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Organocatalytic Reduction of Aromatic Nitro Compounds: The Use of Solid-Supported Phenyl(2-quinolyl)methanol

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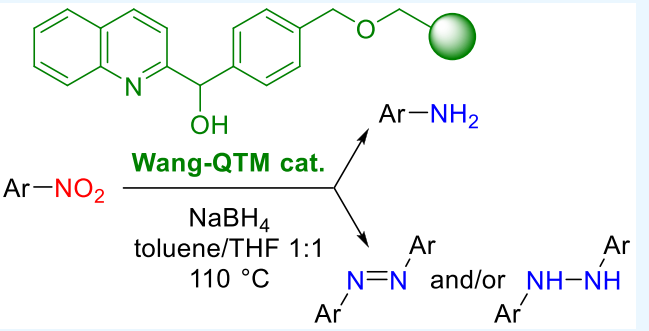
ABSTRACT: The reduction of aromatic nitro compounds has been performed employing a catalytic amount of Wang resin-supported phenyl(2-quinolyl)methanol (Wang-PQM) in the presence of an excess of $NaBH_4$ to regenerate the reactive reducing species at the end of the process. The reduction products are easily isolated through a simple filtration/extraction protocol, and the catalyst can be efficiently recovered and recycled. The condensation route is generally preferred, and azo- and/or hydrazoarenes can be easily prepared in high yields.



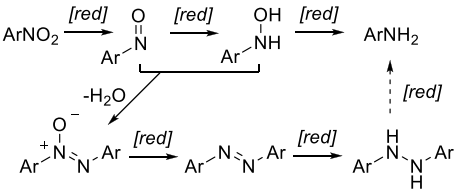
INTRODUCTION

Previous results from our laboratory showed the application of pyridyl- and quinolyl-methanols as transition-metal-free reducing agents for nitro aromatic and heteroaromatic compounds, thanks to their reactivity as NADH 1,4-dihydropyridine mimics. Incidentally, the most studied 1,4-dihydropyridine mimic Hantzsch ester is not able to reduce nitro aromatic and heteroaromatic compounds. The corresponding aniline derivatives, the synthetic applications of which are well established in several domains, were easily recovered operating in thermal conditions (70−110 °C) with 3 equiv of the reducing agent, according to the reaction stoichiometry,[1] or by using the reducing compound as organocatalyst in conjunction with $NaBH_4$ or $NaCNBH_3$, that are not able, alone, to reduce the nitro to amino group.[2] The second approach appeared more efficient thanks to the use of little amounts (0.5 equiv instead of 3 equiv) of phenyl(2-quinolyl)methanol (PQM), shorter reaction times in the presence of $NaBH_4$, and in *situ* regeneration of the reducing agent in "a continuous" process, but suffers from lower selectivity toward aniline formation. In the latter conditions, a competitive pathway leading to condensation products (i.e., azoxy, azo, and/or hydrazo derivatives) was commonly observed, according to the Haber mechanism (Scheme 1).[3]

Compounds bearing the *N*−*N* bond, however, are very useful precursors in dyes, pigments, electronics, and drug industries,[4] and in particular, they found applications in the domain of liquid crystals and polymer materials.[5] Natural and synthetic azoxy and azo derivatives showed biological activities as antitumor, antimicrobial, and antibacterial agents[6] and more recently were exploited as *ortho*-directing group in selective C−H functionalization of arenes.[7] Due to the complexity of the above reaction mechanism, the aim to perform selective and high-yielding processes is a challenging issue, and recently, interesting results have been obtained using, for instance, metal nanoclusters/nanoparticles[8] as catalysts to push the reaction toward the desired product.

On the other hand, in the last decades, the solid-phase organic synthesis (SPOS) has grown significantly, mainly thanks to a facile recovery of reagents and/or reaction products by simple filtration, avoiding chromatographic and solvent- and time-consuming separation.[9] Recently, supported reagents and catalysts have been successfully prepared using different supports and applied in several domains. For instance, NADH models were prepared and grafted on Merrifield resin,[10] polysiloxane,[11] magnetic nanoparticles (MNPs),[12] as

Scheme 1. Haber Mechanism for Nitroarene Reduction



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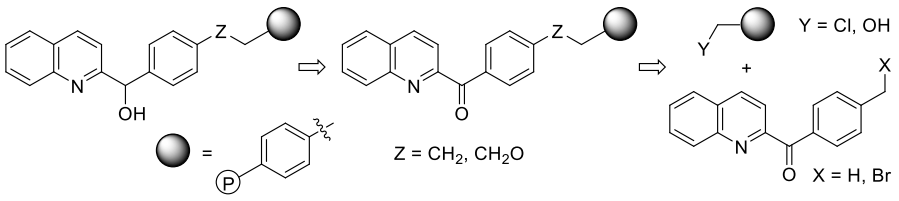
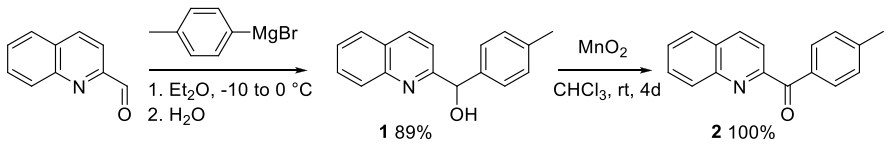


Figure 1. Retrosynthetic analyses to access solid-supported PQMs.

Scheme 2. Synthesis of QTM (1) and QTK (2)



well as soluble polymers,[13] and applied in the reduction of carbonyl derivatives, activated olefins, imines, and so on.

On this basis, the present work is focused on the synthesis of solid-supported phenyl(2-quinolyl)methanols, as well as their applications as hydrogen donors in transition-metal-free reductions of nitroarenes.

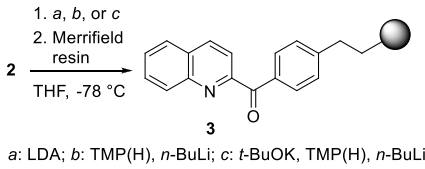
RESULTS AND DISCUSSION

The foreseen strategy to prepare the solid-supported reagents could involve the treatment of a polystyrene resin (i.e., Merrifield or Wang resin) with PQM derivatives, suitably functionalized on the aromatic ring. Some retrosynthetic analyses are depicted in Figure 1.

For this purpose, (2-quinolyl)tolylmethanol (QTM, **1**)[14] was synthesized from 2-quinolinecarbaldehyde and tolyl magnesium bromide in 89% yield, according to Uenishi's procedure,[15] and quantitatively converted into (2-quinolyl) tolyl ketone (QTK, **2**),[14a,16] by oxidation with MnO_2 (Scheme 2).[17]

QTK **2** was then treated with lithium diisopropylamide (LDA) or lithium tetramethylpiperidide (LTMP) and reacted with Merrifield resin at −78 °C to give the solid-supported Merrifield-QTK (**3**) (Scheme 3). Unluckily, a scarce

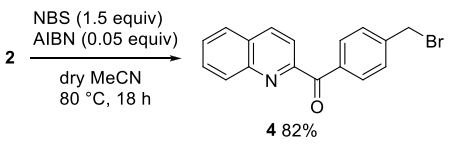
Scheme 3. Synthesis of Merrifield-QTK (3)



functionalization of the resin (23−42% loading, by elemental analyses) was observed, and high amounts of unreacted **2**[18] were recovered. These unsatisfactory results could be ascribed to the high delocalization of the negative charge in the carbanion intermediate, obtained by deprotonation of **2**, likely responsible for difficult interactions with the resin and/or unfavorable side reactions.

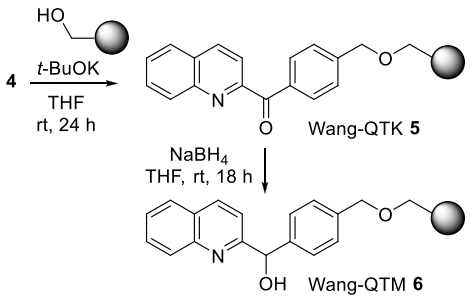
On this ground, attention was devoted to other resins: in particular the Wang resin, bearing a hydroxybenzyl moiety, was the reagent of choice. A simple approach to the supported system could involve the treatment of the Wang resin with the bromomethyl ketone **4**, to generate an ether functionality (see Figure 1, with Z = CH_2O). The (4-bromomethylphenyl) (2-quinolyl) ketone (QTK-Br, **4**) was synthesized from **2** in 82% yield by treatment with *N*-bromosuccinimide (NBS) (Scheme 4).

Scheme 4. Synthesis of (4-bromomethylphenyl)(2-quinolyl)methanone (4)



The following reaction of **4** with the Wang resin (substitution 2.53 mmol/g) was performed in tetrahydrofuran as solvent, to favor the swelling of the resin, in the presence of *t*-BuOK at room temperature. Wang-QTK (**5**) was isolated by filtration and washed with water and THF to remove the salts and unreacted **4**, and the following reduction with $NaBH_4$ afforded Wang-QTM (**6**) quantitatively (Scheme 5).

Scheme 5. Synthesis of Wang-QTM (6)



The reaction conditions for the synthesis of **5** were carefully explored, particularly the kind of base and solvent employed, and satisfactory results with a loading of ca. 90% were obtained performing two consecutive functionalizations on the same resin (see the Experimental Section). The final reduction step allowed a complete recovery of the supported reagent, without significant loading change.

From a qualitative point of view, the resin functionalization was evaluated via IR spectroscopy. The comparison of the IR spectra of Wang resin and Wang-QTK (**5**) showed a significant decrease of the strong absorption band at 3359 cm^{-1},

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ACS Omega XXXX, XXX, XXX−XXX

associated with the OH stretching in the Wang resin, and the appearance of a new band at 1659 cm^{-1} for the carbonyl absorption in compound **5**, diagnostic for the resin functionalization. The conversion of **5** into **6** was confirmed by the disappearance of the latter band, with a concomitant increase of the OH stretching band at 3364 cm^{-1} (see the Supporting Information, Figure S1, IR spectra b and c).

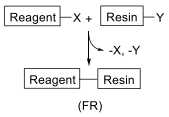
A quantitative evaluation of the grafting of **4** on the resin support was performed via elemental analyses (Table 1).

Table 1. Elemental Analyses of Wang Resin and Functionalized Wang Resins

entry	supported reagent	N (%)	C (%)	H (%)	estimated loading (L), %
1	Wang[a] (2.53 mmol/g)		84.60	7.35	
2	Wang-QTK (1st funct)	1.31	82.30	6.86	60[b]
3	Wang-QTK (2nd funct)	1.97	83.23	6.70	90[b]
4	Wang-QTM	1.92	82.61	6.73	88[c]

[a]Minimal formula calculated from elemental analysis: $C_{28}H_{29}O_2$. [b]Estimated from the ratio of the percentage of nitrogen determined via elemental analysis in the functionalized resin and the calculated percentage of nitrogen for the totally functionalized resin Wang-QTK (minimal formula $C_{45}H_{40}NO_3$, N 2.18%, C 84.08%, H 6.27%). [c]Estimated from the ratio of the percentage of nitrogen determined via elemental analysis in the functionalized resin and the calculated percentage of nitrogen for the totally functionalized resin Wang-QTM (minimal formula $C_{45}H_{42}NO_3$, N 2.17%, C 83.82%, H 6.57%).

From the data of loading (L), a calculation for estimating the formula weight for the functionalized resin (FW_{FR}) was proposed in eq 1:



$$FW_{FR} = [MW(Reagent) + FW(Resin)].L + FW(ResinY).(1 - L) \quad (1)$$

where MW(Reagent) and FW(Resin) are the residual molecular weight and molecular formula of the reagent and resin, respectively, after reacting group removal, while FW(ResinY) is the formula weight of the unreacted resin.

From the experimental viewpoint, considering the loading, the equivalent weight (EW_{FR}) of the functionalized resin has been calculated by eq 2 to evaluate the amount of functionalized resin corresponding to 1 equiv of supported reagent to apply in the reaction:

$$EW_{FR} = \frac{FW_{FR}}{L} \quad (2)$$

For Wang-QTK (**5**) and Wang-QTM (**6**), the 90% and 88% loading allows an estimation of, respectively, an FW_{FR} of 616.0 and 612.8 g/mol corresponding to an EW_{FR} of 684.4 and 696.4 g/equiv (lower loading is responsible for a higher EW_{FR}; see the Supporting Information).

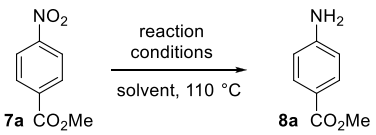
Before applying Wang-QTM (**6**) as reducing agent, its stability was tested by heating the resin overnight in toluene/THF[19] at 110 °C. In these reaction conditions, commonly applied in the reduction processes, the supported reagent appeared perfectly stable (no changes were observed in the IR spectrum and via elemental analysis).

Then, with Wang-QTM in hand, the reduction of nitroarenes was investigated. The stoichiometry of the thermal reduction of electron-poor nitroarenes required a 3:1 ratio PQM/$ArNO_2$ and heating at 70−110 °C for 14−72 h.[1d] Then, the behavior of resin **6** was studied with methyl 4-nitrobenzoate (**7a**) as the substrate. By comparison, the reduction of **7a** with PQM in toluene at 110 °C was studied first and was completed in 18 h, either with or without AcOH, leading to aniline **8a** in 71% and 93% yields, respectively, with a better result in the absence of acid catalysis (Table 2, entries 1 and 2; see the Supporting Information). Using Wang-QTM (**6**), in toluene/THF 1:1 as solvent, higher amounts of **6** (ca. 6−7 equiv) were employed to favor the process, because of the heterogeneous conditions. The reaction was very slow; however, after 4 days at 110 °C, a total conversion of **7a** was observed, and compound **8a** was recovered in 86% yield by resin filtration and evaporation of the solution (Table 2, entry 3). The recovered Wang-QTK (**5**) was then reduced to Wang-QTM (**6**) with $NaBH_4$ and applied again in the reduction of nitro ester **7a** to evaluate the turnover. Unfortunately, a significant decrease in the resin efficiency already at the second cycle was observed, with only partial conversion of **7a** into **8a** (^{1}H NMR, entries 4 and 5, Table 2).

Nevertheless, being reminiscent of the reactivity of PQM [and phenyl (2-quinolyl) ketone, PQK] as organocatalyst in conjunction with $NaBH_4$, which requires minor amounts of reducing agent and lower reaction times,[2] the use of Wang-QTM (**6**) [or Wang-QTK (**5**)] and $NaBH_4$ in the organocatalyzed nitroarene reduction was then explored.

The treatment of 4-nitroaniline (**7b**) gave rise to a clean reaction, and *p*-phenylendiamine (**8b**) was isolated in 74% yield (Table 3, entry 1), after water addition, resin filtration, and extraction.[20] Moreover, the use of recovered **6** (up to the

Table 2. Thermal Reactions of PQM and Wang-QTM (6) with 7a



entry	reducing agent	solvent	AcOH	time (h)	conversion[a] (%)	yield[b] (%)
1	PQM (3.1 equiv)	toluene	20 mol %	18	100	71
2	PQM (3.1 equiv)	toluene		18	100	93
3	Wang-QTM (**6**); 1st cycle (6 equiv)	toluene/THF 1:1		96	100	86[c]
4	Wang-QTM (**6**); 2nd cycle (6 equiv)	toluene/THF 1:1		96	84	ca. 80[a]
5	Wang-QTM (**6**); 3rd cycle (6 equiv)	toluene/THF 1:1		104	75	ca. 70[a]

[a]Determined via ^{1}H NMR analysis. [b]Isolated yields. [c]Compound **8a** was recovered by filtration.

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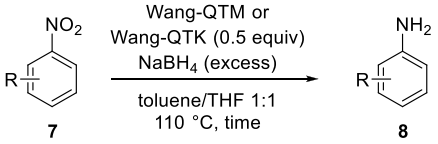
Table 3. Organocatalyzed Nitroarene Reductions with Wang-QTM/Wang-QTK: Synthesis of Anilines 8



7 8

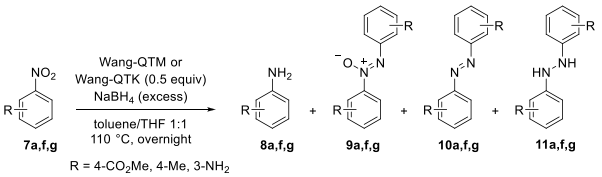
entry	R	time (h)	conversion[a] (%)	yield[b] (%)
1	**7b** (R = 4-NH_2)	14	100	74
2	**7c** (R = 2-NH_2)	20	100	96
3	**7d** (R = 2-Cl)	24	50	ca. 50[a]
4	**7e** (R = 4-OMe)	14	100	71

[a]Determined via ^{1}H NMR analysis. [b]Isolated yields.

fourth cycle) showed no significant changes in the reaction outcomes. Also, 2-nitroaniline (**7c**) was totally converted after 20 h into *o*-phenylendiamine (**8c**), isolated in 96% yield (Table 3, entry 2). Unfortunately, in these cases only partial conversions of the starting material were observed when the recycled resin was used, even for longer reaction times (20−48 h). By heating 1-chloro-2-nitrobenzene (**7d**) for 24 h in the above conditions only a 50% conversion of **7d** into 2-chloroaniline (**8d**) was detected (Table 3, entry 3) without any improvement by heating the reaction mixture for 48 h. On the other hand, 4-nitroanisole (**7e**) was totally reduced in 14 h to 4-anisidine (**8e**), isolated in 71% yields (Table 3, entry 4), but partial conversions of the starting material were observed when the recycled resin was applied.

Conversely, when **7a** was heated overnight with **5** or **6** (ca. 0.5 equiv of reducing agent) in toluene/THF 1:1 at 110 °C in the presence of an excess of $NaBH_4$ (molar ratio 1:4), a very complex reaction mixture containing aniline **8a** and different condensation products (^{1}H NMR) was obtained (Scheme 6).

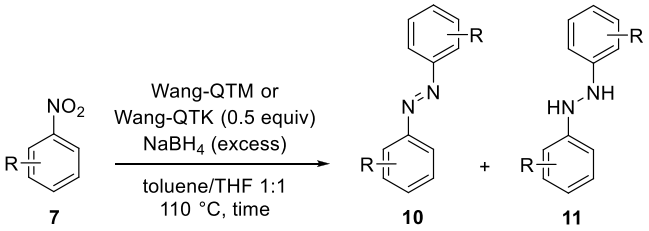
Scheme 6. Organocatalyzed Reductions of Nitroarenes 7a, 7f, and 7g with Wang-QTM/Wang-QTK



Analogous results were observed with 4-nitrotoluene (**7f**) and 3-nitroaniline (**7g**): in these cases the starting material was completely consumed, but mixtures of anilines **8f** and **8g** and azo and hydrazo derivatives **10f**, **10g**, **11f**, and **11g** were formed (Scheme 6), with ratios **8f**/**10f**/**11f** and **8g**/**10g**/**11g** ca. 1/2.5/3 and 1/1.6/0.5, respectively (^{1}H NMR). No significant changes were detected operating for longer reaction times.

The above results match with those obtained using PQM as organocatalyst,[2] albeit with significant benefits thanks to an easier recovery of the reducing agent as well as the aniline products. However, as previously observed, in these conditions the aniline formation is limited to a few substrates (in general holding electron-donating substituents),[21] able to follow the direct route in nitroarene reduction (see Scheme 1), while most nitro derivatives showed a different reactivity, according to a commonly preferred condensation pathway (see Table 4).

Table 4. Organocatalyzed Nitroarene Reductions with Wang-QTM/Wang-QTK: Synthesis of Azo and/or Hydrazo Derivatives 10 and 11



7 10 11

entry	R	time (h)	conversion[a] (%)	yield[b] (%)
1	**7h** (R = H)	24	100	**11h** 96
2	**7i** (R = 3-Cl)	17	100	**11i** 98
3	**7j** (R = 4-Cl)	17	100	**11j** 92
4	**7k** (R = 2-CN)	24	100	**11k** 74 (R = 2-$CONH_2$)
5	**7l** (R = 3-CN)	17	100	**11l** 92
6	**7m** (R = 4-CN)	24	100	**11m** 85
7	**7n** (R = 3-COMe)	15	100	**10n**/**11n** (3.5:1)[c] 98 [R = CH(OH)Me]
8	**7n** (R = 3-COMe)	24	100	**10n**/**11n** (1:1)[c] 97 [R = CH(OH)Me]
9	**7n** (R = 3-COMe)	72	100	**10n**/**11n** (1:10)[c,d] 97 [R = CH(OH)Me]
10	**7o** (R = 4-COMe)	15	100	**10o** 98 [R = CH(OH)Me]
11	**7o** (R = 4-COMe)	24	100	**10o**/**11o** (3:1)[c,e] 92 [R = CH(OH)Me]
12	**7p** (R = 3-CHO)	24	100	**10p**/**11p** (1:5)[c] 92 (R = CH_2OH)
13	**7q** (R = 4-CHO)	24	100	**10q**/**11q** (1:2)[c] 85 (R = CH_2OH)
14	**7r** (R = 2-CHO)	24	100	complex mixture

[a]Determined via ^{1}H NMR analysis. [b]Isolated yields. [c]The azo/idrazo ratio was determined via ^{1}H NMR analysis. [d]After the acquisition of the ^{13}C NMR spectrum (15 h), a partial oxidation into the azo-alcohol **10n** was observed (ratio **10n**/**11n** ca. 1:5). [e]Operating for 72 h, a further conversion into **11o** was observed (ratio **10o**/**11o** ca. 1:3), but a more complex reaction mixture was obtained.

In fact, when nitrobenzene (**7h**) was heated in the above conditions for 24 h, the starting material was totally converted into the hydrazo derivative **11h**, isolated in 96% yield after resin filtration and extraction (Table 4, entry 1). Also, 1-chloro-3-nitrobenzene (**7i**) and 1-chloro-4-nitrobenzene (**7j**), after heating for 17 h, were exclusively transformed into hydrazo compounds **11i** and **11j**, recovered in 98% and 92% yields (Table 4, entries 2 and 3).

A peculiar behavior was observed for 2-nitrobenzonitrile (**7k**) (Table 4, entry 4). The hydrazo-amide **11k** was obtained in 74% yield after 24 h of heating and a total conversion of the starting material, likely via hydrolysis of the CN group. However, the CN group of *meta* and *para* isomers **7l** and **7m** was perfectly stable, and hydrazo-nitriles **11l** and **11m** were isolated in 92% and 85% yields, respectively (Table 4, entries 5 and 6).

When the above protocol was applied to carbonyl derivatives, the first reduction step involved C═O conversion to the corresponding alcohol function. Starting from 3-nitroacetophenone **7n**, different mixtures of azo and hydrazo alcohols **10n** and **11n** were recovered, depending on reaction times (Table 4, entries 7−9). The failure in the isolation of pure hydrazo alcohol **11n** was likely related to its facile oxidation to the azo derivative **10n**, as reported in the literature

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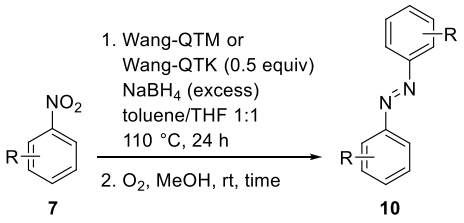
ACS Omega XXXX, XXX, XXX−XXX

for electron-rich hydrazo compounds.[8a] Indeed, the **10n**/**11n** mixture (ratio 1:10) obtained after 72 h of heating, was converted into an almost 1:1 mixture after 3 weeks at 4 °C. A similar behavior was observed for 4-nitroacetophenone **7o**, transformed into azo- and hydrazo-alcohols **10o** and **11o**. By heating at 110 °C for 15 h, the azo derivative **10o** was quantitatively recovered as the sole reaction product (Table 4, entry 10). After 24 h of heating, a 3:1 mixture of **10o** and **11o** was formed (Table 4, entry 11), but prolonged reaction times (72 h) led to a further increase of **11o** as well as the formation of complex reaction crudes. Similarly, 3- and 4-nitrobenzaldehydes **7p** and **7q** were converted into azo- and hydrazo-alcohols **10p**, **10q**, **11p**, and **11q**, while *ortho*-nitrobenzaldehyde (**7r**) led to a complex reaction mixture (Table 4, entries 12−14). As previously observed for nitroacetophenones **7n** and **7o**, the easy oxidation of hydrazo-alcohols **11n**−**11q** to the corresponding azo-alcohols **10n**−**10q** (even during workup) was responsible for the recovery of mixtures of azo/hydrazo derivatives.

According to the literature data,[8a] the azo-alcohols **10n**−**10q** were easily isolated in high yields as the sole reaction products by applying the above reduction protocol in association with a following oxidation step, using molecular oxygen (balloon) at room temperature in MeOH for 2 h (Table 5, entries 6−9).

Table 5. Organocatalyzed Nitroarene Reductions with Wang-QTM/Wang-QTK: Synthesis of Azo Derivatives 10



entry	R	time	conversion[a] (%)	yield[b] (%)
1	**7h** (R = H)	24 h	100	92
2	**7i** (R = 3-Cl)	28 days[c]	100	96
3	**7j** (R = 4-Cl)	24 h	100	92
4	**7l** (R = 3-CN)	18 days[c]	100	93
5	**7n** (R = 3-COMe)	2 h	100	98 [R = CH(OH)Me]
6	**7o** (R = 4-COMe)	2 h	100	98 [R = CH(OH)Me]
7	**7p** (R = 3-CHO)	2 h	100	92 (R = CH_2OH)
8	**7q** (R = 4-CHO)	2 h	100	86 (R = CH_2OH)

[a]Determined via ^{1}H NMR analysis. [b]Isolated yields. [c]Comparable results were obtained performing the oxidation step in $CDCl_3$ as the solvent.

Even azo derivatives **10h**−**j** and **10l** were prepared through the above methodology, but the final oxidation of the hydrazoarenes required 24 h for nitro derivatives **7h** and **7j** (Table 5, entries 1 and 3) and very long reaction times for **7i** and **7l** (Table 5, entries 2 and 4). The easier oxidation of 1,2-bis(4-chlorophenyl)hydrazine **11j** (from **7j**) with respect to 1,2-bis(3-chlorophenyl)hydrazine **11i** (from **7i**) could be likely ascribed to the activation of the NH−NH moiety via the electron-donating +M effect of the chlorine atom at the *para*-position. On the whole, these results appear quite interesting because the oxidation of hydrazobenzenes to azo compounds is generally performed with transition metal reagents (as stoichiometric oxidants or catalysts), and only recently, good outcomes were reported via metal-free strategies. For instance, reduced graphene oxide/air,[22] *tert*-BuOK/air,[23] TEMPO/air,[24] NO_x/O_2,[25] TCCA,[26] TBN/air,[27] molecular iodine/air,[28] and HBr/H_2O_2[29] were efficiently applied while the simple use of oxygen in MeCN was ineffective.[27]

When the above reactions were carried out with recycled resin, comparable results were obtained up to the 30th cycle (Table 6), showing a high turnover for the application of Wang-PQM as organocatalyst in the reduction of nitroarenes to azo and hydrazo compounds.

Table 6. Synthesis of Azo and Hydrazo Derivatives 10 and 11: Evaluation of the Resin Recycling

entry	nitroarene	product	resin cycle	yield[a] (%)
1	**7h** (R = H)	**11h**	1st	96
			14th	96
2	**7j** (R = 4-Cl)	**11j**	2nd	92
			18th	91
3	**7k** (R = 2-CN)	**11k** (R = 2-$CONH_2$)	3rd	74
			27th	71
4	**7m** (R = 4-CN)	**11m**	5th	85
			8th	82
5	**7n** (R = 3-COMe)	**10n**/**11n** (1:1)[b] [R = CH(OH)Me]	19th	97
			30th	95
6	**7p** (R = 3-CHO)	**10p**/**11p** (1:7) (R = CH_2OH)	16th	92
			21st	89

[a]Isolated yields. [b]After 24 h of heating.

Control experiments were performed in the same reaction conditions by using $NaBH_4$ as the only reducing agent. Operating in the absence of **6**, less clean reactions were observed for nitriles **7l** and **7m**, but hydrazo compounds **11l** and **11m** were again obtained in high yields after 24 h of heating. By contrast, nitroarenes **7f**, **7h**−**7j**, and **7n**−**7p** reacted more slowly and were converted almost exclusively into the corresponding azoxy derivatives **9**, isolated in high yields (see the Supporting Information).

CONCLUSIONS

The ability of PQMs to organocatalyze the reduction of various nitroarenes in a selective way either to anilines or to azo/hydrazo compounds has been confirmed in this study with key improvement in the use of the resin-supported organocatalyst Wang-QTM or Wang-QTK. This methodology solves the two main drawbacks associated to the application of PQMs in nitroarene reduction, namely, the high amount of reducing agent required (according to the reaction stoichiometry) and the chromatographic separation of reagents and products. With the achievements described in this paper, and the recyclability of the resin shown, the process is now ascribable as one of the most convenient syntheses of azo and hydrazo derivatives via nitro compound reduction.

EXPERIMENTAL SECTION

General. Chemicals were purchased from commercial suppliers and used as received. Melting points were taken on a Stuart Scientific 200 SIMP3 apparatus and are uncorrected. Silica gel plates (Merck F_{254}) and silica gel 60 (Merck, 230−

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ACS Omega XXXX, XXX, XXX−XXX

400 mesh) were used for TLC and flash chromatographies (FC), respectively; petroleum ether (PE) employed for crystallization and chromatographic workup refers to the fraction of bp 30−50 and 40−70 °C, respectively. IR spectra were recorded with a Shimadzu FT-IR 84 00S spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded with Varian Mercuryplus 400 and Varian Inova instruments, operating at 400 and 100 MHz, respectively. Elemental analyses were performed with Thermoscientific FlashSmart elemental analyzer CHNS/O.

Synthesis of (2-Quinolyl)(4-tolyl)methanol (QTM, 1). A 1.0 M solution of 4-tolylmagnesium bromide in THF (33.1 mmol, 33.1 mL) was added dropwise to an ice-cooled solution of 2-quinolinecarbaldehyde (4 g, 25.45 mmol) in anhydrous diethyl ether (300 mL), at such a rate to maintain the internal reaction temperature below 0 °C. At the end of the addition, the mixture was stirred at 0 °C for 30 min and then for 2 h at room temperature, quenched with ice−water (10 mL), and extracted with EtOAc (3× 80 mL). The collected organic phases were washed with water (2× 50 mL) and brine (2× 50 mL) and dried over anhydrous Na_2SO_4. After evaporation of the solvent, the residue was purified by flash chromatography (PE/EtOAc 4:1 v/v) affording compound **1** (R_f = 0.38, 5.64 g, 89%) that was crystallized from *i*-Pr_2O/Et_2O 1:1 v/v, as a white solid, mp 107−108 °C, the identity of which was confirmed by comparison with literature data.[14]

Oxidation of Alcohol 1 to (Quinol-2-yl)(p-tolyl)-methanone (QTK, 2). Activated MnO_2 (1.5 g) was added to a solution of alcohol **1** (1.05 g, 4.2 mmol) in $CHCl_3$ (20 mL), and the mixture was stirred at room temperature for 4 days. Then, filtration on Celite and evaporation of the solution allowed the isolation of QTK (**2**) (1.03 g, 99%), the identity of which was confirmed by comparison with literature data.[14a,16]

Synthesis of [4-(Bromomethyl)phenyl](quinol-2-yl)-methanone (QTK-Br, 4). In a screw-cap Pirex tube, a mixture of ketone **2** (0.247 g, 1 mmol), *N*-bromosuccinimide (0.267 g, 1.5 mmol), and azobisisobutyronitrile (AIBN) (0.008 g, 0.05 mmol) was deaerated by vacuum-nitrogen treatment (3 cycles), added with dry MeCN (5 mL), and heated for 20 h at 80 °C. After solvent evaporation, the reaction crude was subjected to flash chromatography resolution (toluene). The first moving band (R_f = 0.46) led to a 1:15 mixture of QTK-Br and [4-(dibromomethyl)phenyl](quinol-2-yl)methanone (QTK-Br_2) (0.061 g, ca. 15%), as a light yellow solid. ^{1}H NMR ($CDCl_3$) δ: 8.36 (d, J = 8.5 Hz, 1H), 8.26 (d, J = 8.3 Hz, 2H), 8.19 (d, J = 8.5 Hz, 1H), 8.14 (d, J = 8.5 Hz, 1H), 7.92 (d, J = 8.1 Hz, 1H), 7.80 (t, J = 7.2 Hz, 1H), 7.73−7.50 (m, 3H), 6.69 (s, 1H, $CHBr_2$), [4.55 (s, 2H, CH_2Br)].[30]

The second band afforded QTK-Br (**4**) (R_f = 0.33, 0.267 g, 82%), that was crystallized from PE/Et_2O 5:1 as an orange solid, mp = 91−92 °C. IR, ν_{max} (KBr): 3035, 2981, 1663, 1602, 1325, 1159, 923, 765, 602 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 8.35 (d, J = 8.5 Hz, 1H), 8.22 (d, J = 8.3 Hz, 2H), 8.19 (d, J = 8.3 Hz, 1H), 8.12 (d, J = 8.5 Hz, 1H), 7.91 (d, J = 8.0 Hz, 1H), 7.79 (t, J = 7.8 Hz, 1H), 7.66 (t, J = 7.9 Hz, 1H), 7.53 (d, J = 8.2 Hz, 2H), 4.54 (s, 2H). ^{13}C NMR ($CDCl_3$) δ: 193.0 (s), 154.3 (s), 146.6 (s), 142.6 (s), 137.2 (d), 136.0 (s), 132.0 (d), 130.5 (d), 130.2 (d), 128.95 (s), 128.8 (d), 128.6 (d), 127.7 (d), 120.7 (d), 32.4 (t). Anal. Calcd for $C_{17}H_{12}BrNO$: C, 62.60; H, 3.71; N, 4.29. Found: C, 62.25; H, 3.99; N, 4.51.

From the last moving band, unreacted **2** (R_f = 0.20, 0.007 g, 3%) was recovered.

*Synthesis of Resin-Supported Wang-QTK (**5**).* (a) In a screw-cap Pirex tube, Wang resin 2.53 mmol/g (0.395 g, 1 mmol), QTK-Br (**4**) (0.979 g, 3 mmol), and *t*-BuOK (0.224 g, 2 mmol) were degassed by vacuum-nitrogen treatment. Then, dry THF (10 mL) was added, and the mixture was kept for 24 h at room temperature under stirring. The reaction was quenched with water (3 mL), and the solid was filtered and widely washed with H_2O, THF, MeOH, and Et_2O. Wang-QTK (**5**) was isolated by filtration as a pale solid (0.531 g). Anal. Calcd for $C_{45}H_{40}NO_3$: C, 84.08; H, 6.27; N, 2.18. Found: C, 82.30; H, 6.86; N, 1.31. The ratio between the experimental and theoretical nitrogen percentages for Wang-QTK (**5**) allowed estimating a 60% resin loading (see, Table 1).

Unreacted **4** was recovered (0.741 g) by extraction of the aqueous solution with EtOAc (3× 20 mL), drying on anhydrous Na_2SO_4, and solvent evaporation.

(b) Operating as above, the previously functionalized resin **5** (0.531 g) was added with QTK-Br (**4**) (0.326 g, 1 mmol), *t*-BuOK (0.112 g, 1 mmol), and dry THF (10 mL) and stirred at room temperature for 24 h. After workup, Wang-QTK (**5**) was recovered by filtration as a pale solid (0.598 g). IR, ν_{max} (KBr): 3443, 3056, 3022, 2918, 2851, 1659, 1607, 1510, 1452, 1377, 1315, 1242, 1015, 822, 768, 700 cm^{-1}. Anal. Calcd for $C_{45}H_{40}NO_3$: C, 84.08; H, 6.27; N, 2.18. Found: C, 83.23; H, 6.70; N, 1.97. The ratio between the experimental and theoretical nitrogen percentages for Wang-QTK (**5**) allowed estimating a 90% resin loading (see, Table 1).

Unreacted **4** was recovered (0.199 g) by extraction of the aqueous solution, as described before.

Synthesis of Resin-Supported Wang-QTM (6). In a screw-cap Pyrex tube, a suspension of Wang-QTK (**5**) (0.598 g) and $NaBH_4$ (0.302 g, 8 mmol) in THF (14 mL) and MeOH (1 mL) was stirred at room temperature for 18 h. Wang-QTM (**6**) was isolated (0.562 g, 94%) by filtration and washing with H_2O (5 mL), THF (5 mL), MeOH (3× 5 mL), and Et_2O (2× 5 mL) as an ivory solid. IR, ν_{max} (KBr): 3364, 3024, 2920, 2855, 1601, 1510, 1452, 1383, 1242, 1173, 1067, 1015, 824, 760, 700 cm^{-1}. Anal. Calcd for $C_{45}H_{42}NO_3$: C, 83.82; H, 6.57; N, 2.17. Found: C, 82.61; H, 6.73; N, 1.92. The ratio between the experimental and theoretical nitrogen percentages for Wang-QTM (**6**) allowed estimating a 88% resin loading (see, Table 1).

Reduction of Methyl-4-nitrobenzoate (7a) with Wang-QTM (6). In a screw-cap Pyrex tube, a mixture of methyl-4-nitrobenzoate (**7a**) (0.018g, 0.1 mmol) and Wang-QTM (**6**) (0.418 g, corresponding to 0.6 mmol of QTM) was degassed by several vacuum-nitrogen cycles. Toluene (2.5 mL) and freshly distilled THF (2.5 mL) were added, and the mixture was heated at 110 °C for 4 days. The resin (a mixture of **5** and **6**) (0.401 g) was recovered by filtration and washing with distilled THF (3× 5 mL), MeOH (3× 5 mL), and Et_2O (5 mL). Methyl-4-amino-benzoate (**8a**) (0.013 g, 86%) was easily isolated from the mother liquors by evaporation of the solvent. Its identity was confirmed by comparison with an authentic sample.

General Procedure for the Organocatalytic Reduction of Nitroarenes with Wang-QTK (5) or Wang-QTM (6) and $NaBH_4$. In a screw-cap Pyrex tube, nitro compound 7 (0.25 mmol), Wang-QTK (**5**) or Wang-QTM (**6**) (0.09 g, corresponding to 0.13 mmol of QTK/QTM), and $NaBH_4$ (0.038 g, 1 mmol) in toluene (0.5 mL) and THF (0.5 mL) were heated at 110 °C for the reported time. The reaction mixture was quenched with water (3 mL), and the resin was

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recovered by filtration and washed with freshly distilled THF (2× 1 mL) and EtOAc (3× 3 mL). The solution was washed with water (2× 10 mL) and brine (10 mL), and the organic phase was dried on anhydrous Na_2SO_4 and evaporated under reduced pressure to give the reduction product. The resin was further washed using THF (3 mL), MeOH (3× 3 mL), and Et_2O (3× 3 mL), dried under vacuum, and reused for the following reaction.

*Reduction of 4-Nitroaniline (**7b**).* Starting from 4-nitroaniline (**7b**) (0.035 g), after 14 h of heating, *p*-phenylendiamine (**8b**) was recovered (0.020 g, 74%). Its identity was confirmed by comparison with an authentic sample.

*Reduction of 2-Nitroaniline (**7c**).* By heating 2-nitroaniline (**7c**) (0.035 g) for 20 h, *o*-phenylendiamine (**8c**) (0.026 g, 96%) was recovered and its identity confirmed by comparison with an authentic sample.

*Reduction of 1-Chloro-2-nitrobenzene (**7d**).* After heating 1-chloro-2-nitrobenzene (**7d**) (0.039 g) for 24 h, ^{1}H NMR analysis evidenced the formation of a clean 1:1 mixture (0.035 g) of unreacted **7d** and 2-chloroaniline (**8d**) (ca. 50% yield) identified by comparison with an authentic sample.

*Reduction of 4-Nitroanisole (**7e**).* After heating 4-nitroanisole (**7e**) (0.038 g) for 14 h, 4-aminoanisole (**8e**) (0.022 g, 71%) was recovered and its identity confirmed by comparison with an authentic sample.

*Reduction of Nitrobenzene (**7h**).* Starting from nitrobenzene (**7h**) (0.031 g, 0.026 mL), the reaction mixture was heated for 24 h, and hydrazobenzene (**11h**) (0.022 g, 96%)[31] was recovered.

*Reduction of 1-Chloro-3-nitrobenzene (**7i**).* The reaction mixture obtained from 1-chloro-3-nitrobenzene (**7i**) (0.039 g) was heated for 17 h. Workup allowed the recovery of 1,2-bis(3-chlorophenyl)hydrazine (**11i**) (0.031 g, 98%).[32]

*Reduction of 1-Chloro-4-nitrobenzene (**7j**).* The treatment of reaction crude obtained from 1-chloro-4-nitrobenzene (**7j**) (0.039 g), after heating for 17 h, allowed the recovery of 1,2-bis(4-chlorophenyl)hydrazine (**11j**) (0.029 g, 92%).[31]

*Reduction of 2-Nitrobenzonitrile (**7k**).* Starting from 2-nitrobenzonitrile (**7k**) (0.037 g), the reaction mixture was heated for 24 h, and 2,2′-(hydrazine-1,2-diyl)dibenzamide (**11k**) (0.025 g, 74%) was recovered as red-orange crystals, mp 108−109 °C (from diethyl ether/PE). IR, ν_{max} (KBr): 3412, 3323, 3194, 3045, 1660, 1618, 1585, 1543, 1400, 1317, 1258, 748 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 7.36 (d, J = 7.9 Hz, 2H), 7.22 (t, J = 7.7 Hz, 2H), 6.67 (d, J = 8.2 Hz, 2H), 6.63 (t, J = 7.6 Hz, 2H), 6.18−5.22 (vbr s, 6H). ^{13}C NMR ($CDCl_3$) δ: 171.85 (s), 149.3 (s), 132.95 (d), 128.0 (d), 117.4 (d), 116.4 (d), 113.9 (s). Anal. Calcd for $C_{14}H_{14}N_4O_2$: C, 62.21; H, 5.22; N, 20.73. Found: C, 62.53; H, 5.02; N, 20.51.

*Reduction of 3-Nitrobenzonitrile (**7l**).* The treatment of the reaction crude obtained from 3-nitrobenzonitrile (**7l**) (0.037 g), after heating for 17 h, allowed the recovery of 3,3′-(hydrazine-1,2-diyl)dibenzonitrile (**11l**) (0.027 g, 92%) as a yellow oil. IR, ν_{max} (liquid film): 3337, 3055, 2228, 1603, 1584, 1474, 785, 683 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 7.32 (t, J = 7.9 Hz, 2H), 7.15 (d, J = 7.6 Hz, 2H), 7.08 (br s, 2H), 7.03 (m, 2H), 5.89 (br s, 2H). ^{1}H NMR (CD_3OD) δ: 7.30 (t, J = 8.2 Hz, 2H), 7.09−7.01 (m, 6H). ^{13}C NMR (CD_3OD) δ: 151.5 (s), 131.3 (d), 123.2 (d), 120.2 (s), 117.6 (d), 115.4 (d), 113.8 (s).[33] Anal. Calcd for $C_{14}H_{10}N_4$: C, 71.78; H, 4.30; N, 23.92. Found: C, 71.51; H, 4.65; N, 23.78.

*Reduction of 4-Nitrobenzonitrile (**7m**).* By heating 4-nitrobenzonitrile (**7m**) (0.037 g) for 17 h, 4,4′-(hydrazine-1,2-diyl)dibenzonitrile (**11m**) (0.025 g, 85%)[31] was isolated.

*Reduction of 3-Nitroacetophenone (**7n**).* (a) Starting from 3-nitroacetophenone (**7n**) (0.041 g), after 15 h of heating, a mixture of 1,2-bis[3-(1-hydroxyethyl)phenyl]diazene (**10n**) and 1,2-bis[3-(1-hydroxyethyl)phenyl]hydrazine (**11n**) (ratio 3.5:1, ^{1}H NMR) was isolated (0.033 g, 98%). ^{1}H NMR ($CDCl_3$) δ: 7.91 (s, 2H), 7.81 (m, 2H), 7.48 (m, 4H), [7.14 (t, J = 7.8 Hz, 2H)], [6.83 (s, 2H)], [6.78 (d, J = 7.6 Hz, 2H)], [6.71 (m, 2H)], [5.66 (br s, 2H)], 4.99 (q, J = 6.4 Hz, 2H), [4.76 (q, J = 6.4 Hz, 2H)], 2.41 (br s, 2H + 2H), 1.54 (d, J = 6.5 Hz, 6H), [1.41 (d, J = 6.3 Hz, 6H)].[34]

(b) Starting from 3-nitroacetophenone (**7n**) (0.041 g), after 24 h of heating, a 1:1 mixture (^{1}H NMR) of **10n** and **11n** was isolated (0.033 g, 97%).

(c) By heating 3-nitroacetophenone (**7n**) (0.041 g) for 72 h, a 1:10 mixture (^{1}H NMR) of **10n** and **11n** was recovered (0.033 g, 97%). ^{1}H NMR ($CDCl_3$) δ: 7.19 (t, J = 7.8 Hz, 2H), 6.89 (s, 2H), 6.83 (d, J = 7.6 Hz, 2H), 6.76 (m, 2H), 5.66 (br s, 2H), 4.82 (q, J = 6.4 Hz, 2H), 1.99−1.59 (vbr s, 2H), 1.46 (d, J = 6.4 Hz, 6H).[35] ^{13}C NMR ($CDCl_3$) δ: 149.1 (s), 147.3 (s), 129.5 (d), 116.9 (d), 111.4 (d), 109.3 (d), 70.4 (d), 25.0 (q).[35]

*Reduction of 4-Nitroacetophenone (**7o**).* (a) Starting from 4-nitroacetophenone (**7o**) (0.041 g), after 15 h of heating, 1,2-bis[4-(1-hydroxyethyl)phenyl]diazene (**10o**) was isolated as a yellow-orange solid (0.033 g, 98%).[36]

(b) By heating **7o** (0.041 g) for 24 h, a mixture (ca. 3:1, ^{1}H NMR) of **10o** and 1,2-bis[4-(1-hydroxyethyl)phenyl]-hydrazine (**11o**) was isolated as a yellow-orange oil (0.031 g, 92%). ^{1}H NMR ($CDCl_3$) δ: 7.90 (d, J = 8.2 Hz, 4H), 7.52 (d, J = 8.3 Hz, 4H), [7.22 (d, J = 8.5 Hz, 4H)], [6.82 (d, J = 8.3 Hz, 4H)], [5.64 (br s, 2H)], 4.98 (q, J = 6.5 Hz, 2H), [4.81 (q, J = 6.4 Hz, 2H)], 2.21−1.81 (vbr s, 2H + 2H), 1.54 (d, J = 6.5 Hz, 6H), [1.46 (d, J = 6.4 Hz, 6H)].[34]

*Reduction of 3-Nitrobenzaldehyde (**7p**).* The treatment of the reaction crude obtained by heating 3-nitrobenzaldehyde (**7p**) (0.038 g) for 24 h allowed the recovery of a mixture (ratio 1:5, ^{1}H NMR) of 1,2-bis(3-hydroxymethylphenyl)-diazene (**10p**)[37] and 1,2-bis(3-hydroxymethylphenyl)-hydrazine (**11p**)[38] (0.028 g, 92%).

*Reduction of 4-Nitrobenzaldehyde (**7q**).* By heating 4-nitrobenzaldehyde (**7q**) (0.038 g) for 24 h, a mixture (ratio 1:2, ^{1}H NMR) of 1,2-bis(4-hydroxymethylphenyl)diazene (**10q**)[8a,39] and 1,2-bis(4-hydroxymethylphenyl)hydrazine (**11q**) (0.026 g, 85%) was recovered. ^{1}H NMR ($CDCl_3$) δ: [7.91 (d, J = 8.0 Hz, 4H)], [7.51 (d, J = 8.1 Hz, 4H)], 7.21 (d, J = 8.3 Hz, 4H), 6.83 (d, J = 8.0 Hz, 4H), 5.66 (br s, 2H), [4.79 (s, 4H)], 4.57 (s, 4H).[34]

General Procedure for the Organocatalytic Reduction of Nitroarenes with Wang-QTK (5) or Wang-QTM (6)/$NaBH_4$ Followed by Oxidation with O_2. Operating as reported in the previous general procedure, the reaction product, obtained by heating the nitro compound **7** (0.25 mmol) at 110 °C for 24 h, was dissolved in MeOH (10 mL) and kept under stirring for the reported time at room temperature under an O_2 atmosphere (balloon). The corresponding azo derivative was then recovered by solvent evaporation under reduced pressure.

*Reduction of Nitrobenzene (**7h**): Synthesis of Azobenzene (**10h**).* Starting from nitrobenzene (**7h**) (0.031 g, 0.026 mL),

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the recovered hydrazobenzene was stirred for 24 h under an O_2 atmosphere leading to **10h** (0.021 g, 92%).[31]

*Reduction of 1-Chloro-3-nitrobenzene (**7i**): Synthesis of 1,2-Bis(3-chlorophenyl)diazene (**10i**).* The reaction product obtained from 1-chloro-3-nitrobenzene (**7i**) (0.039 g) was kept for 28 days under an O_2 atmosphere to give **10i** (0.030 g, 96%).[36]

*Reduction of 1-Chloro-4-nitrobenzene (**7j**): Synthesis of 1,2-Bis(4-chlorophenyl)diazene (**10j**).* By stirring for 24 h under an oxygen atmosphere, the hydrazo derivative coming from 1-chloro-4-nitrobenzene (**7j**) (0.039 g) was converted into diazene **10j** (0.029 g, 92%).[31]

*Reduction of 3-Nitrobenzonitrile (**7l**): Synthesis of 3,3′-(Diazene-1,2-diyl)dibenzonitrile (**10l**).* By keeping the hydrazo compound obtained from 3-nitrobenzonitrile (**7l**) (0.037 g) in an oxygen atmosphere for 18 days, the diazene **10l** (0.027 g, 93%) was isolated as the sole reaction product.[39]

*Reduction of 3-Nitroacetophenone (**7n**): Synthesis of 1,2-Bis[3-(1-hydroxyethyl)phenyl]diazene (**10n**).* Starting from 3-nitroacetophenone (**7n**) (0.041 g), **10n** was isolated (0.033 g, 98%) after 2 h of stirring under an O_2 atmosphere as an orange oil. IR, ν_{max} (liquid film): 3368, 3075, 2972, 2922, 2851, 1603, 1444, 1144, 1072, 805, 698 cm^{-1}. ^1H NMR ($CDCl_3$) δ: 7.94 (s, 2H), 7.84 (m, 2H), 7.53−7.50 (m, 4H), 5.03 (q, J = 6.5 Hz, 2H), 1.73 (br s, 2H), 1.57 (d, J = 6.5 Hz, 6H). ^{13}C NMR ($CDCl_3$) δ: 152.7 (s), 147.0 (s), 129.3 (d), 128.0 (d), 122.3 (d), 119.4 (d), 70.2 (d), 25.3 (q). Anal. Calcd for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.36. Found: C, 70.93; H, 6.94; N, 10.59.

*Reduction of 4-Nitroacetophenone (**7o**): Synthesis of 1,2-Bis[4-(1-hydroxyethyl)phenyl]diazene (**10o**).* The diazene **10o**[36] was isolated (0.033 g, 98%) after 2 h of stirring under an O_2 atmosphere, from 4-nitroacetophenone (**7o**) (0.041 g).

*Reduction of 3-Nitrobenzaldehyde (**7p**): Synthesis of 1,2-Bis(3-hydroxymethylphenyl)diazene (**10p**).* Starting from 3-nitrobenzaldehyde (**7p**) (0.038 g), diazene **10p** (0.028 g, 92%) was isolated after 2 h of stirring under an O_2 atmosphere.[37]

*Reduction of 4-Nitrobenzaldehyde (**7q**): Synthesis of 1,2-Bis(4-hydroxymethylphenyl)diazene (**10q**).* From 4-nitrobenzaldehyde (**7q**) (0.038 g), after 2 h of stirring under an O_2 atmosphere, **10q** (0.026 g, 86%) was recovered.[8a,39] ^1H NMR (CD_3OD) δ: 7.89 (d, J = 8.4 Hz, 4H), 7.53 (d, J = 8.5 Hz, 4H), 4.69 (s, 4H). ^{13}C NMR (CD_3OD) δ: 151.8 (s), 144.8 (s), 127.1 (d), 122.4 (d), 63.2 (t).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c04196.

Some experimental details, IR spectra of solid-supported derivatives, ^1H NMR spectra of known synthesized compounds, and ^1H and ^{13}C NMR spectra of new products (PDF)

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Notes

The authors declare no competing financial interest.

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(17) QTM (**1**) was tested as a reducing agent for nitroarenes in the same reaction conditions applied for PQM (see ref 1d), and no significant changes were observed (see the Supporting Information).

(18) Operating with LDA, alcohol **1** was isolated from the reaction mixture, via reduction of **2**.

(19) The system toluene/THF was the solvent of choice to favor the resin swelling and to guarantee the required reaction temperature.

(20) The use of minor amounts of $NaBH_4$ (2−3 equiv) and/or shorter reaction times (8 h) resulted in a partial conversion of the starting material and/or lower yields.

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