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Christopher D McTiernan, Xavier Leblanc, and Juan C. Scaiano

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Heterogeneous Titania-Photoredox/Nickel Dual Catalysis: Decarboxylative Cross-Coupling of Carboxylic Acids with Aryl lodides

Christopher D. McTiernan, Xavier Leblanc, and Juan. C. Scaiano*

Department of Chemistry and Biomolecular Sciences and Centre for Catalysis Research and Innovation, University of Ottawa, 10 Marie Curie, Ottawa ON K1N 6N5, Canada

ABSTRACT: The efficient, mild, and semi-heterogeneous decarboxylative cross-coupling of a variety alkyl carboxylic acids with aryl iodides has been accomplished through a merger of TiO_2 photoredox and nickel cross-coupling chemistries. The protocol is tolerant to a wide range of substituted aryl iodides and alkyl carboxylic acids. Through replacement of the commonly employed Ir transition metal complexes with P25 TiO_2 as photocatalyst we show that these transformations can be heterogenized with little effect on the efficiency of these transformations, while at the same time decreasing the associated costs due to the reusability and inexpensive nature of the TiO_2 photocatalyst.

Keywords: Heterogeneous, Dual Catalysis, Nickel, Titania, Decarboxylative Cross-Coupling, Photoredox

When one thinks of important recent developments in synthetic organic chemistry, probably one of the most impactful has to be the introduction of transition-metal catalyzed cross-coupling reactions. As a tool in forming C-C, C-N, and C-O bonds, these methods have found applications in a variety of chemical syntheses, due to their well-known reliability, selectivity, and predictability. While there is currently a variety of different cross-coupling methods one can choose from (Heck,¹ Suzuki-Miyaura,² Negishi,³ Stille,⁴ Kumada-Corriu,⁵ Sonogashira,⁶ Buchwald-Hartwig,⁷ and Hiyama⁸) all of these methods require that the nucleophilic coupling partner be functionalized with a transition-metal activated handle such as Grignards, stannanes, and boronic acids. While many of these reagents can be purchased or synthesized in few steps, they tend to be relatively expensive, may require harsh synthesis conditions, and in some cases be difficult to handle due to their high reactivity. For these reasons, there has been interest in developing new techniques and methods, which would allow the use of less expensive and readily available starting materials containing non-traditional leaving groups/handles (e.g. –COOH) as competent coupling partners in a variety of different cross-coupling reactions.9

It has been recently shown that a merger of visible-light photoredox and transition-metal catalysis can create dual catalytic systems, which can be used to forge C-C bonds between a variety of nonconventional coupling partners. While there has been a surge in the use of Ni in these dual catalytic systems, other transition-metals such as Pd,¹⁰ Cu,¹¹ and Au¹² can also act synergistically when coupled with appropriately selected photoredox systems.

Since the work of Molander¹³ and MacMillan¹⁴ demonstrated that alkyl radicals generated through photoredox mediated singleelectron transfer (SET) could be efficiently intercepted by Ni(II) complexes and that the convergent Ni(III)(alkyl)(Ar) complex could undergo reductive elimination to furnish the desired crosscoupled product, there have been a number of reports which have looked to both better understand and expand this chemistry.^{15,16}

While the end product of these dual photoredox-Ni catalytic systems are quite diverse, the actual catalytic system employed to bring about these changes are quite conventional. That is, most systems are derived from homogeneous Ir or Ru photocatalysts and some type of bipyridinium functionalized homogeneous Ni complex. The only criteria for the photocatalyst being that the SET redox potentials be favorable for both *in-situ* generation of the desired radical and for turnover of the Ni catalyst. Although the Ir and Ru photocalysts have shown great promise in these dual catalytic systems, we, along with other groups have demonstrated that in many cases one can replace these relatively expensive transitionmetal photocatalysts with cheaper alternatives such as organic dyes¹⁷ (Methylene Blue, Eosin-Y, 9-Mesityl-10-methylacridinium) and organic/inorganic semiconductors (α -Sexithiophene,¹⁸ TiO_2^{19}) to generate the required radical intermediates with little or no sacrifice in efficiency and in some cases these alternatives actually outperform their transition-metal counterparts.

As it had been previously demonstrated that TiO_2 and Ptmodified TiO_2 can be employed as heterogeneous photoredox catalyst in the oxidative decarboxylation of carboxylic acids,^{20,21} we began to wonder whether we could substitute the highly oxidizing Iridium (III) photocatalyst $Ir[dF(CF_3)ppy]_2(dtbbpy)$ PF₆, typically used in the dual photoredox/Ni decarboxylative cross-couplings, with TiO_2 . Just as in the case of Ir, TiO_2 will be responsible for both generation of the alkyl radicals and turnover of the Ni catalytic cycle. The proposed mechanism for the dual TiO_2 -photoredox/Ni is presented in Scheme 1. The idea being that upon excitation of the TiO_2 photocatalyst the highly oxidizing holes in the valence band (VB) of the semiconductor would oxidatively decarboxylate the carboxylic acid to furnish the alkyl radical,²¹ while the strongly reducing electrons of the conduction band (CB) would in turn provide a site for reduction of the Ni(II) and Ni(I) complexes to their active Ni(0) species.



Scheme 1. Proposed Mechanism for the Dual TiO₂-Photoredox-Ni-Catalyzed Decarboxylative Arylation

We present here our recent findings on the semi-heterogeneous dual TiO_2 -photoredox/Ni mediated decarboxylative crosscoupling of carboxylic acids with aryl-iodides. The main goal of this work is to illustrate that one can replace the commonly employed Ir and Ru photocatalysts utilized in these dual-catalytic systems, with a inexpensive, reusable, easily removed and environmentally benign photocatalyst such as P25 TiO₂.

We began our studies on the decarboxylative cross-coupling of carboxylic acids with aryl-iodides using a catalytic system comprising P25 TiO₂ as photoredox catalyst, a variety of Ni(II) and Ni(0) precursor complexes, 4,4'-di-tert-butyl-2,2'-bipyridine (dtbbpy) as ligand for the Ni complex, Cs₂CO₃ as base, and a UVA-Visible light source for irradiation (Luzchem Inc. Solar Simulator fitted with a longpass λ >375 filter). Utilizing N-Boc-proline and Methyl 4-Iodobenzoate as model coupling partners, we performed test and control reactions under a variety of different conditions in order to optimize the procedure (Table 1). From these initial tests it was found that the optimal solvent for this particular catalytic system is acetonitrile (MeCN) [Table 1, entries 1 and 4] and that while the reaction can tolerate the presence of oxygen, its removal through a 20 minute argon purge drastically increases the efficiency of the reaction [Table 1, entries 3 and 8]. While the drastically different results in dimethylformamide (DMF) and MeCN may be simply explained by interference due to readily oxidizable amine impurities in the DMF,²² the increase in efficiency observed in the absence of oxygen may be due to the fact that, when present oxygen can be readily reduced by electrons in the CB of TiO_2 (E^{ox} [CB] = -2.0 V vs. SCE)²³ to give superoxide $(O_2^{\bullet-})$ $(E^{\text{red}}[O_2/O_2^{\bullet-}] = -0.8 \text{ V} \text{ vs.}$ SCE)²⁴ which may disrupt the catalytic cycle directly or indirectly as it may compete with the reduction of the Ni(I) complex to its corresponding Ni(0) complex, a key step in the proposed mechanism (Scheme 1). Although the observed effect of O₂ in our system is opposite to that observed by Oderinde and co-workers for a similar transformation utilizing an Ir[dF(CF₃)ppy]₂(dtbbpy)PF₆, it should be pointed out that they believe that the presence of O2 is assisting the intersystem crossing (ISC) process, resulting in a more efficient formation of the strongly oxidizing triplet excited state of ${}^{*}Ir(III) (E_{1/2}^{red} [{}^{*}Ir(III)/Ir(II)] = 1.21 \text{ V vs. SCE}).^{16} \text{ While}$ such an explanation is plausible for transition metal and organic based photocatalysts, as excitation of TiO2 does not lead to the

formation of singlet and triplet excited states, such an enhancement would not be expected in our system.

Table 1. Optimization of Reaction Conditions^a

	' \	0.5 eq. TiO ₂ 10 mol% Ni Catalyst 15 mol% dtbbpy, 1 eq CsCO ₃ 5 mL Solvent, Atm Light Source		N Boc CO ₂ Me	
Boc OH Boc-Pro-OH	CO ₂ Me Methyl 4-lodobenzoate				
0.6 mmol	0.4 mmol				
Entry	Ni Catalyst	Solvent	Atm.	Time	Isolated Yield
1	NiCl ₂ •glyme	DMF	Air	72 h	0%
2	NiCl ₂ •glyme	DMF	Argon	72 h	0%
3	NiCl ₂ •glyme	MeCN	Air	36 h	56%
4	NiCl ₂ •glyme	MeCN	Air	72 h	93%
5	NiCl ₂ •glyme	MeCN	Air	72 h	$0\%^b$
6	NiCl ₂ •glyme	MeCN	Air	72 h	0% ^c
7	NiCl ₂ •glyme	MeCN	Argon	3 h	19%
8	NiCl ₂ •glyme	MeCN	Argon	6 h	61%
9	NiCl ₂ •glyme	MeCN	Argon	18 h	95%
10	NiCl ₂ •glyme	MeCN	Argon	72 h	$0\%^b$
11	NiCl ₂ •glyme	MeCN	Argon	72 h	0%
12	NiCl ₂ •glyme	MeCN	Argon	18 h	$Trace^d$
13	None	MeCN	Argon	18 h	0%
14	NiCl ₂ •glyme	MeCN	Argon	18 h	Trace ^e
15	NiCl ₂ •glyme	MeCN	Argon	18 h	Trace ^f
16	Ni(acac)2	MeCN	Argon	18 h	8%
17	$Ni(COD)_2$	MeCN	Argon	18 h	>95%

^{*a*}Reaction conditions: Boc-Pro-OH (0.6 mmol), Methyl 4-Iodobenzoate (0.4 mM), P25 TiO₂ (0.5 eq.), dtbbpy (15 mol%), CsCO₃ (1 eq.), solvent (5mL). Irradiated with solar simulator $\lambda > 375$ nm. ^{*b*} no light. ^{*c*} no light and 50°C. ^{*d*} no base. ^{*c*} no P25 TiO₂, ^{*f*} no base.

In addition to solvent and atmosphere, we have also performed control reactions under dark conditions at both room temperature and 50 °C to ensure that it is excitation of the photocatalyst that brings about the desired transformation and not just heating caused by light absorption (Table 1, entries 5,6 10, and 11). From Table 1 it also evident that the photocatalyst, Ni complex, dttbpy ligand, and base are all critical components of the system as their omission results in little or no desired product even after 18 h of irradiation. Lastly, due to the fact that the added Ni complex is only a precursor for the NiCl₂•dtbbpy complex utilized in these transformations, we explored whether or not we could exchange the NiCl₂•glyme with other Ni sources such as $Ni(acac)_2$ and $Ni(COD)_2$. As observed in Table 1, entry 16; when $Ni(acac)_2$ is used as precatalyst the efficiency of the reaction falls drastically with only 8% of the desired cross-coupled product obtained after 18 h of reaction. However, when we switch to the Ni(0) precatalyst, $Ni(COD)_2$, there appears to be no observable change in the efficiency of the transformation. While the Ni(0) catalyst has the advantage that it does not require an initial reduction by the TiO2 to become active, this may not be that advantageous as reduction of Ni(II) to Ni(0) by the CB electrons is quite thermodynamically favorable $(E_{1/2}^{\text{red}} [\text{Ni}^{\text{II}}/\text{Ni}^{0}] = -1.2$ V vs. SCE).²⁵ The Ni(COD)₂ precatalyst is also air sensitive and therefore extra care must be taken when it is employed. For these reasons we have preferred to utilize NiCl₂•glyme as our precatalyst. **Table 2. TiO₂ Photoredox/Ni Dual Catalytic Decarboxylative Cross-Coupling: Aryl-Iodide Scope**



With the optimized conditions in hand, we then set out to test our system in the cross-coupling of a variety of substituted aryl-Iododes with our model alkyl carboxylic acid (N-Boc-pro). As illustrated in Table 2 our dual-catalytic system is capable of coupling a number of electron-deficient aryl-iodides with N-Boc-proline in moderate to excellent yields (37-95%) under relatively short irradiation times (18h). Table 2 shows that our procedure is tolerant to a variety of different functional groups, such as esters, acetyls, aldehydes, CF₃, fluorine, and nitriles. However, it should be mentioned that the presence of ether, alcohol, amine, or nitro functionalities on the aryl-iodide coupling partner either slow or completely shut down the catalytic cycle. While in some cases these may be due to the radical trapping ability of some of these functionalities, the electron donating nature of these substituents may be inhibiting oxidative addition of the Ni(0) complex into the aryl-iodide preventing formation of the Ni(II) intermediate, which would then trap the alkyl radical formed upon oxidative decarboxylation. It is important to note that while we have previously illustrated that one can utilize TiO₂ as photoredox catalysts in the reductive dehalogenation of aryl-iodides, we have observed no corresponding hydrodehalogenated products under these reaction conditions. We do however find trace amounts of the corresponding phenol.

Once we had demonstrated that the aryl-iodide coupling partner could be modified, we set out to do the same thing with the carboxylic acid component. The holes produced in the VB (E^{red} [VB] = 1.0 V vs. SCE) of TiO2 upon excitation make it a moderately oxidizing inorganic semiconductor. Considering that the oxidation potential of N-Boc-pro $(E_{1/2}^{ox} [N-Boc-pro] = 0.95 V vs. SCE)$ is just within the potential window of the TiO2 photocatalyst, it was necessary to find alkyl carboxylic acid type substrates which were more easily oxidized to expand the scope and illustrate the procedures broad applicability. With this in mind, we set out to cross-couple our model aryl-iodide (Methyl 4-Iodobenzoate) with a variety of substituted and unsubstituted phenylacetic acids. Table 3 shows that we have successfully coupled various phenylacetic acid derivatives to methyl 4-iodobenzoate under our optimized conditions. As expected substrates bearing electron-donating substituents gave the best results, owing to their lower oxidation potential. While the ability to cross-couple electron deficient phenylacetic acids is ultimately dependent on the oxidation potential of the substrate, it appears as though some withdrawing functionalities may be tolerated.

 Table 3. TiO2 Photoredox/Ni Dual Catalytic Decarboxylative

 Cross-Coupling: Carboxylic Acid Scope



Interestingly many of the phenylacetic acid derivatives are classified as Non-Steroidal Anti-Inflammatory Drugs (NSAIDs); this protocol provides a quick and simple route to their modification and functionalization with orthogonal handles for further modification. For the most part derivatives substituted in the alpha position display lower reactivity than their unsubstituted counterparts (Table 3, entries 30-32). While it would be easy to attribute this decrease in reactivity to steric effects, this is complicated by the fact that the more sterically hindered diphenylacetic acid (Table 3, entry 33) appears to be a suitable coupling partner, giving similar yields to the unsubstituted derivatives. However, this difference in reactivity could possibly be related to the higher stability of the resulting diphenyl methyl radical.²⁶ Lastly, substrates containing aromatic ketone chromophores (Table 3, entry 34 and 35) are also exceptional coupling partners, giving moderate to good yields with little to no background reaction.

In an attempt to broaden the applicability of this procedure we have substituted the aryl iodide coupling partner with its bromide and chloride analogues. However after 72 h of irradiation of N-Boc-Proline and either Methyl 4-Bromobenzoate or Methyl 4-Chlorobenzoate, under our optimized reaction conditions, we did not obtain any of the desired product. A possible explanation for the observed lack of reactivity may be that the reduction potential of the corresponding Ni(I)Cl or Ni(I)Br species (formed after reductive elimination) is outside the potential window attainable by the TiO₂ photocatalyst and thus the Ni(0) species required for the initial transmetallation step cannot be regenerated.

While easy photocatalyst removal is one of the key advantages of our semi-heterogeneous catalytic system, another benefit of heterogeneous catalysts is that in many cases they can be reused after isolation. While in some cases catalyst reusability has a large impact on the economical feasibility of a given protocol or the scale up of the reaction, the abundance and relatively low cost of TiO_2 its reusability not critical. However, environmental issues are still important and we thus explored the reusability of TiO₂ towards our model reaction. As shown if Figure 1, the TiO₂ photocatalyst shows only a slight decrease in efficiency towards the cross-coupling reaction over 5 trials (approx. 15-20%), indicating that it is exceptionally reusable. It is important to note that in each trial 10 mol% of fresh NiCl₂•dtbbpy complex was added.



Figure 1. TiO_2 reusability in the photoredox/nickel dual catalytic decarboxylative cross-coupling of N-Boc-proline with Methyl 4-Iodobenzoate.

In conclusion, we have demonstrated that P25 TiO₂ can be utilized as an efficient heterogeneous photoredox catalyst in the decarboxylative cross-coupling of carboxylic acids with aryl iodides under dual photoredox/Ni catalysis conditions. The scope can likely be extended to include heteroaryl iodides. While the system has some limitations in comparison to its homogeneous counterparts, the inexpensive and heterogeneous nature of the TiO₂ photocatalyst make the catalytic system quite attractive even without considering its easy reusability.

AUTHOR INFORMATION

* E-mail: titoscaiano@mac.com

ORCID

Juan C. Scaiano: 0000-0002-4838-7123

Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Supporting Information

Details on reaction conditions, spectral data on products, UV-Vis spectra, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org

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