


 Cite this: *RSC Adv.*, 2021, 11, 6776

t-BuOK mediated oxidative coupling amination of 1,4-naphthoquinone and related 3-indolynaphthoquinones with amines†

 Yu Dong,^a Ting Mei,^a Qi-Qi Luo,^a Qiang Feng,^a Bo Chang,^a Fan Yang,^a Hong-wei Zhou,^a Zhi-Chuan Shi,^b Ji-Yu Wang^b and Bing He^{*a}

The transition-metal free amination of 1,4-naphthoquinone and related 3-indolynaphthoquinones with amines, such as various (hetero)aromatic amine and aliphatic amine via *t*-BuOK-mediated oxidative coupling at room temperature has been developed. This reaction provides efficient access to the biologically important and synthetically useful 2-amino-1,4-naphthoquinones and 2-amino-3-indolynaphthoquinones with good yields under mild conditions. The present protocol is simple, practical and shows good functional group tolerance. In addition, the obtained 2-amino-3-indolynaphthoquinones were further transformed to synthesize polycyclic N-heterocycles.

 Received 9th January 2021
 Accepted 1st February 2021

DOI: 10.1039/d1ra00193k

rsc.li/rsc-advances

Introduction

The quinone scaffold can be found not only in various natural products and pharmaceutical compounds¹ but it is also well-known as a versatile building block extensively applied in organic synthesis and functional materials.² Among the derivatives of quinone, the 2-amino-1,4-naphthoquinone (**I**) moiety is found in a considerable number of natural product antibiotics (Fig. 1).³ The representative compounds include the quinone-fused polycyclic N-heterocycles calothrixin A (antiproliferative and potent antimalarial)⁴ and hygrocins A, isolated during the purification of the immunosuppressive agent rapamycin from *Streptomyces hygroscopicus* ATC25293.⁵ Additionally, 2-amino-1,4-naphthoquinone is also important as an intermediate for the synthesis of biologically active compounds.⁶

2-Amino-1,4-naphthoquinone has demonstrated that the amino group in the naphthoquinone structure can change the electron-accepting capacity and therefore result in increased biological activities.⁷ What's more, this type of compound possesses several interesting biological properties such as antibacterial,⁸ antifungal,⁹ and anticancer activities.¹⁰ Therefore, much effort has been devoted to developing synthetic methods for the construction of 2-amino-1,4-naphthoquinone derivatives. The reaction of amines with 1,4-naphthoquinone derivatives to give 2-amino-1,4-naphthoquinone have been

developed with two general methods. On the one hand, 2-amino-1,4-naphthoquinones are prepared by oxidative addition coupling of amines to naphthoquinones in the presence of catalysts such as CeCl₃·7H₂O,¹¹ FeCl₃,¹² Cu(OAc)₂,¹³ I₂,¹⁴ Au¹⁵ and HClO₄·SiO₂.¹⁶ Wang reported that 2-amino-1,4-naphthoquinones were obtained by combine the nitro reduction with the 1,4-nucleophilic addition of amines to 1,4-naphthoquinones.¹⁷ On the other hand, nucleophilic substitution reactions of 2-halonaphthoquinones,¹⁸ or 2-methoxynaphthoquinone derivatives¹⁹ also can afford 2-amino-1,4-naphthoquinones. The studies reported that the use of water was beneficial, resulting in nucleophilic substitution and addition reactions with quinones.²⁰ The use of a bentonitic clay and ultrasonic irradiation were reported to give moderate to excellent yields of 2-amino-1,4-naphthoquinones.²¹

With the objective of studying concise routes into natural products, their analogues, and polyheteroaromatic systems

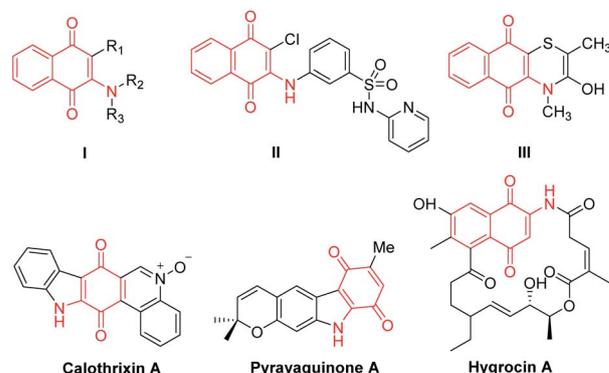


Fig. 1 Representative biological compounds containing 2-amino-quinones skeleton.

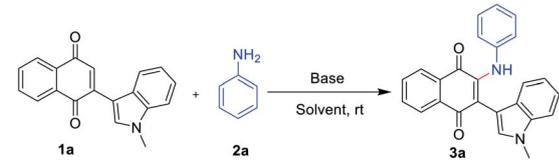
^aCollege of Chemistry and Life Science, Institute of Functional Molecules, Chengdu Normal University, Chengdu, 611130, P. R. China

^bSouthwest Minzu University, Chengdu 610041, P. R. China

^cChengdu Institute of Organic Chemistry, Chinese Academy of Sciences, Chengdu 610041, P. R. China

† Electronic supplementary information (ESI) available. See DOI: 10.1039/d1ra00193k



Table 1 Optimization of the reaction conditions^a


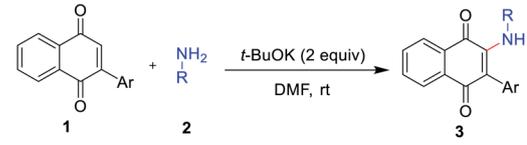
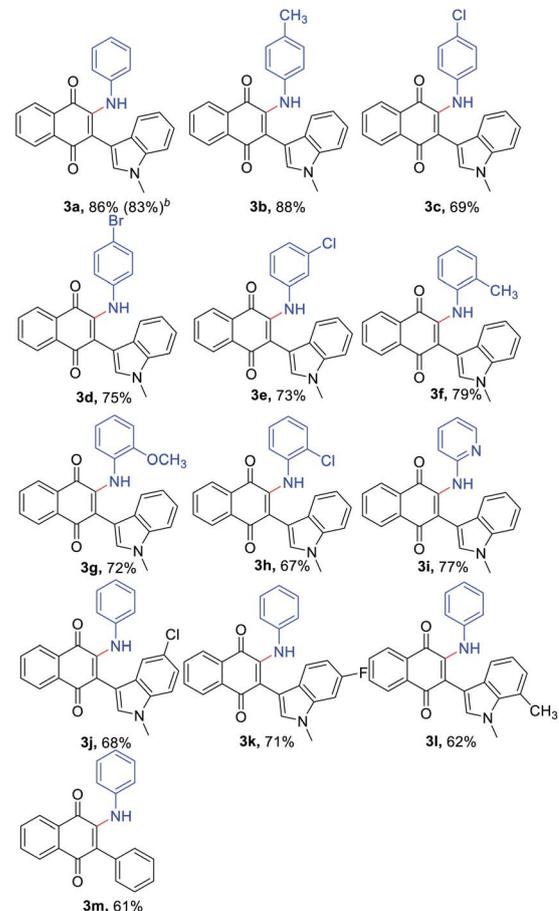
Entry	Base (equiv.)	Solvent (2 mL)	Time (h)	Yield ^b (%)
1	<i>t</i> -BuOK (1.5)	DMF	6	53
2	K ₂ CO ₃ (1.5)	DMF	6	NR
3	NaOH (1.5)	DMF	6	33
4	CH ₃ ONa (1.5)	DMF	6	NR
5	CS ₂ CO ₃ (1.5)	DMF	6	NR
6	Et ₃ N (1.5)	DMF	6	NR
7	DMAP (1.5)	DMF	6	NR
8	<i>t</i> -BuOK (1.5)	DMAC	6	41
9	<i>t</i> -BuOK (1.5)	HFIP	6	NR
10	<i>t</i> -BuOK (1.5)	Dioxane	6	NR
11	<i>t</i> -BuOK (1.5)	DMSO	6	35
12	No	DMF	6	NR
13	<i>t</i> -BuOK (2)	DMF	6	71
14 ^c	<i>t</i> -BuOK (2)	DMF	6	78
15 ^c	<i>t</i> -BuOK (2)	DMF	2	86

^a Reaction conditions: **1a** (0.3 mmol), **2a** (0.45 mmol, 1.5 equiv.), base (1.5–2.0 mmol), solvent (2.0 mL), 2–6 h, air, at room temperature.
^b Isolated yield. ^c **2a** (0.6 mmol, 2 equiv.), DMF = *N,N*-dimethylformamide; DMAP = 4-dimethylaminopyridine; DMSO = dimethyl sulfoxide; HFIP = 1,1,1,3,3,3-hexafluoroisopropanol; NR = no reaction.

with the 2-amino-1,4-naphthoquinone moiety, we initially investigated a synthetic protocol. To the best of our knowledge, an efficient synthesis of 2-amino-1,4-naphthoquinones *via* a *t*-BuOK mediated direct amination has not yet been reported. As always, we have been interested in the synthesis of indolynaphthoquinones and related derivatives. In consideration of the important pharmaceutical applications of the unique 2-amino-1,4-naphthoquinones structural motif, we report herein a simple and practical method for the synthesis of 2-amino-1,4-naphthoquinones and 2-amino-3-indolynaphthoquinones by the *t*-BuOK mediated oxidative coupling amination of 1,4-naphthoquinone and related 3-indolynaphthoquinones with amines.

Results and discussion

Our investigation to explore amination began with the reaction of indolynaphthoquinone (**1a**) and aniline (**2a**) (see Table 1, as well as Tables S1–S4 in the ESI[†]). The reaction of *t*-BuOK (1.5 equiv.), and DMF (2 mL), at room temperature under air atmosphere, for 6 h (Table 1, entry 1), afforded the desired product **3a** in 53% isolated yield. Encouraged by this result, subsequently, variation of K₂CO₃ to NaHCO₃, KOH, NaOH, CH₃ONa, Cs₂CO₃, Et₃N, or DMAP did not show any improvement (entries 2–7; see ESI[†]). The use of DMF as a solvent was crucial, as the reaction gave poor results in other solvents such

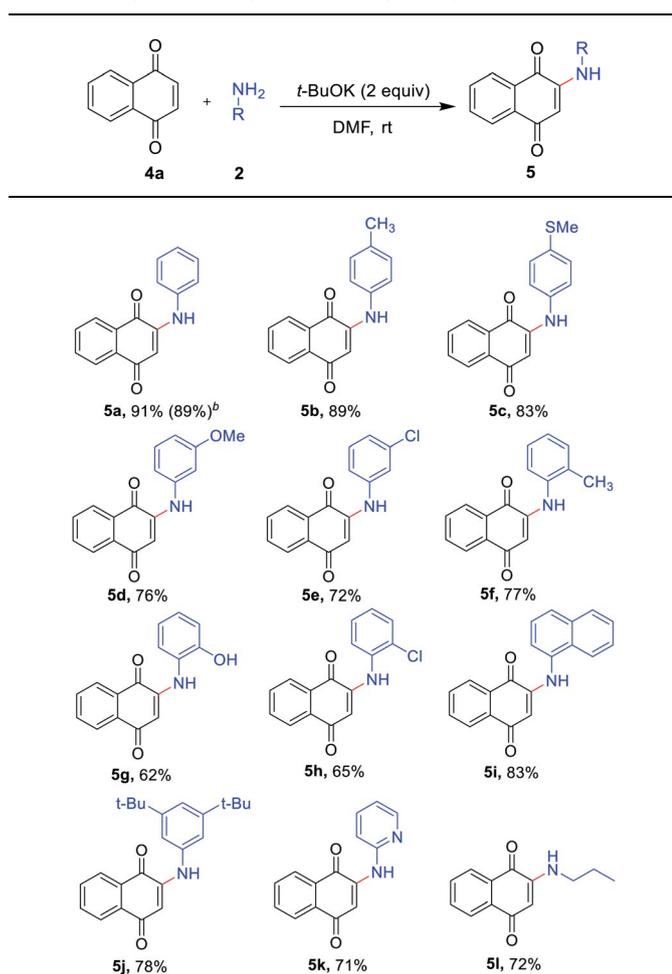
Table 2 Scopes with respect to 3-arylnaphthoquinones with amines^a



^a Reaction conditions: **1** (0.3 mmol), **2** (0.6 mmol), *t*-BuOK (2.0 equiv.), DMF (2.0 mL), 2 h, air, rt. Isolated yield. ^b In a 5 mmol scale.

as DMAC, HFIP, dioxane, DCE, PhCF₃ or DMSO, (entries 8–11; see ESI[†]). The reaction performed under an air atmosphere in the absence of base afforded no product (entry 12), which showed that the base played a pivotal role in obtaining the desired product. Afterward, the amount of *t*-BuOK or **2a** were further screened (entries 13–14; see ESI[†]). It was found that the yields of the product increased with the improved in the amount of *t*-BuOK or **2a**. Therefore, the optimal conditions for the preparation of 2-amino-1,4-naphthoquinones and 2-amino-3-indolynaphthoquinones were obtained: **2a** (2 equiv.), *t*-BuOK (2 equiv.), in DMF (2 mL) at room temperature for 2 h (Table 1, entry 15).

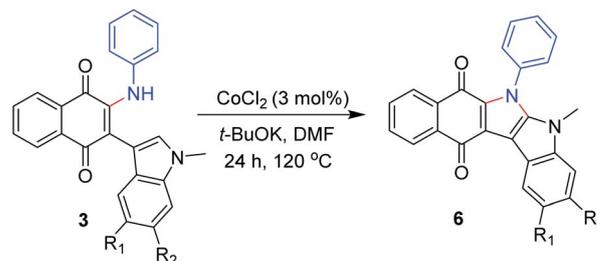
With the optimized reaction conditions in hand, subsequently, a series of substituted indolynaphthoquinones and amines were tested for the amination (Table 2). To find the



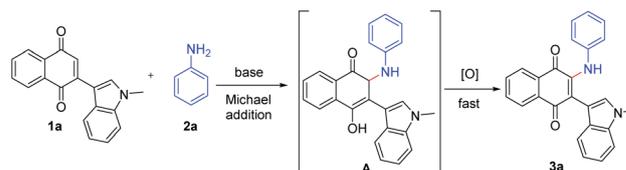
Table 3 Scopes with respect to 1,4-naphthoquinone with amines^a

^a Reaction conditions: 1,4-naphthoquinone (0.3 mmol), 2 (0.6 mmol), *t*-BuOK (2.0 equiv.), DMF (2.0 mL), 2 h, air, rt. Isolated yield. ^b In a 5 mmol scale.

substrate scope leading to 3, a variety of substituted anilines were sequentially coupled with 3-indolynaphthoquinone (1a) afforded the corresponding products 3 in good yields in spite of the electronic nature of aniline (3a–h, Table 2). In a 5 mmol scale reaction, 3a could be obtained in 83% yield, which indicates this transformation could be conducted in a larger scale. It is noteworthy that the valuable groups (F, Cl, Br) could be readily tolerated, which provides an opportunity for further elaboration. Even heteroanilines are well tolerated in this reaction. The use of aminopyridine provides moderate yields of the desired products (3i). The strongly coordinating groups (pyridine), which were employed as reagents for direct C–H functionalization, were fully tolerated with high chemoselectivity and regioselectivity. Next, a variety of indolynaphthoquinones were also examined as substrates for the reaction strategy. The reaction conditions are mild and notably compatible with chloro, fluoro, and methyl on the aryl ring (3j–l, Table 2). In addition, phenylnaphthoquinone was treated with



Scheme 1 R_1 and $\text{R}_2 = \text{H}$ unless otherwise stated. 6a R_1 and $\text{R}_2 = \text{H}$, 81%; 6b $\text{R}_1 = \text{Cl}$, 62%; 6c $\text{R}_2 = \text{F}$, 56%.



Scheme 2 Plausible reaction mechanism.

2a under the optimized reaction conditions for the synthesis of 3m with moderate yields.

The reaction scope was next examined by using different substituted anilines with 1,4-naphthoquinone 4a as a model substrate (Table 3). Various anilines with different electronic and steric nature were tolerated under the reaction conditions to afford 2-amino-1,4-naphthoquinones 5a–5h in moderate to high yields. In a 5 mmol scale reaction, 5a could be obtained in 89% yield, which indicates this transformation could be conducted in a larger scale. Naphthylamine and disubstituted aniline were also suitable reaction partners to give corresponding products 5i and 5j. Especially, heteroanilines and aliphatic amine were amenable under our reaction conditions and provided the expected coupling product 5k and 5l.

Polycyclic N-heterocycles are the key structural element of natural products, drugs and functional materials.²² Therefore, a Co-catalyzed intramolecular cyclization reaction of some of the 2-amino-3-indolynaphthoquinones derivatives 3 allowed the generation of polycyclic N-heterocycles derivatives 6 in moderate yields (Scheme 1).

On the basis of our and previous reports,²³ a possible reaction mechanism was proposed (Scheme 2). Initially, the Michael addition of indolynaphthoquinone (1a) and aniline (2a) in the presence of base gave the intermediate A, which was immediately oxidized to the product 3a by O_2 or the oxidative naphthoquinone.

Conclusions

In conclusion, we have developed a practical and efficient strategy for *t*-BuOK-mediated oxidative coupling amination of 1,4-naphthoquinone and related 3-indolynaphthoquinones with amines at room temperature. A series of 2-amino-1,4-naphthoquinones and 2-amino-3-indolynaphthoquinones were conveniently synthesized in good yields under air



conditions. The reaction took place under mild conditions, displayed excellent functional group compatibility, and did not use metals. In addition, the obtained 2-amino-3-indolynaphthoquinones derivatives were conducted further transformation to synthesize polycyclic N-heterocycles.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We are grateful for the financial support from the Foundation of Applied Basic Research Project of Sichuan Provincial Science and Technology Department (2018JY0262 and 2017JY0177).

Notes and references

- (a) C. Puder, K. Wagner, R. Vettermann, R. Hauptmann and O. Potterat, Terphenylquinone Inhibitors of the Src Protein Tyrosine Kinase from *Stilbella* sp, *J. Nat. Prod.*, 2005, **68**, 323–326; (b) J.-K. Liu, Natural Terphenyls: Developments since 1877, *Chem. Rev.*, 2006, **106**, 2209–2223; (c) C. Asche, Antitumor quinones, *Mini-Rev. Med. Chem.*, 2005, **5**, 449–467.
- (a) A. Skrzyńska, M. Romaniszyn, D. Pomikło and Ł. Albrecht, The Application of 2-Benzyl-1,4-naphthoquinones as Pronucleophiles in Aminocatalytic Synthesis of Tricyclic Derivatives, *J. Org. Chem.*, 2018, **83**, 5019–5026; (b) J. Blom, T. K. Johansen, F. Jensen and K. A. Jørgensen, Dynamic resolution of 2-cyclohexylidene acetaldehydes through organocatalytic dienamine [4+2] cycloaddition, *Chem. Commun.*, 2016, **52**, 7153–7156.
- (a) A. K. Jordão, J. Novais, B. Leal, A. C. Escobar, H. M. dos Santos Júnior, H. C. Castro and V. F. Ferreira, Synthesis using microwave irradiation and antibacterial evaluation of new N,O-acetals and N,S-acetals derived from 2-amino-1,4-naphthoquinones, *Eur. J. Med. Chem.*, 2013, **63**, 196–201; (b) K. W. Wellington and N. I. Kolesnikova, A laccase-catalysed one-pot synthesis of aminonaphthoquinones and their anticancer activity, *Bioorg. Med. Chem.*, 2012, **20**, 4472–4481.
- P. H. Bernardo, C. L. L. Chai, G. A. Heath, P. J. Mahon, G. D. Smith, P. Waring and B. A. Wilkes, Synthesis, electrochemistry, and bioactivity of the cyanobacterial calothrixins and related quinones, *J. Med. Chem.*, 2004, **47**, 4958–4963.
- P. Cai, F. Kong, M. E. Ruppen, G. Glasier and G. T. Carter, Hygroscins A and B, Naphthoquinone Macrolides from *Streptomyces hygroscopicus*, *J. Nat. Prod.*, 2005, **68**, 1736–1742.
- P. A. Aristoff and P. D. Johnson, Synthesis of CBI-PDE-I-dimer, the benzannelated analog of CC-1065, *J. Org. Chem.*, 1992, **57**, 6234–6239.
- M. Aguilar-Martínez, G. Cuevas, M. Jiménez-Estrada, I. González, B. Lotina-Hennsen and N. Macías-Ruvalcaba, An Experimental and Theoretical Study of the Substituent Effects on the Redox Properties of 2-[(R-phenyl)amine]-1,4-naphthalenediones in Acetonitrile, *J. Org. Chem.*, 1999, **64**, 3684–3694.
- A. P. Neves, C. C. Barbosa, S. J. Greco, M. D. Vargas, L. C. Visentin, C. B. Pinheiro, A. S. Mangrich, J. P. Barbosa and G. L. d. Costa, Novel aminonaphthoquinone Mannich bases derived from lawsone and their copper (II) complexes: synthesis, characterization and antibacterial activity, *J. Braz. Chem. Soc.*, 2009, **20**, 712–727.
- A. P. Neves, C. C. Barbosa, S. J. Greco, M. D. Vargas, L. C. Visentin, C. B. Pinheiro, A. S. Mangrich, J. P. Barbosa and G. L. d. Costa, Novel aminonaphthoquinone Mannich bases derived from lawsone and their copper (II) complexes: synthesis, characterization and antibacterial activity, *J. Braz. Chem. Soc.*, 2009, **20**, 712–727.
- A. I. Francisco, A. Casellato, A. P. Neves, J. W. de Mesquita Carneiro, M. D. Vargas, L. do Canto Visentin, A. Magalhães, C. A. Câmara, C. Pessoa, L. V. Costa-Lotufo, J. D. B. Marinho-Filho and M. O. De Moraes, Novel 2-(R-phenyl)amino-3-(2-methylpropenyl)-[1,4]-naphthoquinones: Synthesis, Characterization, Electrochemical Behavior and Antitumor Activity, *J. Braz. Chem. Soc.*, 2010, **21**, 169–178.
- E. Leyva, L. I. López, S. E. Loredó-Carrillo, M. Rodríguez-Kessler and A. Montes-Rojas, Synthesis, spectral and electrochemical characterization of novel 2-(fluoroanilino)-1,4-naphthoquinones, *J. Fluorine Chem.*, 2011, **132**, 94–101.
- E. Leyva, K. M. Baines, C. G. Espinosa-González, D. A. Magaldi-Lara, S. E. Loredó-Carrillo, T. A. De Luna-Méndez and L. I. López, 2-(Fluoro-) and 2-(methoxyanilino)-1,4-naphthoquinones. 2-(Fluoro-) and 2-(methoxyanilino)-1,4-naphthoquinones. Synthesis and mechanism and effect of fluorine substitution on redox reactivity and NMR, *J. Fluorine Chem.*, 2015, **180**, 152–160.
- C. d. S. Lisboa, V. G. Santos, B. G. Vaz, N. C. de Lucas, M. N. Eberlin and S. J. Garden, C–H Functionalization of 1,4-Naphthoquinone by Oxidative Coupling with Anilines in the Presence of a Catalytic Quantity of Copper(II) Acetate, *J. Org. Chem.*, 2011, **76**, 5264–5273.
- B. Liu and S. J. Ji, Facile Synthesis of 2-Amino-1,4-naphthoquinones Catalyzed by Molecular Iodine Under Ultrasonic Irradiation, *Synth. Commun.*, 2008, **38**, 1201–1211.
- C. Jiang and S. Wang, Gold (III)-catalyzed 1,4-nucleophilic addition: facile approach to prepare 2-amino-1,4-naphthalenedione and 6-amino-5,8-quinolinedione derivatives, *Synlett*, 2009, 1099–1102.
- U. Sharma, D. Katoch, S. Sood, N. Kumar, B. Singh, A. Thakur and A. Gulati, Synthesis, antibacterial and antifungal activity of 2-amino-1,4-naphthoquinones using silica-supported perchloric acid (HClO₄-SiO₂) as a mild, recyclable and highly efficient heterogeneous catalyst, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, 2013, **52**, 1431–1440.
- X.-L. Chen, Y. Dong, S. He, R. Zhang, H. Zhang, L. Tang, X.-M. Zhang and J.-Y. Wang, A one-pot approach to 2-(N-substituted amino)-1,4-naphthoquinones with use of nitro



- compounds and 1,4-naphthoquinones in water, *Synlett*, 2019, **30**, 615–619.
- 18 (a) S. N. Falling and H. Rapoport, Application of iminium salts to the synthesis of naphthoquinone mitosene analogs, *J. Org. Chem.*, 1980, **45**, 1260–1270; (b) N. L. Agarwal and W. Schaefer, Quinone chemistry, reaction of 2,3-dichloro-1,4-naphthoquinone with arylamines in pyridine, *J. Org. Chem.*, 1980, **45**, 5139–5143; (c) E. A. Couladouros, Z. F. Plyta and V. P. Papageorgiou, A general procedure for the efficient synthesis of (alkylamino) naphthoquinones, *J. Org. Chem.*, 1996, **61**, 3031–3033; (d) T. Win and S. Bittner, Novel 2-amino-3-(2,4-dinitrophenylamino) derivatives of 1,4-naphthoquinone, *Tetrahedron Lett.*, 2005, **46**, 3229–3231.
- 19 (a) C. A. Camara, A. C. Pinto, M. A. Rosa and M. D. Vargas, Secondary amines and unexpected 1-aza-anthraquinones from 2-methoxylapachol, *Tetrahedron*, 2001, **57**, 9569–9574; (b) A. I. Francisco, M. D. Vargas, J. W. d. M. Carneiro, M. Lanznaster, J. C. Torres, C. A. Camara and A. C. Pinto, General method for the high yield preparation of 2-(4-X-phenylene)amine-1,4-naphthoquinones (X=ferrocenyl, OMe, Me, I, Cl, and NO₂) from 2-methoxy-1,4-naphthoquinone and investigation of H⁺ and Mg²⁺ catalysts with DFT calculations, *J. Mol. Struct.*, 2008, **891**, 228–232.
- 20 J. S. Yadav, B. V. S. Reddy, T. Swamy and K. S. Shankar, Green protocol for conjugate addition of amines to p-quinones accelerated by water, *Monatsh. Chem.*, 2008, **139**, 1317.
- 21 E. Leyva, L. I. López, E. Moctezuma and H. de Lasa, A Bentonitic Clay Assisted Method for the Preparation of 2-(R-Anilino)-1,4-Naphthoquinones, *Top. Catal.*, 2008, **49**, 281.
- 22 (a) R. K. Konidena, W. J. Chung and J. Y. Lee, C1-, C2-, and C3-Modified Carbazole Derivatives as Promising Host Materials for Phosphorescent Organic Light-Emitting Diodes, *Org. Lett.*, 2020, **22**, 2786–2790; (b) D. Bader, J. Fröhlich and P. Kautny, Thienopyrrolo[3,2,1-jk]carbazoles: Building Blocks for Functional Organic Materials, *J. Org. Chem.*, 2020, **85**, 3865–3871.
- 23 (a) Y. Dong, J. Yang, H. Zhang, X.-Y. Zhan, S. He, Z.-C. Shi, X.-M. Zhang and J.-Y. Wang, Cobalt-Catalyzed Cycloamination: Synthesis and Photophysical Properties of Polycyclic N-Heterocycles, *Org. Lett.*, 2020, **22**, 5151–5156; (b) H.-B. Zhang, L. Liu, Y.-J. Chen, D. Wang and C.-J. Li, Synthesis of Aryl-Substituted 1,4-Benzoquinone via Water-Promoted and In(OTf)₃-Catalyzed in situ Conjugate Addition-Dehydrogenation of Aromatic Compounds to 1,4-Benzoquinone in Water, *Adv. Synth. Catal.*, 2006, **348**, 229–235; (c) See ref. 13 and 16.

