes without available β-H atoms, first reported by Catellani and coworker,[18] or forego use of alkenes altogether.[19] Perhaps the most general approach thus far was disclosed by Glorius and coworkers earlier this year.[20] They reported using an internal diazinecarboxylate oxidant and Rh(III)-catalyzed directed C–H functionalization to couple arenes with electron-poor alkenes yielding 2-substituted aminoindolines. The 1-amino group can then be removed in a subsequent step to reveal the NH-indoline.

We began our development of a complementary and general approach to indoline synthesis by testing conditions similar to those of Heck reactions (Table 1, entry 1), and found that for a variety of electrophiles, aniline protecting groups, bases, and phosphine and N-type ligands, only Heck products were observed. Finally, upon using the N-heterocyclic carbene (NHC) ligand IPr, we were able to detect a small amount of indoline product (entry 2). We were gratified to see that the indoline product was produced in high selectivity (>19:1) compared to the sum of all other products. This suggests that, not only was β-H elimination suppressed, but also that alkene migratory insertion had been highly selective for arene insertion at the internal position, a difficult step given the electronically unbiased nature of aliphatic terminal alkenes. Although similar results had been seen in nickel-catalyzed Heck reactions previously, only sterically demanding phosphine ligands had been used successfully. [12] After this initial result, we attempted optimization of various reaction parameters,[21] but quickly discovered that catalytic turnover from Ni(II) was likely not feasible since formation of indoline products was only observed upon exposure of the reaction mixture to air during workup. Csp^3–N bond reductive elimination from low-valent Group 10 metals is known in rare cases,[18,22] and Hillhouse and coworker had previously demonstrated that it could occur stoichiometrically after extended reaction times at room

temperature when β-H elimination was not possible.[13a] However, consistent with our results, they demonstrated that reductive elimination was made far more facile by oxidation to Ni(III) by a number of stoichiometric oxidants, including oxygen.

If oxidation to Ni(III) is necessary for reductive elimination, single electron reduction of the Ni(I) species formed therein would also be necessary to transition from a stoichiometric to a catalytic manifold, a scenario, in theory, fulfilled by a photoredox catalytic cycle. Spurred by the recent reports of Molander[7] and Doyle and MacMillan,[8] we were excited to find that the addition of the visible light photoredox catalyst $Ru(bpy)_3(PF_6)_2$ under conditions similar to those reported by Molander (acetone, 2,6-lutidine) produced significantly more indoline product than the same reaction without photoredox catalyst (Table 1, entries 4, 5). Further optimization using triethylamine furnished, for the first time, yields in excess of the catalyst loading (entry 6). Use of aryl iodides rather than bromides and blue LEDs to shorten reaction times provided the optimal conditions for excellent yields of indoline product (entry 8). Again, we were gratified to see that under these conditions, indoline products were produced in high selectivities (>19:1) over Heck products.

With these optimized conditions in hand, we explored the scope of this transformation (Scheme 3). Substitution at the 4- or 5-positions of the 2-iodoacetanilide electrophile was well-tolerated with both electron donating (e.g., **6b**) and electron withdrawing (e.g., **6c**) substituents. However, substitution at the 3- or 6- positions of the arene resulted in substantially lower yields (**6f** and **6g**). In several cases, reaction yields were improved by slightly elevated temperatures (35 °C) and longer reaction times, although generally greater amounts of products corresponding to β-H elimination were observed at higher temperatures.

The substrate scope of alkene coupling partners is significantly broader (Scheme 4). A variety of functional groups are well tolerated in the indoline formation, including trimethylsilyl groups (**6i**), protected alcohols and amines (**6j**, **6n**), ketones (**6m**), and alkyl chlorides (**6o**). Styrene was also a competent coupling partner and gave the same 3-substituted indoline product **6p** as aliphatic alkenes despite the overwhelming preference for arene insertion to the terminal position of such alkenes. For styrenyl substrates, increased amounts of Heck products were observed, but 2-substituted indoline products were not observed by ^{1}H NMR analysis. Styrenes substituted with electron donating and electron withdrawing groups were also competent reaction partners (**6q**, **6r**). Only terminal monosubstituted alkenes were reactive under these conditions; internal and 1,1-disubstituted alkenes gave no desired product.

We next set out to probe the mechanism of this reaction. The intermediacy of a discrete Heck reaction followed by hydroamination was ruled out by reacting **5d** with 1-octene in the presence of independently synthesized Heck product **7a** (Scheme 5a).[23] No formation of product **6a** arising from **7a** was observed, suggesting that it is not a competent intermediate. Next, we sought to investigate whether oxidation to Ni(III) was indeed responsible for product formation (Scheme 5b). 2-Iodoacetanilide (**5a**) was submitted to stoichiometric reaction conditions without photoredox catalyst for 12 hours. This mixture was then split into portions and exposed to various oxidants, before filtration through alumina under inert

atmosphere and GC analysis. When no oxidant was added, very little indoline was observed, and a number of other products were formed in trace amounts. However, when stirred open to air or $PhI(OAc)_2$ was added, significant amounts of product **6a** (75 and 60% respectively) were observed with good selectivity for the desired indoline product. The addition of catalytic $Ru(bpy)_3(PF_6)_2$ surprisingly did not produce significant amounts of **6a**, possibly because of the larger than normal excess of Ni species compared to photoredox catalyst leading to unselective or unproductive oxidation/reduction and/or to photoredox catalyst death. Given that stoichiometric oxidants do successfully increase the amount of C–N bond formation as expected, a necessary oxidation to Ni(III) prior to product formation is still likely.

We provisionally propose the catalytic cycle shown in Scheme 6, and several lines of evidence support the steps depicted. Crystal structures of oxidative addition and migratory insertion complexes were obtained,[24] and the formation of complexes **10** and **12** were studied by ^1H NMR.[21] The feasibility of the proposed redox steps were further examined by performing cyclic voltammetry (CV) studies on Ni(0) complex **10** and Ni(II) complex **12**. The Ni(0/I) oxidation of **10** was irreversible, so an exact $E_{1/2}$ value could not be calculated.[25] The potential wave of the Ni(I/0) transition of **10** peaks at −1.12V vs. Fc/Fc⁺ (or ~−0.74V vs. SCE)[26] suggesting that it should be easily reduced by $Ru(bpy)_3^+$ [$E_{1/2}^{II/I}$ = −1.33V vs. SCE in MeCN].[9] The Ni(III/II) transition of **12** is reversible, and $E_{1/2}^{III/II}$ = −0.20V vs. Fc/Fc⁺ (or ~+0.18V vs. SCE), suggesting that it should also be easily oxidized by $*Ru(bpy)_3^{2+}$ [$E_{1/2}^{II/I}$ = +0.77V vs. SCE in MeCN].[9] The selectivity for desired reaction formation in the presence of so many redox-active species rather than off-cycle redox events is impressive.[27] Also, for the first time, the photoredox cycle appears to oxidize and reduce nickel directly, rather than generating free carbon-based radicals which are then trapped by nickel. Several mechanistic puzzles still remain, however, including why both iodide and *N*-acetyl protecting group are necessary for good reaction yields[21] and the exact role of triethylamine, so further mechanistic studies are needed to further elucidate the mechanism of this complex transformation.

In summary, the first general annulation reaction of 2-iodoaniline derivatives and terminal alkenes to form indolines has been developed. Using a nickel/NHC catalytic system, high selectivities for insertion to the terminal position of both aliphatic and styrenyl alkenes is achieved. Moreover, Csp^3–N bond formation is achieved by leveraging the various oxidation states available to nickel within the same reaction system using photoredox catalysis as a powerful tool. We envision that using similar dual catalytic systems will enable other reactions for which reductive elimination would otherwise be particularly challenging.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. (a) Tasker SZ, Standley EA, Jamison TF. Nature. 2014; 509:299. [PubMed: 24828188] (b) Ananikov VP. ACS Catal. 2015; 5:1964.

2. Camasso NM, Sanford MS. Science. 2015; 347:1218. [PubMed: 25766226]

3. Yamaguchi J, Muto K, Itami K. Eur J Org Chem. 2013:19.

4. (a) Montgomery J. Angew Chem, Int Ed. 2004; 43:3890.(b) Standley EA, Tasker SZ, Jensen KL, Jamison TF. Acc Chem Res. 2015; 48:1503. [PubMed: 25905431]

5. The radical nature of oxidative addition of an alkyl halide often involves the brief intermediacy of a Ni(II) species as well: Breitenfeld J, Ruiz J, Wodrich MD, Hu X. J Am Chem Soc. 2013; 135:12004. [PubMed: 23865460] Schley ND, Fu GC. J Am Chem Soc. 2014; 136:16588. [PubMed: 25402209]

6. (a) Everson DA, Shrestha R, Weix DJ. J Am Chem Soc. 2010; 132:920. [PubMed: 20047282] (b) Biswas S, Weix DJ. J Am Chem Soc. 2013; 135:16192. [PubMed: 23952217]

7. Tellis JC, Primer DN, Molander GA. Science. 2014; 345:433. [PubMed: 24903560]

8. Zuo Z, Ahneman DT, Chu L, Terrett JA, Doyle AG, MacMillan DWC. Science. 2014; 345:437. [PubMed: 24903563]

9. Prier CK, Rankic DA, MacMillan DWC. Chem Rev. 2013; 113:5322. [PubMed: 23509883]

10. Recent studies have also suggested trapping of a radical by Ni(0), rather than Ni(II): Gutierrez O, Tellis JC, Primer DN, Molander GA, Kozlowski MC. J Am Chem Soc. 2015; 137:4896. [PubMed: 25836634]

11. (a) Noble A, McCarver SJ, MacMillan DWC. J Am Chem Soc. 2015; 137:624. [PubMed: 25521443] (b) Primer DN, Karakaya I, Tellis JC, Molander GA. J Am Chem Soc. 2015; 137:2195. [PubMed: 25650892] (c) Xuan J, Zeng TT, Chen JR, Lu LQ, Xiao WJ. Chem Eur J. 2015; 21:4962. [PubMed: 25688851]

12. (a) Tasker SZ, Gutierrez AC, Jamison TF. Angew Chem, Int Ed. 2014; 53:1858.(b) Matsubara R, Gutierrez AC, Jamison TF. J Am Chem Soc. 2011; 133:19020. [PubMed: 22066899]

13. (a) Koo K, Hillhouse GL. Organometallics. 1995; 14:4421.(b) Lin BL, Clough CR, Hillhouse GL. J Am Chem Soc. 2002; 124:2890. [PubMed: 11902877]

14. Larock RC, Yum EK. J Am Chem Soc. 1991; 113:6689.

15. Liu D, Zhao G, Xiang L. Eur J Org Chem. 2010:3975.

16. Hartwig JF. Nature. 2008; 455:314. [PubMed: 18800130]

17. Larock RC, Berrios-Peña N, Narayanan K. J Org Chem. 1990; 55:3447.

18. Catellani M, Del Rio A. Russ Chem Bull. 1998; 47:928.

19. (a) Thansandote P, Raemy M, Rudolph A, Lautens M. Org Lett. 2007; 9:5255. [PubMed: 18001046] (b) Gilmore CD, Allan KM, Stoltz BM. J Am Chem Soc. 2008; 130:1558. [PubMed: 18193875]

20. Zhao D, Vásquez-Céspedes S, Glorius F. Angew Chem, Int Ed. 2015; 54:1657.

21. See Supporting Information for more details.

22. Ni: Miura T, Morimoto M, Yamauchi M, Murakami M. J Org Chem. 2010; 75:5359. [PubMed: 20604510] Pd: Marquard SL, Rosenfeld DC, Hartwig JF. Angew Chem, Int Ed. 2010; 49:793.Hanley PS, Marquard SL, Cundari TR, Hartwig JF. J Am Chem Soc. 2012; 134:15281. [PubMed: 22934822]

23. Qin L, Ren X, Lu Y, Li Y, Zhou J. Angew Chem, Int Ed. 2012; 51:5915.

24. CCDC 1403188 and 1403189 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

25. Pletcher, D.; Greef, R.; Peat, R.; Peter, LM.; Robinson, J. Instrumental Methods in Electrochemistry. Horwood; Chichester: 2001.

26. Pavlishchuk VV, Addison AW. Inorg Chim Acta. 2000; 298:97.

27. The need for Et$_3$N or i-Pr$_2$EtN for good yields is curious since the large excess of these amines relative to Ni should result in their oxidation by *Ru(bpy)$_3$$^{2+}$ as well. Whether amine oxidation modulates the oxidizing strength of the photoredox catalyst acting as a SET relay for Ni oxidation, acts to build up the reducing Ru(bpy)$_3$$^+$, or is irrelevant (with Et$_3$N acting solely as a base) is unclear.
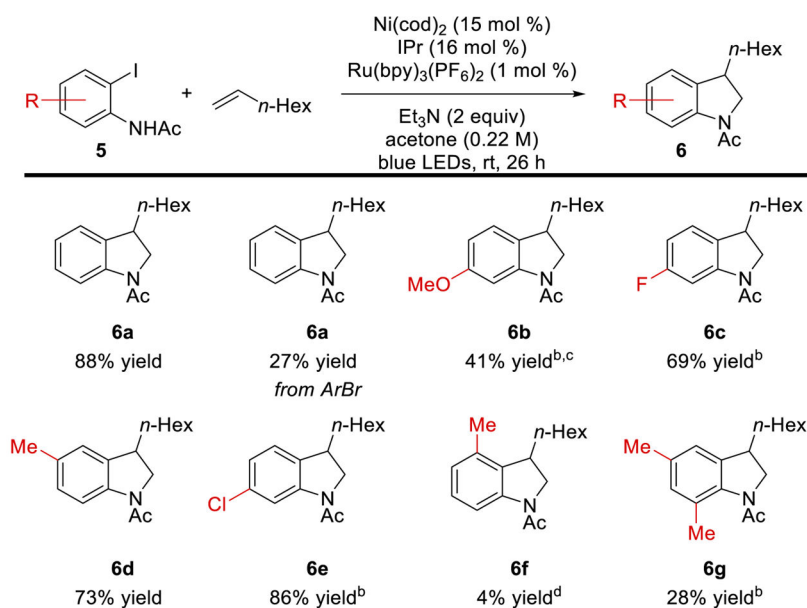
Weix, 2010, 2013[6]

Molander,[7] MacMillan and Doyle,[8] 2014
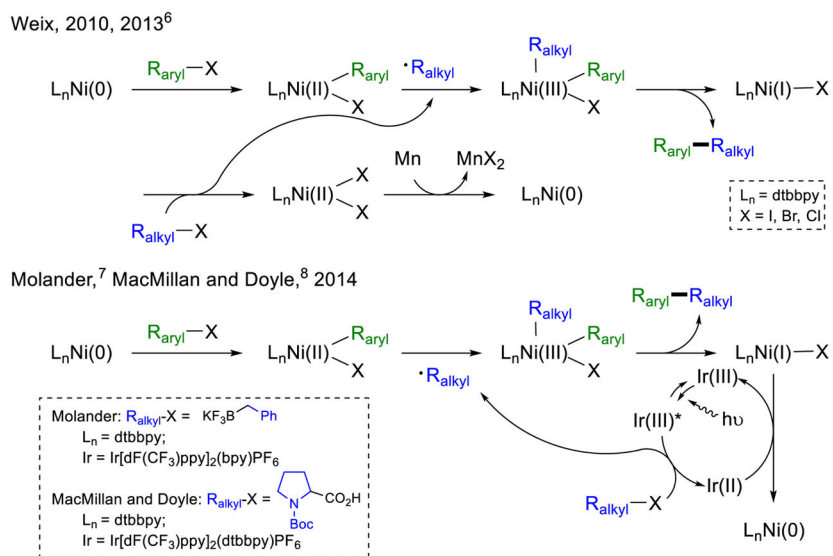
Scheme 1.
Recent examples of catalytic reactions involving four different oxidation states of nickel.
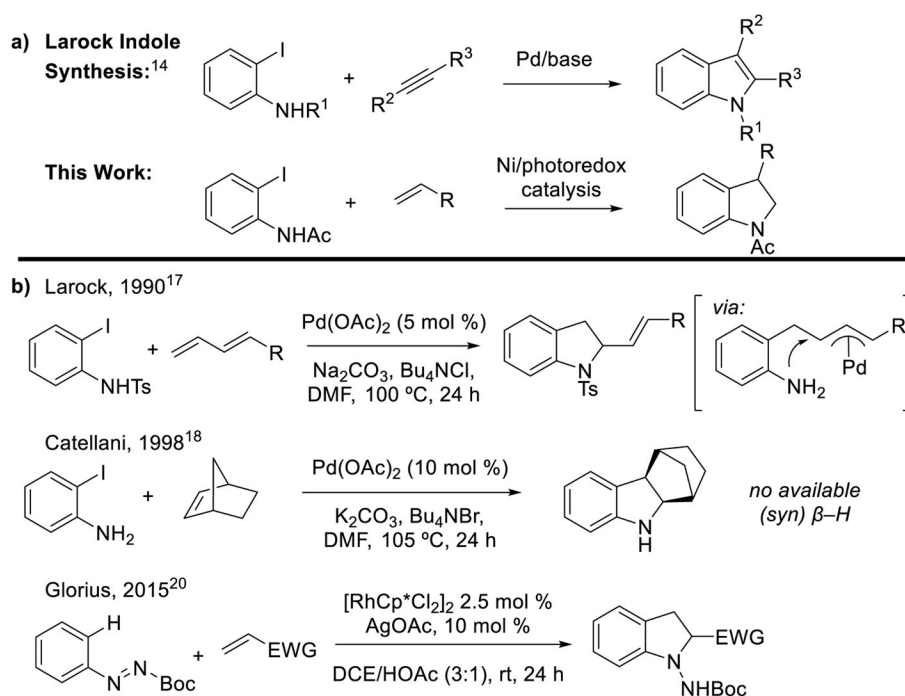
Scheme 2.
Synthesis of indolines and indoles via an intermolecular alkene or alkyne annulation strategy.
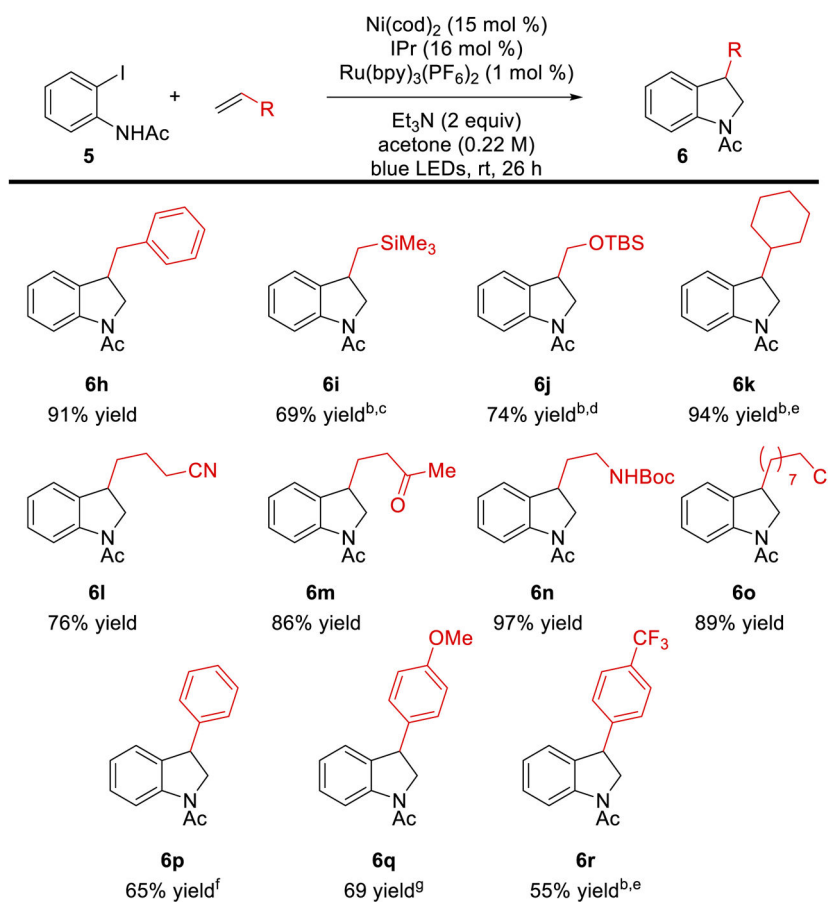
Scheme 3. Scope of aryl electrophile[a]

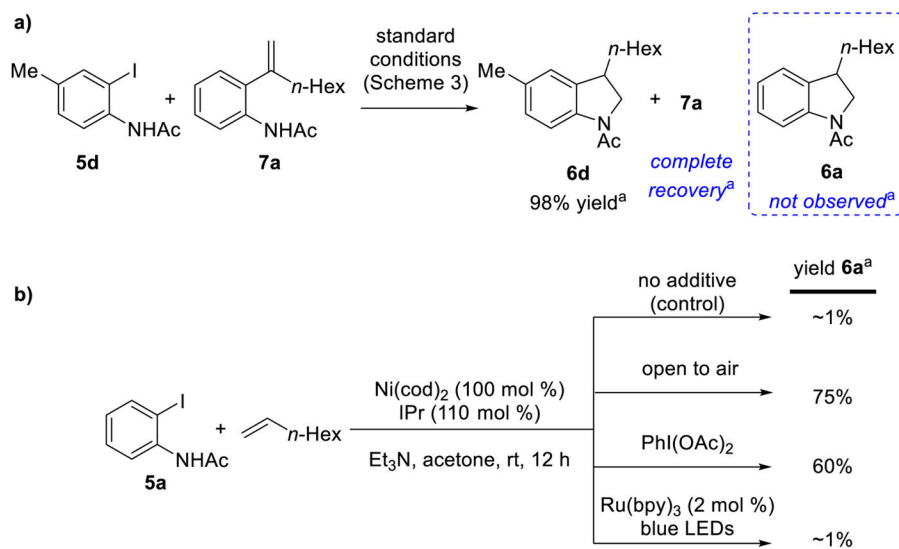[a]All yields are isolated yields. Selectivity **6** to sum of **7**–**9** >19:1 unless otherwise noted. Reaction conditions: Ni(cod)$_2$ (15 mol %), IPr (16 mol %), Ru(bpy)$_3$(PF$_6$)$_2$ (1 mol %), Et$_3$N (2 equiv), Acetone (0.22 M), blue LEDs, rt, 26 [b] Ru(bpy)$_3$(PF$_6$)$_2$ (2 mol %), CFL, 35 °C, 48 h. [c] 7:1 [d] GC yield.
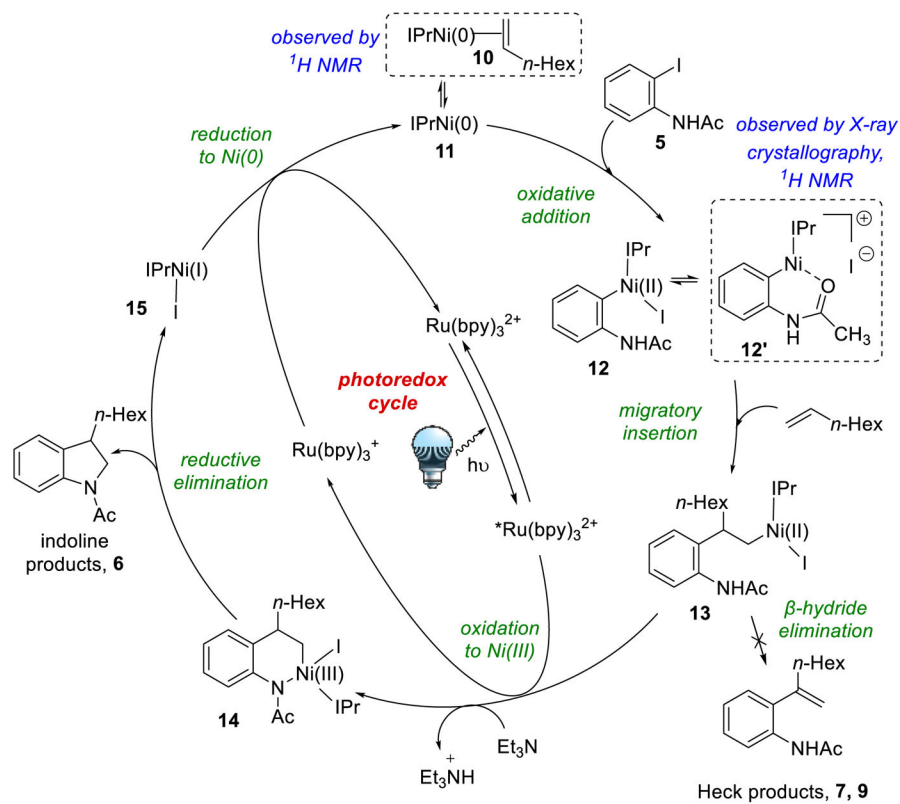
Scheme 4. Scope of alkene coupling partner[a]

[a]All yields are isolated yields. Selectivity **6** to sum of **7**–**9** >19:1 unless otherwise noted. Reaction conditions: Ni(cod)$_2$ (15 mol %), IPr (16 mol %), Ru(bpy)$_3$(PF$_6$)$_2$ (1 mol %), Et$_3$N (2 equiv), Acetone (0.22 M), blue LEDs, rt, 26 h [b] Ru(bpy)$_3$(PF$_6$)$_2$ (2 mol %), CFL, 35 °C, 48 h. [c] 5:1 [d] 12:1 [e] 9:1 [f] 8:1 [g] 11:1.

a)

5d + **7a** → standard conditions (Scheme 3) → **6d** 98% yield[a] + **7a** *complete recovery*[a]

6a *not observed*[a]

b)

5a + ethylene-n-Hex, Ni(cod)$_2$ (100 mol %), IPr (110 mol %), Et$_3$N, acetone, rt, 12 h

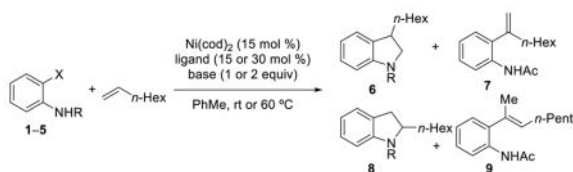|	yield **6a**[a]
no additive (control)	~1%
open to air	75%
PhI(OAc)$_2$	60%
Ru(bpy)$_3$ (2 mol %) blue LEDs	~1%

Scheme 5. Mechanistic studies

[a]GC yield using dodecane as an internal standard.

Scheme 6.
Proposed mechanism.

Table 1

Reaction optimization.

	X; R	ligand	base	yield 6[a]
1	OTf; Piv (**1**)	phosphine, PyBOX, phenanthroline-type	various organic/inorganic	0%
2	**1**	IPr	LiOt-Bu	7%
3	Cl (**2**), OTf (**3**), Br (**4**), I (**5**); Ac	IPr	LiOt-Bu	10–14%[b]
4[c]	Br; Ac (**4**)	IPr	2,6-lutidine	5%
5[c,d]	**4**	IPr, Ru(bpy)$_3$	2,6-lutidine	15%
6[c,d]	**4**	IPr, Ru(bpy)$_3$, 66 h	Et$_3$N	33%
7[c,d]	I; Ac (**5**)	IPr, Ru(bpy)$_3$, 48 h	Et$_3$N	90%
8[c,e]	**5**	IPr, Ru(bpy)$_3$, 26 h	Et$_3$N	88%
9[c,f]	**5**	IPr, Ru(bpy)$_3$, 26 h	Et$_3$N	9%[g]

[a] yield **6** determined by GC using dodecane as an internal standard, selectivity **6** to sum of Heck (**7**), isomerized Heck (e.g., **9**), and 2-alkyl indoline (**8**) >19:1 unless otherwise noted

[b] 10:1

[c] Acetone (0.22 M)

[d] Compact fluorescent light (CFL), (2 mol %) Ru(bpy)$_3$(PF$_6$)$_2$

[e] blue LEDs, (1 mol %) Ru(bpy)$_3$(PF$_6$)$_2$

[f] reaction run in absence of light, (1 mol %) Ru(bpy)$_3$(PF$_6$)$_2$

[g] 9:1.