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]

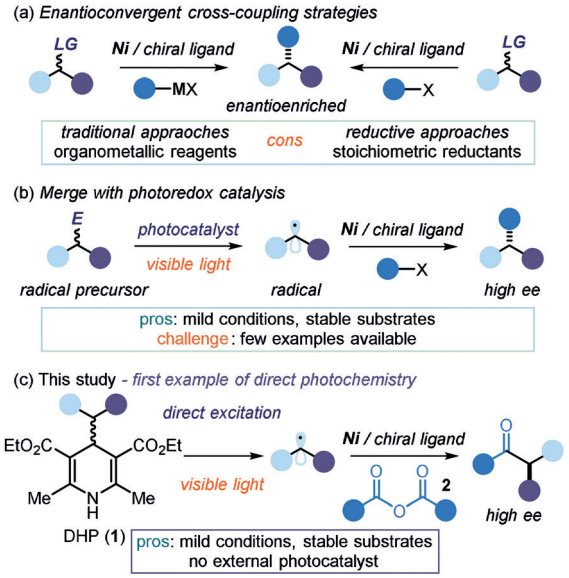

Figure 1. a) Enantioconvergent nickel-catalyzed strategies via traditional nucleophile–electrophile coupling (left) and reductive (right) cross-electrophile coupling. b) Enantioselective dual photoredox-nickel catalysis approaches via radical manifolds. c) The proposed asymmetric catalytic cross-coupling 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**$^{\bullet+}$/**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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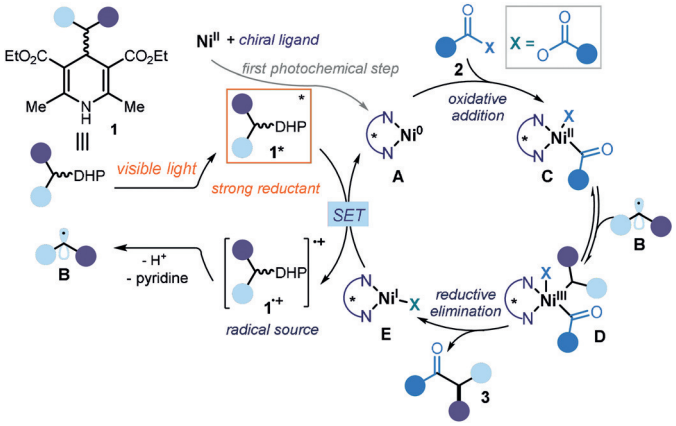
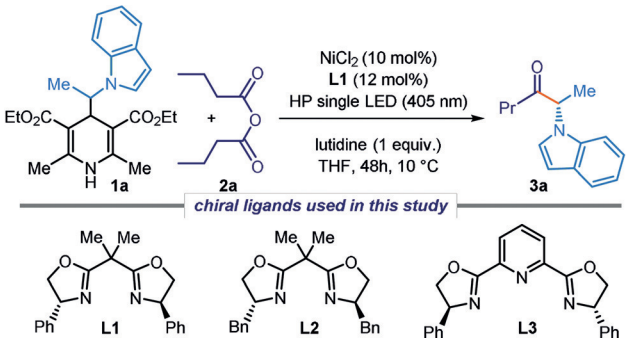


Figure 2. Proposed catalytic mechanism for the visible-light-driven asymmetric nickel-catalyzed acyl cross-coupling process.

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

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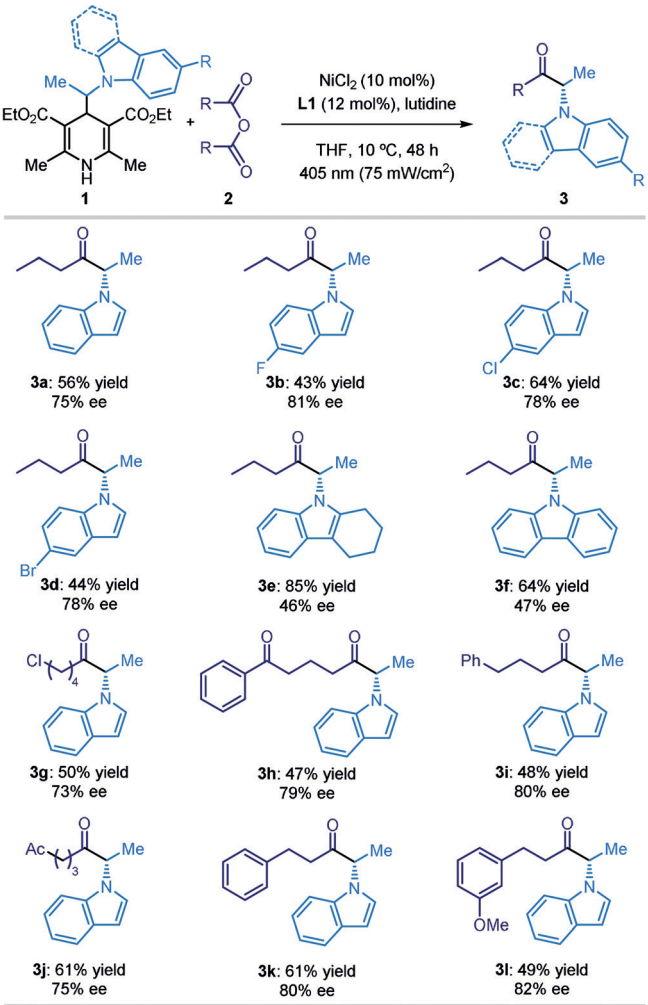

Figure 3. Synthesis of *N*-alkylated chiral indoles: survey of the DHPs **1** and anhydrides **2** that can participate in the photochemical nickel-catalyzed asymmetric cross-coupling. Reaction performed at 10 °C for 48 h on a 0.1 mmol scale using THF as solvent (0.6 mL), 2 equiv of **1**, 1 equiv of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

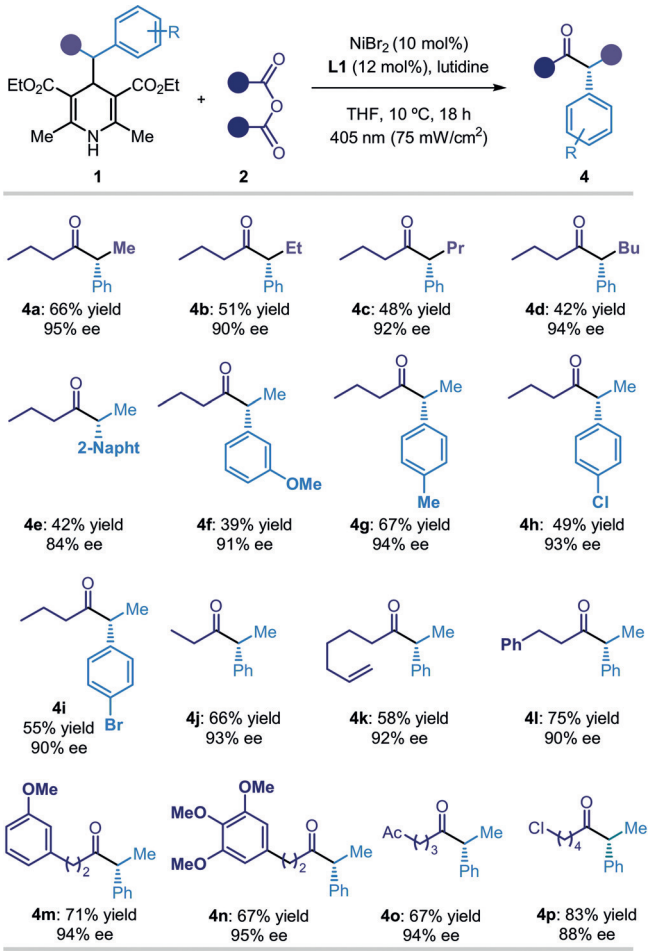

Figure 4. Synthesis of α-aryl ketones: survey of the DHPs **1** and anhydrides **2** that can participate in the photochemical nickel-catalyzed asymmetric cross-coupling. Reaction performed at 10 °C for 18 h on a 0.1 mmol scale using THF as solvent (0.6 mL), 2 equiv of **1**, 1 equiv of lutidine under 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.

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Conflict of interest

The authors declare no conflict of interest.

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