RSC Advances

PAPER

View Article Online
View Journal | View Issue

Cite this: *RSC Adv.*, 2023, **13**, 4865

An investigation of the allylation cascade reactions of substituted indigos†

Matthew J. Perry, [a] Anthony C. Willis, [b] John B. Bremner[a] and Paul A. Keller *[a]

In a continuation of the exploration of indigo cascade reactions, a series of –OMe, –Ph, –Br and $-NO_2$ substituted indigos **1a–i** were synthesised to probe electronic effects upon the outcome of allylation cascade reactions. When indigos **1a–i** in the presence of base were reacted with allyl bromide, spiroindolinepyridoindolones **17–25** (36–75%) were obtained as the major products in each case, marking a shift in outcome relative to that previously reported for unsubstituted indigo. In electron-rich derivatives (–OMe, –Ph), *C*-allylspiroindolinepyridoindolediones **26–29** (3–11%) were also isolated, which are most likely formed *via* a Claisen rearrangement of the respective spiroindolinepyridoindolones **18–21**. Additionally, the isolation of diallylbiindolone **16**, oxazinobiindole **30** and *N*,*N*′-diallyl-3,3′-bis(allyloxy) biindole **31** each represented novel polyheterocyclic derivatives, providing intriguing new mechanistic insights, reaction pathways and in the case of **30** the first common heterocyclic skeletal outcome shared in both allylation and propargylation cascade reactions of indigo.

Received 23rd January 2023
Accepted 31st January 2023

DOI: 10.1039/d3ra00481c

rsc.li/rsc-advances

Introduction

Indigo **1** and its derivatives have been the focus of intensive study in recent years due to their presence in biologically active natural products[1–3] and unique photophysical[4] and semiconducting properties.[5,6] The industrial-scale synthesis and high degree of functionality of indigo **1** also make it an ideal target for use as an advanced synthetic building block for the synthesis of more complex heterocycles, as exemplified by the cascade reactions of indigo **1**. Under basic conditions, one-pot reactions of indigo **1** with aziridine,[7] oxirane,[7] allyl[8,9] and propargyl[10,11] halides have provided access to diverse polyheterocyclic architectures with a range of anticancer, antitubercular and antimalarial activities, and materials with high fluorescence quantum yields and ready access to triplet states.

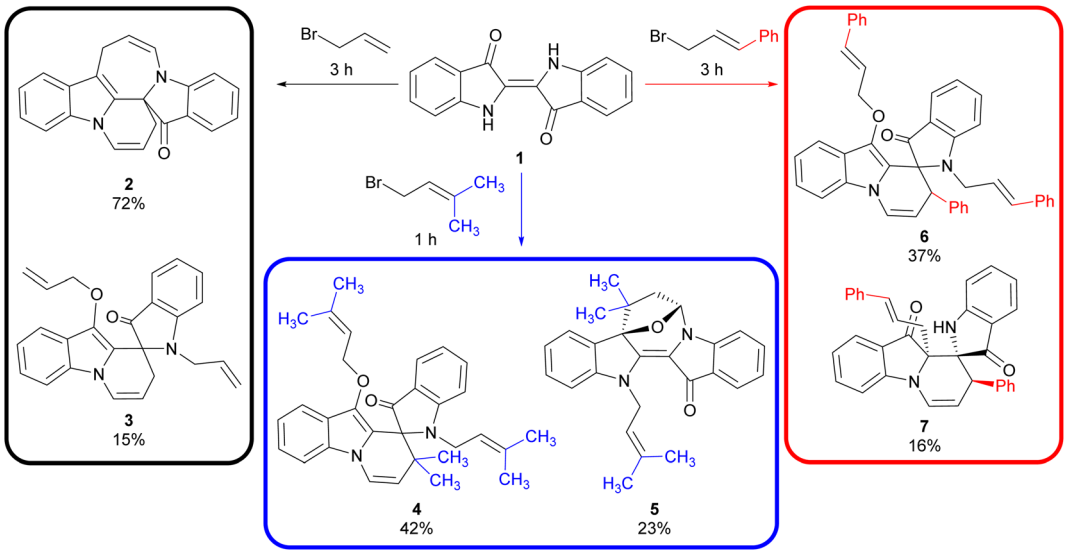
Due to the complex multi-step mechanisms involved in the cascade reactions of indigo **1** and the numerous mechanistic branchpoints available, the ability to accurately predict the outcome of any given cascade reaction has not yet been attained. Minor changes in the cascade reaction conditions were observed to lead to significantly altered outcomes, particularly when substituted electrophiles were employed.[7–11] This was evident in the allylation cascade reactions, where the use of allyl bromide led to the production of pyridoindoloazepinoindolone **2** and spiroindolinepyridoindolone **3** in 72% and 15% yield, respectively (Scheme 1). In contrast, the use of 1-bromo-3-methyl-2-butene led to the synthesis of spiroindolinepyridoindolone analogue **4** (42%) as the major product along with epoxyazepinodiindolone **5** (23%, Scheme 1).[9] Likewise, the use of cinnamyl bromide again produced the equivalent spiroindolinepyridoindolone **6** as the major outcome (37%) in addition to *C*-cinnamylated spiroindolinepyridoindoledione **7** (16%), highlighting the variability of outcome when substituted electrophiles are utilised (Scheme 1).[9]

Although intuitive mechanisms have been proposed to account for the outcomes observed in the cascade reactions of indigo **1**, the isolation of key intermediates and direct evidence to substantiate the reported mechanisms is required. A deeper understanding of these mechanisms could also enable accurate prediction of cascade reaction outcomes and the ability to tune the reaction conditions to favour the formation of specific heterocyclic targets. To this point, all investigations into the cascade reactions of indigo **1** have focused upon changing the nature of the electrophile with no equivalent studies associated with the use of functionalised indigos. The use of indigos substituted with a spectrum of EDGs and EWGs could provide a more thorough understanding of how electronic factors affect key mechanistic branchpoints and provide a further insight into these cascade reactions. Reported herein is the synthesis of a range of substituted indigos, their evaluation in allylation

[a]*School of Chemistry and Molecular Bioscience, Molecular Horizons, and Illawarra Health and Medical Research Institute, University of Wollongong, Wollongong, NSW, 2522, Australia. E-mail: keller@uow.edu.au*

[b]*Research School of Chemistry, Australian National University, Canberra, ACT, 2601, Australia*

† Electronic supplementary information (ESI) available: Full experimental procedures, ^{1}H and ^{13}C NMR spectra of all compounds, structural elucidation of novel heterocyclic motifs and crystallographic data. CCDC 2219386. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d3ra00481c



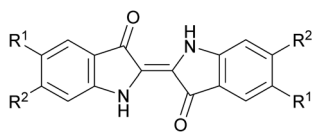
Scheme 1 The cascade reactions of indigo **1** with allyl bromide, 1-bromo-3-methyl-2-butene and cinnamyl bromide electrophiles. Reaction conditions: (i) DMF, N_2, 30 min; (ii) Cs_2CO_3, 4 Å M.S., N_2, 85–88 °C, 30 min; (iii) electrophile, 1–3 h. Note – the relative stereochemistry is shown for compounds **5** and **7**.

cascade reactions, and the mechanistic implications arising from these outcomes.

Results and discussion

The synthesis of substituted indigos

To systematically investigate the use of substituted indigos in the allylation cascade reaction, indigos substituted in the 5,5′- and 6,6′-positions with –OMe, –Br, –Ph and –NO_2 functionalities (Fig. 1) were targeted. The one-pot Baeyer–Drewson indigo synthesis was used due to its procedural simplicity.[12] Bromo- and methoxy-substituted 2-nitrobenzaldehyde starting materials were commercially available, while phenyl-substituted derivatives were prepared *via* a Suzuki coupling of $PhB(OH)_2$ with the respective bromo-derivatives (see ESI,† Section S1.1). The methoxy-, bromo- and phenyl-substituted 2-nitrobenzaldehydes **8a–g** were dissolved in acetone, stirred overnight with 1 M NaOH, the precipitate filtered, rinsed with organic solvents and where necessary recrystallised from ethyl benzoate to yield the respective 5,5′- and 6,6′-dibromo-, diphenyl-, and dimethoxy-indigos **1a–g** in 22–58% yield (Table 1).

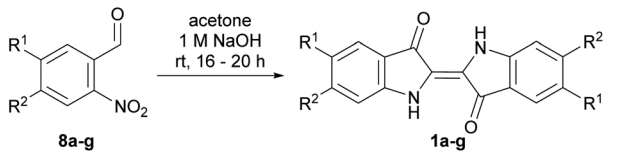


R^1 = OMe, R^2 = H **1a**
R^1 = OMe, R^2 = OMe **1b**
R^1 = H, R^2 = OMe **1c**
R^1 = Ph, R^2 = H **1d**
R^1 = H, R^2 = Ph **1e**
R^1 = Br, R^2 = H **1f**
R^1 = H, R^2 = Br **1g**
R^1 = NO_2, R^2 = H **1h**
R^1 = H, R^2 = NO_2 **1i**

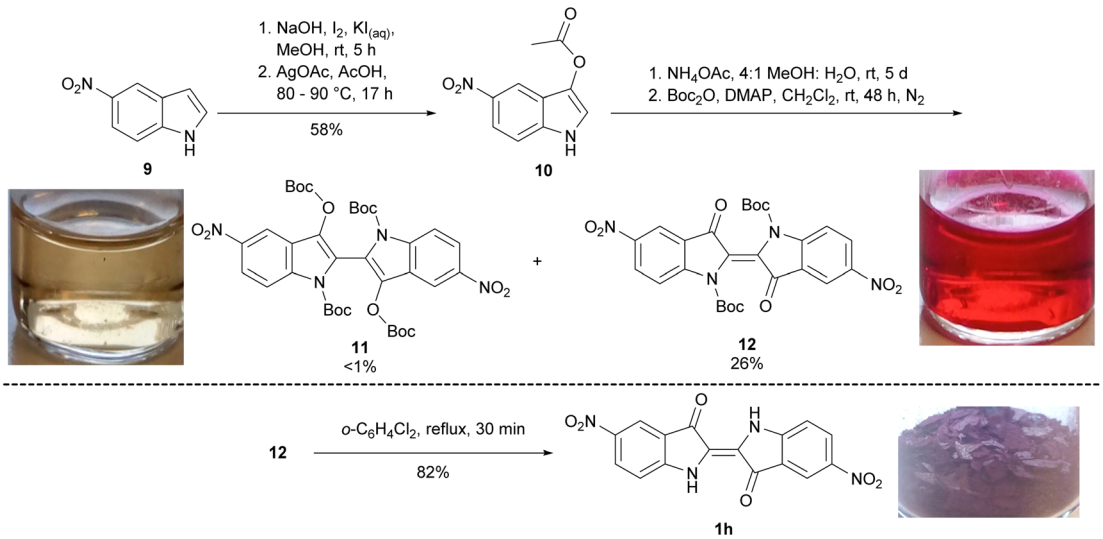
Fig. 1 Substituted indigos targeted for investigation in allylation cascade reactions.

To synthesise 5,5′-dinitroindigo **1i**, a literature procedure[13] was modified, wherein 5-nitroindole **9** was 3-iodinated, and the product converted to 3-acetoxy-5-nitroindole **10** in the presence of AgOAc (58% yield over two steps, Scheme 2). Attempted hydrolysis of 3-acetoxy-5-nitroindole **10** under acidic or basic conditions produced 5,5′-dinitroindigo **1h** as a crude solid which could not be further purified by washing with organic solvents or recrystallisation. Therefore, a known hydrolysis procedure[14] was modified, in which 3-acetoxy-5-nitroindole **10** was dissolved in MeOH and a solution of NH_4OAc in H_2O added and stirred for 5 days. The resulting precipitate was filtered, dried, reacted with Boc_2O and DMAP for 48 h and upon purification, yielded *N*,*N*′,*O*,*O*′-tetraBoc-5,5′-dinitrobiindole-3,3′-diol **11** (<1%) and *N*,*N*′-diBoc-5,5′-dinitroindigo **12** (26%, Scheme 2). Finally, heating *N*,*N*′-diBoc-5,5′-dinitroindigo **12** at reflux in 1,2-

Table 1 The synthesis of methoxy-, phenyl- and bromo-substituted indigos



Entry	R^1	R^2		Time	Yield	
1	OMe	H	**8a**	16 h	**1a**	58%
2	OMe	OMe	**8b**	20 h	**1b**	22%
3	H	OMe	**8c**	20 h	**1c**	30%
4	Ph	H	**8d**	20 h	**1d**	36%
5	H	Ph	**8e**	20 h	**1e**	28%
6	Br	H	**8f**	16 h	**1f**	35%
7	H	Br	**8g**	20 h	**1g**	32%

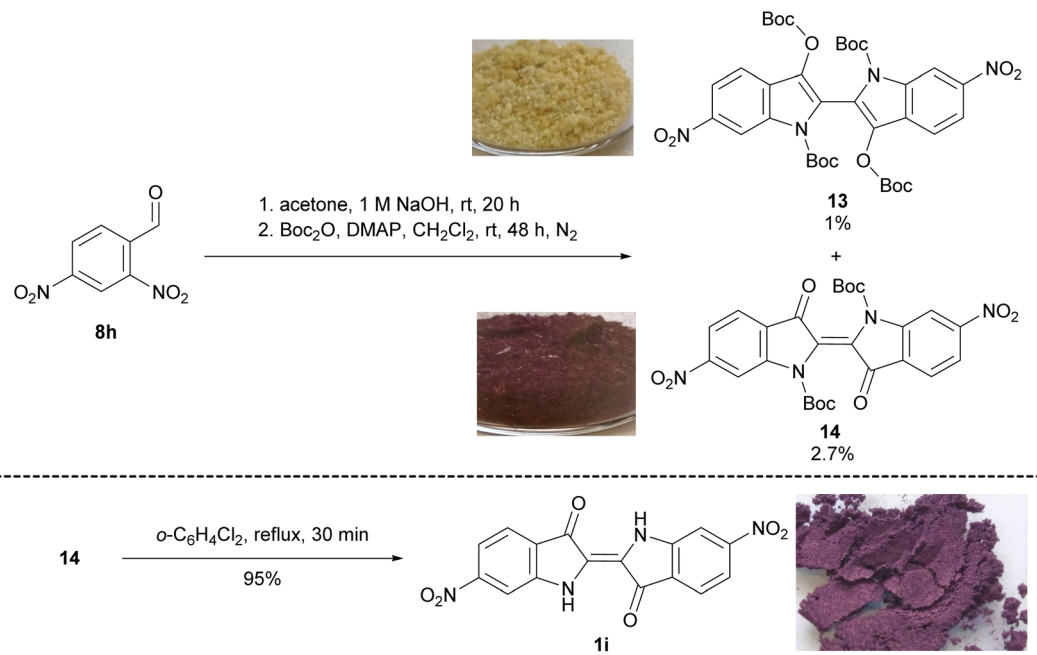


Scheme 2 The synthesis of 5,5′-dinitroindigo **1h**. The image of compound **1h** and solutions of **11** and **12** in CH_2Cl_2 were taken under ambient lighting.

dichlorobenzene enabled thermal Boc-deprotection to yield 5,5′-dinitroindigo **1h** in 82% yield.

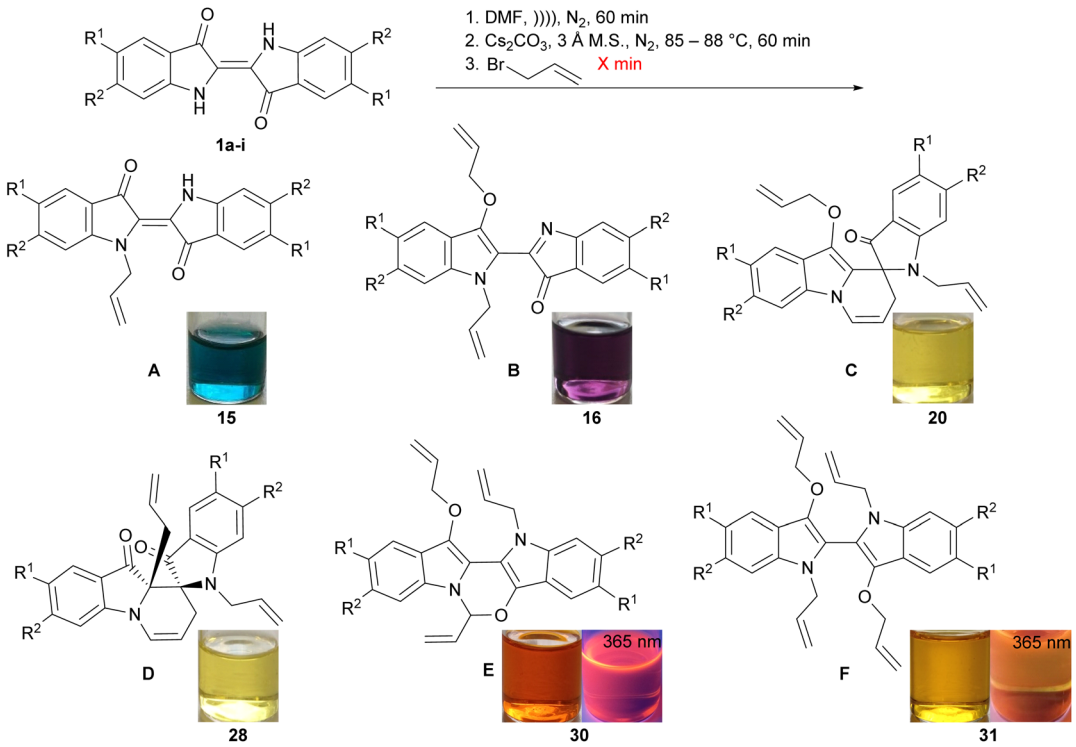
Initial attempts involving the Baeyer–Drewson synthesis with 2,4-dinitrobenzaldehyde **8h** produced 6,6′-dinitroindigo **1i** in poor yield with impurities inseparable by recrystallisation or washing with organic solvents. Therefore, 2,4-dinitrobenzaldehyde **8h** was reacted with acetone and 1 M NaOH for 20 h, the crude indigo was filtered, air-dried and reacted with Boc_2O and DMAP in CH_2Cl_2 for 48 h. Subsequent multiple rounds of column chromatography and recrystallisation yielded *N*,*N*′,*O*,*O*′-tetraBoc-6,6′-dinitrobiindole-3,3′-diol **13** (1%) and *N*,*N*′-diBoc-6,6′-dinitroindigo **14** (2.7%, Scheme 3). Finally, the heating of *N*,*N*′-diBoc-6,6′-dinitroindigo **14** in 1,2-dichlorobenzene at reflux for 30 min furnished 6,6′-dinitroindigo **1i** in excellent yield (95%), partly compensating for the very low yield of **14**. Attempts to optimise the yield of indigo **1i** in the initial step of this reaction were unsuccessful, suggesting an alternative route is required to improve the yield.

The isolation of *N*,*N*′,*O*,*O*′-tetraBoc-dinitrobiindole-3,3′-diols **11** and **13** was unexpected due to the two-electron reduction of the indigo moiety to a leucoindigo required to enable their formation. Initially, the synthesis of **13** (Scheme 3) was thought



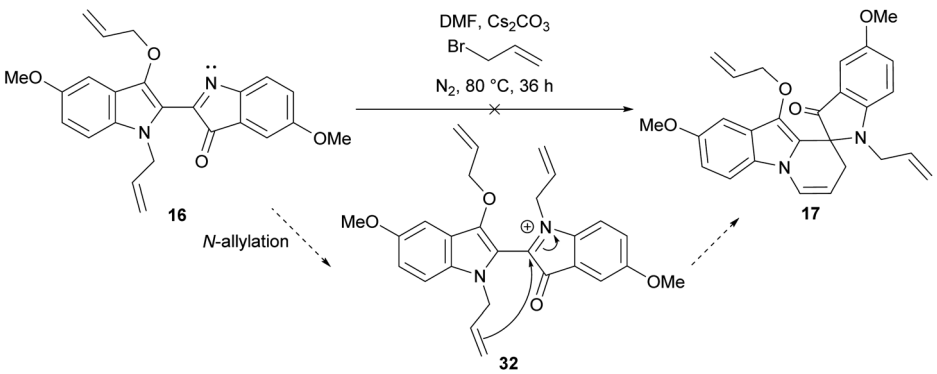
Scheme 3 The synthesis of 6,6′-dinitroindigo **1i**. Images of compounds **13**, **14** and **1i** were taken under ambient lighting.

Table 2 The allylation of substituted indigos. Images of solutions of **15**, **16**, **20**, **28**, **30** and **31** in CH_2Cl_2 were taken under ambient lighting or with 365 nm UV irradiation. Note – the relative stereochemistry is shown for spiroindolinepyridoindoledione **D**

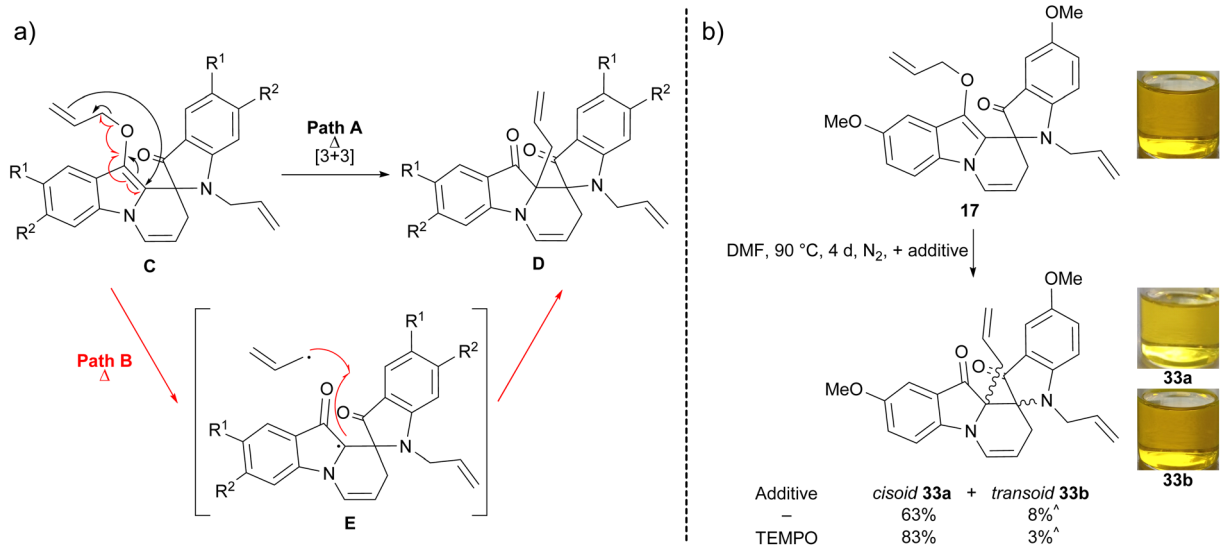


Entry	R^1	R^2		X min	A		B		C		D		E		F	
1	OMe	H	**1a**	2	15	6%	**16**	3%[b]	**17**	37%	—		—		—	
2	OMe	H	**1a**	5	—		**16**	3%[b]	**17**	69%	—		—		—	
3	OMe	OMe	**1b**	60	—		—		**18**	56%	**26**	10%	—		—	
4	H	OMe	**1c**	60	—		—		**19**	43%[c]	**27**	11%[d]	—		—	
5	Ph	H	**1d**	17	—		—		**20**	75%	**28**	3%[b]	—		—	
6	H	Ph	**1e**	45	—		—		**21**	58%	**29**	3%[b]	—		—	
7	Br	H	**1f**	5	—		—		**22**[a]	62%	—		—		—	
8	H	Br	**1g**	60	—		—		**23**	69%	—		—		—	
9	NO_2	H	**1h**	70	—		—		**24**	51%	—		—		—	
10	H	NO_2	**1i**	8	—		—		**25**	36%	—		**30**	13%	**31**	1%

[a] X-ray quality crystals obtained – see ESI, Section S5. [b] Presence of some grease/impurities in sample – <10 mg isolated precluding further purification. [c] Corrected yield (NMR). [d] Small amount of grease present in final sample.



Scheme 4 The proposed mechanism[8] and investigation into the role of diallylbiindolone **16** as an intermediate to spiroindolinepyridoindolone **17**.



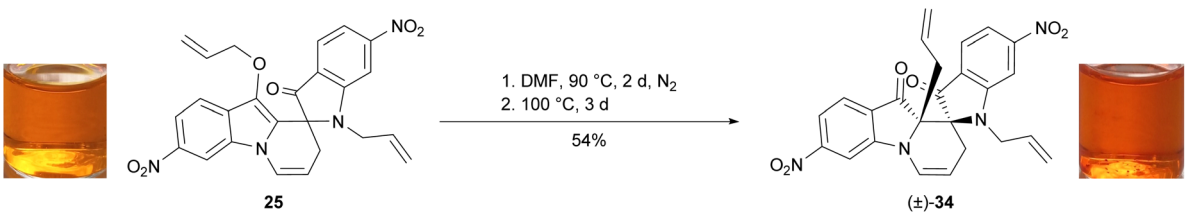
Scheme 5 The (a) proposed mechanism of spiroindolinepyridoindolone **C** conversion to *C*-allylspiroindolinepyridoindoledione **D** *via* a Claisen rearrangement (**Path A**) or radical mechanism (**Path B**) and (b) mechanistic investigation of *C*-allylspiroindolinepyridoindoledione **33a–b** formation. ^ presence of some grease in sample.

to be occurring as a result of disproportionation of the nitrobenzaldehyde **8h** *via* a Cannizzaro reaction,[15] however the isolation of **13** through a different synthetic pathway that did not utilise nitrobenzaldehyde starting materials suggested another mechanism of reduction was contributing to this result. One alternative mechanism of reduction could involve *tert*-butoxide, a by-product of Boc_2O hydrolysis in the Boc-protection reactions. *tert*-Butoxide has been previously observed to reduce Ag(I) and Au(I) to the respective Ag(0) and Au(0) nanoparticles.[16]

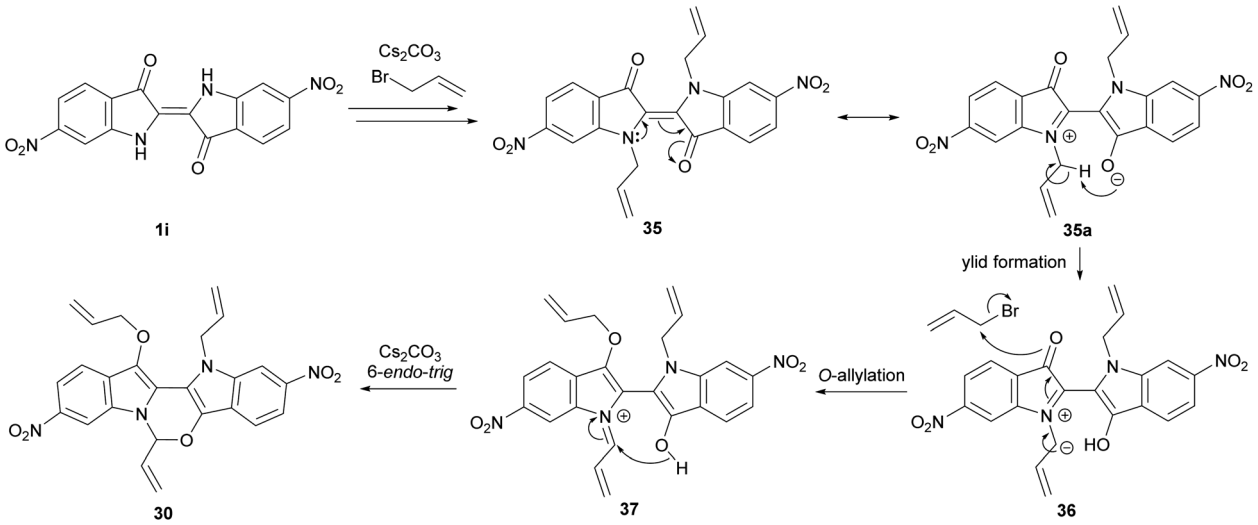
The allylation of substituted indigos

The investigation of the effects of substituted indigos on allylation cascade outcomes (Table 2) began with optimisations using 5,5′-dimethoxyindigo **1a**. Therefore, a suspension of 5,5′-dimethoxyindigo **1a** in DMF was sonicated for 60 min, cannulated into a flask containing pre-dried Cs_2CO_3 and activated 3 Å M.S. and heated at 85–88 °C for 60 min. Treatment with allyl bromide for 2 min followed by reaction workup, two rounds of column chromatography and recrystallisation yielded *N*-allyl-5,5′-dimethoxyindigo **A** (**15**, 6%), diallylbiindolone **B** (**16**, 3%) and spiroindolinepyridoindolone **C** (**17**, 37%, Table 2, entry 1). Repetition of this reaction with allyl bromide until the consumption of the *N*-allyl-5,5′-dimethoxyindigo **15** as determined by TLC analysis (5 min reaction time) led to the isolation of diallylbiindolone **16** in 3% yield and spiroindolinepyridoindolone **17** in an improved yield of 69% (Table 2, entry 2). Application of the optimised reaction conditions to indigos **1b–i** with quenching upon the disappearance of *N*-allylindigos by TLC analysis led to the isolation of spiroindolinepyridoindolones **C** (**18–25**) as the major products in 36–75% yield (Table 2, entry 3–10). In the reactions of 5,5′,6,6′-tetramethoxy-, 6,6′-dimethoxy-, 5,5′-diphenyl- and 6,6′-diphenylindigos **1b–e**, *C*-allylspiroindolinepyridoindolediones **D** (**26–29**) were also isolated in 3–11% yields (Table 2, entry 3–6). The reaction of 6,6′-dinitroindigo **1i** was also observed to generate the novel oxazinodiindole derivative **E** (**30**, 13%) and *N*,*N*′-diallyl-3,3′-bis(allyloxy)biindole **F** (**31**, 1%) as additional minor outcomes (Table 2, entry 10).

The structure of diallylbiindole **16** was confirmed by the presence of strong 2D HMBC and HSQC correlations between the allyl substituents and the indole ring system and a ^{13}C resonance at 156.4 ppm, characteristic of the imine moiety (see ESI,† Section S4.3). The generated spiroindolinepyridoindolones **17–25** showed similar spectral characteristics to those previously reported derivatives,[8,9] with further confirmation provided by NMR analysis and an X-ray crystal



Scheme 6 The synthesis of 6,3′-dinitrospiroindolinepyridoindoledione **34**.

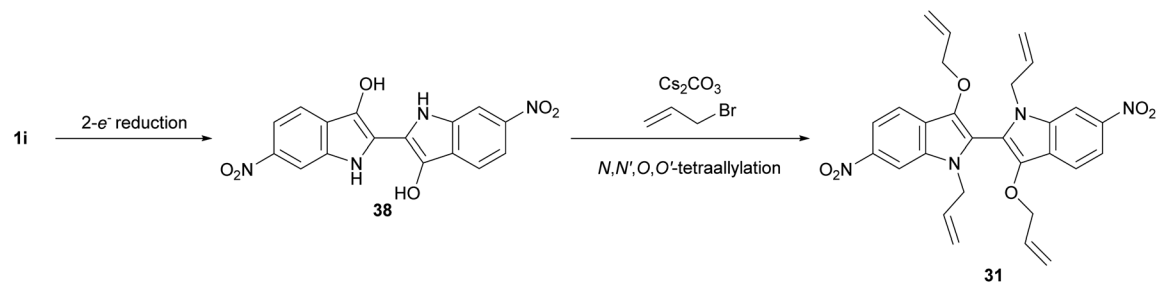


Scheme 7 The proposed mechanism of oxazinodiindole **30** formation.[11]

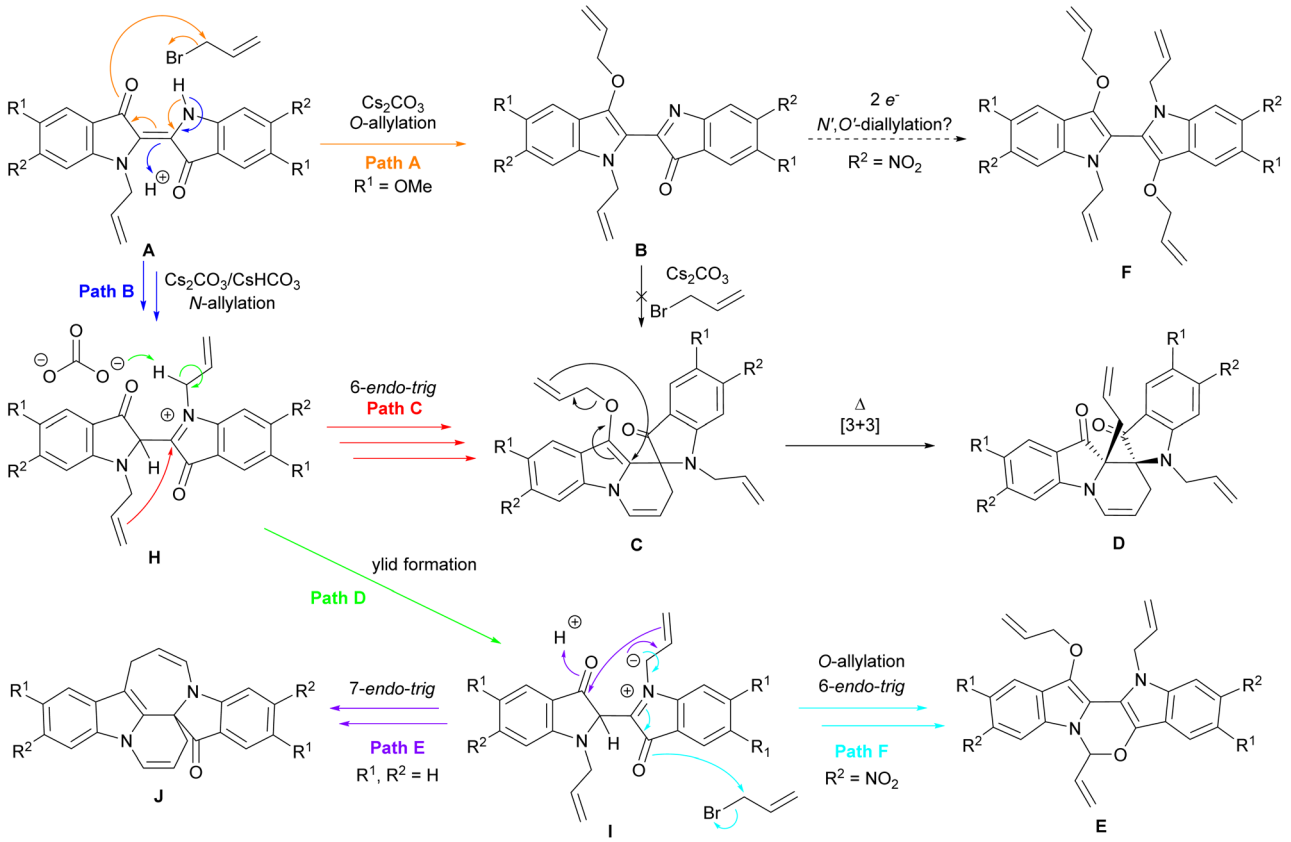
structure of 5,2′-dibromo derivative **22** (see ESI,† Section S4.4 and S5). Key evidence suggesting the formation of *C*-allylspiroindolinepyridoindoledione **27** included the presence of two ^{13}C resonances at 197.2 and 195.9 ppm, corresponding to two carbonyl moieties, and strong HMBC correlations from the spirocyclic carbon and the carbonyl at 195.9 ppm to the *C*-allyl methylene protons (see ESI,† Section S4.5). All *C*-allylspiroindolinepyridoindolediones **26–29** showed similar spectral characteristics and were all found to possess transoid relative stereochemistry (*vide infra*). The structure of oxazinobiindole **30** was determined based primarily upon the characteristic methine ^{1}H and ^{13}C NMR resonances at 6.81 ppm and 84.0 ppm, respectively, and relevant 2D COSY, HMBC and NOESY correlations to the vinyl pendant (see ESI,† Section S4.6). The simple ^{1}H NMR and ^{13}C NMR spectrum of *N*,*N*′-diallyl-3,3′-bis(allyloxy)biindole **31** suggested the structure was symmetrical. The structure of *N*,*N*′-diallyl-3,3′-bis(allyloxy)biindole **31** was proposed based upon analysis of the ^{1}H NMR spectrum which showed resonances assigned to two distinct allyl substituents. Analysis of the ^{13}C NMR spectrum showed an absence of resonances corresponding to carbonyl moieties. Importantly, the HRMS spectrum showed a peak at 537.1735, assigned to $[M + Na]^+$ of the tetra-allylated **31** (see ESI,† Section S4.7).

Mechanistic insights

The synthesis of spiroindolinepyridoindolones **C** (**17–25**) as the major outcome of all the substituted indigo allylation reactions represented a shift from the allylation of indigo **1** itself, wherein spiroindolinepyridoindolone **3** represented a minor product (Scheme 1).[9] The isolation of diallylbiindolone **16** was an intriguing outcome as the *N*-allylation of diallylbiindolone **16** to iminium intermediate **32** followed by 6-*exo-trig* cyclisation would furnish spiroindolinepyridoindolone **17**, making it a potential mechanistic intermediate (Scheme 4).[8] Treatment of diallylbiindolone **16** with Cs_2CO_3 and allyl bromide in DMF at 80 °C, however, showed baseline decomposition and the presence of unreacted **16** after 36 h, suggesting **16** is not a key intermediate involved in the generation of spiroindolinepyridoindolone **17** (Scheme 4). The isolation of *C*-allylspiroindolinepyridoindolediones **D** (**26–29**) was not the first observation of this scaffold, which has been isolated in the cascade reaction of indigo **1** with cinnamyl bromide (**7**, Scheme 1).[9] The simplest mechanism to account for the formation of spiroindolinepyridoindoledione **D** is a thermally-induced Claisen rearrangement of spiroindolinepyridoindolone **C** (Scheme 5a, Path A). Alternatively, a radical mechanism is possible, wherein homolytic cleavage of the allyl ether of spiroindolinepyridoindolone **C**



Scheme 8 The proposed mechanism of *N*,*N*′-diallyl-3,3′-bis(allyloxy)biindole **31** formation.



Scheme 9 The updated mechanistic pathways of indigo allylation cascade reactions. Note – the relative stereochemistry is shown for spiroindolinepyridoindoledione **D**.

would generate an allyl radical and captodatively-stabilised radical **E**, which upon unification would yield *C*-allylspiroindolinepryridoindoledione **D**, as was previously proposed in the synthesis of cinnamyl *C*-allylspiroindolinepyridoindoledione **7** (Scheme 5a, Path B).[9]

To confirm the spiroindolinepyridoindolediones **D** form through a thermal electrocyclic process, a solution of 5,2′-dimethoxyspiroindolinepyridoindolone **17** in DMF was heated at 90 °C for 4 days, to yield cisoid- and transoid-spiroindolinepyridoindolediones **33a–b** in 63% and 8% yield, respectively (Scheme 5b). Repetition of this reaction with the addition of TEMPO as a radical scavenger also yielded cisoid- and transoid-spiroindolinepyridoindolediones **33a–b** in 83% and 3% yield respectively, suggesting this reaction proceeds *via* a Claisen rearrangement rather than a radical pathway (Scheme 5b). The cisoid- and transoid-isomers **33a–b** were distinguished *via* NMR spectroscopy based upon differences in allyl methylene peak splittings due to restricted rotation in **33a** and *N*-allyl substituent deshielding in **33b**, thought to be the result of its closer proximity to the pyridoindolone aromatic ring relative to **33a** (see ESI,† Sections S4.8 and S4.9). The cisoid-spiroindolinepyridoindoledione **33a** possessed identical spectral characteristics to derivatives **26–29**, strongly suggesting **26–29** also have cisoid relative stereochemistry.

The generation of the *C*-allylspiroindolinepyridoindolediones **D** appeared to follow a positive correlation with electron-richness, with the greatest yields observed in reactions with methoxy-and phenyl-substituted indigos, while no formation was observed in bromo- and nitro-substituted indigos (Table 2). In the case of 5,5′-dimethoxyindigo **1a** (Table 2, entry 1–2), the lack of *C*-allylspiroindolinepyridoindoledione **D** formation *in situ* was proposed to be due to a shorter heating time (2–5 min), which was shown to be the case with the isolation of **33a–b** in high yield upon heating 5,2′-dimethoxyspiroindolone **17** at 90 °C for 4 days (Scheme 5b). To determine if electron-deficient derivatives of type **D** are accessible, 6,3′-dinitrospiroindolinepyridoindolone **25** was heated in DMF at 90 °C for 2 days, however no consumption of starting material was observed by TLC analysis. The reaction was therefore heated at 100 °C for a further 3 days, which upon workup, column chromatography and recrystallisation furnished 6,3′-dinitrospiroindolinepyridoindoledione **34** in 54% yield (Scheme 6).

Oxazinodiindole **30** represented a novel structural motif for the allylation cascade reactions, having only been observed in propargylation reactions previously,[11] while also representing the first cascade product unifying allylation and propargylation reaction mechanisms. Analogous to the mechanism previously proposed for propargyl oxazinodiindole,[11] *N*,*N*′-diallylation of 6,6′-dinitroindigo **1i** was proposed to produce **35**, which mesomerises to enolate-iminium intermediate **35a** and upon intramolecular methylene proton abstraction forms ylid **36** (Scheme

7). The formation of a methylene-based iminium ion and *O*-propargylation would generate **37**, which could undergo a base-mediated 6-*endo-trig* cyclisation to provide oxazinodiindole **30**. The isolation of *N*,*N*′-diallyl-3,3′-bis(allyloxy)biindole **31** also represented a new motif generated in the cascade reactions of indigo. Compound **31** was proposed to form *via* a 2-e$^-$ reduction of 6,6′-dinitroindigo **1i** to 6,6′-dinitroleucoindigo **38** followed by tetra-allylation, though *N*-allylation or *N*,*N*′-diallylation followed by reduction and *O*-allylation may also occur (Scheme 8). Another possibility is that diallylbiindole type **B** is reduced and alkylated to generate *N*,*N*′-diallyl-3,3′-bis(allyloxy)biindole **31**, which could explain the lack of diallylbiindole **B** products in electron-deficient derivatives. While DMF could be a reductant *in situ*,[17–20] this is unlikely as repetition of this reaction using anhydrous MeCN as the solvent also led to the formation of *N*,*N*′-diallyl-3,3′-bis(allyloxy)biindole **31**, suggesting an alternate reductive process is present (see ESI,† Section S1.2). Another possibility is that indigo **1i** is the reductant, generating diallylbiindole **31** and indigo oxidative by-products such as isatin and anthranilic acids *in situ*.

These investigations have provided substantial insights into the allylation cascade reactions of indigo and further expanded the mechanistic pathway (Scheme 9). Upon the formation of *N*-allylindigo **A** *in situ*, *O*-allylation to generate diallylbiindolone **B** (**Path A**) was shown to exist as a mechanistic pathway when $R^1 = OMe$, though it is hypothesised that when $R^2 = NO_2$, **B** may be reduced and alkylated to generate *N*,*N*′-diallyl-3,3′-diallyloxybiindole **F**. The attempted *N*-allylation and cyclisation of **B** did not produce spiroindolinepyridoindolone **C** as predicted previously, suggesting the formation of *N*,*N*′-diallyl intermediate **H** (**Path B**) followed by 6-*endo-trig* cyclisation and *O*-allylation (**Path C**) is the dominant pathway contributing to the synthesis of spiroindolinepyridoindolones **C**. Further, spiroindolinepyridoindolones **C** were shown to undergo thermal Claisen rearrangement to generate *C*-allylspiroindolinepyridoindolediones **D**. Diallyl intermediate **H** was also suggested to generate ylid **I** (**Path D**), which was thought to be a mechanistic branchpoint giving rise to either azepinoindolone **J** (**Path E**) when $R^1 = R^2 = H$,[8,9] or oxazinobiindole **E** when $R^2 = NO_2$ (**Path F**).

Conclusions

A variety of substituted indigos **1a–i** were successfully synthesised and evaluated in allylation cascade reactions, leading to the isolation of diallylbiindolone **16**, oxazinobiindole **30** and *N*,*N*′-diallyl-3,3′-bis(allyloxy)biindole **31** as novel polyheterocyclic architectures. The isolation of these products provided evidence for, and therefore strong support of, the proposed mechanisms of indigo cascade reactions. These mechanistic investigations could also, with further development, enable the synthesis of specific cascade products by modifying the substituents attached to indigo and the electrophile. The isolation of tetra-alkylated dinitrobiindole derivatives **11**, **13** and **31** also suggest that electron-deficient indigos more readily participate in redox processes, providing another avenue for future investigation.

Experimental details

Detailed experimental data and characterisation can be found in the ESI, Section S2.† General procedures for indigo synthesis and allylation cascade reactions are provided below for convenient reference.

General procedure A: the Baeyer–Drewson indigo synthesis

Following a modified procedure,[21] to a solution of substituted 2-nitrobenzaldehydes **8a–g** (1.0 eq.) in acetone (1.8 mL mmol^{-1}), was added NaOH (1 M, 0.9 mL mmol^{-1}) dropwise over 5–20 min at 2 °C. Upon addition, the ice bath was removed and the reaction stirred at rt. After 16–20 h, the reaction was diluted with H_2O (4 mL mmol^{-1}) and the precipitate filtered, rinsed with H_2O until the filtrate was colourless (5 × 20–50 mL) and EtOAc (5 × 20–50 mL) until the filtrate was colourless or pale blue. Upon air drying, the crude solid was recrystallised (EtOBz, 10 mg mL^{-1}) and the precipitate or crystals filtered and washed with EtOAc (3 × 20–50 mL) to yield substituted indigos **1a–g**.

General procedure B: the allylation of substituted indigos

A suspension of substituted indigos **1a–i** (1.0 eq.) in anhydrous DMF (40 mL mmol^{-1}) was sonicated for 60 min under a N_2 atmosphere. The suspension was transferred to a flask containing pre-dried Cs_2CO_3 (4.0 eq.) and activated 3 Å M.S. (2 g mmol^{-1}) and plunged into a pre-heated oil bath at 85–88 °C under N_2 with stirring. After 60 min, the N_2 flow was cut and allyl bromide (5.0 eq.) was added and stirred for 2–70 min. The reaction was quenched with ice (200 g mmol^{-1}) and diluted with brine (to 400 mL mmol^{-1}). This mixture was extracted with EtOAc (4 × 40–100 mL mmol^{-1}), and the combined organic phases washed with H_2O (5 × 50 mL mmol^{-1}) and brine (2 × 25 mL mmol^{-1}), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was subjected to multiple rounds of purification by silica gel column chromatography, PTLC and/or recrystallisation to furnish the titled cascade products **15–31**.

Author contributions

Matthew Perry: conceptualization; formal analysis; investigation; methodology; visualisation; writing – original draft preparation; writing – review and editing; Anthony Willis: formal analysis; investigation; methodology; John Bremner: conceptualization; formal analysis; methodology; writing – review and editing; Paul Keller: conceptualization; formal analysis; methodology; project administration; supervision; writing – review and editing.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

MJP acknowledges the Australian Government Research Training Program (AGRTP) scholarship for financial assistance through

this research. All research was performed with assistance and resources from the School of Chemistry and Molecular Bioscience (UOW) and the Research School of Chemistry (ANU).

References

1 J. Bush, B. Long, J. Catino and W. Bradner, *J. Antibiot.*, 1987, **40**, 668–678.
2 D. M. Roll, C. M. Ireland, H. S. Lu and J. Clardy, *J. Org. Chem.*, 1988, **53**, 3276–3278.
3 S. Omura, Y. Iwai, A. Hirano, A. Nakagawa, J. Awaya, H. Tsuchiya, Y. Takahashi and R. Asuma, *J. Antibiot.*, 1977, **30**, 275–282.
4 C.-Y. Huang, A. Bonasera, L. Hristov, Y. Garmshausen, B. M. Schmidt, D. Jacquemin and S. Hecht, *J. Am. Chem. Soc.*, 2017, **139**, 15205–15211.
5 O. Pitayatanakul, T. Higashino, T. Kadoya, M. Tanaka, H. Kojima, M. Ashizawa, T. Kawamoto, H. Matsumoto, K. Ishikawa and T. Mori, *J. Mater. Chem. C*, 2014, **2**, 9311–9317.
6 E. D. Głowacki, L. Leonat, G. Voss, M.-A. Bodea, Z. Bozkurt, A. M. Ramil, M. Irimia-Vladu, S. Bauer and N. S. Sariciftci, *AIP Adv.*, 2011, **1**, 042132.
7 N. M. Butler, R. Hendra, J. B. Bremner, A. C. Willis, L. Lucantoni, V. M. Avery and P. A. Keller, *Org. Biomol. Chem.*, 2018, **16**, 6006–6016.
8 M. K. Abdel-Hamid, J. B. Bremner, J. Coates, P. A. Keller, C. Miländer, Y. S. Torkamani, B. W. Skelton, A. H. White and A. C. Willis, *Tetrahedron Lett.*, 2009, **50**, 6947–6950.
9 A. Shakoori, J. B. Bremner, M. K. Abdel-Hamid, A. C. Willis, R. Haritakun and P. A. Keller, *Beilstein J. Org. Chem.*, 2015, **11**, 481–492.
10 A. Shakoori, J. B. Bremner, A. C. Willis, R. Haritakun and P. A. Keller, *J. Org. Chem.*, 2013, **78**, 7639–7647.
11 P. M. McCosker, N. M. Butler, A. Shakoori, M. K. Volland, M. J. Perry, J. W. Mullen, A. C. Willis, T. Clark, J. B. Bremner and D. M. Guldi, *Chem.–Eur. J.*, 2021, **27**, 3708–3721.
12 F. Sánchez-Viesca, M. Berros and R. Gómez, *Am. J. Chem.*, 2016, **6**, 18–22.
13 Y. Tanoue, K. Sakata, M. Hashimoto, M. Hamada, N. Kai and T. Nagai, *Dyes Pigm.*, 2004, **62**, 101–105.
14 C. Ramesh, G. Mahender, N. Ravindranath and B. Das, *Tetrahedron*, 2003, **59**, 1049–1054.
15 T. A. Geissman, in *Organic Reactions*, ed. R. Adams, John Wiley and Sons, Inc., Illinois, 1944, vol. 2, pp. 94–113.
16 J. F. Gomes, A. C. Garcia, E. B. Ferreira, C. Pires, V. L. Oliveira, G. Tremiliosi-Filho and L. H. S. Gasparotto, *Phys. Chem. Chem. Phys.*, 2015, **17**, 21683–21693.
17 M. M. Heravi, M. Ghavidel and L. Mohammadkhani, *RSC Adv.*, 2018, **8**, 27832–27862.
18 I. Pastoriza-Santos and L. M. Liz-Marzán, *Adv. Funct. Mater.*, 2009, **19**, 679–688.
19 I. Pastoriza-Santos and L. Liz-Marzán, *Pure Appl. Chem.*, 2000, **72**, 83–90.
20 Y. Feng, K. Zhang, B. Yan, S. Li and Y. Du, *Catalysts*, 2016, **6**, 103.
21 J. Yang, Y. Jiang, Z. Tu, Z. Zhao, J. Chen, Z. Yi, Y. Li, S. Wang, Y. Yi, Y. Guo and Y. Liu, *Adv. Funct. Mater.*, 2019, **29**, 1804839.