

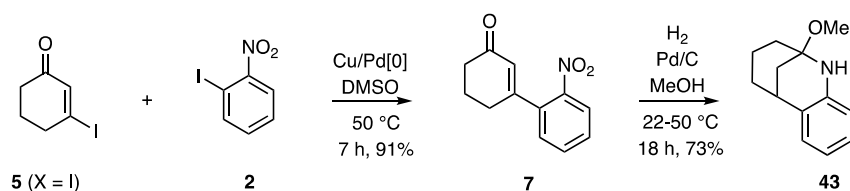
The Palladium-Catalyzed Ullmann Cross-Coupling of β -Iodoenones and β -Iodoacrylates with *o*-Halonitroarenes or *o*-Iodobenzonitriles and the Reductive Cyclization of the Resulting Products to Give Diverse Heterocyclic Systems

Faiyaz Khan, Michael Dlugosch, Xin Liu, Marium Khan, Martin G. Banwell,* Jas S. Ward and Paul D. Carr

Research School of Chemistry, Institute of Advanced Studies

The Australian National University, Canberra, ACT 2601, Australia

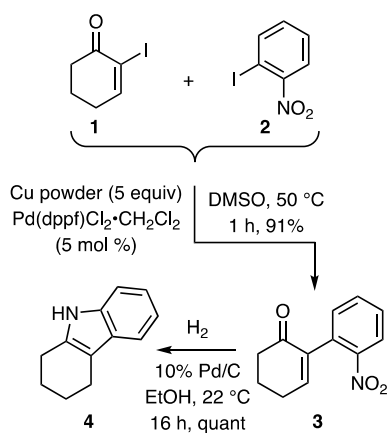
Supporting Information Placeholder



ABSTRACT: The palladium-catalyzed Ullmann cross-coupling of β -iodo-enones and -acrylates such as **5** (X = I) with *o*-halogenated nitroarenes or benzonitriles including **2** affords products such as compound **7**. These can be engaged in a range of reductive cyclization reactions leading to heterocyclic frameworks such as the 3,4-benzomorphan derivative **43**.

Sometime ago, we described¹ the palladium-catalysed Ullmann cross-coupling of α -iodinated α,β -unsaturated ketones and related compounds with *o*-halonitroarenes, thus providing the corresponding α -arylated enone. The conversion **1** + **2** \rightarrow **3** shown in Scheme 1 is representative of such cross electrophile couplings² that are generally high yielding and proceed under mild conditions. Furthermore, coupling products such as **3** can be reductively cyclized to give, for example, the tetrahydrocarbazole **4** in high yield.

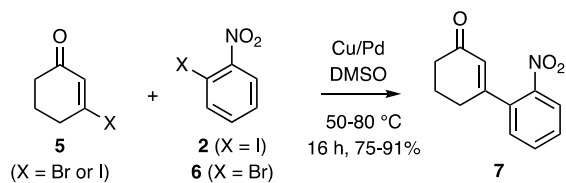
Scheme 1: Previously reported¹ palladium-catalyzed Ullmann cross-coupling of compounds **1** and **2** and the reductive cyclization of product **3** leading to indole **4**.



cols to the preparation of quinolones, 2-quinolones, phenanthridines, 6(5*H*)-phenanthridinones, oxindoles, carbazoles and carbolines.³ In addition, we have been able to apply them in total synthesis of a range of natural products and various analogues.⁴ A number of other groups have also employed these protocols in the synthesis of various biologically active systems.⁵

We now report on the effective participation of β -iodinated α,β -unsaturated ketones and acrylates in related processes that have provided a means for the rapid construction of a diverse range of novel heterocyclic systems. Our initial studies involved, as shown in Scheme 2, examining the cross-coupling of the readily available β -halo-2-cyclohexen-1-ones **5** (X = Br or I)⁶ with *o*-halonitrobenzenes **2** and **6** in anticipation of forming the β -arylated 2-cyclohexen-1-one **7**.

Scheme 2: The palladium-catalyzed Ullmann cross-coupling of β -halo-2-cyclohexen-1-ones **5** with *o*-halonitrobenzenes **2** or **6** to form the β -arylated 2-cyclohexen-1-one **7**.



In the intervening period, we have extended these proto-

Products of this type, which have been prepared previously by less direct methods,⁷ were targeted, as they have been shown to engage in efficient reductive cyclisation reactions to form carbazolones, including one that has served as a precursor to the carbazole alkaloid clausenale.^{7b} A series of cross-coupling experiments involving both the brominated and iodinated forms of coupling partners, viz. compounds **2**, **5** and **6**, were examined as were various coupling conditions. The outcomes of these trials established that the best coupling partners were the iodides. Thus, on using these in conjunction with 5 equivalents of copper powder, 5 mol % Pd(dppf)Cl₂·CH₂Cl₂ and DMSO as solvent then the reaction proceeded at 50 °C in 16 h to give compound **7** in 91% yield. The structure of compound **7** was confirmed by single-crystal X-ray analysis, details of which are provided in the Supporting Information (SI). Cross-couplings involving **5** (X = Br) and **2** or **5** (X = I) and **6** required heating to 80 °C and produced compound **7** in 75% and 83% yields, respectively while reaction of bromides **5** (X = Br) and **6** under the same conditions gave product **7** in 79% yield. Attempts were made to effect a carbonylative cross-coupling of the iodinated reaction partners by carrying out the reaction under a carbon monoxide atmosphere but only product **7** (75%) was obtained. None of the hoped-for diketone was observed.

Encouraged by these results, we sought to extend them to the preparation of various related systems. For example, the readily prepared⁶ β-iodinated 2-cyclopenten-1-ones **8** and **9** (Figure 1) also engaged in cross-coupling reactions with compound **2** to give the anticipated products **10** (93%) and **11** (49%), respectively. Each of these was fully characterized by the usual range of spectroscopic methods. In a similar manner, the bromonitropyridines **12**,^{3e} **13**^{3e} and **14**^{3e} were cross-coupled with enone **5** (X = I) and thus afforded the β-arylated enones **15** (69%), **16** (91%) and **17** (89%), respectively. β-Iodoalkenones incorporating an exocyclic olefinic residue also participate in these same types of reactions as evidenced by the successful cross-coupling of the readily available substrate **18**⁶ with arene **13** to give compound **19** (87%), the structure of which was confirmed by X-ray analysis (see SI).

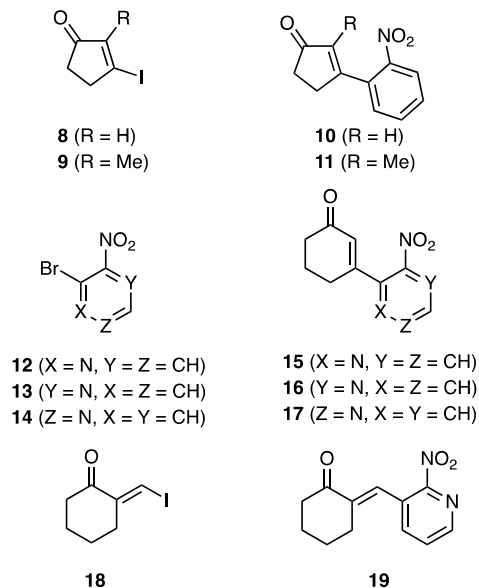


Figure 1: Substrates **8**, **9**, **12-14** and **18** and the cross-coupling products **10**, **11**, **15-17** and **19**.

o-Iodobenzonitriles also cross-couple with β-iodoenones as evidenced by the successful reaction of the easily accessible⁸ compounds **20**, **21**, **22** and **23** (Figure 2) with β-iodocyclohex-2-en-1-one [**5** (X = I)] to give products **24** (40%), **25** (61%), **26** (34%) and **27** (75%), respectively. The poorer yields associated with these *o*-iodobenzonitrile-based couplings are attributed to the weaker electron-withdrawing capacities of the nitrile group, as compared to the nitro-group and, therefore, the intervention of competing homo-couplings of the reaction partners.

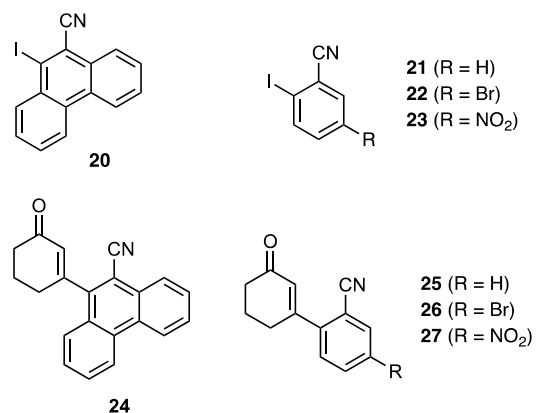


Figure 2: *o*-Iodobenzonitriles **20-23** and the products, **24-27**, arising from their cross-coupling with **5** (X = I).

β-Iodinated acrylates proved to be generally competent partners in palladium-catalysed Ullmann cross-couplings with *o*-iodo-nitrobenzenes and -benzonitriles. For example, when methyl (*Z*)-3-iodobut-2-enoate (**28**)⁹ (Figure 3) was reacted with compounds **13**, **14**, **20**, **23** and **29**¹⁰ under the usual conditions then the cross-coupling products **30** (84%), **31** (69%), **32** (55%), **33** (43%) and **34** (59%), respectively, were obtained.

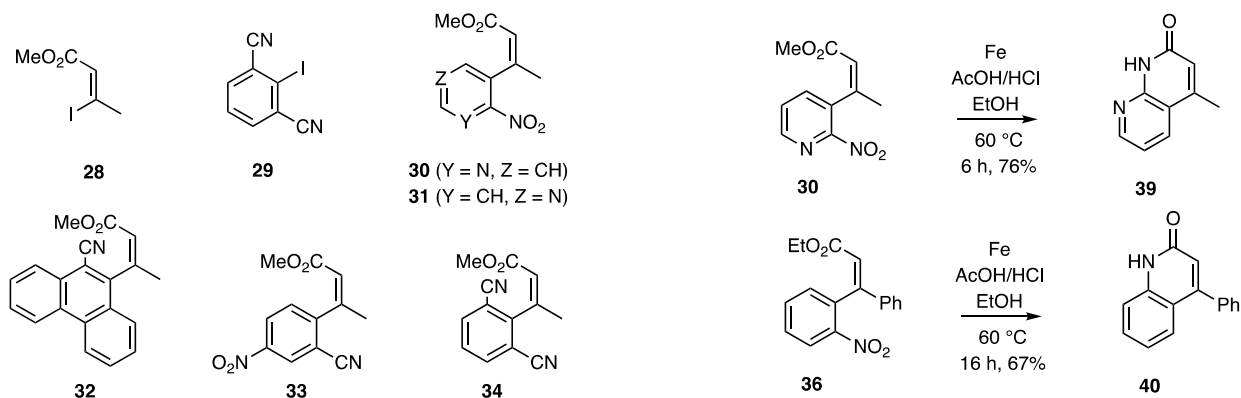


Figure 3: β -Iodoacrylate **28** and the products, **30-34**, arising from its cross-coupling with *o*-iodonitroarenes and -benzonitriles.

The ethyl β -iodocinnamate (**35**)⁹ (Figure 4) behaved in a similar fashion. Thus, cross-coupling of this compound with *o*-iodonitro-benzene (**2**) afforded product **36**¹¹ (61%) while the coupling of compounds **15** and **35** gave ester **37** (50%). The analogous reaction of substrates **16** and **35** gave ester **38** (81%).

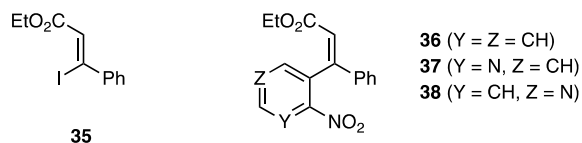


Figure 4: β -Iodocinnamate **35** and the products, **36-38**, arising from its cross-coupling with certain *o*-halonitroarenes.

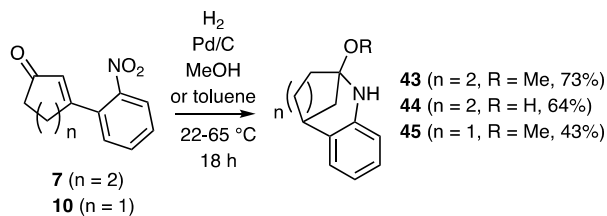
Many of the cross-coupling products described above engage in useful reductive cyclisation processes and thus giving rise, in a direct manner, to heterocyclic frameworks of synthetic and/or biological relevance. For example, on exposing an ethanolic solution of coupling product **30** (Scheme 3) to iron filings in the presence of acetic and hydrochloric acid then reduction of the nitro-group occurred with the product aniline undergoing spontaneous cyclization onto the pendant ester residue and thus forming the 8-azaquinolone **39**¹² in 76% yield.

Scheme 3: The reductive cyclization of the cross-coupling products **30** and **36** leading to heterocycles **39-41**

Under analogous conditions, cinnamate **36** was converted into the quinolone **40**¹³ (67%) while when the same substrate was exposed to hydrogen in the presence of 10% palladium on carbon more extensive reduction occurred to afford the dihydroquinolone **41**¹⁴ (85%). Given the ease of formation of the substrates through the title cross-coupling reactions, these conversions provide especially concise routes to quinolones and their 8-aza analogues, classes of compounds that have attracted considerable attention because of, *inter alia*, their enzyme inhibiting and DNA intercalating properties.¹³⁻¹⁵ 1,8-Naphthyridines, another medicinally significant class of compound,¹⁶ are also available via related protocols as highlighted by the conversion **19** \rightarrow **42** shown above. This proceeds in 74% yield when a mixture of iron powder and calcium chloride in ethanol is used as the reducing medium and a basic workup is employed.

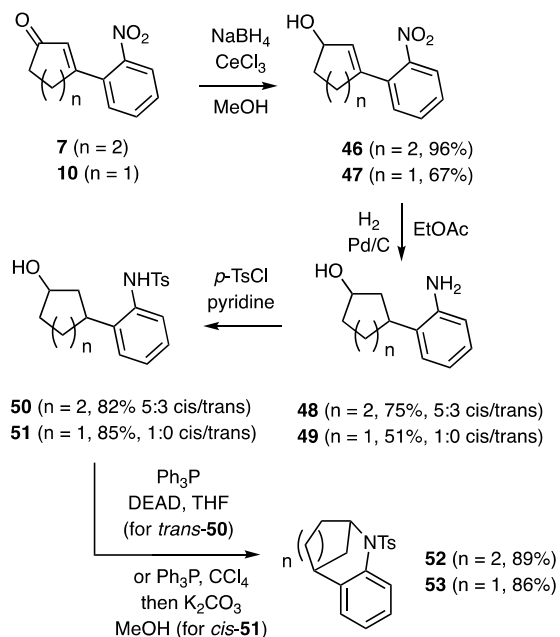
Quite distinct reductive cyclisation processes are observed when employing the β -arylated-2-cycloalken-1-one coupling products as substrates. Thus, as shown in Scheme 4, exposure of a methanolic solution of compound **7** to hydrogen in the presence of Pd on C afforded the 3,4-benzomorphan **43** (73%) while analogous treatment of a toluene solution of the same substrate afforded compound **44**¹⁷ (64%) bearing a bridgehead hydroxyl group. In a similar manner, a methanolic solution of the cross-coupling product **10** was converted into the B-norbencomorphan **45** (43%). The structures of compounds **43** and **45** were confirmed through X-ray analyses, details of which are provided in the SI.

Scheme 4: The reductive cyclization of the cross-coupling products **7** and **10** leading to heterocycles **43-45**



Deoxygenated variants of compounds **43-45** were readily prepared by the pathways shown in Scheme 5.

Scheme 5: Conversion of the cross-coupling products **7** and **10** into the bridged heterocyclic compounds **52** and **53**



Thus, Luche-type reductions of compounds **7** and **10** afforded the corresponding allylic alcohols **46** (96%) and **47** (67%), respectively. These 1,2-reduction products underwent catalytic hydrogenation (and accompanying hydrogenolysis of the nitro group) in ethyl acetate to give the saturated amino-alcohols **48** (75% of a 5:3 mixture of *cis*- and *trans*-isomers) and **49** (51% of *cis*-isomer only), respectively. The two-fold reduction products **48** and **49** were then converted, under standard conditions, into the corresponding sulfonamides **50** (82% of a 5:3 mixture of *cis*- and *trans*-isomers) and **51** (85% of *cis*-isomer only). Compound *trans*-**50**, for which a single-crystal X-ray analysis was obtained (see SI for details), readily engaged in a Mitsunobu cyclization reaction on exposure to Ph_3P /diethyl azodicarboxylate (DEAD) and so affording 3,4-benzomorphan **52** (89%). Unsurprisingly, congener *cis*-**50** failed to cyclize under these same conditions. On the other hand, successive treatment of compound *cis*-**51** under Appel conditions using CCl_4 and Ph_3P gave what is presumed to be the corresponding *trans*-chloride and on treating this with potassium carbonate in methanol it cyclized to give the norbenzomorphan **53** in 86% yield.

Presumably, these protocols could be readily adapted to the preparation of the non-racemic forms of these heterocycles through, for example, the enantioselective 1,2-reduction of the starting enones **7** and **10**. Given the extensive and ongoing interest in benzomorphan and related systems,¹⁸ the processes outlined in Schemes 4 and 5 should be of considerable utility in a range of settings.

The possibilities for reductive cyclization of the above-mentioned cross-coupling products extend beyond those delineated above as evidenced, by, for example, the report¹¹ that compound **36** (prepared by different means to those described here) can be engaged in a Cadogan cyclisation to give 2-carboethoxy-3-phenylindole in 90% yield. As such, the work detailed above serves to highlight the capacities of title cross electrophile coupling reactions to deliver a wide-range of products capable of engaging in various useful reductive cyclisation processes and thus forming new or otherwise difficult-to-access heterocyclic systems.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free-of-charge on the ACS Publications website at DOI: 10.1021/acs.orglett.XXXXXX.

Experimental procedures, spectroscopic data, NMR spectra of compounds **5** (X = I and Br), **7**, [1,1'-bi(cyclohexane)]-1,1'-diene-3,3'-dione, **8-11**, **15-19**, **24-27**, **30-34**, **36-47**, **49**, *trans*-**50**, *cis*-**50**, *cis*-**51**, **52**, **53** (PDF) together with the X-ray data for compounds **7**, **19**, **39**, **43**, **45**, and *trans*-**50** (*cis*)

Accession Codes

CCDC 1832167, 1832168, 1832169, 1832170, 1832171 and 1832172 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

AUTHOR INFORMATION

Corresponding Author

*E-mail: Martin.Banwell@anu.edu.au

ORCID

Martin G. Banwell: [0000-0002-0582-475X](https://orcid.org/0000-0002-0582-475X)

Author Contributions

The manuscript was written through contributions from all of the authors. All of the authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGEMENTS

We thank the Australian Research Council for financial support. FK is the grateful recipient of a scholarship provided by the Australian National University, XL acknowledges the support of Circa Pty Ltd (Melbourne) while MK thanks the Higher Education Commission of Pakistan for funding.

REFERENCES

1. Banwell, M. G.; Kelly, B. D.; Kokas, O. J.; Lupton, D. W. *Org. Lett.*, **2003**, *5*, 2497.
2. For some key articles on cross electrophile couplings, see: (a) Knappke, C. E. I.; Grupe, S.; Gärtner, D.; Corpet, M.; Gosmini, C.; von Wangelin, A. J. *Chem. Eur. J.*, **2014**, *20*, 6828; (b) Everson, D. A.; Weix, D. J. *J. Org. Chem.*, **2014**, *79*, 4793; (c) Hanna, L. E.; Jarvo, E. R. *Angew. Chem. Int. Ed.*, **2015**, *54*, 15618; (d) Weix, D. J. *Acc. Chem. Res.*, **2015**, *48*, 1767; (e) Poremba, K. E.; Kadunce, N. T.; Suzuki, N.; Cherney, A. H.; Reisman, S. E. *J. Am. Chem. Soc.*, **2017**, *139*, 5684.
3. (a) Banwell, M. G.; Lupton, D. W.; Ma, X.; Renner, J.; Sydnes, M. O. *Org. Lett.*, **2004**, *6*, 2741; (b) Some, S.; Ray, J. K.; Banwell, M. G.; Jones, M. T. *Tetrahedron Lett.*, **2007**, *48*, 3609; (c) Banwell, M. G.; Jones, M. T.; Loong, D. T. J.; Lupton, D. W.; Pinkerton, D. M.; Ray, J. K.; Willis, A. C. *Tetrahedron*, **2010**, *66*, 9252; (d) Yan, Q.; Gin, E.; Wasinska-Kalwa, M.; Banwell, M. G.; Carr, P. D. *J. Org. Chem.*, **2017**, *82*, 4148; (e) Yan, Q.; Gin, E.; Banwell, M. G.; Willis, A. C.; Carr, P. D. *J. Org. Chem.*, **2017**, *82*, 4328.
4. See: Tang, F.; Banwell, M. G.; Willis, A. C. *J. Org. Chem.* **2016**, *81*, 10551 and references cited therein.
5. (a) Herzon, S. B.; Myers, A. G. *J. Am. Chem. Soc.*, **2005**, *127*, 5342; (b) Nicolaou, K. C.; Nold, A. L.; Li, H. *Angew. Chem. Int. Ed.*, **2009**, *48*, 5860.
6. Piers, E.; Grierson, J. R.; Lau, C. K.; Nagakura, I. *Can. J. Chem.*, **1982**, *60*, 210.
7. (a) Klement, T.; Rottländer, M.; Tucker, C. E.; Majid, T. N.; Knochel, P.; Venegas, P.; Chaiez, G. *Tetrahedron*, **1996**, *52*, 7201; (b) Scott, T. L.; Yu, X.; Gorugantula, S. P.; Carrero-Martinez, G.; Söderberg, B. C. G. *Tetrahedron*, **2006**, *62*, 10835.
8. (a) Moss, R. A.; Bracken, K.; Emge, T. J. *J. Org. Chem.*, **1995**, *60*, 7739; (b) Du, B.; Jiang, X.; Sun, P. *J. Org. Chem.*, **2013**, *78*, 2786.
9. Akpınar, G. E.; Kus, M.; Ucüncü, M.; Karakus, E.; Artok, L. *Org. Lett.*, **2011**, *13*, 748.
10. Martin, J. C.; Krizan, T. D. *J. Org. Chem.*, **1982**, *47*, 2681.
11. Yamamoto, Y.; Yamada, S.; Nishiyama, H. *Adv. Synth. Catal.*, **2011**, *353*, 701.
12. Chunavala, K. C.; Adimurthy, S. *Synth. Comm.* **2011**, *41*, 1843.
13. Han, J.; Wu, X.; Zhang, Z.; Wang, L. *Tetrahedron Lett.*, **2017**, *58*, 3433.
14. Linsenmeier, A. M.; Braje, W. M. *Tetrahedron*, **2015**, *71*, 6913.
15. See, for example: Poppe, L.; Tegley, C. M.; Li, V.; Lewis, J.; Zondlo, J.; Yang, E.; Kurzeja, R. J. M.; Syed, R. *J. Am. Chem. Soc.*, **2009**, *131*, 16654.
16. Madaan, A.; Verma, R.; Kumar, V.; Singh, A. T.; Jain, S. K.; Jaggi, M. *Arch. Pharm. Chem. Life Sci.*, **2015**, *348*, 837.
17. Reisman, S. E.; Ready, J. M.; Weiss, M. M.; Hasuoka, A.; Hirata, M.; Tamaki, K.; Ovaska, T. V.; Smith, C. J.; Wood, J. L. *J. Am. Chem. Soc.*, **2008**, *130*, 2087.
18. Li, Y.; Feng, C.; Shi, H.; Xu, X. *Org. Lett.*, **2016**, *18*, 324.