Palladium-Catalyzed Ullmann Cross-Coupling Reactions for the Synthesis of Heterocyclic Compounds

A thesis submitted for the Degree of
Doctor of Philosophy
of The Australian National University

by

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Declaration

I declare that the material presented in this thesis represents the result of original work carried out by me during the period 2015-2019 and has not been presented for examination for any other degree. The body of this thesis by publication is comprises four journal articles and these are preceded by a synopsis. Wherever appropriate, established methodologies have been acknowledged by citation of the original publication.

Faiyaz Khan

September, 2019
Acknowledgments

First, I would like to thank my supervisor Professor Martin Banwell. Any period of doctoral studies is typically met with highs and lows, which I've now experienced first-hand. If not for Martin's constant support, emotional and scientific, I would never have made it this far. For this I am eternally grateful.

I owe a significant debt to Brett Schwartz, with whom I shared many years in lab 3.25 and who thus contributed significantly to the development of my experimental skills and as a researcher more generally. The times we spent chatting about our shared hobbies and the constant lab jukebox made my day-to-day lab experiences all the more enjoyable. Special thanks to Shen Tan, my first lab mentor during an undergraduate project, who laid the foundation for the skills, achievements and the passion for chemistry I've accumulated to this day.

To the many members of the Banwell Group, past and present, I thank you for making the experience an enjoyable one. Special thanks to Michael Dlugosch, Jiri Mikusek, Nadia Gao, Xin Liu, Hannah Bollard, Yen Vo, Xiang Ma, Joshua Buckler and Jeremy Nugent who were my lab mates in 3.25 at various times and/or colleagues and collaborators. To the visiting and undergraduate students I've mentored over the years, thank you for allowing me to discover my passion for teaching which has been one of the most rewarding experiences during my time at the ANU. I thank all of the technical staff in the Research School of Chemistry for the important work done every day to ensure the smooth operation of the entire facility.

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Publications

The following publications have resulted from the candidate’s research work carried out during the course of his studies for the Degree of Doctor of Philosophy:


Relative Contributions to Publications

Publication 1: The Palladium-Catalyzed Ullmann Cross-Coupling Reaction: A Modern Variant on a Time-Honored Process

This is a review article that was written by Professor Martin Banwell. It incorporates descriptions of research on palladium-catalyzed Ullmann cross-coupling reactions conducted by the co-authors including the candidate.

Publication 2: Palladium-Catalyzed Ullmann Cross-Coupling of β-Iodoenones and β-Iodoacrylates with o-Halonitroarenes or o-Iodobenzonitriles and Reductive Cyclisation of the Resulting Products To Give Diverse Heterocyclic Systems

This is a full paper detailing extensive experimental work on a methodology involving the palladium-catalyzed Ullmann cross-coupling reaction and the reductive cyclisation of those products derived from this process. The candidate carried out 50% of the experimental work reported in the paper. In addition, the candidate collated and formatted 50% of the reported spectral data presented in the Supporting Information document. The candidate also wrote 50% of the Experimental Section and conducted relevant literature surveys. Professor Martin Banwell wrote the body of the paper.

Publication 3: Reductive Cyclisation of o-Nitroarylated-α,β-unsaturated Aldehydes and Ketones with TiCl3/HCl or Fe/HCl Leading to 1,2,3,9-Tetrahydro-4H-carbazol-4-ones and Related Heterocycles

This is a full paper detailing extensive experimental work on a methodology concerned with producing distinct reductive cyclisation products from the same substrate by varying the nature of the reagent employed for such purposes. The candidate carried out 25% of the experimental work reported in the paper. In addition, the candidate collated and formatted 40% of the spectral data presented in the Supporting Information document. The candidate also wrote 40% of the
Experimental Section and conducted relevant literature surveys. Professor Martin Banwell wrote the body of the paper.

**Publication 4: Tandem Ullmann–Goldberg Cross-Coupling/Cyclopalladation–Reductive Elimination Reactions and Related Sequences Leading to Polyfunctionalized Benzofurans, Indoles, and Phthalanes**

This is a full paper detailing extensive experimental work on developing a methodology allowing for the synthesis of benzofurans, indoles and phthalanes using a tandem (one-pot) Ullmann–Goldberg cross-coupling/cyclopalladation–reductive elimination reaction. The candidate carried out 50% of the experimental work reported in the paper. In addition, the candidate collated and formatted 50% of the reported spectral data presented in the Supporting Information document. The candidate also wrote the whole of the Experimental Section and conducted relevant literature surveys as well as coordinating the research and data-recording/reporting activities of most of the other co-authors. Professor Martin Banwell wrote the body of the paper.
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Abstract

This thesis comprises four scientific articles (Publications 1-4) and is preceded by an overview (synopsis) that contextualizes all of this published work.

**Publication 1** is an invited review article that details the development of the palladium-catalyzed Ullmann cross-coupling reaction within the Banwell Group. Specifically, it describes the extensive efforts directed towards modernizing the Ullmann reaction so as to circumvent the harsh (and therefore restrictive) conditions associated with this classic protocol. The reductive cyclisation of the ensuing cross-coupling products is also discussed as a means of forming a range of heterocyclic systems of relevance to medicinal or natural products chemistry. As such **Publication 1** serves to contextualize the research described in **Publications 2-3**.

**Publication 2** describes work directed towards engaging β-iodinated α,β-unsaturated carbonyl compounds in palladium-catalyzed Ullmann cross-couplings with o-halonitroarenes as well as the less reactive o-halobenzonitriles. The reductive cyclisation of the products of such reactions allows access to various heterocyclic frameworks including benzomorphan that, hitherto, have been inaccessible via such simple pathways.

**Publication 3** details methods for the reductive cyclisation of o-nitroarylated α,β-unsaturated carbonyl compounds arising from the palladium-catalyzed Ullmann cross-coupling reaction. Specifically, complementary modes of reductive cyclisation are observed on using titanium trichloride/HCl or H₂/Pd on C and so allowing for different heterocyclic systems to be obtained from the same substrate. Such processes significantly enhance the utility of the products available through the palladium-catalyzed Ullmann cross-coupling reaction.

**Publication 4** describes a protocol related to the palladium-catalyzed Ullmann cross-coupling reaction for the one-pot synthesis of functionalized benzofurans, indoles and phthalanes. Specifically, it details a tandem Ullmann–Goldberg cross-coupling/cyclopalladation–reductive elimination reaction sequence employing
iodophenols or iodoanilines and β-halogenated α,β-unsaturated carbonyl compounds as coupling partners (substrates). The overall process involves the simultaneous exposure of such substrates to a combination of Cu[I]- and Pd[0]-catalysts.
Thesis Overview

The formation of new carbon–carbon bonds, a fundamental aspect of organic synthesis, has been revolutionized with the advent of cross-coupling protocols catalyzed by transition metal complexes. These cross-coupling reactions have been applied, in both academia and the pharmaceutical industry, to the synthesis of a wide range of natural products and other biologically active compounds and so demonstrating it is one of the most useful and important types of transformations in modern organic chemistry. Seminal publications on the most frequently utilized variants of such processes has been authored by Heck, Negishi, and Suzuki (in collaboration with Miyaura). They represent some of the most widely read articles in organic chemistry and are so fundamental in nature that they now form the basis of many undergraduate chemistry courses around the world. The award of the 2010 Nobel Prize in chemistry to Heck, Negishi and Suzuki serves to further emphasize the significance of such cross-coupling protocols.

The basic process involved in these reactions is the linking of two coupling partners, normally an electrophilic one (typically an organohalide or pseudohalide) with a nucleophilic one, the precise form of which defines the name of the process involved. While these reactions often proceed in high yield under mild conditions, the nucleophilic partner (typically an organometallic) is regularly prepared from the corresponding halide and is often highly reactive or toxic (as is the case with many organostannanes). The constant desire to reduce step-count and improve atom-efficiency in organic transformations has prompted extensive research in a closely related field, namely cross-electrophile couplings. In such reactions, two distinct electrophilic partners are coupled to provide a cross-coupling product, avoiding the need to employ stoichiometric quantities of an organometallic species.

An early form of such reactions involved the Ullmann coupling of electron deficient aryl halides in the presence of copper at elevated temperatures (> 200 °C) and so producing biaryls. Unfortunately, this classical method is normally confined to the formation of symmetrical biaryls through homo-coupling processes. When attempts are made to cross-couple two distinct halides under the same conditions, cross-
coupling products are usually only formed in modest yield because of competing homocoupling processes. However, the simple expedient of adding palladium to the Ullmann coupling reaction allows for the cross-coupling of a wide range of different pairs of organo-halides wherein the halide is attached to a sp$^2$-hybridised carbon. Significantly, not only do the desired cross-coupling reactions take place in high yield but distinctly lower operating temperatures (ca. 50-80 °C) are now involved.

The research described in this thesis focuses on the continued development and use of the palladium-catalyzed Ullmann cross-coupling and related reactions for the synthesis of pharmacologically relevant heterocyclic frameworks. The mechanism originally proposed (by Shimizu and collaborators) for this cross-coupling reaction is shown in Scheme 1.$^5$

![Scheme 1: Proposed Mechanism for the Palladium-Catalyzed Ullmann Cross-Coupling Reaction (X = halogen)](image)

Thus, the active Pd[0] catalyst, which can be formed in situ, undergoes oxidative addition to the less electron-deficient coupling partner (I) containing a sp$^2$-hybridised carbon-halogen bond and so forming the Pd[II] complex II. The more electron-deficient coupling partner (III), typically an o-halogenated nitroarene, reacts with Cu[0] to form, after halogen-metal exchange, organocuprate IV. Transmetalation of
complex II and organocuprate IV then affords the Pd[II] species V that undergoes reductive elimination to form the cross-coupled product VI as well as regenerating the Pd[0] catalyst that can re-enter the reaction cycle.

Summaries of the four research publications co-authored by the candidate, which build upon the original work conducted within the Banwell Group on the palladium-catalyzed Ullmann cross-coupling reaction, are now presented.


This review details the extensive efforts within the Banwell Group to examine the scope and limitations the palladium-catalyzed Ullmann cross-coupling process and using the products of such reactions as key intermediates in natural product synthesis or in the construction of pharmacologically significant heterocyclic frameworks. It serves to contextualize the candidate’s other published research in the area. A typical reaction sequence using the title process is highlighted in Scheme 2, wherein an electron-deficient iodoarene such as compound 1 and an α-iodoenone such as compound 2 are heated with copper powder and a source of palladium(0) in DMSO, normally at 80 °C or below. Under such conditions the cross-coupling product 3 is formed in good yield and reductive cyclisation of this species then affords, in a generally efficient manner, tetrahydrocarbazole 4.6

![Scheme 2: A Representative Palladium-Catalyzed Ullmann Cross-Coupling/Reductive Cyclisation Sequence](image)

Within the Banwell Group, the title reaction has been exploited in numerous syntheses of natural products and/or pharmacologically active agents and these
often involve reductive cyclisation of the initially-formed cross-coupling product. Examples of the end-products arising from the successful application of such sequences are shown in Figure 1 and include the carbazole clauszoline K (4), the ring-fused indoles (±)-gilbertine (6) and (±)-1-acetylaspidolbidine (7) as well as the pyrrole-fused quinoline marinoquinoline A (8).

![Chemical structures](image)

**Figure 1**: Examples of Natural Products Prepared Using the Palladium-Catalyzed Ullmann Cross-Coupling Reactions in Combination with Reductive Cyclization Protocols.

**Publication 2**: Palladium-Catalyzed Ullmann Cross-Coupling of β-Iodoenones and β-Iodoacrylates with o-Halonitroarenes or o-Iodobenzonitriles and Reductive Cyclisation of the Resulting Products To Give Diverse Heterocyclic Systems (*Org. Lett.* 2018, 20, 2770-2773)

While investigating the use o-halobenzonitriles as substrates for the palladium-catalyzed Ullmann cross-coupling, it was discovered that previously unexplored β-iodoenones were competent, if not superior reaction partners to their α-iodinated counterparts. The scope and limitations of processes involving such substrates are the subject of the work described in **Publication 2**. In particular, the cross-couplings of a variety of β-halogenated α,β-unsaturated carbonyl compounds with o-iodonitroarene 1 or o-bromonitropyridine 15 were shown to afford, after reductive cyclisation of the primary products of reaction, a range of heterocyclic systems.
(Scheme 3) that have only been accessible previously by multi-step reaction sequences.\(^{12}\)

\[
\begin{align*}
\text{Scheme 3: The Outcomes of Applying Palladium-Catalyzed Ullmann Cross-Coupling/Reductive Cyclisation Sequences to Various } \beta\text{-Iodinated } \alpha,\beta\text{-unsaturated Carbonyl Compounds}
\end{align*}
\]

So, for example, using reaction sequences starting with the cyclic \(\beta\)-iodoenones 9 and 12 the \(\beta\)-nitroarylated products 10 and 13, respectively, were obtained and reductive cyclisation of these using hydrogen in the presence of 10\% Pd/C and acetic acid then gave the 3,4-benzomorphan 11 and the lower homologue (a B-norbenzomorphan) 14, respectively. By using a variety of other coupling partners as well as different reductive cyclisation regimes the versatility of such simple reaction sequences has been demonstrated. For example, the reductive cyclisation of the cross-coupling product 17 under appropriately mild conditions provides the fused 1,8-naphthyridine 18, a key member of a family of compounds known for their wide spectrum of biological activities.\(^{13}\) The use of non-cyclic ketones such as \(\beta\)-iodocinnamate 19 in an analogous sequence provides the 2-tetrahydroquinolone 21 after reductive cyclisation of the initial cross-coupling product 20.
In summary, this work highlights the use of β-halogenated α,β-unsaturated carbonyl compounds in palladium-catalyzed Ullmann cross-couplings and constitutes an important extension of previous work carried out within the Banwell Group.

**Publication 3: Reductive Cyclisation of α-Nitroarylated-α,β-unsaturated Aldehydes and Ketones with TiCl₃/HCl or Fe/HCl Leading to 1,2,3,9-Tetrahydro-4H-carbazol-4-ones and Related Heterocycles** *(J. Org. Chem. 2018, 83, 12023-12033)*

Publication 3 reports on the discovery that treating cross-coupling products such as the α-nitroarylated-enone 3 (Scheme 4) with titanium trichloride in a hydrochloric acid solution provides the indole product 22 rather than the tetrahydrocarbazole 4 that is formed on treating the same substrate with dihydrogen in the presence of Pd on C. The application of these two, distinct, reductive cyclisation pathways to a variety of palladium-catalyzed Ullmann cross-coupling products is detailed.

![Scheme 4: Complementary Modes of Reductive Cyclisation of α- and β-Nitroarylated-α,β-unsaturated Ketones](image)

In one intriguing variant of these TiCl₃-based reductive cyclisation protocols wherein a ketone such as acetone is included in the reaction mixture then not only was the direct reduction product observed, namely an aniline such as 23, but the solvent-incorporated dihydroquinolone 24 was co-produced. The scope and limitations of such novel processes were examined and established that a range of novel,
heterocyclic systems could be formed, including ones incorporating, for example, added benzophenone.


Previous attempts to utilize ortho-substituted haloarenes other than the highly electron-deficient o-halonitroarenes such as 1 or 15 in the palladium-catalyzed Ullmann cross-coupling reactions had met with limited success. Such outcomes are attributed to the weaker electron-withdrawing properties of substituents other than the nitro group. During investigations on the use of o-iodophenol 25 in the title reaction, the benzofuran 27 (Scheme 5) was produced, albeit initially in modest yield. After some further studies it was established that by adding a base to the reaction mixture or replacing the copper powder with copper(I) iodide, greater quantities of compound 27 could be obtained and, significantly, in a one-pot process.

Scheme 5: One-pot Synthesis of Benzofuran 27 via a Tandem Ullmann–Goldberg Cross-Coupling/Cyclopalladation–Reductive Elimination Reaction

The development of such observations into a useful new method for forming benzofurans, indoles and related heterocyclic systems forms the basis of Publication 4. The fact that copper powder was not necessary for such reactions to
proceed indicated that a palladium-catalyzed Ullmann cross-coupling was not involved. Rather, and as suggested by various control experiments, an Ullmann–Goldberg coupling of iodophenol 25 and β-iodoenone 26 was taking place to afford the (isolable) aryl ether 28 that engages in a cyclopalladation/reductive elimination sequence to give the observed benzofuran 27.

This reaction sequence was applied to various combinations of either phenols or anilines (as the nucleophilic coupling partners) and β-halogenated-α,β-unsaturated ketones and so affording a range of benzofurans and indoles by a pathway that complements the palladium-catalyzed Ullmann cross-coupling/reductive cyclisation protocols detailed in Publication 1.
References


Statement of Contribution

This thesis is submitted as a Thesis by Compilation in accordance with https://policies.anu.edu.au/ppl/document/ANUP_003405

I declare that the research presented in this Thesis represents original work that I carried out during my candidature at the Australian National University, except for contributions to multi-author papers incorporated in the Thesis where my contributions are specified in this Statement of Contribution.

Authors: Fayyaz Khan, Michael Dlugosch, Xin Liu, and Martin G. Banwell
Publication outlet: Accounts of Chemical Research, 2018, 51, 1784
Current status of paper: Published
Contribution to paper: This is a review article that was written by Professor Martin Banwell. It incorporates descriptions of research on palladium-catalyzed Ullmann cross-coupling reactions conducted by the co-authors including Mr Khan.
Senior author or collaborating authors endorsement:

Title: Palladium-Catalyzed Ullmann Cross-Coupling of β-Iodoenones and β-Iodoacylates with o-Halonitroarenes or o-Iodobenzonitriles and Reductive Cyclization of the Resulting Products To Give Diverse Heterocyclic Systems
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Contribution to paper: This is a full paper detailing extensive experimental work on a methodology involving the palladium-catalyzed Ullmann cross-coupling and the reductive cyclisation of those products. Mr Khan carried out 50% of the experimental work reported in the paper. In addition, Mr Khan collated and formatted 50% of the reported spectral data presented in the Supporting Information document. Mr Khan also wrote 50% of the Experimental Section and conducted relevant literature surveys. Professor Martin Banwell wrote the body of the paper.
Senior author or collaborating authors endorsement:

Title: The Reductive Cyclization of o-Nitroarylated-ω,β-unsaturated Aldehydes and Ketones with TiCl$_4$/HCl or Fe/HCl Leading to 1,2,3,9-Tetrahydro-4H-carbazol-4-ones and Related Heterocycles
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Contribution to paper: This is a full paper detailing extensive experimental work on a methodology focusing on producing multiple reductive cyclisation products from the same coupling product. Mr Khan carried out 25% of the experimental work reported in the paper. In addition, Mr Khan collated and formatted 40% of the reported spectral data presented in the Supporting Information document. Mr Khan also wrote 40% of the Experimental Section and conducted relevant literature surveys. Professor Martin Banwell wrote the body of the paper.
Title: Tandem Ullmann–Goldberg Cross-Coupling/Cyclopalladation-Reductive Elimination Reactions and Related Sequences Leading to Polyfunctionalized Benzofurans, Indoles, and Phthalanes

Authors: Faizay Khan, Mehwish Fatima, Moheb Shirzaei, Yen Vo, Madushani Amarasiri, Martin G. Banwell, Chenxi Ma, Jas S. Ward, and Michael G. Gardiner

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Contribution to paper: This is a full paper detailing extensive experimental work on a methodology involving the synthesis of benzofurans, indoles and phthalanes from a tandem Ullmann–Goldberg cross-coupling/cyclopalladation-reductive elimination reaction. Mr Khan carried out approximately half (ca. 50%) of the experimental work reported in the paper. In addition, Mr Khan collated and formatted approximately half (ca. 50%) of the reported spectral data presented in the Supporting Information document. Mr Khan also wrote the whole of the Experimental Section and conducted relevant literature surveys. Professor Martin Banwell wrote the body of the paper.

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Publication One

The Palladium-Catalyzed Ullmann Cross-Coupling Reaction: A Modern Variant on a Time-Honored Process

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The Palladium-Catalyzed Ullmann Cross-Coupling Reaction: 
A Modern Variant on a Time-Honored Process

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CONSPECTUS: Cross-coupling reactions, especially those that are catalyzed by palladium, have revolutionized the way in which carbon–carbon bonds can be formed. The most commonly deployed variants of such processes are the Suzuki–Miyaura, Mizoroki–Heck, Stille, and Negishi cross-coupling reactions, and these normally involve the linking of an organohalide or pseudohalide (such as a triflate or nonaflate) with an organo-metallic or -metalloid such as an organo-boron, -magnesium, -tin, or -zinc species. Since the latter type of coupling partner is often prepared from the corresponding halide, methods that allow for the direct cross-coupling of two distinct halogen-containing compounds would provide valuable and more atom-economical capacities for the formation of carbon–carbon bonds. While the venerable Ullmann reaction can in principle achieve this, it has a number of drawbacks, the most significant of which is that homocoupling of the reaction partners is a competitive, if not the dominant, process. Furthermore, such reactions normally occur only under forcing conditions (viz., often at temperatures in excess of 250 °C). As such, the Ullmann reaction has seen only limited application in this regard, especially as a mid- to late-stage feature of complex natural product synthesis. This Account details the development of the palladium-catalyzed Ullmann cross-coupling reaction as a useful method for the assembly of a range of heterocyclic systems relevant to medicinal and/or natural products chemistry. These couplings normally proceed under relatively mild conditions (<100 °C) over short periods of time and, usually, to the exclusion of (unwanted) homocoupling events. The keys to success are the appropriate choice of coupling partners, the form of the copper metal employed, and the choice of reaction solvent. At the present time, the cross-coupling partners capable of engaging in the title reaction are confined to halogenated and otherwise electron-deficient arenes and, as complementary reactants, α- or β-halogenated, αβ-unsaturated aldehydes, ketones, esters, lactones, lactams, and cycloimides. Nitro-substituted (and halogenated) arenes, in particular, serve as effective participants in these reactions, and the products of their coupling with the above-mentioned carbonyl-containing systems can be manipulated in a number of different ways. Depending on the positional relationship between the nitro and carbonyl groups in the cross-coupling product, the reduction of the former group, which can be achieved under a range of different conditions, provides, through intramolecular nucleophilic addition reactions, including Schiff base condensations, access to a diverse range of heterocyclic systems. These include indoles, quinolines, quinolones, isoquinolines, carbazoles, and carbolines. Tandem variants of such cyclization processes, in which Raney cobalt is used as a catalyst for the chemoselective reduction (by dihydrogen) of nitro and nitrile groups (but not olefins), allow for the assembly of a range of structurally challenging natural products, including marinoquinoline A, (±)-1-acetylaspidolbidine, and (±)-gilbertine.

1. INTRODUCTION

Arguably, carbon–carbon bond formation is the most important process in organic chemistry, and the development of means for doing so has been a source of conscious effort for almost two centuries.¹ In modern times, cross-coupling reactions, perhaps most especially those catalyzed by palladium, nickel, copper, and iron species, have revolutionized the way in which more complex organic compounds are assembled from simpler ones.² Named reactions such as the Suzuki–Miyaura, Mizoroki–Heck, Stille, Sonogashira, and Negishi cross-couplings immediately spring to mind in considering such matters.²⁴ The coupling partners involved in these processes are normally an organohalide or pseudohalide (e.g., a triflate or nonaflate) and an organo-metallic species that is, more often than not, obtained from a halide precursor. In view of this and the frequently unstable/sensitive nature of the organometallic species, there have been many efforts directed at effecting the reductive cross-coupling of two structurally distinct organohalides, the most conspicuous examples of which involve adaptations of the venerable Wurtz¹ and Ullmann³ reactions. In their traditional forms, however, these processes have not found extensive application because of competition from homocoupling reactions and/or the need to use rather aggressive reaction conditions that are incompatible with other functionalities.

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present in the substrates. In recent times, so-called cross-electrophile couplings (XECs), especially ones carried out in reductive mode and often involving multimetallic catalysts, have come to the fore, with notable contributions having been reported in the past few years by various groups. The versatility of such processes is quickly becoming apparent. Herein we detail the outcomes of our own ongoing work concerned with the development of the palladium-catalyzed Ullmann cross-coupling reaction of structurally distinct, sp²-hybridized, halogen-associated electrophiles with one another. These reactions enable the construction of products that are useful in their own right and/or can participate in reductive cyclization reactions and thus affording various heterocyclic motifs encountered in a range of interesting natural products.

2. THE CLASSICAL ULLMANN REACTION
The Ullmann reaction (Scheme 1) was first reported in 1901 and in the intervening period has found extensive application in chemical synthesis, most notably in the reductive coupling of aryl halides (e.g., 1) to form the corresponding symmetrical biaryls (e.g., 2). Its limitations also became evident rather quickly. These include the need to use high reaction temperatures (>200 °C), the attendant functional group incompatibilities, an inability to cleanly generate unsymmetrical biaryls from two structurally distinct aryl halide precursors (because of competing homocoupling processes), and the frequently erratic yields obtained. Manifold efforts to redress such deficiencies have been undertaken over the years, including through the application of on-surface processes, the introduction of metal-chelating species, and the use of varying forms of copper as well as other metal species. These have had useful impacts, as summarized in a range of recent review articles.

3. DISCOVERY OF THE PALLADIUM-CATALYZED ULLMANN CROSS-COUPING REACTION
Some years ago, in connection with work directed toward establishing a total synthesis of the alkaloid rhazinal, a potent spindle toxin, we required access to an arylated pyrrole. We initially attempted to prepare this key intermediate through conventional Ullmann cross-coupling of commercially available o-bromonitrobenzene (1) with the known iodinated pyrrole 3 (see Scheme 2), but only traces of target 4 were obtained. Upon undertaking an extensive literature survey, we came across the work of Thompson and Shimizu, both of whom reported that the synthesis of certain arylated pyridines through the Ullmann cross-coupling of the relevant aryl halide and halogenated pyridine is greatly facilitated by the addition of a palladium catalyst. Upon applying such observations to our system, using DMF as solvent and three equivalents of compound 1, we were able to obtain, under ultrasonication conditions, target 4 in 88% yield (based on recovered starting material (brsm)), with the major byproduct being 2,2′-dinitrobiphenyl (2) (55%) (Scheme 2).

These observations triggered extensive studies of the title process that continue in our group to this day. These studies have provided, through the reductive cyclization of the initially formed cross-coupling products, useful new means for the construction of a wide range of heterocyclic compounds, including ones embodying previously unreported frameworks. Details of these processes are presented in the following sections and categorized according to the heterocyclic frameworks that are generated.

4. APPLICATION TO THE SYNTHESIS OF HETEROCYCLES

4.1. Indoles
Our first efforts to comprehensively develop the title reaction involved the cross-coupling of readily available α-haloenones and -enals with o-halonitroarenes and the reductive cyclization of the ensuing α-arylated-enones and -enals to give indoles, including annulated variants. The simple reaction sequences shown in Scheme 3 serve to highlight the possibilities for the assembly of such heterocycles, and others have since exploited these processes in the total synthesis of a range of natural products. Some of our own efforts in this regard are detailed in the next section.

In the course of optimizing these sorts of cross-coupling processes, we established that a range of different sources of Pd[0] can be used, that DMSO appears to be the optimal solvent, that electron-deficient, halogenated arenes are required, and that a lower reaction temperature leads to a better ratio of cross-coupling to homocoupling products. Indeed, in favorable circumstances the cross-coupling reactions can be conducted at near ambient temperatures and essentially to the exclusion of the homocoupling process. Thus, a close to 1:1 ratio of coupling partners could often be employed, an important consideration in exploiting these processes in complex natural product synthesis, where such transformations are exploited at a late stage. Mechanistically speaking, we believe that these couplings proceed as suggested by Shimizu.
(see the penultimate section for details), wherein palladium\([0]\) oxidatively adds to the \(\alpha\)-iodo-enone or -enal and the resulting palladium\([II]\) complex reacts with the ortho-cuprated nitro-arene arising from the other coupling partner, thereby producing a palladated intermediate that undergoes reductive elimination to deliver the observed product (and, of course, regenerates the Pd\([0]\) catalyst). The nature of the copper used in these reactions has some impact on the efficiency of the process, with freshly prepared activated copper \(12\) being particularly effective though somewhat tedious to prepare. The simple expedient of adding some sand to the reaction mixture containing normal copper powder (copper bronze), and thus continuously generating a fresh metal surface through abrasion, is an operationally simple means of achieving often equivalent outcomes. Furthermore, adding small amounts of cuprous iodide to the starting reaction mixture can enhance the desired process,\(^{11b}\) although the precise origins of this benefit remain to be fully understood.

Highly functionalized indolic substructures are encountered in therapeutically significant alkaloids such as vincristine (Scheme 4), and we sought to establish methods for assembling these using our protocols.\(^{13}\) In a representative process, \(\alpha\)'-carbomethoxylated cycloheptenone \(12\) was subjected to Pinhey arylation with plumbated indole \(13\), thereby affording compound \(14\), which was itself engaged in a Johnson-type \(\alpha\)-iodination\(^{14}\) reaction to afford iodide \(15\). The palladium-catalyzed Ullmann cross-coupling of this last compound with \(o\)-iodonitrobenzene \(5\) gave product \(16\), which upon reductive cyclization afforded bis(indole) \(17\) embodying key structural elements associated with the “Southern” hemisphere of vincristine.
4.2. Oxindoles

Oxindoles, which represent privileged structures in medicinal chemistry and motifs encountered in biologically active natural products,\textsuperscript{15} are readily obtained using analogous processes wherein an \( \alpha \)-brominated \( \alpha,\beta \)-unsaturated cycloimide, lactam, or lactone is used as the coupling partner in a reaction with an \( o \)-halonitroarene and the product of this process then subjected to reductive cyclization.\textsuperscript{15} The efficient and \textsuperscript{18} (Scheme 5) to produce arylated \( N \)-methylmaleimide \textsuperscript{19} followed by its reductive cyclization under standard conditions to give oxindole \textsuperscript{20} is illustrative of these types of processes.

4.3. Quinolines and Related Heterocycles

A further extension of our original processes, as shown in Scheme 3, has allowed the formation of quinolones and related systems. In such cases (Scheme 6), the electrophiles employed are \( \beta \)-halo-enals, -enones, or -esters. So, for example, the cross-coupling of arene \textsuperscript{2} with aldehyde \textsuperscript{21} affords arylated enal \textsuperscript{22}, which, upon reductive cyclization, produces cyclopenta-annulated quinolone \textsuperscript{23}. In a related but less efficient manner, cross-coupling of compounds \textsuperscript{2} and \textsuperscript{24} affords ester \textsuperscript{25} which upon reductive cyclization delivers the \( 2 \)-quinolone \textsuperscript{26}. By similar means a range of alternately substituted/annulated quinolones, phenanthridines, and \( 6(5H) \)-phenanthridinones can be obtained. The capacity to generate electrophiles such as \textsuperscript{21} directly from the corresponding ketone (in this case cyclopentenone) through a Vilsmeier–Haack haloformylation reaction is likely to enhance the utility of these processes.\textsuperscript{16}

4.4. Carbazoles

When \( \alpha \)-iodocyclohex-2-en-1-ones are cross-coupled with halogenated nitroarenes such as \textsuperscript{1} and \textsuperscript{5} using the protocols detailed above and the aryl enone products are subjected to reductive cyclization, tetrahydrocarbazoles are obtained. Given
that their fully aromatic counterparts (viz., carbazoles) are encountered in a wide range of biologically active natural products, we sought to produce such heterocycles using variations of our earlier protocols. The routes to clauszoline K and karapinchamine A shown in Scheme 7 are illustrative of the possibilities the title reaction offers in this regard. Thus, reductive cross-coupling of electrophiles 27 and 28 under our now standard conditions afforded product 29 (80%), which upon reductive cyclization using dihydrogen in the presence of Raney nickel afforded tetralydrocarbazole 30 (65%). This could then be oxidized to its fully aromatic counterpart, namely carbazole 31 (88%), upon exposure to 10% Pd on C in diphenyl ether at 210 °C (various attempts to effect the conversion 29 → 31 in a direct manner, or at least in a one-pot-process, have been unsuccessful to date). Upon exposure of compound 31 to 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) it was oxidized, in 66% yield, to the natural product clauszoline K (32). On the other hand, treatment of compound 31 with BBr3 effected cleavage of the associated ether residue and, thereby, the formation of the anticipated phenolic product 33 (84%). Deprotonation of the latter compound with n-butyllithium and reaction of the ensuing anion with geranyl bromide resulted in alkylation at nitrogen and the formation of the carbazole-containing natural product karapinchamine A (34), which was obtained in 50% yield.

4.5. Carbolines

There are four isomeric carbolines, namely, the α, β, γ, and δ forms (35–38, respectively; Figure 1), and each of these frameworks is encountered in both natural products and pharmacologically active agents. While various methods have been developed for their synthesis, a unified approach to them had remained elusive until our recent deployment of the title cross-coupling reaction for this purpose.

An illustrative example of our approach is presented in Scheme 8. It starts with the palladium-catalyzed Ullmann cross-coupling of bromonitropyridine 39 with readily available α-iodinated cyclohexenone 40. Engaging the ensuing product 41 (80%) in a reductive cyclization reaction gives tetrahydrocarboline 42 (83%), which is then dehydrogenated to give the fully aromatic compound 43 (83%) representing the structure of the natural product harman.

The challenge associated with deploying this type of approach to the carbolines is the need to construct the requisite polysubstituted pyridine-based coupling partner. Thus, for example, the nitrination reaction associated with the synthetic sequence leading to compound 39 also produced a regiosomer, and these could only be separated from one another by HPLC techniques.

4.6. β-Haloenones and Related Compounds as Cross-Coupling Partners

Recently we have established that β-haloenones such as 44 couple particularly effectively with electrophiles including 5 (Scheme 9) to form the anticipated cross-coupling product 45 (91%), a compound that upon exposure to standard reductive cyclization conditions using methanol as the solvent affords 3,4-benzomorphan 46 in 73% yield. In a further illustration of the extensive utility of these types of processes, the coupling of brominated pyridine 47 with the β-iodinated crontonate 48 proceeded with retention of configuration and afforded the anticipated product 49 (84%). Reductive cyclization of this last compound using iron filings in an acidic medium then gave the 1,8-naphthyridin-2(1H)-one 50 (76%). Interestingly, o-iodobenzoazinones can be engaged in related couplings, although these are less efficient than those involving iodinated nitroarenes, presumably because of the weaker electron-withdrawing properties of the cyano group.

4.7. Formation of Unsymmetrical Biaryls

An obvious application of the title reaction is in the production of unsymmetrical biaryls. While we have yet to explore such processes in any comprehensive fashion, early indications have been very positive. Thus, as shown in Scheme 10 for example, the cross-coupling of aryl iodide 51 with bromide 52 under our by now standard conditions provided the desired biaryl 53 (60%). This last compound was readily elaborated to the alkaloid zephycandidine III, a natural product reported to possess acetylcholinesterase (AChE) inhibitory properties, which were not evident in the synthetically derived material despite the spectroscopic equivalence of the natural and synthetic materials. More pertinent to the present discussion is that all our attempts to prepare compound 53 and related systems using Suzuki–Miyaura cross-coupling reactions were unsuccessful.

5. APPLICATION TO THE TOTAL SYNTHESIS OF NATURAL PRODUCTS

As our understanding of the palladium-catalyzed Ullmann cross-coupling reaction has developed, we have been exploiting it on an increasingly frequent basis in developing syntheses of various natural products. Such is our confidence in the reliability of the process that we have often deployed it at relatively advanced stages of synthetic pathways, normally in

Figure 1. The four isomeric carbolines.
conjunction with reductive cyclization reactions that enable the conversion of the cross-coupling products into various heterocyclic frameworks. Specific examples are given in the following sections.

5.1. Synthesis of Marinoquinoline A

As part of an ongoing interest in the cross-coupling chemistries of pyrroles, we were attracted to the development of a synthesis of marinoquinoline A, an alkaloid isolated from a marine gliding bacterium that displays AChE inhibitory and antimalarial activities. The route that we ultimately established in obtaining this compound is shown in Scheme 11. It starts with the palladium-catalyzed Ullmann cross-coupling of o-bromonitrobenzene (1) with iodinated pyrrole 54 to afford the target 55 in 74% yield. Significantly, all of our attempts to effect the Suzuki–Miyaura cross-coupling of compound 54 with o-nitrophenylboronic acid failed. In a related vein, when o-iodonitrobenzene (5) was used as a coupling partner in this process, its homocoupling (to give 2,2′-dinitrobiphenyl) became the dominant process. Such outcomes highlight the capacity to facilitate cross-coupling processes by attenuating the reactivity of one substrate through changing the associated halogen.

The elaboration of coupling product 55 to the target alkaloid was straightforward and involved the initial addition of methyllithium to the associated aldehyde residue and oxidation of the resulting alcohol, 56, to the corresponding methyl ketone 57 using the Dess–Martin periodinane (DMP). Reductive cyclization of this last compound to the target framework was effected using magnesium in methanol, and this was accompanied by cleavage of the tosyl group, thus affording marinoquinoline A (58) in 85% yield.

5.2. Total Syntheses of the Aspidosperma Alkaloids Aspidospermidine, Limaspermidine, and 1-Acetylaspidoalbidine and Approaches to Vindoline

In a more elaborate reaction sequence and as part of an ongoing campaign to develop a synthesis of the binary indole–indoline alkaloid vincristine (see Scheme 4), we first developed a route to the alkaloid aspidospermidine. This entailed, as one of two key steps, the cross-coupling of α-iodinated cyclohexenone 59 with arene 5 to afford product 60 in 75% yield (Scheme 12). Compound 60 was readily elaborated to azide 61 that upon heating engaged in an intramolecular [3 + 2] cycloaddition reaction followed by nitrogen extrusion to afford azidine 62, thereby establishing the piperidine ring associated with the final product. Various straightforward steps, including a TiCl₄-mediated reductive cyclization reaction, were
then deployed in elaborating compound 62 to aspidospermidine.

A related but more convergent protocol was employed in obtaining the alkaloid limaspermidine.24 As shown in Scheme 13, compounds 5 and 63 were cross-coupled to give the α-arylated enone 64 (85%). When this was subjected to reductive cyclization using dihydrogen in the presence of Raney cobalt, the indole-annulated and cis ring-fused octahydroquinoline 65 was obtained in 85% yield. This conversion involves the selective reduction of the nitro and cyano groups within substrate 64 while the enone moiety remains intact. As a result, the associated ketone carbonyl engages in an intramolecular Schiff base condensation reaction with the aniline or N-hydroxyaniline arising from reduction of the nitro group while the 1° amine arising from the cyano residue undergoes a hetero-Michael addition reaction, thus forming both the indole and piperidine rings in a one-pot operation. The use of properly prepared Raney cobalt is critical to the success of this transformation because of the chemoselectivities it allows for. If the more active Raney nickel is used as the catalyst, then reduction of the carbon–carbon double bond of the enone residue also occurs, with the result that piperidine ring formation does not take place.24 Elaboration of compound 65 to (±)-limaspermidine was achieved over four additional steps, including several closely related to those employed in the conversion of compound 62 into (±)-aspidospermidine (Scheme 12). Two additional steps, including an oxidative cyclization reaction employing mercuric acetate, were required to convert (±)-limaspermidine into (±)-1-acetylaspidolabdine.24

The extension of the protocols defined above in an enantioselective approach to the alkaloid vindoline (representing a crucial substructure of vincristine) is shown in Scheme 14.26 Cross-coupling of iodinated nitroarene 66 with homochiral α-iodinated cyclohexenone 67 (a compound obtained from an enzymatically derived cis-1,2-dihydrocatechol27) gave the anticipated product 68 in 92% yield. Reduction of this last compound using dihydrogen in the presence of Raney cobalt resulted in the formation of the tandem reductive cyclization product 69 (85%) embodying a cis ring-fused octahydroquinoline. Over a further four steps this could be elaborated to the hexacyclic compound 70 embodying many of the features of vindoline, which we are seeking to convert into that alkaloid.

5.3. Formal Total Synthesis of the Cage-like Alkaloid Kopsihainanine A

The tandem reductive cyclizations of the palladium-catalyzed Ullmann cross-coupling products 64 and 68 are presumed to proceed under kinetic control, thus affording cis ring-fused products. Given that trans ring-fused perhydroquinolines are encountered in a range of natural products, we sought methods to access such systems. Despite extensive investigations of the cyclization reactions, including examination of a range of modifications to the conditions employed, the cis ring-fused products were invariably formed on an exclusive basis.
Therefore, we sought ways to effect epimerization at the ring-junction carbon center bearing the piperidine nitrogen. This turned out to be a straightforward process, as illustrated in our formal total synthesis of the cage-like alkaloid kopsihainanine A (Scheme 15). The reductive cyclization product could be converted, over five steps, into the angularly allylated congener, which upon exposure to iodosobenzene in dichloromethane at ambient temperatures was oxidized to the corresponding imine. Upon reduction of compound with sodium borohydride, the epimeric octahydroquinoline was obtained. Since this last compound has previously been converted into kopsihainanine A, the illustrated synthetic sequence constitutes a formal total synthesis of the racemic modification of this alkaloid.

5.4. Syntheses of the Uleine Alkaloids and Approaches to the Strychnos Alkaloids

Another cross-coupling/tandem reductive cyclization sequence, shown in Scheme 16, has allowed syntheses of various members of the uleine family of alkaloids. Cross-coupling of compounds 5 and 74 under the usual conditions afforded the anticipated product (88%), and the reductive cyclization of this with dihydrogen in the presence of Raney cobalt afforded the tetracyclic product (60%) as a result of the same type of tandem processes as shown in Schemes 13 and 14. Selective Boc protection of the piperidine nitrogen within compound afforded carboxylate, and this could be elaborated over two steps, including a pyridinium chlorochromate-mediated oxidation reaction to introduce a carbonyl moiety at the methylene adjacent to the indole ring, to hydroxyketone. Reaction of this last compound with methyllithium proceeded smoothly, and the resulting tertiary alcohol engaged in a cycloetherification reaction upon treatment with protic acid. Cleavage of the Boc group also occurred under these conditions, and the resulting 2° amine was subjected to reductive N-methylation to afford (±)-gilbertine.

By means of closely related protocols, the somewhat simpler uleine alkaloids shown in Figure 2 could also be prepared in a...
stereoselective manner,\textsuperscript{29b} while the ABCDE ring system of the \textit{Strychnos} alkaloids proved accessible by similar means.\textsuperscript{30}

6. MECHANISTIC AND SYNTHETIC OVERVIEW

Our current thinking about the title process is dominated by the original mechanistic proposals of Shimizu.\textsuperscript{9} Thus, as shown in Scheme 17, aryl iodide 79 is presumed to react with the added copper through an oxidative addition/reductive deiodination process to give arylcopper(I) 80, representing the aryl anion synthon 81. This reacts with the aryl cation synthon 82, which is produced through oxidative addition of Pd[0] to the carbonyl-containing coupling partner 83, thus affording intermediate 84. The coupling event presumably

Scheme 16. Total Synthesis of the Alkaloid (±)-Gilbertine

Scheme 17. Mechanistic and Synthetic Analysis of a Key Example of the Palladium-Catalyzed Ullmann Cross-Coupling Reaction and Certain Currently Problematic Substrates

Figure 2. Structures of the simpler uleine alkaloids.
involves nucleophilic substitution at the palladium of intermediate 84 by organometallic 80, and after reductive elimination product 85 is formed. Concurrently, of course, a Pd[0] species is formed and re-enters the catalytic cycle. Presumably, analogous pathways are involved in the potentially broadly applicable couplings shown in Schemes 9 and 10. Currently problematic substrates are also shown in Scheme 17.

While the majority of the title cross-coupling reactions we have studied to date are of the general form shown in Scheme 17, their utility is considerable because of the differing modes of reductive cyclization that can be applied to the products 85. Thus, as demonstrated in the multitude of settings presented above, when such products incorporate a nitro group, cyclizations using dihydrogen in the presence of various catalysts provide a range of indoles of the general form 86. Using TiCl₃ or iron filings in acidic media for the same purpose provides alternate cyclization products, while recent but thus far unpublished work has shown that certain nitro-containing coupling products 85 (X = CN) can be converted into isoquinolines of the general form 87.

It remains to be seen precisely how far palladium-catalyzed Ullmann cross-coupling reactions can be extended beyond those involving substrates incorporating the strongly electron-attracting nitro and nitrile groups. Therefore, one of the challenges in this regard will be defining, if possible, how to engage more electron-rich coupling partners in analogous reactions.

7. FUTURE PROSPECTS

As is the case with other emergent XEC processes, the title one is proving effective in a range of settings, most particularly when combined with reductive cyclization reactions that thereby afford heterocyclic compounds. Investigations of intramolecular variants of the title XECs are also likely to be profitable areas of research. Furthermore, our recent discovery that γ-halobenzonitriles are also capable of engaging in palladium-catalyzed Ullmann cross-coupling reactions suggests that access to other types of heterocyclic systems (e.g., 87) will become available through the reductive cyclization of such products. Of course, the development of a more detailed mechanistic understanding of the palladium-catalyzed Ullmann cross-coupling reaction, including the role of additives such as cuprous iodide, will provide an important basis for further developments in the area.

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■ REFERENCES

(1) The Kolbe synthesis of acetic acid from carbon disulfide was reported over 170 years ago. See: Kolbe, H. Beiträge zur Kenntniss der gepaarten Verbindungen. Ann. Chem. Pharm. 1845, 54, 145–188. It is arguably the first “conscious” synthesis involving C–C bond formation. Indeed, Kolbe is attributed with the introduction of the term “synthesis” in the manner that it is used today. The Wurtz coupling reaction was first reported in 1885. See: Wurtz, A. Sur une nouvelle classe de radicaux organiques. Ann. Chem. Phys. 1885, 44, 275–312.


(6) The homo- and cross-coupling of aryl halides using palladium catalysts without copper present have also been described as “Pd-catalyzed Ullmann coupling reaction” (sic). See: Ohtaka, A.; Sakon, A.; Yasui, A.; Kawaguchi, T.; Hamasaka, G.; Uozumi, Y.; Shinagawa, T.; Shimomura, O.; Nomura, R. Catalytic specificity of linear polystyrene-stabilized Pd nanoparticles during Ullmann coupling reaction in water and the associated mechanism. J. Organomet. Chem. 2018, 854, 87–93. In contrast, the present discussion of this topic is concerned with processes in which both palladium and copper are present.


(27) For a recent review of the other applications of these enzymatically-derived compounds in chemical synthesis, see: Taher, E. S.; Banwell, M. G.; Buckler, J. N.; Yan, Q.; Lan, P. The Exploitation of Enzymatically-Derived cis-1,2-Dihydrocarboxates and Related Compounds in the Synthesis of Biologically Active Natural Products. Chem. Rev. 2018, 118, 239–264.


(32) Cadogan-type cyclizations of compounds related to 49 (Scheme 9) have been reported. See: Yamamoto, Y.; Yamada, S.;...

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

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Supporting Information

ABSTRACT: The palladium-catalyzed Ullmann cross-coupling of β-iodoenones and β-iodoacrylates such as 5 (X = I) with o-halonitroarenes and o-iodobenzonitriles 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 3,4-benzomorphan derivative 43.

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

In the intervening period, we have extended these protocols to the preparation of quinolones, 2-quinolones, phenanthridines, 6(5H)-phenanthridinones, oxindoles, carbazoles, and carbolines.3 In addition, we have been able to apply them in the 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. As shown in Scheme 2, our initial studies involved an examination of the cross-coupling of readily available β-halo-2-cyclohexen-1-ones 5 (X = Br, I)6 with o-halonitrobenzene 2 or 6 in anticipation of forming β-arylated 2-cyclohexen-1-one 7.

Products of this type, which have been prepared previously by less direct methods,7 were targeted because they have been

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shown to engage in efficient reductive cyclization reactions to form carbazoles, including one that has served as a precursor to the carbazole alkaloid clausenalene. A series of cross-coupling experiments involving both the brominated and iodinated forms of the 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, when these were used in conjunction with 5 equiv of copper powder, 5 mol % Pd(dppf)Cl2, CH2Cl2, and DMSO as the solvent, 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% yield, respectively, while the 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 prepared 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, bromonitropyridines 12, 13, 14 were cross-coupled with enone 5 (X = I) to afford 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 with arene 13 to give compound 19 (87%), the structure of which was confirmed by X-ray analysis (see the SI).

β-Iodobenzonitriles also cross-couple with β-iodoenones, as demonstrated by the successful reaction of the easily accessible compounds 20, 21, 22, and 23 (Figure 2) with 5 (X = I) to give products 24 (40%), 25 (61%), 26 (34%), and 27 (79%), respectively. The poorer yields associated with these o-iodobenzonitrile-based couplings are attributed to the weaker electron-withdrawing capacities of the nitrile group compared with the nitro group and, therefore, the intervention of competing homocouplings of the reaction partners. β-Iodinated acrylates proved to be generally competent partners in palladium-catalyzed Ullmann cross-couplings with o-iodonitrobenzenes and o-iodobenzonitriles. For example, when methyl (Z)-3-iodobut-2-enoate (28) (Figure 3) was reacted with compounds 13, 14, 20, 23, and 29 under the usual conditions, the cross-coupling products 30 (84%), 31 (69%), 32 (55%), 33 (43%), and 34 (59%), respectively, were obtained.

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

Many of the cross-coupling products described above engage in useful reductive cyclization processes, thus giving rise, in a direct manner, to heterocyclic frameworks of synthetic and/or biological relevance. For example, upon exposure of 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 and the product aniline underwent spontaneous cyclization onto the pendant ester residue, thus forming 8-azaquinolone 39 in 76% yield.

Under analogous conditions, cinnamate 36 was converted into quinolone 40 (67%) while when the same substrate was exposed to hydrogen in the presence of 10% palladium on carbon more extensive reduction occurred to a dihydridroquinolone 41 (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 → 42 shown in Scheme 3. 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 cyclization processes are observed when the β-aryl-2-cycloalken-1-one coupling products are employed 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 3,4-benzomorphan 43 (73%), while analogous treatment of a toluene solution of the same substrate afforded compound 44 (64%) bearing a bridgehead hydroxyl group. In a similar manner, a methanolic solution of cross-coupling product 10 was converted into B-norbenzomorphan 45 (43%). The structures of compounds 43 and 45 were confirmed through X-ray analyses, details of which are provided in the SI.

Deoxygenated variants of compounds 43−45 were readily prepared by the pathways shown in Scheme 5. 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 saturated amino alcohols 48 (75% yield of a 5:3 mixture of cis and trans isomers) and 49 (51% yield of the cis isomer only), respectively. The twofold reduction products 48 and 49 were then converted, under standard conditions, into the corresponding sulfonamides 50 (82% yield of a 5:3 mixture of cis and trans isomers) and 51 (85% yield of the cis isomer only). Compound trans-50, for which a single-crystal X-ray analysis was obtained (see the SI for details), readily engaged in a Mitsunobu cyclization reaction upon exposure to Ph3P/diethyl azodicarboxylate (DEAD), affording 3,4-benzomorphan 52 (89%). Unsurprisingly, the congener cis-50 failed to cyclize under these same conditions. On the other hand, successive treatment of compound cis-51 under Appel conditions using CCl4 and Ph3P gave what is presumed to be the corresponding trans-chloride, which upon
treatment with potassium carbonate in methanol cyclized to give norbenzomorpham S3 in 86% yield.

Presumably, these protocols could be readily adapted to the preparation of the nonracemic forms of these heterocycles through, for example, enantioselective 1,2-reduction of the starting enones 7 and 10. In view of the extensive and ongoing interest in benzomorphans 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 report19 that compound 36 (prepared by different means than those described here) can be engaged in a Cadogan cyclization to give 2-carboethoxy-3-phenylindole in 90% yield. As such, the work described here) can be engaged in a Cadogan cyclization to give a wide range of products capable of engaging in various useful reductive cyclization processes, 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.8b01015.

Experimental procedures, spectroscopic data, crystallographic data, and NMR spectra of compounds S (X = I, Br), S1, S1, S1, bis(cyclohexane)]-1,1’-dione-3,3’-dione, 8–11, 15–19, 24–27, 30–34, 36–47, 49, trans-50, cis-50, cis-51, 52, 53 and trans-N-(2-(3-chlorocyclopentyl)phenyl)-4-methylbenzenesulfonamid (PDF)

**Accession Codes**

CCDC 1832167–1832172 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.

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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**

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**REFERENCES**

Supporting Information for:

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

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1H and 13C 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 and trans-N-(2-(3-chlorocyclopentyl)phenyl)-4-methylbenzenesulfonamide S36
General Experimental Protocols

Unless otherwise specified, proton ($^1$H) and carbon ($^{13}$C) NMR spectra were recorded at room temperature in base-filtered CDCl$_3$ on a spectrometer operating at 400 MHz for proton and 100 MHz for carbon nuclei. For $^1$H NMR spectra, signals arising from the residual protio-forms of the solvent were used as internal standards. $^1$H NMR data are recorded as follows: chemical shift ($\delta$) [multiplicity, coupling constant(s) $J$ (Hz), relative integral] where multiplicity is defined as: $s =$ singlet; $d =$ doublet; $t =$ triplet; $q =$ quartet; $m =$ multiplet or combinations of the above. The signal due to residual CHCl$_3$ appearing at $\delta_H$ 7.26 and the central resonance of the CDCl$_3$ “triplet” appearing at $\delta_C$ 77.0 were used to reference $^1$H and $^{13}$C NMR spectra, respectively. IR spectra were recorded, using neat samples, on an attenuated total reflectance (ATR) infra-red spectrometer. Low-resolution ESI mass spectra were recorded on a single quadrupole liquid chromatograph-mass spectrometer, while high-resolution measurements were conducted on a time-of-flight instrument. Low- and high-resolution EI mass spectra were recorded on a magnetic-sector machine. Melting points were measured on an automated melting point system and are uncorrected. Analytical thin layer chromatography (TLC) was performed on aluminum-backed 0.2 mm thick silica gel 60 F$_{254}$ plates. Eluted plates were visualized using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included phosphomolybdic acid : ceric sulfate : sulfuric acid (conc.) : water (37.5 g : 7.5 g : 37.5 g : 720 mL) or potassium permanganate : potassium carbonate : 5% sodium hydroxide aqueous solution : water (3 g : 20 g : 5 mL : 300 mL). Flash chromatographic separations were carried out following protocols defined by Still et al.$^1$ with silica gel 60 (40–63 µm) as the stationary phase and using the AR- or HPLC-grade solvents indicated. Starting materials, reagents and drying agents as well as other inorganic salts were generally available from commercial sources and used as supplied. Tetrahydrofuran (THF), diethyl ether, methanol, acetonitrile and dichloromethane were dried using a solvent purification system that is based upon a technology originally described by Grubbs et al.$^2$ Where necessary, reactions were performed under a nitrogen atmosphere.
Specific Chemical Transformations

**Compound 5 (X = I)**

\[
\text{\chem{5 (X = I)}}
\]

A magnetically stirred solution of triphenylphosphine (2.89 g, 11.0 mmol) in dry acetonitrile (50 mL) maintained at 22 °C was treated, in portions, with powdered molecular iodine (2.79 g, 11.0 mmol). After 0.5 h the reaction mixture was treated with triethylamine (1.53 mL, 11.0 mmol) then cyclohexane-1,3-dione (1.12 g, 10.0 mmol) and the resulting mixture heated under reflux for 16 h. The cooled reaction mixture was then concentrated under reduced pressure and the residue thus obtained stirred vigorously with diethyl ether (30 mL) and the supernatant liquid decanted. This process was repeated twice more and the combined organic phases then diluted with 40-60 petroleum ether (50 mL) to precipitate triphenylphosphine oxide. The ensuing mixture was filtered through a plug of TLC-grade silica gel topped with diatomaceous earth and the filtrate concentrated under reduced pressure to afford compound 5 (X = I) (1.84 g, 83%) as a light-yellow oil. The spectral data obtained on this material matched those published in the literature.\(^3\)

**Compound 5 (X = Br)**

\[
\text{\chem{5 (X = Br)}}
\]

A magnetically stirred solution of triphenylphosphine (4.33 g, 16.5 mmol) in dry acetonitrile (75 mL) maintained at 0 °C was treated, dropwise via addition funnel, with a solution of molecular bromine (851 µL, 16.5 mmol) in dry acetonitrile (8.25 mL). The resulting mixture was then warmed to 22 °C and after 0.5 h it was treated with triethylamine (2.30 mL, 16.5 mmol) then cyclohexane-1,3-dione (1.68 g, 15.0 mmol) before being stirred at 22 °C for 16 h then concentrated under reduced pressure. The residue thus obtained was stirred vigorously with diethyl ether (30 mL) and the supernatant liquid decanted. This process was repeated twice more and the combined organic phases then diluted with 40-60 petroleum ether (50 mL) to precipitate triphenylphosphine oxide. The ensuing mixture was filtered through a plug of TLC-grade silica gel topped with diatomaceous earth and the filtrate concentrated under reduced pressure to afford compound 5 (X = Br) (2.05 g, 78%) as a light-yellow oil. The spectral data obtained on this material matched those published in the literature.\(^5\)
Compound 7

A magnetically stirred suspension of compound 5 (X = I) (222 mg, 1.00 mmol), o-iodonitrobenzene (2) (498 mg, 2.00 mmol) and copper powder (318 mg, 5.00 mmol) in dry DMSO (5 mL) maintained at 50 °C was treated with Pd(dppf)Cl₂•CH₂Cl₂ (41 mg, 0.05 mmol). After 18 h the reaction mixture was cooled to 22 °C, diluted with ethyl acetate (5 mL) and the ensuing mixture filtered through a plug of TLC-grade silica gel topped with diatomaceous earth and the solids so retained were washed with ethyl acetate (20 mL). The combined filtrates were washed with ammonia (2 x 25 mL of a 5% v/v aqueous solution), water (2 x 25 mL) and brine (1 x 25 mL) before being dried (Na₂SO₄), filtered, then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (1:9 v/v diethyl ether/toluene elution) and thus affording, after concentration of the appropriate fractions (Rf = 0.2), compound 7 (198 mg, 91%) as a pale-yellow, crystalline solid, m.p. = 74 °C.

¹H NMR (400 MHz, CDCl₃) δ 8.10 (d, J = 7.8 Hz, 1H), 7.67 (t, J = 7.8 Hz, 1H), 7.55 (t, J = 7.8 Hz, 1H), 7.30 (d, J = 7.8 Hz, 1H), 5.98 (s, 1H), 2.58–2.48 (complex m, 4H), 2.25–2.17 (complex m, 2H).

¹³C NMR (100 MHz, CDCl₃) δ 199.0, 160.8, 146.8, 136.7, 134.0, 129.8, 129.7, 127.7, 125.1, 37.4, 31.0, 23.4.

IR (ATR) νmax 2938, 2870, 1659, 1521, 1345, 1257, 1190, 959, 895, 856, 788, 742, 703 cm⁻¹.

MS (ESI, +ve) m/z 240 [(M+Na)+, 100%].

HRMS m/z 218.0813 [M+H]+ (calcd for C₁₂H₁₁NO₃, 218.08112).

Cross-coupling reactions of compound 5 (X = I) such as the one detailed immediately above sometimes delivered small quantities of the corresponding homo-coupling product, viz. [1,1'-bi(cyclohexane)]-1,1'-diene-3,3'-dione and so an authentic sample of this material was produced by the method detailed immediately below.

[1,1'-Bi(cyclohexane)]-1,1'-diene-3,3'-dione

A magnetically stirred mixture of compound 5 (X = I) (222 mg, 1.00 mmol) and copper powder (318 mg, 5.00 mmol) in dry DMSO (5 mL) was heated at 80 °C (41 mg, 0.05 mmol) for 22 h then cooled to 22 °C, diluted with ethyl acetate (5 mL) then filtered through a plug of
TLC-grade silica gel topped with diatomaceous earth and the solids so retained were washed with ethyl acetate (20 mL). The combined filtrates were washed with ammonia (1 x 25 mL of a 5% v/v aqueous solution), water (1 x 25 mL) and brine (1 x 25 mL) before being dried (Na2SO4), filtered, then concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 2:3 v/v ethyl acetate/40-60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions (Rf = 0.2), the title compound\(^5\) (46 mg, 48%) as a brown powder, m.p. = 104 °C.

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 6.29 (s, 2H), 2.52 (td, \(J = 6.2\) and 1.2 Hz, 4H), 2.44 (t, \(J = 6.2\) Hz, 4H), 2.12–2.02 (complex m, 4H).

\(^13\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 199.8, 156.7, 128.1, 37.6, 26.0, 22.4.

IR (ATR) \(\nu_{\text{max}}\) 2951, 2881, 1661, 1637, 1575, 1415, 1328, 1263, 1186, 1144, 899, 770 cm\(^{-1}\).

MS (ESI, +ve) \(m/z\) 213 [(M+Na)+, 100%].

HRMS \(m/z\) 191.1062 [M+H]+ (calcd for C\(_{12}\)H\(_{14}\)O\(_2\), 191.1067).

**Compound 8**

![Image of Compound 8]

A magnetically stirred solution of triphenylphosphine (2.89 g, 11.0 mmol) in dry acetonitrile (50 mL) maintained at 22 °C was treated, in portions, with powdered molecular iodine (2.92 g, 11.5 mmol). After 0.5 h the reaction mixture was treated with triethylamine (1.67 mL, 12.0 mmol) and cyclopentene-1,3-dione (981 mg, 10.0 mmol) then it was heated under reflux 16 h before being cooled and concentrated under reduced pressure. The residue thus obtained was stirred vigorously with diethyl ether (30 mL) and the supernatant liquid decanted. This process was repeated twice more and the combined organic phases then diluted with 40-60 petroleum ether (50 mL) to precipitate triphenylphosphine oxide. The ensuing mixture was filtered through a plug of TLC-grade silica gel topped with diatomaceous earth and the filtrate concentrated under reduced pressure to afford compound 8 (1.37 g, 66%) as a white, crystalline solid. The spectral data obtained on this material matched those published in the literature.\(^3\)

**Compound 9**

![Image of Compound 9]

A magnetically stirred solution of triphenylphosphine (2.89 g, 11.0 mmol) in dry acetonitrile (50 mL) maintained at 22 °C was treated, in portions, with powdered molecular iodine (2.92 g, 11.5 mmol). After 0.5 h the reaction mixture was treated with triethylamine (1.67 mL, 12.0 mmol) and 2-methylcyclopentene-1,3-dione (1.12 g, 10.0 mmol) before being heated under reflux for 18 h. The cooled reaction mixture was concentrated under reduced pressure and the residue thus obtained stirred vigorously with diethyl ether (30 mL) and the supernatant liquid decanted. This process was repeated twice more and the combined organic phases then diluted with 40-60 petroleum ether (50 mL) to precipitate triphenylphosphine oxide. The ensuing mixture was filtered through a plug of TLC-grade silica gel topped with diatomaceous earth and the filtrate concentrated under reduced pressure to afford 9 (1.80 g,
81%) as a pale-yellow, crystalline solid. The spectral data obtained on this material matched those published in the literature.

**Compound 10**

A magnetically stirred suspension of compound 8 (728 mg, 3.50 mmol), o-iodonitrobenzene (2) (1.74 g, 7.00 mmol) and copper powder (1.11 g, 17.5 mmol) in dry DMSO (15 mL) maintained at 50 °C was treated with Pd(dppf)Cl₂•CH₂Cl₂ (143 mg, 0.18 mmol). The ensuing mixture was stirred at 50 °C for 17 h then cooled to 22 °C and diluted with ethyl acetate (15 mL) before being filtered through a plug of TLC-grade silica gel topped with diatomaceous earth. The solids so retained were washed with ethyl acetate (60 mL) and the combined filtrates washed with ammonia (2 x 75 mL of a 5% v/v aqueous solution), water (2 x 75 mL) and brine (1 x 75 mL) before being dried (Na₂SO₄), filtered, then concentrated under reduced pressure. The ensuing residue was subjected to flash column chromatography (silica, 1:9 v/v diethyl ether/toluene elution) and thus affording, after concentration of the appropriate fractions (Rf = 0.2), compound 10 (663 mg, 93%) as a pale-yellow powder, m.p. = 89 °C.

**¹H NMR** (400 MHz, CDCl₃) δ 8.06 (dd, J = 7.8 and 1.0 Hz, 1H), 7.69 (td, J = 7.8 and 1.0 Hz, 1H), 7.57 (td, J = 7.8 and 1.0 Hz, 1H), 7.38 (dd, J = 7.8 and 1.0 Hz, 1H), 6.17 (t, J = 1.9 Hz, 1H), 2.95–2.86 (complex m, 2H), 2.64–2.57 (complex m, 2H).

**¹³C NMR** (100 MHz, CDCl₃) δ 208.5, 173.9, 147.1, 133.7, 132.6, 132.0, 130.2, 129.4, 124.9, 35.7, 31.9.

**IR** (ATR) ν_max 3065, 2929, 2850, 1702, 1686, 1592, 1509, 1437, 1345, 1321, 1287, 1254, 1184, 1083, 876, 849, 788, 746 cm⁻¹.

**MS** (ESI, +ve) m/z 226 [(M+Na)⁺, 100%].

**HRMS** m/z 226.0482 [M+Na]⁺ (calcd for C₁₁H₉NO₃, 226.0480).

**Compound 11**

A magnetically stirred suspension of compound 9 (516 mg, 2.32 mmol), o-iodonitrobenzene (2) (1.16 g, 4.65 mmol), copper(I) iodide (221 mg, 1.16 mmol) and copper powder (738 mg, 11.6 mmol) in dry DMSO (10 mL) maintained at 50 °C was treated with Pd(dppf)Cl₂•CH₂Cl₂ (190 mg, 0.23 mmol). After 23 h the reaction mixture was cooled to 22 °C then diluted with ethyl acetate (10 mL) before being filtered through a plug of TLC-grade silica gel topped with diatomaceous earth and the solids so retained were washed with ethyl acetate (30 mL). The combined filtrates were washed with ammonia (2 x 40 mL of a 5% v/v aqueous solution), water (2 x 40 mL) and brine (1 x 40 mL) before being dried (Na₂SO₄), filtered, then concentrated under reduced pressure. The residue so obtained was subjected to flash column
chromatography (silica, 1:9 v/v diethyl ether/toluene elution) and thus affording, after concentration of the appropriate fractions ($R_f = 0.2$), compound 11 (247 mg, 49%) as a pale-yellow oil.

$^1$H NMR (400 MHz, CDCl$_3$) δ 8.02 (dd, $J = 8.2$ and 1.2 Hz, 1H), 7.6 (td, $J = 7.5$ and 1.2 Hz, 1H), 7.50 (m, 1H), 7.22 (dd, $J = 7.5$ and 1.2 Hz, 1H), 2.69 (m, 2H), 2.45 (m, 2H), 1.44 (t, $J = 2.2$ Hz, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 208.3, 166.2, 146.8, 138.0, 133.8, 132.8, 129.4, 129.1, 124.7, 34.2, 30.6, 8.4.

IR (ATR) $\nu_{\text{max}}$ 2919, 1698, 1464, 1515, 1382, 1353, 1337, 1219, 1102, 857, 787, 753, 707, 698 cm$^{-1}$.

MS (ESI, +ve) $m/z$ 240 [(M+Na)$^+$, 100%].

HRMS $m/z$ 218.0822 [M+H]$^+$ (calcd for C$_{12}$H$_{11}$NO$_3$, 218.0817).

Compound 15

![Compound 15](attachment:image)

A magnetically stirred suspension of compound 5 (X = I) (1.32 g, 5.91 mmol), copper(I) iodide (845 mg, 4.44 mmol) and copper powder (600 mg, 2.96 mmol) in dry DMSO (40 mL) maintained at 50 °C was treated with Pd(dppf)Cl$_2$•CH$_2$Cl$_2$ (241 mg, 0.30 mmol). After 0.75 h the reaction mixture was treated, dropwise over 1 h, with a solution of 2-bromo-3-nitopyridine (12) (600 mg, 2.96 mmol) in dry DMSO (10 mL). After a further 4 h the reaction mixture was cooled to 22 °C before being diluted with ethyl acetate (20 mL). The ensuing mixture was filtered through a plug of TLC-grade silica gel topped with diatomaceous earth and the solids thus retained were washed with ethyl acetate (40 mL). The combined filtrates were washed with ammonia (2 x 60 mL of a 5% v/v aqueous solution), water (2 x 60 mL) and brine (1 x 60 mL) before being dried (Na$_2$SO$_4$), filtered and then concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 4:6 v/v ethyl acetate/40-60 petroleum ether elution) and so affording, after concentration of the appropriate fractions ($R_f = 0.2$ in 1:1 v/v ethyl acetate/40-60 petroleum ether), compound 15 (650 mg, 69%) as an oily, brown solid.

$^1$H NMR (400 MHz, CDCl$_3$) δ 8.80 (d, $J = 4.6$ Hz, 1H), 8.27 (d, $J = 8.2$ Hz, 1H), 7.50 (m, 1H), 5.96 (s, 1H), 2.68 (t, $J = 6.3$ Hz, 2H), 2.48 (t, $J = 6.3$ Hz, 2H), 2.19 (p, $J = 6.3$ Hz, 2H).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 198.5, 158.0, 152.8 (4), 144.3, 132.6, 128.1, 123.9, 37.2, 28.7, 22.8.

IR (ATR) $\nu_{\text{max}}$ 2980, 1669, 1593, 1524, 1346, 1325, 1251, 959, 818, 762, 725 cm$^{-1}$.

MS (ESI, +ve) $m/z$ 241 [(M+Na)$^+$, 100%].

HRMS $m/z$ 219.0769 [M+H]$^+$ (calcd for C$_{11}$H$_{10}$N$_2$O$_3$, 219.0770).
Compound 16

A magnetically stirred suspension of compound 5 (X = I) (1.96 g, 8.83 mmol), 3-bromo-2-nitropyridine (13) (900 mg, 4.41 mmol), copper(I) iodide (1.26 g, 6.62 mmol) and copper powder (1.15 g, 18.1 mmol) in dry DMSO (44 mL) maintained at 50 °C was treated with Pd(dppf)Cl₂•CH₂Cl₂ (241 mg, 0.30 mmol). After 5 h the reaction mixture was cooled to 22 °C then diluted with ethyl acetate (20 mL). The ensuing mixture was filtered through a plug of TLC-grade silica gel topped with diatomaceous earth and the solids so retained were washed with ethyl acetate (40 mL). The combined filtrates were washed with ammonia (2 x 60 mL of a 5% v/v aqueous solution), water (2 x 60 mL) and brine (1 x 60 mL) before being dried (Na₂SO₄), filtered, then concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 1:4 v/v ethyl acetate/40-60 petroleum ether elution) and so affording, after concentration of the appropriate fractions (Rf = 0.2), compound 16 (894 mg, 91%) as a yellow, crystalline solid, m.p. = 90-93 °C.

¹H NMR (400 MHz, CDCl₃) δ 8.59 (dd, J = 4.7 and 1.7 Hz, 1H), 7.81 (dd, J = 7.7 and 1.7 Hz, 1H), 7.67 (dd, J = 7.7 and 4.7 Hz, 1H), 6.00 (s, 1H), 2.56-2.51 (complex m, 4H), 2.20 (m, 2H).

¹³C NMR (100 MHz, CDCl₃) δ 198.3, 156.7, 155.1, 148.8, 139.7, 130.8, 128.8, 128.3, 37.3, 30.3, 23.2.

IR (ATR) νmax 3061, 2950, 2886, 1537, 1346, 1238, 1188, 982, 958, 807, 703 cm⁻¹.

MS (ESI, +ve) m/z 241 [(M+Na)⁺, 100%], 219 [(M+H)⁺, 10%].

HRMS m/z 219.0755 [M+H]⁺ (calcd for C₁₁H₁₀N₂O₃ 219.0764).

Compound 17

A magnetically stirred suspension of compound 5 (X = I) (80.0 mg, 0.36 mmol), 3-bromo-4-nitropyridine (14) (102 mg, 0.50 mmol) and copper powder (160 mg, 2.52 mmol) in dry DMSO (4 mL) maintained at 80 °C was treated with Pd₂(dba)_₃•CHCl₃ (37.3 mg, 0.036 mmol). After 16 h the reaction mixture was cooled to 22 °C, diluted with ethyl acetate (4 mL), filtered through a plug of TLC-grade silica gel topped with diatomaceous earth and the solids so retained were washed with ethyl acetate (10 mL). The combined filtrates were washed with ammonia (2 x 20 mL of a 5% v/v aqueous solution), water (2 x 20 mL) and brine (1 x 20 mL) before being dried (Na₂SO₄), filtered, then concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 1:9 to 4:6 v/v diethyl ether/40-60 petroleum ether elution) and so affording, after concentration of the
appropriate fractions ($R_f = 0.2$ in 1:1 v/v ethyl acetate/40-60 petroleum ether), compound 17 (70 mg, 89%) as a clear, colorless oil.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.87 (d, $J = 5.3$ Hz, 1H), 8.66 (s, 1H), 7.85 (d, $J = 5.3$ Hz, 1H), 6.01 (s, 1H), 2.51 (m, 4H), 2.19 (m, 2H).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 198.1, 155.9, 152.2, 151.0, 129.6, 129.1, 117.0, 37.2, 30.6, 23.2 (signal due to one carbon obscured or overlapping).

IR (ATR) $\nu_{\text{max}}$ 2925, 1669, 1554, 1530, 1348, 1246, 728, 689, 672 cm$^{-1}$.

MS (ESI, +ve) $m/z$ 241 [(M+Na)$^+$, 100%], 219 [(M+H)$^+$, 18%].

HRMS $m/z$ 219.0766 [M+H]$^+$ (calcd for C$_{11}$H$_{10}$N$_2$O$_3$, 219.0764).

**Compound 18**

![Compound 18](image)

Compound 18 was prepared using a procedure reported earlier.$^3$ Thus, a magnetically stirred solution of triphenylphosphine (2.16 g, 8.25 mmol) in dry acetonitrile/HMPA (55 mL of a 10:1 v/v mixture) maintained at 22 °C was treated, in portions, with powdered molecular iodine (2.10 g, 8.25 mmol). After 0.5 h the reaction mixture was treated with triethylamine (1.20 mL, 8.25 mmol) and a solution of (E)-2-(hydroxymethylene)cyclohexan-1-one$^3$ (800 mg, 6.35 mmol) in dry acetonitrile (10 mL). The resulting mixture was stirred at 22 °C for 15 h then concentrated under reduced pressure. The residue thus obtained was dissolved in ethyl acetate (50 mL) and the resulting solution washed with water (3 x 30 mL) before being dried (Na$_2$SO$_4$), filtered then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:20 v/v ethyl acetate/40-60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions ($R_f = 0.5$), compound 18 (1.18 g, 79%) as a light-yellow oil. The spectral data acquired on this material were identical, in all respects, with those reported in the literature.$^3$

**Compound 19**

![Compound 19](image)

A magnetically stirred suspension of compound 18 (472 g, 2.00 mmol), 3-bromo-2-nitropyridine (13) (808 mg, 4.00 mmol), copper(I) iodide (570 g, 3.00 mmol) and copper powder (512 mg, 8.00 mmol) in dry DMSO (20 mL) maintained at 50 °C was treated with Pd(dppf)Cl$_2$$^\bullet$CH$_2$Cl$_2$ (16 mg, 0.02 mmol). After 5 h the reaction mixture was cooled to 22 °C then diluted with ethyl acetate (20 mL) and the ensuing mixture filtered through a plug of TLC-grade silica gel topped with diatomaceous earth. The solids so retained were washed with ethyl acetate (40 mL) and the combined filtrates were washed with ammonia (2 x 60 mL of a 5% v/v aqueous solution), water (2 x 60 mL) and brine (1 x 60 mL) before being dried (Na$_2$SO$_4$), filtered and then concentrated under reduced pressure. The residue thus obtained
was subjected to flash column chromatography (silica, 1:4 v/v ethyl acetate/40-60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions ($R_f = 0.2$), compound 19 (402 mg, 87%) as a yellow, crystalline solid, m.p. = 95-98 °C.

$^1$H NMR (400 MHz, [(CD$_3$)$_2$CO]) $\delta$ 8.56 (dd, $J = 4.6$ and 1.5 Hz, 1H), 8.12 (dd, $J = 7.7$ and 1.5 Hz, 1H), 7.85 (dd, $J = 7.7$ and 4.6 Hz, 1H), 7.32 (t, $J = 4.6$ Hz, 1H), 2.64 (m, 2H), 2.51 (m, 2H), 1.93 (m, 2H), 1.76 (m, 2H).

$^{13}$C NMR (100 MHz, [(CD$_3$)$_2$CO]) $\delta$ 200.0, 148.8, 142.3, 142.2, 128.7, 126.8, 125.9, 41.0, 29.2, 24.4, 24.1. (resonance due to one carbon obscured or overlapping).

IR (ATR) $\nu_{\text{max}}$ 2941, 2868, 1690, 1595, 1540, 1405, 1360, 1142, 862, 813 cm$^{-1}$.

MS (ESI, +ve) $m/z$ 255 [(M+Na)$^+$, 100%].

HRMS $m/z$ 233.0912 [M+H]$^+$ (calcd for C$_{12}$H$_{12}$N$_2$O$_3$, 233.0921).

**Compound 24**

![Image of compound 24]

A magnetically stirred suspension of compound 5 ($X = I$) (84.4 mg, 0.38 mmol), compound 20$^\theta$ (126 mg, 0.38 mmol) and copper powder (170 mg, 2.68 mmol) in dry DMSO (5 mL) maintained at 80 °C was treated with Pd$_2$(dba)$_3$•CHCl$_3$ (39.3 mg, 0.038 mmol). After 16 h the reaction mixture was cooled to 22 °C, diluted with ethyl acetate (5 mL), filtered through a plug of TLC-grade silica gel topped with diatomaceous earth and the solids so retained were washed with ethyl acetate (20 mL). The filtrate was washed with ammonia (2 x 25 mL of a 5% v/v aqueous solution), water (2 x 25 mL) and brine (1 x 25 mL) before being dried (Na$_2$SO$_4$), filtered, then concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 1:9 to 4:6 v/v diethyl ether/40-60 petroleum ether elution) and so affording, after concentration of the appropriate fractions ($R_f = 0.2$ in 2:3 v/v diethyl ether/40-60 petroleum ether elution), compound 24 (45 mg, 40%) as a white, crystalline solid, m.p. = 163 °C.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.75 (m, 2H), 8.36 (d, $J = 9.3$ Hz, 1H), 7.94–7.74 (complex m, 4H), 7.70 (m, 1H), 6.26 (s, 1H), 2.89 (m, 1H), 2.71 (m, 3H), 2.41 (m, 2H).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 198.6, 158.6, 145.9, 132.0, 131.6, 130.2, 129.8, 128.7(0), 127.6(9), 128.4, 128.1, 127.6, 127.1, 126.6, 123.5, 123.1, 116.6, 107.1, 37.6, 31.3, 23.4.

IR (ATR) $\nu_{\text{max}}$ 3340, 3067, 2949, 2240, 1678, 1450, 907, 757, 725 cm$^{-1}$.

MS (ESI, +ve) $m/z$ 320 [(M+Na)$^+$, 100%].

HRMS $m/z$ 320.1049 [M+Na]$^+$ (calcd for C$_{21}$H$_{15}$NO, 320.1051).
Compound 25

![Image of Compound 25]

A magnetically stirred suspension of compound 5 (X = I) (222 mg, 1.00 mmol), compound 21 (458 mg, 2.00 mmol), triphenylarsine (61.0 mg, 0.20 mmol) and copper powder (318 mg, 5.00 mmol) in dry DMSO (5 mL) maintained at 80 °C was treated with Pd[db(dba)]3•CHCl3 (52 mg, 0.05 mmol). After 20 h the reaction mixture was cooled to 22 °C, diluted with ethyl acetate (5 mL) and the resulting mixture filtered through a plug of TLC-grade silica gel topped with diatomaceous earth and the solids so retained were washed with ethyl acetate (20 mL). The combined filtrates were washed with ammonia (2 x 25 mL of a 5% v/v aqueous solution), water (2 x 25 mL) and brine (1 x 25 mL) before being dried (Na2SO4), filtered then concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 1:9 v/v ethyl acetate/40-60 petroleum ether elution) and so affording, after concentration of the appropriate fractions (Rf = 0.3), compound 25 (120 mg, 61%) as a white, crystalline solid, m.p. = 86 °C.

1H NMR (400 MHz, CDCl3) δ 7.73 (dd, J = 7.7 and 1.4 Hz, 1H), 7.63 (td, J = 7.7 and 1.4 Hz, 1H), 7.48 (m, 1H), 7.39 (dd, J = 7.8 and 1.4 Hz, 1H), 6.20 (s, 1H), 2.80 (m, 2H), 2.54 (m, 2H), 2.21 (m, 2H).

13C NMR (100 MHz, CDCl3) δ 198.9, 158.6, 144.5, 133.9, 133.2, 130.1, 129.2, 128.1, 117.9, 110.2, 37.4, 30.2, 23.3.

IR (ATR) νmax 2949, 2870, 2226, 1669, 1615, 1346, 1326, 1248, 1189, 957, 894, 764 cm⁻¹.

MS (ESI, +ve) m/z 220 [(M+Na)⁺, 100%].

HRMS m/z 220.0733 [M+Na]⁺ (calcd for C13H11NO, 220.0738).

Compound 26

![Image of Compound 26]

A magnetically stirred suspension of compound 5 (X = I) (84.4 mg, 0.38 mmol), compound 22 (176 mg, 0.57 mmol) and copper powder (160 mg, 2.52 mmol) in dry DMSO (5 mL) maintained at 80 °C was treated with Pd[db(dba)]3•CHCl3 (39.3 mg, 0.038 mmol). After 16 h the reaction mixture was cooled to 22 °C, diluted with ethyl acetate (5 mL) and the resulting mixture filtered through a plug of TLC-grade silica gel topped with diatomaceous earth. The solids so retained were washed with ethyl acetate (20 mL) and the filtrate was washed with ammonia (2 x 25 mL of a 5% v/v aqueous solution), water (2 x 25 mL) and brine (1 x 25 mL) before being dried (Na2SO4), filtered then concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 2:8 to 1:1 v/v ethyl acetate/40-60 petroleum ether elution) and so affording, after concentration of the appropriate
fractions ($R_f = 0.6$ in 2:3 v/v ethyl acetate/40-60 petroleum ether elution), compound 26 (36 mg, 34%) as a white, crystalline solid, m.p. = 123 °C.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.85 (d, $J = 2.0$ Hz, 1H), 7.75 (dd, $J = 8.4$ and 2.0 Hz, 1H), 7.26 (d, $J = 8.4$ Hz, 1H), 6.18 (m, 1H), 2.80–2.73 (complex m, 2H), 2.56–2.49 (complex m, 2H), 2.24–2.15 (complex m, 2H).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 198.5, 157.3, 143.3, 136.4, 136.3, 130.3, 129.6, 123.0, 116.5, 112.0, 37.3, 30.1, 23.2.

IR (ATR) $\nu_{max}$ 3062, 2951, 2869, 2227, 1669, 1547, 1346, 1252, 822 cm$^{-1}$.

MS (ESI, +ve) $m/z$ 300 and 298 [(M+Na$^+$), 98 and 100 %].

HRMS $m/z$ 297.9843 [M+Na$^+$] (calcd for C$_{13}$H$_{10}$BrNO, 297.9843).

**Compound 27**

A magnetically stirred suspension of compound 5 (X = I) (84.4 mg, 0.38 mmol), compound 23$^6$ (176 mg, 0.57 mmol) and copper powder (160 mg, 2.52 mmol) in dry DMSO (5 mL) maintained at 80 °C was treated with Pd$_2$(dba)$_3$•CHCl$_3$ (39.3 mg, 0.038 mmol). After 16 h the reaction mixture was cooled to 22 °C, diluted with ethyl acetate (5 mL) and the resulting mixture filtered through a plug of TLC-grade silica gel topped with diatomaceous earth and the solids so retained were washed with ethyl acetate (20 mL). The combined filtrates were washed with ammonia (2 x 25 mL of a 5% v/v aqueous solution), water (2 x 25 mL) and brine (1 x 25 mL) before being dried (Na$_2$SO$_4$), filtered then concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 2:8 to 1:1 v/v ethyl acetate/40-60 petroleum ether elution) and so affording, after concentration of the appropriate fractions ($R_f = 0.6$ in 2:3 v/v ethyl acetate/40-60 petroleum ether elution), compound 27 (73 mg, 79%) as a red, crystalline solid, m.p. = 152 °C.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.60 (d, $J = 2.2$ Hz, 1H), 8.47 (dd, $J = 8.6$ and 2.2 Hz, 1H), 7.61 (d, $J = 8.6$ Hz, 1H), 6.24 (t, $J = 1.7$ Hz, 1H), 6.24 (t, $J = 5.9$ and 1.7 Hz, 2H), 2.58 (dd, $J = 7.6$ and 5.9 Hz, 2H), 2.26 (m, 2H).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 198.9, 155.9, 150.1, 147.6, 131.1, 129.6, 128.9, 127.8, 115.8, 111.8, 37.2, 29.8, 23.1.

IR (ATR) $\nu_{max}$ 3081, 2953, 2233, 1673, 1526, 1353, 1324, 1247, 744 cm$^{-1}$.

MS (ESI, +ve) $m/z$ 265 [(M+Na$^+$), 100 %].

HRMS $m/z$ 265.0591 [M+Na$^+$] (calcd for C$_{13}$H$_{10}$N$_2$O$_3$ 265.0589).
Compound 30

A magnetically stirred suspension of compound 28 (79.1 mg, 0.35 mmol), 3-bromo-2-nitropyridine (12) (102 mg, 0.50 mmol) and copper powder (160 mg, 2.52 mmol) in dry DMSO (5 mL) maintained at 80 °C was treated with Pd$_2$(dba)$_3$•CHCl$_3$ (29.0 mg, 0.028 mmol). After 16 h the reaction mixture was cooled to 22 °C then diluted with ethyl acetate (5 mL) before being filtered through a plug of TLC-grade silica gel topped with diatomaceous earth and the solids so retained were washed with ethyl acetate (20 mL). The combined filtrates were washed with ammonia (2 x 25 mL of a 5% v/v aqueous solution), water (2 x 25 mL) and brine (1 x 25 mL) before being dried (Na$_2$SO$_4$), filtered then concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 4:6 to 1:1 v/v ethyl acetate/40-60 petroleum ether elution) and so affording, after concentration of the appropriate fractions ($R_f$ = 0.3 in 3:7 v/v ethyl acetate/40-60 petroleum ether elution), compound 30 (66 mg, 84%) as a yellow, crystalline solid, m.p. = 68 °C.

$^1$H NMR (400 MHz, CDCl$_3$) δ 8.56 (dd, $J$ = 4.5 and 1.8 Hz, 1H), 7.68 (dd, $J$ = 7.6 and 1.8 Hz, 1H), 7.62 (dd, $J$ = 7.6 and 4.5 Hz, 1H), 6.00 (q, $J$ = 1.5 Hz, 1H), 3.52 (s, 3H), 2.29 (d, $J$ = 1.5 Hz, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 165.4, 154.8, 150.5, 147.5, 139.0, 132.0, 128.0, 118.9, 51.5, 26.1.

IR (ATR) $\nu_{\text{max}}$ 2953, 1714, 1650, 1539, 1359, 1249, 1172, 1042, 859, 814, 659 cm$^{-1}$.

MS (ESI, +ve) $m/z$ 245 [(M+Na)$^+$, 100 %].

HRMS $m/z$ 245.0536 [M+Na]$^+$ (calcd for C$_{10}$H$_{10}$N$_2$O$_4$ 245.0538).

Compound 31

A magnetically stirred suspension of compound 28 (22.6 mg, 0.10 mmol), 3-bromo-4-nitropyridine (14) (40.6 mg, 0.20 mmol) and copper powder (31.8 mg, 0.50 mmol) in dry DMSO (1 mL) maintained at 55 °C was treated with Pd(dppf)Cl$_2$•CH$_2$Cl$_2$ (8.2 mg, 0.010 mmol). After 18 h the reaction mixture was cooled to 22 °C, diluted with ethyl acetate (5 mL), filtered through a plug of TLC-grade silica gel topped with diatomaceous earth and the solids so retained were washed with ethyl acetate (10 mL). The filtrate was washed with ammonia (2 x 15 mL of a 5% v/v aqueous solution), water (2 x 15 mL) and brine (1 x 15 mL) before being dried (Na$_2$SO$_4$), filtered, then concentrated under reduced pressure. The residue obtained was subjected to flash chromatography (silica, 1:9 v/v diethyl ether/toluene elution) and thus affording, after concentration of the appropriate fractions ($R_f$ = 0.12 in 1:9 v/v diethyl ether/toluene elution) and thus affording, after concentration of the appropriate fractions ($R_f$ = 0.12 in 1:9 v/v diethyl ether/toluene elution), compound 31 (15.3 mg, 69%) as a clear, colorless oil.

$^1$H NMR (400 MHz, CDCl$_3$) δ 8.82 (d, $J$ = 5.4 Hz, 1H), 8.55 (s, 1H), 7.91 (d, $J$ = 5.4 Hz, 1H), 6.08 (d, $J$ = 1.5 Hz, 1H), 3.53 (s, 3H), 2.29 (d, $J$ = 1.5 Hz, 3H). Irradiation of the
resonance at δ 2.29 led to a significant enhancement of the one at δ 6.08 and so establishing the illustrated Z-configuration about the acrylate double-bond.

\[ ^{13}C\text{ NMR } (100\text{ MHz, CDCl}_3)\delta 165.4, 152.3, 150.8, 150.6, 149.7, 130.8, 119.9, 116.5, 51.5, 26.3.\]

IR (ATR) \(v_{\text{max}}\) 2953, 1716, 1650, 1532, 1442, 1243, 1163, 1047, 858, 676 cm\(^{-1}\).

MS (ESI, +ve) \(m/z\) 245 [(M+Na)\(^+\), 100\%].

HRMS \(m/z\) 245.0539 [M+Na]\(^+\) (calcd for C\(_{10}\)H\(_{10}\)N\(_2\)O\(_4\) 245.0538).

**Compound 32**

![Chemical Structure](image)

A magnetically stirred suspension of compound 28 (84.4 mg, 0.38 mmol), compound 20 (160 mg, 0.49 mmol) and copper powder (160 mg, 2.52 mmol) in dry DMSO (5 mL) maintained at 80 °C was treated with Pd\(_2\)(dba)\(_3\)•CHCl\(_3\) (39.3 mg, 0.030 mmol). After 16 h the reaction mixture was cooled to 22 °C, diluted with ethyl acetate (5 mL), filtered through a plug of TLC-grade silica gel topped with diatomaceous earth and the solids so retained were washed with ethyl acetate (20 mL). The combined filtrates were washed with ammonia (2 x 25 mL of a 5\% v/v aqueous solution), water (2 x 25 mL) and brine (1 x 25 mL) before being dried (Na\(_2\)SO\(_4\)), filtered, then concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 1:4 to 1:1 v/v ethyl acetate/40-60 petroleum ether elution) and so affording, after concentration of the appropriate fractions (\(R_f\) = 0.2), compound 32 (62 mg, 55\%) as a pink, crystalline solid, m.p. = 153-155 °C.

\[ ^1\text{H NMR } (400\text{ MHz, CDCl}_3)\delta 8.75 (d, J = 8.4 Hz, 1H), 8.72 (m, 1H), 8.31 (m, 1H), 7.86 (dd, J = 8.4 and 1.6 Hz, 1H), 7.80 (m, 1H), 7.77–7.73 (complex m, 2H), 7.65 (m, 1H), 6.46 (q, J = 1.6 Hz, 1H), 3.48 (s, 3H), 2.40 (d, J = 1.6 Hz, 3H).\]

Irradiation of the resonance at δ 2.40 led to a significant enhancement of the one at δ 6.46 and so establishing the illustrated Z-configuration about the acrylate double-bond.

\[ ^{13}C\text{ NMR } (100\text{ MHz, CDCl}_3)\delta 164.9, 152.2, 147.8, 131.8, 129.7, 129.6, 128.8, 128.2, 128.0, 127.9, 127.6, 126.5, 126.3, 123.5, 123.1, 122.4, 116.9, 106.0, 51.4, 26.0.\]

IR (ATR) \(v_{\text{max}}\) 2950, 2220, 1723, 1438, 1450, 1208, 1158, 1133, 1044, 759, 725 cm\(^{-1}\).

MS (ESI, +ve) \(m/z\) 340 [(M+K)\(^+\), 100\%], 324 [(M+Na)\(^+\), 90\%].

HRMS \(m/z\) 324.1003 [M+Na]\(^+\) (calcd for C\(_{20}\)H\(_{15}\)NO\(_2\), 324.1000).

**Compound 33**

![Chemical Structure](image)

A magnetically stirred suspension of compound 28 (84.4 mg, 0.38 mmol), compound 23 (155 mg, 0.56 mmol) and copper powder (160 mg, 2.52 mmol) in dry DMSO (5 mL) maintained at 80 °C was treated with Pd\(_2\)(dba)\(_3\)•CHCl\(_3\) (31.1 mg, 0.030 mmol). After 16 h the reaction mixture was cooled to 22 °C, diluted with ethyl acetate (5 mL) and the resulting mixture...
filtered through a plug of TLC-grade silica gel topped with diatomaceous earth and the solids so retained were washed with ethyl acetate (20 mL). The combined filtrates were washed with ammonia (2 x 25 mL of a 5% v/v aqueous solution), water (2 x 25 mL) and brine (1 x 25 mL) before being dried (Na$_2$SO$_4$), filtered then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:4 to 1:1 v/v diethyl ether/40-60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions ($R_f$ = 0.3), compound 33 (36 mg, 43%) as a white, crystalline solid, m.p. = 106-107 °C.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.54 (d, $J$ = 2.3 Hz, 1H), 8.43 (dd, $J$ = 8.6 and 2.3 Hz, 1H), 7.43 (d, $J$ = 8.6 Hz, 1H), 6.19 (q, $J$ = 1.6 Hz, 1H), 3.60 (s, 3H), 2.26 (d, $J$ = 1.6 Hz, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 165.1, 152.2, 150.6, 146.9, 128.7, 127.8, 127.5, 121.5, 115.6, 112.3, 51.7, 26.0.

IR (ATR) $\nu_{max}$ 2954, 2236, 1721, 1606, 1529, 1439, 1353, 1241, 1166, 1042, 797 cm$^{-1}$.

MS (ESI, +ve) $m/z$ 269 [(M+Na)$^+$, 100 %].

HRMS $m/z$ 269.0539 [M+Na]$^+$ (calcd for C$_{12}$H$_{10}$N$_2$O$_4$, 269.0538).

**Compound 34**

\[ \begin{array}{c}
\text{MeO} \\
\text{C} \\
\text{C} \\
\text{CN} \\
\end{array} \]

A magnetically stirred suspension of compound 28 (84.4 mg, 0.38 mmol), compound 29
(134 mg, 0.53 mmol) and copper powder (160 mg, 2.52 mmol) in dry DMSO (5 mL) maintained at 80 °C was treated with Pd$_2$(dba)$_3$$\cdot$CHCl$_3$ (31.1 mg, 0.030 mmol). After 16 h the reaction mixture was cooled to 22 °C, diluted with ethyl acetate (5 mL) then filtered through a plug of TLC-grade silica gel topped with diatomaceous earth and the solids so retained were washed with ethyl acetate (20 mL). The combined filtrates were washed with ammonia (2 x 25 mL of a 5% v/v aqueous solution), water (2 x 25 mL) and brine (1 x 25 mL) before being dried (Na$_2$SO$_4$), filtered then concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 1:4 to 1:1 v/v diethyl ether/40-60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions ($R_f$ = 0.2), compound 34 (50 mg, 59%) as a clear, colorless oil.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.90 (d, $J$ = 7.8 Hz, 2H), 7.54 (t, $J$ = 7.8 Hz, 1H), 6.28 (d, $J$ = 1.6 Hz, 1H), 3.61 (s, 3H), 2.30 (d, $J$ = 1.6 Hz, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 164.9, 149.9, 149.1, 136.5, 128.5, 123.0, 115.9, 112.2, 51.8, 25.1.

IR (ATR) $\nu_{max}$ 2954, 2236, 1719, 1654, 1455, 1434, 1352, 1244, 1166, 1041, 808, 760 cm$^{-1}$.

MS (ESI, +ve) $m/z$ 249 [(M+Na)$^+$, 100 %].

HRMS $m/z$ 249.0647 [M+Na]$^+$ (calcd for C$_{13}$H$_{10}$N$_2$O$_2$, 249.0640).
Compound 36

A magnetically stirred suspension of compound 35\textsuperscript{8} (100 mg, 0.33 mmol), compound 5 (X = I) (124 mg, 0.50 mmol) and copper powder (160 mg, 2.52 mmol) in dry DMSO (5 mL) maintained at 80 °C was treated with Pd\textsubscript{2}(dba)\textsubscript{3}•CHCl\textsubscript{3} (31.1 mg, 0.030 mmol). After 16 h the reaction mixture was cooled to 22 °C, diluted with ethyl acetate (5 mL) and the ensuing mixture filtered through a plug of TLC-grade silica gel topped with diatomaceous earth and the solids so retained were washed with ethyl acetate (20 mL). The combined filtrates were washed with ammonia (2 x 25 mL of a 5% v/v aqueous solution), water (2 x 25 mL) and brine (1 x 25 mL) before being dried (Na\textsubscript{2}SO\textsubscript{4}), filtered and then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:9 to 1:1 v/v diethyl ether/40-60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions ($R_f = 0.3$ in 1:4 v/v diethyl ether/40-60 petroleum ether elution), compound 36\textsuperscript{10} (60 mg, 61%) as a clear, yellow oil.

$^1$H NMR (400 MHz, CDCl\textsubscript{3}) $\delta$ 8.12 (dd, $J$ = 8.3 and 1.4 Hz, 1H), 7.60 (td, $J$ = 7.5 and 1.3 Hz, 1H), 7.49 (m, 1H), 7.29–7.18 (complex m, 6H), 6.41 (s, 1H), 3.92 (m, 2H), 1.03 (t, $J$ = 7.2 Hz, 3H).

$^{13}$C NMR (100 MHz, CDCl\textsubscript{3}) $\delta$ 165.5, 153.5, 138.3, 135.2, 133.3, 131.2, 129.9, 128.9, 128.7, 127.6, 127.2, 124.7, 117.2, 60.4, 14.1.

IR (ATR) $\nu_{\text{max}}$ 3036, 1712, 1625, 1523, 1346, 1168, 1032, 771, 69 cm$^{-1}$.

MS (ESI, +ve) $m/z$ 320 [(M+Na)$^+$, 100 %].

HRMS $m/z$ 320.0899 [M+Na]$^+$ (calcd for C\textsubscript{17}H\textsubscript{15}NO\textsubscript{4}, 320.0899).

Compound 37

A magnetically stirred suspension of compound 35\textsuperscript{8} (130 mg, 0.43 mmol), 3-bromo-2-nitropyridine (13) (122 mg, 0.60 mmol) and copper powder (160 mg, 2.52 mmol) in dry DMSO (5 mL) maintained at 80 °C was treated with Pd\textsubscript{2}(dba)\textsubscript{3}•CHCl\textsubscript{3} (31.1 mg, 0.030 mmol). After 16 h the reaction mixture was cooled to 22 °C, diluted with ethyl acetate (5 mL), filtered through a plug of TLC-grade silica gel topped with diatomaceous earth and the solids so retained were washed with ethyl acetate (20 mL). The combined filtrates were washed with ammonia (2 x 25 mL of a 5% v/v aqueous solution), water (2 x 25 mL) and brine (1 x 25 mL) before being dried (Na\textsubscript{2}SO\textsubscript{4}), filtered and then concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 3:7 v/v ethyl acetate/40-60 petroleum ether elution) and so affording, after concentration of the appropriate fractions ($R_f = 0.5$), compound 37 (65 mg, 50%) as a white, crystalline solid, m.p. = 102-103 °C.
$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.64 (dd, $J = 4.6$ and 1.8 Hz, 1H), 7.76 (dd, $J = 7.7$ and 1.7 Hz, 1H), 7.67 (dd, $J = 7.7$ and 4.6 Hz, 1H), 7.47–7.29 (complex m, 5H), 6.52 (s, 1H), 4.00 (m, 2H), 1.14 (t, $J = 7.2$ Hz, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 165.2, 155.9, 150.5, 148.0, 141.2, 137.6, 130.4, 129.9, 129.0, 127.7(3), 127.7(0), 118.3, 60.7, 14.1.

IR (ATR) $\nu_{\max}$ 3061, 2983, 1709, 1624, 1540, 1367, 1349, 1270, 1175, 1093, 1027, 771 cm$^{-1}$.

MS (ESI, +ve) $m/z$ 321 [(M+Na)$^+$, 100 %].

HRMS $m/z$ 321.0851 [M+Na$^+$] (calcd for C$_{16}$H$_{14}$N$_2$O$_4$, 321.0851).

**Compound 38**

![Structure of Compound 38](image)

A magnetically stirred suspension of compound 35$^8$ (380 mg, 1.26 mmol), 3-bromo-4-nitropyridine (14) (510 mg, 2.52 mmol) and copper powder (400 mg, 6.29 mmol) in dry DMSO (5 mL) maintained at 55 °C was treated with PdCl$_2$(dppf)$\cdot$CH$_2$Cl$_2$ (103 mg, 0.13 mmol). After 16 h the reaction mixture was cooled to 22 °C, diluted with ethyl acetate (5 mL) and the resulting mixture filtered through a plug of TLC-grade silica gel topped with diatomaceous earth and the solids so retained washed with ethyl acetate (20 mL). The combined filtrates were washed with ammonia (2 x 25 mL of a 5% v/v aqueous solution), water (2 x 25 mL) and brine (1 x 25 mL) before being dried (Na$_2$SO$_4$), filtered and then concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 1:9 to 1:1 v/v diethyl ether/40-60 petroleum ether elution) and so affording, after concentration of the appropriate fractions ($R_f = 0.3$ in 3:7 v/v ethyl acetate/40-60 petroleum ether elution), compound 38 (303 mg, 81%) as a clear, yellow oil.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.91 (broad s, 1H), 8.64 (broad s, 1H), 7.99 (d, $J = 5.4$ Hz, 1H), 7.42–7.29 (complex m, 5H), 6.59 (s, 1H), 4.03 (m, 2H), 1.15 (t, $J = 7.2$ Hz, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 165.3, 153.3, 152.5, 151.3, 149.7, 137.7, 130.4, 129.0, 127.5, 119.2, 60.8, 14.1 (two resonances obscured or overlapping).

IR (ATR) $\nu_{\max}$ 2982, 1711, 1624, 1533, 1352, 1268, 1177, 1028, 847, 770, 676 cm$^{-1}$.

MS (ESI, +ve) $m/z$ 321 [(M+Na)$^+$, 100 %].

HRMS $m/z$ 321.0844 [M+Na$^+$] (calcd for C$_{16}$H$_{14}$N$_2$O$_4$, 321.0851).
Compound 39

\[
\text{HN}_\text{O}
\]

A magnetically stirred mixture of compound 30 (55.4 mg, 0.25 mmol), glacial acetic acid (1 mL) and iron powder (30.0 mg, 0.54 mmol) in ethanol (5 mL) maintained at 22 °C was treated with hydrochloric acid (2 drops of a 37% aqueous solution). After 1 h the reaction mixture was quenched with sodium bicarbonate (10 mL of a saturated aqueous solution) and extracted with ethyl acetate (2 x 5 mL). The combined organic phases were dried (Na$_2$SO$_4$), filtered and then concentrated under reduced pressure to give compound 39\(^{11}\) (30.4 mg, 76%) as a brown solid, no m.p., decomposition above 200 °C.

\(^1\)H NMR (400 MHz, CDCl$_3$) $\delta$ 9.78 (broad s, 1H), 8.57 (d, $J = 4.1$ Hz, 1H), 7.99 (d, $J = 7.8$ Hz, 1H), 7.22 (m, 1H), 6.57 (s, 1H), 2.48 (s, 3H).

\(^{13}\)C NMR (100 MHz, CDCl$_3$) $\delta$ 163.7, 150.4, 149.8, 147.2, 133.4, 122.4, 118.4, 115.9, 18.5.

IR (ATR) $\nu_{\text{max}}$ 2874, 1664, 1612, 1564, 1423, 1388, 1086, 966, 862, 779, 672, 510 cm$^{-1}$.

MS (ESI, +ve) m/z 183 [(M+Na)$^+$, 100%].

HRMS m/z 183.0536 [M+Na]$^+$ (calcd for C$_9$H$_8$N$_2$O, 183.0534).

Compound 40

\[
\text{HN}_\text{O}
\]

A magnetically stirred mixture of compound 36 (20.3 mg, 0.068 mmol), glacial acetic acid (1 mL) and iron powder (50.0 mg, 0.94 mmol) in ethanol (5 mL) maintained at 60 °C was treated with hydrochloric acid (2 drops of a 37% aqueous solution). After 16 h the reaction mixture was cooled to 22 °C then quenched with sodium bicarbonate (10 mL of a saturated aqueous solution) and extracted with ethyl acetate (2 x 5 mL). The combined organic phases were dried (Na$_2$SO$_4$), filtered then concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 1:1 v/v ethyl acetate/40-60 petroleum ether elution) and so affording, after concentration of the appropriate fractions ($R_f$ = 0.2), compound 40\(^{12}\) (10.1 mg, 67%) as a white, crystalline solid, m.p. = 189-191 °C.

\(^1\)H NMR (400 MHz, CDCl$_3$) $\delta$ 12.64 (broad s, 1H), 7.57–7.46 (complex m, 8H), 7.17 (m, 1H), 6.71 (s, 1H).

\(^{13}\)C NMR (100 MHz, CDCl$_3$) $\delta$ 164.6, 153.9, 139.4, 137.6, 131.2, 129.3(3), 129.3(0), 129.1, 127.2, 123.0, 121.3, 120.1, 117.1.

IR (ATR) $\nu_{\text{max}}$ 2957, 2920, 2851, 1661, 1610, 1563, 1432, 1386, 876, 751, 700 cm$^{-1}$.

MS (ESI, +ve) m/z 465 [(2M+Na)$^+$, 100%], 244 [(M+Na)$^+$, 78%].

HRMS m/z 244.0744 [M+Na]$^+$ (calcd for C$_{15}$H$_{11}$NO, 244.0738).
**Compound 41**

![Chemical Structure](image)

A magnetically stirred mixture of compound 36 (27.4 mg, 0.092 mmol) and 10% palladium on carbon (27 mg) in dry ethanol (5 mL) maintained at 22 °C was placed under a hydrogen atmosphere. After 16 h the reaction mixture was filtered through a pad of diatomaceous earth and the filtrate concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 4.6 to 1:1 v/v diethyl ether/40-60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions ($R_f = 0.4$), compound 41\textsuperscript{13} (17.5 mg, 85%) as a white, crystalline solid, m.p. = 177-179 °C.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.96 (broad s, 1H), 7.39–7.30 (complex m, 2H), 7.30–7.27 (complex m, 1H), 7.23–7.17 (complex m, 3H), 7.02–6.89 (complex m, 2H), 6.82 (d, $J = 7.9$ Hz, 1H), 4.30 (t, $J = 7.5$ Hz, 1H), 2.93 (m, 2H).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 170.3, 141.5, 137.1, 129.1, 128.6, 128.2, 128.0, 127.4, 126.9, 123.5, 115.6, 42.2, 38.6.

IR (ATR) $\nu_{\text{max}}$ 3212, 2911, 1679, 1593, 1486, 1376, 1245, 1159, 754, 700 cm$^{-1}$.

MS (ESI, +ve) $m/z$ 246 [(M+Na)$^+$, 100%].

HRMS $m/z$ 246.0894 [M+Na]$^+$ (calcld for C$_{15}$H$_{13}$NO, 246.0895).

**Compound 42**

![Chemical Structure](image)

A magnetically stirred mixture of compound 19 (232 mg, 1.00 mmol) and iron powder (168 mg, 3.00 mmol) in a mixture of ethanol and water (10 mL of a 7:3 v/v mixture) maintained at 22 °C was treated with calcium chloride (333 mg, 3.00 mmol). The resulting mixture was heated under reflux and after 2 h the reaction mixture was cooled to 22 °C then treated with sodium hydroxide (200 mg, 5.00 mmol) then heated under reflux again. After 1 h the reaction mixture was cooled to 22 °C before diluted with ethyl acetate (20 mL) then filtered through a plug of TLC-grade silica gel topped with diatomaceous earth. The solids so retained were washed with ethyl acetate (2 x 20 mL) and the separated organic phase associated with the combined filtrates dried (MgSO$_4$) before being concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 1:99 v/v methanol/ethyl acetate elution) and so affording, after concentration of the appropriate fractions ($R_f = 0.2$), compound 42\textsuperscript{14} (136 mg, 74%) as a yellow solid, no m.p., decomposition above 118 °C.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.01 (dd, $J = 4.3$ and 2.0 Hz, 1H), 8.07 (dd, $J = 8.1$ and 2.0 Hz, 1H), 7.83 (s, 1H), 7.39 (dd, $J = 8.1$ and 4.3 Hz, 1H), 3.23 (t, $J = 6.6$ Hz, 2H), 3.00 (t, $J = 6.0$ Hz, 2H), 2.01 (m, 2H), 1.91 (m, 2H).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 163.3, 154.8, 152.6, 136.1, 135.6, 132.4, 121.5, 121.3, 33.9, 29.2, 23.0, 22.8.
**Compound 43**

![Image of compound 43]

A magnetically stirred suspension of compound 7 (1.00 g, 4.56 mmol) and 10% palladium on carbon (460 mg) in dry methanol (50 mL) maintained at 50 °C was placed under a hydrogen atmosphere. After 2 h the reaction mixture was cooled to 22 °C then filtered through a pad of diatomaceous earth and the filtrate concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 5:95 v/v ethyl acetate/40-60 petroleum ether elution) and so affording, after concentration of the appropriate fractions (Rf = 0.11 in 1:9 v/v ethyl acetate/40-60 petroleum ether elution), compound 43 (684 mg, 73%) as white crystals, m.p. = 108 °C.

**1H NMR (400 MHz, CDCl3)** δ 7.02 (m, 1H), 6.94 (dd, J = 7.3 and 1.3 Hz, 1H), 6.63 (m, 1H), 6.55 (dd, J = 8.0 and 1.3 Hz, 1H), 3.82 (s, 1H), 3.32 (s, 3H), 3.14 (m, 1H), 2.26 (m, 1H), 1.79 (m, 2H), 1.72–1.64 (complex m, 3H), 1.65–1.46 (complex m, 2H).

**13C NMR (100 MHz, CDCl3)** δ 145.8, 128.0, 127.2, 125.7, 117.3, 113.3, 83.9, 48.4, 41.5, 36.3, 34.0, 32.0, 19.5.

**IR (KBr) νmax** 3315, 2943, 1606, 1274, 1114, 1067, 753 cm⁻¹.

**MS (ESI, +ve) m/z** 226 [(M+Na)⁺, 45%], 204 [(M+H)⁺, 100].

**HRMS m/z** 204.1389 [M+H]⁺ (calcd for C_{13}H_{17}NO, 204.1388).

**Compound 44**

![Image of compound 44]

A magnetically stirred suspension of compound 7 (100 mg, 0.46 mmol) and 10% palladium on carbon (46 mg) in dry toluene (5 mL) maintained at 50 °C was placed under a hydrogen atmosphere. After 1 h the reaction mixture was cooled to 22 °C then filtered through a pad of diatomaceous earth and the filtrate concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 1:4 v/v ethyl acetate/40-60 petroleum ether elution) and so affording, after concentration of the appropriate fractions (Rf = 0.4), compound 44₁⁵ (55.2 mg, 64%) as a clear, yellow oil.
$^{1}$H NMR (400 MHz, CDCl$_{3}$) $\delta$ 7.01 (m, 1H), 6.94 (dd, $J$ = 7.5 and 1.6 Hz, 1H), 6.65 (m, 1H), 6.50 (dd, $J$ = 7.5 and 1.6 Hz, 1H), 4.17 (m, 1H), 3.12 (t, $J$ = 3.3 Hz, 1H), 2.24 (broad s, 1H), 2.03–1.90 (complex m, 2H), 1.90–1.82 (complex m, 2H), 1.70–1.59 (complex m, 2H), 1.61–1.44 (complex m, 2H).

$^{13}$C NMR (100 MHz, CDCl$_{3}$) $\delta$ 144.9, 128.1, 127.3, 125.7, 117.8, 113.2, 80.5, 40.9, 38.8, 36.7, 33.5, 19.5.

IR (KBr) $\nu_{\text{max}}$ 3361, 2930, 2847, 1608, 1493, 1478, 1300, 1267, 1127, 1080, 979, 910, 744 cm$^{-1}$.

MS (ESI, +ve) $m/z$ 212 [(M+Na)$^+$, 100%], 190 [(M+H)$^+$, 70%].

HRMS $m/z$ 190.1236 [M+H]$^+$ (calcd for C$_{12}$H$_{15}$NO, 190.1232).

**Compound 45**

![Compound 45](image)

A magnetically stirred suspension of compound 10 (52.4 mg, 0.26 mmol) and 10% palladium on carbon (26 mg) in dry, degassed methanol (20 mL) maintained at 65 °C was treated with glacial acetic acid (0.2 mL) then placed under a hydrogen atmosphere. After 20 h the reaction mixture was cooled to 22 °C, filtered through a pad of diatomaceous earth and the filtrate concentrated under reduced pressure. The ensuing residue was portioned between diethyl ether (10 mL) and sodium bicarbonate (10 mL of a saturated aqueous solution) then the separated aqueous phase was extracted with diethyl ether (2 x 10 mL) and the combined organic phases washed with brine (1 x 20 mL) before being dried (Na$_2$SO$_4$), filtered and concentrated under reduced pressure to give compound 45 (22 mg, 43%) as a white, crystalline solid, m.p. = 77 °C ($R_f$ = 0.1 in 1:9 v/v diethyl ether/ n-hexane).

$^{1}$H NMR (400 MHz, CDCl$_{3}$) $\delta$ 7.00 (m, 1H), 6.90 (m, 1H), 6.64 (m, 1H), 6.58 (m, 1H), 3.83 (broad s, 1H), 3.46 (s, 3H), 3.03 (m, 1H), 2.21–2.05 (complex m, 4H), 1.99–1.89 (complex m, 2H).

$^{13}$C NMR (100 MHz, CDCl$_{3}$) $\delta$ 143.9, 131.6, 127.2, 126.6, 118.5, 115.5, 94.3, 52.3, 40.7, 40.0, 35.6, 34.4.

IR (ATR) $\nu_{\text{max}}$ 3339, 2941, 2855, 1606, 1493, 1470, 1318, 1298, 1245, 1217, 1199, 1150, 1112, 1070, 1034, 1001, 942, 747 cm$^{-1}$.

MS (ESI, +ve) $m/z$ 190 [(M+H)$^+$, 69%], 158 (62), 153 (100), 102 (93).

HRMS $m/z$ 190.1233 [M+H]$^+$ (calcd for C$_{12}$H$_{15}$NO, 190.1232).
Compound 46

A magnetically stirred solution of compound 7 (652 mg, 3.0 mmol) and cerium(III) chloride heptahydrate (1.23 g, 3.3 mmol) in dry methanol/dichloromethane (6 mL of a 1:1 v/v mixture) maintained at 0 °C was treated, in portions, with sodium borohydride (125 mg, 3.30 mmol). After 2 h the reaction mixture was concentrated under reduced pressure and the residue dissolved in diethyl ether (10 mL) and the resulting mixture treated hydrochloric acid (10 mL of a 1 M aqueous solution). The separated aqueous phase was extracted with diethyl ether (2 x 10 mL) and the combined organic phases washed with brine (1 x 30 mL) before being dried (Na$_2$SO$_4$), filtered, then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:9 v/v diethyl ether/dichloromethane elution) and thus affording, after concentration of the appropriate fractions ($R_f = 0.3$), compound 46 (631 mg, 96%) as a clear, yellow oil.

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.88 (dd, $J = 8.1$ and 1.3 Hz, 1H), 7.55 (td, $J = 7.6$ and 1.3 Hz, 1H), 7.40 (td, $J = 8.1$ and 1.4 Hz, 1H), 7.29 (dd, $J = 7.6$ and 1.3 Hz, 1H), 5.67 (m, 1H), 4.30 (m, 1H), 2.31–2.14 (complex m, 2H), 1.99–1.86 (complex m, 2H), 1.80–1.66 (complex m, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 148.3, 139.9, 138.5, 133.0, 130.8, 128.5, 128.1, 124.3, 65.7, 31.4, 29.7, 19.5.

IR (ATR) $\nu_{	ext{max}}$ 3342, 2937, 2863, 1521, 1346, 1049, 972, 912, 859, 785, 746 cm$^{-1}$.

MS (ESI, +ve) $m/z$ 242 [(M+Na)$^+$, 100%].

HRMS $m/z$ 242.0794 [M+Na]$^+$ (calcd for C$_{12}$H$_{13}$NO$_3$, 242.0793).

Compound 47

A magnetically stirred solution of compound 10 (609 mg, 3.0 mmol) and cerium(III) chloride heptahydrate (1.23 g, 3.3 mmol) in methanol/dichloromethane (12 mL of a 1:1 v/v mixture) maintained at 0 °C was treated, in portions, with sodium borohydride (125 mg, 3.30 mmol). After 0.5 h the reaction mixture was concentrated under reduced pressure and the ensuing residue dissolved in diethyl ether (10 mL). The resulting solution was treated with hydrochloric acid (10 mL of a 1 M aqueous solution) and the separated aqueous phase extracted with diethyl ether (2 x 10 mL). The combined organic phases were washed with brine (1 x 30 mL) before being dried (Na$_2$SO$_4$), filtered and then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:9 v/v diethyl ether/dichloromethane elution) and so affording, after concentration of the appropriate fractions ($R_f = 0.3$), compound 47 (414 mg, 67%) as a clear, yellow oil.
$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.80 (dd, $J = 8.1$ and 1.3 Hz, 1H), 7.51 (td, $J = 7.5$ and 1.3 Hz, 1H), 7.41–7.30 (complex m, 2H), 5.82 (q, $J = 2.0$ Hz, 1H), 4.94 (broad s, 1H), 2.71 (m, 1H), 2.57 (s, 1H), 2.54–2.46 (complex m, 1H), 2.45–2.36 (complex m, 1H), 1.86 (m, 1H).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 148.4, 144.1, 133.0, 132.7, 132.1, 130.6, 128.4, 124.0, 77.6, 34.3, 34.0.

IR (ATR) $\nu_{\text{max}}$ 3338, 2937, 2854, 1520, 1345, 1274, 1239, 1048, 966, 854, 784, 744 cm$^{-1}$.

MS (ESI, +ve) $m/z$ 228 [(M+Na)$^+$, 100%], 214 [(M+Na)$^+$, 34%], 192 [(M+H)$^+$, 34%].

HRMS $m/z$ 228.0638 [M+Na]$^+$ (calcd for C$_{11}$H$_{11}$NO$_3$, 228.0637).

**Compound 48**

![Compound 48](image)

A magnetically stirred mixture of compound 46 (798 mg, 3.64 mmol) and 10% palladium on carbon (80 mg) in dry methanol (8 mL) maintained at 22 °C was placed under a hydrogen atmosphere. After 2.5 h the reaction mixture was filtered through a pad of diatomaceous earth and the filtrate concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 2.5:47.5:50 v/v/methanol/ethyl acetate/40-60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions ($R_f = 0.6$ in 5:95 v/v methanol/ethyl acetate elution), compound 48 (524 mg, 75%) as a clear, light-brown oil. The product decomposes rapidly at ambient temperatures and so it was used immediately in the next step of the reaction sequence.

IR (ATR) $\nu_{\text{max}}$ 3349, 2927, 2855, 1621, 1496, 1453, 1293, 1251, 1051, 976, 959, 748 cm$^{-1}$.

MS (ESI, +ve) $m/z$ 405 [(2M+Na)$^+$, 48%], 214 [(M+Na)$^+$, 100%], 192 [(M+H)$^+$, 34%].

HRMS $m/z$ 192.1381 [M+H]$^+$ (calcd for C$_{12}$H$_{17}$NO, 192.1383).

**Compound 49**

![Compound 49](image)

A magnetically stirred mixture of compound 47 (235 mg, 1.14 mmol) and 10% palladium on carbon (24 mg) in dry methanol (5 mL) maintained at 22 °C was placed under a hydrogen atmosphere. After 2 h the reaction mixture was filtered through a pad of diatomaceous earth and the filtrate concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:4 to 1:1 v/v diethyl ether/dichloromethane elution) and thus affording, after concentration of the appropriate fractions ($R_f = 0.2$), compound 49 (102 mg, 51%) as a clear, light-brown oil.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.19 (dd, $J = 7.6$ and 1.5 Hz, 1H), 7.05 (m, 1H), 6.76 (m, 1H), 6.67 (dd, $J = 7.8$ and 1.2 Hz, 1H), 4.46 (m, 1H), 3.33 (broad s, 2H), 3.07 (m, 1H), 2.45–2.31...
(complex m, 1H), 2.12–1.94 (complex m, 2H), 1.93–1.80 (complex m, 2H), 1.80–1.73 (complex m, 1H) (resonance due to one proton not observed).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 144.2, 129.0, 127.8, 127.1, 118.7, 116.2, 73.8, 40.9, 40.0, 36.0, 29.5.

IR (ATR) $\nu_{\text{max}}$ 3350, 3244, 2951, 2865, 1617, 1495, 1454, 1295, 1078, 983, 748 cm$^{-1}$.

MS (ESI, +ve) $m/z$ 200 [(M+Na)$^+$, 50%], 178 [(M+H)$^+$, 100], 160 (100).

HRMS $m/z$ 178.1232 [M+H]$^+$ (calcd for C$_{11}$H$_{15}$NO, 178.1232).

$cis$- and $trans$- Forms of Compound 50

A magnetically stirred solution of compound 48 (524 mg, 2.74 mmol) and pyridine (665 µL, 8.22 mmol) in dry dichloromethane (5.5 mL) maintained at 0 °C was treated, in portions, with $p$-toluenesulfonyl chloride (575 mg, 3.01 mmol) then warmed to 22 °C. After 16 h the reaction mixture was treated with heptane (20 mL) then concentrated under reduced pressure. This dilution/concentration process was repeated twice more in order to remove pyridine. The residue thus obtained was subjected to flash column chromatography (silica, 2:3 v/v ethyl acetate/40–60 petroleum ether elution) and so affording, two fractions, A and B.

Concentration of fraction A ($R_f$ = 0.2) gave compound $trans$-50 (304 mg, 32%) as a white crystalline solid, m.p. = 145 °C.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.71 (s, 1H), 7.65 (d, $J$ = 8.3 Hz, 2H), 7.36 (m, 1H), 7.24 (d, $J$ = 8.3 Hz, 2H), 7.20–7.11 (complex m, 3H), 4.20 (t, $J$ = 2.9 Hz, 1H), 3.01 (s, 1H), 2.91 (m, 1H), 2.37 (s, 3H), 1.84 (m, 1H), 1.74 (m, 1H), 1.68–1.55 (complex m, 1H), 1.43 (m, 3H), 1.32–1.20 (complex m, 1H), 1.01 (d, $J$ = 12.5 Hz, 1H).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 143.7, 141.9, 136.9, 133.1, 129.7, 127.4, 127.3, 127.2, 126.9, 126.6, 66.7, 40.4, 32.8, 32.0, 31.1, 21.6, 20.4.

IR (ATR) $\nu_{\text{max}}$ 3521, 3345, 3284, 2928, 1491, 1406, 1327, 1163, 1091, 976, 808, 756, 664 cm$^{-1}$.

MS (ESI, +ve) $m/z$ 368 [(M+Na)$^+$, 100%].

HRMS $m/z$ 368.1292 [M+Na]$^+$ (calcd for C$_{19}$H$_{23}$NO$_3$S, 368.1291).

Concentration of fraction B ($R_f$ = 0.1) gave compound $cis$-50 (469 mg, 50%) as a white powder, m.p. = 152 °C.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.77 (d, $J$ = 8.3 Hz, 2H), 7.25–7.22 (complex m, 3H), 7.21–7.11 (complex m, 3H), 6.38 (s, 1H), 3.51 (m, 1H), 2.48 (m, 1H), 2.40 (s, 3H), 1.99 (d, $J$ = 11.2 Hz, 1H), 1.75 (m, 1H), 1.54 (m, 2H), 1.33–1.09 (complex m, 4H) (resonance due to OH group proton not observed).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 143.9, 141.7, 136.7, 132.7, 129.7, 127.5, 127.4, 127.3, 127.0 126.7, 70.7, 42.8, 36.1, 35.1, 32.5, 24.4, 21.6.

IR (ATR) $\nu_{\text{max}}$ 3249, 2925, 1492, 1401, 1330, 1161, 1092, 915, 809, 756, 706, 671 cm$^{-1}$.

MS (ESI, +ve) $m/z$ 368 [(M+Na)$^+$, 100%].

HRMS $m/z$ 368.1288 [M+Na]$^+$ (calcd for C$_{19}$H$_{23}$NO$_3$S, 368.1291).
Compound \textit{cis}-51

A magnetically stirred solution of compound 49 (165 mg, 0.93 mmol) and pyridine (226 \(\mu\)L, 2.79 mmol) in dry dichloromethane (5 mL) maintained at 0 °C was treated, in portions, with \(p\)-toluenesulfonyl chloride (186 mg, 0.98 mmol) then warmed to 22 °C. After 19 h the reaction mixture was treated with heptane (20 mL) then concentrated under reduced pressure. This dilution/concentration process was repeated twice more in order to remove pyridine. The residue so obtained was subjected to flash column chromatography (silica, 1:9 v/v diethyl ether/dichloromethane elution) and thus affording, after concentration of the appropriate fractions \((R_f = 0.2)\), compound \textit{cis}-51 (262 mg, 85%) as a clear, colorless oil.

\(^1\text{H} \text{NMR} \) (400 MHz, CDCl\(_3\)) \(\delta\) 8.49 (broad s, 1H), 7.78–7.66 (m, 2H), 7.37 (dd, \(J = 8.1\) and 1.3 Hz, 1H), 7.24–7.17 (complex m, 3H), 7.09 (m, 1H), 6.99 (m, 1H), 6.94 (m, 1H), 4.80 (m, 1H), 2.93 (t, \(J = 3.4\) Hz, 1H), 2.36 (s, 3H), 2.18 (m, 1H), 1.78 (dt, \(J = 12.9\) and 2.6 Hz, 1H), 1.74–1.62 (complex m, 3H), 1.54–1.47 (complex m, 1H), 1.47–1.40 (complex m, 1H), 1.31–1.20 (complex m, 1H).

\(^{13}\text{C} \text{NMR} \) (100 MHz, CDCl\(_3\)) \(\delta\) 143.7, 137.2, 136.8, 134.5, 130.0, 129.6, 127.4, 127.1, 125.2, 122.6, 74.0, 41.6, 40.7, 36.4, 30.9, 21.6.

IR (ATR) \(\nu_{\text{max}}\) 3503, 3270, 2955, 2870, 1492, 1341, 1158, 1090, 814, 756, 661 cm\(^{-1}\).

MS (ESI, +ve) m/z 354 [(M+Na\(^+\)], 100\%].

HRMS m/z 354.1141 [M+Na\(^+\)] (calcd for C\(_{18}\)H\(_{21}\)NO\(_3\)S, 354.1140).

\textbf{Compound 52}

A magnetically stirred solution of compound \textit{trans}-50 (81.4 mg, 0.24 mmol) and triphenylphosphine (148 mg, 0.57 mmol) in dry tetrahydrofuran (5 mL) maintained at 0 °C was treated, dropwise, with DEAD (92 \(\mu\)L, 0.59 mmol). After 16 h the reaction mixture was concentrated under reduced pressure and the residue so obtained subjected to flash column chromatography (silica, 1:9 v/v ethyl acetate/40-60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions \((R_f = 0.3)\), compound 52 (69 mg, 89%) as a clear, colorless oil.

\(^1\text{H} \text{NMR} \) (400 MHz, CDCl\(_3\)) \(\delta\) 7.87 (m, 1H), 7.62 (m, 2H), 7.21 (d, \(J = 8.1\) Hz, 2H), 7.09 (m, 1H), 6.99 (m, 1H), 6.94 (m, 1H), 4.80 (m, 1H), 2.93 (t, \(J = 3.4\) Hz, 1H), 2.36 (s, 3H), 2.18 (m, 1H), 1.78 (dt, \(J = 12.9\) and 2.6 Hz, 1H), 1.74–1.62 (complex m, 3H), 1.54–1.47 (complex m, 1H), 1.47–1.40 (complex m, 1H), 1.31–1.20 (complex m, 1H).

\(^{13}\text{C} \text{NMR} \) (100 MHz, CDCl\(_3\)) \(\delta\) 143.6, 138.5, 137.2, 130.7, 129.8, 129.0, 127.1, 126.7, 122.9, 119.5, 52.3, 33.9, 33.7(2), 33.6(9), 28.4, 21.6, 17.3.

IR (ATR) \(\nu_{\text{max}}\) 2931, 2853, 1489, 1453, 1341, 1158, 1089, 871, 814, 674 cm\(^{-1}\).

MS (ESI, +ve) m/z 677 [(2M+Na\(^+\)], 78\%], 350 [(M+Na\(^+\)], 100\%], 328 [(M+H\(^+\)], 5].
**HRMS** m/z 328.1361 [M+H]$^+$ (calcd for C$_{19}$H$_{21}$NO$_2$S, 328.1366).

**trans-N-(2-(3-Chlorocyclopentyl)phenyl)-4-methylbenzenesulfonamide**

![Chemical structure](image)

A magnetically stirred solution of compound *cis*-51 (61 mg, 0.18 mmol) and triphenylphosphine (97 mg, 0.37 mmol) in dry dichloromethane (2 mL) maintained at 0 °C was treated, dropwise, with carbon tetrachloride (107 µL, 1.10 mmol) then warmed to 22 °C. After 15 h the reaction mixture was concentrated under reduced pressure and the residue so obtained subjected to flash column chromatography (silica, dichloromethane elution). After concentration of the appropriate fractions ($R_f = 0.4$), the title halide (55.7 mg, 87%) was obtained as a clear, colorless oil.

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.61 (d, $J = 8.2$ Hz, 2H), 7.34 (dd, $J = 7.6$ and 1.6 Hz, 1H), 7.23 (d, $J = 8.2$ Hz, 2H), 7.20–7.10 (complex m, 3H), 6.73 (s, 1H), 4.49 (m, 1H), 3.38 (m, 1H), 2.39 (s, 3H), 2.28 (m, 1H), 2.07–1.95 (complex m, 2H), 1.87 (dd, $J = 9.0$ and 4.2 Hz, 2H), 1.51–1.37 (complex m, 1H).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 143.9, 139.9, 136.6, 133.7, 129.8, 127.5, 127.4, 127.0, 126.9, 126.7, 61.4, 45.0, 37.2, 36.4, 32.3, 21.6.

IR (ATR) $\nu_{\text{max}}$ 3267, 2972, 1492, 1399, 1328, 1156, 1091, 904, 813, 757, 732, 662 cm$^{-1}$.

**MS** (ESI, +ve) m/z 374 and 372 [(M+Na)$^+$, 38 and 100%].

**HRMS** m/z 350.0962 [M+H]$^+$ (calcd for C$_{18}$H$_{20}$$_{35}$ClNO$_2$S, 350.0976).

**Compound 53**

![Chemical structure](image)

A magnetically stirred solution of the above-mentioned *trans-N-(2-(3-chlorocyclopentyl)-phenyl)-4-methylbenzenesulfonamide* (55.7 mg, 0.16 mmol) in dry methanol (16 mL) maintained at 55 °C was treated with potassium carbonate (110 mg, 0.80 mmol). After 18 h the reaction mixture was cooled to 22 °C then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, dichloromethane elution) and thus affording, after concentration of the appropriate fractions ($R_f = 0.6$), compound 53 (49.6 mg, 99%) as a white, crystalline solid, m.p. =111 °C.

$^1$H NMR (400 MHz, CDCl$_3$) δ 7.85 (m, 1H), 7.65 (d, $J = 8.0$ Hz, 2H), 7.21 (d, $J = 8.0$ Hz, 2H), 7.11 (m, 1H), 6.94 (m, 2H), 5.08 (m, 1H), 2.99 (s, 1H), 2.37 (s, 3H), 2.17–2.04 (complex m, 1H), 1.99–1.89 (complex m, 1H), 1.87–1.74 (complex m, 2H), 1.48 (m, 2H).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 143.7, 137.1, 135.2, 134.8, 129.7, 127.9, 127.2, 127.1, 123.7, 121.1, 58.5, 41.4 35.9, 31.9, 31.4, 21.6.
IR (ATR) $\nu_{\text{max}}$ 2947, 2866, 1600, 1483, 1455, 1342, 1226, 1165, 1155, 1090, 812, 757, 680 cm$^{-1}$.

**MS (ESI, +ve)** $m/z$ 336 [(M+Na)$^+$, 100%].

**HRMS** $m/z$ 314.1196 [M+H]$^+$ (calcd for $\text{C}_{18}\text{H}_{19}\text{NO}_2\text{S}$, 314.1209).
X-ray Crystallographic Studies

Crystallographic Data

Crystallographic Data for Compound 7

C_{12}H_{11}NO_3, M = 217.22, T = 150 K, monoclinic, space group P2_1/c, Z = 4, a = 9.3274(2), b = 14.6679(2), c = 7.9674(1) Å; β = 107.026(2)°; V = 1042.27(3) Å^3, D_x = 1.384 g cm^{-3}, 2088 unique data (2θ_{max} = 147.2°), R = 0.042 [for 1953 reflections with I > 2.0σ(I)]; Rw = 0.111 (all data), S = 1.02.

Crystallographic Data for Compound 19

C_{12}H_{22}N_3O_3, M = 232.24, T = 150 K, monoclinic, space group C2/c, Z = 8, a = 7.87923(6), b = 19.95864(19), c = 13.93593(11) Å; β = 92.3804(7)°; V = 2189.66(3) Å^3, D_x = 1.409 g cm^{-3}, 2224 unique data (2θ_{max} = 147.2°), R = 0.035 [for 2127 reflections with I > 2.0σ(I)]; Rw = 0.035 (all data), S = 1.01.

Crystallographic Data for Compound 39

C_{18}H_{22}N_3O_5, M = 374.40, T = 150 K, triclinic, space group P\overline{T}, Z = 2, a = 7.0058(2), b = 9.5456(3), c = 13.6950(46) Å; α = 79.998(3)°, β = 83.227(3)°, γ = 85.094(2)°; V = 893.65(5) Å^3, D_x = 1.391 g cm^{-3}, 3597 unique data (2θ_{max} = 147.8°), R = 0.035 [for 3346 reflections with I > 2.0σ(I)]; Rw = 0.102 (all data), S = 0.97.

Crystallographic Data for Compound 43

C_{13}H_{22}N_2O, M = 203.28, T = 150 K, monoclinic, space group P2_1/c, Z = 4, a = 8.5291(3), b = 18.2560(5), c = 7.6050(3) Å; β = 112.547(4)°; V = 1093.63(6) Å^3, D_x = 1.235 g cm^{-3}, 2919 unique data (2θ_{max} = 60°), R = 0.044 [for 2299 reflections with I > 2.0σ(I)]; Rw = 0.117 (all data), S = 1.06.

Crystallographic Data for Compound 45

C_{12}H_{22}NO, M = 189.25, T = 150 K, orthorhombic, space group Pccn, Z = 8, a = 19.6584(2), b = 13.0353(1), c = 7.9633(1) Å; V = 2040.62(4) Å^3, D_x = 1.232 g cm^{-3}, 2048 unique data (2θ_{max} = 147.4°), R = 0.038 [for 1926 reflections with I > 2.0σ(I)]; Rw = 0.105 (all data), S = 1.06.

Crystallographic Data for Compound trans-50

C_{10}H_{23}NO_3S, M = 345.44, T = 150 K, triclinic, space group P\overline{T}, Z = 4, a = 9.4185(4), b = 12.9752(7), c = 16.0422(8) Å; α = 70.958(5)°, β = 77.623(4)°, γ = 78.202(4)°; V = 1790.80(16) Å^3, D_x = 1.281 g cm^{-3}, 7108 unique data (2θ_{max} = 147.6°), R = 0.048 [for 6495 reflections with I > 2.0σ(I)]; Rw = 0.048 (all data), S = 1.05.

Structure Determinations

The image for compound 43 was measured on a diffractometer (Mo Kα, graphite monochromator, λ = 0.71073 Å) fitted with an area detector and the data extracted using the DENZO/Scalepack package.\textsuperscript{16} Images for compounds 7, 19, 39, 45, and trans-50 were measured on a diffractometer (Cu Kα, mirror monochromator, λ = 1.54184 Å) fitted with an area detector and the data extracted using the CrysAlis package.\textsuperscript{17} The structure solutions for all six compounds were either solved by direct methods (SIR92) and refined using the CRYSTALS program package, or solved with ShelXT\textsuperscript{18} and refined using ShelXL\textsuperscript{19} in OLEX2.\textsuperscript{20} Atomic coordinates, bond lengths and angles, and displacement parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC nos. 1832167, 1832168, 1832169, 1832170, 1832171 and 1832172). These data can be obtained free-of-charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.
Figure S1: Structure of compound 7 (CCDC 1832167). Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.
Figure S2: Structure of compound 19 (CCDC 1832168). Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.
Figure S3: Structure of compound 39 (CCDC 1832169) and associated water molecules. Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.
Figure S4: Structure of compound 43 (CCDC 1832170). Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.
Figure S5: Structure of compound 45 (CCDC 1832171). Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.
Figure S6: Structure of compound trans-50 (CCDC 1832171). Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.
References

400 MHz $^1$H NMR Spectrum of Compound 5 (X = I)
(recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 5 ($X = I$)
(recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 5 (X = Br) (recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 5 (X = Br)
(recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 7
(recorded in CDCl$_3$)
$^{13}$C NMR Spectrum of Compound 7
(recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of [1,1'-Bi(cyclohexane)]-1,1'-diene-3,3'-dione (recorded in CDCl$_3$)

400 MHz $^1$H NMR Spectrum of [1,1'-Bi(cyclohexane)]-1,1'-diene-3,3'-dione (recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of [1,1'-Bi(cyclohexane)]-1,1'-diene-3,3'-dione (recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 8 (recorded in CDCl$_3$)
$^{13}$C NMR Spectrum of Compound 8
(recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 9
(recorded in CDCl$_3$)

* = decomposition product

CHCl$_3$
100 MHz $^{13}$C NMR Spectrum of Compound 9
(recorded in CDCl$_3$)

$^{*}$ = decomposition product
400 MHz $^1$H NMR Spectrum of Compound 10
(recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 10
(recorded in CDCl$_3$)

![Compound 10](image)
400 MHz $^1$H NMR Spectrum of Compound 11
(recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 11
(recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 15
(recorded in CDCl$_3$)

![NMR Spectrum Image]

Chemical Shift (ppm)

CHCl$_3$
100 MHz $^{13}$C NMR Spectrum of Compound 15
(recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 16
(recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 16 (recorded in CDCl$_3$)
400 MHz 1H NMR Spectrum of Compound 17 (recorded in CDCl₃)
100 MHz $^{13}$C NMR Spectrum of Compound 17 (recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 18
(recorded in CDCl$_3$)

* = decomposition product

CHCl$_3$

hexanes
$100 \text{ MHz } ^{13}\text{C NMR Spectrum of Compound 18}$

(recorded in CDCl$_3$)

* = decomposition product

CDCl$_3$
400 MHz $^1$H NMR Spectrum of Compound 19 
[recorded in $(CD_3)_2CO$]

$^1$H NMR Spectrum of Compound 19
100 MHz $^{13}$C NMR Spectrum of Compound 19
[recorded in (CD$_3$)$_2$CO]
400 MHz $^1$H NMR Spectrum of Compound 24
(recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 24
(recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 25
(recorded in CDCl$_3$)

H$_2$O
hexanes
100 MHz $^{13}$C NMR Spectrum of Compound 25
(recorded in CDCl$_3$)

[Diagram of compound 25]
400 MHz $^1$H NMR Spectrum of Compound 26
(recorded in CDCl$_3$)

* = impurity
100 MHz $^{13}$C NMR Spectrum of Compound 26
(recorded in CDCl$_3$)

* = impurity
400 MHz $^1$H NMR Spectrum of Compound 27 (recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 27
(recorded in CDCl$_3$)

* = impurity

CDCl$_3$
400 MHz $^1$H NMR Spectrum of Compound 30 (recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 30 (recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 31
(recorded in CDCl$_3$)

![NMR Spectrum of Compound 31](image)
100 MHz $^{13}$C NMR Spectrum of Compound 31
(recorded in CDCl$_3$)

![NMR spectrum diagram]
400 MHz $^1$H NMR Spectrum of Compound 32
(recorded in CDCl$_3$)

$\text{MeO}_2\text{C}$

$\text{CN}$

$\text{CHCl}_3$

$\text{H}_2\text{O}$

hexanes
100 MHz $^{13}$C NMR Spectrum of Compound 32
(recorded in CDCl$_3$)

![Compound 32](image)
$400 \text{ MHz } ^1\text{H NMR Spectrum of Compound 33}$

(recorded in CDCl$_3$)
$100\ \text{MHz}$ $^{13}\text{C}$ NMR Spectrum of Compound 33
(recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 34
(recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 34
(recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 36
(recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 36 (recorded in CDCl$_3$)

$^{13}$C NMR Spectrum of Compound 36 (recorded in CDCl$_3$)

* = impurity
400 MHz $^1$H NMR Spectrum of Compound 37
(recorded in CDCl$_3$)

CHCl$_3$

H$_2$O

hexanes
$^{13}$C NMR Spectrum of Compound 37 (recorded in CDCl$_3$)

100 MHz
400 MHz $^1$H NMR Spectrum of Compound 38
(recorded in CDCl$_3$)
$^{13}$C NMR Spectrum of Compound 38
(recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 39 (recorded in CDCl$_3$)
100 MHz $^{13}\text{C}$ NMR Spectrum of Compound 39
(recorded in CDCl$_3$)

![Chemical Structure of Compound 39]
400 MHz $^1$H NMR Spectrum of Compound 40
(recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 40
(recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 41
(recorded in CDCl$_3$)

* = impurity

H grease

H$_2$O

CHCl$_3$
100 MHz $^{13}$C NMR Spectrum of Compound 41
(recorded in CDCl$_3$)

41
400 MHz $^1$H NMR Spectrum of Compound 42
(recorded in CDCl$_3$)

$\text{CH}_3\text{Cl}_3$

N

N

$\text{(CH}_3\text{)}_2\text{CO}$
100 MHz $^{13}$C NMR Spectrum of Compound 42
(recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 43
(recorded in CDCl₃)
100 MHz $^{13}$C NMR Spectrum of Compound 43 (recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 44
(recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 44
(recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 45
(recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 45
(recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 46
(recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 46
(recorded in CDCl$_3$)

![NMR Spectrum Diagram]
400 MHz $^1$H NMR Spectrum of Compound 47 (recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 47
(recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 49
(recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 49
(recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound trans-50
(recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound \textit{trans-50} (recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound $cis$-50
(recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound $cis$-$50$
(recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound cis-51
(recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound cis-51 (recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 52
(recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 52
(recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of 
cis-N-(2-(3-chlorocyclopentyl)phenyl)-4-methylbenzenesulfonamide 
(recorded in CDCl$_3$)

* = impurity

CH$_2$Cl$_2$  
H$_2$O
100 MHz $^{13}$C NMR Spectrum of 
$cis$-$N$-(2-(3-chlorocyclopentyl phenyl)-4-methylbenzenesulfonamide
(recorded in CDCl$_3$)

* = impurity
400 MHz $^1$H NMR Spectrum of Compound 53
(recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 53
(recorded in CDCl$_3$)
Reductive Cyclisation of o-Nitroarylated-α,β-unsaturated Aldehydes and Ketones with TiCl₃/HCl or Fe/HCl Leading to 1,2,3,9-Tetrahydro-4H-carbazol-4-ones and Related Heterocycles

Yun Qiu, Michael Dlugosch, Xin Liu, Faiyaz Khan, Jas S. Ward, Ping Lan and Martin G. Banwell

Reductive Cyclization of o-Nitroarylated-α,β-unsaturated Aldehydes and Ketones with TiCl₃/HCl or Fe/HCl Leading to 1,2,3,9-Tetrahydro-4H-carbazol-4-ones and Related Heterocycles

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*Supporting Information

ABSTRACT: Compounds such as 3, the product of a palladium[0]-catalyzed Ullmann cross-coupling of o-iodonitrobenzene and 2-iodocyclohex-2-en-1-one, undergo complementary modes of reductive cyclization depending upon the conditions employed. Thus, on treatment with hydrogen in the presence of palladium on carbon, the tetrahydrocarbazole 4 is formed, while reaction of the same substrate (3) with TiCl₃ in acetone affords the 1,2,3,9-tetrahydro-4H-carbazol-4-one 6.

INTRODUCTION

Sometime ago,¹ we reported that 2-iodocyclohex-2-en-1-one (1) (Scheme 1) could be efficiently cross-coupled with o-iodonitrobenzene (2) in the presence of copper bronze and catalytic quantities of palladium[0] at 50 °C. Catalytic hydrogenation of the resulting o-nitroarylated cyclohexenone 3 then afforded the tetrahydrocarbazole 4. We have since extended this two-step and related reaction sequences in a variety of settings, including ones that have led to a range of alkaloids as well as medicinally relevant heterocycles.²

We now report that by treating cross-coupling products such as 3 with titanium trichloride/HCl or iron/HCl at ambient conditions, quite distinct reductive cyclization processes take place to give heterocyclic systems of biological interest.

RESULTS AND DISCUSSION

As shown in Scheme 2, when compound 3 is treated with either titanium trichloride/HCl or iron/HCl at ambient conditions, the resulting 1,2,3,9-tetrahydro-4H-carbazol-4-one 6 and the direct reduction of nitroarene 7 to aniline 8 are obtained. The mechanism for these reactions is proposed to involve a nucleophilic attack at the α-carbon of the α,β-unsaturated aldehyde or ketone, followed by a β-elimination to give the carbazole core.

Scheme 1. Palladium-Catalyzed Ullmann Cross-Coupling/Reductive Cyclization Sequence Leading to Tetrahydrocarbazole 4

Scheme 2. Reductive Cyclization of Compound 3 via N-Hydroxyindole 5 to 1,2,3,9-Tetrahydro-4H-carbazol-4-one 6 and the Direct Reduction of Nitroarene 7 to Aniline 8

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temperatures for brief periods, then the primary product of the reaction is the N-hydroxytetrahydro-4H-carbazol-4-one 5, the structure of which was confirmed by single-crystal X-ray analysis (see the SI for details). Furthermore, when compound 3 or 5 was exposed to the same reagents for extended periods of time, then the previously reported tetrahydro-4H-carbazol-4-one 6 was obtained. Under optimal conditions (TiCl₃/HCl is generally the preferred reducing agent), the latter product could be obtained, as the exclusive one, from precursor 3 in 82% yield. Fe/HCl was much less effective in these conversions (see the Experimental section and SI for details). While the precise mode of the formation of product 5 from substrate 3 remains to be established, it is clear that the former compound is a precursor to tetrahydrocarbazol-4-one 6. The formation of compound 6 by the means just described is closely related to a protocol recently reported by Zhu and co-workers as a key step in their elegant total synthesis of aspidospermidine. 6

The cyclization process appears to be sensitive to stereo-electronic effects, as evidenced by the conversion of the cyclopentenone-appended nitroarene 7 into the corresponding aniline 8 (80%) rather than the lower homologue of heterocycle 6. Interestingly, analogous treatment of the cycloheptenone-appended nitroarene (viz. the higher homologue of compound 3) only led to complex mixtures of products.

The complementary nature of the original mode of reductive cyclization of the palladium-catalyzed Ullmann cross-coupling products and the one that can normally be best effected using TiCl₃/HCl is emphasized through the example shown in Scheme 3. Thus, cross-coupling of electrophiles 9 and 2 using copper in the presence of catalytic Pd[0] afforded product 10 (80%), and on treatment of this with hydrogen in the presence of 10% palladium on carbon then the previously reported gem-dimethylated tetrahydrocarbazole 11 is obtained in 92% yield. In contrast, on treating the same substrate with TiCl₃/HCl in acetone at ambient temperatures, then compound 12, an established precursor to demethoxyxarazomycin B, is obtained in 82% yield.

The utility of the "new" mode of reductive cyclization in establishing multiheteroatom-containing ring systems is revealed through the examples shown in Scheme 4. Thus, exposure of the previously reported coupling product 13 to TiCl₃/HCl gives the 7-azaindole 14 (54%), while the products derived from the cross-coupling of the homochiral iodide 15 with aryl iodides 2 and 16, namely, compounds 17 (69%) and 18 (91%), respectively, react with TiCl₃/HCl (in the former case) or Fe/HCl (in the latter case) to afford the tetracyclic products 19 (97% from 17) and 20 (58% from 18). The spectral data derived from these products were in complete accord with the assigned structures, and a single-crystal X-ray analysis of compound 19 was obtained.

Acyclic ketones behave similarly as shown in Scheme 5. So, the Johnson α-iodination of chalcone (21) afforded a chromatographically separable mixture of compounds 22 (58%) and 23 (10%) that, upon palladium-catalyzed Ullmann cross-coupling with compound 16, afforded the anticipated products 24 and 25 (59–85% combined yield). The structure of the former product (24) was confirmed by single-crystal X-ray analysis. Since the cross-couplings of the geometrically pure E- and Z-isomeric forms of 22 and 23 are each accompanied by some double-bond isomerization, it was most convenient to carry the mixture of iodinated products through the illustrated reaction sequence rather than separating these. Subjection of these cross-coupling products, either separately or as a mixture, to reductive cyclization with hydrogen in the presence of 10% palladium on carbon afforded the 3-benzyl-7-azaindole 26 (63–80%), while treatment of the same substrates with TiCl₃ gave the 3-benzoyl-7-azaindole 27 in 15–49% yield. The structure of product 26 was confirmed by single-crystal X-ray analysis.

In contrast to the outcomes detailed immediately above, when the readily obtained α-iodinated cinnamonaldehyde (Scheme 6) was subjected to palladium-catalyzed Ullmann cross-coupling with compound 2 and the ensuing product, 32 (77%), treated with TiCl₃ then a slowly interconverting mixture of the partially chromatographically separable and isomeric cyclization products 33 and 34 was obtained (55% combined yield). The structure of oxindole 33, a known
antiproliferative agent,\textsuperscript{15} was confirmed by single-crystal X-ray analysis.

Very recently, we detailed\textsuperscript{16} the cross-coupling of various \(\beta\)-iodoeneones and related compounds with \(\alpha\)-iodonitrobenzene (2) to afford products, such as compound 35 (Scheme 7). Accordingly, we sought to establish how this nitroarene and its homologue 36 would behave on exposure to TiCl\(_3\)/HCl. In the event, when treated under our now standard conditions, each produced the corresponding aniline, viz. compounds 37 (quant.) and 38 (98%), respectively, with the structure of the latter being confirmed by single-crystal X-ray analysis.

A more intriguing outcome was observed when an acetone solution of the nonmethylated cross-coupling product 39 (Scheme 8) was treated with TiCl\(_3\) at ambient temperatures. Under these conditions, the chromatographically separable products 40 (40%) and 41 (60%) were obtained, and their structures established by single-crystal X-ray analysis. Compound 40 is undoubtedly the primary product of the reaction and the precursor to the other through its Schiff base condensation with acetone to give imine 42 and electrocyclic ring closure of this to give compound 43 that engages in a prototropic shift with accompanying re-aromatization to deliver the secondary product 41. Consistent with this proposal, when THF solutions of compound 40 were treated, at 22 °C, with methyl ethyl ketone, cyclohexanone, or benzaldehyde then the cycloadducts 44 (73%), 45 (64%), and 46 (quant.), respectively, are obtained. The structures of products 44 and 45 were confirmed by single-crystal X-ray analysis (see the SI for details).
CONCLUSIONS

The reductive cyclization processes detailed above considerably enhance the utility of the various products available through the palladium-catalyzed Ullmann cross-coupling of o-halotriazolylarenes with either α- or β-iodinated-α,β-unsaturated enones and related systems. The resulting, and in some instances previously unreported, heterocyclic ring systems should serve as useful scaffolds in a range of settings.

EXPERIMENTAL SECTION

General Experimental Procedures. Unless otherwise specified, proton (1H) and carbon (13C) NMR spectra were recorded at room temperature in base-filtered CDCl3, on a spectrometer operating at 400 MHz for proton and 100 MHz for carbon nuclei. For 1H NMR spectra, signals arising from the residual proto-forms of the solvent were used as internal standards. 1H NMR data are recorded as follows: chemical shift (δ) (multiplicity, coupling constant(s) J (Hz), relative integral) where multiplicity is defined as s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; or combinations of the above. The signal due to residual CHCl3 appearing at δ6.85 and the central resonance of the CDCl3 triplet appearing at δ7.26, 7.70 ppm were used to reference 1H and 13C NMR spectra, respectively. IR spectra were recorded, using neat samples, on an attenuated total reflectance (ATR) infrared spectrometer. Low-resolution ES mass spectra were recorded on a single quadrupole liquid chromatograph–mass spectrometer, while high-resolution measurements were conducted on a time-of-flight instrument. Low- and high-resolution EI mass spectra were recorded on a magnetic-sector instrument. Melting points were measured on an automated melting point system and are uncorrected. Analytical thin layer chromatography (TLC) was performed on aluminum-backed 0.2 mm thick silica gel 60 F254 plates. Eluted plates were visualized using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included phosphomolybdic acid/ceric sulfate/sulfuric acid (conc.), water (37.5 g:7.5 g:37.5 g:720 mL) or potassium permanganate/potassium carbonate:5% sodium hydroxide aqueous solution:water (3 g:20 g:5 mL:300 mL). Column chromatographic separations were carried out following protocols defined by Still et al. with silica gel 60 (40–63 μm) as the stationary phase and using the AR- or HPLC-grade solvents indicated. Starting materials, reagents, and drying agents as well as other inorganic salts were generally available from commercial sources and used as supplied. Tetrahydrofuran (THF), diethyl ether, methanol, and dichloromethane were dried using a solvent purification system that is based upon a technology originally described by Grabus et al. Where necessary, reactions were performed under a nitrogen atmosphere.

Specific Chemical Transformations. Compound 5. Method i: A magnetically stirred mixture of compound 3 (217 mg, 1.00 mmol) in acetone (5 mL) maintained at 22 °C was treated with titanium(III) chloride (5.0 mL of a 12% w/v solution in hydrochloric acid, 4.79 mmol). After 1 h, the reaction mixture was diluted with ethyl acetate (20 mL), washed with water (3 × 10 mL), dried (Na2SO4), filtered, and then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:1 v/v ethyl acetate/40–60 petroleum ether elution) and thus afforded, after concentration of the appropriate fractions (Rf = 0.2), compound 6 (42 mg, 91%) as a white, crystalline solid. mp 174 °C (lit5a mp 173–174 °C). 1H NMR (400 MHz, CDCl3, δ): 11.84 (s, 1H), 7.59 (m, 1H), 7.39 (dd, J = 8.0 and 1.4 Hz), 7.15 (m, 2H), 2.96 (t, J = 6.2 Hz, 2H), 2.42 (t, J = 6.2 Hz, 2H), 2.10 (m, 2H). 13C NMR (100 MHz, CDCl3, δ): 192.9, 152.3, 153.8, 124.5, 122.4, 121.5, 120.2, 111.7, 111.5, 37.8, 23.4, 22.7. IR (ATR) νmax = 3056, 2954, 1604, 1576, 1462, 1445, 1411, 1257, 1177, 1145, 1016, 753 cm−1. MS [ESI (+)] m/z: 208 [M+Na]+, 739, 186 [M+H]+. Calculated for C16H16NO3: 286.0913; found, 286.0912.

Method ii: A magnetically stirred solution of compound 5 (100 mg, 0.46 mmol) in hydrochloric acid (5 mL of a 3 M aqueous solution) was maintained at ca. 100 °C with a magnetic stirrer for 1 h. After 1 h, the mixture was cooled to 22 °C, diluted with ethyl acetate (20 mL), washed with water (2 × 20 mL) and then filtered through a plug of TCL-grade silica topped with diatomaceous earth, and the solids so retained were washed with ethyl acetate (1 × 10 mL) and then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:1 v/v ethyl acetate/40–60 petroleum ether elution) and thus afforded, after concentration of the appropriate fractions (Rf = 0.2), compound 6 (10 mg, 12%) as a white, crystalline solid. This material was identical, in all aspects, with that obtained by Method i.

Compound 6. Method i: A magnetically stirred solution of compound 5 (50 mg, 0.25 mmol) in acetone (1.3 mL) maintained at 22 °C was treated with titanium(III) chloride (1.3 mL of a 12% w/v solution in hydrochloric acid, 1.24 mmol). After 1 h, the reaction mixture was quenched with sodium carbonate (5 mL of a saturated aqueous solution), and the resulting heterogeneous mixture was filtered through diatomaceous earth. The solids so retained were washed with ethyl acetate (10 mL), the combined filtrates were separated, and the aqueous phase was extracted with ethyl acetate (2 × 5 mL). The combined organic phases were washed with water (20 mL), dried (Na2SO4), filtered, and then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:1 v/v ethyl acetate/40–60 petroleum ether elution) and thus afforded, after concentration of the appropriate fractions (Rf = 0.2), compound 6 (42 mg, 91%) as a white, crystalline solid. mp 174 °C (lit5a mp 173–174 °C). 1H NMR (400 MHz, DMSO-d6, δ): 11.84 (s, 1H), 7.95 (m, 1H), 7.39 (dd, J = 8.0 and 1.4 Hz), 7.15 (m, 2H), 2.96 (t, J = 6.2 Hz, 2H), 2.42 (t, J = 6.2 Hz, 2H), 2.10 (m, 2H). 13C NMR (100 MHz, DMSO-d6, δ): 192.9, 152.3, 153.8, 124.5, 122.4, 121.5, 120.2, 111.7, 111.5, 37.8, 23.4, 22.7. IR (ATR) νmax = 3056, 2954, 1604, 1576, 1462, 1445, 1411, 1257, 1177, 1145, 1016, 753 cm−1. MS [ESI (+)] m/z: 208 [M+Na]+, 739, 186 [M+H]+. Calculated for C16H16NO3: 286.0913; found, 286.0912.

Method ii: A magnetically stirred solution of compound 5 (100 mg, 0.46 mmol) in hydrochloric acid (5 mL of a 3 M aqueous solution) was maintained at ca. 100 °C with a magnetic stirrer for 1 h. After 1 h, the mixture was cooled to 22 °C, diluted with ethyl acetate (20 mL), washed with water (2 × 20 mL) and then filtered through a plug of TCL-grade silica topped with diatomaceous earth, and the solids so retained were washed with ethyl acetate (1 × 10 mL). The combined filtrates were washed with water (2 × 20 mL) and then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:1 v/v ethyl acetate/40–60 petroleum ether elution) and thus afforded, after concentration of the appropriate fractions (Rf = 0.2), compound 6 (42 mg, 91%) as a white, crystalline solid. This material was identical, in all aspects, with that obtained by Method i.
118.8, 118.7, 117.0, 35.2, 27.2. IR (ATR) υ\textsubscript{max}: 3422, 3357, 2921, 2688, 1724, 1688, 1622, 1492, 1543, 1299, 1137, 935, 751 cm\(^{-1}\). MS (ESI, +) (m/z): 196 [M+Na]+, 100%. HRMS (ESI, +): [M + Na]+ Calcd for C\(_{14}\)H\(_{18}\)N, 200.1434; found, 200.1433.

**Compound 12.** A magnetically stirred solution of compound 10 (50 mg, 0.20 mmol) in acetone (3 mL) maintained at 22 °C was treated with titanium(III) chloride (1.25 mL of a 12% w/v solution in hydrochloric acid, 1.20 mmol). After 16 h, the reaction mixture was cooled to 22 °C and then quenched with Na\(_2\)CO\(_3\) (10 mL of a saturated aqueous solution), and the resulting heterogeneous mixture filtered through a plug of diatomaceous earth. The solids so retained were washed with ethyl acetate (1 × 20 mL), and the aqueous phase associated with the combined filtrates was extracted with ethyl acetate (2 × 10 mL). The combined organic phases were washed with brine (1 × 50 mL), dried (Na\(_2\)SO\(_4\)), and filtered before being concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:8 v/v ethyl acetate/dichloromethane elution) and thus afforded, after concentration of the appropriate fractions (R\(_f\) = 0.2), compound 12 (35 mg, 82%) as a white, crystalline solid, mp 258 °C (lit. 8 mp 270–274 °C).¹ H NMR (400 MHz, CDCl\(_3\), δ): 8.80 (broad s, 1H), 8.26 (m, 1H), 7.38 (m, 1H), 7.24 (m, 2H), 2.68 (dd, J = 7.0 and 6.0 Hz, 2H), 2.10 (dd, J = 7.0 and 6.0 Hz, 2H), 1.48 (s, 6H). ¹³C NMR (100 MHz, CDCl\(_3\), δ): 194.0, 158.3, 153.6, 124.9, 123.4, 122.7, 121.7, 111.4, 111.0, 38.6, 35.4, 32.1, 27.4. IR (ATR) υ\textsubscript{max}: 3186, 2962, 1625, 1615, 1582, 1474, 1413, 1421, 1201, 881, 756 cm\(^{-1}\). MS (ESI, +) (m/z): 449 [2M+Na]+, 586, 236 [M+Na]+, 85 [M+H]+, 100. HRMS (ESI, +): [M + H]+ Calcd for C\(_{14}\)H\(_{18}\)N\(_2\), 214.1227; found, 214.1226.

**Compound 14.** A magnetically stirred solution of compound 13 (109 mg, 0.50 mmol) in acetone (2.5 mL) maintained at 22 °C was treated with titanium(III) chloride (2.5 mL of a 12% w/v solution in hydrochloric acid, 2.39 mmol). After 16 h, the reaction mixture was quenched with sodium carbonate (10 mL of a 0.5 M aqueous solution), and the resulting heterogeneous mixture filtered through a plug of diatomaceous earth. The solids so obtained were washed with ethyl acetate (1 × 20 mL), and the aqueous phase associated with the combined filtrates was extracted with ethyl acetate (2 × 10 mL). The combined organic phases were washed with brine (1 × 50 mL), dried (Na\(_2\)SO\(_4\)), and filtered before being concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, ethyl acetate elution) and thus afforded, after concentration of the appropriate fractions (R\(_f\) = 0.2), compound 14 (35 mg, 82%) as a white, crystalline solid, mp 179 °C (lit. 170–172 °C).¹ H NMR (400 MHz, CDCl\(_3\), δ): 13.01 (broad s, 1H), 8.55 (dd, J = 7.7 and 1.4 Hz, 1H), 8.31 (d, J = 4.9 Hz, 1H), 7.29 (m, 1H), 3.13 (s, J = 6.2 Hz, 2H), 2.65 (s, J = 6.4 Hz, 2H), 2.40-2.26 (complex m, 2H). ¹³C NMR (100 MHz, CDCl\(_3\), δ): 194.0, 152.5, 148.8, 141.8, 130.5, 118.5, 118.2, 114.9, 23.3, 23.4. IR (ATR) υ\textsubscript{max}: 449 [2M+Na]+, 586, 236 [M+Na]+, 85 [M+H]+, 100. HRMS (ESI, +): [M + H]+ Calcd for C\(_{14}\)H\(_{18}\)N\(_2\), 214.1227; found, 214.1226.

**Compound 15.** A magnetically stirred solution of levojuglone (1.50 g, 11.9 mmol) in dry dichloromethane (15 mL) maintained at 22 °C was treated, in portions, with powdered molecular iodine (4.53 g, 17.8 mmol) and then pyridine (10 mL). After 48 h, the reaction mixture was quenched with sodium sulfite (30 mL of a saturated aqueous solution) and then stirred vigorously until two clear layers were formed. The separated aqueous phase was extracted with ethyl acetate (2 × 20 mL), and the organic phase subjected to flash chromatography (silica, 1:8 v/v diethyl ether/40–60 petroleum ether elution) and thus afforded, after concentration of the appropriate fractions (R\(_f\) = 0.3), compound 15 (1.30 g, 92%) as a white, crystalline solid, mp 64 °C (lit. 60 °C). MS (ESI, +) (m/z): 543 [M+H]+, 75% [M+Na]+, 100%. HRMS (ESI, +): [M + Na]+ Calcd for C\(_{14}\)H\(_{18}\)O\(_4\), 246.1126; found, 246.1126.

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m, 2H). 13C NMR (100 MHz, CDCl3, δ): 185.7, 148.5, 142.7, 137.3,
133.5, 131.5, 129.8, 128.8, 124.6, 101.3, 72.1, 66.8. IR (ATR) νmax:
3278, 2924, 1651, 1479, 1452, 1076, 869 cm−1. MS (ESI, +) (m/z):
238 [(M+Na)+, 100%]. HRMS (ESI, +): [M + H]+ Calcd for
C12H10NO3, 216.0655; found, 216.0658.
Compound 20. A magnetically stirred solution of compound 18
(52 mg, 0.21 mmol) and hydrochloric acid (9 mL of a 1 M aqueous
solution) in 1,2-dimethoxyethane (5 mL) maintained at 50 °C was
treated with iron powder (59 mg, 1.10 g.atom). After 18 h, the
reaction mixture was cooled to 22 °C, diluted with ethyl acetate (10
mL), and then ﬁltered through a plug of TLC-grade silica topped with
diatomaceous earth, and the solids so retained were washed with ethyl
acetate (1 × 10 mL). The combined ﬁltrates were washed with water
(2 × 20 mL) and brine (1 × 20 mL) before being dried (Na2SO4),
ﬁltered, and then concentrated under reduced pressure. The ensuing
residue was subjected to ﬂash column chromatography (silica, 2:1 v/v
ethyl acetate/40−60 petroleum ether elution) and thus aﬀorded, after
concentration of the appropriate fractions (Rf = 0.2), compound 20
(26 mg, 58%) as a white, crystalline solid, mp 275 °C. 1H NMR (400
MHz, acetone-d6, δ): 8.37 (m, 1H), 8.25 (dd, J = 7.8 and 1.6 Hz, 1H),
7.29 (dd, J = 7.8 and 4.8 Hz, 1H), 5.95 (d, J = 4.6 Hz, 1H), 5.44 (s,
1H), 4.11 (dd, J = 7.2 and 4.6 Hz, 1H), 3.96 (d, J = 7.2 Hz, 1H)
(signal due to N−H group proton not observed). 13C NMR (100
MHz, acetone-d6, δ): 186.5, 152.2, 149.8, 145.6, 129.6, 119.4, 117.4,
107.1, 103.1, 72.1, 68.0. IR (ATR) νmax: 2981, 2888, 1679, 1592,
1480, 1426, 1109, 1075, 889, 805 cm−1. MS (ESI, +) (m/z): 239 [(M
+Na)+, 100%], 217 [(M+H)+, 10]. HRMS (ESI, +): [M + H]+ Calcd
for C11H9N2O3, 217.0608; found, 217.0609.
Compounds 22 and 23. A magnetically stirred solution of transchalcone (21) (475 mg, 2.28 mmol) in dry dichloromethane (7 mL)
maintained at 22 °C was treated, in portions, with powdered
molecular iodine (2.00 g, 7.98 mmol) and then pyridine (7 mL). After
48 h, the reaction mixture was quenched with sodium sulﬁte (30 mL
of a saturated aqueous solution), and vigorous stirring continued until
two clear layers had formed. The separated aqueous phase was
extracted with dichloromethane (2 × 10 mL), and the combined
organic phases were washed with sodium sulﬁte (1 × 60 mL of a
saturated aqueous solution), hydrochloric acid (1 × 500 mL of a 0.5
M aqueous solution), and brine (1 × 50 mL) before being dried
(Na2SO4) and then ﬁltered through a plug of TLC-grade silica. The
ﬁltrate was concentrated under reduced pressure, and the residue so
obtained was subjected to ﬂash column chromatography (silica, 5:95
to 1:9 v/v diethyl ether/40−60 petroleum ether gradient elution).
Two fractions, A and B, were thus obtained.
Concentration of fraction A (Rf = 0.5 in 1:9 diethyl ether/40−60
petroleum ether) gave compound 2212 (439 mg, 58%) as a lightyellow oil. 1H NMR (400 MHz, CDCl3, δ): 8.01−7.92 (complex m,
2H), 7.58−7.40 (complex m, 6H), 7.17 (m, 3H). 13C NMR (100
MHz, CDCl3, δ): 193.0, 148.5, 135.5, 135.3, 132.7, 130.2, 130.0,
129.4, 128.5, 128.4, 103.5. IR (ATR) νmax: 3057, 3024, 2923, 1657,
1595, 1446, 1238, 1176, 1059, 748, 689 cm−1. MS (ESI, +) (m/z):
357 [(M+Na)+, 100%]. HRMS (ESI, +): [M + H]+ Calcd for
C15H12IO, 334.9927; found, 334.9916.
Concentration of fraction B (Rf = 0.6 in 1:9 diethyl ether/40−60
petroleum ether) gave compound 2312 (79 mg, 10%) as a light-yellow
oil. 1H NMR (400 MHz, CDCl3, δ): 7.98 (m, 2H), 7.53 (m, 2H),
7.40 (m, 2H), 7.16 (m, 5H). 13C NMR (100 MHz, CDCl3, δ): 193.6,
143.4, 136.0, 134.0, 132.5, 129.9, 128.8, 128.7, 128.5, 128.1, 92.7. IR
(ATR) νmax: 3058, 3024, 2924, 1659, 1596, 1447, 1221, 1173, 1012,
750, 685 cm−1. MS (ESI, +) (m/z): 357 [(M+Na)+, 100%]. HRMS
Compounds 24 and 25. Method i: A magnetically stirred mixture
of compound 22 (160 mg, 0.48 mmol), 3-bromo-2-nitropyridine (16)
(155 mg, 0.76 mmol), and copper powder (182 mg, 2.87 g.atom) in
dry DMSO (5 mL) maintained at 80 °C was treated with Pd2(dba)3
(43 mg, 0.05 mmol). After 16 h, the reaction mixture was cooled to
22 °C, diluted with ethyl acetate (10 mL), and then ﬁltered through a
plug of TLC-grade silica topped with diatomaceous earth. The solids
so retained were washed with ethyl acetate (1 × 5 mL), and the
combined ﬁltrates were washed with ammonia (2 × 10 mL of a 5% v/

MS (ESI, +) (m/z): 307 [(M+Na+MeOH)+, 100%], 275 [(M+Na)+,
55]. HRMS (ESI, +): [M + H]+ Calcd for C6H6IO3, 252.9356; found,
252.9361.
Compound 17. A magnetically stirred suspension of compound 15
(297 mg, 1.2 mmol), o-iodonitrobenzene (2) (200 mg, 0.79 mmol),
and copper powder (250 mg, 4.0 g.atom) in dry DMSO (6 mL)
maintained at 80 °C was treated with Pd2(dba)3 (72 mg, 0.08 mmol).
After 16 h, the reaction mixture was cooled to 22 °C, diluted with
ethyl acetate (5 mL), and then ﬁltered through a plug of TLC-grade
silica topped with diatomaceous earth. The solids so retained were
washed with ethyl acetate (1 × 10 mL), and the combined ﬁltrates
were washed with ammonia (2 × 15 mL of a 5% v/v aqueous
solution), water (2 × 15 mL), and then brine (1 × 15 mL) before
being dried (Na2SO4), ﬁltered, and concentrated under reduced
pressure. The ensuing residue was subjected to ﬂash column
chromatography (silica, 2:8 to 1:1 v/v diethyl ether/40−60 petroleum
ether elution) and thus aﬀorded, after concentration of the
appropriate fractions (Rf = 0.3 in 4:6 v/v ethyl acetate/40−60
petroleum ether), compound 17 (135 mg, 69%) as a white, crystalline
solid, mp 137 °C. 1H NMR (400 MHz, acetone-d6, δ): 7.92 (m, 1H),
7.53 (m, 1H), 7.27−7.18 (complex m, 2H), 5.88 (d, J = 4.5 Hz, 1H),
5.38 (s, 1H), 4.03 (dd, J = 7.1 and 4.5 Hz, 1H), 3.84 (d, J = 7.1 Hz,
1H) (resonance due to one proton not observed). 13C NMR (100
MHz, acetone-d6, δ): 186.8, 151.6, 137.1, 125.1, 124.4, 123.3, 121.5,
113.4, 108.3, 103.2, 72.2, 68.0. IR (ATR) νmax: 2967, 2899, 1703,
1523, 1354, 1108, 984, 895, 794 cm−1. MS (ESI, +) (m/z): 270 [(M
+Na)+, 100%]. HRMS (ESI, +): [M + H]+ Calcd for C12H10NO5,
248.0553; found, 248.0553.
Compound 18. A magnetically stirred suspension of compound 15
(2.77 g, 11.0 mmol), 3-bromo-2-nitropyridine (16)8 (1.0 g, 5.0
mmol), copper(I) iodide (1.43 g, 7.5 mmol), and copper powder
(1.58 g, 25.0 g.atom) in dry DMSO (50 mL) maintained at 50 °C was
treated with Pd(dppf)Cl2·CH2Cl2 (204 mg, 0.25 mmol). After 5 h,
the reaction mixture was cooled to 22 °C, diluted with ethyl acetate
(20 mL), and then ﬁltered through a plug of TLC-grade silica topped
with diatomaceous earth. The solids so retained were washed with
ethyl acetate (1 × 40 mL), and the combined ﬁltrates were washed
with ammonia (2 × 25 mL of a 5% v/v aqueous solution), water (2 ×
25 mL), and then brine (1 × 25 mL) before being dried (Na2SO4),
ﬁltered, and concentrated under reduced pressure. The residue so
obtained was subjected to ﬂash column chromatography (silica, 1:4 v/
v ethyl acetate/40−60 petroleum ether elution) and thus aﬀorded,
after concentration of the appropriate fractions (Rf = 0.2), compound
18 (1.133 g, 91%) as a yellow, crystalline solid, mp 170 °C. 1H NMR
(400 MHz, CDCl3, δ): 8.59 (dd, J = 4.7 and 1.7 Hz, 1H), 7.79 (dd, J
= 7.6 and 1.7 Hz, 1H), 7.65 (dd, J = 7.6 and 4.7 Hz, 1H), 7.32 (d, J =
4.8 Hz, 1H), 5.51 (s, 1H), 5.20 (t, J = 4.6 Hz, 1H), 4.05−3.96
(complex m, 2H). 13C NMR (100 MHz, CDCl3, δ): 185.4, 156.8,
148.8, 144.4, 141.6, 134.7, 128.1, 123.5, 101.3, 72.3, 66.9. IR (ATR)
νmax: 2971, 2888, 1702, 1541, 1407, 1364, 1101, 984, 930, 890, 819,
647 cm−1. MS (ESI, +) (m/z): 271 [(M+Na)+, 100%]. HRMS (ESI,
+): [M + H]+ Calcd for C11H9N2O5, 249.0506; found, 249.0509.
Compound 19. A magnetically stirred solution of compound 18
(40 mg, 0.16 mmol) in THF (1.7 mL) maintained at 22 °C was
treated with titanium(III) chloride (0.85 mL of a 12% w/v solution in
hydrochloric acid, 0.81 mmol). After 18 h, the reaction mixture was
quenched with sodium carbonate (5 mL of a saturated aqueous
solution), and the resulting heterogeneous mixture was ﬁltered
through a pad of diatomaceous earth. The solids so retained were
washed with ethyl acetate (1 × 10 mL), the combined ﬁltrates were
separated, and the aqueous phase was extracted with ethyl acetate (2
× 5 mL). The combined organic phases were washed with brine (1 ×
30 mL), dried (Na2SO4), ﬁltered, and concentrated under reduced
pressure. The residue so obtained was subjected to ﬂash column
chromatography (silica, 4:6 v/v ethyl acetate/40−60 petroleum ether
elution) and thus aﬀorded, after concentration of the appropriate
fractions (Rf = 0.4), compound 19 (34 mg, 97%) as a white,
crystalline solid, mp > 250 °C. 1H NMR (400 MHz, CDCl3, δ): 8.09
(d, J = 8.1 Hz, 1H), 7.65 (m, 1H), 7.56 (m, 1H), 7.28−7.24 (complex
m, 2H), 5.51 (s, 1H), 5.19 (t, J = 4.6 Hz, 1H), 4.06−3.95 (complex
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v aqueous solution), water (2 × 10 mL), and brine (1 × 10 mL) before being dried (Na$_2$SO$_4$) filtered, and then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 3:7 to 1:1 v/v ethyl ether/40–60 petroleum ether gradient elution) and so afforded two fractions, A and B.

Concentration of fraction A ($R_f$ = 0.3 in 3:7 ethyl acetate/40–60 petroleum ether) gave compound 24 (122 mg, 77%) as a light-yellow oil. $^1$H NMR (400 MHz, CDCl$_3$, δ): 8.53 (dd, $J$ = 4.6 and 1.8 Hz, 1H), 8.16 (dd, $J$ = 7.8 and 1.8 Hz, 1H), 7.90 (m, 2H), 7.62 (dd, $J$ = 7.8 and 4.6 Hz, 1H), 7.40–7.22 (complex m, 3H), 7.17–7.08 (complex m, 5H). $^{13}$C NMR (100 MHz, CDCl$_3$, δ): 195.6, 156.4, 147.8, 141.9, 138.3, 135.9, 134.3, 133.7, 133.4, 130.0, 129.4, 129.1, 128.3, 128.2(1), 128.9(9), 127.3. IR (ATR) $\nu_{max}$: 3060, 2982, 1647, 1541, 1447, 1365, 1231, 695 cm$^{-1}$. MS (ESI, +) ($[M+H]^+$, 100%). HRMS (ESI, +): [M + H$^+$] $^+$ Calcd for C$_{20}$H$_{17}$N$_2$, 285.1386; found, 285.1388.

This material was identical, in all aspects, with that obtained by Method i.

Compound 27. A magnetically stirred mixture of compound 24 (45 mg, 0.14 mmol) in THF (5 mL) maintained at 22 °C was treated with titanium(III) chloride (0.9 mL of a 12% w/v solution in hydrochloric acid, 0.86 mmol). After 16 h, the reaction mixture was quenched with sodium carbonate (10 mL of a saturated aqueous solution), and the resulting heterogeneous mixture was filtered through a pad of diatomaceous earth. The solids so retained were washed with ethyl acetate (1 × 20 mL), the combined filtrates were separated, and the aqueous phase was extracted with ethyl acetate (4 × 10 mL). The combined organic phases were washed with brine (1 × 50 mL), dried (Na$_2$SO$_4$), and filtered before being concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 2.8 to 1:1 v/v ethyl acetate/40–60 petroleum ether gradient elution) and thus afforded, after concentration of the appropriate fractions ($R_f$ = 0.2 in 3:7 v/v ethyl acetate/40–60 petroleum ether), compound 27 (20 mg, 49%) as a yellow, crystalline solid, mp 159 °C. $^1$H NMR (400 MHz, CDCl$_3$, δ): 8.37 (d, $J$ = 7.9 Hz, 1H), 8.15 (broad s, 1H), 7.64 (m, 2H), 7.52 (m, 4H), 7.34 (m, 4H), 7.21 (m, 4H). $^{13}$C NMR (100 MHz, CDCl$_3$, δ): 192.7, 148.1, 145.4, 142.5, 139.3, 131.7, 131.5, 129.8, 129.6, 129.3, 128.4, 127.8, 117.9, 111.6 (one signal obscured or overlapping). IR (ATR) $\nu_{max}$: 2917, 2849, 1615, 1459, 1435, 1292, 936, 896, 766, 730, 698 cm$^{-1}$. MS (ESI, +) ($m/z$): 321 [M+Na$^+$], 100%; 299 [M+H$^+$], 70%; 259 [M+H$^+$·2H$_2$O$^+$], 100%. HRMS (ESI, +): [M + H$^+$] $^+$ Calcd for C$_{32}$H$_{22}$N$_2$O$_2$, 499.1179; found, 499,1181.

Method ii: Compound 25 was subjected to reductive cyclization in the same manner as described immediately above in Method i. Subjection of the product mixture obtained on workup to flash column chromatography (silica, 2.8 to 1:1 v/v ethyl acetate/40–60 petroleum ether gradient elution) afforded, after concentration of the appropriate fractions ($R_f$ = 0.2 in 3:7 v/v ethyl acetate/40–60 petroleum ether), compound 27 (15%) as a yellow, crystalline solid. This material was identical, in all aspects, with that obtained by Method i.

Compound 32. A magnetically stirred mixture of compound 31 (516 mg, 2.00 mmol), o-iodonitrobenzene (2) (996 mg, 4.00 mmol), and copper powder (636 mg, 10.0 g atom) in dry DMSO (10 mL) maintained at 50 °C was treated with Pd(dppf)Cl$_2$CH$_2$Cl$_2$ (82 mg, 0.10 mmol). After 4 h, the reaction mixture was cooled to 22 °C and then diluted with ethyl acetate (10 mL) before being filtered through a plug of TLC-grade silica topped with diatomaceous earth. The solids so retained were washed with ethyl acetate (1 × 30 mL), and the combined filtrates were washed with ammonia (2 × 40 mL of a 5% w/v aqueous solution), water (2 × 40 mL), and brine (1 × 40 mL) before being dried (Na$_2$SO$_4$), filtered, and then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, toluene elution) and then afforded, after concentration of the appropriate fractions ($R_f$ = 0.3), compound 32 (390 mg, 77%) as a clear, yellow oil. $^1$H NMR (400 MHz, CDCl$_3$, δ): 7.93 (s, 1H), 8.23 (m, 1H), 7.63–7.56 (complex m, 2H), 7.54 (s, 1H), 7.37–7.22 (complex m, 3H), 7.17 (complex m, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$, δ): 191.8, 148.9, 139.7, 133.9, 133.3, 132.0, 130.5, 130.4, 129.6(1), 129.5(9), 128.7, 125.0 (one signal obscured or overlapping). IR (ATR) $\nu_{max}$: 2018, 83, 760, 673, 516, 479, 397, 364 cm$^{-1}$. MS (ESI, +) ($m/z$): 326 [M+Na$^+$], 100%; 294 [M$^+$], 50%; 254 [M$^+$·H$_2$O$^+$], 100%. HRMS (ESI, +): [M + H$^+$] $^+$ Calcd for C$_{32}$H$_{22}$NO, 454.1604; found, 453.1601.

Compounds 33 and 34. A magnetically stirred solution of compound 32 (134 mg, 0.53 mmol) in acetone (5 mL) maintained at 22 °C was treated with titanium(III) chloride (3.18 mmol). After 23 h, the reaction mixture was quenched with sodium carbonate (10 mL of a saturated aqueous solution), and the resulting heterogeneous mixture was filtered through a pad of diatomaceous earth. The solids so retained were washed with ethyl acetate (1 × 20 mL), the combined filtrates were separated, and the aqueous phase was extracted with ethyl acetate (2 × 20 mL). The combined organic phases were washed with brine (1 × 50 mL), dried (Na$_2$SO$_4$), and filtered before being...
Concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:9 v/v diethyl ether/dichloromethane elution) and thus afforded a partially separable, ca. 5:3:1, and slowly interconverting mixture of compounds 33 and 34 (64 mg, 55%) as an oily solid. Rf = 0.2 and 0.4, respectively. 1H NMR (400 MHz, CDCl3, δ) (for compound 33): 8.20 (s, 1H), 7.85 (s, 1H), 7.70–7.60 (complex m, 3H), 7.52–7.41 (complex m, 3H), 7.22 (m, 1H), 6.88 (m, 2H). 13C NMR (100 MHz, CDCl3, δ) (for compound 33): 170.1, 141.6, 137.7, 135.0, 129.8, 129.5, 128.8, 127.6, 123.2, 122.0, 121.9, 110.2. 13C NMR (100 MHz, CDCl3, δ) (for a ca. 3:1 mixture of compounds 33 and 34): 170.0, 167.7, 141.4, 139.6, 136.7(1), 137.5(9), 134.8, 133.7, 131.9, 130.6, 139.9, 129.7, 128.9, 128.6, 127.4, 126.2, 125.3, 125.0, 121.8(1), 121.5(9), 121.7, 119.3, 110.1, 109.5. IR (ATR) νmax: 3348, 3234, 2970, 2872, 722, 696 cm−1. MS (ESI, +) (m/z): 465 ([M+Na]+ 60%), 244 ([M+Na]+ 100%), 222 ([M+H]+ 13). HRMS (ESI, +): [M + H]+ Calcd for C13H16NO, 202.1226; found, 202.1219.

The residue so obtained was subjected to flash column chromatography (silica, 1:9 v/v diethyl ether/40–60 petroleum ether elution) and then subjected to flash column chromatography (silica, 1:9 v/v diethyl ether/40–60 petroleum ether elution) and thus afforded, after concentration of the appropriate fractions (Rf = 0.6), compound 38 (40 mg, 98%) as light-yellow crystals, mp 73 °C. 1H NMR (400 MHz, CDCl3, δ): 7.13 (m, 1H), 6.92 (dd, J = 7.6 and 1.7 Hz, 1H), 6.79 (m, 1H), 6.74 (dd, J = 7.9 and 1.1 Hz, 1H), 3.57 (broad s, 2H), 2.55 (m, 4H), 2.10 (m, 2H), 1.65 (t, J = 2.0 Hz, 3H). 13C NMR (100 MHz, CDCl3, δ): 199.6, 154.9, 141.5, 133.6, 128.8, 127.1, 126.8, 114.5, 37.9, 31.9, 22.9, 12.3. IR (ATR) νmax: 3459, 3362, 2945, 2923, 1606, 1618, 1494, 1452, 1354, 1106, 750 cm−1. MS (ESI, +) (m/z): 224 ([M+Na]+ 100%), 202 ([M+H]+ 28). HRMS (ESI, +): [M + H]+ Calcd for C12H14NO, 202.1226; found, 202.1219.

Method ii: Reduction of complex 36 with TiCl3/HCl in the same manner as detailed above but using acetone instead of THF as the solvent gave, after workup and flash chromatography, compound 38 (80%) as light-yellow crystals. This material was identical, in all aspects, with that obtained by Method i.

Compounds 40 and 41. A magnetically stirred mixture of compound 39 (200 mg, 0.92 mmol) in acetone (10 mL) maintained at 22 °C was treated with titanium(III) chloride (5.0 mL of a 12 w/v solution in hydrochloric acid, 4.79 mmol). After 16 h, the reaction mixture was quenched with sodium carbonate (40 mL). The combined organic phases were washed with brine (10 mL), dried (Na2SO4), and then concentrated under reduced pressure. The residue so obtained was subjected to flash chromatography (silica, 1:9 v/v diethyl ether/40–60 petroleum ether elution) and thus afforded two fractions, A and B.

Concentration of fraction A (Rf = 0.4 in 1:1 v/v diethyl ether/40–60 petroleum ether elution) gave compound 40 (80 mg, 40%) as orange-colored crystals, mp 90 °C. 1H NMR (400 MHz, CDCl3, δ): 7.16 (m, 1H), 7.07 (dd, J = 7.8 and 1.7 Hz, 1H), 6.78 (m, 1H), 6.73 (dd, J = 8.1 and 1.2 Hz, 1H), 6.26 (t, J = 1.6 Hz, 1H), 3.84 (broad s, 2H), 2.67 (m, 2H), 2.51 (m, 2H), 2.15 (m, 2H). 13C NMR (100 MHz, CDCl3, δ): 199.6, 161.2, 142.8, 129.7, 127.9, 125.5, 118.3, 116.2, 37.3, 30.2, 23.1. IR (ATR) νmax: 3443, 3354, 2925, 1655, 1608, 1490, 1449, 1244, 1188, 747 cm−1. MS (ESI, +) (m/z): 210 ([M+Na]+ 100%), 188 ([M+H]+). HRMS (ESI, +): [M + H]+ Calcd for C12H14NO, 188.1070; found, 188.1072.

Concentration of fraction B (Rf = 0.5 in 1:1 v/v diethyl ether/40–60 petroleum ether elution) gave compound 41 (35 mg, 60%) as red-colored crystals, mp 113 °C. 1H NMR (400 MHz, CDCl3, δ): 7.21 (dd, J = 7.9 and 1.5 Hz, 1H), 7.11 (m, 1H), 6.65 (m, 1H), 6.45 (dd, J = 8.0 and 1.2 Hz, 1H), 3.64 (broad s, 1H), 2.69 (t, J = 6.1 Hz, 2H), 2.43 (dd, J = 7.4 and 6.1 Hz, 2H), 2.03 (m, 2H, 1.52 (s, 6H). 13C NMR (100 MHz, CDCl3, δ): 196.8, 148.2, 145.2, 133.8, 131.7, 125.5, 125.2, 120.2, 117.5, 113.8, 53.8, 38.7, 29.0, 25.9, 21.6. IR (ATR) νmax: 3336, 2952, 2925, 1637, 1607, 1380, 1269, 743 cm−1. MS (ESI, +) (m/z): 250 ([M+Na]+ 100%), 228 ([M+H]+). HRMS (ESI, +): [M + H]+ Calcd for C14H16NO, 228.1384; found, 228.1384.

Compound 44. A magnetically stirred solution of compound 40 (35 mg, 0.19 mmol, 1.0 equiv) in butanone (5 mL) was treated with HCl (100 μL of a 12 M aqueous solution), and the ensuing mixture was maintained at 22 °C for 16 h. The resulting mixture was quenched with sodium carbonate (5 mL of a saturated aqueous solution).
solution), and the separated aqueous layer was extracted with ethyl acetate (3 x 5 mL). The combined organic phases were then dried (Na₂SO₄), filtered, and concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 5:3:5 v/v diethyl ether/40–60 petroleum ether elution) to afford, after concentration of the appropriate fractions (Rₛ = 0.6 in 3:7 v/v diethyl ether/40–60 petroleum ether elution), compound 44 (33 mg, 73%) as a red, crystalline solid, mp 118 °C. ¹H NMR (400 MHz, CDCl₃, δ): 7.19 (dd, J = 7.9 and 1.3 Hz, 1H), 7.07 (m, 1H), 6.59 (m, 1H), 6.41 (dd, J = 8.0 and 1.1 Hz, 1H), 3.54 (broad s, 1H), 2.70 (m, 1H), 2.45 (m, 3H), 2.04 (m, 2H), 1.49 (s, 3H), 1.34 (m, 1H), 0.87 (t, J = 7.4 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃, δ): 197.1, 149.2, 145.8, 131.9(1), 131.8(2), 125.3, 119.5, 116.9, 113.3, 57.3, 38.8, 33.8, 28.5, 26.1, 21.7, 9.3 (AR (ATR) v₄max 3499, 2937, 2923, 2871, 1638, 1609, 1566, 1455, 1378, 1262, 1152 cm⁻¹, MS (ESI, +) (m/z): 264 [M +Na⁺, 100%], 242 [(M+H)⁺, 37], HRMS (ESI, +): [M + H]⁺ Calcd for C₁₃H₁₈NO 242.1545; found, 242.1547.

Compound 45. A magnetically stirred solution of compound 40 (65 mg, 0.35 mmol, 1.0 equiv) and cyclohexanone (136 mg, 1.39 mmol, 64%), mp 136–145 °C, was then added (so as to reduce the excess cyclohexenone). The mixture was stirred at 22 °C for 201.26. T = 150 K. Monoclinic, space group P2₁/c, Z = 4, a = 13.9326(4), b = 31.3218(6), c = 7.6013(1) Å, β = 98.270(2)°. V = 3282.67(11) Å³. D₄ = 1.222 g cm⁻³. 6365 unique data (20max = 144.2°). R = 0.058 [for 5008 reflections with I > 2σ(I)]. Rₛ = 0.163 (all data). S = 1.07.

Crystallographic Data for Compound 46. C₁₅H₁₇NO. M = 221.25. T = 150 K. Monoclinic, space group P2₁/c, Z = 4, a = 10.2353(2), b = 22.2268(5), c = 12.2592(3) Å, β = 95.1122(2)°. V = 1087.55(5) Å³. D₄ = 1.351 g cm⁻³. 2147 unique data (20max = 148.4°). R = 0.052 [for 2026 reflections with I > 2σ(I)]. Rₛ = 0.044 (all data). S = 4.03.

Crystallographic Data for Compound 47. C₁₅H₁₇NO. M = 187.23. T = 150 K. Monoclinic, space group P2₁/c, Z = 2, a = 7.0538(7), b = 8.4543(7), c = 8.3005(10) Å, β = 99.725(10)°. V = 887.89(1) Å³. D₄ = 1.275 g cm⁻³. 1859 unique data (20max = 52.8°). R = 0.038 [for 1663 reflections with I > 2σ(I)]. Rₛ = 0.081 (all data). S = 1.09.

Crystallographic Data for Compound 48. C₁₅H₁₇NO. M = 277.29. T = 150 K. Monoclinic, space group P2₁/c, Z = 4, a = 8.8038(8), b = 18.8775(9), c = 11.2318(10) Å, β = 109.578(10)°. V = 1199.72(19) Å³. D₄ = 1.258 g cm⁻³. 2446 unique data (20max = 52.8°). R = 0.039 [for 2055 reflections with I > 2σ(I)]. Rₛ = 0.107 (all data). S = 1.04.

Crystallographic Data for Compound 49. C₁₅H₁₇NO. M = 239.04. T = 150 K. Monoclinic, space group P2₁/c, Z = 4, a = 9.8386(3), b = 12.2110(3), c = 12.1822(4) Å, β = 108.645(2)°. V = 1322.90(7) Å³. D₄ = 1.202 g cm⁻³. 2640 unique data (20max = 147.2°). R = 0.082 [for 2373 reflections with I > 2σ(I)]. Rₛ = 0.044 (all data). S = 1.06.

Crystallographic Data for Compound 50. C₁₅H₁₇NO. M = 267.36. T = 150 K. Monoclinic, space group P2₁/c, Z = 4, a = 11.0667(3), b = 10.0284(2), c = 14.0170(3) Å, β = 112.696(3)°. V = 1435.16(6) Å³. D₄ = 1.237 g cm⁻³. 2883 unique data (20max = 148.0°). R = 0.047 [for 2635 reflections with I > 2σ(I)]. Rₛ = 0.132 (all data). S = 1.06.

Structure Determinations. The images for compounds S, 19, 24, 26, 33, 38, 40, 41, 44, and 45 were measured on either a SuperNova (Cu Kr, mirror monochromator, λ = 1.54184 Å) or Xcalibur (Mo Kr, mirror monochromator, λ = 0.71073 Å) diffractometer fitted with an area detector, and the data were extracted using the Crystals.log package. The structures of these compounds were solved with ShelXTₚ and refined using ShelXL₂¹ in OLEX2. Atomic coordinates, bond lengths and angles, and displacement parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC no. 1852687-1852695 and 1855327). These data can be obtained free-of-charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing 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.
X-ray derived plots for compounds 5, 6, 13, 14, 15, 32–34, 36–38, 40, 41, and 44–46 (PDF).

Accession Codes
CCDC 1852687–1852695 and 1853327 contain the supplementary crystallographic data for this article. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, 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.

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Notes
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References

(9) Yan, Q.; Gao, E.; Banwell, M. G.; Willis, A. C.; Carr, P. D. A Unified Approach to the α, β, γ, and δ-Carbolines via their 6,7,8,9-Tetrahydrocounterparts. J. Org. Chem. 2017, 82, 4328–4335.
Supporting Information for

The Reductive Cyclization of o-Nitroarylated-α,β-Unsaturated Aldehydes and Ketones with TiCl₃/HCl or Fe/HCl Leading to 1,2,3,9-Tetrahydro-4H-carbazol-4-ones and Related Heterocycles

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400 MHz $^1$H NMR Spectrum of Compound 5 (prepared by Method i)
[recorded in (CD$_3$)$_2$SO]
100 MHz $^{13}$C NMR Spectrum of Compound 5 (prepared by Method i) [recorded in (CD$_3$)$_2$SO]
400 MHz $^1$H NMR Spectrum of Compound 6 (prepared by Method i)
[recorded in (CD$_3$)$_2$SO]
100 MHz $^{13}$C NMR Spectrum of Compound 6 (prepared by Method i) [recorded in $(\text{CD}_3)_2\text{SO}$]

![NMR Spectrum](image)

157.2
164.3
153.8
125.3
124.4
122.8
120.2
115.7
111.5

$(\text{CD}_3)_2\text{SO}$

$(\text{CH}_3)_2\text{CO}$
400 MHz $^1$H NMR Spectrum of Compound 8 (recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 8
(recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 9
(recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 9 (recorded in CDCl$_3$)
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100 MHz $^{13}$C NMR Spectrum of Compound 10
(recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 11
(recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 11
(recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 12 (recorded in CDCl$_3$)
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(recorded in CDCl$_3$)

$^1$H NMR spectrum showing peaks at various ppm values, labeled with CHCl$_3$, (CH$_3$)$_2$CO, and hexanes.
100 MHz $^{13}$C NMR Spectrum of Compound 14
(recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 15
(recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 15
(recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 17
[recorded in (CD$_3$)$_2$CO]

400 MHz $^1$H NMR Spectrum of Compound 17
[recorded in (CD$_3$)$_2$CO]

Partial protio-forms of (CD$_3$)$_2$CO

H grease
100 MHz $^{13}$C NMR Spectrum of Compound 17
[recorded in (CD$_3$)$_2$CO]

![NMR Spectrum](image-url)
400 MHz $^1$H NMR Spectrum of Compound 18
(recorded in CDCl$_3$)
$100 \text{ MHz } ^{13}\text{C NMR Spectrum of Compound 18 (recorded in CDCl}_3$)
400 MHz $^1$H NMR Spectrum of Compound 19 (recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 19 (recorded in CDCl$_3$)

19
400 MHz $^1$H NMR Spectrum of Compound 20
[recorded in (CD$_3$)$_2$CO]

partial protio-forms of (CD$_3$)$_2$CO

H$_2$O
100 MHz $^{13}$C NMR Spectrum of Compound 20
[recorded in (CD$_3$)$_2$CO]
400 MHz $^1$H NMR Spectrum of Compound 22
(recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 22
(recorded in CDCl$_3$)

\[
\text{Ph} = \text{O} = \text{Ph}
\]

CDCl$_3$
400 MHz $^1$H NMR Spectrum of Compound 23 (recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 23 (recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 24 (prepared by Method i) (recorded in CDCl$_3$)

![NMR Spectrum](image-url)
100 MHz $^{13}$C NMR Spectrum of Compound 24
(prepared by Method i)
(recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 25 (prepared by Method i) (recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 25
(prepared by Method i)
(recorded in CDCl$_3$)

CDCl$_3$

Et$_2$O

hexanes

Et$_2$O
400 MHz $^1$H NMR Spectrum of Compound 26 (prepared by Method i) (recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 26 (prepared by Method i) (recorded in CDCl$_3$)

Ph

NH

26

CDCl$_3$

Et$_2$O

hexanes

Et$_2$O

0 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
400 MHz $^1$H NMR Spectrum of Compound 27 (prepared by Method i) (recorded in CDCl$_3$)

![Compound 27](image)

S48
100 MHz $^{13}$C NMR Spectrum of Compound 27 (prepared by Method i) (recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 32
(recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 32
(recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 33
(recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 33
(recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 33/34 (recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 36
(recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 36
(recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 37 (recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 37 (recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 38 (recorded in CDCl$_3$)

H$_2$O

C$_6$H$_{12}$

H grease

CHCl$_3$
100 MHz $^{13}$C NMR Spectrum of Compound 38
(recorded in CDCl$_3$)

$^{38}$

CDCl$_3$

Et$_2$O

H

grease

10 20 30 40 50 60 70 80 90 100 110 120 130 140 150 160 170 180 190 200 ppm
400 MHz $^1$H NMR Spectrum of Compound 40
(recorded in CDCl$_3$)

CHCl$_3$

H$_2$O

C$_6$H$_{12}$
silicon grease

H grease
100 MHz $^{13}$C NMR Spectrum of Compound 40
(recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 41
(recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 41
(recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 44
(recorded in CDCl$_3$)

CHCl$_3$

Et$_2$O

Et$_2$O
$^{13}$C NMR Spectrum of Compound 44
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(recorded in CDCl$_3$)

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Tandem Ullmann–Goldberg Cross-Coupling/Cyclo palladation-Reductive Elimination Reactions and Related Sequences Leading to Polyfunctionalized Benzofurans, Indoles, and Phthalanes

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Supporting Information

ABSTRACT: On exposure to a combination of Cu[I]- and Pd[0]-based catalysts, compounds such as 1 and 7 engage in tandem Ullmann–Goldberg cross-coupling and cyclopalladation-reductive elimination reactions to give benzofurans such as 8. Related reactions involving hetero-Michael additions of o-halogenated phenols or anilines to propiolates and the Pd[0]-catalyzed cyclization of the resulting conjugates provide, in a one-pot process, alternately functionalized benzofurans, indoles, or phthalanes.

Benzofurans and indoles represent privileged heterocyclic frameworks, not least because they have found extensive applications in medicinal chemistry and materials science.1,2 They are also encountered in many biologically active natural products.3 While numerous methods have been devised for their assembly,4 new and convergent means for doing so and that allow for the introduction of novel functionalities remain of considerable interest.5−7 In this connection, we envisaged (Scheme 1) that an o-halophenol (1) could be fused with a 3-halo cyclohexenone (2) to give, via an initial and Cu[I]-catalyzed Ullmann–Goldberg cross-coupling reaction,8 the ether 3. On exposure of the last compound to Pd[0], the initially formed oxidative addition product 4 should engage in a cyclopalladation-reductive elimination reaction sequence and so deliver the annulated benzofuran 5.6 Overall, a reverse of the bond-forming steps used in the Larock protocol9,10 is involved here, as is a C–H activation step. Compound 5 embodies key structural elements of the benzofuran-containing and neurologically active ribisin class of natural product, compound 6 (ribisin C) being a notable example.11 Replacing the o-halophenol (1) in such a sequence with the analogous aniline should deliver the corresponding indole.12 Herein we detail the implementation of such reaction sequences in a tandem manner and extensions of these to the construction of a range of alternately substituted benzofurans and indoles as well as related heterocyclic frameworks.

The outcomes of our initial studies of the proposed process are shown in Table 1. So, a DMSO solution of a 1:1.5 mixture of the iodinated substrates 1 (X = I) and 2 (Y = I)13 was treated with cuprous iodide (0.5 mol equivalents), Pd2(dba)3 (5 mol %), and triethylamine (2 mol equivalents) at 120 °C for 20 h (entry 1), and under such conditions, the benzofuran 514 was obtained in 43% yield, and its structure was confirmed by single-crystal X-ray analysis. (See the Supporting Information for details.) The stepwise addition of the copper salt then Pd2(dba)3 (entry 2) resulted in a 61% yield of the same product. Under the same conditions, 3-bromoenone 2 (Y = Br)10 also coupled to 1 (X = I) (entry 3) to give benzofuran 5, albeit in somewhat lower (47%) yield. In contrast, the equivalent process involving o-bromophenol 1 (X = Br) and iodo enone 2 (Y = I) (entry 4) now just delivered the Ullmann–Goldberg product 3 (X = Br) in 32% yield. Similarly, when both coupling partners incorporated bromine (entry 5), the same product [viz. 3 (X = Br)] was obtained but now in just 19% yield. The enol triflate 2 (Y = OTf) reacted in a similar fashion provided that 5 mol % of tetra-n-butylammonium bromide (TBAB) was added to the reaction mixture (entry 6), a requirement we attribute to the need for the in situ formation of 2 (X = Br) (through a halogen for the pseudohalogen exchange process of some sort) that then couples in the previously observed manner. On just adding CuI to the reaction mixture (entry 7) and heating this to 80 °C for 2 h, substrates 1 (X = I) and 2 (Y = I) only engaged in the Ullmann–Goldberg reaction and thereby formed the enol ether 3 (X = I) that was obtained in 63% yield. On resubjecting compound 3 to the same reaction conditions but now with just Pd[0] present (entry 8), benzofuran 5 was obtained (91%). Significantly, when a DMSO solution of substrates 1 (X = I) and 2 (Y = I) was treated with Pd2(dba)3 (0.05 mol equivalents) and triethylamine (no cuprous iodide present) at 120 °C, no reaction took place. This outcome suggests that the first step of the successful reaction sequence.

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Scheme 1. Proposed Tandem Ullmann−Goldberg Cross-Coupling/Cyclopalladation-Reductive Elimination Reaction Sequence Leading from Substrates 1 and 2, via Intermediates 3 and 4, to Benzofuran 5

![Scheme 1](image)

**Table 1. Optimization of Conditions for Effecting the Conversion 1 + 2 → 5**

<table>
<thead>
<tr>
<th>entry</th>
<th>substrates(s)</th>
<th>additives</th>
<th>time/temperature</th>
<th>product (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 (X = I)</td>
<td>CuI, Pd[0]</td>
<td>20 h/120 °C</td>
<td>5 (43%)</td>
</tr>
<tr>
<td>2</td>
<td>2 (Y = I)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1 (X = I)</td>
<td>CuI, Pd[0]</td>
<td>2 h then 20 h/60 then 120 °C</td>
<td>5 (61%)</td>
</tr>
<tr>
<td>2</td>
<td>2 (Y = I)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1 (X = I)</td>
<td>CuI, Pd[0]</td>
<td>2 h then 20 h/60 then 120 °C</td>
<td>5 (47%)</td>
</tr>
<tr>
<td>2</td>
<td>2 (Y = Br)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1 (X = Br)</td>
<td>CuI, Pd[0]</td>
<td>2 h then 20 h/60 then 120 °C</td>
<td>3 (X = Br)</td>
</tr>
<tr>
<td>2</td>
<td>2 (Y = I)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1 (X = Br)</td>
<td>CuI, Pd[0]</td>
<td>2 h then 20 h/80 then 120 °C</td>
<td>3 (X = Br)</td>
</tr>
<tr>
<td>2</td>
<td>2 (Y = Br)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>1 (X = Br)</td>
<td>CuI, Pd[0]</td>
<td>2 h then 20 h/60 then 120 °C</td>
<td>5 (15%)</td>
</tr>
<tr>
<td>2</td>
<td>2 (Y = Br)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>1 (X = I)</td>
<td>CuI</td>
<td>2 h/80 °C</td>
<td>3 (X = I)</td>
</tr>
<tr>
<td>2</td>
<td>2 (Y = I)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>3 (X = I)</td>
<td>Pd[0]</td>
<td>20 h/120 °C</td>
<td>3 (X = I)</td>
</tr>
<tr>
<td>9</td>
<td>1 (X = I)</td>
<td>Pd[0]</td>
<td>20 h/120 °C</td>
<td>NR^d</td>
</tr>
<tr>
<td>2</td>
<td>1 (Y = I)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

^a0.5 mol equivalents of CuI and 5 mol % of Pd[0] used together with 2 mol equiv of Et3N. ^b5 mole % used except for Entries 4 and 5 where 10 mole % used. ^cInitial reaction mixture containing just the copper salt was stirred for 2 h at 60 °C, then a source of Pd[0] was added and the reaction mixture was heated to 120 °C for 20 h. ^dNR = no reaction.

(leading to 5) is indeed an Ullmann−Goldberg reaction and not, for example, a conjugate addition/elimination reaction.

The optimized protocol defined in entry 2 could be extended to the synthesis of other benzofurans with, for example, the cyclohexenones 7 (X = I, OTf, or Br) and 9,10,12 (Figure 1) coupling to phenol 1 (X = I) to give the anticipated product 8 (10, 30, and 59%, respectively). Acyclic iodides such as the crotonate 9 and cinnamate 10 also couple in an analogous manner to 1 (X = I), thus affording the 2,3-disubstituted benzofurans 11 (42%) and 12 (84%), respectively, while the iodinated cyclopentenone 13 also coupled to the same phenol to give compound 14 (47%). Interestingly, the readily prepared 2-methyl-3-iodoenone 15 only coupled to o-iodophenol to give the Ullmann−Goldberg product 16 (39%). This could not be engaged in a carbopalladation-reductive elimination sequence, an outcome that might be attributed to steric effects.

Indoles are also available using the present methods, as demonstrated by the cross-coupling of o-iodoaniline (17) (Scheme 2) with enone 7 (Y = Br) to give the cyclohexannulated indole 18 (60%), the structure of which was also confirmed by single-crystal X-ray analysis. The non-isolable enamine 19 is presumably the precursor to the observed product 18.

Scheme 2. Tandem Ullmann−Goldberg/Cyclopalladation-Reductive Elimination Reaction Sequence Leading from Substrates 17 and 7 (Y = Br) to Indole 18 and the Presumed Intermediate 19

![Scheme 2](image)
Extensions to this basic process provided indoles 20–23 (65%), 21 (45%), 22 (63%), and 23 (52%) (Figure 2) through the couplings of the reaction partners 17 + 2 (Y = I), 17 + 9, 17 + 10, and 17 + 13, respectively.

![Figure 2](image)

Figure 2. Indoles 20–23 arising from the tandem Ullmann–Goldberg coupling/cyclopalladation-reductive elimination of o-iodoaniline (17) with iodides 2 (X = I), 9, 10, and 13.

Open-chain analogues of enol ether 3 (X = I) and enamine 19 could, in principle, be obtained through the conjugate addition of o-halogenated phenols or anilines to, for example, propiolates and related alkynes incorporating an electron-withdrawing group. Consistent with such expectations, when compounds 1 (X = I) and 17 were treated with dimethyl acetylenedicarboxylate (DMAD, 24) (Figure 3) in the presence of triethylamine and Pd[0], then benzo-furan 25 (40%) and indole 26 (67%), respectively, were obtained. The hetero-Michael addition products 27 (62%) and 28 (84%) were obtained as single geometric isomers when the relevant reaction partners were treated with the amine alone. Furthermore, the exposure of adducts 27 and 28 to Pd[0] resulted in their cyclization to give heterocycles 25 (37%) and 26 (66%), respectively. Under the same conditions, propiolates 29 and 30 reacted in a regioselective manner with o-iodophenol (1 (X = I)) to give benzo-furans 31 (42%) and 11 (43%), respectively, while analogous reactions involving o-iodoaniline (17) afforded indoles 32 (41%) and 21 (53%).

Phthalanes can be obtained by related means (Figure 4). For example, when a DMF solution of o-iodobenzyl alcohol (33) and DMAD (24) was exposed to Au[1] and Pd[0], the isolable Michael addition product 34 (obtained as a single geometric isomer of undefined configuration) cyclized, presumably now in a Heck process, to give product 35 (30%). Similarly, the terminal alkyne 29 coupled to compound 33 to give phthalane 36 (41%).

![Figure 3](image)

Figure 3. Propiolates 24, 29, and 30 that engage in hetero-Michael addition/cyclopalladation-reductive elimination reactions with compounds 1 (X = I) and 17, leading to 3-substituted and 2,3-disubstituted benzo-furans and indoles.

![Figure 4](image)

Figure 4. Phthalanes 35 and 36 available through hetero-Michael addition/Heck cyclization reactions of o-iodobenzyl alcohol (33) with certain propiolates.

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.or-lett.9b02235.

Experimental procedures, spectroscopic data, copies of the NMR spectra of compounds 2 (Y = Br, I and OTf), 3 (X = Br and I), 5, 8, 11, 12, 14–16, 18, 20–23, 25–28, 31, 32, and 34–36 together with the X-ray data and the derived ORTEPs for compounds 5, 14, 18, 21, 22, and 26 (PDF).

Accession Codes

CCDC 1935464–1935469 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 emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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The authors declare no competing financial interest.

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Org. Lett. 2019, 21, 6342–6346
drazones: Novel Approaches to the Synthesis of Polysubstituted Indoles and 1,4-Diaryldiquinolines. Chem. Commun. 2016, 52, 6312–


(9) Lan, P.; Banwell, M. G.; Willis, A. C. Chemoenzymatic Total Synthesis of 3,4-Dihydropyridine-2-carboxylic Acid and 3-

(10) Piers, E.; Grierson, J. R.; Lau, C. K.; Nagakura, J. Synthesis of β-

(11) Aljaar, N.; Malakar, C. C.; Conrad, J.; Strobel, S.; Schleid, T.; Beihuss, U. Cu-Catalyzed Reaction of 1,2-Dihalobenzenes with 1,3-
Cyclohexanediol for the Synthesis of 3,4-Dihydrobenzo[b,d]-


(13) Khan, F.; Dlugosch, M.; Liu, X.; Khan, M.; Banwell, M. G.; Ward, J. S.; Carr, P. D. Palladium-Catalyzed Ullmann Cross-Coupling of β-Iodoenones and β-Iodoacrylates with α-Halotriarenens or α-


(15) Chatterjee, J. N.; Sahai, R. P. Syntheses of Furano Compounds. Part XLIV. Syntheses of 2-Carboxybenzo[b]furan-3-acetic Acid and 3-

(16) Qu, Y.; Dlugosch, M.; Liu, X.; Khan, F.; Ward, J. S.; Lan, P.; Banwell, M. G. Reductive Cyclization of α-Nitroarylated-α,β-
Unsaturated Aldehydes and Ketones with TiCl 4/HCl or Fe/HCl Leading to 1,2,3,9-

(17) Zuo, Y.; He, X.; Ning, Y.; Wu, Y.; Shang, Y. Rh(III)-Catalyzed C-H Activation/Intramolecular Cyclization: Access to N-Acyl-2,3-
Dihydro-1H-carbazol-4(9H)ones from Cyclic 2-Diazolic, 3,6-diketones and N-Arylamides. ACS Omega 2017, 2, 8507–8516.

(18) Liu, X.-G.; Li, Z.-H.; Xie, J.-W.; Liu, P.; Zhang, J.; Dai, B. Copper-Catalyzed Synthesis of 2,3-Disubstituted Indoles from ortho-

(19) (a) Guo, X.; Han, J.; Liu, Y.; Qin, M.; Zhang, X.; Chen, B. Synthesis of 2,3-Disubstituted NH Indoles via Rhodium(III)-

(20) Sørensen, U. S.; Pombo-Villar, E. Synthesis of Cyclopenta[b]-


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SUPPORTING INFORMATION FOR:

Tandem Ullmann-Goldberg Cross-Coupling/Cyclopalladation-Reductive Elimination Reactions and Related Sequences Leading to Polyfunctionalized Benzofurans, Indoles and Phthalanes

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$^1$H and $^{13}$C NMR Spectra of Compounds 2 (Y = Br), 2 (Y = I), 2 (Y = OTf), 3 (X = Br), 3 (X = I), 5, 8, 11, 12, 14-16, 18, 20-23, 25-28, 31, 32 and 34-36. S28

S1
General Experimental Protocols

Unless otherwise specified, proton ($^1$H) and carbon ($^{13}$C) NMR spectra were recorded at room temperature in base-filtered CDCl$_3$ on a spectrometer operating at 400 MHz for proton and 100 MHz for carbon nuclei. For $^1$H NMR spectra, signals arising from the residual protio-forms of the solvent were used as the internal standards. $^1$H NMR data are recorded as follows: chemical shift ($\delta$) [multiplicity, coupling constant(s) $J$ (Hz), relative integral] where multiplicity is defined as: $s =$ singlet; $d =$ doublet; $t =$ triplet; $q =$ quartet; $m =$ multiplet or combinations of the above. The signal due to residual CHCl$_3$ appearing at $\delta_H$ 7.26 and the central resonance of the CDCl$_3$ “triplet” appearing at $\delta_C$ 77.0 were used to reference $^1$H and $^{13}$C NMR spectra, respectively. Infrared spectra were recorded, using neat samples, on an attenuated total reflectance (ATR) infrared spectrometer. Low-resolution ESI mass spectra were recorded on a single quadrupole liquid chromatograph-mass spectrometer, while high-resolution measurements were conducted on a time-of-flight instrument. Low- and high-resolution EI mass spectra were recorded on a magnetic-sector machine. Melting points were measured on an Optimelt automated melting point system and are uncorrected. Analytical thin layer chromatography (TLC) was performed on aluminum-backed 0.2 mm thick silica gel 60 F$_{254}$ plates as supplied by Merck. Eluted plates were visualized using a 254 nm UV lamp and/or by treatment with a suitable dip followed by heating. These dips included phosphomolybdic acid : ceric sulfate : sulfuric acid (conc.) : water (37.5 g : 7.5 g : 37.5 g : 720 mL) or potassium permanganate : potassium carbonate : 5% sodium hydroxide aqueous solution : water (3 g : 20 g : 5 mL : 300 mL). Flash chromatographic separations were carried out following protocols defined by Still et al.$^1$ with silica gel 60 (40–63 $\mu$m) as the stationary phase and using the AR- or HPLC-grade solvents indicated. Starting materials and reagents were generally available from the Sigma–Aldrich, Merck, TCI, Strem or Lancaster Chemical Companies and were used as supplied. Drying agents and other inorganic salts were purchased from the AJAX, BDH or Unilab Chemical Companies. Acetonitrile, tetrahydrofuran (THF), methanol and dichloromethane were dried using a Glass Contour solvent purification system that is based upon a technology originally described by Grubbs et al.$^2$ Petroleum ether refers to the fraction boiling between 40 and 60 °C. Where necessary, reactions were performed under an nitrogen atmosphere.
Specific Chemical Transformations

**Compound 2 (Y = Br)**

![Chemical Structure](image1)

A magnetically stirred solution of triphenylphosphine (1.44 g, 5.50 mmol) in dry acetonitrile (25 mL) maintained at 0 °C was treated, dropwise, with a solution of molecular bromine (283 µL, 5.50 mmol) in dry acetonitrile (2.30 mL). The resulting mixture was warmed to 22 °C and after 0.5 h it was treated with triethylamine (836 µL, 6.00 mmol) then 5,5-dimethyl-1,3-cyclohexanedione (700 mg, 5.00 mmol) before being stirred under reflux for 16 h. The cooled reaction mixture was concentrated under reduced pressure and the residue thus obtained stirred vigorously with diethyl ether (20 mL) and the supernatant liquid then decanted. This process was repeated twice more and the combined organic phases then diluted with 40-60 petroleum ether (30 mL) to precipitate residual triphenylphosphine oxide. The ensuing mixture was filtered through a plug of TLC-grade silica gel topped with diatomaceous earth and the filtrate concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:9 v/v diethyl ether/pentane elution) and thus affording, after concentration of the appropriate fractions (R_f = 0.2), compound 2 (Y = Br) (697 mg, 69%) as a clear, pale-yellow oil. The spectral data obtained on this material matched those reported in the literature.

**Compound 2 (Y = I)**

![Chemical Structure](image2)

A magnetically stirred solution of triphenylphosphine (2.96 g, 11.3 mmol) in dry acetonitrile (50 mL) maintained at 22 °C was treated, in portions, with powdered molecular iodine (3.00 g, 11.8 mmol). After 0.5 h the reaction mixture was treated with triethylamine (1.72 mL, 12.3 mmol) then 5,5-dimethyl-1,3-cyclohexanedione (1.44 g, 10.3 mmol) and the resulting mixture heated under reflux for 16 h. The cooled reaction mixture was concentrated under reduced pressure and the residue thus obtained stirred vigorously with diethyl ether (30 mL) before the supernatant liquid was decanted. This process was repeated twice more and the combined organic phases then diluted with 40-60 petroleum ether (50 mL) to precipitate residual triphenylphosphine oxide. The ensuing mixture was filtered through a plug of TLC-grade silica gel topped with diatomaceous earth and the filtrate concentrated under reduced pressure to afford compound 2 (Y = I) (1.95 g, 76%) as a clear, colourless oil. The spectral data obtained on this material matched those reported in the literature.
**Compound 2 (Y = OTf)**

![Structure of Compound 2](image)

A magnetically stirred solution of 5,5-dimethyl-1,3-cyclohexanedione (421 mg, 3.00 mmol) in dry dichloromethane (15 mL) maintained at −78 °C was treated with pyridine (483 µL, 6.00 mmol). After 10 min the reaction mixture was treated, dropwise over 5 minutes at −78 °C, with trifluoromethanesulfonic anhydride (605 µL, 3.60 mmol). After 0.33 h the reaction mixture was allowed to warm to 22 °C over 1 h then quenched with hydrochloric acid (10 ml of a 1 M aqueous solution). The separated aqueous phase was extracted with dichloromethane (2 x 10 mL) and the combined organic phases were washed with sodium bicarbonate (1 x 20 mL of a saturated aqueous solution), water (1 x 20 mL) and brine (1 x 20 mL) before being dried (Na₂SO₄), filtered then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:19 v/v diethyl ether/40-60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions ($R_f = 0.1$), compound 2 (Y = OTf) (751 mg, 92%) as a clear, pale-yellow oil. The spectral data obtained on this material matched those reported in the literature.

**Compound 3 (X = Br)**

![Structure of Compound 3](image)

A magnetically stirred solution of compound 2 (Y = I) (125 mg, 0.50 mmol), o-bromophenol [1 (X = Br)] (130 mg, 0.75 mmol) and copper(I) iodide (48 mg, 0.25 mmol) in dry DMSO (5 mL) maintained at 60 °C was treated with triethylamine (139 µL, 1.00 mmol). After 2 h the reaction mixture was treated with Pd₃(dba)₃ (46 mg, 0.050 mmol) then heated to 120 °C. After 20 h the reaction mixture was cooled to 22 °C, diluted with ethyl acetate (5 mL) and the ensuing mixture filtered through a plug of TLC-grade silica topped with diatomaceous earth and the solids so retained were washed with ethyl acetate (20 mL). The combined filtrates were washed with ammonia (2 x 25 mL of a 5% v/v aqueous solution), water (1 x 25 mL) and brine (1 x 25 mL) before being dried (Na₂SO₄), filtered, then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:3 v/v diethyl ether/40-60 petroleum ether elution elution) and thus affording, after concentration of the appropriate fractions ($R_f = 0.2$), compound 3 (X = Br) (47 mg, 32%) as a clear, yellow oil.

**1H NMR** (400 MHz, CDCl₃) $\delta$ 7.62 (d, $J = 8.0$ Hz, 1H), 7.34 (t, $J = 7.7$ Hz, 1H), 7.20-7.06 (complex m, 2H), 4.96 (s, 1H), 2.56 (s, 2H), 2.25 (s, 2H), 1.16 (s, 6H).

**13C NMR** (100 MHz, CDCl₃) $\delta$ 199.2, 175.3, 149.9, 134.0, 128.9, 127.6, 123.4, 116.0, 104.9, 50.7, 41.9, 32.8, 28.3.

**IR** (ATR) $\nu_{\text{max}}$ 2960, 1658, 1617, 1469, 1366, 1213, 1134, 1046, 762, 659 cm$^{-1}$. 

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240
MS (ESI, +ve) m/z 615, 613 and 611 [(2M+Na)^+], 50, 100, 50%, 319 and 317 [(M+Na)^+], 65 and 66), 297 and 295 [(M+H)^+], 19 and 19.

HRMS m/z 295.0330 [M+H]^+ (calcd for C_{14}H_{15}BrO_2, 295.0328).

**Compound 3 (X = I)**

![Compound 3](image)

A magnetically stirred solution of compound 2 (Y = I) (104 mg, 0.42 mmol) and o-iodophenol [1 (X = I)] (137 mg, 0.62 mmol) and copper(I) iodide (40 mg, 0.21 mmol) in dry DMSO (5 mL) maintained at 60 °C was treated with triethylamine (116 µL, 0.83 mmol). After 2 h the reaction mixture was cooled to 22 °C, diluted with ethyl acetate (5 mL) and the ensuing mixture filtered through a plug of TLC-grade silica topped with diatomaceous earth and the solids so retained were washed with ethyl acetate (20 mL). The combined filtrates were washed with ammonia (2 x 25 mL of a 5% v/v aqueous solution), water (1 x 25 mL) and brine (1 x 25 mL) before being dried (Na_2SO_4), filtered, then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:3 v/v diethyl ether/40-60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions (R_f = 0.2), compound 3 (X = I) (90 mg, 63%) as a clear, yellow oil.

1^H NMR (400 MHz, CDCl_3) δ 7.84 (d, J = 7.8 Hz, 1H), 7.37 (t, J = 7.8 Hz, 1H), 7.06 (d, J = 7.8 Hz, 1H), 6.99 (t, J = 7.8 Hz, 1H), 4.95 (s, 1H), 2.57 (s, 2H), 2.25 (s, 2H), 1.17 (s, 6H).

13^C NMR (100 MHz, CDCl_3) δ 199.2, 175.3, 152.8, 140.0, 129.9, 127.8, 122.6, 105.1, 90.0, 50.7, 42.1, 32.9, 28.4.

IR (ATR) ν max 2958, 1657, 1617, 1575, 1464, 1368, 1208, 1135, 1021, 764 cm\(^{-1}\).

MS (ESI, +ve) m/z 707 [(2M+Na)^+], 100%, 365 [(M+Na)^+], 46], 343 [(M+H)^+, 70].

HRMS m/z 365.0009 [M+Na]^+ (calcd for C_{14}H_{13}I_{13}O_2, 365.0009).

**Compound 5**

![Compound 5](image)

A magnetically stirred solution of compound 2 (Y = I) (58 mg, 0.23 mmol), o-iodophenol [1 (X = I)] (76 mg, 0.35 mmol) and copper(I) iodide (22 mg, 0.12 mmol) in dry DMSO (2.3 mL) maintained at 60 °C was treated with triethylamine (64 µL, 0.46 mmol). After a further 2 h the reaction mixture was treated with Pd_2(dba)_3 (11 mg, 0.012 mmol) then heated to 120 °C. After 20 h the reaction mixture was cooled to 22 °C, diluted with ethyl acetate (3 mL) and the ensuing mixture filtered through a plug of TLC-grade silica topped with diatomaceous earth and the solids so retained were washed with ethyl acetate (12 mL). The combined filtrates were washed with ammonia (2 x 15 mL of a 5% v/v aqueous solution), water (1 x 15 mL) and brine (1 x 15 mL) before being dried (Na_2SO_4), filtered, then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:3 v/v diethyl ether/40-60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions (R_f = 0.2), compound 5 (X = I) (50 mg, 63%) as a clear, yellow oil.
chromatography (silica, 2:8 v/v diethyl ether/40-60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions ($R_f = 0.3$), compound 5 (30 mg, 61%) as a yellow, crystalline solid, m.p. = 119-120 °C (lit. m.p. = 121-122 °C).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.06 (m, 1H), 7.48 (m, 1H), 7.33 (m, 2H), 2.91 (s, 2H), 2.49 (s, 2H), 1.21 (s, 6H).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 194.1, 169.9, 154.9, 124.8, 124.4, 123.6, 121.7, 115.3, 111.1, 52.2, 37.7, 35.2, 28.7.

IR (ATR) $\nu_{max}$ 2960, 1665, 1479, 1444, 1406, 1173, 1040, 840, 748, 672 cm$^{-1}$.

MS (ESI, +ve) $m/z$ 215 [(M+H)$^+$, 100%].

HRMS $m/z$ 215.1071 [M+H]$^+$ (calcd for C$_{14}$H$_{14}$O$_2$, 215.1071).

**Compound 8**

![8]

A magnetically stirred solution of compound 7 (X = Br) (100 mg, 0.57 mmol), o-iodophenol [1 (X = I)] (189 mg, 0.86 mmol) and copper(I) iodide (54 mg, 0.29 mmol) in dry DMSO (5 mL) maintained at 60 °C was treated with triethylamine (159 µL, 1.14 mmol). After 2 h the reaction mixture was treated with Pd$_2$(dba)$_3$ (26 mg, 0.029 mmol) then heated to 120 °C. After a further 20 h the reaction mixture was cooled to 22 °C, diluted with ethyl acetate (5 mL) and the ensuing mixture filtered through a plug of TLC-grade silica topped with diatomaceous earth and the solids so retained were washed with ethyl acetate (20 mL). The combined filtrates were washed with ammonia (2 x 25 mL of a 5% v/v aqueous solution), water (1 x 25 mL) and brine (1 x 25 mL) before being dried (Na$_2$SO$_4$), filtered, then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:9 v/v ethyl acetate/40-60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions ($R_f = 0.3$), compound 5 (63 mg, 59%) as a clear, brown oil.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.00 (m, 1H), 7.47 (m, 1H), 7.32 (m, 2H), 3.04 (t, $J = 6.3$ Hz, 3H), 2.61 (t, $J = 6.5$ Hz, 2H), 2.28 (m, 2H).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 194.7, 170.8, 154.5, 124.9, 124.4, 123.7, 121.8, 116.5, 111.0, 37.9, 23.8, 22.5.

IR (ATR) $\nu_{max}$ 2959, 1676, 1482, 1451, 1169, 1012, 751 cm$^{-1}$.

MS (ESI, +ve) $m/z$ 209 [(M+Na)$^+$, 100%], 187 [(M+H)$^+$, 25].

HRMS $m/z$ 187.0749 [M+H]$^+$ (calcd for C$_{12}$H$_{10}$O$_2$, 187.0754).

**Compound 11**

![11]

A magnetically stirred solution of compound 7 (X = Br) (100 mg, 0.57 mmol), o-iodophenol [1 (X = I)] (189 mg, 0.86 mmol) and copper(I) iodide (54 mg, 0.29 mmol) in dry DMSO (5 mL) maintained at 60 °C was treated with triethylamine (159 µL, 1.14 mmol). After 2 h the reaction mixture was treated with Pd$_2$(dba)$_3$ (26 mg, 0.029 mmol) then heated to 120 °C. After a further 20 h the reaction mixture was cooled to 22 °C, diluted with ethyl acetate (5 mL) and the ensuing mixture filtered through a plug of TLC-grade silica topped with diatomaceous earth and the solids so retained were washed with ethyl acetate (20 mL). The combined filtrates were washed with ammonia (2 x 25 mL of a 5% v/v aqueous solution), water (1 x 25 mL) and brine (1 x 25 mL) before being dried (Na$_2$SO$_4$), filtered, then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:9 v/v ethyl acetate/40-60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions ($R_f = 0.3$), compound 5 (63 mg, 59%) as a clear, brown oil.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.00 (m, 1H), 7.47 (m, 1H), 7.32 (m, 2H), 3.04 (t, $J = 6.3$ Hz, 3H), 2.61 (t, $J = 6.5$ Hz, 2H), 2.28 (m, 2H).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 194.7, 170.8, 154.5, 124.9, 124.4, 123.7, 121.8, 116.5, 111.0, 37.9, 23.8, 22.5.

IR (ATR) $\nu_{max}$ 2959, 1676, 1482, 1451, 1169, 1012, 751 cm$^{-1}$.

MS (ESI, +ve) $m/z$ 209 [(M+Na)$^+$, 100%], 187 [(M+H)$^+$, 25].

HRMS $m/z$ 187.0749 [M+H]$^+$ (calcd for C$_{12}$H$_{10}$O$_2$, 187.0754).
Method i: A magnetically stirred solution of compound 9\textsuperscript{6} (100 mg, 0.44 mmol), o-iodophenol [1 (X = I)] (146 mg, 0.66 mmol) and copper(I) iodide (42 mg, 0.22 mmol) in dry DMSO (5 mL) maintained at 60 °C was treated with triethylamine (123 µL, 0.88 mmol). After 2 h the reaction mixture was treated with Pd\textsubscript{2}(dba)\textsubscript{3} (20 mg, 0.022 mmol) then heated to 120 °C. After a further 20 h the reaction mixture was cooled to 22 °C, diluted with ethyl acetate (5 mL) and the ensuing mixture filtered through a plug of TLC-grade silica topped with diatomaceous earth and the solids so retained were washed with ethyl acetate (20 mL). The combined filtrates were washed with ammonia (2 x 25 mL of a 5% v/v aqueous solution), water (1 x 25 mL) and brine (1 x 25 mL) before being dried (Na\textsubscript{2}SO\textsubscript{4}), filtered and then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:5 v/v ethyl acetate/40-60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions (R\textsubscript{f} = 0.6), compound 11\textsuperscript{7} (35 mg, 42%) as a clear, colorless oil.

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) δ 7.95 (m, 1H), 7.42 (m, 1H), 7.30 (m, 2H), 3.95 (s, 3H), 2.77 (s, 3H).

\textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) δ 164.9, 163.7, 153.6, 126.1, 124.3, 123.7, 121.7, 110.7, 108.9, 51.4, 14.4.

IR (ATR) ν\textsubscript{max} 2952, 1712, 1454, 1237, 1106, 1085, 785, 750 cm\textsuperscript{-1}

MS (ESI, +ve) m/z 245 [(M+Na+MeOH)\textsuperscript{+}, 100%], 191 [(M+H)\textsuperscript{+}, 40].

HRMS m/z 191.0706 [M+H]\textsuperscript{+} (calcd for C\textsubscript{11}H\textsubscript{10}O\textsubscript{3}, 191.0708).

Method ii: A magnetically stirred solution of compound 30 (135 mg, 1.35 mmol), o-iodophenol [1 (X = I)] (200 mg, 0.91 mmol) and triethylamine (251 µL, 1.80 mmol) in dry DMSO (3 mL) maintained at 80 °C in a sealed tube was treated with Pd\textsubscript{2}(dba)\textsubscript{3} (41 mg, 0.045 mmol). After 24 h the reaction mixture was cooled to 22 °C, diluted with water (10 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic phases were dried (Na\textsubscript{2}SO\textsubscript{4}), filtered, then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:2:3 v/v/v ethyl acetate/dichloromethane/40-60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions (R\textsubscript{f} = 0.7), compound 11 (75 mg, 43%) as a clear, colorless oil. This material was identical with that obtained via Method i.

**Compound 12**

![Image of Compound 12]

A magnetically stirred solution of compound 10\textsuperscript{5} (74 mg, 0.25 mmol), o-iodophenol [1 (X = I)] (81 mg, 0.37 mmol) and copper(I) iodide (23 mg, 0.12 mmol) in dry DMSO (2.5 mL) maintained at 60 °C was treated with triethylamine (68 µL, 0.49 mmol). After 3 h the reaction mixture was treated with Pd\textsubscript{2}(dba)\textsubscript{3} (11 mg, 0.012 mmol) then heated to 120 °C. After a further 18 h the reaction mixture was cooled to 22 °C, diluted with ethyl acetate (2.5 mL) and the ensuing mixture filtered through a plug of TLC-grade silica topped with diatomaceous earth and the solids so retained were washed with ethyl acetate (10 mL). The combined filtrates were washed with ammonia (2 x 20 mL of a 5% v/v aqueous solution), water (1 x 20 mL) and brine (1 x 20 mL) before being dried (Na\textsubscript{2}SO\textsubscript{4}), filtered and then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:3 v/v dichloromethane/40-60 petroleum ether elution) and thus affording, after
concentration of the appropriate fractions ($R_f = 0.2$), compound $12^{7}$ (55 mg, 84%) as a clear, yellow oil.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.12-7.97 (complex m, 3H), 7.60-7.44 (complex m, 4H), 7.37 (m, 2H), 4.42 (q, $J = 7.1$ Hz, 2H), 1.42 (t, $J = 7.1$ Hz, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 164.0, 160.7, 153.8, 130.2, 129.6, 129.5, 128.0, 127.1, 125.2, 124.0, 122.7, 111.1, 109.0, 60.6, 14.3.

IR (ATR) $\nu_{\text{max}}$ 2984, 1712, 1454, 1443, 1224, 1195, 1090, 748, 691 cm$^{-1}$.

MS (ESI, +ve) $m/z$ 289 [(M+Na)$^+$, 100%], 267 [(M+H)$^+$, 10].

HRMS $m/z$ 289.0841 [M+Na]$^+$ (calcld for C$_{17}$H$_{14}$O$_3$, 289.0841).

**Compound 14**

![Chemical structure of Compound 14](image)

A magnetically stirred solution of compound $13^{3}$ (100 mg, 0.48 mmol), o-iodophenol [1 (X = I)] (158 mg, 0.72 mmol) and copper(I) iodide (46 mg, 0.24 mmol) in dry DMSO (5 mL) maintained at 60 °C was treated with triethylamine (0.134 µL, 0.96 mmol). After 2 h the reaction mixture was treated with Pd$_2$(dba)$_3$ (22 mg, 0.024 mmol) then heated to 120 °C. After a further 24 h the reaction mixture was cooled to 22 °C, diluted with ethyl acetate (5 mL) and then the ensuing mixture was filtered through a plug of TLC-grade silica topped with diatomaceous earth and the solids so retained were washed with ethyl acetate (25 mL). The combined filtrates were washed with ammonia (2 x 25 mL of a 5% v/v aqueous solution), water (1 x 25 mL) and brine (1 x 25 mL) before being dried (Na$_2$SO$_4$) and filtered before being concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:9 v/v ethyl acetate/40-60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions ($R_f = 0.2$), compound $14^{8}$ (39 mg, 47%) as a light brown, crystalline solid, m.p. = 141-142 °C.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.83 (m, 1H), 7.53 (m, 1H), 7.38-7.31 (complex m, 2H), 3.16 (m, 2H), 3.08 (m, 2H)

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 194.9, 186.7, 161.3, 125.4, 124.6, 124.4, 121.5, 121.4, 112.2, 41.3, 22.7.

IR (ATR) $\nu_{\text{max}}$ 2917, 2851, 1689, 1591, 1481, 1436, 1038, 818, 755 cm$^{-1}$.

MS (ESI, +ve) $m/z$ 173 [(M+H)$^+$, 100%].

HRMS $m/z$ 173.0604 [M+H]$^+$ (calcld for C$_{11}$H$_8$O$_2$, 173.0603).

**Compound 15**

![Chemical structure of Compound 15](image)

A magnetically stirred solution of triphenylphosphine (2.89 g, 11.0 mmol) in dry acetonitrile (50 mL) maintained at 22 °C was treated, in portions, with powdered molecular iodine (2.92
g, 11.5 mmol). After 0.5 h the reaction mixture was treated with triethylamine (1.67 mL, 12.0 mmol) then 2-methyl-1,3-cyclohexanedione (1.26 g, 10.0 mmol) and the resulting mixture heated under reflux for 20 h. The cooled reaction mixture was then concentrated under reduced pressure and the residue thus obtained was stirred vigorously with diethyl ether (40 mL) and the supernatant liquid decanted. This process was repeated twice more and the combined organic phases then diluted with 40-60 petroleum ether (90 mL) to precipitate triphenylphosphine oxide before being filtered and then concentrated under reduced pressure. The resulting oily solid was filtered through a plug of TLC-silica gel topped with diatomaceous earth and the solids thus retained washed with dichloromethane/40-60 petroleum ether (300 mL of a 1:1 v/v mixture) and the filtrate concentrated under reduced pressure to afford compound 15 (2.01 g, 85%) as a white, crystalline solid m.p. = 63.5 °C. The spectral data obtained on this material matched those reported in the literature.  

**Compound 16**

![Compound 16](image)

A magnetically stirred solution of compound 15 (118 mg, 0.50 mmol), o-iodophenol [1 (X = I)] (220 mg, 1.00 mmol) and copper(I) iodide (24 mg, 0.13 mmol) in dry DMSO (5 mL) maintained at 60 °C was treated with triethylamine (349 µL, 2.50 mmol). After 2 h the reaction mixture was treated with Pd2(dba)3 (23 mg, 0.025 mmol) then heated to 120 °C. After a further 20 h the reaction mixture was cooled to 22 °C, diluted with ethyl acetate (5 mL) and the ensuing mixture filtered through a plug of TLC-grade silica topped with diatomaceous earth and the solids so retained were washed with ethyl acetate (20 mL). The combined filtrates were washed with ammonia (2 x 25 mL of a 5% v/v aqueous solution), water (1 x 25 mL) and brine (1 x 25 mL) before being dried (Na2SO4), filtered then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:9 v/v ethyl acetate/40-60 petroleum spirit elution) and thus affording, after concentration of the appropriate fractions (Rf = 0.1), compound 16 (63 mg, 39%) as a clear, yellow oil.

**1H NMR** (400 MHz, CDCl3) δ 7.81 (dd, J = 7.9 and 1.5 Hz, 1H), 7.32 (m, 1H), 6.98-6.87 (complex m, 2H), 2.40 (t, J = 6.6 Hz, 2H), 2.24 (m, 2H), 1.94 (m, 2H), 1.83 (s, 3H).

**13C NMR** (100 MHz, CDCl3) δ 199.2, 168.3, 153.9, 139.7, 129.6, 126.5, 120.5, 119.6, 89.7, 36.6, 27.0, 20.9, 8.0.

**IR** (ATR) νmax 2954, 2857, 1633, 1575, 1463, 1375, 1347, 1258, 1219, 1195, 1115, 1083, 1019, 762 cm⁻¹

**MS** (ESI, +ve) m/z 351 [(M+Na)⁺, 100%].

Compound 18

A magnetically stirred solution of compound 7³ (X = Br) (100 mg, 0.57 mmol), o-iodoaniline (17) (188 mg, 0.86 mmol) and copper(I) iodide (54 mg, 0.29 mmol) in dry DMSO (5 mL) maintained at 60 °C was treated with triethylamine (159 µL, 1.14 mmol). After 2 h the reaction mixture was treated with Pd₂(dba)₃ (26 mg, 0.028 mmol) then heated to 120 °C. After 24 h the reaction mixture was cooled to 22 °C, diluted with ethyl acetate (5 mL) and the ensuing mixture filtered through a plug of TLC-grade silica topped with diatomaceous earth and the solids so retained were washed with ethyl acetate (5 mL). The combined filtrates were washed with ammonia (2 x 25 mL of a 5% v/v aqueous solution), water (1 x 25 mL) and brine (1 x 25 mL) before being dried (Na₂SO₄), filtered and then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 3:7 v/v ethyl acetate/40-60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions (Rᵣ = 0.1), compound 18⁹ (64 mg, 60%) as a white, crystalline solid, m.p. = 220-221 °C.

¹H NMR (400 MHz, DMSO-d₆) δ 11.84 (broad s, 1H), 7.89 (m, 1H), 7.39 (d, J = 7.9 Hz, 1H), 7.21-7.07 (complex m, 2H), 2.96 (t, J = 6.2 Hz, 2H), 2.42 (t, J = 6.5 Hz, 2H), 2.11 (m, 2H).

¹³C NMR (100 MHz, DMSO-d₆) δ 192.9, 152.3, 135.8, 124.5, 122.4, 121.5, 120.2, 111.7, 111.5, 37.8, 23.4, 22.7.

IR (ATR) νₘₐₓ 3061, 2917, 2854, 1603, 1575, 1456, 1177, 1015, 752 cm⁻¹.

MS (ESI, +ve) m/z 208 [(M+Na)+, 100%], 186 [(M+H)+, 16].

HRMS m/z 208.0740 [M+Na]+ (calcd for C₁₁H₁₁NO, 208.0738).

Compound 20

A magnetically stirred solution of compound 2 (Y = I) (100 mg, 0.40 mmol), o-iodoaniline (17) (132 mg, 0.60 mmol) and copper(I) iodide (38 mg, 0.20 mmol) in dry DMSO (4 mL) maintained at 60 °C was treated with triethylamine (120 µL, 0.80 mmol). After 2 h the reaction mixture was treated with Pd₂(dba)₃ (18 mg, 0.019 mmol) then heated to 120 °C. After a further 20 h the reaction mixture was cooled to 22 °C, diluted with ethyl acetate (4 mL) and the ensuing mixture filtered through a plug of TLC-grade silica topped with diatomaceous earth and the solids so retained were washed with ethyl acetate (15 mL). The combined filtrates were washed with ammonia (2 x 20 mL of a 5% v/v aqueous solution), water (1 x 20 mL) and brine (1 x 20 mL) before being dried (Na₂SO₄), filtered, then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 3:7 v/v ethyl acetate/40-60 petroleum ether elution) and thus
affording, after concentration of the appropriate fractions ($R_f = 0.4$), compound 20$^{10}$ (55 mg, 65%) as a brown powder, m.p. = 96-97 °C (lit.$^{10}$ m.p. = 94-96 °C).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.53 (broad s, 1H), 8.21 (d, $J = 7.2$ Hz, 1H), 7.35 (d, $J = 7.4$ Hz, 1H), 7.27 – 7.18 (complex m, 2H), 2.84 (s, 2H), 2.47 (s, 2H), 1.17 (s, 6H)

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 193.6, 149.8, 135.8, 124.7, 123.2, 122.5, 121.5, 112.3, 110.8, 52.3, 37.4, 35.7, 29.7, 28.7.

IR (ATR) $\nu_{max}$ 3186, 2962, 2918, 2852, 1608, 1456, 1142, 1061, 733, 614 cm$^{-1}$

MS (ESI, +ve) $m/z$ 236 [(M+Na)$^+$, 100%], 214 [(M+H)$^+$, 15].

HRMS $m/z$ 236.1050 [M+Na]$^+$ (calcd for C$_{14}$H$_{15}$NO, 236.1051).

**Compound 21**

\[
\begin{array}{c}
\text{CO}_2\text{Me} \\
\text{N}
\end{array}
\]

Method i: A magnetically stirred solution of compound 9$^5$ (100 mg, 0.44 mmol), o-iodoaniline (17) (146 mg, 0.66 mmol) and copper(I) iodide (42 mg, 0.22 mmol) in dry DMSO (5 mL) maintained at 60 °C was treated with triethylamine (123 µL, 0.88 mmol). After 2 h the reaction mixture was treated with Pd$_2$(dba)$_3$ (20 mg, 0.022 mmol) then heated to 120 °C. After a further 20 h the reaction mixture was cooled to 22 °C, diluted with ethyl acetate (5 mL) and the ensuing mixture filtered through a plug of TLC-grade silica topped with diatomaceous earth and the solids so retained were washed with ethyl acetate (20 mL). The combined filtrates were washed with ammonia (2 x 25 mL of a 5% v/v aqueous solution), water (1 x 25 mL) and brine (1 x 25 mL) before being dried (Na$_2$SO$_4$), filtered then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:4 v/v ethyl acetate/40-60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions ($R_f = 0.5$), compound 21$^{11}$ (38 mg, 45%) light-brown, crystalline solid m.p. = 164 °C.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.33 (broad s, 1H), 8.02 (d, $J = 7.5$ Hz, 1H), 7.23 (d, $J = 7.2$ Hz, 1H), 7.18-7.09 (complex m, 2H), 3.86 (s, 3H), 2.67 (s, 3H)

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 166.5, 143.9, 134.4, 127.1, 122.4, 121.7, 121.3, 110.4, 104.5, 50.8, 14.2.

IR (ATR) $\nu_{max}$ 3271, 1669, 1460, 1264, 1204, 733, 704 cm$^{-1}$.

MS (ESI, +ve) $m/z$ 212 [(M+Na)$^+$, 100%], 190 [(M+H)$^+$, 22].

HRMS $m/z$ 212.0863 [M+H]$^+$ (calcd for C$_{11}$H$_{11}$NO$_2$, 212.0868).

Method ii: A magnetically stirred solution of compound 30 (134 mg, 1.37 mmol), o-iodoaniline (17) (200 mg, 0.91 mmol) and triethylamine (251 µL, 1.80 mmol) in dry DMSO (3 mL) maintained at 80 °C in a sealed tube was treated with Pd$_2$(dba)$_3$ (42 mg, 0.045 mmol). After 24 h the reaction mixture was cooled to 22 °C, diluted with water (10 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic phases were dried (Na$_2$SO$_4$), filtered, then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:2:3 v/v/v ethyl acetate/dichloromethane/40-60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions ($R_f = 0.6$), compound 21 (91 mg, 53%) as a light-brown, crystalline solid, m.p. = 164 °C. This material was identical, in all respects, to that obtained via Method i.
Compound 22

A magnetically stirred solution of compound 10 (100 mg, 0.33 mmol), o-iodoaniline (17) (109 mg, 0.50 mmol) and copper(I) iodide (32 mg, 0.17 mmol) in dry DMSO (3 mL) maintained at 60 °C was treated with triethylamine (92 µL, 0.66 mmol). After 2 h the reaction mixture was treated with Pd(dba)$_2$ (15 mg, 0.16 mmol) then heated to 120 °C. After a further 20 h the reaction mixture was cooled to 22 °C, diluted with ethyl acetate (3 mL) and the ensuing mixture filtered through a plug of TLC-grade silica topped with diatomaceous earth and the solids so retained were washed with ethyl acetate (12 mL). The combined filtrates were washed with ammonia (2 x 15 mL of a 5% v/v aqueous solution), water (1 x 15 mL) and brine (1 x 15 mL) before being dried (Na$_2$SO$_4$), filtered then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:19 v/v ethyl acetate/40-60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions ($R_f = 0.4$), compound 22 (55 mg, 63%) as a yellow powder, m.p. = 145-146 °C (lit.$^{12}$ m.p. = 147-149 °C).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.42 (broad s, 1H), 8.23 (m, 1H), 7.67 (m, 2H), 7.51-7.44 (complex m, 3H), 7.41 (m, 1H), 7.33-7.26 (complex m, 2H), 4.32 (q, $J = 7.1$ Hz, 2H), 1.33 (t, $J = 7.1$ Hz, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 165.3, 144.4, 135.1, 132.0, 129.6, 129.2, 128.1, 127.6, 123.2, 122.2, 122.1, 110.9, 104.8, 59.7, 14.3.

IR (ATR) $\nu_{max}$ 3291, 2922, 1668, 1446, 1426, 1277, 1211, 1127, 1048, 742, 696 cm$^{-1}$.

MS (ESI, +ve) $m/z$ 288 [(M+Na)$^+$, 100%], 266 [(M+H)$^+$, 31].

HRMS $m/z$ 266.1183 [M+H]$^+$ (calcd for C$_{17}$H$_{15}$NO$_2$, 266.1181).

Compound 23

A magnetically stirred solution of compound 13 (100 mg, 0.48 mmol), o-iodoaniline (17) (157 mg, 0.72 mmol) and copper(I) iodide (46 mg, 0.24 mmol) in dry DMSO (5 mL) maintained at 60 °C was treated with triethylamine (134 µL, 0.96 mmol). After 2 h the reaction mixture was treated with Pd(dba)$_2$ (22 mg, 0.024 mmol) then heated to 120 °C. After a further 20 h the reaction mixture was cooled to 22 °C, diluted with ethyl acetate (5 mL) and the ensuing mixture filtered through a plug of TLC-grade silica topped with diatomaceous earth and the solids so retained were washed with ethyl acetate (20 mL). The combined filtrates were washed with ammonia (2 x 25 mL of a 5% v/v aqueous solution), water (1 x 25 mL) and brine (1 x 25 mL) before being dried (Na$_2$SO$_4$), filtered then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:19 v/v ethyl acetate/40-60 petroleum ether elution) and thus
affording, after concentration of the appropriate fractions ($R_f = 0.4$), compound 23\textsuperscript{13} (43 mg, 52%) as a brown powder, m.p. = 253-255 °C (lit. \textsuperscript{13}m.p. = 259.5-260.5 °C).

\textsuperscript{1}H NMR (400 MHz, DMSO-$d_6$) $\delta$ 7.66 (d, $J = 7.7$ Hz, 1H), 7.45 (d, $J = 8.0$ Hz, 1H), 7.32-7.05 (complex m, 2H), 3.36 (broad s, 1H), 3.07 (t, $J = 4.8$ Hz, 2H), 2.81 (t, $J = 4.8$ Hz, 2H).

\textsuperscript{13}C NMR (100 MHz, DMSO-$d_6$) $\delta$ 195.2, 168.3, 142.7, 123.4, 122.0, 121.4, 119.9, 119.6, 113.1, 41.1, 21.5.

IR (ATR) $\nu_{\max}$ 3199, 2928, 1652, 1470, 1429, 1050, 739, 639 cm$^{-1}$.

MS (ESI, +ve) $m/z$ 194 [(M+Na)$^+$, 100%], 172 [(M+H)$^+$, 8].

HRMS $m/z$ 172.0761 [M+H]$^+$ (calcd for C\textsubscript{11}H\textsubscript{9}NO, 172.0762).

**Compound 25**

![Chemical Structure of Compound 25](image)

A magnetically stirred solution of dimethyl acetylenedicarboxylate (50 mg, 0.35 mmol), o-iodophenol [1 (X = I)] (116 mg, 0.53 mmol) and triethylamine (98 µL, 0.70 mmol) in dry DMSO (4 mL) maintained at 120 °C was treated with Pd\textsubscript{2}(dba)$_3$ (16 mg, 0.018 mmol). After 8 h the reaction mixture was cooled to 22 °C, diluted with water (50 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic phases were dried (Na\textsubscript{2}SO\textsubscript{4}), filtered and then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:3 v/v ethyl acetate/40-60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions ($R_f = 0.6$), compound 25\textsuperscript{14} (32 mg, 40%) as a yellow powder, m.p. = 65 °C.

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) $\delta$ 7.93 (d, $J = 7.9$ Hz, 1H), 7.60 (d, $J = 8.4$ Hz, 1H), 7.50 (m, 1H), 7.39 (m, 1H), 4.02 (s, 6H).

\textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) $\delta$ 162.8, 159.1, 154.1, 145.5, 128.1, 125.4, 124.8, 122.9, 118.2, 112.2, 52.9, 52.5.

IR (ATR) $\nu_{\max}$ 2953, 1733, 1582, 1438, 1367, 1305, 1294, 1243, 1212, 1159, 1147, 1066, 749 cm$^{-1}$.

MS (ESI, +ve) $m/z$ 257 [(M+Na)$^+$, 100%].

HRMS $m/z$ 257.0426 [M+Na]$^+$ (calcd for C\textsubscript{12}H\textsubscript{10}O\textsubscript{5}, 257.0426).

**Compound 26**

![Chemical Structure of Compound 26](image)

A magnetically stirred solution of dimethyl acetylenedicarboxylate (50 mg, 0.35 mmol), o-iodoaniline (\textsuperscript{17}) (116 mg, 0.53 mmol) and triethylamine (98 µL, 0.70 mmol) in dry DMSO (4 mL) maintained at 60 °C was treated with Pd\textsubscript{2}(dba)$_3$ (16 mg, 0.018 mmol). After 8 h the reaction mixture was cooled to 22 °C, diluted with water (50 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic phases were dried (Na\textsubscript{2}SO\textsubscript{4}), filtered and then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:3 v/v ethyl acetate/40-60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions ($R_f = 0.6$), compound 26\textsuperscript{14} (32 mg, 40%) as a yellow powder, m.p. = 65 °C.

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) $\delta$ 7.93 (d, $J = 7.9$ Hz, 1H), 7.60 (d, $J = 8.4$ Hz, 1H), 7.50 (m, 1H), 7.39 (m, 1H), 4.02 (s, 6H).

\textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) $\delta$ 162.8, 159.1, 154.1, 145.5, 128.1, 125.4, 124.8, 122.9, 118.2, 112.2, 52.9, 52.5.

IR (ATR) $\nu_{\max}$ 2953, 1733, 1582, 1438, 1367, 1305, 1294, 1243, 1212, 1159, 1147, 1066, 749 cm$^{-1}$.

MS (ESI, +ve) $m/z$ 257 [(M+Na)$^+$, 100%].

HRMS $m/z$ 257.0426 [M+Na]$^+$ (calcd for C\textsubscript{12}H\textsubscript{10}O\textsubscript{5}, 257.0426).
chromatography (silica, 1:3 v/v ethyl acetate/40-60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions ($R_f = 0.3$), compound $26^{15}$ (53 mg, 67%) as a yellow, crystalline solid, m.p. = 106 °C (lit. $^{15}$ m.p. = 114-116 °C).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.29 (broad s, 1H), 8.06 (d, $J = 8.2$ Hz, 1H), 7.44 (dd, $J = 8.2$ and 1.1 Hz, 1H), 7.38 (ddd, $J = 8.2$, 7.0 and 1.2 Hz, 1H), 7.29 (d, $J = 7.0$ Hz, 1H), 3.99 (s, 6H).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 164.5, 161.3, 134.7, 128.0, 126.8, 126.0, 122.8, 122.6, 112.0, 111.8, 52.7, 51.9.

IR (ATR) $\nu$$_{\text{max}}$ 3308, 2951, 1695, 1537, 1443, 1249, 1219, 1070, 749 cm$^{-1}$.

MS (ESI, +ve) $m/z$ 256 [(M+Na)$^+$, 100%].

HRMS $m/z$ 256.0584 [M+Na]$^+$ (calcd for C$_{12}$H$_{11}$NO$_4$, 256.0586).

**Compound 27**

![Image of Compound 27](image)

A magnetically stirred solution of dimethyl acetylenedicarboxylate (50 mg, 0.35 mmol) and o-iodophenol [1 (X = I)] (116 mg, 0.53 mmol) in dry DMSO (4 mL) maintained at 80 °C was treated with triethylamine (98 µL, 0.70 mmol). After 8 h the reaction mixture was cooled to 22 °C, diluted with water (50 mL) and extracted with ethyl acetate (3 x 50 mL). The combined organic phases were dried (Na$_2$SO$_4$), filtered and then concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:9 v/v ethyl acetate/40-60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions ($R_f = 0.2$), compound 27 (60 mg, 62%) as a clear, colorless oil and as a single geometric isomer.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.87 (d, $J = 7.8$ Hz, 1H), 7.39 (t, $J = 7.8$ Hz, 1H), 7.15 (d, $J = 7.8$ Hz, 1H), 7.01 (t, $J = 7.8$ Hz, 1H), 5.01 (s, 1H), 3.94 (s, 3H), 3.68 (s, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 165.5, 162.8, 159.2, 152.7, 140.4, 130.1, 128.1, 121.9, 99.3, 89.1, 53.1, 51.8.

IR (ATR) $\nu$$_{\text{max}}$ 2952, 1750, 1719, 1636, 1464, 1437, 1364, 1210, 1129, 780 cm$^{-1}$.

MS (ESI, +ve) $m/z$ 385 [(M+Na)$^+$, 100%].

HRMS $m/z$ 384.9550 [M+Na]$^+$ (calcd for C$_{12}$H$_{11}$IO$_5$, 384.9549).

**Compound 28**

![Image of Compound 28](image)

A magnetically stirred solution of o-iodoaniline (17) (1.10 g, 5.00 mmol) in dry methanol (10 mL) maintained at 0 °C was treated, dropwise, with dimethyl acetylenedicarboxylate (782 mg, 5.50 mmol) before being warmed to 22 °C. After 2 h the reaction mixture was concentrated under reduced pressure, diluted with diethyl ether (20 mL), washed with water (2 x 10 mL) and brine (1 x 20 mL) then dried (Na$_2$SO$_4$), filtered and concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:19...
v/v diethyl ether/40-60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions \((R_f = 0.1)\), compound 28\(^{16}\) (1.52 g, 84%) as a yellow, crystalline solid, m.p. = 75 °C (lit.\(^{16}\) m.p. = 73-75 °C) and as a single geometric isomer.

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 9.62 (s, 1H), 7.82 (d, \(J = 7.9\) Hz, 1H), 7.24 (m, 1H), 6.86-6.69 (complex m, 2H), 5.55 (s, 1H), 3.77 (s, 3H), 3.68 (s, 3H).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 169.5, 164.4, 146.8, 141.8, 139.4, 128.7, 125.6, 120.7, 95.8, 91.9, 52.8, 51.5.

IR (ATR) \(\nu_{\text{max}}\) 2591, 1735, 1668, 1607, 1581, 1435, 1215, 1145, 1011, 821, 751, 642 cm\(^{-1}\).

MS (ESI, +ve) \(m/z\) 416 [(M+Na+MeOH)+, 34%], 384 [(M+Na)+, 100], 362 [(M+H)+, 5].

HRMS \(m/z\) 361.9888 [M+H]+ (calcd for C\(_{12}\)H\(_{12}\)INO\(_4\), 361.9889).

**Compound 31**

![Compound 31](attachment:image)

A magnetically stirred solution of compound 29 (120 µL, 1.35 mmol), o-iodophenol [1 (X = I)] (200 mg, 0.90 mmol) and triethylamine (251 µL, 1.80 mmol) in dry DMSO (3 mL) maintained at 80 °C in a sealed tube was treated with Pd\(_2\)(dba)\(_3\) (42 mg, 0.045 mmol). After 24 h the reaction mixture was cooled to 22 °C, diluted with water (10 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic phases were dried (Na\(_2\)SO\(_4\)), filtered then concentrated under reduced pressure and the residue so obtained was subjected to flash column chromatography (silica, 1:2:3 v/v/v ethyl acetate/dichloromethane/40-60 petroleum ether elution). Concentration of the appropriate fractions \((R_f = 0.7)\) then afforded compound 31\(^{17}\) (67 mg, 42%) as a clear, yellow oil.

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.26 (s, 1H), 8.05 (m, 1H), 7.54 (m, 1H), 7.37 (m, 2H), 3.94 (s, 3H).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 163.8, 155.5, 150.9, 125.3, 124.5, 124.1, 122.0, 114.4, 111.6, 51.6.

IR (ATR) \(\nu_{\text{max}}\) 3148, 2953, 1721, 1566, 1451, 1287, 1234, 1123, 1050, 149 cm\(^{-1}\).

MS (EI, +ve) \(m/z\) 176 (M\(^{+}\), 50%), 145 (100).

HRMS \(m/z\) 176.0474 [M+H]+ (calcd for C\(_{10}\)H\(_{8}\)O\(_3\), 176.0473).

**Compound 32**

![Compound 32](attachment:image)

A magnetically stirred solution of compound 29 (120 µL, 1.35 mmol), o-iodoaniline (17) (200 mg, 0.91 mmol) and triethylamine (251 µL, 1.80 mmol) in dry DMSO (3 mL) maintained at 80 °C in a sealed tube was treated with Pd\(_2\)(dba)\(_3\) (42 mg, 0.045 mmol). After 24 h the reaction mixture was cooled to 22 °C, diluted with water (10 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic phases were dried (Na\(_2\)SO\(_4\)), filtered then concentrated under reduced pressure. The residue so obtained was subjected to flash column...
chromatography (silica, 1:2:3 v/v/v ethyl acetate/dichloromethane/40-60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions (R_f = 0.6), compound 32^18 (65 mg, 41%) as a white, crystalline solid, m.p. = 123 °C (lit. m.p. = 149-151 °C).

^1H NMR (400 MHz, CDCl_3) δ 8.61 (broad s, 1H), 8.20 (m, 1H), 7.93 (s, 1H), 7.43 (m, 1H), 7.32-7.25 (complex m, 2H), 3.93 (s, 3H).

^13C NMR (100 MHz, CDCl_3) δ 165.6, 136.0, 130.9, 125.8, 123.2, 122.1, 121.5, 111.4, 108.9, 51.1.

IR (ATR) ν_{max} 3325, 1695, 1533, 1442, 1193, 1169, 1125, 1050, 780, 754 cm^{-1}.

MS (ESI, +ve) m/z 198 [(M+Na)^+, 100%], 176 [(M+H)^+, 38].

HRMS m/z 198.0533 [M+Na]^+ (calcd for C_{10}H_{19}NO_{2}, 198.0531).

**Compound 34**

![Compound 34](image)

A magnetically stirred solution of 2-iodobenzyl alcohol (33)^19 (300 mg, 1.28 mmol) in dry dichloromethane (10 mL) was treated, dropwise, with dimethyl acetylenedicarboxylate (157 µL, 1.28 mmol) and then Echavarren’s gold catalyst (CAS No. 866641-66-9, 50 mg, 0.06 mmol). The resulting mixture was heated at 45 °C for 16 h then cooled and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 5:10:85 v/v/v ethyl acetate/dichloromethane/40-60 petroleum ether elution) to afford, after concentration of the appropriate fractions (R_f = 0.2), compound 34 (280 mg, 58%) as a white, crystalline solid, m.p. = 49 °C and as a single geometric isomer.

^1H NMR (400 MHz, CDCl_3) δ 7.82 (d, J = 7.8 Hz, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.39 (t, J = 7.8 Hz, 1H), 7.02 (t, J = 7.8 Hz, 1H), 6.31 (s, 1H), 5.17 (s, 2H), 3.85 (s, 3H), 3.75 (s, 3H).

^13C NMR (100 MHz, CDCl_3) δ 164.6, 163.2, 153.5, 139.1, 138.7, 129.6, 129.1, 128.4, 109.9, 97.1, 78.9, 53.0, 51.8.

IR (ATR) ν_{max} 2946, 1727, 1699, 1623, 1434, 1363, 1226, 1122, 1007, 886, 743, 657 cm^{-1}.

MS (ESI, +ve) m/z 399 [(M+Na)^+, 100%].

HRMS m/z 398.9703 [M+Na]^+ (calcd for C_{13}H_{13}IO_{5}, 398.9705).

**Compound 35**

![Compound 35](image)

A round-bottom flask was charged with compound 34 (100 mg, 0.26 mmol) and Pd_2(dba)_3 (12 mg, 0.013 mmol) then evacuated before being refilled with nitrogen and treated with triethylamine (74 µL, 0.53 mmol) and degassed DMF (2 mL). The resulting mixture was heated at 120 °C for 6 h then cooled to 22 °C before being diluted with ethyl acetate (10 mL). The solution thus obtained was washed with water (2 x 5 mL) then dried (Na_2SO_4), filtered
and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 20:80 v/v ethyl acetate/40-60 petroleum ether elution) and thus affording, after concentration of the appropriate fractions ($R_f = 0.2$), compound 35 (32 mg, 48%) as a clear, colorless oil.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.38-7.21 (complex m, 4H), 5.35 (d, $J = 12.2$ Hz, 1H), 5.22 (d, $J = 12.2$ Hz, 1H), 3.75 (s, 3H), 3.70 (s, 3H), 3.51 (d, $J = 16.3$ Hz, 1H), 2.86 (d, $J = 16.3$ Hz, 1H).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 172.6, 169.9, 139.0, 138.8, 129.1, 127.9, 122.0, 121.2, 88.0, 73.8, 52.8, 52.0, 43.4.

IR (ATR) $\nu_{\text{max}}$ 2954, 1732, 1436, 1255, 1199, 1167, 1052, 1014, 780, 739, 698 cm$^{-1}$.

MS (ESI, +ve) $m/z$ 273 [(M+Na)$^+$, 100%].

HRMS $m/z$ 273.0734 [M+Na]$^+$ (calcd for C$_{13}$H$_{14}$O$_5$, 273.0739).

**Compound 36**

A magnetically stirred solution of compound 33 (100 mg, 1.35 mmol) in dry DMSO (3 mL) maintained at 22 ºC in a sealed tube was treated with sodium hydride (15 mg, 0.65 mmol). After 0.25 h the reaction mixture was treated with Pd$_2$(dba)$_3$ (42 mg, 0.045 mmol), triethylamine (110 µL, 0.86 mmol) and compound 29 (58 µL, 0.65 mmol) before being heated to 80 ºC. After 24 h the reaction mixture was cooled to 22 ºC then diluted with water (10 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic phases were dried (Na$_2$SO$_4$), filtered then concentrated under reduced pressure and the residue so obtained subjected to flash column chromatography (silica, 1:2:3 v/v/v ethyl acetate/dichloromethane/40-60 petroleum ether elution). Concentration of the appropriate fractions ($R_f = 0.6$) then afforded compound 36$^{20}$ (33 mg, 41%) as a yellow, crystalline solid, m.p. = 99 ºC (lit.$^{20}$ m.p. = 105-105 ºC).

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.60 (m, 1H), 7.51 (m, 1H), 7.43 (m, 2H), 5.58 (s, 2H), 5.53 (s, 2H), 3.77 (s, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 168.0, 166.8, 141.4, 132.9, 131.4, 128.5, 121.5, 121.3, 85.7, 51.0 (one signal obscured or overlapping).

IR (ATR) $\nu_{\text{max}}$ 2948, 1699, 1644, 1295, 1152, 1067, 1003, 769 cm$^{-1}$.

MS (ESI, +ve) $m/z$ 213 [(M+Na)$^+$, 100%].

HRMS $m/z$ 213.0529 [M+Na]$^+$ (calcd for C$_{11}$H$_{10}$O$_3$, 213.0528).
Crystallographic Studies.

Crystallographic Data.

Compound 5. C_{14}H_{10}O_{2} \( M = 214.25 \), \( T = 150 \) K, monoclinic, space group \( P2_1/n \), \( Z = 4 \), \( a = 9.3811(6) \) Å, \( b = 11.9699(7) \) Å, \( c = 9.7738(8) \) Å; \( \beta = 97.017(6) \), \( V = 1089.29(13) \) Å³, \( D_x = 1.306 \) Mg m⁻³, 2456 unique data \( (2\theta_{\text{max}} = 58.254^\circ) \), \( R = 0.0508 \) [for 1907 reflections with \( I > 2.0\sigma(I) \)]; \( R_w = 0.1177 \) (all data), \( S = 1.053 \).

Compound 14. C_{14}H_{20}O_{2}, \( M = 172.17 \), \( T = 150 \) K, triclinic, space group \( P-1 \) (No. 2), \( Z = 2 \), \( a = 6.5623(4) \) Å, \( b = 7.4117(6) \) Å, \( c = 9.4839(8) \) Å; \( \alpha = 67.098(8)^\circ \), \( \beta = 73.107(6)^\circ \), \( \gamma = 74.123(6)^\circ \), \( V = 399.78(6) \) Å³, \( D_x = 1.430 \) Mg m⁻³, 1851 unique data \( (2\theta_{\text{max}} = 58.386^\circ) \), \( R = 0.0467 \) [for 1590 reflections with \( I > 2.0\sigma(I) \)]; \( R_w = 0.1164 \) (all data), \( S = 1.068 \).

Compound 18. C_{12}H_{11}NO, \( M = 185.23 \), \( T = 150 \) K, orthorhombic, space group \( Pn\overline{1}a_{2} \), \( Z = 4 \), \( a = 9.8208(8) \) Å, \( b = 10.9059(8) \) Å, \( c = 8.6381(7) \) Å; \( V = 925.18(7) \) Å³, \( D_x = 1.330 \) Mg m⁻³, 1242 unique data \( (2\theta_{\text{max}} = 58.8^\circ) \), \( R = 0.035 \) [for 1187 reflections with \( I > 2.0\sigma(I) \)]; \( R_w = 0.082 \) (all data), \( S = 1.01 \).

Compound 21. C_{12}H_{11}NO_{2} \( M = 189.21 \), \( T = 150 \) K, monoclinic, space group \( Cc \), \( Z = 8 \), \( a = 6.9018(3) \) Å, \( b = 16.7805(6) \) Å, \( c = 16.7244(7) \) Å; \( \beta = 101.100(4)^\circ \), \( V = 1900.71(14) \) Å³, \( D_x = 1.322 \) Mg m⁻³, 3397 unique data \( (2\theta_{\text{max}} = 56.806^\circ) \), \( R = 0.0410 \) [for 3106 reflections with \( I > 2.0\sigma(I) \)]; \( R_w = 0.0957 \) (all data), \( S = 1.070 \).

Compound 22. C_{12}H_{10}NO_{2} \( M = 265.31 \), \( T = 150 \) K, monoclinic, space group \( P2_1/c \), \( Z = 4 \), \( a = 13.7205(7) \) Å, \( b = 10.8238(5) \) Å, \( c = 8.9624(5) \) Å; \( \beta = 90.504(4) \), \( V = 1330.94(12) \) Å³, \( D_x = 1.3240 \) Mg m⁻³, 2716 unique data \( (2\theta_{\text{max}} = 52.74^\circ) \), \( R = 0.0388 \) [for 2299 reflections with \( I > 2.0\sigma(I) \)]; \( R_w = 0.0976 \) (all data), \( S = 1.0484 \).

Compound 26. C_{12}H_{11}NO_{4} \( M = 233.22 \), \( T = 150 \) K, orthorhombic, space group \( Pbca \), \( Z = 8 \), \( a = 8.0517(4) \) Å, \( b = 15.1149(6) \) Å, \( c = 18.0630(8) \) Å; \( V = 2198.28(17) \) Å³, \( D_x = 1.409 \) Mg m⁻³, 3369 unique data \( (2\theta_{\text{max}} = 63.624^\circ) \), \( R = 0.0510 \) [for 2590 reflections with \( I > 2.0\sigma(I) \)]; \( R_w = 0.1231 \) (all data), \( S = 1.080 \).

Structure Determinations.

Data for compounds 5, 14, 18, 21 and 26 were measured on a Rigaku SuperNova diffractometer (using MoKα, graphite monochromator, \( \lambda = 0.71073 \) Å), while data for compound 22 were measured on a Rigaku xCalibur diffractometer (MoKα, graphite monochromator, \( \lambda = 0.71073 \) Å). Data collection, cell refinement and data reduction employed the CrysAlis PRO program²¹ while SHELXT²² and SHELXL²³ were used for structure solution and refinement. Atomic coordinates, bond lengths and angles, and displacement parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC nos. 1935464-1935469). These data can be obtained free-of-charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.
Figure S1: Structure of compound 5 (CCDC 1935464). Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.
Figure S2: Structure of compound 14 (CCDC 1935465). Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.
Figure S3: Structure of compound 18 (CCDC 1935466). Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.
**Figure S4**: Structure of compound 21 (CCDC 1935467). Anisotropic displacement ellipsoids show 30% probability levels. For clarity, only one of two crystallographically independent molecules in the asymmetric unit is shown (both have similar geometries). Hydrogen atoms are drawn as circles with small radii.
Figure S5: Structure of compound 22 (CCDC 1935468). Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.
Figure S6: Structure of compound 26 (CCDC 1935469). Anisotropic displacement ellipsoids show 30% probability levels. Hydrogen atoms are drawn as circles with small radii.
References


10. Zuo, Y.; He, X.; Ning, Y.; Wu, Y.; Shang, Y. Rh(III)-Catalyzed C-H Activation/Intramolecular Cyclization: Access to N-Acyl-2,3-dihydro-1H-carbazol-


400 MHz $^1$H NMR Spectrum of Compound 2 ($Y = \text{Br}$) (recorded in CDCl$_3$)

2 ($Y = \text{Br}$)

CHCl$_3$
100 MHz $^{13}$C NMR Spectrum of Compound 2 (Y = Br) (recorded in CDCl$_3$)

2 (Y = Br)
400 MHz $^1$H NMR Spectrum of Compound 2 (Y = I)
(recorded in CDCl$_3$)
$100$ MHz $^{13}$C NMR Spectrum of Compound 2 ($Y = I$) (recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 2 ($Y = OTf$) (recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 2 (Y = OTf) (recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 3 (X = Br) (recorded in CDCl$_3$)

$\text{CHCl}_3$

3 (X = Br)
$^{13}$C NMR Spectrum of Compound 3 (X = Br)
(recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 3 ($X = I$) (recorded in CDCl$_3$)

![Chemical structure of Compound 3 ($X = I$)](image)

3 ($X = I$)
100 MHz $^{13}$C NMR Spectrum of Compound 3 ($X = I$) (recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 5
(recorded in CDCl$_3$)

[Chemical Structure Image]

$\text{CHCl}_3$
100 MHz $^{13}$C NMR Spectrum of Compound 5
(recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 8
(recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 8 (recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 11
(recorded in CDCl$_3$)

[Chemical structure image]

- CHCl$_3$
- H$_2$O
100 MHz $^{13}$C NMR Spectrum of Compound 11
(recorded in CDCl$_3$)

![Chemical Structure of 11](image)

CDCl$_3$
400 MHz $^1$H NMR Spectrum of Compound 12
(recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 12 (recorded in CDCl₃)
400 MHz $^1$H NMR Spectrum of Compound 14
(recorded in CDCl$_3$)

* = impurity

CHCl$_3$

C$_6$H$_{12}$

H$_2$O

H grease
100 MHz $^{13}$C NMR Spectrum of Compound 14
(recorded in CDCl$_3$)

* = impurity
400 MHz $^1$H NMR Spectrum of Compound 15
(recorded in CDCl$_3$)

![](image)

CHCl$_3$
100 MHz $^{13}$C NMR Spectrum of Compound 15
(recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 16
(recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 16
(recorded in CDCl$_3$)

16
400 MHz $^1$H NMR Spectrum of Compound 18
[recorded in (CD$_3$)$_2$SO]

H$_2$O

partial protio-forms of (CD$_3$)$_2$SO
100 MHz $^{13}$C NMR Spectrum of Compound 18
[recorded in (CD$_3$)$_2$SO]
400 MHz $^1$H NMR Spectrum of Compound 20
(recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 20
(recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 21
(recorded in CDCl$_3$)

H$_2$O
H grease
100 MHz $^{13}$C NMR Spectrum of Compound 21 (recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 22
(recorded in CDCl$_3$)

$\text{CHCl}_3$

$\text{H}_2\text{O}$

$\text{H grease}$

\[
\text{CO}_2\text{Et}
\]
100 MHz $^{13}$C NMR Spectrum of Compound 22
(recorded in CDCl$_3$)

![Chemical Structure](image)
400 MHz $^1$H NMR Spectrum of Compound 23
[recorded in (CD$_3$)$_2$SO]
100 MHz $^{13}$C NMR Spectrum of Compound 23
[recorded in (CD$_3$)$_2$SO]
400 MHz $^1$H NMR Spectrum of Compound 25
(recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 25 (recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 26
(recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 26 (recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 27
(recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound **27**
(recorded in CDCl$_3$)

![Chemical Structure](image)
400 MHz $^1$H NMR Spectrum of Compound 28
(recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 28 (recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 31
(recorded in CDCl$_3$)

\[ \text{CHCl}_3 \]

31
100 MHz $^{13}$C NMR Spectrum of Compound 31 (recorded in CDCl$_3$)
400 MHz $^1$H NMR Spectrum of Compound 32 (recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 32 (recorded in CDCl$_3$)
400 MHz $^1H$ NMR Spectrum of Compound 34
(recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 34 (recorded in CDCl$_3$)

$\text{CDCl}_3$

34
400 MHz $^1$H NMR Spectrum of Compound 35
(recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 35
(recorded in CDCl$_3$)

![Chemical Structure of Compound 35](attachment:image.png)
400 MHz $^1$H NMR Spectrum of Compound 36 (recorded in CDCl$_3$)
100 MHz $^{13}$C NMR Spectrum of Compound 36 (recorded in CDCl$_3$)

![Structural formula of Compound 36](image)

CDCl$_3$