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Eosin Y Catalyzed Visible Light Oxidative C−C and C−P bond Formation

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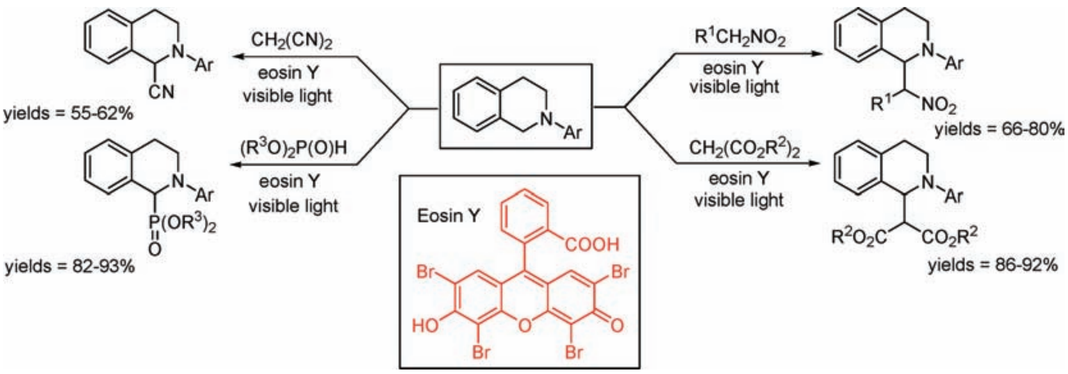
ABSTRACT



Eosin Y catalyzes efficiently the visible light mediated coupling of sp^3 C−H bonds adjacent to the nitrogen atom in tetrahydroisoquinoline derivatives in the absence of an external oxidant. Nitroalkanes, dialkyl malonates, malononitrile, and dialkyl phophonates were used as pronucleophiles in this metal-free, visible light oxidative coupling reaction.

Sunlight is an abundant, renewable, and clean energy resource for chemistry.[1] Visible light accounts for the major part of the incoming solar radiation, and therefore visible light should be used to drive chemical transformations. However, most organic molecules do not absorb light in the visible region of light. This restricts the application of photochemical reactions and, thus, motivates the development of efficient visible light photocatalysts for chemical transformations in organic synthesis.[2] Such photoredox catalysts absorb visible light and utilize the collected energy for electron transfer to or from organic molecules to initiate chemical reactions.

In the past decade tris(bipyridine) ruthenium and iridium complexes have been used as visible light photoredox catalysts in dehalogenation,[2d,3] reduction,[4] oxidation,[5] and asymmetric alkylation reactions.[6] Yoon and co-workers have used the same ruthenium complex as a photocatalyst in inter- and intramolecular $[2 + 2]$ enone cycloadditions.[2b,7] Currently, Stephenson used these catalysts for an oxidative coupling reaction of nitroalkanes with *N*-arylamines in visible light.[8] However, the iridium and ruthenium catalysts are expensive and toxic. The use of organic dyes, which are environmentally friendly, inexpensive, and easy to handle as photoredox catalysts, would be a superior alternative to inorganic transition metal photocatalysts.

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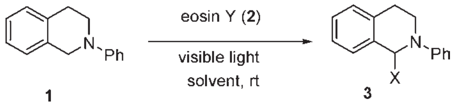
10.1021/ol201376v

Table 1. Oxidative Trapping of Iminium Ion with Different Pronucleophiles

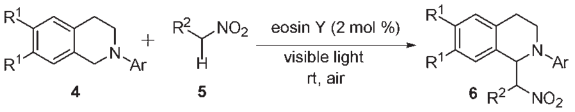


entry	conditions[a]	yield[b] (%)
1	**2** (1 mol %), CH_3NO_2, 12 h; X = CH_2NO_2	74
2	**2** (2 mol %), CH_3NO_2, 8 h; X = CH_2NO_2	80
3	**2** (5 mol %), CH_3NO_2, 8 h; X = CH_2NO_2	80
4	**2** (2 mol %), $C_7H_{12}O_4$, 10 h; X = $C_7H_{11}O_4$	92[c]
5	**2** (2 mol %), $C_5H_8O_4$, 10 h; X = $C_5H_7O_4$	88[c]
6	**2** (2 mol %), DMF, 10 h; X = CN	62
7	**2** (2 mol %), DMF, 3 h; X = $C_4H_{10}O_3P$	86
8	No catalyst, CH_3NO_2, 180 h; X = CH_2NO_2	78
9	**2** (2 mol %), no light, CH_3NO_2, 72 h; X = CH_2NO_2	0

[a] With the exception of entries 6 and 7, in all cases nucleophiles were used as solvents. [b] Isolated yields after purification by chromatography. [c] Isolated yields after removal of the excess solvent by distillation.

Direct formation of C–C and C–P bonds by C–H activation is a challenging research area in organic synthesis. In the past years many elegant methodologies were developed,[9] but those required transition metal catalysts and harsh conditions. We reported here the metal-free visible light photoredox catalysis for C–C and C–P bond formation using the organic dye eosin Y to initiate a single electron transfer process without exclusion of moisture or air in visible light. We focused our initial studies on the oxidative coupling reaction of **1** with nitromethane using the reaction conditions reported by Stephenson and coworkers,[8] but replacing the tris(bipyridine) ruthenium complex as the visible light photoredox catalyst by the organic dye eosin Y (2 mol %). The desired product **3** was obtained in 80% isolated yield after 8 h of irradiation with green LED light (Table 1, entry 2). Under these conditions (2 mol % of **2**, 530 nm) we also examined other pronucleophiles, such as dialkyl malonates, malononitrile, and dialkyl phosphonates at room temperature (Table 1, entries 4, 5, 6, and 7). In all cases, we obtained the desired products in good yields and found that for efficient conversion both light and catalyst are required (Table 1, entries 8 and 9).

Table 2. Oxidative Coupling Reaction of Tetrahydroisoquinolines with Nitroalkanes[a,c,d]

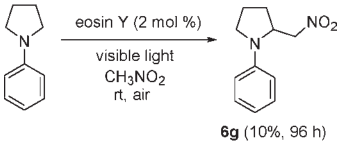


entry	R^1	Ar	R^2	product	time (h)	yield[b] (%)
1	H	Ph	H	**6a**	8	80
2	H	4-BrC_6H_4	H	**6b**	10	76
3	H	4-$MeOC_6H_4$	H	**6c**	10	78
4	OMe	Ph	H	**6d**	8	74
5	H	Ph	Me	**6e**[c]	12	75
6	H	Ph	Et	**6f**[d]	14	66

[a] The reaction was performed with **4** (0.25 mmol) and eosin Y (0.02 equiv) in 1.0 mL of **5**. [b] Isolated yield after purification on SiO_2. [c] dr = 2:1. [d] dr = 1.4:1.

Various *N*-aryl tetrahydroisoquinoline derivatives were reacted with nitromethane, nitroethane, or 1-nitropropane and gave the desired coupling products in good yields (66–80%; Table 2). Nitromethane always gave better results than other nitroalkanes (**6a** vs **6e** and **6f**), and the reaction was insensitive to electronic effects on the aromatic rings (**6a**, **6b**, and **6c**). In the case of nonactivated amine (Scheme 1), a low yield was obtained after 96 h of irradiation.

Scheme 1. Reaction of 1-Phenylpyrrolidine with Nitromethane



Dialkyl malonates gave *β*-diester amines in excellent yields from the reaction with tetrahydroisoquinoline derivatives using 2 mol % of eosin Y as the photocatalyst

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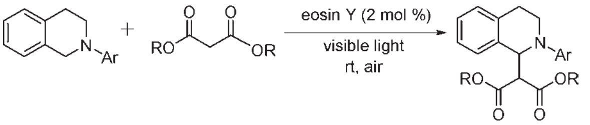
[9] For C–C bond reactions, see: (a) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215–1292. (b) Liu, C.; Zhang, H.; Shi, W.; Lei, A. *Chem. Rev.* **2011**, *111*, 1780–1824. (c) Fagnoni, M.; Dondi, D.; Ravelli, D.; Albini, A. *Chem. Rev.* **2007**, *107*, 2725–2756. (d) Hoffmann, N. *Pure. Appl. Chem.* **2007**, *79*, 1949–1958. (e) Klussmann, M.; Sureshkumar, D. *Synthesis* **2011**, *3*, 353–369. (f) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335–344. (g) Li, Z.; MacLeod, P. D.; Li, C.-J. *Tetrahedron: Asymmetry* **2006**, *17*, 590–597. (h) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2005**, *127*, 3672–3673. (i) Li, Z.; Cao, L.; Li, C.-J. *Angew. Chem., Int. Ed.* **2007**, *46*, 6505–6507. (j) So, M.-H.; Liu, Y.; Ho, C.-M.; Che, C.-M. *Chem.—Asian J.* **2009**, *4*, 1551–1561. (k) Griesbeck, A. G.; Hoffmann, N.; Warzecha, K.-D *Acc. Chem. Res.* **2007**, *40*, 128–140. (l) Hoffmann, N. *Chem. Rev.* **2008**, *108*, 1052–1103. (m) Griesbeck, A. G.; Abe, M.; Bondock, S. *Acc. Chem. Res.* **2004**, *37*, 919–928. (n) Zeug, N.; Bücheler, J.; Kisch, H. *J. Am. Chem. Soc.* **1985**, *107*, 1459–1464. (o) For more reactions, see: Albini, A.; Fragnoni, M. *Handbook of Synthetic Photochemistry*; Wiley-VCH: Weinheim, 2010. (p) Mattay, J. *Top. Curr. Chem. 156 (Photoinduced Electron Transfer I)*, 1990. (q) Mattay, J. *Top. Curr. Chem. 168 (Photoinduced Electron Transfer V)*, 1993. For C–P bond reactions, see: (r) Stradiotto, M.; Fujdala, K. L.; Tilley, T. D. *Helv. Chem. Acta* **2001**, *84*, 2958–2970. (s) Basle, O.; Li, C.-J. *Chem. Commun.* **2009**, 4124–4126. (t) Bidan, G.; Genies, M. *Tetrahedron* **1981**, *37*, 2297–2301. (u) Bidan, G.; Genies, M.; Renaud, R. *Electrochim. Acta* **1981**, *26*, 275–282. (v) Han, W.; Ofial, A. R. *Chem. Commun.* **2009**, 6023–6025. (w) Rueping, M.; Zhu, S.; Koenigs, R. M. *Chem. Commun.* **2011** (DOI: 10.1039/c1cc12907d).

and green light irradiation at 530 nm at room temperature. Excellent product yields (86−92%; Table 3) were obtained when dialkyl malonates were used as solvents. After the reaction excess dialkyl malonates were distilled off using Kugelrohr distillation[10] yielding the analytically pure reaction products. These results compare favorably with literature reported results by Li and co-workers[11] and Liang et al.[12]

Table 3. Oxidative Coupling Reaction of Tetrahydroisoquinolines with Dialkyl Malonates[a]



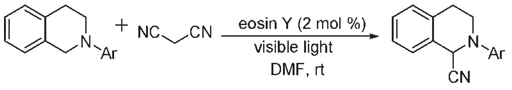
4 **7** **8**

entry	Ar	R	product	time (h)	yield[b] (%)
1	Ph	Et	**8a**	10	92
2	Ph	Me	**8b**	10	88
3	4-MeOC$_6$H$_4$	Et	**8c**	12	91
4	4-MeOC$_6$H$_4$	Me	**8d**	12	90
5	2-MeOC$_6$H$_4$	Et	**8e**	14	89
6	2-MeOC$_6$H$_4$	Me	**8f**	14	86

[a] The reaction was performed with **4** (0.25 mmol) and eosin Y (0.02 equiv) in 1.0 mL of **7**. [b] Isolated yield after distillation of excess solvent.

In addition to nitroalkanes and dialkyl malonates, the photocatalytic reaction was applied to malononitrile. Surprisingly, α-amino nitriles were obtained as the sole products instead of the expected *β*-dicyano substituted derivatives when malononitrile was treated with tetrahydroisoquinolines in DMF at room temperature (Table 4). Amino nitriles are synthetically useful intermediates. The nitrile functionality can be hydrolyzed to give α-amino acids or can be converted into α-amino aldehydes or α-amino alcohols. The photocatalytic reaction is an alternative synthetic route to α-amino nitriles avoiding toxic cyanides and expensive metals.[12,13]

Table 4. Oxidative Synthesis of α-Amino Nitriles[a]



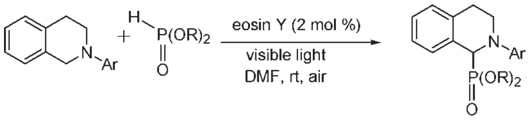
4 **9** **10**

entry	Ar	product	time (h)	yield[b] (%)
1	Ph	**10a**	10	62
2	4-BrC$_6$H$_4$	**10b**	12	56
3	4-MeOC$_6$H$_4$	**10c**	10	60
4	2-MeOC$_6$H$_4$	**10d**	10	58

[a] The reaction was run with **4** (0.25 mmol), malononitrile (1.5 equiv), and eosin Y (0.02 equiv) in 1.0 mL DMF. [b] Isolated yield after purification on SiO$_2$.

The success of C−C bond formation by using eosin Y encouraged us to investigate C−P bond reactions. A variety of methods have been described for the synthesis of α-amino phosphonates,[9r−w] but those typically require metal catalysts and expensive reagents. To avoid these catalysts, we applied our methodology for the synthesis of α-amino phophonates. Various tetrahydoisoquinolines were reacted with dialkyl phosphonates, and representative results are listed in Table 5. The desired products were obtained in good to excellent yields.

Table 5. Oxidative Synthesis of α-Amino Phosphonates[a]



4 **11** **12**

entry	Ar	R	product	time (h)	yield[b] (%)
1	Ph	Et	**12a**	3	86
2	Ph	Bn	**12b**	4	92
3	4-BrC$_6$H$_4$	Et	**12c**	2	82
4	4-BrC$_6$H$_4$	Bn	**12d**	3	88
5	4-MeOC$_6$H$_4$	Et	**12e**	3	93
6	4-MeOC$_6$H$_4$	Bn	**12f**	3	91
7	2-MeOC$_6$H$_4$	Et	**12g**	3	91
8	2-MeOC$_6$H$_4$	Bn	**12h**	3	90

[a] The reaction was run with **4** (0.25 mmol), dialkyl phosphonate (4 equiv), and eosin Y (0.02 equiv) in 1.0 mL of DMF. [b] Isolated yield after purification on SiO$_2$.

The mechanism of the eosin Y photocatalysis has not been investigated in detail at this stage. However, on the basis of our results using nitroalkanes, dialkyl malonates, and dialkyl phosphonates as pronucleophiles in the photoreaction and the litreature reports[8,14] the following mechanism can be suggested (Scheme 2). A single electron transfer from **4** to the excited state of eosin Y gave an

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(10) Diethyl malonate and dimethyl malonates were distilled approximately at 80 °C and 0.5 mm of Hg.

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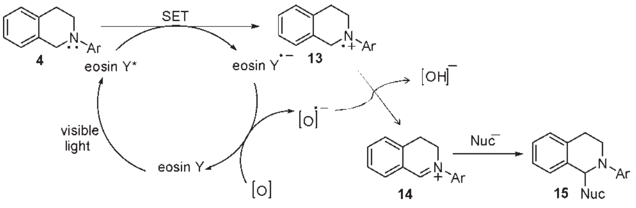
aminyl cation radical **13**, which then lost a hydrogen atom by a radical anion to generate iminium ion **14**.[15] Subsequently, trapping of **14** with pronucleophiles resulted in the desired product **15**. The formation of α-amino nitriles may result from cyanide ion addition to the iminium ion **14**, whereby cyanide ions may be formed by oxidative cleavage of the malononitrile C−CN bond.[11,12a,16]

Scheme 2. Proposed Reaction Mechanism



Iridium- and ruthenium-based photocatalysts mediate the visible light oxidative coupling of tetrahydroisoquinoline derivatives with nitroalkanes, as recently disclosed by Stephenson et al. Our experiments have shown that the transition metal catalysts can be replaced by the redox active organic dye eosin Y yielding comparable yields. Using these organic photocatalysts, the scope of the reaction was extended to dialkyl malonate, malononitrile, and dialkyl phosphonates as pronucleophiles. Continuing from these results we successfully replaced other reagents $PhI(IOAc)_2$ (for cyanation) and CuBr-O_2 (for phosphonation). Due to the similar redox properties of eosin Y and the previously used $Ru(bpy)_3$ complexes we propose a similar mechanism of the reaction. However, alternative mechanistic pathways are equally likely and ongoing investigations must prove the correct mechanistic picture.

Acknowledgment. This work was supported by the GRK 1626 (Chemical Photocatalysis) of German Science Foundation (DFG).

Supporting Information Available. Experimental procedures and spectral characterization of all compounds are available. This material is available free of charge via the Internet at http://pubs.acs.org

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[15] We were able to detect hydrogen peroxide as a byproduct of the reaction using the starch-iodine test (see Supporting Information). This experimental result supports that the iminium ion is likely to be an intermediate.

[16] (a) C−CN bond cleaved by Cu^{II}: Marlin, D. S.; Olmstead, M. M.; Mascharak, P. K. *Angew. Chem., Int. Ed.* **2001**, *40*, 4752–4754. (b) Kharasch, M. S.; Sosnovsky, G. *Tetrahedron* **1958**, *3*, 105–112. (c) Choudary, B. M.; Reddy, P. N. *J. Mol. Catal.* **1996**, *112*, 385–388.