Enantioselective Catalysis

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Photochemical Asymmetric Nickel-Catalyzed Acyl Cross-Coupling

*Eugenio Gandolfo, Xinjun Tang, Sudipta Raha Roy, and Paolo Melchiorre**

Abstract: *Photochemical enantioselective nickel-catalyzed cross-coupling reactions are difficult to implement. We report a visible-light-mediated strategy that successfully couples symmetrical anhydrides and 4-alkyl dihydropyridines (DHPs) to afford enantioenriched α-substituted ketones under mild conditions. The chemistry does not require exogenous photocatalysts. It is triggered by the direct excitation of DHPs, which act as a radical source and as a reductant, facilitating the turnover of the chiral catalytic nickel complex.*

Nickel catalysis has experienced great advances in the past decade, with valuable cross-coupling processes being developed to produce natural products, polymers, and pharmaceuticals.[1] Recent efforts have also demonstrated how nickel-catalyzed cross-coupling strategies can be used to prepare chiral molecules.[2] For example, there are effective methods for achieving enantioconvergent carbon–carbon bond formation using racemic alkyl electrophiles and traditional[3] or reductive[4] cross-coupling processes (Figure 1 a). However, these methods require highly nucleophilic organometallic reagents or stoichiometric reductants, respectively. This reduces their practicality. Recently, the combination of nickel catalysis and photoredox catalysis[5] has provided a versatile tool to mitigate some of these issues (Figure 1 b). This approach exploits the ability of visible-light-activated photocatalysts to generate, on excitation, alkyl radicals upon single-electron transfer (SET) activation of low-energy, bench-stable substrates and under mild conditions.[6] Crucially, the photoredox catalyst also modulates the oxidation state of nickel complexes by SET reduction, which is essential for catalyst turnover. Despite the potential practical advantages of this approach, only a few asymmetric catalytic examples has been developed to date.[7]

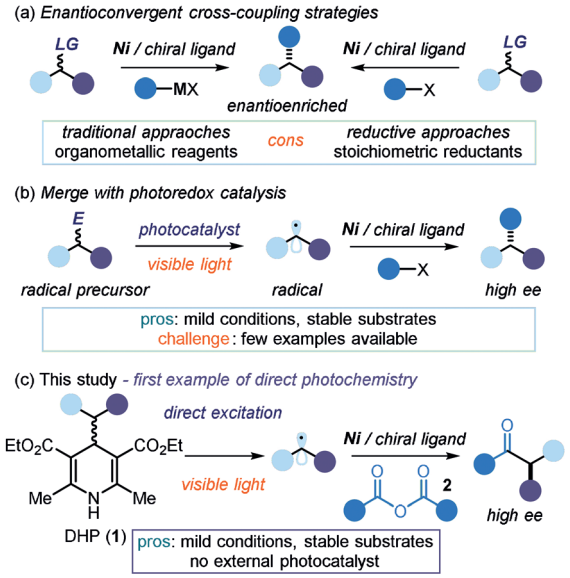

Figure 1. a) Enantioconvergent nickel-catalyzed strategies via traditional nucleophile–electrophile coupling (left) and reductive (right) cross-electrophile coupling. b) Enantioselective dual photoredox-nickel catalysis approaches via radical manifolds. c) The proposed asymmetric catalytic cross-coupling strategy exploits the ability of 4-alkyl-1,4-dihydropyridines (DHPs, **1**) to generate radicals upon visible-light excitation. X: halides and pseudo-halides; LG: leaving group; E: electrophore.

Our laboratory recently reported a complementary photochemical approach for nickel cross-coupling[8] that exploits the direct excitation of 4-alkyl-1,4-dihydropyridines (DHPs, **1**) to generate alkyl radicals.[9,10] We demonstrated that the excited state of DHPs acts simultaneously as a strong SET reductant, thus modulating the nickel oxidation state, and as a radical source. We recently wondered if the dual reactivity profile of the excited **1** could be used to expand the potential of asymmetric nickel-catalyzed cross-coupling technology. Here, we detail how this design plan was translated in experimental reality, leading to the development of a visible-light-induced enantioselective process under mild conditions, using readily available and stable reagents, and without the need for exogenous photocatalysts (Figure 1 c).

The catalytic cycle of our proposed photochemical asymmetric cross-coupling process is outlined in Figure 2. We selected symmetrical anhydrides **2** as electrophiles because nickel has a propensity to activate these substrates.[11] The crucial mechanistic aspect is that, upon excitation, the racemic alkyl-DHPs **1** can act as precursors of alkyl radicals and as strong reducing agents (E (**1a**$^{+}$/**1a***) ≈ −1.6 V vs. Ag/Ag^{+} in CH_3CN, as estimated from electrochemical and spectroscopic measurements applying the Rehm-Weller approximation).[12] The latter property is essential to restore

[*] Prof. Dr. P. Melchiorre
ICREA
Passeig Lluís Companys 23, 08010 Barcelona (Spain)
E. Gandolfo, Dr. X. Tang, Dr. S. Raha Roy, Prof. Dr. P. Melchiorre
ICIQ – Institute of Chemical Research of Catalonia, the Barcelona Institute of Science and Technology
Avenida Països Catalans 16-43007, Tarragona (Spain)
E-mail: pmelchiorre@iciq.es
Homepage: http://www.iciq.org/research/research_group/prof-paolo-melchiorre/
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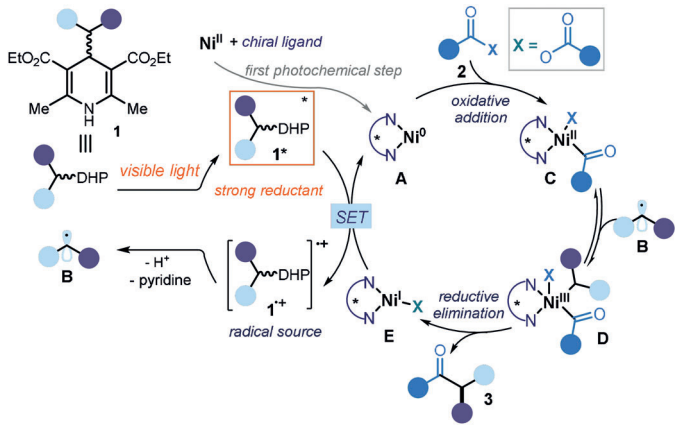
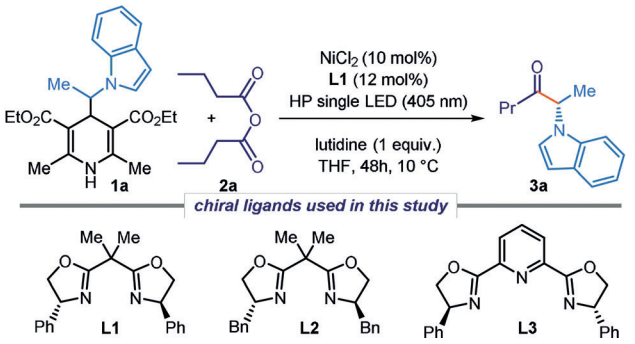


Figure 2. Proposed catalytic mechanism for the visible-light-driven asymmetric nickel-catalyzed acyl cross-coupling process.

the catalytically active nickel intermediate and to secure turnover. In the first catalytic cycle, the excited-state intermediate **1*** would reduce, by two discrete SET events, the Ni^{II} precatalyst to afford the active Ni^0 intermediate **A** ($E_p(Ni^{II}/Ni^0) = -1.2$ V versus SCE in DMF).[13] The resulting, highly unstable radical cation $\mathbf{1}^{\bullet+}$ would then undergo homolytic cleavage to generate a secondary $C(sp^3)$-centered radical **B**. Oxidative addition into the $C(sp^2)$–O bond of the anhydride **2** would afford the Ni^{II}–acyl complex **C**, which would intercept the stabilized secondary radical, leading to the Ni^{III} intermediate **D**. Reductive elimination would then provide the cross-coupling chiral ketone product **3**. We anticipated that an appropriate chiral ligand would provide control of the stereoselectivity.[14] Finally, the generated Ni^I complex would undergo SET reduction by the excited alkyl-DHPs **1***, completing the nickel catalytic cycle while regenerating the $C(sp^3)$ radical intermediate **B**.

To validate our plan, the commercially available and stable butyric anhydride **2a** was selected as the acyl precursor (Table 1). For the radical precursor, we chose the indole-containing racemic DHP **1a** because this would form product **3a** bearing a stereogenic center α to the indole nitrogen. This structural motif is synthetically interesting because it is found in many natural products and pharmaceutical drugs.[15] However, it is a difficult target as testified to by the paucity of asymmetric catalytic protocols available for the preparation of enantioenriched *N*-alkylated indoles.[16] We conducted our experiments in THF under irradiation by a single high-power visible-light-emitting diode (LED, $\lambda_{max} = 405$ nm) with an irradiance of 75 mW cm^{-2}, as controlled by an external power supply (full details of the illumination set-up are reported in the Supporting Information). By examining a range of reaction parameters, we determined that $NiCl_2$ and the chiral box ligand **L1**[17] can accomplish the enantioconvergent photochemical cross-coupling in good yield and high *ee* (**3a** formed in 65 % yield and 75 % *ee*; entry 1). Other nickel salts provided slightly improved stereocontrol, but at the expense of chemical yield (entries 2 and 3). Because of the good compromise between reactivity and enantioselectivity, we selected $NiCl_2$ for further optimization. No improvement was achieved with other solvents (entries 4 and 5) or chiral

Table 1: Optimization studies and control experiments.[a]



Entry	Deviation	Yield [%][b]	*ee* [%]
1	none	65 (56)[c]	75
2	$NiBr_2$ instead of $NiCl_2$	53	80
3	$NiCl_2$dme instead of $NiCl_2$	48	80
4	acetonitrile instead of THF	43	28
5	dioxane instead of THF	38	77
6	L2 instead of L1	31	12
7	L3 instead of L1	34	0
8	no light	0	–
9	no catalyst $NiCl_2$	0	–

[a] Reaction performed in THF [0.167 M] at 10 °C for 48 h on a 0.1 mmol scale using 2 equiv of **1a** and 1 equiv of lutidine as base under illumination by a single high-power (HP) LED ($\lambda_{max} = 405$ nm) with an irradiance of 75 mW cm^{-2}. [b] Yield determined by ^{1}H NMR analysis of the crude mixture using mesitylene as the internal standard. [c] The number in parentheses indicates the yield of the isolated **3a** after chromatography purification on silica gel.

ligands, including representative examples that have been useful in other nickel-catalyzed enantioconvergent cross-couplings (entries 6 and 7).[3,4] Control experiments confirmed that the reaction could not proceed in the absence of light or a nickel catalyst (entries 7 and 8).

Using the optimized conditions described in Table 1, entry 1, we tested the generality of the photochemical cross-coupling process (Figure 3). We first evaluated the scope of the radical precursors **1**. Several halogen substituents on the indole scaffold were tolerated well, affording the corresponding *N*-alkylated chiral indoles in good yields and stereoselectivity (products **3b–d**). A carbazole scaffold was also introduced within the final products, albeit at the expense of stereoselectivity (adducts **3e** and **3f**). We then evaluated different anhydrides as acyl coupling partners. Different substitution patterns were tolerated, including an aryl moiety (products **3i**, **3k**, **3l**), a ketone (**3h** and **3j**), and an alkyl chloride (**3g**). We failed to synthesize DHP radical precursors **1** bearing a substitution pattern other than methyl. This limitation is somehow mitigated by the ability to forge a ketone moiety with a methyl α-stereogenic center. This is an important synthetic achievement,[18] for which there are few effective catalytic asymmetric protocols.

We then sought to extend the applicability of this photochemical cross-coupling strategy to the stereocontrolled preparation of acyclic α,α-aryl,alkyl ketones, which are versatile synthetic intermediates for the synthesis of natural products and pharmaceutical agents.[19] This required the preparation of racemic DHP radical precursors bearing both

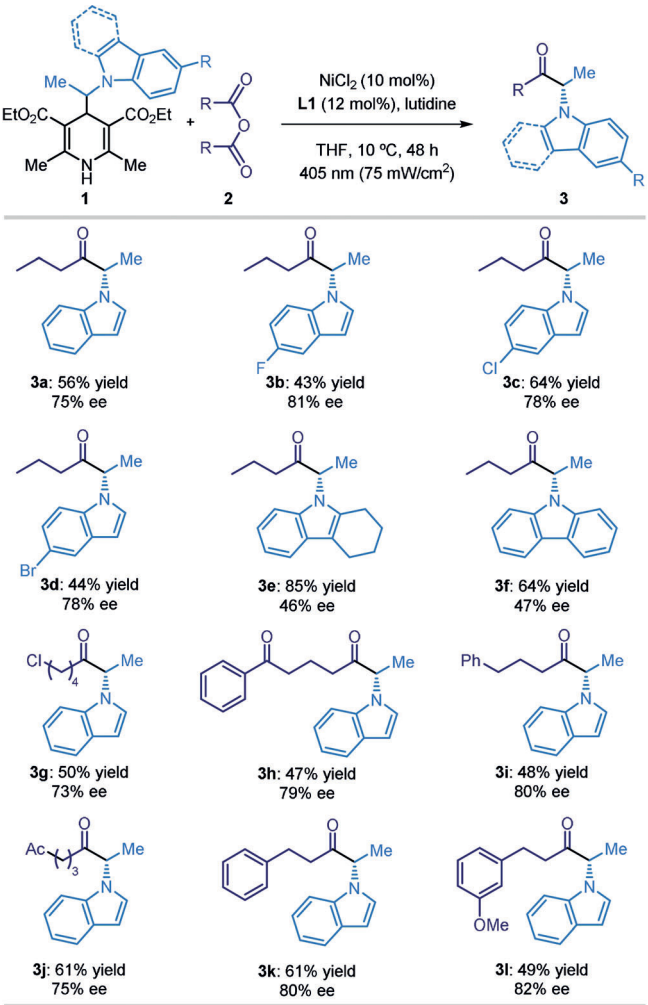


Figure 3. Synthesis of *N*-alkylated chiral indoles: survey of the DHPs **1** and anhydrides **2** that can participate in the photochemical nickel-catalyzed asymmetric cross-coupling. Reaction performed at 10 °C for 48 h on a 0.1 mmol scale using THF as solvent (0.6 mL), 2 equiv of **1**, 1 equiv of lutidine under illumination by a single high-power (HP) LED (λ_{max} = 405 nm) with an irradiance of 75 mW cm^{-2}. Ac: acetyl.

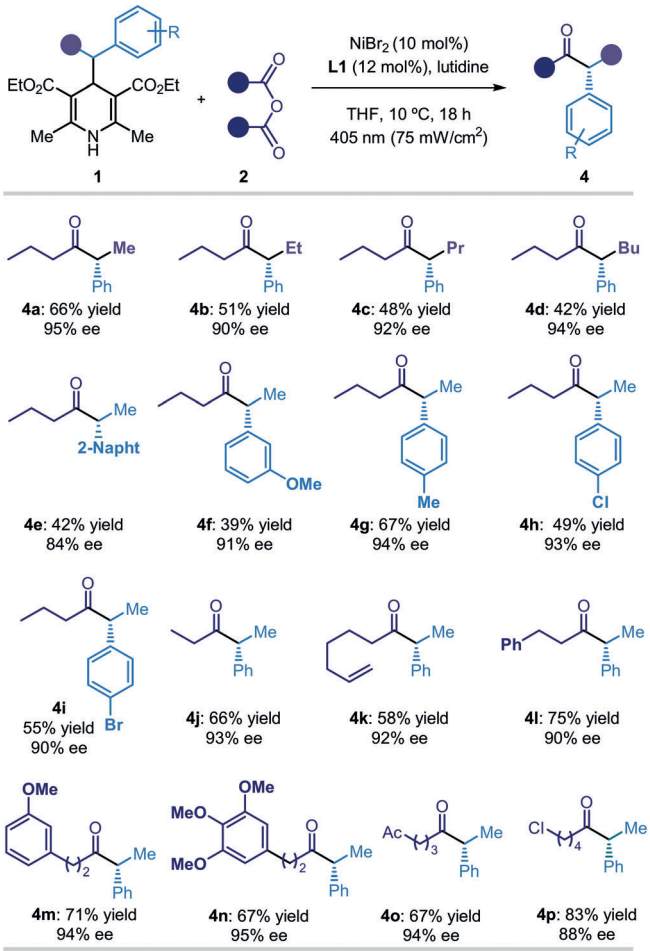


Figure 4. Synthesis of α-aryl ketones: survey of the DHPs **1** and anhydrides **2** that can participate in the photochemical nickel-catalyzed asymmetric cross-coupling. Reaction performed at 10 °C for 18 h on a 0.1 mmol scale using THF as solvent (0.6 mL), 2 equiv of **1**, 1 equiv of lutidine under illumination by a single high-power (HP) LED (λ_{max} = 405 nm) with an irradiance of 75 mW cm^{-2}. Ac: acetyl.

an aryl and alkyl moiety. A quick re-optimization of the reaction conditions identified $NiBr_2$ as the best catalyst to promote the asymmetric acyl cross-coupling using anhydrides, which afforded the target chiral α-aryl ketones **4** with high enantioselectivity (Figure 4).[20] Concerning the radical precursor, this protocol offered a wide scope since alkyl chains of different length could be readily accommodated (products **4a–d**). A variety of α-methyl α-aryl ketones were synthesized with high stereocontrol and good chemical yield. The process tolerated aromatic rings adorned with electron-donating and electron-withdrawing groups at the *para* position (**4g–i**). A *meta*-substituted ring decreased the yield (**4f**), while *ortho*-substitution suppressed the reactivity (result not shown, a complete list of unsuccessful substrates is reported in Figure S6 of the Supporting Information). A naphthyl ring was also tolerated (**4e**).

A wide functional group tolerance was achieved for the acyl fragment. For example, an olefin was included in the final product (**4k**) without the occurrence of side reactions.

In summary, we have shown that the excited state chemistry of DHPs **1** can be combined with a chiral nickel catalyst. We have used this approach to stereoselectively couple radicals with symmetric anhydrides. The resulting chiral ketones, which contain different groups at the α-stereogenic center, including an (1*H*-indol-1-yl) moiety, are synthesized with good stereocontrol. We believe that this visible-light-mediated strategy, which does not require external photoredox catalysts, can provide a reliable platform for other applications in enantioselective catalytic cross-coupling processes.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: asymmetric catalysis · cross-coupling · nickel catalysis · photochemistry · radical chemistry

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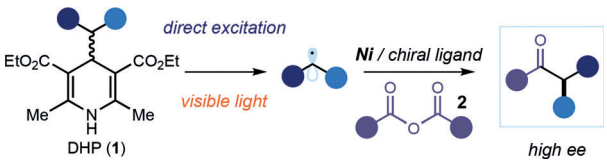
Communications

Enantioselective Catalysis

E. Gandolfo, X. Tang, S. Raha Roy, P. Melchiorre* ——— ■■■■–■■■■

Photochemical Asymmetric Nickel-Catalyzed Acyl Cross-Coupling



Light it up: Photochemical enantioselective nickel-catalyzed cross-coupling reactions are difficult to implement. A visible-light-mediated strategy is reported that couples anhydrides **2** and 4-alkyl dihydropyridines **1** (DHPs) to afford enantioenriched α-amino and α-aryl ketones under mild conditions. The chemistry, which does not require exogenous photocatalysts, is triggered by the direct excitation of DHPs, which generate radicals while facilitating the turnover of the nickel catalyst.

