RESEARCH ARTICLE doi.org/10.1002/adsc.202201123

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Advanced Synthesis & Catalysis

Towards a More Sustainable Photocatalyzed α-Arylation of Amines: Green Solvents, Catalyst Recycling and Low Loading

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Manuscript received: October 12, 2022; Revised manuscript received: December 29, 2022;
Version of record online: January 17, 2023

Dedicated to Professor David A. Evans (1941–2022) in memory of his prominent contributions to the field of synthetic organic chemistry.

Supporting information for this article is available on the WWW under https://doi.org/10.1002/adsc.202201123

Abstract: A more sustainable and efficient protocol for the photocatalytic α-amino arylation promoted by *fac*-Ir(ppy)$_3$ was developed. Three noteworthy results were achieved: i) the replacement of toxic medium DMA with the greener solvents NBP and NHP, and the concurrent improvement of the process efficiency by lowering both the amine and the base amount; ii) the development of a recycling protocol for both the sustainable solvent NHP and the commercially available costly photocatalyst *fac*-Ir(ppy)$_3$, achieving environmental and economic benefits. This approach to the photocatalyst recovery avoids very demanding catalyst structural modifications; iii) the protocol in green solvents proved to be scalable up to 10 mmol of limiting reagent, maintaining excellent performance also lowering the photocatalyst loading down to 0.05 mol%. This is the first example of photocatalytic α-arylation of amines promoted by such a low amount of catalyst. Lastly, the versatility of this approach was demonstrated by extending the use of the green solvent NBP to another photoredox process.

Keywords: Amines α-Arylation; Green Solvents; Photocatalyst Recycling; Sustainable Chemistry; Photocatalysis; Iridium; Radical Reactions

Introduction

Photoredox catalysis has seen an outstanding growth over the past decade, proving to be a very powerful tool to accomplish several synthetic transformations not only difficult to achieve otherwise, but also under more sustainable conditions.[1] In particular, processes involving radical species (previously requiring harsh conditions and/or toxic reagents) have greatly benefited from the development of milder, safer and energetically more favorable photoredox catalytic protocols,[2] leading to remarkable applications in medicinal[3] and materials[4] chemistry. Different classes of photoredox catalysts (transition-metal complexes, inorganic semiconductors and organic dyes) have been investigated aiming to achieve highly efficient, robust and broadly applicable transformations. However, despite the remarkable results obtained, the sustainability profile of many proposed reactions is not suitable for large-scale applications.[5] When the scale of reactants, by-products, solvents, exotherms, waste, etc. increases, safety, environmental and economic impacts of the process become crucial.[6] The decreased efficiency of photocatalytic transformations attributed to limited light penetration in large batch reactors and the exothermicity can be overcome exploiting continuous flow processing.[7] However, operating in flow generally prevents the use of heterogeneous reaction mixtures and a very demanding optimization is usually required to convert a protocol from batch to flow. Moreover, many other parameters of a photocatalytic process must be evaluated and implemented to increase the reaction scale, among which: i) the sustainability of the medium, ii) the

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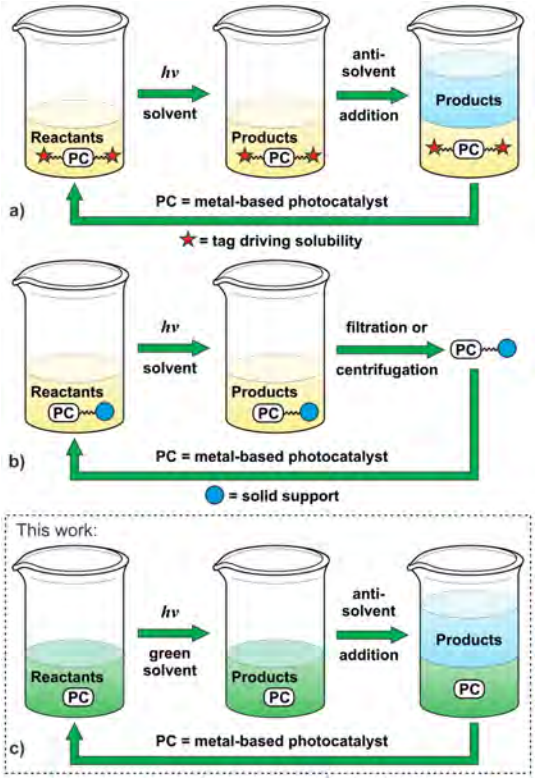
absence of sacrificial reagents (redox-neutral conditions), iii) the catalyst sustainability profile, iv) the process productivity. As part of our experience in developing sustainable catalytic processes,[8] we focused our attention on the sustainability issues related to solvent and metal-based photocatalyst. Solvents represent the main source of waste produced by chemical industrial transformations and, on the basis of their dangerousness and toxicity, they heavily affect the process safety and productivity.[9] In the peculiar case of photoredox catalysis, the solvent plays a pivotal role in determining the solubility and the stability/reactivity not only of reactants and catalyst but also, most importantly, of excited states and reactive intermediates (e.g., radicals). A large part of proposed photocatalytic transformations is carried out in undesirable solvents, such as polar aprotic (DMSO, DMA, DMF, DME, etc.) or halogenated ones, and, to date, few concrete efforts have been devoted to develop photoredox processes in truly sustainable organic media[10] other than water.[11] Although the use of water (or water mixtures) is very promising, it is not compatible with several transformations and photocatalysts. Therefore, the implementation of photoredox protocols in more lipophilic green solvents is highly desirable, making the industrial application of several photocatalytic processes feasible and profitable.

The photocatalysts also play a critical role in determining the sustainability profile and the large-scale applicability of a transformation, especially when metal-complexes based on expensive and scarcely available metals are employed.[12] Moreover, metal traces can inevitably contaminate the resultant products, leading to a highly negative impact on its performance in medicinal or material chemistry. Recently, several known or newly developed metal-free organic dyes have been employed,[13] however, the achieved performances (redox properties, lifetime and nature of the reactive excited states, etc.)[14] are often inferior and, in some cases, insufficient. Among the metal-based photoredox catalysts, $Ru(bpy)_3^{2+}$ and *fac*-$Ir(ppy)_3$ complexes and their derivatives are certainly the most powerful and extensively applied ones.[15] Unfortunately, iridium and ruthenium are among the rarest elements on Earth, hence the extremely high cost severely limits their large-scale applications. In addition, organometallic photocatalysts have a significant environmental impact due to the slow degradation and the action as fluorescent pollutants. For these reasons, one of the current main challenges is the recycling and reuse of Ru- and, especially, Ir-based photocatalysts, achieving both environmental and economic benefits. Some authors have tackled this feat[16] and two are the main adopted strategies (Scheme 1): a) modifying the solubility profile of the photocatalyst, to confine it in a specific solvent (homogeneous systems); b) supporting the photocatalyst to easily separate it (heterogeneous systems). Despite the remarkable results obtained, these two approaches both suffer from a significant disadvantage, which consists in the need to structurally modify the photocatalyst. The synthetic pathway to reach the desired functionalized catalysts is often a cumbersome process with a prominent impact in terms of costs, time and environment.[17]



Scheme 1. Strategies adopted for photocatalyst recycling.

Based on this state of the art, our aim was to further improve the sustainability of a homogeneous photoredox transformation proving that this class of reactions is concretely usable for large-scale applications. In particular, we focused on proving that: i) some photoredox catalytic reactions can proceed in green organic solvents, ii) suitable strategies enable the recovery of the homogeneous precious metal-based photocatalyst in its *commercially available form*, avoiding the demanding structural modification (Scheme 1, c).

To the best of our knowledge, only two examples are present in the literature reporting on the recycling of *commercial* iridium photocatalysts. In 2015, Rueping and coworkers[18] proposed a protocol in which the cationic $Ir(ppy)_2(bpy)PF_6$ (3 mol%) was recycled 8 times in the (*E*) to (*Z*) isomerization of highly apolar olefins, a process involving an energy transfer (ET) mechanism. However, ionic liquid $bmimBF_4$ (not

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considered as green solvent)[19] or toxic DMF[20] were used as reaction medium. In 2018, Zhang and co-workers[21] proposed a photoinduced atom transfer radical polymerization (ATRP) promoted by *fac*-Ir(ppy)$_3$ (2.5 mol%). Exploiting the water-solubility of both the monomers and the obtained polymer, the photocatalyst can be separated in the organic phase and recycled 5 times. However, the need for few specific water-soluble reagents significantly limits the wide applicability of this protocol for the photocatalyst reuse. Aiming to go beyond the reported methods for iridium-photocatalysts recycling, i) we selected a process involving a SET mechanism to be carried out in a green solvent under mild and improved conditions, ii) we envisaged to recycle the commercially available catalyst separating it from reactants and products with *similar solubility profiles*. It is important to underline that this kind of reactive system is representative of most of the photoredox processes recently proposed for synthetic purposes.

The photocatalytic transformation to be studied was selected on the basis of its ability to produce scaffolds of industrial interest. In particular, we focused on α-amino C–H arylation, being α-arylamino structural motif present in several medicinally relevant compounds (Figure 1),[22] including top-selling pharmaceuticals.[23]

Several catalytic methods of amines α-arylation have been described,[24] however, their sustainability and large-scale applicability are very often limited by high amounts of metals, excess of oxidants, harsh conditions, and/or toxic solvents. The visible light-mediated photoredox catalysis has recently offered a viable sustainable alternative approach,[25] characterized by mild conditions, green energy source, redox-neutral systems, low loading of metal-catalysts. However, in most cases, toxic polar aprotic solvents are used as reaction media. Based on the photocatalytic amines α-arylation protocol proposed by MacMillan and coworkers,[25b,e] we planned to efficiently perform the same reaction in a green solvent and to recycle the precious photocatalyst.

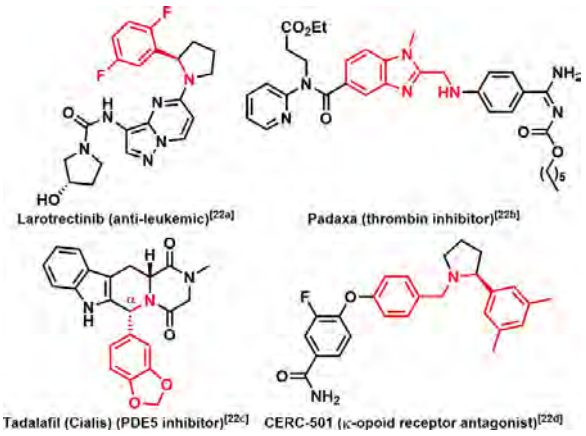

Figure 1. Some bioactive compounds containing the α-arylamino motif.

Results and Discussion

Our first investigations were carried out on the model system composed by *N*-phenyl pyrrolidine **1 a** and 1,4-dicyanobenzene (DCB, **2 a**), applying the reaction conditions reported in the literature[25e] and aiming to identify a suitable green solvent for this transformation (Table 1). To efficiently replace toxic dimethylacetamide (DMA) we tested some polar solvents starting from 1-methyl-2-pyrrolidone (NMP) as representative of its green higher analogues. Using a 462 nm LED strip, we were delighted by a good **3 aa** yield (51%, entry 1).

Shorter or longer reaction times did not affect very much the yield (see Supporting Information) and we decided to compare different solvents at 24 hours. The reaction performance improved when a more potent (50 W) 456 nm Kessil lamp was used (entry 2). Once demonstrated the good reactivity in NMP, a series of 2-pyrrolidones was evaluated as sustainable solvents.

In fact, longer 2-alkylpyrrolidones show lower toxicity,[26] generating metabolites different from those produced by *N*-Me oxidation in DMF[27] or NMP.[28] 1-Butyl-2-pyrrolidone (NBP,[29] entry 3) and 1-octyl-2-pyrrolidone (NOP,[30] entry 5) provided high product yields (72–75%), significantly better than 1-cyclohexyl-2-pyrrolidone (NCP,[31] entry 4), 1-benzyl-2-pyrrolidone (NBnP,[32] entry 6) and 1-hydroxyethyl-2-pyrrolidone (HEP,[33] entry 7). As last member of this family we evaluated 2-pyrrolidone (NHP,[34] entry 8), which, although not considered a fully green solvent, is a component of some foods and, thanks to its low toxicity, is used as excipient in veterinary pharmaceutical products and as vehicle for dermally administered human medicines.[35] It also finds application as a cosolvent and plasticiser in aqueous coatings, co-solvent for water-based ink formulations, intermediate in the pharmaceutical industry (e. g. Piracetam), solvent in the manufacture of membrane filters (for e. g. sterile filtration of drugs such as pharmaceutical proteins, wine filtration systems, etc.).[36] Applied in our photocatalytic process, NHP yielded a very good result (75%). Some other sustainable solvents[9a,d] were tested: in anisole, tBuOAc and dimethyl carbonate (DMC) (entries 9–11, respectively) the reaction did not proceed, probably because of the very low reagents solubility. No product was also observed in MeOH and cyrene (entries 12–13), whereas MeCN provided a very low yield (entry 14). Lastly, we were pleased to find out that the green solvents sulfolane and γ-valerolactone (GVL) led to good results (71 and 75%

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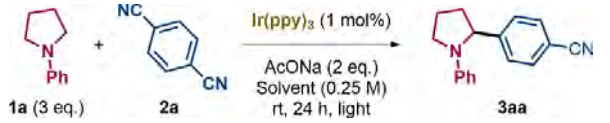
Table 1. Reaction medium optimization.[a]



1a (3 eq.) 2a 3aa

Entry	Solvent	Light Source	**3aa** Yield (%)[b]
1	NMP	LED strip, 462 nm	51
2	NMP	Kessil 50 W, 456 nm	80
3	NBP	Kessil 50 W, 456 nm	72
4	NCP	Kessil 50 W, 456 nm	51
5	NOP	Kessil 50 W, 456 nm	75
6	NBnP	Kessil 50 W, 456 nm	44
7	HEP	Kessil 50 W, 456 nm	41
8	NHP	Kessil 50 W, 456 nm	75
9	PhOMe	Kessil 50 W, 456 nm	np
10	*t*BuOAc	Kessil 50 W, 456 nm	np
11	DMC	Kessil 50 W, 456 nm	np
12	MeOH	Kessil 50 W, 456 nm	np
13	Cyrene	Kessil 50 W, 456 nm	np
14	MeCN	Kessil 50 W, 456 nm	28
15	Sulfolane	Kessil 50 W, 456 nm	71
16	GVL	Kessil 50 W, 456 nm	75

[a] Reaction conditions: **2a** (0.1 mmol), **1a** (3 eq.), *fac*-Ir(ppy)$_3$ (1 mol%), NaOAc (2 eq.), distilled solvent (0.4 mL), rt.
[b] Determined by ^{1}H NMR spectroscopic analysis of the crude using methyl acetoacetate as internal standard. eq. = equivalents, ppy = 2-phenylpyridinato; rt = room temperature; h = hours; np = no product.

yield, entries 15–16). The solvents screening provided a remarkable achievement, proving that the photoredox catalytic α-arylation of amines can be efficiently carried out in green organic media. To the best of our knowledge, this is the first photoredox transformation taking place in green *N*-alkylpyrrolidones (other than toxic NMP), 2-pyrrolidone (NHP), sulfolane or γ-valerolactone (GVL). To further improve the efficiency and the sustainability of the process we optimized the amount of both starting amine **1a** and base, selecting the best performing solvents (Table 2).

Table 2. Reaction conditions optimization.[a]

Entry	Solvent	**1a** [eq.], NaOAc [eq.]	**3aa** Yield (%)[b]
1	NOP	1.5, 2	78
2	NOP	1.5, 1.5	72
3	NBP	1.5, 1.5	84
4	NHP	1.5, 1.5	86
5	Sulfolane	1.5, 2	60
6	Sulfolane	1.5, 1.5	50
7	GVL	2, 2	75
8	GVL	1.5, 2	48

[a] Reaction conditions: **2a** (0.1 mmol), *fac*-Ir(ppy)$_3$ (1 mol%), Kessil 50 W 456 nm, distilled solvent (0.4 mL), rt, 24 h.
[b] Determined by ^{1}H NMR spectroscopic analysis of the crude using methyl acetoacetate as internal standard.

Although the authors of the reference protocol[25e] proved that a remarkable excess of amine and base was required to achieve good performance, we gradually lowered the reagents equivalents (see Supporting Information) demonstrating that, in pyrrolidones as solvents, satisfactory results can be obtained using only a moderate excess of both amine and base (entries 1–4). Conversely, sulfolane and GVL were more sensitive to these variations (entries 5–8). With the optimized conditions in our hands, we explored the structural scope of the process (Scheme 2) in NBP and NHP, as the best performing and most sustainable solvents (NBP: 57.4 €/L and NHP: 32.3 €/Kg by VWR International; NOP: 231 €/L by Merck).

The reactivity of different amines **1** was evaluated obtaining good to excellent yields (Scheme 2). Five-, six- and seven-membered rings proved to be suitable substrates, also including heteroatoms (products **3ea** and **3fa**). Moreover, remarkable results were also achieved with acyclic amines (products **3ha** and **3ia**). Some different *N*-substituents were tolerated (products **3ba**, **3ca**, **3ja** and **3ka**) and the excellent performance provided by the drug-like scaffolds indoline **1j** and 1,2,3,4-tetrahydroquinoline **1k** were noteworthy (products **3ja** and **3ka**). Afterwards, we moved to aryl-donors scope, however, we observed a decrease of products yields when the aromatic ring became less electron-poor, as evident by comparing products **3aa**, **3ac** and **3ad** (Scheme 2). The low reactivity of 1,2-dicyanobenzene **2b** was in accordance with the results already reported in other solvents.[25e] Conversely, good performance were achieved with heteroaromatic aryl-donors (**2e–h**) and, in particular, with drug-like bicyclic systems of benzothiazole and benzoimidazole (products **3af** and **3ag–h**, respectively). It is worth mentioning that in these latter cases, the leaving group was a chloride and not a cyanide, and, unlike us, the authors of the reference protocol[25e] were forced to use a different photocatalyst ($Ir(ppy)_2(dtbbpy)PF_6$) to obtain good results. These observations prompted us to

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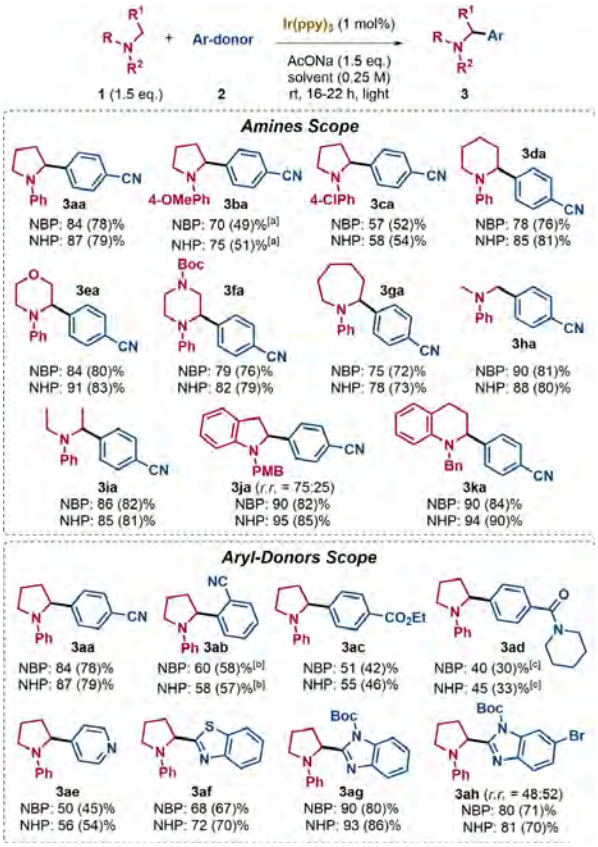
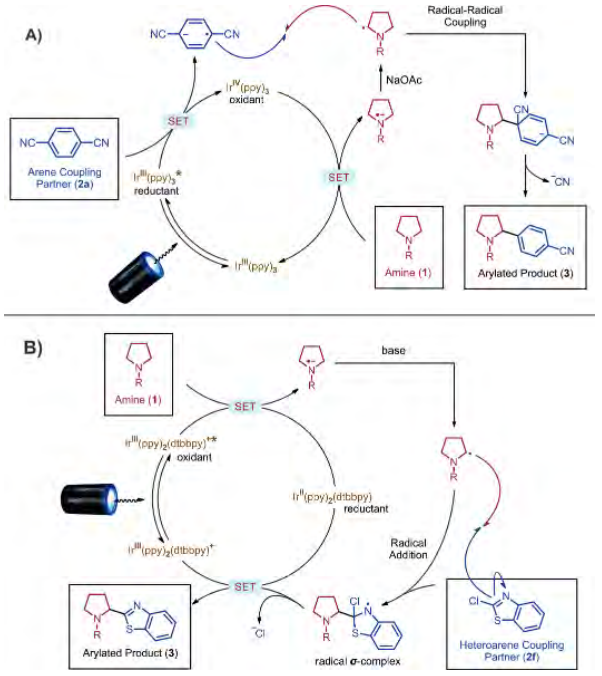


Scheme 2. Reaction scope. Optimized reaction conditions: **1** (1.5 eq.), **2** (0.1 mmol), *fac*-Ir(ppy)$_3$ (1 mol%), NaOAc (1.5 eq.), distilled NBP or NHP (0.4 mL), Kessil 50 W 456 nm, rt, 16–22 h. The aryl-donors were cyanoarenes except for **2 f**–**2 h**, which were aromatic chlorides. All the products were obtained as racemates. NMR yields determined by ^{1}H NMR spectroscopic analysis of the crude using methyl acetoacetate as internal standard. Yields after purification reported in brackets. [a] Product degradation (see Supporting Information). [b] 5 mol% of catalyst. [c] Reaction time: 66 h. r.r.: regioisomeric ratio.

think about the reaction mechanism. MacMillan and coworkers proposed two different pathways (Scheme 3) for this transformation depending on the aryl-donor **2**.

In the presence of easy reducible substrates (as DCB **2 a**) an oxidative quenching of the excited Ir(III)-complex is active (Scheme 3A),[25e] providing the arene radical anion and the Ir(IV) species. The latter is able to oxidize the amine **1** to radical cation regenerating the initial *fac*-Ir(ppy)$_3$ complex. The sequence of α–C–H deprotonation, radical-radical coupling and cyanide elimination yields the arylated product **3**. When the direct reduction of the aryl-donor is too unfavourable, as reported by MacMillan for Cl-benzothiazole with *fac*-Ir(ppy)$_3$, the first step should be the amine oxidation operated by a sufficiently oxidizing photocatalyst (Scheme 3B).[25b] The neutral α-amino radical, generated by deprotonation of the radical cation, adds to the electrophilic arene providing a radical σ-complex, which is reduced restoring the initial catalyst and, by losing an anionic leaving group, it yields the arylated product **3**. In our system, based on *fac*-Ir(ppy)$_3$ as photocatalyst, the initial reductive quenching coupled with the amine oxidation (Scheme 3B) is very unlikely due to the low reduction potential of *fac*-Ir(ppy)$_3$ [$E_{1/2}$ (Ir^{III*}/Ir^{II}) = +0.31 V vs SCE;[14] $E_{1/2}^{ox}$ (*N*,*N*-dimethylaniline) = −0.71 V vs SCE[37]]. The most likely pathway is the oxidative quenching (Scheme 3A) and the significantly better results obtained in our conditions with Cl-benzothiazole **2 f** and Cl-benzoimidazoles **2 g**–**h** could be due to a beneficial effect of NBP or NHP on the potentials of the involved species. Stern-Volmer experiments carried out in NBP confirmed a significant quenching of the excited *fac*-Ir(ppy)$_3$ by benzoimidazole **2 g** (see Supporting Information).



Scheme 3. Possible mechanistic pathways.

Once demonstrated efficiency, sustainability and applicability of our protocol in green solvent compared to the previously reported process, we moved to the evaluation of the recycling of the commercially available photocatalyst *fac*-Ir(ppy)$_3$. The major issue related to the selective separation of catalyst from reactants and products is their similar solubility profile.[38] Our investigation began testing some extracting solvents applied to the best performing green reaction media (Table 3).

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Table 3. Extracting solvents investigation.[a]

Entry	Reaction Solvent	Extraction Solvent (conditions)	**3** Yield (%)[b]
1	NOP	Cy (0.5 mL)	ns
2	NOP	Hex (0.5 mL)	ns
3	NBP	Cy (0.5 mL)	ns
4	NBP	Hex (0.5 mL)	ns
5	Sulfolane	Cy (9×1 mL)	23
6	Sulfolane	Hex (9×1 mL)	11
7	GVL	Cy (10×1.5 mL)	75[c]
8	GVL	Hex (14×1.5 mL)	40
9	NHP	Cy (14×1.5 mL)	51
10	NHP	Hex (13×1.5 mL)	34
11	NHP	Cy:CPME 97:3 (14×1.5 mL)	65
12	NHP	Cy:EtOAc 98:2 (14×1.5 mL)	85
13	NHP	MeCy:EtOAc 98:2 (14×1.5 mL)	19
14	NHP	Cy:EtOAc 98:2 (14×1.5 mL)	74[d]
15	NHP	Cy:EtOAc 98:2 (14×1.5 mL)	57[e]

[a] Reaction conditions: **2a** (0.1 mmol), **1a** (1.5 eq.), NaOAc (the best amount for each solvent reported in Table 2), *fac*-Ir(ppy)$_3$ (1 mol%), Kessil 50 W 456 nm, distilled solvent (0.25 M), rt, 22 h.

[b] Determined by ^{1}H NMR spectroscopic analysis of the extracted crude using methyl acetoacetate as internal standard.

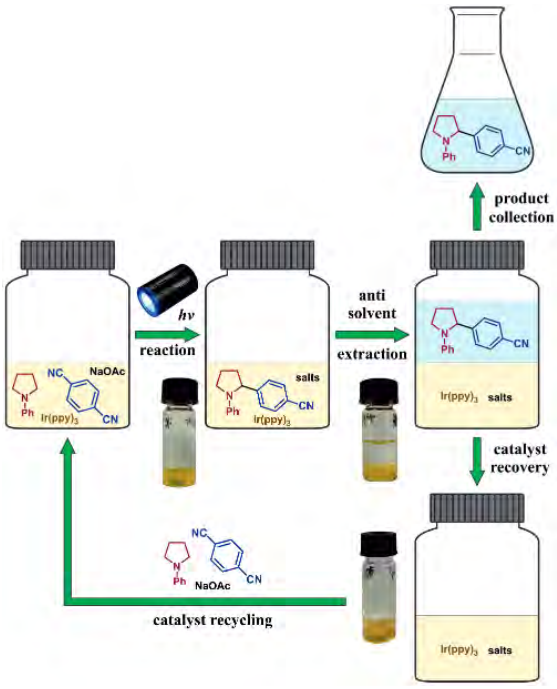
[c] Reaction and extracting solvents partially miscible, a significant amount of reaction solvent was extracted dragging *fac*-Ir(ppy)$_3$.

[d] **1d** used as amine.

[e] **2e** used as aryl-donor. ns = no separation, reaction solvent and extracting solvent are miscible. Cy = cyclohexane, Hex = hexane, CPME = cyclopentyl methylether, MeCy = methyl cyclohexane.

Aiming to confine the photocatalyst in the polar reaction solvent, we tried to extract the product with apolar solvents, such as cyclohexane or hexane. Unfortunately, the alkyl pyrrolidones NOP and NBP were miscible and no separation was observed (entries 1–4). With sulfolane we obtained two phases but a low amount of product was extracted (entries 5–6), with hexane working worse than cyclohexane. GVL allowed to separate 40% of product with hexane (entry 8), whereas cyclohexane was partially miscible, extracting not only the arylated amine but also GVL and *fac*-Ir(ppy)$_3$ (entry 7). The best results were achieved with NHP, being more polar and providing a good phase separation. Cyclohexane was able to extract 51% of product (entry 9) and the performance improved by adding a small portion of a more polar solvent. Among the sustainable solvents, we tested CPME[39] (entry 11) and EtOAc[40] (entry 12), with the latter enabling the full extraction of the product. The attempt to replace cyclohexane with greener methyl cyclohexane[40] failed (entry 13). Lastly, we were pleased to find out that not only arylated pyrrolidine **3aa** (entry 12) but also arylated piperidine **3da** (entry 14) and the pyridine-derived amine **3ae** (entry 15) were fully extracted exploiting the developed protocol. The last result is noteworthy, because the high polarity of **3ae** could make the extraction from the catalyst-containing NHP phase particularly difficult.

Once identified a satisfactory extraction protocol, we investigated the recyclability of the catalytic *fac*-Ir(ppy)$_3$ in our reaction system. We carried out the α-arylation alternatively on two different amines (**1a** and **1d**) to monitor the full product extraction in each cycle. After product removal, the NHP phase containing the photocatalyst was dried, new reagents (**1**, **2** and base) were added and, after freeze-pump-thaw treatment, the mixture was irradiated (Scheme 4, see Supporting Information for details). The α-arylation was successfully carried out with the same *fac*-Ir(ppy)$_3$ (1 mol%) in the same NHP for 15 runs (Table 4, 1.072 mmol of arylated product with 0.001 mmol of photocatalyst). In the 16th and 17th cycles a significant reactivity drop was observed with both the amines **1a** and **1d**. Since the reaction mixture looked cloudy probably due to the accumulated salts, we washed the NHP phase (see Supporting Information for details) obtaining a performance improvement (18th and 19th



Scheme 4. *fac*-Ir(ppy)$_3$ recycling in NHP.

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Table 4. Recyclability of catalytic *fac*-Ir(ppy)$_3$ (1 mol%) in NHP.[a]

Run	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19
Amine	**1 a**	**1 d**	**1 a**	**1 d**	**1 a**	**1 d**	**1 a**	**1 d**	**1 a**	**1 d**	**1 a**	**1 d**	**1 a**	**1 d**	**1 a**	**1 d**	**1 a**	**1 d**	**1 a**
Time (h)	16	19	72	22	22	22	22	72	22	17	44	72	22	22	22	22	96	96	22
3 Yield (%)[b]	70	71	61	88	71	70	84	71	84	75	75	62	65	63	62	23	36	51[c]	41

[a] Reaction conditions: **2 a** (0.1 mmol), **1** (1.5 eq.), NaOAc (1.5 eq.), *fac*-Ir(ppy)$_3$ (1 mol%), Kessil 50 W 456 nm, distilled NHP (0.25 M), rt. Crude mixtures extracted with Cy/EtOAc = 98/2 as reported in Table 3, entries 12 and 14.
[b] Determined by ^{1}H NMR spectroscopic analysis of the extracted crude using methyl acetoacetate as internal standard.
[c] Before setting this reaction the NHP phase was washed with aqueous Na_2CO_3 (see Supporting Information).

cycles). It should be noted that the variability in the reaction yields observed during the different recycling runs is a common phenomenon in photoredox catalytic reactions, since it is extremely difficult to reproduce the exact experimental setup between different runs.[41] On the other hand, it is important to note that, after several cycles, the yields were comparable or higher than those obtained in the first cycles, proving the effective photocatalyst recycling.

Prompted by the obtained good results, we planned to halve the catalyst amount and to recycle 0.5 mol% of *fac*-Ir(ppy)$_3$ (Table 5). In this case the α-arylation also proceeded with good to excellent results for 11 cycles, providing 0.752 mmol of product with 0.0005 mmol of photocatalyst. Moreover, three different amines (**1 a**, **1 d**, **1 h**) were employed, proving not only the process efficiency using 0.5 mol% of catalyst, but also the broad applicability of the developed extracting and recycling protocol. Finally, it is worth noting that the extraction mixture cyclohexane/EtOAc = 95/5 can be also employed in the products extraction and catalyst recycling (see Supporting Information). A more polar extraction mixture represents a further tool useful for the extraction and separation of more polar products.

The next step of our investigation focused on the scalability of the photocatalytic α-arylation reaction in green solvents (Table 6).

We selected NBP as the best performing green solvent and NHP as the most useful recycling medium. At first, we lowered the catalyst loading and, gratifyingly, we demonstrated that our conditions allowed to achieve excellent performance in both solvents even using 0.1 mol% of *fac*-Ir(ppy)$_3$ (entries 2 and 9). A further photocatalyst decrease at this concentration (0.25 M) led to a notable drop in the product yield (entries 3 and 10). On this basis, we increased the reaction scale by ten times (1 mmol of limiting reagent **2 a**, 0.1 mol% of catalyst) pleasingly maintaining the same good results (entry 4), although some set-up changes were required to compensate for the longer optical path and for the increased thickness of the reactor walls (see Supporting Information for details). The excellent performance on 1 mmol scale with 0.1 mol% of *fac*-Ir(ppy)$_3$ was also confirmed on dimethylaniline **1 h** (entries 5 and 11), proving the broad applicability of this protocol. To the best of our knowledge, this is the first example of photocatalytic α-arylation of amines promoted by such a low loading of catalyst. However, aiming to further improve this result, we evaluated whether a good performance could be obtained with less catalyst by lowering the solvent volume. Pleasingly, the transformation smoothly proceeded at higher concentrations (0.5 and 1 M, see Supporting Information), allowing us to save not only the solvent but also the photocatalyst. In fact, we were able to obtain excellent performance in both NBP and NHP using the unprecedented photocatalyst loading 0.05 mol% (Table 6, entries 6–7 and 12–13). These results are particularly remarkable because they were obtained also by applying the protocol to the gram-scale (10 mmol, 1.28 g of the limiting reagent **2 a**) in both NBP and NHP. We also investigated the impact of the higher reaction concentration on the extraction process (see Supporting Information). We were delighted to observe a beneficial effect, allowing us to

Table 5. Recyclability of catalytic *fac*-Ir(ppy)$_3$ (0.5 mol%) in NHP.[a]

Run	1	2	3	4	5	6	7	8	9	10	11
Amine	**1 d**	**1 h**	**1 a**	**1 h**	**1 d**	**1 h**	**1 d**	**1 h**	**1 d**	**1 d**	**1 a**
Time (h)	17	19	18	18	38	20	17	21	20	19	18
3 Yield (%)[b]	81	80	60	58	71	76	60	54	79	70[c]	63

[a] Reaction conditions: **2 a** (0.1 mmol), **1** (1.5 eq.), NaOAc (1.5 eq.), *fac*-Ir(ppy)$_3$ (0.5 mol%), Kessil 50 W 456 nm, distilled NHP (0.25 M), rt. Crude mixtures extracted with Cy/EtOAc = 98/2 as reported in Table 3, entries 12 and 14.
[b] Determined by ^{1}H NMR spectroscopic analysis of the extracted crude using methyl acetoacetate as internal standard.
[c] Before setting this reaction the NHP phase was washed with aqueous Na_2CO_3 (see Supporting Information).

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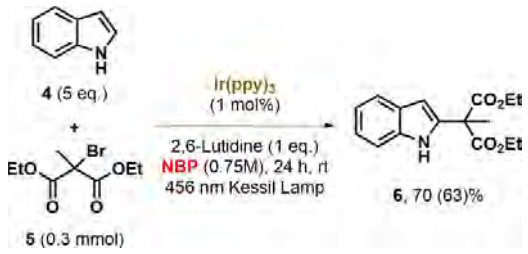
Table 6. Study on the scalability of the α-arylation reaction.[a]

Entry	Reaction Scale, Amine	*fac*-Ir(ppy)$_3$ (mol%)	Solvent	**3** Yield (%)[b]
1	**2 a** (0.1 mmol), **1 a**	0.5	NBP (0.25 M)	72
2	**2 a** (0.1 mmol), **1 a**	0.1	NBP (0.25 M)	78
3	**2 a** (0.1 mmol), **1 a**	0.05	NBP (0.25 M)	56
4[c]	**2 a** (1 mmol), **1 a**	0.1	NBP (0.25 M)	83 (79)
5[c]	**2 a** (1 mmol), **1 h**	0.1	NBP (0.25 M)	89 (80)
6[c]	**2 a** (1 mmol), **1 h**	0.05	NBP (0.5 M)	95
7[c]	**2 a** (10 mmol), **1 h**	0.05	NBP (1 M)	>95 (85)
8	**2 a** (0.1 mmol), **1 a**	0.5	NHP (0.25 M)	82
9	**2 a** (0.1 mmol), **1 a**	0.1	NHP (0.25 M)	86
10	**2 a** (0.1 mmol), **1 a**	0.05	NHP (0.25 M)	38
11[c]	**2 a** (1 mmol), **1 h**	0.1	NHP (0.25 M)	77 (70)
12[c]	**2 a** (1 mmol), **1 a**	0.05	NHP (0.5 M)	83
13[c]	**2 a** (10 mmol), **1 h**	0.05	NHP (1 M)	93 (80)

[a] Reaction conditions in vial (0.1 mmol of **2 a**): **1** (1.5 eq.), NaOAc (1.5 eq.), *fac*-Ir(ppy)$_3$ as photocatalyst, Kessil 50 W 456 nm, distilled solvent, rt, 22 h. For catalyst loading 0.1 and 0.05 mol% a stock solution (1.25 mM) was used.
[b] Determined by ^{1}H NMR spectroscopic analysis of the crude using methyl acetoacetate as internal standard. Yields after purification reported in brackets.
[c] Reaction carried out in Schlenk tube irradiated by two lamps (see Supporting Information).

fully extract the product saving a significant amount of the extraction solvent (more than half), also in the 10 mmol scale process (Table 6, entry 13; see Supporting Information for details).

As last remark we extended the use of the green solvent NBP to a different photoredox catalytic reaction: the intermolecular C–H functionalization of indole with a tertiary alkyl halide (Scheme 5).[42]



Scheme 5. Photoredox catalytic alkylation of indole carried out in NBP.

Although this process is not optimized, the obtained good result demonstrates that NBP can be a suitable solvent for different photocatalytic transformations and a good candidate as green alternative to polar aprotic solvents.

Conclusion

In summary, we developed a more sustainable and efficient protocol for the photocatalytic α-amino C–H arylation promoted by *fac*-Ir(ppy)$_3$. In particular, three main goals were achieved: i) we successfully replaced the toxic polar aprotic medium DMA with the greener solvents NBP and NHP, also improving the process efficiency by lowering the amount of both amine reagent and base; ii) we developed a protocol enabling the recycling of the solvent NHP and the commercially available costly photocatalyst *fac*-Ir(ppy)$_3$, achieving environmental and economic benefits. Moreover, this approach avoids the very demanding process of catalyst structural modification, usually required for

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the photocatalyst recovery; iii) we demonstrated the scalability of our protocol in green solvents up to 10 mmol, maintaining excellent performance also lowering the photocatalyst loading to 0.05 mol%. To the best of our knowledge, this is the first example of photocatalytic α-arylation of amines promoted by such a low amount of catalyst. Lastly, we showed that the use of NBP as green solvent can be extended to different photoredox catalytic processes, helping to improve the sustainability profile of this type of transformations. Although more progresses need to be made to make the photocatalytic α-amino arylation effectively applicable on a large scale, our work significantly improves the sustainability of some aspects of the process. Indeed, remarkable results were obtained by running the photocatalytic process in alternative and more benign solvents and by lowering the photocatalyst loading and the solvent amount. However, the recycling protocol still needs further attention, because, although the catalyst is effectively recycled, the quantitative product recovery actually needs significant amount of solvent. Our efforts were aimed to demonstrate the possibility to increase the sustainability profile of photoredox catalytic transformations, to make them more efficient and to expand their applicability on the larger scale.

Experimental Section

General Procedure for Photoredox α-Arylation of Amines in Green Solvents on 0.1 mmol Scale

A 4 mL screw cap septum vial equipped with a magnetic stirring bar was charged with the amine **1** (1.5 eq), the aryl-donor **2** (0.1 mmol, 1 eq), sodium acetate (1.5 eq) and the photocatalyst (*fac*-Ir(ppy)$_3$, 1 mol%, 0.01 eq). The reaction vessel was then purged with a stream of Argon and 400 µL (0.25 M) of NBP or NHP (previously distilled and degassed with Argon bubbling for 5 minutes) were added via syringe. The vial was sealed with grease on the septum and with parafilm and placed approximately 10 cm from a 50 W 456 nm Kessil® Lamp. In order to maintain the temperature between 25 and 30 °C a fan was employed to blow air over the vial. After the reported time, the reaction was diluted with ca. 3 mL of ethyl acetate and added to a separatory funnel containing 5 mL of a saturated aqueous solution of K_2CO_3. The organic layer was separated and the aqueous layer was extracted with EtOAc (2 × 5 mL). The combined organic extracts were washed with brine, dried over sodium sulphate, and concentrated in vacuo. Purification of the crude by flash chromatography on silica gel afforded the desired product.

General Procedure for Photocatalyst Recycling

The first reaction was set up exactly as previously described. For the subsequent runs, after addition of new reagents (**1**, **2** and the base) to the recycled NHP containing the photocatalyst, the reaction mixture was degassed with 3 cycles of freeze – pump – thaw (3 × 10 minutes, backfilling with Argon). After the indicated time, the vial was opened and 1.5 mL of the anti-solvent (cyclohexane: ethyl acetate 98:2) was added. The vial was sealed, vigorously shaken and the two phases were allowed to settle. At this point, approximately 1.4 mL of the anti-solvent were removed by means of a 1 mL Hamilton® syringe. This procedure was repeated 13 times. Since small quantities of NHP (containing traces of catalyst) were extracted as microemulsion, the collected anti-solvent was cooled to 0 °C for a few minutes in order to freeze the extracted NHP. The anti-solvent containing the product was easily removed and the NHP was transferred to the reaction vessel by means of 1 mL of ethyl acetate. The mixture contained in the reaction vessel was dried under vacuum and then reused for the following run. The collected anti-solvent containing the product was dried under reduced pressure and analyzed by ^{1}H NMR spectroscopy adding methyl acetoacetate (0.1 mmol) as internal standard.

Acknowledgements

We acknowledge Ministero dell'Università e della Ricerca (PRIN2017 – 20174SYJAF_001, SURSUMCAT), University of Bologna (RFO) and Fondazione Carisbo (project 18668 "Tecnologie avanzate per il controllo e lo sviluppo di molecole innovative per la salute") for the financial support. Funding provided by Universita degli Studi di Bologna within the CRUI-CARE Agreement.

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