Novel Approaches Towards the Synthesis of Morphinan Derivatives

By

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February 2023

Declaration

I hereby declare that, except for where specific reference is made to other sources, the work contained within this thesis is the original work of my own research since the registration of the PhD degree in April 2019, and any collaboration is clearly indicated. This thesis has been composed by myself and has not been submitted, in whole or part, for any other degree, diploma or other qualification.

The following thesis contains results reported in the following publications:

Novel process for the synthesis of noroxymorphone from morphine

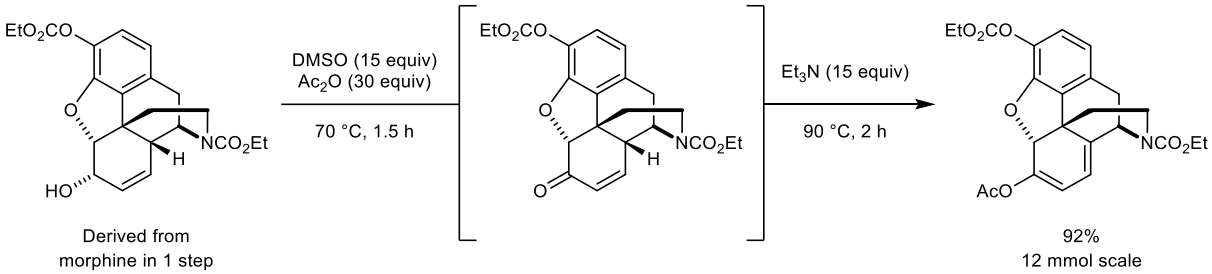
D. Gorbachev, H. W. Lam, A. Saxena, N. S. Saxena, WO2022144911A1, **2022**

Synthesis of New Morphinan Opioids by TBADT-Catalyzed Photochemical Functionalization at the Carbon Skeleton

D. Gorbachev, E. Smith, S. P. Argent, G. N. Newton, H. W. Lam, *Chem. Eur. J.*, **2022**, *28*, e202201478

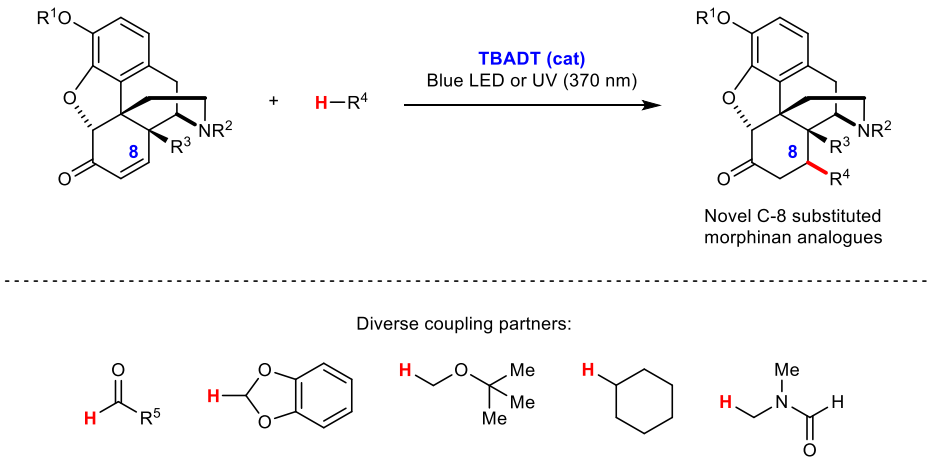
Abstract

The following work contains two chapters, encompassing two projects. The first chapter describes improvements to the current state-of-the-art process route for the conversion of morphine to a valuable pharmaceutical intermediate noroxymorphone. A mild and industrially applicable Albright-Goldman oxidation was implemented as a key step to improve the process. Utilisation of the Albright-Goldman conditions allowed the combination of the oxidation step with the subsequent diene-forming step, thereby making the overall process more concise and reducing the number of required manipulations. These features are particularly advantageous when applied to the large-scale industrial manufacture.



One-pot Albright-Goldman oxidation/ diene formation

The second chapter describes the successful application of TBADT photocatalysis towards functionalisation of the morphinan scaffold. A series of novel 8-substituted morphinan derivatives were synthesized using a range of coupling partners containing various functional groups. This work demonstrated the utility and applicability of TBADT catalysis towards late-stage functionalisation of natural products under mild conditions.



Acknowledgements

First and foremost, I would like to extend my gratitude to my supervisor – Professor Hon Wai Lam. Thank you for hiring me and giving me the opportunity to practice the art of chemistry. You have taught me lessons that go beyond the lab – most importantly, about the value of time. Thank you for your time, patience, and guidance throughout this journey.

I would also like to thank Aakarsh Saxena and Rusan Pharma for sponsoring my PhD studentship and the opportunity to work on an incredibly exciting project. I really hope that this work has paved the way for more fruitful collaborations in the future.

From the bottom of my heart, I would like to thank the amazing people whom I've had the privilege of calling my lab mates for the past few years – the Laminators. We've been through some real highs and lows together, but if I were to do it all over again, I wouldn't choose anyone else to do it with. Members past and present, you will forever live in my heart rent free. Alistair, Harley, Luke, Simone, Jack, Elliot, Hongyi, Raja, Kieran, Johnny and Rob – I salute you all and thank you for the countless great memories. From the long games of Risk to poker nights and Hooters debauchery, we really did it all. An honourable mention must also go out to Tom, a fellow Laminator in spirit.

This work would not have been possible without the tremendous support from my family – not only in these past three years, but throughout my entire life. My parents Ella and Vladimir, who have always nurtured my curiosity and encouraged me to pursue my dreams – thank you for your unconditional love. I would have never achieved this without you.

To my dear fiancée Pollyanna – you are the wind in my sails, and you gave me the motivation to get through the challenge of thesis-writing. You inspire me with your hard work and dedication to be the best person that you can be, and I learn from you every day.

Finally, I would like to thank perhaps the single most important person on my chemistry journey – my school chemistry teacher Mike Scamell. You have opened the door to the wonderful and mysterious world of chemistry for me and it has been a crazy adventure ever since. The world is a better place because of people like you.

Contents

List of Abbreviations

cAMP	cyclic adenosine monophosphate
CNS	central nervous system
Cp	cyclopropyl
DCC	*N,N*'-dicyclohexylcarbodiimide
DOP	delta opioid receptor
DMSO	dimethyl sulfoxide
Equiv	equivalents
EtOAc	ethyl acetate
EWG	electron-withdrawing group
GPCR	G-protein-coupled receptor
HAT	hydrogen atom transfer
HOMO	highest occupied molecular orbital
HRMS	high resolution mass spectrometry
IPA	isopropanol
IR	infrared
KOP	kappa opioid receptor
LMCT	ligand-to-metal charge transfer
LUMO	lowest unoccupied molecular orbital
Me	methyl
MHz	megahertz
MOP	mu opioid receptor
Ms	mesyl
m.p.	melting point
ND	not determined
NMR	nuclear magnetic resonance
NOP	nociceptin opioid receptor
PC	photocatalyst
Ph	phenyl
PMB	*para*-methoxybenzyl
POM	polyoxometalate
RT	room temperature
SAR	structure-activity relationship
TBADT	*tert*-butylammoniumdecatungstate

TBDMS	*tert*-butyldimethylsilyl
TBHP	*tert*-butyl hydroperoxide
Tf	triflate
THF	tetrahydrofuran
TPP	tetraphenylporphyrin
TIPS	triisopropylsilyl
TLC	thin-layer chromatography
W	watt

Chapter 1: Process Development for Opiate-Derived Pharmaceutical Agents

1. Introduction

1.1. Historical Background

Opiates are generally described as drugs derived from opium - the dried latex material obtained from the opium poppy plant (*Papaver somniferum*).[1] The term *opiate* encompasses a range of naturally occurring opium alkaloids as well as their semisynthetic congeners. The term *opioid* is even more inclusive and can be applied to all drugs, natural and synthetic, that interact with the opioid receptor system. Morphine (**1**), the prototypical opiate drug, is one of the major alkaloid constituents of the opium poppy latex, representing 10% - 20% of its weight.[2] Other major opium alkaloid constituents of synthetic and pharmaceutical interest include codeine (**2**), thebaine (**3**) and oripavine (**4**) (Figure 1).

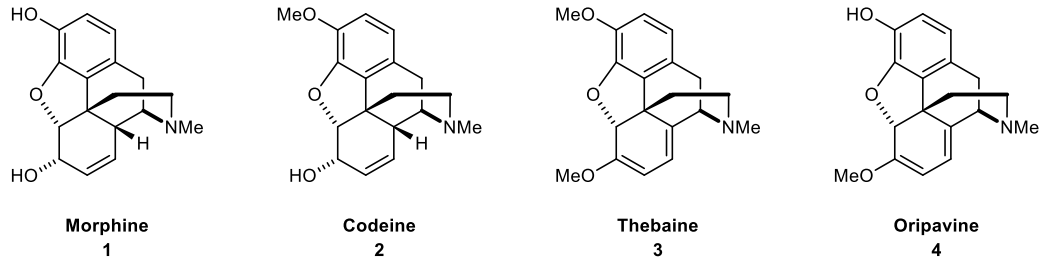
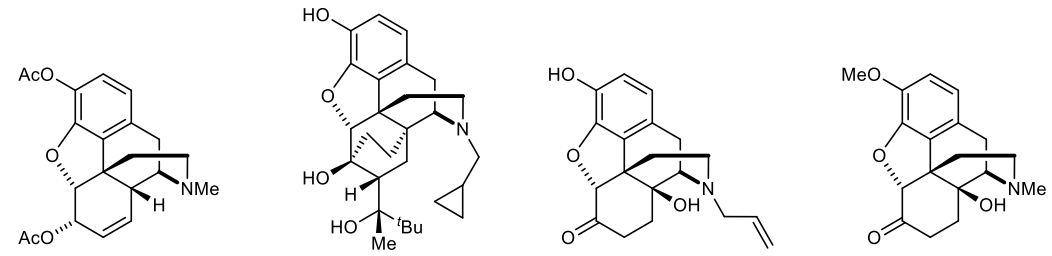


Figure 1: Major opium-derived alkaloids

Opium is widely considered to be one the oldest medicines known to mankind – written records detailing the use of opium as an analgesic date as far back as 1500 BC.[3] However, it was only in 1805 that crystalline morphine was isolated for the first time from opium by Sertürner.[4] Sertürner's isolation of crystalline material launched a century-long effort to identify the structure of morphine. In 1925 the structure of morphine was proposed by Robinson, which was ultimately proved to be correct after Gates completed the first total synthesis of morphine in 1952, and a few years later, in 1955 Crowfoot-Hodgkin published a crystallographic study of morphine hydroiodide dihydrate.[5–7]

Despite the lengthy process of the elucidation of morphine's structure, the first chemical modifications to morphine were made much earlier. For example, diacetylmorphine (**5**) (heroin, Figure 2) was synthesised in 1874 and marketed as a cough suppressant by Bayer.[8] Starting from rudimentary chemical manipulations on morphine, the desire to develop an improved analgesic with diminished abuse potential has been driving the majority of synthetic

efforts in the field of opioid chemistry. As a result, a vast number of semi-synthetic and synthetic opioids has been generated over the years that have become indispensable in the clinical setting. Notable examples of such drugs include buprenorphine (**6**), naloxone (**7**) and oxycodone (**8**) (Figure 2).



Diacetylmorphine (heroin) **5** | **Buprenorphine** **6** | **Naloxone** **7** | **Oxycodone** **8**

Figure 2: Medicinally important opiate drugs

In fact, a large number of the clinically useful opioid drugs were developed before the discovery of the endogenous peptide agonists (*vide infra*) and many even before the opioid receptors in the human body were characterised.

The extensive array of the existing opioid drugs can generally be classified based on two pharmacological parameters – the type of opioid receptor targeted by a given drug, and the effect elicited on the receptor by the drug (i.e. agonistic, antagonistic etc.).[9] The following section will present a concise overview of opioid pharmacology.

1.2. Opioid Pharmacology

The modern era of opioid research began with the discovery of opioid receptors in 1973.[10,11] Martin provided evidence for opioid receptor multiplicity, i.e. the existence of multiple opioid receptors by demonstrating that a series of opioid compounds displayed different *in vivo* pharmacological profiles.[12] It was proposed that opioids interact with three different types of receptors, designated *μ*-, *κ*- and *σ*- after their prototypical agonists – morphine (**1**), ketocyclazocine (**9**), and SKF-10047 (**10**) (*N*-allylnormetazocine) respectively (Figure 3).

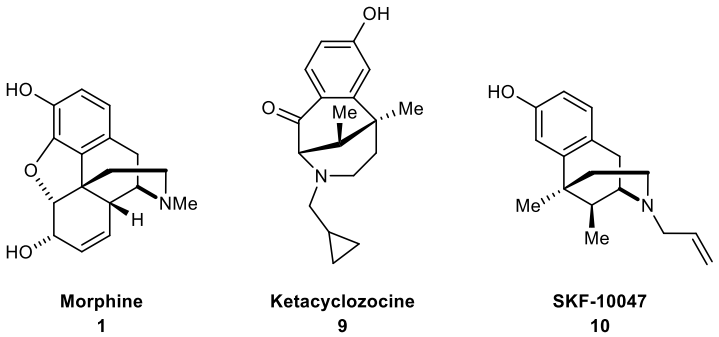


Figure 3: Prototypical agonists for μ-, κ- and σ-recepotors

Broad pharmacological effects of these ligands on the respective receptor subtypes were described as morphine-induced analgesia, ketocyclazocine-induced dysphoria and SKF-10047-induced psychotomimesis. However, the *σ*-receptor is no longer considered to be an opioid receptor, as later findings by Su have shown that it has only low affinity for naltrexone, which is a universal high-affinity blocker for all opioid receptor subtypes.[13] Consequently, *σ*-receptor has been treated as a receptor type of its own, rather than an opioid receptor subtype.[14]

In 1975 the first endogenous opioid receptor ligands met-enkephalin (**11**) and leu-enkephalin (**12**) were discovered by Hughes *et al.* along with a new type of receptor, the *δ*-receptor, which they targeted (Figure 4).[15,16] Both of these ligands were identified as pentapeptides derived from a pro-hormone precursor proenkephalin. Other endogenous opioid peptides that were discovered later include dynorphins A and B, which possess agonistic activity at the *κ*-opioid receptor, and β-endorphin, which exhibits agonistic activity at the *μ*-opioid receptor.[17]

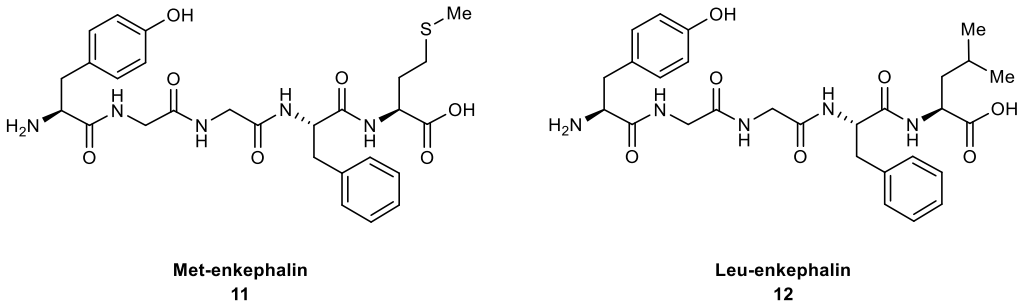


Figure 4: Endogenous δ-opioid receptor ligands

The final addition to the canonical family of the opioid receptors was made in 1994 when Mollereau identified a new receptor through gene encoding experiments, which showed more than 60% homology with the three known classical opioid receptors, and was

thus deemed an opioid receptor on structural grounds.[18] The new receptor was subsequently named the nociceptin (NOP) receptor and its endogenous ligand nociceptin/orphanin FQ (N/OFQ) was isolated from brain tissue soon thereafter.[19]

The four opioid receptors μ (MOP), κ (KOP), δ (DOP) and nociceptin (NOP) are widely distributed throughout the central nervous system and, to a lesser extent, in the periphery, occupying regions in the gastrointestinal tract, the heart and vas deferens.[20,21] Stimulation of any of the four opioid receptors produces analgesia, along with a range of other physiological effects, which are receptor specific. Activation of the MOP receptors causes analgesia, but also sedation, respiratory depression, bradycardia, nausea, vomiting and a reduction in gastric motility. Activation of DOP receptors can cause spinal and supraspinal analgesia and reduce gastric motility, while KOP receptor stimulation produces spinal analgesia, diuresis and dysphoria.[9] Analgesic effects mediated by the NOP receptors are more complex compared to other opioid receptors – depending on the exposure to exogenous opioid agonists the NOP receptors can either block or facilitate the analgesic effect of opioids.[22]

All four opioid receptors are G-protein-coupled receptors (GPCRs). Despite producing different functional effects, all of them display similar cellular response upon activation (Figure 5). Binding of an opioid agonist to a G-protein-coupled opioid receptor on the transmembrane portion of the receptor leads to the closing of voltage sensitive calcium channels, stimulation of potassium efflux leading to hyperpolarization and reduced cyclic adenosine monophosphate (cAMP) production via inhibition of adenylyl cyclase. Overall, this results in reduced net neuronal cell excitability, which in turn leads to a reduction in transmission of nerve impulses along with inhibition of neurotransmitter release.[17] In the central nervous system (CNS) this series of cellular events eventually leads to activation of a number of inhibitory pathways and ultimately the production of opioid-mediated analgesic effect.

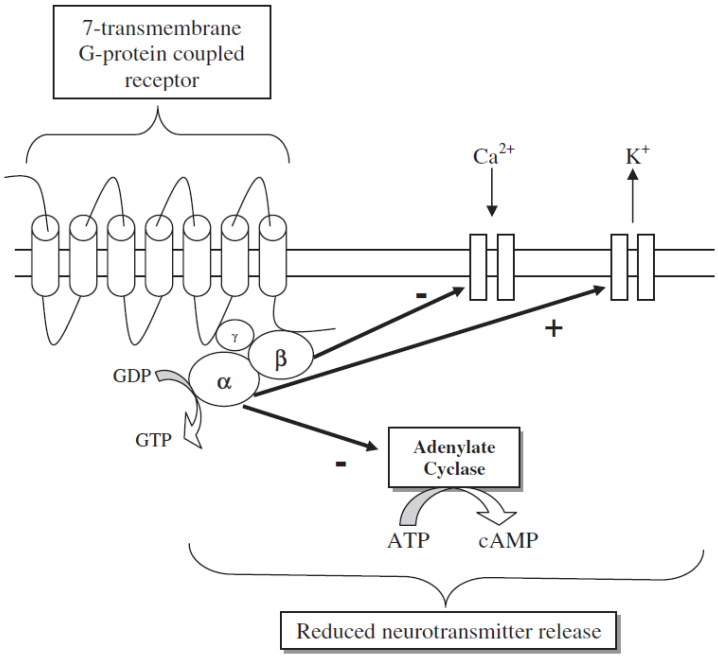


Figure 5: Cellular events following opioid agonist binding / receptor activation[17]

1.3. Total Synthesis of Morphine and Related Alkaloids

To this day, opiates remain the mainstay in the management of moderate to severe pain conditions.[23] Thus, the medical community requires a constant supply of morphine and other analgesics for pain control. The unnatural opiate derivatives of morphine are all produced by semisynthesis from the naturally occurring alkaloids, harvested primarily in Asia and Tasmania.[24] According to a 2018 report from the International Narcotics Control Board, the global production of morphine for medical use from opium poppy was estimated at 747 tons that year.[25]

There is currently no other practical source of opiates, whether by chemical synthesis or through fermentation, that would compete with the cost of isolation from the opium poppy. However, in the event of a natural or political emergency in the opium poppy-producing regions, alternative approaches would receive increased credibility. In order for its *de novo* synthesis to be competitive with isolation, morphine would need to be synthesised in 6-8 steps from inexpensive materials.[26]

Since the disclosure of Gates' seminal work on the first total synthesis of morphine in 1952, more than 30 total and formal syntheses of morphine and related alkaloids have been

published.[27] The unwavering interest from the synthetic community is a testament not only to the medical importance of morphine but also to the complex nature of its chemical structure. Morphine's pentacyclic structure comprises a reduced phenanthrene-like core, containing rings A, B and C, as well as piperidine ring D and dihydrofuran ring E (Figure 6). There are five contiguous stereocenters, one of which is a benzylic quaternary carbon centre (C-13). These structural features make the total synthesis of morphine a challenging undertaking.

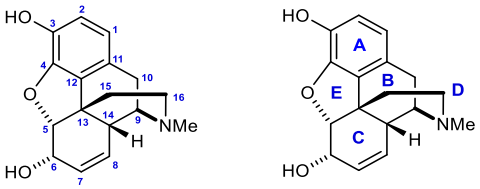
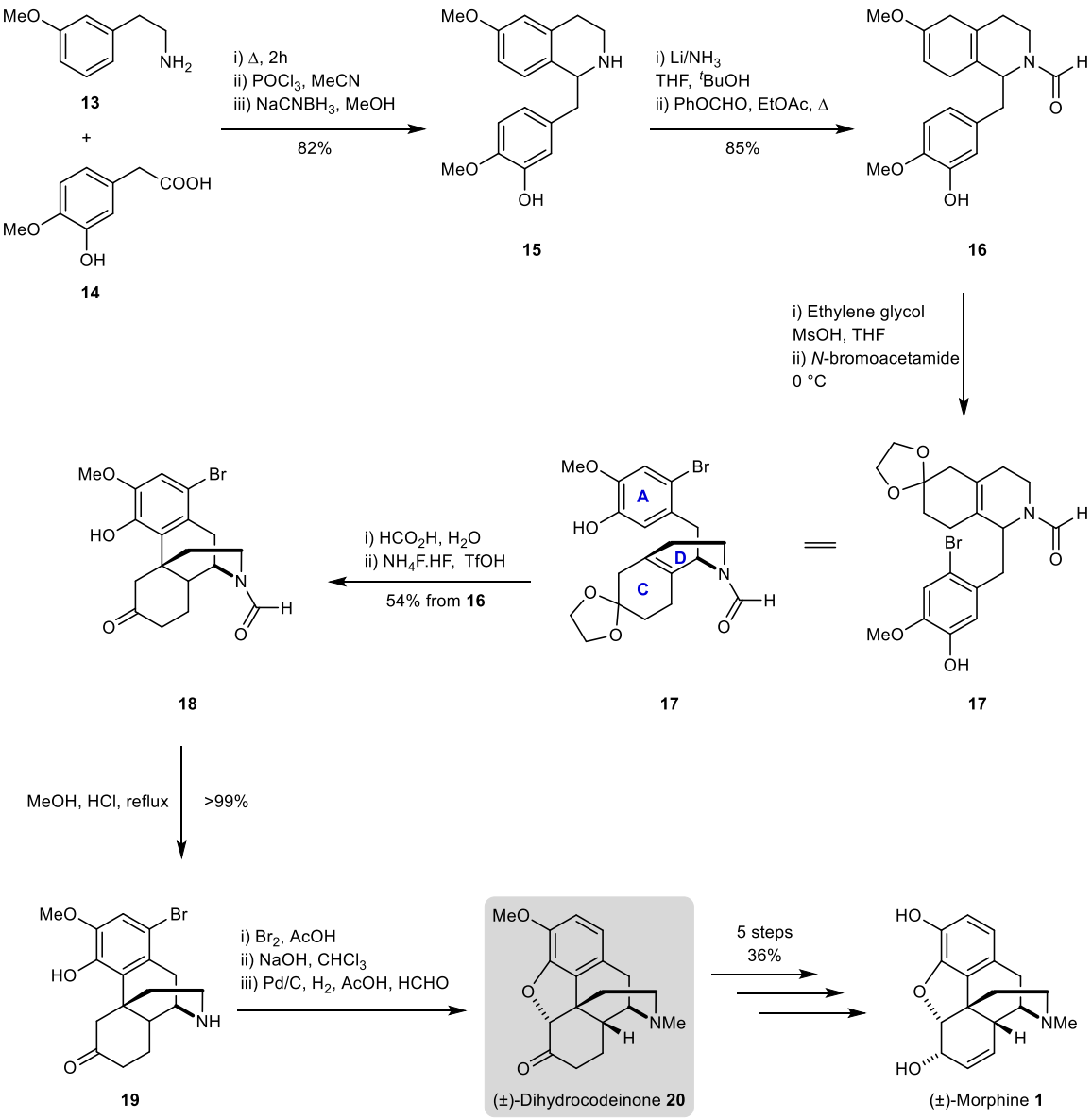


Figure 6: Morphine ring nomenclature and atom numbering

The most efficient synthesis of racemic morphine to date remains the procedure disclosed by Rice in 1980 (Scheme 1).[28] Rice utilised a biomimetic approach inspired by the biosynthesis of morphine in the opium poppy plant. Condensation of amine **13** and acid **14** followed by a Bischler-Napieralski reaction and subsequent imine reduction using sodium cyanoborohydride established rings A, C and D (compound **15**). Birch reduction and subsequent *N*-formylation with phenyl formate gave the methyl enol ether **16**. Ketalisation and bromination of the aromatic ring to protect the *para* position afforded intermediate **17** as the precursor for the key electrophilic cyclisation reaction originally described by Grewe.[29] This transformation was achieved *via* treatment of intermediate **17** with formic acid to release the *β,γ*-unsaturated ketone and subsequent exposure to $NH_4{\cdot}HF$ in neat triflic acid. This key step results in formation of the quaternary C-13 carbon centre (albeit in a non-stereoselective fashion) and completes morphine's phenanthrene-like core (compound **18**).



Scheme 1: Rice's total synthesis of (±)-dihydrocodeinone

Intermediate **18** was then deformylated to give amine **19** and the E-ring closure was achieved through *α*-bromination of the ketone followed by cyclisation with the phenol/ phenoxide. Finally, a one-pot reductive amination/aryl debromination furnished racemic dihydrocodeinone **20**. Attainment of dihydrocodeinone thus represented a formal synthesis of morphine since the conversion of this material to morphine had been previously described.[30,31] Worth noting is that the whole synthesis required isolation of only six intermediates, all obtained sufficiently pure for immediate further use. However, the final product was furnished as a racemic mixture of (±)-dihydrocodeinone **20**, which is less than ideal, since only (−)-morphine exhibits significant analgesic effect.

Although a number of stereoselective approaches to morphine and codeine have been reported, notably procedures disclosed by Trost, Hudlicky, Fukuyama and Gaunt,[32–35] all of them suffer from low overall yields (<7%), large number of steps and utilisation of expensive starting materials and reagents. Thus, a truly practical, industrially applicable and economically viable stereoselective total synthesis of morphine remains a lofty goal.

1.4. Industrial Synthesis of Opiate-Derived Pharmaceuticals

The industrial preparation of many opiate-derived pharmaceuticals, specifically those derived from morphine (**1**), thebaine (**3**) and oripavine (**4**) is presented with two major challenges: introduction of the C-14 hydroxyl group and the exchange of the *N*-methyl group for another alkyl substituent (Figure 7).[36]

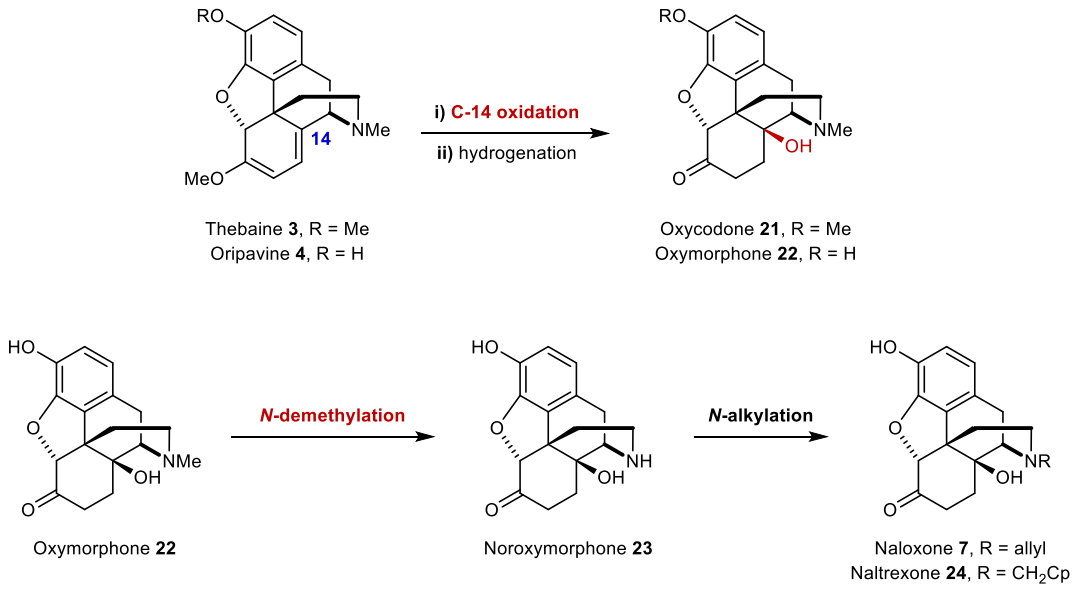


Figure 7: Two major challenges in industrial synthetic transformations of natural opiate alkaloids

The C-14 oxidation is most easily accomplished by oxidation of either thebaine (**3**) or oripavine (**4**) due to the presence of the diene moiety in the C-ring of these compounds. For this reason, thebaine (**3**) and oripavine (**4**) are the preferred starting materials in the industrial production of C-14 hydroxylated derivatives (e.g. oxycodone (**21**), naloxone (**7**)) despite the significantly lower content of these natural alkaloids in the opium poppy plant, compared to morphine (**1**). Approaches to this transformation include addition of singlet oxygen to

thebaine (**3**) and subsequent reduction of the resulting endoperoxide **25** or treatment of thebaine (**3**) with formic acid and hydrogen peroxide (Figure 8).[37–39]

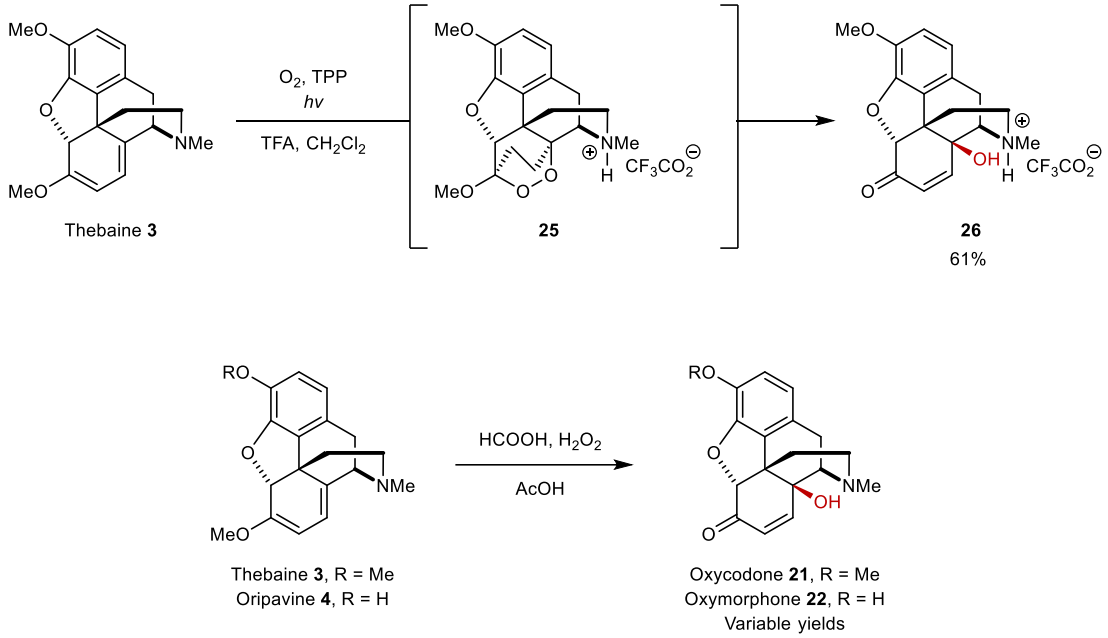


Figure 8: Approaches to C-14 oxidation via thebaine and oripavine

The second challenge, the *N*-demethylation, represents a crucial step in the semi-synthesis of medicinally important opiates. The replacement of the naturally occurring *N*-methyl moiety with other alkyl substituents is desired, since the biological activity of drugs derived from opiate alkaloids is very sensitive to the nature of nitrogen substituents.[40] This transformation has been approached using a variety of different methods such as using demethylation with hard electrophiles, dialkyl azodicarboxylates, *N*-oxide intermediates and palladium-mediated protocols.[41] The secondary amine subsequently serves as an important intermediate in the synthesis of pharmaceutical agents such as buprenorphine (**6**), naloxone (**7**) and naltrexone (**24**).[42–45]

N-Demethylation of morphine derivatives with cyanogen bromide (von Braun demethylation) and various alkyl chloroformates are two of the earliest approaches towards this transformation, with the latter still being widely used today on industrial scale (Figure 9).[46–49] Both approaches require multiple steps and often harsh conditions to effect the demethylation.

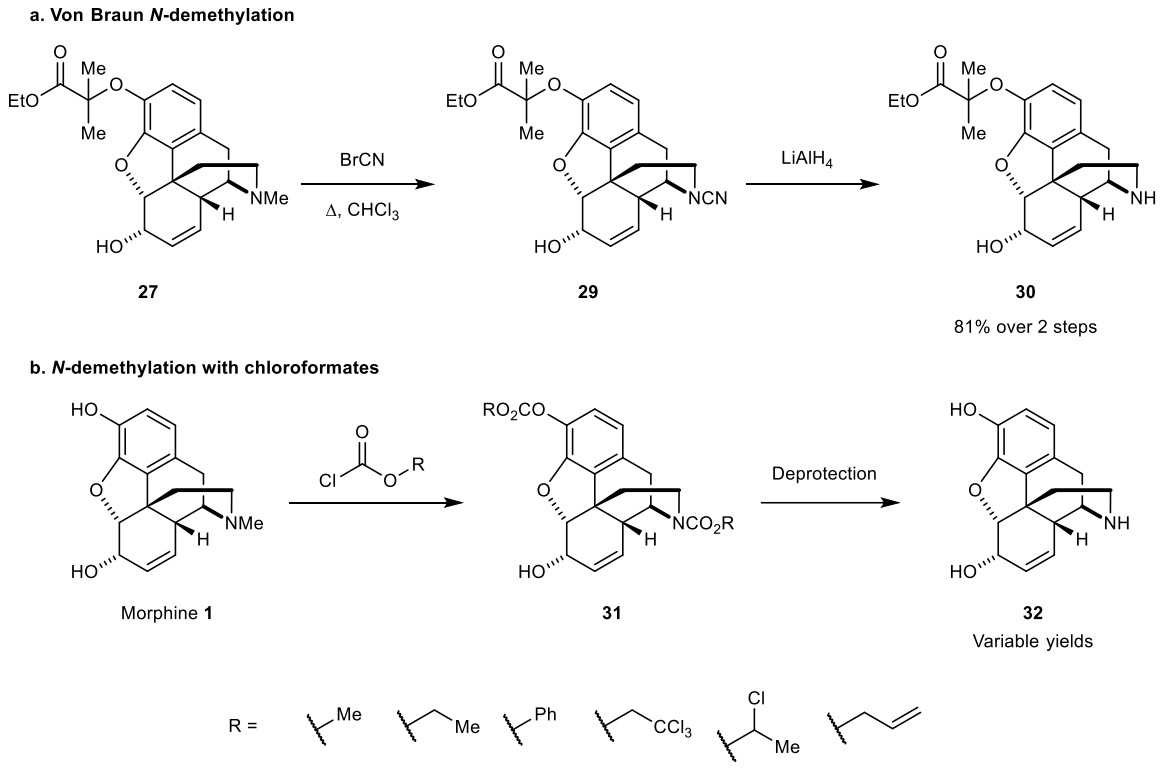


Figure 9: Approaches to N-demethylation of opiate alkaloids utilising hard electrophiles

More recently, photochemical *N*-demethylation of various opiates under visible light irradiation in the presence of photosensitisers has been reported by Scammells, albeit in low yields.[50] The same group has also produced a modified Polonovski protocol wherein over two steps the tertiary amine is oxidised to the corresponding *N*-oxide followed by an iron-mediated reduction/demethylation reaction to produce the desired secondary amine.[51] A palladium-mediated approach was developed by Hudlicky for the *N*-demethylation of hydrocodone, which has been applied on industrial scale.[52,53]

In summary, the challenges associated with conversion of opiates such as morphine (**1**), thebaine (**3**) and oripavine (**4**) into valuable pharmaceutical intermediates have been adequately addressed thus far. However, there is a heavy reliance on the use of thebaine (**3**) and oripavine (**4**) in the preparation of 14-hydroxylated derivatives due to the presence of the diene moiety in these alkaloids, which facilitates the otherwise challenging C-14 oxidation. As previously discussed, thebaine (**3**) and oripavine (**4**) are less abundant alkaloid components of the opium poppy compared to morphine (**1**) and are consequently more expensive to use as starting materials. Therefore, development of process routes in which morphine (**1**) is utilised as a starting material for the production of 14-hydroxylated opiate derivatives such as noroxymorphone (**23**) is highly desirable. In fact, industry experts speculate that

production of noroxymorphone (**23**) from morphine (**1**) would be approximately 60% less expensive compared to production from thebaine (**3**) and 30% less expensive compared to production from oripavine (**4**) (Figure 10, A. Saxena, Rusan Pharma Ltd., personal correspondence, 2019).

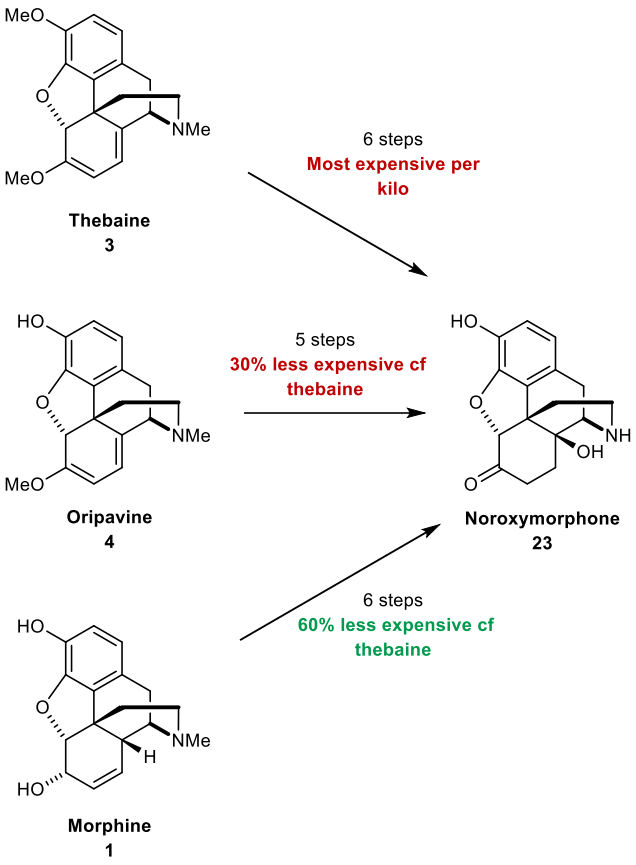


Figure 10: Comparison of cost of using the three major opium alkaloids as starting materials for production of noroxymorphone

The current state-of-the-art process for the industrial-scale chemical transformation of morphine to noroxymorphone is demonstrated in patent EP 3 024 835 B1 “Novel Synthesis of Noroxymorphone from Morphine”.[54] The route in question comprises six steps and proceeds in 64% overall yield (Figure 11).

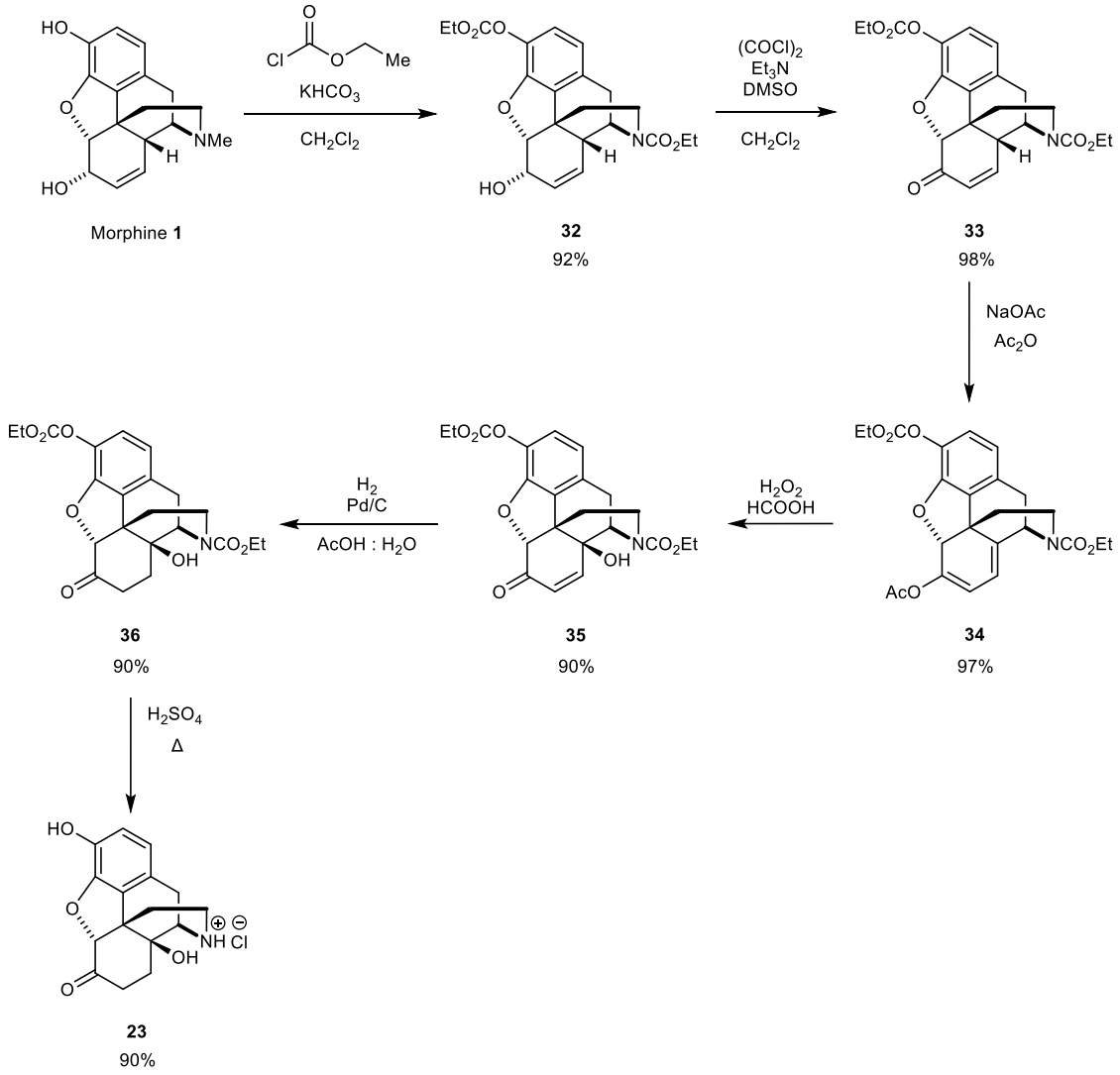


Figure 11: State-of-the-art industrial process for the conversion of morphine (1) into noroxymorphone (23)

The first step involves *N*-demethylation of the tertiary amine with subsequent protection of the newly formed secondary amine and phenol moieties as a carbamate and a carbonate, respectively to give species **32**. The secondary alcohol in the 6-position is then oxidised under Swern conditions with oxalyl chloride, triethylamine and DMSO at −78 °C. Ketone **33** is subsequently converted into the dienol acetate **34** by heating in acetic anhydride with sodium acetate acting as a base. Peroxyacid oxidation of **34** achieves the challenging formation of the C-14 hydroxyl group centre, along with the formation of enone within the C ring. The penultimate step of the process involves catalytic reduction of **35** with Pd/C and hydrogen gas to afford **36**, which is finally hydrolysed under harsh conditions with concentrated sulfuric acid to give the final product noroxymorphone (**23**), which is precipitated directly from the reaction mixture and purified by recrystallisation.

2. Results and Discussion

2.1. Aims and Objectives

Despite the appealing brevity and high overall yield of the current state-of-the-art process for the industrial-scale conversion of morphine to noroxymorphone, certain drawbacks are evident.

Firstly, and perhaps most importantly, Swern oxidation of the secondary alcohol **32** is not well suited for industrial scale application: the requirement of maintaining the temperature at −78 °C in order to avoid side-product formation is impractical within an industrial setting. Additionally, oxalyl chloride is acutely toxic by inhalation which makes its use on industrial scale undesirable.

Secondly, the reduction of enone **35** also stands out as a step poorly suited for industrial application. While catalytic heterogenous reductions with pyrophoric catalysts such as Pd/C and hydrogen gas can be performed on industrial scale, an alternative procedure which does not require the use of a pyrophoric catalyst and a flammable gas would be highly desirable for the process in question.

The present investigation therefore aimed to address the abovementioned shortcomings and improve the route for the conversion of morphine into noroxymorphone by:

- Identifying alternative conditions for the oxidation of secondary alcohol **32**
- Identifying an alternative method of reducing enone **35**

2.2. Process Development – Alternative Oxidation Conditions

As described above, oxidation of the secondary alcohol **32** is performed using the Swern oxidation protocol which is a modification of an earlier Pfitzner-Moffatt reaction.[55] Both reactions effect oxidation of alcohols through the activation of DMSO; oxalyl chloride acts as the activating agent in the Swern protocol, while the original Pfitzner-Moffatt protocol employs 1,3-dicyclohexylcarbodiimide (DCC). Alternative DMSO-activating agents such as sulfur trioxide pyridine complex (Parikh-Doering), phosphorus pentoxide (Albright-Onodera) and trifluoracetic acid anhydride, among others, are well known.[56] Thus, it was decided that

a good starting point for the present investigation would be the identification of an alternative activating agent that would replace the highly toxic oxalyl chloride and would enable the reaction to be performed at a less extreme temperature.

Among the protocols for activated DMSO-mediated oxidations the relatively underused Albright-Goldman oxidation stands out as particularly attractive from an industrial point of view. Reported in 1967, the Albright-Goldman protocol employs acetic anhydride as the activating agent and can be performed at room temperature, resulting in a particularly mild oxidation process.[57] Despite only a small number of literature examples showing the utility of the Albright-Goldman oxidation in complex natural product substrates, the protocol has been applied to a morphinan scaffold by Broka, effecting oxidation of the secondary alcohol **37** in good yield (Figure 12).[58] Thus, Albright-Goldman oxidation appeared as a good potential alternative to the Swern oxidation in the synthetic route to noroxymorphone.

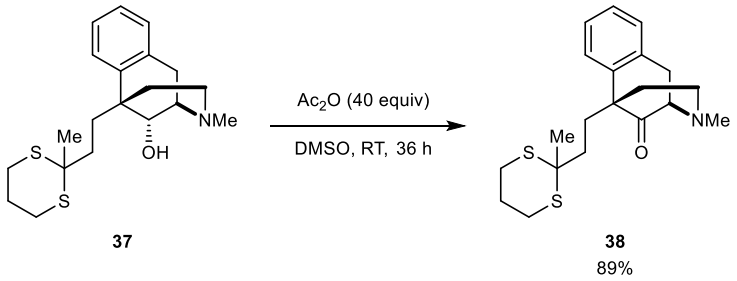


Figure 12: Literature precedent for Albright-Goldman oxidation on a morphinan scaffold

To test the applicability of the Albright-Goldman oxidation, secondary alcohol **32** was accessed by *N*-demethylation/protection of morphine with ethyl chloroformate using literature conditions.[54] The reaction proceeded cleanly, affording **32** in 97% yield which could be taken to the next step without further purification (Figure 13).

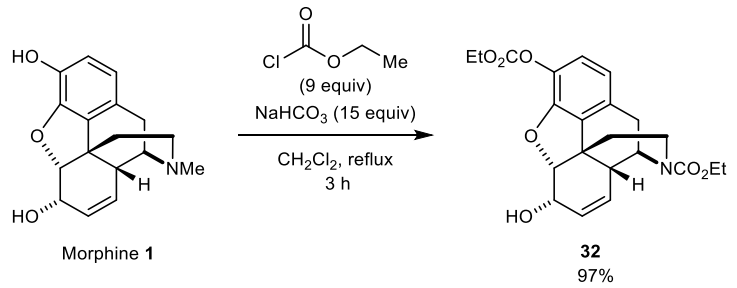


Figure 13: N-demethylation / protection of morphine with ethyl chloroformate

Secondary alcohol **32** was subjected to Albright-Goldman conditions, stirring the substrate in 60 equivalents of acetic anhydride and 30 equivalents of DMSO at room

temperature (Figure 14). Pleasingly, the reaction went to completion in 21 hours and furnished the desired ketone **33** in quantitative yield after an aqueous work-up without the need for further purification.

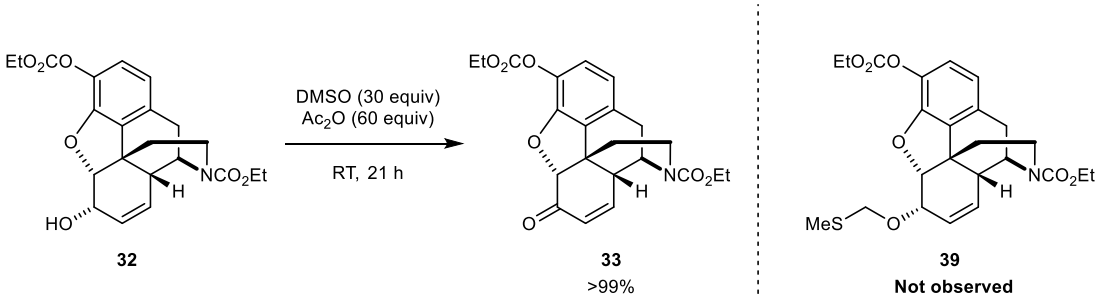


Figure 14: Successful Albright-Goldman oxidation

Importantly, no formation of the undesired methyl thiomethyl ether **39**, a common side product in Pfitzner-Moffat type oxidations, was observed.

It was soon realised that the Albright-Goldman conditions for the oxidation of alcohol **32** might be compatible with the conditions in the subsequent diene **34** formation step. In the patent EP 3 024 835 B1, this step involves heating enone **33** in acetic anhydride with sodium acetate as a base. Because the Albright-Goldman oxidation protocol already utilises a large excess of acetic anhydride and generates acetate anions during the course of the reaction, a possibility was open for combining the two steps in a one-pot process. This would be highly beneficial from a process point of view as it would remove a work-up step and increase the efficiency of the overall process.

Pleasingly, it was found that performing the reaction in a sequential manner, wherein after initial conversion of alcohol **32** to enone **33** (as monitored by TLC) sodium acetate was added to the reaction mixture and heated to 90 °C for 2 hours, produced the desired diene **34** in a 95% yield after aqueous work-up (Figure 15). Importantly, the product was furnished with high purity, allowing it to be taken forward without chromatographic purification, albeit in the form of a viscous residue.

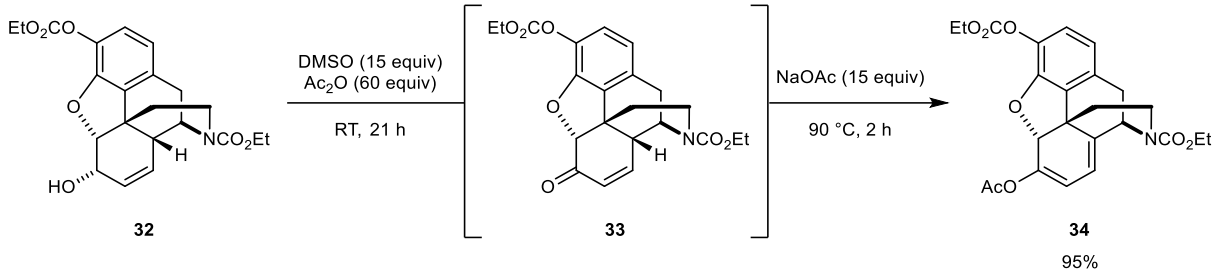


Figure 15: Initial sequential approach to one-pot Albright-Goldman oxidation / diene formation

When sodium acetate was added to the reaction mixture at the start of the reaction and heated to 40 °C for 24 hours, formation of the desired diene **34** was not observed (Figure 16). Instead, acetylation of the secondary alcohol took place to give derivative **40**.

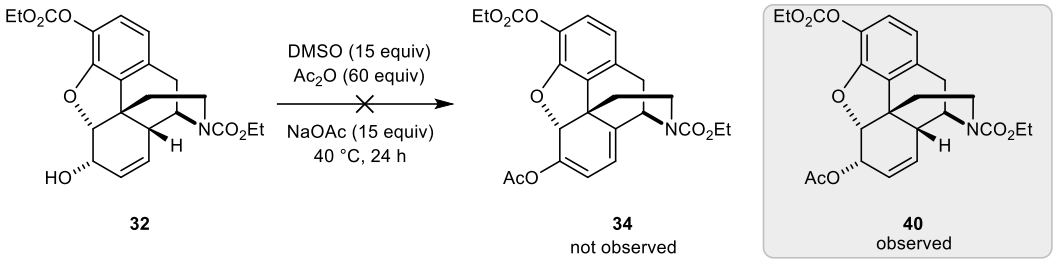


Figure 16: Detrimental effect of base on the Albright-Goldman oxidation

It was also found that the reaction time for the Albright-Goldman oxidation step could be reduced considerably by performing the reaction at elevated temperature. Heating the reaction to 70 °C allowed for complete conversion of alcohol **32** to enone **33** in only 1.5 hours (Figure 17). This reduction in reaction time is beneficial, because from an industrial process standpoint prolonged reaction times are undesirable. Importantly, the reaction profile remained unchanged compared to the room temperature protocol, with no formation of side products being observed.

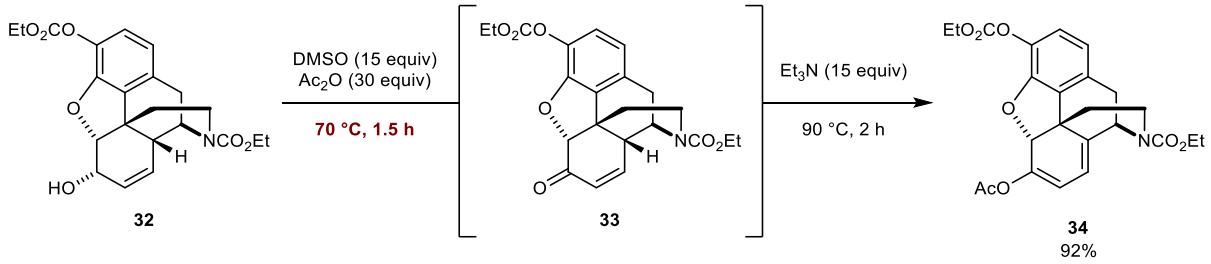


Figure 17: Modified one-pot Albright-Goldman oxidation / diene formation procedure

Further minor improvements of the process included reduction in the number of equivalents of both acetic anhydride and DMSO required in the oxidation step, effectively

increasing the concentration of the reaction, as well as substituting sodium acetate for triethylamine, a cheaper base, in the diene forming step (Figure 17). Scalability of the one-pot process was also demonstrated by performing the reaction on a 12 mmol scale, furnishing the desired product **34** in 92% yield.

Attempts at performing the Albright-Goldman oxidation directly on morphine (**1**) prior to demethylation/protection did not yield the desired oxidation product **41** (Figure 18). Instead, a mixture of mono- and bis-acetylated derivatives **42** and **43** was observed. Presumably this pattern of reactivity is due to the basic nature of the tertiary amine centre of morphine and the reaction outcome mirrors that of Albright-Goldman oxidation on the protected species **32** where base (sodium acetate) is added to the reaction mixture (Figure 16).

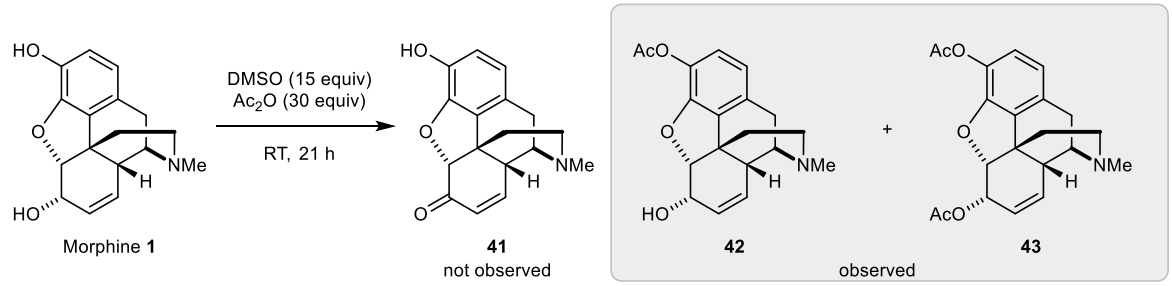
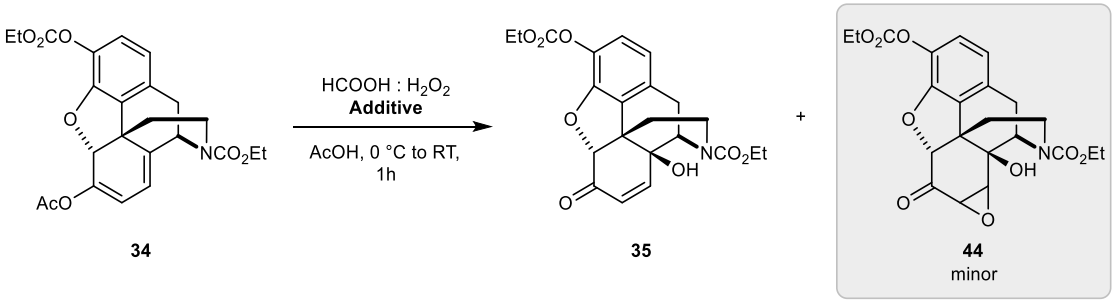


Figure 18: Unsuccessful Albright-Goldman oxidation on morphine

With easy access to large quantities of the intermediate diene **34** in hand, efforts were made to reproduce literature conditions for the C-14 oxidation.[54] Oxidation is effected by performic acid which is pre-formed by stirring formic acid in an aqueous solution (50%) of hydrogen peroxide.

Initial attempts to oxidise **34** using previously reported process conditions yielded the desired product **35** in a moderate isolated yield of 43% (Table 1, entry 1). The epoxidized side product **44**, which was detected by HRMS and ^{1}H NMR spectroscopy but not isolated, was also observed.

Table 1: C-14 oxidation optimisation



Entry[a]	Equivalents of H_2O_2[b]	Additive (equiv)	Isolated Yield of 35
1	22.0	none	43%
2	10.0	Oxalic acid (0.5)	65%
3	5.0	Oxalic acid (0.5)	89%
4	1.4	Oxalic acid (0.5)	63%
5	5.0	none	87%
6[c]	5.0	none	96%

[a]Reactions performed on 0.22 mmol scale with a 5:1 v:v ratio of HCOOH to H_2O_2. [b]Hydrogen peroxide in the form of 50% aqueous solution. [c]Reaction performed on 3.29 mmol scale

It was evident that when too large an excess of hydrogen peroxide was used to pre-form the peroxy species was detrimental to the yield, possibly due to the over-oxidation of the product. Additionally, reports in the literature suggested that oxalic acid can be used in substoichiometric quantities to prevent formation of the undesired epoxide derivative **44**.[59] Thus, lowering the number of equivalents of hydrogen peroxide to 5.0 together with the addition of 0.5 equivalents of oxalic acid to the reaction mixture improved the yield of the desired product to 89% (Table 1, entry 3) and diminished formation of side product **44** to trace quantities. Lowering the amount of H_2O_2 further to 1.4 equivalents resulted in diminished yield (Table 1, entry 4). A control reaction was performed without addition of oxalic acid which produced an equally good result (Table 1, entry 5), deeming its addition unnecessary. Scaling-up the reaction further improved the yield (Table 1, entry 6). Thus, the final reaction conditions are shown below (Figure 19).

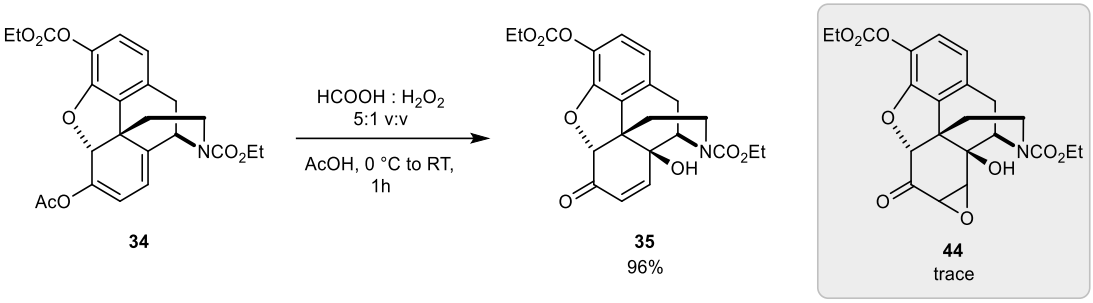


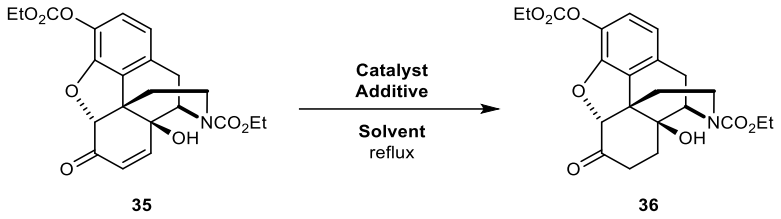
Figure 19: Optimised reaction conditions for C-14 oxidation

2.3. Process Development – Alternative Hydrogenation Conditions

With sufficient quantities of enone **35** in hand, alternative conditions for the reduction step could be investigated. As previously discussed, the state-of-the-art approach to industrial-scale reduction of **35** is through catalytic hydrogenation with Pd/C under hydrogen atmosphere.[54] If the use of hydrogen atmosphere could be avoided, the safety profile of the reaction would be greatly improved.

An alternative approach could involve generation of controlled quantities of hydrogen gas in situ through addition of formic acid to the reaction mixture at elevated temperature. Thus, handling large quantities of hydrogen gas could be avoided. To this end, a range of conditions utilising formic acid as a source of hydrogen gas were investigated and are summarised in Table 2 below.

Table 2: Transfer hydrogenation optimisation



Entry[a]	Catalyst (mol%)	Additive (equiv)	Solvent	Reaction Time (h)	Conversion of 35[b]
1	Pd/C (10 mol%)	HCOOH (10)	EtOH	48	41
2	Pd/C (10 mol%)	HCOOH (20)	EtOH	48	61
3	Pd/C (10 mol%)	HCOOH (30)	EtOH	48	99
4	Pd/C (10 mol%)	HCOOH (30)	EtOH	16	50
5	Pd/C (10 mol%)	HCOOH (30)	IPA	16	87
6[c]	Pd/C (10 mol%)	HCOOH (neat)	neat	16	ND
7	$Pd(OH)_2/C$ (10 mol%)	HCOOH (30)	IPA	16	79
8[d]	Pd/C (10 mol%)	HCOOH (30) and Et_3N (5)	IPA	16	99
9[d]	Pd/C (2 mol%)	HCOOH (30) and Et_3N (5)	IPA	16	99

[a]Reactions performed on 0.06 mmol scale. [b]Determined by ^1H NMR analysis of the crude product. [c]Concentration of 0.3 M in formic acid. [d]Triethylamine and formic acid added separately to the reaction mixture without pre-formation

Full conversion of starting material **35** could be achieved using 10 mol% of Pd/C and 30 equivalents of formic acid in refluxing ethanol over 48 hours (Table 2, entry 3). Lesser quantities of formic acid resulted in incomplete conversion (Table 2, entries 1 and 2)

Clearly, neither the time frame nor the catalyst loading were satisfactory. A large excess of formic acid could be tolerated due to its low cost and availability, but shorter reaction time and lower catalyst loadings were necessary to maximise the efficiency of the process. 50% conversion could be achieved in 16 h (Table 2, entry 4) and therefore this reaction time was subsequently used to screen further conditions. Switching the solvent from ethanol to IPA increased the conversion of starting material **35** to 87% (Table 2, entry 5). Performing reaction in neat formic acid, conversely, resulted in a complex inseparable mixture (Table 2, entry 6). An alternative heterogeneous palladium catalyst $Pd(OH)_2$ (Pearlman's catalyst) was also tested, but only resulted in 79% conversion of starting material (Table 2, entry 7).

A breakthrough was made with addition of triethylamine to the reaction mixture, which presumably reacts with formic acid to form triethylammonium formate *in situ*. Triethylammonium formate is known to be effective at facilitating Pd-catalysed reductions of α, β- unsaturated carbonyl compounds.[60] Thus, adding 5 equivalents of triethylamine to the reaction mixture before heating resulted in full conversion of **35** (Table 2, entry 8). Pleasingly, the catalyst loading could be reduced to 2 mol% while maintaining the full conversion of starting material (Table 2, entry 9). Upon scaling-up, formation of mono deprotected side-product **45** was observed (Figure 20). Performing the reaction on 1.17 mmol scale yielded the desired product **36** in 62% yield as well as **45** in 13% yield after chromatographic purification.

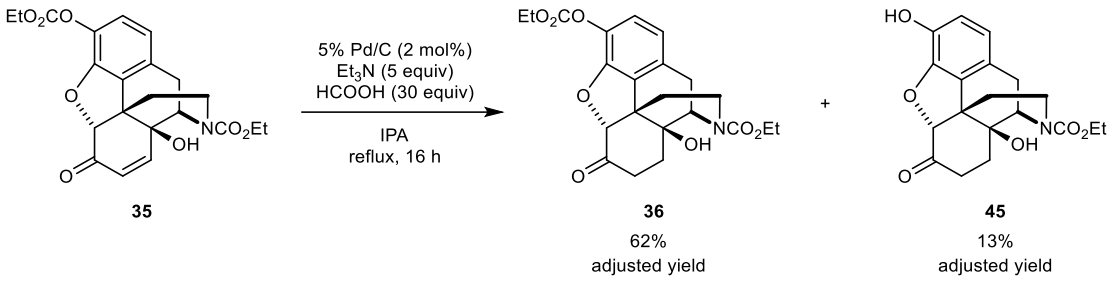


Figure 20: Formation of mono-deprotected side product during transfer hydrogenation upon scale-up

In this instance, the formation of side product **45** is not detrimental since the following step involves the acid-catalysed hydrolysis of the carbonate and carbamate moieties in **36** to furnish noroxymorphone (**23**). Therefore, the crude mixture containing both species **36** and **45** could be used without purification to yield the single desired product noroxymorphone.

Since the final step in the synthesis of noroxymorphone from morphine involves a simple acid hydrolysis to achieve global deprotection, and has been described in the patent

literature, this step was not further investigated in the scope of this project. Thus, synthesis of **36** represented a formal synthesis of noroxymorphone.

2.4. One-pot Albright-Goldman Oxidation/Diene Formation Scope

To further explore the utility of the newly developed one-pot procedure of the Albright-Goldman oxidation/diene formation various functionalities were installed on the secondary alcohol-bearing intermediate and subjected to the reaction conditions. In the first instance, various phenol protecting groups were explored. Benzyl, *para*-methoxybenzyl and allyl protected phenols were all well-tolerated and provided the corresponding products **46-48** in satisfactory yields after chromatographic purification (Figure 21).

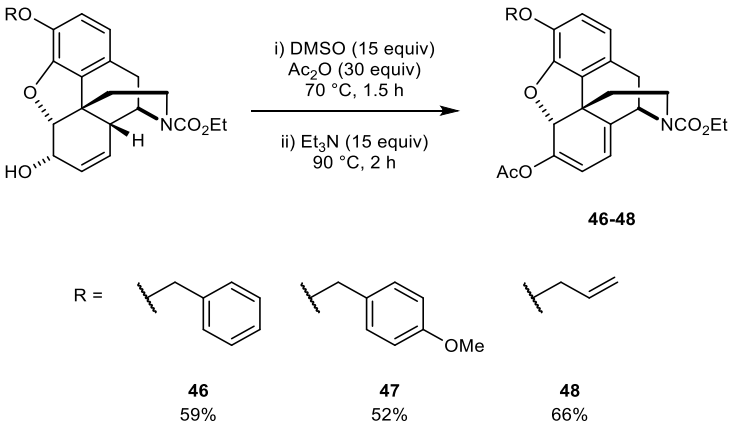


Figure 21: Successful examples of AG oxidation / diene formation with variable substitution at the 3-postion

However, the reaction conditions were found to be too harsh when the phenol moiety was protected as a silyl ether. Subjecting the 3-OTBDMS derivative **49** to the protocol yielded primarily the undesired bis-acetylated derivative **52** (Figure 22). HRMS data suggests that the intermediate enone **50** is formed without the loss of TBDMS group, therefore cleavage of the silyl ether likely occurs at elevated temperature in the second step of the reaction, followed by the attack of the liberated phenol on acetic anhydride to give **52**.

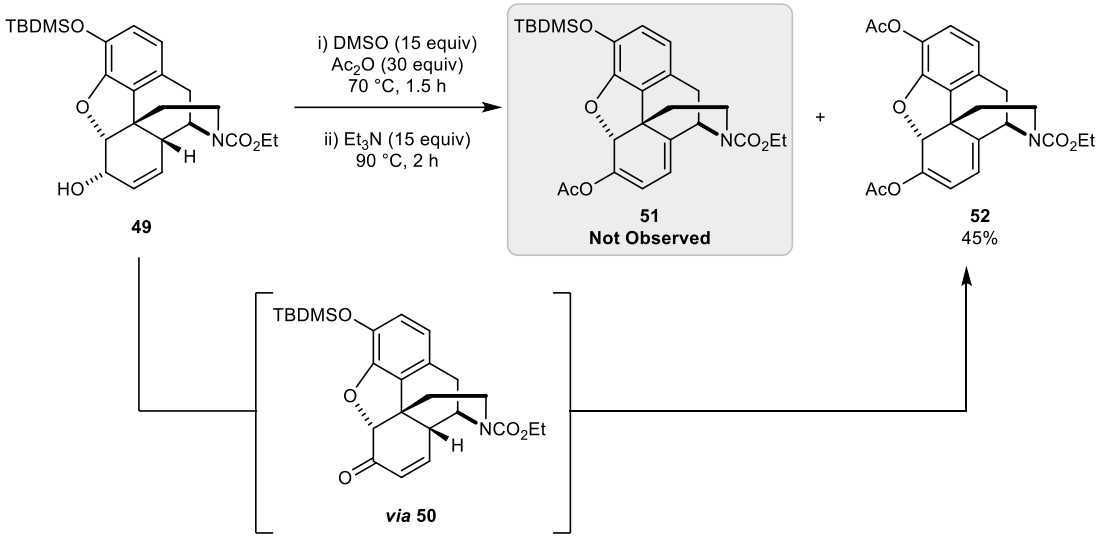


Figure 22: Undesired silyl ether deprotection under AG oxidation / diene formation conditions

Installing a more sterically demanding TIPS moiety on the starting phenol **53** yielded the desired product **55** in low yield, with the majority of the product still residing as the bis-acetylated derivative **56** (Figure 23).

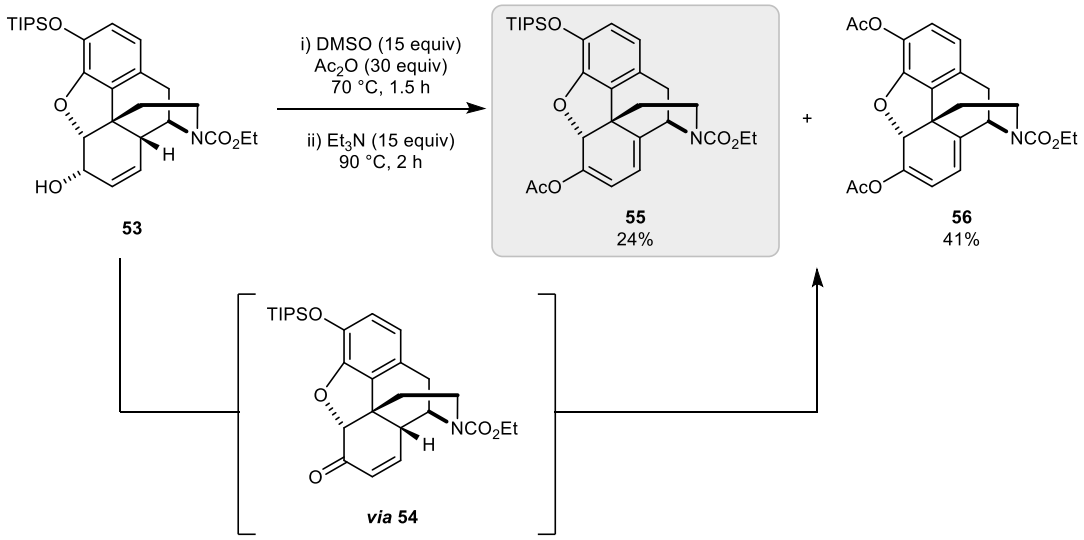


Figure 23: Successful sequence with a TIPS silyl ether-bearing substrate

Next, substitution on the secondary amine was explored. Since previous unsuccessful attempts at performing the Albright-Goldman oxidation directly on morphine (Figure 18) suggested that the presence of Brønsted-basic free amine centre was detrimental to the reaction outcome, alternative functionalities that reduce the basicity of the nitrogen centre were of interest.

In particular, cyanamide **57** was investigated. Cyanamide intermediates are used on industrial scale for the demethylation of natural opiates such as morphine, thebaine and oripavine, therefore these represent an industrially-relevant group of substrates to which the one-pot oxidation/diene formation procedure could be applied.[61] Subjecting cyanamide **57** to the reaction conditions yielded the desired derivative **58** in 26% yield after chromatographic purification (Figure 24). It is of note that no side products were observed in the reaction and the low yield is likely a result of product decomposition on silica during chromatography.

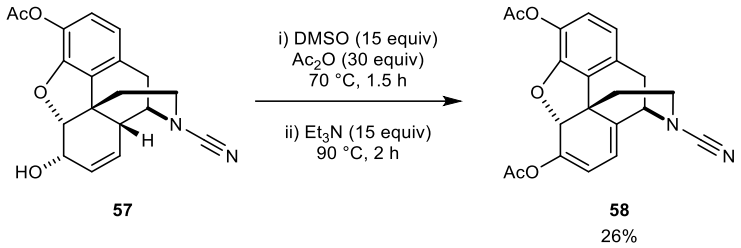


Figure 24: AG oxidation / diene formation on a cyanamide substrate

Finally, it was established that other acid anhydrides could also be used to perform the oxidation/diene formation sequence. Propionic anhydride was successfully employed under the reaction conditions to give the desired propionyl dienol **59** in good yield after chromatographic purification (Figure 25). However, the low cost and availability of acetic anhydride still make it a preferred reactant in this system.

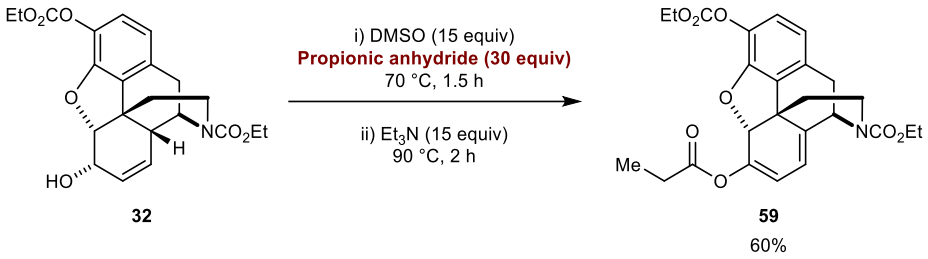


Figure 25: AG oxidation / diene formation with propionic anhydride

2.5. Conclusions and Future Work

In conclusion, improvements have been made to the state-of-the-art process for the conversion of morphine (**1**) into noroxymorphone (**23**). The Swern oxidation has been replaced by a more chemically benign and industrially applicable Albright-Goldman oxidation, which allows the reaction to be performed at room temperature or elevated temperatures

without the formation of undesirable side products. Furthermore, the overall process was made more concise by combining the oxidation and diene formation steps, therefore removing a work-up step in-between and reducing the number of required manipulations.

The modified one-pot procedure has been shown to tolerate a range of protecting groups on the phenol moiety including an acetyl ester, ethylcarbonate, benzyl, 3-methoxybenzyl and allyl functionalities. Phenolic silyl ethers were found to be labile under reaction conditions. Cyanamide functionality, often used in industrial preparations of opiate derivatives, was also shown to be able to withstand the reaction conditions. Finally, propionic anhydride was shown to be effective in facilitating the oxidation/diene formation in place of acetic anhydride.

Alternative hydrogenation conditions were also developed with the view to eliminating the need for handling large quantities of hydrogen gas by employing triethylammonium formate formed *in situ* as a source of hydrogen. These conditions were found to give a crude mixture of the desired product together with a mono-deprotected side product, which could be taken directly to the next step and reacted convergently to give the desired final product noroxymorphone (**23**).

Future work will investigate the possibility of direct C-14 hydroxylation without the introduction of the diene moiety. For example, C-14 oxidation could be performed on enone **33** to yield **35** (Figure 26).

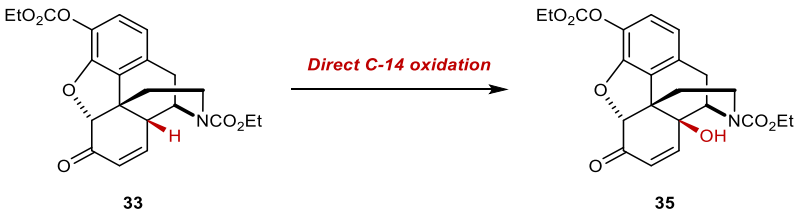


Figure 26: Direct C-14 oxidation via C-H activation

Michels has reported a direct chemical C-14 hydroxylation of codeinone (**60**) under ambient conditions using catalytic quantities of manganese sulfate and sodium thiosulfate in a phosphate buffer (Figure 27).[62] These conditions could be applied to enone **33**.

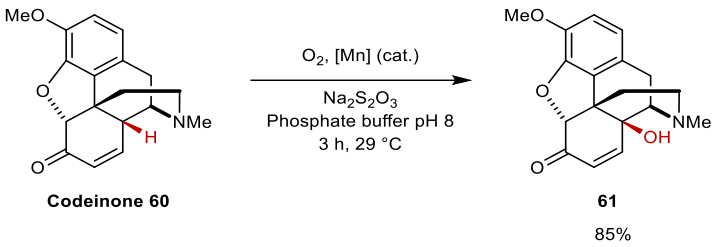


Figure 27: Direct C-14 hydroxylation of codeinone

Direct C-14 hydroxylation would further simplify the route for conversion of morphine (**1**) to noroxymorphone (**23**) thus improving process economics.

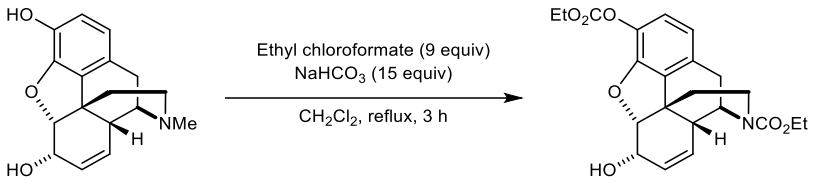
3. Experimental

3.1. General Information

All reactions were carried out under air unless stated otherwise. All commercially available reagents were used as received unless otherwise stated. Pet. ether refers to Sigma-Aldrich product 24587 (petroleum ether boiling point 40-60 °C) or VWR product 23835.328 (petroleum spirit 40-60 °C). Thin layer chromatography (TLC) was performed on Merck DFAlufolien 60F254 0.2 mm precoated plates. Compounds were visualised by exposure to UV light or by dipping the plates into solutions of potassium permanganate or vanillin followed by gentle heating. Flash column chromatography was carried out using silica gel (Fisher Scientific 60 Å particle size 35–70 micron or Fluorochem 60 Å particle size 40–63 micron). Automated column chromatography was conducted using PuriFlash instrument from Interchim. Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. The solvent of recrystallization is reported in parentheses. Infrared (IR) spectra were recorded on a Bruker platinum alpha FTIR spectrometer on the neat compound using the attenuated total refraction technique. NMR spectra were acquired on a Bruker Ascend 400 spectrometer. ^{1}H and ^{13}C NMR spectra were referenced to external tetramethylsilane via the residual protonated solvent (^{1}H) or the solvent itself (^{13}C). All chemical shifts are reported in parts per million (ppm). For $CDCl_3$, the shifts are referenced to 7.26 ppm for ^{1}H NMR spectroscopy and 77.16 ppm for ^{13}C NMR spectroscopy. Abbreviations used in the description of resonances are: s (singlet), d (doublet), t (triplet), q (quartet), quint (quintet), br (broad) and m (multiplet). Coupling constants (*J*) are quoted to the nearest 0.1 Hz. ^{13}C NMR assignments were made using the DEPT sequence with secondary pulses at 90° and 135°. High–resolution mass spectra were recorded using electrospray ionization (ESI).

3.2. Preparation of Intermediates from Morphine

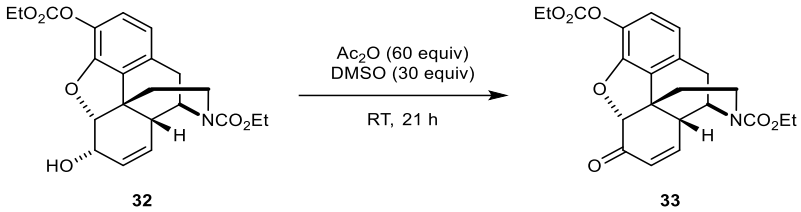
Ethyl (4*R*,4a*R*,7*S*,7a*R*,12b*S*)-9-[(ethoxycarbonyl)oxy]-7-hydroxy-1,2,4,4a,7,7a-hexahydro-3*H*-4,12-methanobenzofuro[3,2-*e*]isoquinoline-3-carboxylate (32)



Morphine **1** **32**

To a stirred suspension of morphine (2.00 g, 7.01 mmol) and sodium bicarbonate (8.82 g, 105 mmol) in CH_2Cl_2 (20 mL) at room temperature was added ethyl chloroformate (6.00 mL, 63.0 mmol) in one portion then the resulting mixture was heated at reflux for 3 h. The reaction mixture was allowed to cool down to room temperature and filtered, washing with CH_2Cl_2 (10 mL). The filtrate was collected and concentrated *in vacuo* to give **32** as a white solid (2.82 g, 97%). R_f = 0.37 (50% EtOAc/Pet. ether); m.p. 152-153 °C (Et_2O); $[\alpha]_D^{20.1}$ −244 (*c* 1.00, $CDCl_3$); IR (ATR) 3515 (OH), 2980, 2861, 1747 (C=O), 1688 (C=O) cm^{-1} ; ^1H NMR (400 MHz, $CDCl_3$) δ 6.84 (1H, d, *J* = 8.3 Hz, Ar**H**), 6.60 (1H, d, *J* = 8.3 Hz, Ar**H**), 5.79 (1H, d, *J* = 8.9 Hz, HOCHC**H**CH), 5.32-5.25 (1H, d, *J* = 8.9 Hz, HOCHCHC**H**), 5.00-4.78 (2H, m, ArOC**H** and C**H**N), 4.38-4.26 (2H, m, $OCO_2C\mathbf{H}_2$), 4.24-4.01 (4H, m, $NCO_2C\mathbf{H}_2$ and C**H**OH and $C\mathbf{H}_aH_bN$), 3.47-3.39 (1H, m, CHO**H**), 3.03-2.93 (1H, m, $CH_a\mathbf{H}_bN$), 2.87 (1H, dd, *J* = 18.8, 6.4 Hz, $ArC\mathbf{H}_aH_b$), 2.74 (1H, d, *J* = 18.8 Hz, $ArCH_a\mathbf{H}_b$), 2.60-2.53 (1H, m, C**H**CHN), 1.99-1.90 (2H, m, $C\mathbf{H}_2CH_2N$), 1.37 (3H, t, *J* = 7.2 Hz, $OCO_2CH_2C\mathbf{H}_3$), 1.34-1.23 (3H, m, $NCO_2CH_2C\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.4 (C), 153.0 (C), 148.7 (C), 135.0 (CH), 132.7 (C), 131.9 (C), 131.6 (C), 126.5 (CH), 121.5 (CH), 120.3 (CH), 92.3 (CH), 65.6 (CH), 65.5 (CH_2), 61.7 (CH_2), 50.1 (CH), 43.1 (C), 39.3 (CH), 37.4 (CH_2), 34.9 (CH_2), 29.7 (CH_2), 14.7 (CH_3), 14.2 (CH_3); HRMS (ESI) exact mass calculated for $[C_{22}H_{26}NO_7]^+$ $[M+H]^+$: 416.1704, found 416.1702.

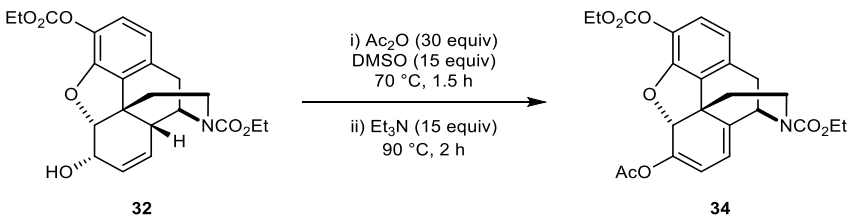
Ethyl (4*R*,4a*R*,7a*R*,12b*S*)-9-[(ethoxycarbonyl)oxy]-7-oxo-1,2,4,4a,7,7a-hexahydro-3*H*-4,12-methanobenzofuro[3,2-*e*]isoquinoline-3-carboxylate (33)



32 33

To a stirred solution of secondary alcohol **32** (1.00 g, 2.40 mmol) in acetic anhydride (13.6 mL, 144 mmol) at room temperature was added DMSO (5.11 mL, 72.0 mmol) then the resulting mixture was stirred for 21 h. The reaction mixture was then diluted with H_2O (50 mL) and extracted with diethyl ether (3 × 25 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution (50 mL), brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give **33** as a white solid (0.99 g, 99%). R_f = 0.20 (50% EtOAc/Pet. ether); m.p. 176-177 °C (Et_2O); $[\alpha]_D^{20.1}$ −160 (*c* 1.00, $CDCl_3$); IR (ATR) 2987, 1768 (C=O), 1674 (C=O), 1624 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.91 (1H, d, *J* = 8.2 Hz, Ar**H**), 6.70-6.61 (2H, m, Ar**H** and O=CCHC**H**), 6.13 (1H, dd, *J* = 10.3, 2.9 Hz, O=CC**H**CH), 5.10-4.86 (1H, m, C**H**N), 4.76 (1H, s, ArOC**H**), 4.35-4.23 (2H, m, $OCO_2C\mathbf{H}_2$), 4.22-3.97 (3H, m, $NCO_2C\mathbf{H}_2$ and $C\mathbf{H}_aH_bN$), 3.09-3.02 (1H, m, C**H**CHN), 2.95-2.77 (3H, m, $CH_a\mathbf{H}_bN$ and $ArC\mathbf{H}_2$), 2.04-1.89 (2H, m, $C\mathbf{H}_2CH_2N$), 1.35 (3H, t, *J* = 7.1 Hz, $OCO_2CH_2C\mathbf{H}_3$), 1.31-1.24 (3H, m, $NCO_2CH_2C\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.9 (C), 155.6 (C), 152.7 (C), 147.8 (C), 147.1 (CH), 133.3 (CH), 133.0 (C), 130.6 (C), 128.9 (C), 122.9 (CH), 120.5 (CH), 88.4 (CH), 65.2 (CH_2), 61.9 (CH_2), 50.1 (CH), 43.6 (C), 40.2 (CH), 37.9 (CH_2), 33.6 (CH_2), 29.5 (CH_2), 14.7 (CH_3), 14.1 (CH_3); HRMS (ESI) exact mass calculated for $[C_{22}H_{24}NO_7]^+$ $[M+H]^+$: 414.1547, found 414.1549.

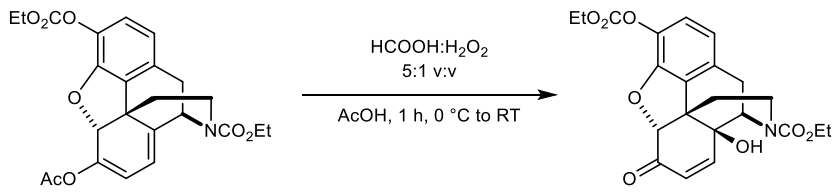
Ethyl (4*R*,7a*R*,12b*S*)-7-acetoxy-9-[(ethoxycarbonyl)oxy]-1,2,4,7a-tetrahydro-3*H*-4,12-methanobenzofuro[3,2-*e*]isoquinoline-3-carboxylate (34)



32 34

To a stirred solution of secondary alcohol **32** (4.98 g, 12.0 mmol) in acetic anhydride (34.0 mL, 360.0 mmol) was added DMSO (13.0 mL, 180.0 mmol) and the resulting mixture stirred at 70 °C for 1.5 h. TLC (50% EtOAc:Pet. ether) indicated full consumption of starting material. Triethylamine (25.0 mL, 180.0 mmol) was then added to the reaction mixture, heated to 90 °C and stirred for 2 h. The reaction mixture was then allowed to cool down to room temperature, diluted with H_2O (130 mL) and extracted with diethyl ether (5 × 100 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (3 × 250mL), H_2O (250 mL), brine (250 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give **34** as a brown oil (5.03 g, 92%). R_f = 0.36 (50% EtOAc/Pet. ether); $[\alpha]_D^{20.1}$ −232 (*c* 1.00, $CDCl_3$); IR (ATR) 2981, 1759 (C=O), 1689 (C=O), 1609 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.89 (1H, d, *J* = 8.2 Hz, Ar**H**), 6.63 (1H, d, *J* = 8.2 Hz, Ar**H**), 5.78 (1H, d, *J* = 6.3 Hz, AcOCC**H**CH), 5.67-5.57 (1H, m, AcOCCHC**H**), 5.54 (1H, s, ArOC**H**), 5.31-5.05 (1H, m, C**H**N), 4.38-4.23 (2H, m, OCO_2CH_2), 4.21-4.01 (3H, m, NCO_2CH_2 and CH_aH_bN), 3.30-3.12 (2H, m, CH_aH_bN and $ArCH_aH_b$), 3.05 (1H, d, *J* = 18.3 Hz, $ArCH_aH_b$), 2.24-2.13 (4H, m, CH_3CO_2C and $CH_aH_bCH_2N$), 1.90-1.79 (1H, m, $CH_aH_bCH_2N$), 1.37 (3H, t, *J* = 7.1 Hz, $OCO_2CH_2CH_3$), 1.32-1.22 (3H, m, $NCO_2CH_2CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0 (C), 155.1 (C), 154.7 (C), 153.0 (C), 147.6 (C), 143.8 (C), 135.9 (C), 133.3 (C), 132.3 (C), 122.2 (CH), 119.8 (CH), 115.5 (CH), 111.1 (CH), 88.3 (CH), 65.1 (CH_2), 61.7 (CH_2), 52.5 (CH), 47.3 (C), 37.9 (CH_2), 37.6 (CH_2), 37.3 (CH_2), 21.1 (CH_3), 14.7 (CH_3), 14.2 (CH_3); HRMS (ESI) exact mass calculated for $[C_{24}H_{26}NO_8]^+$ $[M+H]^+$: 456.1653, found 456.1656.

Ethyl (4*R*,4a*S*,7a*R*,12b*S*)-9-[(ethoxycarbonyl)oxy]-4a-hydroxy-7-oxo-1,2,4,4a,7,7a-hexahydro-3*H*-4,12-methanobenzofuro[3,2-*e*]isoquinoline-3-carboxylate (35)

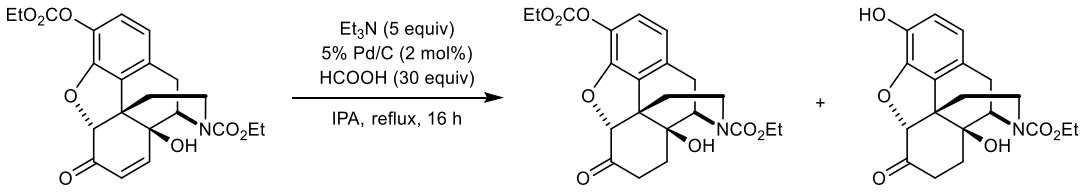


34 **35**

To a stirred solution of diene **34** (1.50 g, 3.29 mmol) in glacial acetic acid (9.10 mL) at 0 °C was added dropwise a pre-stirred (10 min) mixture of 50% aqueous H_2O_2 (1.12 mL, 16.45 mmol, N.B. WILL REACT VIOLENTLY WITH METALS, refer to a relevant SOP before handling) and formic acid (5.60 mL, 5:1 v:v with respect to H_2O_2) over 1 h. After the addition was complete,

the reaction was allowed to stir for a further 30 min, maintaining the temperature at 0 °C. The reaction mixture was then diluted with H_2O (50 mL), slowly neutralised with concentrated ammonium hydroxide and extracted with chloroform (5 × 25 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (50 mL), brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give **35** as an off-white solid (1.36 g, 96%) R_f = 0.17 (50% EtOAc/Pet. ether); m.p. 193-195 °C (Et_2O); $[\alpha]_D^{20.1}$ −164 (*c* 1.00, $CDCl_3$); IR (ATR) 3345 (OH), 1760 (C=O), 1721 (C=O), 1683 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.94 (1H, d, *J* = 8.2 Hz, Ar**H**), 6.86-6.76 (1H, m, O=CCHC**H**), 6.70 (1H, d, *J* = 8.2 Hz, Ar**H**), 6.18 (1H, d, *J* = 10.1 Hz, O=CC**H**CH), 4.81 (1H, s, ArOC**H**), 4.80-4.60 (1H, m, C**H**N), 4.36-4.25 (2H, m, OCO_2CH_2), 4.23-4.01 (3H, m, NCO_2CH_2 and CH_aH_bN), 3.95 (1H, s, O**H**), 3.13-2.96 (2H, m, ArCH_2), 2.95-2.84 (1H, m, CH_aH_bN), 2.59-2.47 (1H, m, $CH_aH_bCH_2N$), 1.79-1.65 (1H, m, $CH_aH_bCH_2N$), 1.37 (3H, t, *J* = 7.1 Hz, $OCO_2CH_2CH_3$), 1.34-1.26 (3H, m, $NCO_2CH_2CH_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 192.9 (C), 156.6 (C), 152.6 (C), 147.9 (CH), 147.3 (C), 133.9 (CH), 133.2 (C), 130.8 (C), 129.9 (C), 123.1 (CH), 120.0 (CH), 87.5 (CH), 67.9 (C), 65.3 (CH_2), 62.3 (CH_2), 55.4 (CH), 47.3 (C), 37.4 (CH_2), 31.9 (CH_2), 27.5 (CH_2), 14.6 (CH_3), 14.1 (CH_3); HRMS (ESI) exact mass calculated for $[C_{22}H_{24}NO_8]^+$ $[M+H]^+$: 430.1496, found 430.1487.

Ethyl (4*R*,4a*S*,7a*R*,12b*S*)-9-[(ethoxycarbonyl)oxy]-4a-hydroxy-7-oxo-1,2,4,4a,5,6,7,7a-octahydro-3*H*-4,12-methanobenzofuro[3,2-*e*]isoquinoline-3-carboxylate (36)



35 **36** 62% **45** 13%

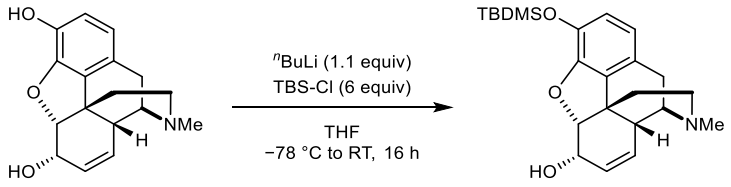
A microwave vial was charged with enone **35** (500 mg, 1.17 mmol), 5% Pd/C (50 mg, 2 mol%), isopropanol (1.5 mL), triethylamine (0.82 mL, 5.85 mmol) and formic acid (1.32 mL, 35.1 mmol), purged with nitrogen, sealed and the resulting mixture was then heated at reflux for 16 h. The reaction mixture was allowed to cool down to room temperature, filtered through a pad of Celite, washing through with chloroform (20 mL). The filtrate was then washed with H_2O (10 mL), saturated aqueous $NaHCO_3$ solution (10 mL), brine (10 mL), dried over $MgSO_4$

and concentrated *in vacuo*. Purification of the crude product by column chromatography (5% to 10% MeOH/CH_2Cl_2) gave **36** as a white foam (312 mg, 62%). The minor side product **45** was also observed in the ^{1}H NMR spectrum of the crude material but was not isolated.

Ketone 36: R_f = 0.17 (50% EtOAc/Pet. ether); m.p. 198-200 °C (Et_2O); $[\alpha]_D^{20.1}$ −268 (*c* 1.00, $CDCl_3$); IR (ATR) 3393 (OH), 2977, 1762 (C=O), 1727 (C=O), 1649 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (1H, d, *J* = 8.2 Hz, Ar**H**), 6.70 (1H, d, *J* = 8.2 Hz, Ar**H**), 4.71 (1H, s, ArOC**H**), 4.60-4.54 (1H, m, C**H**N), 4.37-4.25 (2H, m, $OCO_2C\mathbf{H}_2$), 4.23-4.13 (2H, m, $NCO_2C\mathbf{H}_2$), 4.02-3.98 (1H, m, $C\mathbf{H}_aH_bN$), 3.14-2.92 (4H, m, O**H** and $ArC\mathbf{H}_2$ and $O{=}CC\mathbf{H}_aH_b$), 2.81-2.71 (1H, m, $CH_a\mathbf{H}_bN$), 2.54-2.38 (1H, m, $O{=}CCH_2C\mathbf{H}_aH_b$), 2.31 (1H, dt, *J* = 14.7, 3.2 Hz, $O{=}CCH_a\mathbf{H}_b$), 1.99-1.89 (1H, m, $C\mathbf{H}_aH_bCH_2N$), 1.74-1.61 (1H, m, $C\mathbf{H}_aH_bCH_2N$), 1.60-1.56 (1H, m, $O{=}CCH_2CH_a\mathbf{H}_b$), 1.37 (3H, t, *J* = 7.1 Hz, $OCO_2CH_2C\mathbf{H}_3$), 1.29 (3H, t, *J* = 7.1 Hz, $NCO_2CH_2C\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.7 (C), 156.9 (C), 152.8 (C), 147.8 (C), 133.5 (C), 129.7 (C), 129.5 (C), 123.2 (CH), 119.9 (CH), 90.4 (CH), 70.7 (C), 65.2 (CH_2), 62.1 (CH_2), 56.5 (CH), 50.3 (C), 37.3 (CH_2), 35.6 (CH_2), 31.8 (CH_2), 31.5 (CH_2), 28.7 (CH_2), 14.6 (CH_3), 14.2 (CH_3); HRMS (ESI) exact mass calculated for $[C_{22}H_{26}NO_8]^+$ $[M+H]^+$: 432.1653, found 432.1647.

3.3. Albright-Goldman/Diene Formation Scope

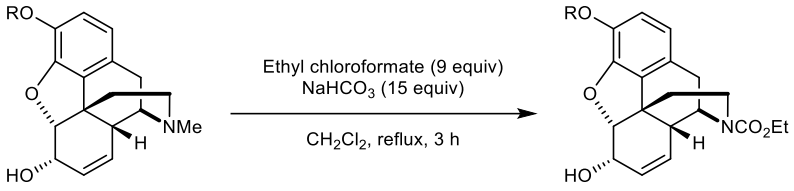
(4*R*,4a*R*,7*S*,7a*R*,12b*S*)-9-[(*tert*-Butyldimethylsilyl)oxy]-3-methyl-2,3,4,4a,7,7a-hexahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-7-ol (62)



To a stirred suspension of morphine (**1**) (0.50 g, 1.75 mmol) in dry THF (2.90 mL) at −78 °C under argon atmosphere was added ^{n}BuLi (2.5 M in hexanes, 1.12 mL, 1.93 mmol) and the resulting mixture stirred for 30 min. A dry solution of *tert*-butyldimethylsilyl chloride (1.58 g, 10.5 mmol) in dry THF (2.9 mL) was then added slowly to the reaction mixture and stirred for 16 h, allowing to warm up to room temperature. The reaction mixture was diluted with H_2O

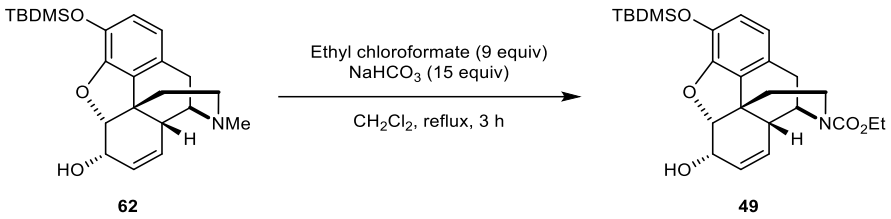
(20 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed with brine (15 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by column chromatography (0-10% 2M NH_3[MeOH]/CH_2Cl_2 gradient) to give **62** as a colourless solid (0.41 g, 59%). R_f = 0.44 (10% 2M NH_3[MeOH]/CH_2Cl_2); m.p. 126-129 °C (Et_2O); $[\alpha]_D^{20.1}$ −58 (*c* 1.00, $CDCl_3$); IR (ATR) 3163 (OH), 2926, 2850 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) 6.57 (1H, d, *J* = 8.1 Hz, Ar**H**), 6.48 (1H, d, *J* = 8.1 Hz, Ar**H**), 5.71-5.62 (1H, m, HOCHC**H**CH), 5.32-5.23 (1H, m, HOCHCHC**H**), 4.85 (1H, dd, *J* = 6.5, 1.3 Hz, ArOC**H**), 4.20-4.12 (1H, m, C**H**OH), 3.39-3.32 (1H, m, C**H**NMe), 3.02 (1H, d, *J* = 18.7 Hz, ArC**H$_a$**H$_b$), 2.82 (1H, br s, O**H**), 2.71-2.64 (1H, m, C**H**CHN), 2.65-2.55 (1H, m, C**H**$_a$H$_b$N), 2.47-2.38 (4H, m, CH$_a$**H**$_b$N and NC**H**$_3$), 2.30 (1H, dd, *J* = 18.7, 6.3 Hz, ArCH$_a$**H**$_b$), 2.07 (1H, td, *J* = 12.4, 5.1 Hz, C**H**$_a$H$_b$CH$_2$N), 1.90-1.80 (1H, m, CH$_a$**H**$_b$CH$_2$N), 0.98 {9H, s, [Si(C)(C**H**$_3$)$_3$]}, 0.19 [3H, s, Si(C**H**$_3$)$_a$(CH$_3$)$_b$], 0.16 [3H, s, Si(CH$_3$)$_a$(C**H**$_3$)$_b$]; ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.3 (C), 137.3 (C), 133.3 (CH), 131.2 (C), 128.3 (CH), 127.6 (C), 121.0 (CH), 119.7 (CH), 90.9 (CH), 66.4 (CH), 58.9 (CH), 46.5 (CH_2), 43.1 (CH_3), 42.9 (C), 40.7 (CH), 35.8 (CH_2), 25.6 (3 × CH_3), 20.6 (CH_2), 18.3 (C), -4.4 (CH_3), -4.6 (CH_3); HRMS (ESI) exact mass calculated for $[C_{23}H_{34}NO_3Si]^+$ $[M+H]^+$: 400.2302, found 400.2308.

General Procedure A: *N*-demethylation/protection



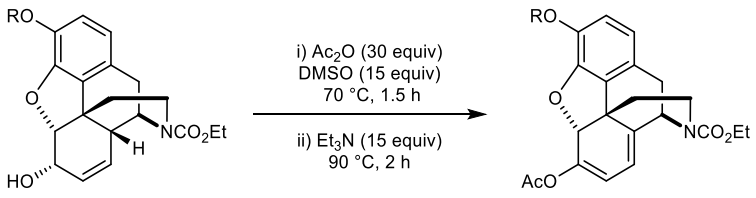
To a stirred suspension of the appropriate tertiary amine (1.0 equiv) and sodium bicarbonate (15 equiv) in CH_2Cl_2 at room temperature was added ethyl chloroformate (9.0 equiv) and the resulting mixture was then heated at reflux for 3 h. The reaction mixture was allowed to cool down to room temperature, filtered and concentrated *in vacuo*. Purification by column chromatography gave the carbamate product.

Ethyl (4*R*,4a*R*,7*S*,7a*R*,12b*S*)-9-[(*tert*-butyldimethylsilyl)oxy]-7-hydroxy-1,2,4,4a,7,7a-hexahydro-3*H*-4,12-methanobenzofuro[3,2-*e*]isoquinoline-3-carboxylate (49)



General Procedure A was followed using amine **62** (100 mg, 0.25 mmol). Purification by column chromatography (0-100% EtOAc/Pet.Ether gradient) gave carbamate **49** as a white solid (94 mg, 83%). R_f = 0.55 (50% EtOAC/Pet.Ether); m.p. 127-130 °C (Et_2O); $[\alpha]_D^{20.1}$ −12 (*c* 1.00, $CDCl_3$); IR (ATR) 3423 (OH), 2927, 2855, 1658 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.60 (1H, d, *J* = 8.1 Hz, Ar**H**), 6.48 (1H, d, *J* = 8.1 Hz, Ar**H**), 5.77-5.68 (1H, m, HOCHC**H**CH), 5.33-5.24 (1H, m, HOCHCHC**H**), 4.98-4.77 (2H, m, ArOC**H** and C**H**N), 4.25-3.91 (4H, m, $NCO_2C\mathbf{H}_2$ and C**H**OH and $C\mathbf{H}_aH_bN$), 3.09-2.94 (1H, m, $CH_a\mathbf{H}_bN$), 2.91-2.79 (2H, m, $ArC\mathbf{H}_aH_b$ and O**H**), 2.71 (1H, d, *J* = 18.6 Hz, $ArCH_a\mathbf{H_b}$), 2.54-2.47 (1H, m, C**H**CHN), 1.99-1.82 (2H, m, $C\mathbf{H}_2CH_2N$), 1.35-1.23 (3H, m, $NCO_2CH_2C\mathbf{H_3}$), 0.98 {9H, s, $[Si(C)(C\mathbf{H}_3)_3]$}, 0.19 [3H, s, $Si(C\mathbf{H}_3)_a(CH_3)_b$], 0.16 [3H, s, $Si(C\mathbf{H}_3)_a(CH_3)_b$]; ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.4 (C), 148.4 (C), 137.6 (C), 134.0 (CH), 130.2 (C), 127.2 (CH), 126.5 (C), 121.5 (CH), 120.1 (CH), 90.8 (CH), 66.1 (CH), 61.5 (CH_2), 50.1 (CH), 43.4 (C), 39.6 (CH), 37.4 (CH_2), 35.6 (CH_2), 29.5 (CH_2), 25.6 (3 × CH_3), 18.3 (C), 14.7 (CH_3), −4.4 (CH_3), −4.6 (CH_3); HRMS (ESI) exact mass calculated for $[C_{25}H_{36}NO_5Si]^+$ $[M+H]^+$: 458.2357, found 458.2357.

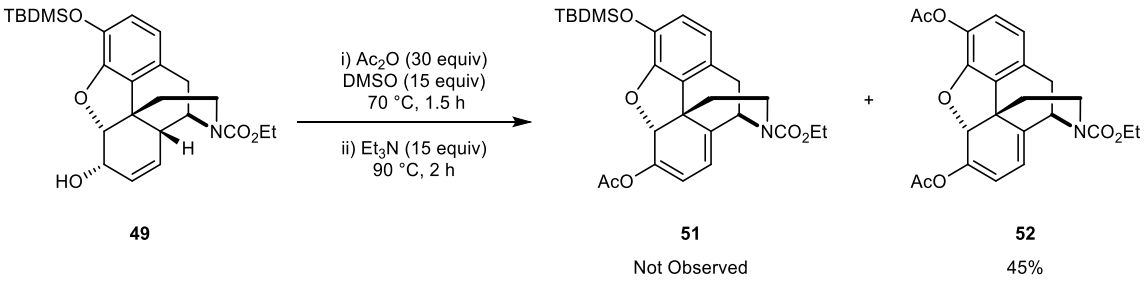
<u>General Procedure B: One-pot Albright-Goldman Oxidation/Diene Formation</u>



To a stirred solution of the appropriate secondary alcohol (1 equiv) in acetic anhydride (30 equiv) was added DMSO (15 equiv) and the resulting mixture stirred at 70 °C for 1.5 h. Triethylamine (15 equiv) was then added to the reaction mixture, heated to 90 °C and stirred

for 2 h. Reaction mixture was then allowed to cool down to room temperature, diluted with H_2O and extracted with diethyl ether. Combined organic extracts were washed with saturated aqueous $NaHCO_3$, H_2O, brine, dried over $MgSO_4$ and concentrated *in vacuo.* Purification by column chromatography gave the diene product.

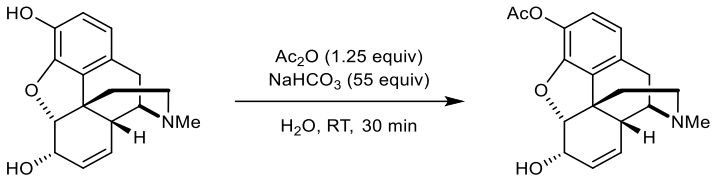
(4*R*,7a*R*,12b*S*)-3-(Ethoxycarbonyl)-2,3,4,7a-tetrahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinoline-7,9-diyl diacetate (52)



49 **51** Not Observed **52** 45%

General Procedure B was followed using secondary alcohol **49** (92 mg, 0.2 mmol). Purification by column chromatography (0-50% EtOAc/Pet. ether gradient) gave diene **52** as a yellow residue (38 mg, 45% adjusted yield). R_f = 0.38 (50% EtOAc/Pet. ether); $[\alpha]_D^{20.1}$ −106 (*c* 1.00, $CDCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (1H, d, *J* = 8.2 Hz, Ar**H**), 6.66 (1H, d, *J* = 8.2 Hz, Ar**H**), 5.81 (1H, d, *J* = 6.3 Hz, AcOCC**H**CH), 5.70-5.59 (1H, m, AcOCCHC**H**), 5.53 (1H, s, ArOC**H**), 5.31-5.09 (1H, m, C**H**N), 4.27-4.02 (3H, m, $NCO_2C\mathbf{H}_2$ and $C\mathbf{H}_aH_bN$), 3.36-3.14 (2H, m, $CH_a\mathbf{H}_bN$ and $ArC\mathbf{H}_aH_b$), 3.07 (1H, d, *J* = 18.3 Hz, $ArCH_a\mathbf{H}_b$), 2.31 (3H, s, $ArOC(O)C\mathbf{H}_3$), 2.25-2.16 (4H, m, $C\mathbf{H}_3CO_2C$ and $C\mathbf{H}_aH_bCH_2N$), 1.92-1.83 (1H, m, $CH_a\mathbf{H}_bCH_2N$), 1.34-1.26 (3H, m, $CH_2C\mathbf{H_3}$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.0 (C), 168.5 (C), 155.1 (C), 147.7 (C), 143.7 (C), 136.0 (C), 133.0 (C), 132.7 (C), 132.0 (C), 122.5 (CH), 119.8 (CH), 115.6 (CH), 111.1 (CH), 88.2 (CH), 61.7 (CH_2), 51.9 (CH), 47.3 (C), 37.9 (CH_2), 37.6 (CH_2), 37.3 (CH_2), 21.1 (CH_3), 20.8 (CH_3), 14.7 (CH_3); HRMS (ESI) exact mass calculated for $[C_{23}H_{23}NNaO_7]^+$ $[M+Na]^+$: 448.1367, found 448.1372.

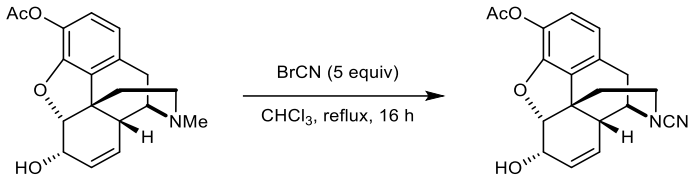
(4*R*,4a*R*,7*S*,7a*R*,12b*S*)-7-Hydroxy-3-methyl-2,3,4,4a,7,7a-hexahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-9-yl acetate (63)



Morphine **1** **63**

To a stirred suspension of sodium bicarbonate (8.0 g, 95.3 mmol) in H_2O (50 mL) was added morphine **1** (0.5 g, 1.75 mmol), followed by a dropwise addition of acetic anhydride (0.83 mL, 2.19 mmol) at room temperature and the resulting mixture stirred for 30 min. The reaction mixture was filtered, extracted with CH_2Cl_2 (3 × 60 mL), combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo* to give **63** as a white foam (524 mg, 92%). R_f = 0.42 (10% 2M NH_3[MeOH]/CH_2Cl_2); m.p. 131-132 °C (Et_2O); $[\alpha]_D^{20.1}$ −208 (*c* 1.00, $CDCl_3$); IR (ATR) 3486 (OH), 2913, 1749 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.73 (1H, d, *J* = 8.2 Hz, Ar**H**), 6.60 (1H, d, *J* = 8.2 Hz, Ar**H**), 5.77-5.69 (1H, m, HOCHC**H**CH), 5.30-5.25 (1H, m, HOCHCHC**H**), 4.91 (1H, dd, *J* = 6.9, 1.1 Hz, ArOC**H**), 4.19-4.11 (1H, m, C**H**OH), 3.36 (1H, dd, *J* = 6.2, 3.3 Hz, C**H**N), 3.16 (1H, br s, O**H**), 3.05 (1H, d, *J* = 18.8 Hz, ArC**H**$_a$H$_b$), 2.76-2.67 (1H, m, C**H**CHN), 2.66-2.56 (1H, m, ArCH$_a$**H**$_b$), 2.44 (3H, s, NC**H**$_3$), 2.38 (1H, td, *J* = 12.5, 3.6 Hz, C**H**$_a$H$_b$N), 2.35-2.28 (1H, m, CH$_a$**H**$_b$N), 2.28 (3H, s, **H**$_3$CCO$_2$), 2.08 (1H, td, *J* = 12.5, 5.1 Hz, C**H**$_a$H$_b$CH$_2$N), 1.94-1.85 (1H, m, CH$_a$**H**$_b$CH$_2$N); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.6 (C), 148.7 (C), 134.2 (CH), 132.7 (C), 132.2 (C), 131.8 (C), 127.7 (CH), 121.1 (CH), 119.9 (CH), 92.3 (CH), 65.8 (CH), 58.9 (CH), 46.4 (CH_2), 43.0 (CH_3), 42.6 (C), 40.3 (CH), 35.1 (CH_2), 20.8 (CH_2), 20.7 (CH_3); HRMS (ESI) exact mass calculated for $[C_{19}H_{22}NO_4]^+$ $[M+H]^+$: 328.1543, found 328.1546.

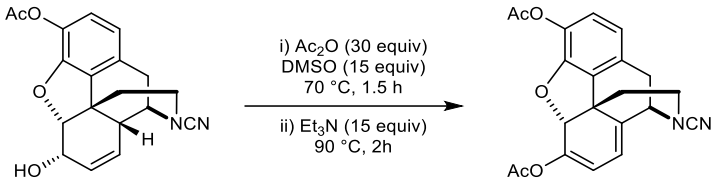
(4*R*,4a*R*,7*S*,7a*R*,12b*S*)-3-Cyano-7-hydroxy-2,3,4,4a,7,7a-hexahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-9-yl acetate (57)



63 **57**

To a stirred solution of amine **63** (245 mg, 0.75 mmol) in $CHCl_3$ (1.4 mL) was added a solution of cyanogen bromide (397 mg, 3.75 mmol) in $CHCl_3$ (0.7 mL) and the resulting mixture was then heated at reflux for 16 h. The reaction mixture was allowed to cool down to room temperature, diluted with $CHCl_3$ (10 mL), washed with 1M HCl (2 × 10 mL), 2M NaOH (2 × 10 mL), brine (10 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography (0-10% 2M NH_3[MeOH]/CH_2Cl_2 gradient) to give **57** as a colourless solid (95 mg, 38%). R_f = 0.56 (10% 2M NH_3[MeOH]/CH_2Cl_2); m.p. 236-240 °C (Et_2O); $[\alpha]_D^{20.1}$ −196 (*c* 1.00, $CDCl_3$); IR (ATR) 3414 (OH), 2921, 2207 (C=N), 1766 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 (1H, d, *J* = 8.2 Hz, Ar**H**), 6.68 (1H, d, *J* = 8.2 Hz, Ar**H**), 5.90-5.83 (1H, m, HOCHC**H**CH), 5.27-5.19 (1H, m, HOCHCHC**H**), 4.95 (1H, d, *J* = 7.0 Hz, ArOC**H**), 4.25-4.15 (1H, m, C**H**OH), 4.06 (1H, dd, *J* = 6.1, 3.7 Hz, C**H**N), 3.39-3.22 (3H, m, C**H**$_2$N and O**H**), 3.11 (1H, d, *J* = 19.0 Hz, ArC**H**$_a$H$_b$), 2.90 (1H, dd, *J* = 19.0, 6.1 Hz, ArCH$_a$**H**$_b$), 2.87-2.84 (1H, m, C**H**CHN), 2.32 (3H, s, **H**$_3$CCO$_2$), 2.23-2.11 (1H, m, C**H**$_a$H$_b$CH$_2$N), 2.02-1.95 (1H, m, CH$_a$**H**$_b$CH$_2$N); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.6 (C), 148.9 (C), 135.9 (CH), 132.4 (C), 130.5 (C), 130.3 (C), 124.9 (CH), 122.2 (CH), 120.4 (CH), 117.5 (C), 91.8 (CH), 65.3 (CH), 57.1 (CH), 43.2 (CH_2), 42.2 (C), 38.6 (CH), 33.8 (CH_2), 29.0 (CH_2), 20.8 (CH_3); HRMS (ESI) exact mass calculated for $[C_{19}H_{19}N_2O_4]^+$ $[M+H]^+$: 339.1339, found 339.1340.

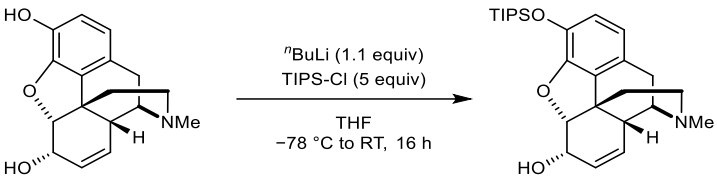
(4*R*,7a*R*,12b*S*)-3-Cyano-2,3,4,7a-tetrahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinoline-7,9-diyl diacetate (58)



57 **58**

General Procedure B was followed using secondary alcohol **57** (68 mg, 0.2 mmol). Purification by column chromatography (0-50% EtOAc/Pet. ether gradient) gave diene **58** as a colourless oil (20 mg, 26%). R_f = 0.47 (50% EtOAc/Pet. ether); $[\alpha]_D^{20.1}$ −168 (*c* 1.00, $CDCl_3$); IR (ATR) 2925, 2206 (C≡N), 1758 (C=O) cm^{-1}; ^1H NMR (400 MHz, CDCl3) δ 6.84 (1H, d, *J* = 8.2 Hz, Ar**H**), 6.68 (1H, d, *J* = 8.2 Hz, Ar**H**), 5.82 (1H, d, *J* = 6.3 Hz, AcOCCHC**H**), 5.69 (1H, d, *J* = 6.3 Hz, AcOCC**H**CH), 5.52 (1H, s, ArOC**H**), 4.31 (1H, d, *J* = 6.7 Hz, C**H**N), 3.50 (1H, td, *J* = 12.9, 3.4 Hz, C**H**$_a$H$_b$N), 3.39-3.31 (2H, m, CH$_a$**H**$_b$N and ArC**H**$_a$H$_b$), 3.20 (1H, dd, *J* = 18.6, 6.7 Hz, ArCH$_a$**H**$_b$), 2.39 (1H, td, *J* = 12.9, 5.5 Hz, C**H**$_a$H$_b$CH$_2$N), 2.30 (3H, s, **H**$_3$CCO$_2$), 2.22 (3H, s, **H**$_3$CCO$_2$Ar), 1.94-1.83 (1H, m, CH$_a$**H**$_b$CH$_2$N); ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.8 (C), 168.4 (C), 147.9 (C), 144.3 (C), 133.3 (C), 133.0 (C), 132.2 (C), 130.8 (C), 122.9 (CH), 119.9 (CH), 117.1 (C), 114.9 (CH), 112.7 (CH), 87.8 (CH), 58.7 (CH), 46.4 (C), 43.1 (CH_2), 36.8 (CH_2), 36.6 (CH_2), 21.1 (CH_3), 20.7 (CH_3); HRMS (ESI) exact mass calculated for $[C_{21}H_{19}N_2O_5]^+$ $[M+H]^+$: 379.1288, found 379.1282.

(4*R*,4a*R*,7*S*,7a*R*,12b*S*)-3-Methyl-9-[(triisopropylsilyl)oxy]-2,3,4,4a,7,7a-hexahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-7-ol (64)

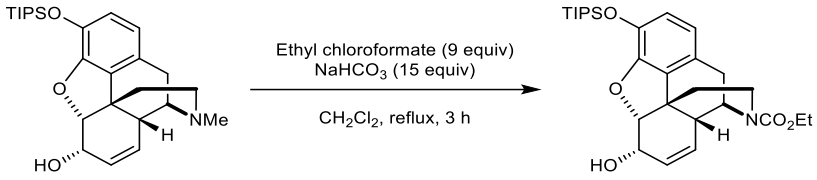


Morphine **1** **64**

To a stirred suspension of morphine (**1**) (0.5 g, 1.75 mmol) in dry THF (5.8 mL) at −78 °C under an argon atmosphere was added ^{n}BuLi (2.5 M in hexanes, 1.12 mL, 1.93 mmol) and the resulting mixture stirred for 30 min, maintaining the temperature. Triisopropylsilyl chloride (1.90 mL, 8.75 mmol) was then added slowly to the reaction mixture and stirred for 16 h,

allowing to gradually warm up to room temperature. The reaction mixture was diluted with H_2O (20 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were washed with brine (30 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude residue was purified by column chromatography (0-10% 2M NH_3[MeOH]/CH_2Cl_2 gradient) to give **64** as a colourless solid (395 mg, 50%). R_f = 0.42 (10% 2M NH_3[MeOH]/CH_2Cl_2); m.p. 86-88 °C (Et_2O); $[\alpha]_D^{20.1}$ −92 (*c* 1.00, $CDCl_3$); IR (ATR) 3141 (OH), 2923, 2864 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.63 (1H, d, *J* = 8.1 Hz, Ar**H**), 6.49 (1H, d, *J* = 8.2 Hz, Ar**H**), 5.71-5.65 (1H, m, HOCHC**H**CH), 5.27-5.21 (1H, m, HOCHCHC**H**), 4.88 (1H, dd, *J* = 1.3, 6.6 Hz, ArOC**H**), 4.22-4.09 (1H, m, C**H**OH), 3.36 (1H, dd, *J* = 6.3, 3.3 Hz, C**H**N), 3.02 (1H, d, *J* = 18.7 Hz, ArC**H**$_a$H$_b$), 2.88 (1H, br s, O**H**), 2.74-2.66 (1H, m, C**H**CHN), 2.66-2.57 (1H, m, C**H**$_a$H$_b$N), 2.50-2.38 (4H, m, NC**H**$_3$ and C**H**$_a$H$_b$N), 2.31 (1H, dd, *J* = 18.7, 6.3 Hz, ArCH$_a$**H**$_b$), 2.09 (1H, td, *J* = 12.5, 5.1 Hz, C**H**$_a$H$_b$CH$_2$N), 1.84 (1H, ddd, *J* = 12.5, 3.7, 1.7 Hz, CH$_a$**H**$_b$CH$_2$N), 1.30-1.18 [3H, m, Si(C**H**)$_3$], 1.12-1.04 {18H, m, Si[CH(C**H**$_3$)$_2$]$_3$}; ^{13}C NMR (101 MHz, $CDCl_3$) δ 148.2 (C), 138.1 (C), 133.6 (CH), 131.2 (C), 128.2 (CH), 127.2 (C), 120.8 (CH), 119.7 (CH), 90.9 (CH), 66.5 (CH), 59.1 (CH), 46.6 (CH_2), 43.1 (CH_3), 43.0 (C), 40.7 (CH), 35.8 (CH_2), 20.7 (CH_2), 18.0 (6 × CH_3), 12.8 (3 × CH); HRMS (ESI) exact mass calculated for $[C_{26}H_{40}NO_3Si]^+$ $[M+H]^+$: 442.2772, found 442.2774.

Ethyl (4*R*,4a*R*,7*S*,7a*R*,12b*S*)-7-hydroxy-9-[(triisopropylsilyl)oxy]-1,2,4,4a,7,7a-hexahydro-3*H*-4,12-methanobenzofuro[3,2-*e*]isoquinoline-3-carboxylate (53)

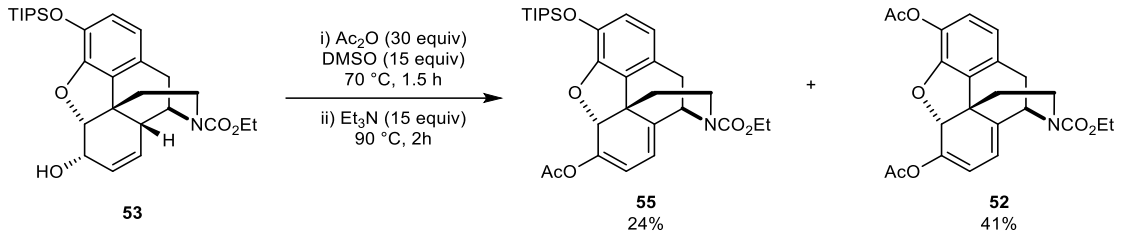


64 **53**

General Procedure A was followed using amine **64** (88 mg, 0.2 mmol). Purification by column chromatography (0-30% EtOAc/Pet.ether gradient) gave carbamate **53** as a colourless waxy solid (55 mg, 55%). R_f = 0.27 (30% EtOAC/cyclohexane); $[\alpha]_D^{20.1}$ −108 (*c* 1.00, $CDCl_3$); IR (ATR) 3563(OH), 2942, 2865, 1690 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.63 (1H, d, *J* = 8.1 Hz, Ar**H**), 6.47 (1H, d, *J* = 8.1 Hz, Ar**H**), 5.74-5.65 (1H, m, HOCHC**H**CH), 5.32-5.21 (1H, m, HOCHCHC**H**), 4.98-4.75 (2H, m, ArOC**H** and C**H**N), 4.23-3.96 (4H, m, NCO$_2$C**H**$_2$ and C**H**OH and C**H**$_a$H$_b$N), 3.09-2.91 (1H, m, CH$_a$**H**$_b$N), 2.90-2.78 (2H, m, ArC**H**$_a$H$_b$ and O**H**), 2.70 (1H, d, *J* = 18.5

Hz, ArCH$_a$**H**$_b$), 2.53-2.46 (1H, m, C**H**CHN), 2.00-1.77 (2H, m, C**H**$_2$CH$_2$N), 1.33-1.17 [6H, m, NCO$_2$CH$_2$C**H**$_3$ and Si(C**H**)$_3$], 1.13-1.04 {18H, m, Si[CH(C**H**$_3$)$_2$]$_3$}; ^{13}C NMR (101 MHz, CDCl$_3$) δ 155.4 (C), 148.2 (C), 138.2 (C), 134.1 (CH), 130.1 (C), 127.2 (CH), 126.2 (C), 121.1 (CH), 120.0 (CH), 90.7 (CH), 66.1 (CH), 61.5 (CH$_2$), 50.1 (CH), 43.4 (C), 39.6 (CH), 37.4 (CH$_2$), 35.6 (CH$_2$), 29.5 (CH$_2$), 17.7 (6 × CH$_3$), 14.7 (CH$_3$), 12.7 (3 × CH); HRMS (ESI) exact mass calculated for [C$_{28}$H$_{42}$NO$_5$Si]$^+$ [M+H]$^+$: 500.2827, found 500.2823.

Ethyl (4*R*,7a*R*,12b*S*)-7-acetoxy-9-((triisopropylsilyl)oxy)-1,2,4,7a-tetrahydro-3*H*-4,12-methanobenzofuro[3,2-*e*]isoquinoline-3-carboxylate (55)

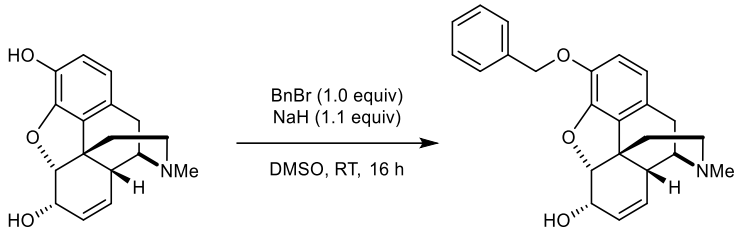


General Procedure B was followed using secondary alcohol **53** (150 mg, 0.3 mmol). Purification by column chromatography (0-20% EtOAc/cyclohexane gradient) gave diene **55** as a yellow residue (32 mg, 24%) followed by diene **52** as a yellow residue (52 mg, 41%).

Diene 55: R$_f$ = 0.49 (20% EtOAc/cyclohexane); ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.65 (1H, d, *J* = 8.2 Hz, Ar**H**), 6.50 (1H, d, *J* = 8.2 Hz, Ar**H**), 5.76 (1H, d, *J* = 6.2 Hz, AcOCC**H**), 5.64-5.54 (1H, m, AcOCCHC**H**), 5.53-5.48 (1H, m, ArOC**H**), 5.26-5.03 (1H, m, C**H**N), 4.24-3.98 (3H, m, NCO$_2$C**H**$_2$ and C**H**$_a$H$_b$N), 3.33-3.07 (2H, m, CH$_a$**H**$_b$N and ArC**H**$_a$H$_b$), 3.00 (1H, d, *J* = 18.0 Hz, ArCH$_a$**H**$_b$), 2.23-2.11 (4H, m, **H**$_3$CCO$_2$ and C**H**$_a$H$_b$CH$_2$N), 1.82-1.74 (1H, m, CH$_a$**H**$_b$CH$_2$N), 1.34-1.20 [6H, m, CH$_2$C**H**$_3$ and Si(C**H**)$_3$], 1.13-1.02 {18H, m, Si[CH(C**H**$_3$)$_2$]$_3$}; ^{13}C NMR (101 MHz, CDCl$_3$) δ 168.8 (C), 155.2 (C), 146.4 (C), 144.2 (C), 138.9 (C), 136.4 (C), 132.3 (C), 126.6 (C), 121.4 (CH), 119.6 (CH), 114.6 (CH), 110.7 (CH), 86.6 (CH), 61.6 (CH$_2$), 52.2 (CH), 47.5 (C), 38.1 (CH$_2$), 37.8 (CH$_2$), 37.5 (CH$_2$), 21.0 (CH$_3$), 17.9 (6 × CH$_3$), 14.7 (CH$_3$), 12.7 (3 × CH); HRMS (ESI) exact mass calculated for [C$_{30}$H$_{42}$NO$_6$Si]$^+$ [M+H]$^+$: 540.2776, found 540.2767.

Diene 52: See Entry **52** (*vide supra)*

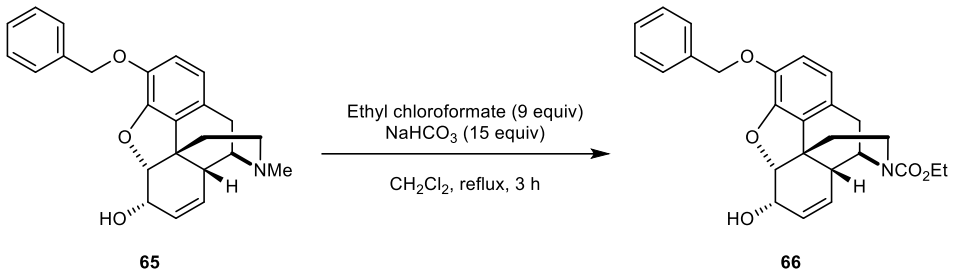
(4*R*,4a*R*,7*S*,7a*R*,12b*S*)-9-(Benzyloxy)-3-methyl-2,3,4,4a,7,7a-hexahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-7-ol (65)



Morphine **1** **65**

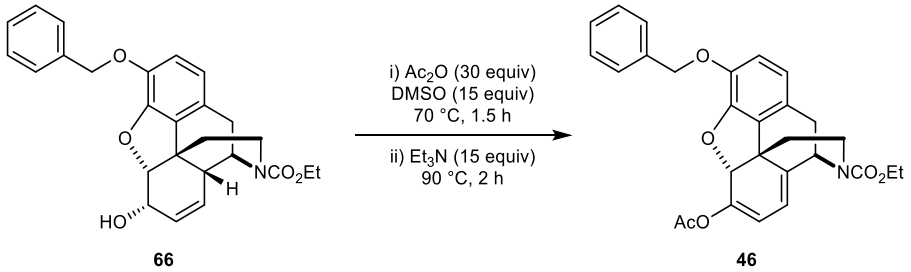
Morphine (**1**) (200 mg, 0.70 mmol) and sodium hydride (60% dispersion in mineral oil, 31 mg, 0.77 mmol) were suspended in DMSO (3.0 mL) and stirred at room temperature for 1 h under an argon atmosphere. A solution of benzyl bromide (83 µL, 0.70 mmol) in diethyl ether (1.0 mL) was then added dropwise to the reaction mixture and stirred for 16 h at room temperature. The reaction mixture was diluted with H_2O (30 mL) and extracted with Et_2O (3 × 30 mL). The combined organic extracts were washed with brine (45 mL) dried over $MgSO_4$ and concentrated *in vacuo* to give **65** as an off-white solid (210 mg, 83%) which was taken forward to the next step without further purification. R_f = 0.31 (10% 2M NH_3[MeOH]/CH_2Cl_2); m.p. 130-132 °C (Et_2O); $[\alpha]_D^{20.1}$ −64 (*c* 1.00, $CDCl_3$); IR (ATR) 3544 (OH), 3026, 2929, 2846, 2797 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.44-7.27 (5H, m, Ph**H**), 6.71 (1H, d, *J* = 8.1 Hz, Ar**H**), 6.53 (1H, d, *J* = 8.1 Hz, Ar**H**), 5.69-5.63 (1H, m, HOCHC**H**CH), 5.31-5.24 (1H, m, HOCHCHC**H**), 5.17 (1H, d, *J* = 12.0 Hz, ArC**H**$_a$H$_b$O), 5.08 (1H, d, *J* = 12.0 Hz, ArCH$_a$**H**$_b$O), 4.87 (1H, d, *J* = 6.6, 1.2 Hz, ArOC**H**), 4.19-4.10 (1H, m, C**H**OH), 3.35 (1H, dd, *J* = 6.2, 3.2 Hz, C**H**N), 3.03 (1H, d, *J* = 18.6 Hz, ArC**H**$_a$H$_b$CH), 2.79 (1H, br s, O**H**), 2.69-2.65 (1H, m, C**H**CHN), 2.63-2.55 (1H, m, C**H**$_a$H$_b$N), 2.44 (3H, s, NC**H**$_3$), 2.41-2.36 (1H, m, CH$_a$**H**$_b$N), 2.29 (1H, dd, *J* = 18.7, 6.2 Hz, ArCH$_a$**H**$_b$CH), 2.07 (1H, td, *J* = 12.4, 5.2 Hz, C**H**$_a$H$_b$CH$_2$N), 1.91-1.83 (1H, m, CH$_a$**H**$_b$CH$_2$N); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.9 (C), 141.2 (C), 137.4 (C), 133.4 (CH), 131.4 (C), 128.5 (2 × CH), 128.3 (CH), 127.9 (CH), 127.8 (C), 127.5 (2 × CH), 119.7 (CH), 115.9 (CH), 91.3 (CH), 71.8 (CH_2), 66.4 (CH), 58.9 (CH), 46.5 (CH_2), 43.1 (CH_3), 42.9 (C), 40.7 (CH), 35.8 (CH_2), 20.5 (CH_2); HRMS (ESI) exact mass calculated for $[C_{24}H_{26}NO_3]^+$ $[M+H]^+$: 376.1907, found 376.1909.

Ethyl (4*R*,4a*R*,7*S*,7a*R*,12b*S*)-9-(benzyloxy)-7-hydroxy-1,2,4,4a,7,7a-hexahydro-3*H*-4,12-methanobenzofuro[3,2-*e*]isoquinoline-3-carboxylate (66)



General Procedure A was followed using amine **65** (188 mg, 0.5 mmol). Purification by column chromatography (0-40% EtOAc/cyclohexane gradient) gave carbamate **66** as a colourless solid (183 mg, 84%). R_f = 0.24 (40% EtOAc/cyclohexane); m.p. 167-169 °C (Et_2O); $[\alpha]_D^{20.1}$ −108 (*c* 1.00, $CDCl_3$); IR (ATR) 3453 (OH), 3031, 2937, 1671 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46-7.27 (5H, m, Ph**H**), 6.75 (1H, d, *J* = 8.2 Hz, Ar**H**), 6.54 (1H, d, *J* = 8.2 Hz, Ar**H**), 5.78-5.66 (1H, m, HOCHC**H**CH), 5.34-5.23 (1H, m, HOCHCHC**H**), 5.18 (1H, d, *J* = 12.0 Hz, ArC**H**$_a$H$_b$O), 5.09 (1H, d, *J* = 12.0 Hz, ArCH$_a$**H**$_b$O), 4.98-4.78 (2H, m, C**H**N and ArOC**H**), 4.25-3.95 (4H, m, $CO_2C\mathbf{H}_2$ and C**H**$_a$H$_b$N and C**H**OH), 3.09-2.92 (1H, m, CH$_a$**H**$_b$N), 2.92-2.80 (1H, m, ArC**H**$_a$H$_b$CH), 2.81-2.68 (2H, m, ArCH$_a$**H**$_b$CH and O**H**), 2.56-2.48 (1H, m, C**H**CHN), 1.99-1.84 (2H, m, C**H**$_2$CH$_2$N), 1.35-1.24 (3H, m, $CH_2C\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.4 (C), 147.0 (C), 141.4 (C), 137.2 (C), 134.2 (CH), 130.3 (C), 128.6 (2 × CH), 128.0 (CH), 127.5 (2 × CH), 127.1 (CH), 126.6 (C), 120.1 (CH), 116.3 (CH), 91.1 (CH), 71.8 (CH_2), 66.1 (CH), 61.6 (CH_2), 50.1 (CH), 43.3 (C), 39.6 (CH), 37.4 (CH_2), 35.5 (CH_2), 29.5 (CH_2), 14.7 (CH_3); HRMS (ESI) exact mass calculated for $[C_{26}H_{28}NO_5]^+$ $[M+H]^+$: 434.1962, found 434.1965.

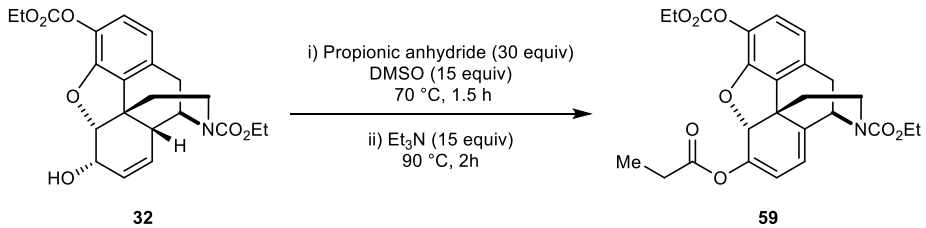
Ethyl (4*R*,7a*R*,12b*S*)-7-acetoxy-9-(benzyloxy)-1,2,4,7a-tetrahydro-3*H*-4,12-methanobenzofuro[3,2-*e*]isoquinoline-3-carboxylate (46)



66 46

General Procedure B was followed using secondary alcohol **66** (87 mg, 0.2 mmol). Purification by column chromatography (0-30% EtOAc/cyclohexane gradient) gave diene **46** as a pale yellow residue (56 mg, 59%). R_f = 0.55 (50% EtOAc/cyclohexane); $[\alpha]_D^{20.1}$ −204 (*c* 1.00, $CDCl_3$); IR (ATR) 2914, 1759 (C=O), 1688 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.46-7.28 (5H, m, Ph**H**), 6.72 (1H, d, *J* = 8.2 Hz, Ar**H**), 6.55 (1H, d, *J* = 8.2 Hz, Ar**H**), 5.79 (1H, d, *J* = 6.2 Hz, AcOCCHC**H**), 5.68-5.58 (1H, m, AcOCC**H**CH), 5.51 (1H, s, ArOC**H**), 5.29-5.07 (3H, m, C**H**N and ArC$\mathbf{H}_2$O), 4.24-4.00 (3H, m, C$\mathbf{H}_2CH_3$ and C$\mathbf{H}_a$H$_b$N), 3.35-3.09 (2H, m, CH$_a\mathbf{H}_b$N and ArC$\mathbf{H}_a$H$_b$CH), 3.02 (1H, d, *J* = 18.1 Hz, ArCH$_a\mathbf{H}_b$CH), 2.25-2.14 (4H, m, $\mathbf{H}_3CCO_2$ and C$\mathbf{H}_a$H$_b$CH$_2$N), 1.89-1.78 (1H, m, CH$_a\mathbf{H}_b$CH$_2$N), 1.34-1.24 (3H, m, CH$_2$C$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.1 (C), 155.1 (C), 145.3 (C), 143.9 (C), 142.2 (C), 137.4 (C), 136.4 (C), 132.5 (C), 128.5 (2 × CH), 127.9 (CH), 127.6 (2 × CH), 127.1 (C), 119.8 (CH), 116.7 (CH), 115.5 (CH), 110.9 (CH), 87.5 (CH), 71.9 (CH_2), 61.6 (CH_2), 52.2 (CH), 47.4 (C), 38.2 (CH_2), 37.8 (CH_2), 37.5 (CH_2), 21.2 (CH_3), 14.7 (CH_3); HRMS (ESI) exact mass calculated for $[C_{28}H_{28}NO_6]^+$ $[M+H]^+$: 474.1911, found 474.1913.

Ethyl (4*R*,7a*R*,12b*S*)-9-[(ethoxycarbonyl)oxy]-7-(propionyloxy)-1,2,4,7a-tetrahydro-3*H*-4,12-methanobenzofuro[3,2-*e*]isoquinoline-3-carboxylate (59)

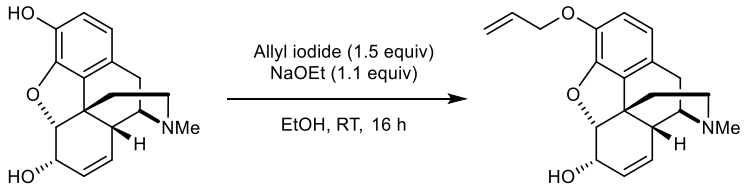


32 59

To a stirred suspension of secondary alcohol **32** (83 mg, 0.2 mmol) in propionic anhydride (0.57 mL, 6.0 mmol) was added DMSO (0.21 mL, 3.0 mmol) and the resulting mixture stirred

at 75 °C for 1.5 h. At this point Et_3N (0.42 mL, 3.0 mmol) was added to the reaction mixture, heated to 90 °C and stirred further for 2 h. The reaction mixture was allowed to cool down to room temperature, diluted with H_2O (10 mL) and extracted with Et_2O (5 × 5 mL). The combined organic extracts were washed with saturated aqueous sodium bicarbonate solution (15 mL), brine (15 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by column chromatography (0-30% EtOAc/cyclohexane gradient) to give **59** as a pale yellow residue (56 mg, 60%). R_f = 0.52 (50% EtOAc/cyclohexane); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (1H, d, *J* = 8.3 Hz, Ar**H**), 6.64 (1H, d, *J* = 8.3 Hz, Ar**H**), 5.78 (1H, d, *J* = 6.3 Hz, CO_2CCHCH), 5.67-5.59 (1H, m, CO_2CCHCH), 5.56 (1H, s, ArOC**H**), 5.30-5.08 (1H, m, C**H**N), 4.31 (2H, q, *J* = 7.1 Hz, OCO_2CH_2), 4.23-4.01 (3H, m, NCH_2CH_3 and CH_aH_bN), 3.31-3.12 (2H, m, CH_aH_bN and $ArCH_aH_b$), 3.06 (1H, d, *J* = 18.3 Hz, $ArCH_aH_b$), 2.49 (2H, q, *J* = 7.6 Hz, $CH_3CH_2CO_2C$), 2.25-2.13 (1H, m, $CH_aH_bCH_2N$), 1.91-1.81 (1H, m, CH_aHCH_2N), 1.37 (3H, t, *J* = 7.1 Hz, $OCO_2CH_2CH_3$), 1.31-1.24 (3H, m, $NCO_2CH_2CH_3$), 1.20 (3H, t, *J* = 7.6 Hz, $CH_3CH_2CO_2C$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.5 (C), 155.1 (C), 152.9 (C), 147.6 (C), 143.8 (C), 135.7 (C), 133.3 (C), 132.2 (C), 122.1 (CH), 119.8 (CH), 115.2 (CH), 111.2 (CH), 88.3 (CH), 65.0 (CH_2), 61.7 (CH_2), 52.5 (CH), 47.3 (C), 37.9 (CH_2), 37.6 (CH_2), 37.3 (CH_2), 29.7 (C), 27.7 (CH_2), 14.7 (CH_3), 14.2 (CH_3), 8.9 (CH_3); HRMS (ESI) exact mass calculated for $[C_{25}H_{28}NO_8]^+$ $[M+H]^+$: 470.1809, found 470.1804.

(4*R*,4a*R*,7*S*,7a*R*,12b*S*)-9-(Allyloxy)-3-methyl-2,3,4,4a,7,7a-hexahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-7-ol (67)

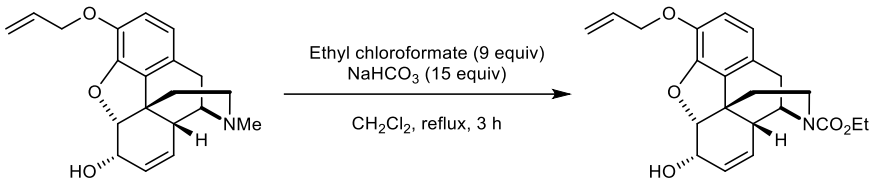


Morphine **1** **67**

To a stirred suspension of morphine (**1**) (500 mg, 1.75 mmol) in EtOH (4.5 mL) was added NaOEt (21 wt. % in ethanol, 0.76 mL, 1.93 mmol) and stirred at room temperature for 20 min under argon. Solution of allyl iodide (0.24 mL, 2.63 mmol) in EtOH (0.8 mL) was then added dropwise over 30 min and the resulting mixture stirred for 16 h at room temperature. The reaction mixture was diluted with H_2O (30 mL), extracted with EtOAc (3 × 20 mL), combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in*

vacuo. The crude mixture was purified by column chromatography (0-5% 2M NH_3[MeOH]/CH_2Cl_2 gradient) to give **67** as a clear colourless oil (274 mg, 48%). R_f = 0.38 (10% 2M NH_3[MeOH]/CH_2Cl_2); $[\alpha]_D^{20.1}$ −108 (*c* 1.00, $CDCl_3$); IR (ATR) 2911, 2848 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.65 (1H, d, J = 8.2 Hz, Ar**H**), 6.52 (1H, d, *J* = 8.2 Hz, Ar**H**), 6.03 (1H, ddt, *J* = 17.2, 10.7, 5.4 Hz, H_2C=C**H**), 5.72-5.63 (1H, m, HOCHC**H**CH), 5.36 (1H, dd, *J* = 17.2, 1.6 Hz, **H**$_a$H$_b$C=CH), 5.30-5.21 (2H, m, HOCHCHC**H** and H$_a$**H**$_b$C=CH), 4.86 (1H, dd, *J* = 6.5, 1.3 Hz, ArOC**H**), 4.61 (1H, dd, *J* = 12.9, 5.4 Hz, C**H**$_a$H$_b$OAr), 4.53 (1H, dd, *J* = 12.9, 5.4 Hz, CH$_a$**H**$_b$OAr), 4.20-4.11 (1H, m, C**H**OH), 3.34 (2H, dd, *J* = 6.4, 3.3 Hz, C**H**N and O**H**), 3.02 (1H, d, *J* = 18.6 Hz, ArC**H**$_a$H$_b$), 2.71-2.62 (1H, m, C**H**CHN), 2.63-2.54 (1H, m, C**H**$_a$H$_b$N), 2.45-2.34 (4H, m, NC**H**$_3$ and CH$_a$**H**$_b$N), 2.28 (1H, dd, *J* = 18.6, 6.4 Hz, ArCH$_a$**H**$_b$), 2.06 2.05 (1H, td, *J* = 12.6, 5.2 Hz, C**H**$_a$H$_b$CH$_2$N), 1.90-1.80 (1H, m, CH$_a$**H**$_b$CH$_2$N); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.7 (C), 140.9 (C), 133.7 (CH), 133.4 (CH), 131.3 (C), 128.3 (CH), 127.6 (C), 119.6 (CH), 117.7 (CH_2), 115.3 (CH), 91.3 (CH), 70.5 (CH_2), 66.4 (CH), 58.8 (CH), 46.4 (CH_2), 43.1 (CH_3), 42.9 (C), 40.7 (CH), 35.8 (CH_2), 20.5 (CH_2); HRMS (ESI) exact mass calculated for $[C_{20}H_{24}NO_3]^+$ [M+H]$^+$: 326.1751, found 326.1751.

Ethyl (4*R*,4a*R*,7*S*,7a*R*,12b*S*)-9-(allyloxy)-7-hydroxy-1,2,4,4a,7,7a-hexahydro-3*H*-4,12-methanobenzofuro[3,2-*e*]isoquinoline-3-carboxylate (68)

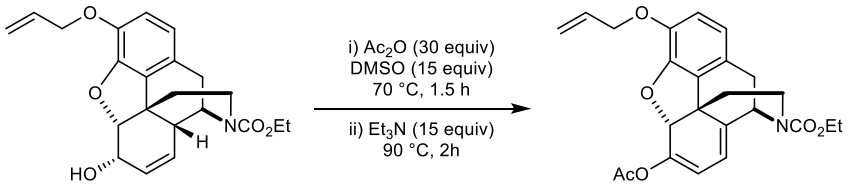


67 68

General Procedure A was followed using amine **67** (200 mg, 0.62 mmol). Purification by column chromatography (0-40% EtOAc/cyclohexane gradient) gave carbamate **68** as a colourless residue (219 mg, 92%). R_f = 0.21 (40% EtOAc/cyclohexane); $[\alpha]_D^{20.1}$ −120 (*c* 1.00, $CDCl_3$); IR (ATR) 3430 (OH), 2931, 1682 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.69 (1H, d, *J* = 8.2 Hz, Ar**H**), 6.53 (1H, d, *J* = 8.2 Hz, Ar**H**), 6.03 (1H, ddt, *J* = 16.2, 10.6, 5.4 Hz, H_2C=C**H**), 5.79-5.70 (1H, m, HOCHC**H**CH), 5.41-5.32 (1H, m, **H**$_a$H$_b$C=CH), 5.32-5.22 (2H, m, HOCHCHC**H** and H$_a$**H**$_b$C=CH), 4.98-4.78 (2H, m, C**H**N and ArOC**H**), 4.62 (1H, dd, *J* = 13.0, 5.4 Hz, C**H**$_a$H$_b$OAr), 4.55 (1H, dd, *J* = 13.0, 5.4 Hz, CH$_a$**H**$_b$OAr), 4.25-3.94 (4H, m, CO_2C**H**$_2$ and C**H**OH and C**H**$_a$H$_b$N), 3.08-

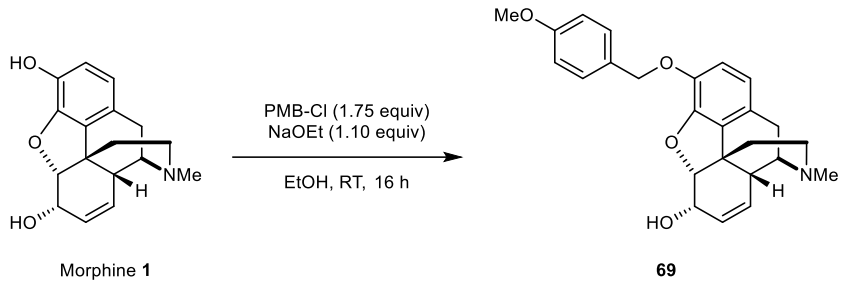
2.90 (2H, m, CH_aH_bN and O**H**), 2.90-2.79 (1H, m, ArC**H**$_a$H$_b$), 2.71 (1H, d, *J* = 18.6 Hz, ArCH$_a$**H**$_b$), 2.56-2.48 (1H, m, C**H**CHN), 1.99-1.84 (2H, m, C**H**$_2$CH$_2$N), 1.32-1.21 (3H, m, C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.4 (C), 146.8 (C), 141.3 (C), 134.2 (CH), 133.6 (CH), 130.2 (C), 127.1 (CH), 126.3 (C), 120.1 (CH), 117.8 (CH_2), 115.7 (CH), 91.1 (CH), 70.5 (CH_2), 66.1 (CH), 61.6 (CH_2), 50.1 (CH), 43.3 (C), 39.6 (CH), 37.4 (CH_2), 35.5 (CH_2), 29.4 (CH_2), 14.7 (CH_3); HRMS (ESI) exact mass calculated for $[C_{22}H_{26}NO_5]^+$ $[M+H]^+$: 384.1805, found 384.1814.

Ethyl (4*R*,7a*R*,12b*S*)-7-acetoxy-9-(allyloxy)-1,2,4,7a-tetrahydro-3*H*-4,12-methanobenzofuro[3,2-*e*]isoquinoline-3-carboxylate (47)



General Procedure B was followed using secondary alcohol **68** (77 mg, 0.2 mmol). Purification by column chromatography (0-30% EtOAc/cyclohexane gradient) gave diene **47** as a clear yellow oil (56 mg, 66%). R_f = 0.44 (40% EtOAc/cyclohexane); $[\alpha]_D^{20.1}$ −208 (*c* 1.00, $CDCl_3$); IR (ATR) 3003, 2916, 1765 (C=O), 1681 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.69 (1H, d, *J* = 8.2 Hz, Ar**H**), 6.56 (1H, d, *J* = 8.2 Hz, Ar**H**), 6.04 (1H, ddt, *J* = 16.3, 10.7, 5.5 Hz, H_2C=C**H**), 5.77 (1H, d, *J* = 6.2 Hz, AcOCC**H**CH), 5.66-5.56 (1H, m, AcOCCHC**H**), 5.48 (1H, s, ArOC**H**), 5.37 (1H, d, *J* = 16.3 Hz, **H**$_a$H$_b$C=CH), 5.27-5.06 (2H, m, H$_a$**H**$_b$C=CH and C**H**N), 4.60 (2H, d, *J* = 5.5 Hz, C**H**$_2$OAr), 4.22-4.00 (3H, m, CO_2C**H**$_2$ and C**H**$_a$H$_b$N), 3.32-3.09 (2H, m, CH_aH_bN and ArC**H**$_a$H$_b$), 3.02 (1H, d, *J* = 18.1 Hz, ArCH$_a$**H**$_b$), 2.22-2.12 (4H, m, **H**$_3$CCO$_2$C and C**H**$_a$H$_b$CH$_2$N), 1.85-1.75 (1H, m, CH$_a$**H**$_b$CH$_2$N), 1.33-1.21 (3H, m, CH$_2$C**H**$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.1 (C), 155.1 (C), 145.1 (C), 143.9 (C), 142.0 (C), 136.3 (C), 133.7 (CH), 132.4 (C), 126.9 (C), 119.7 (CH), 117.7 (CH_2), 116.1 (CH), 115.4 (CH), 110.8 (CH), 87.5 (CH), 70.7 (CH_2), 61.6 (CH_2), 52.2 (CH), 47.4 (C), 38.2 (CH_2), 37.4 (CH_2), 29.7 (CH_2), 21.2 (CH_3), 14.7 (CH_3); HRMS (ESI) exact mass calculated for $[C_{24}H_{26}NO_6]^+$ $[M+H]^+$: 424.1755, found 424.1761.

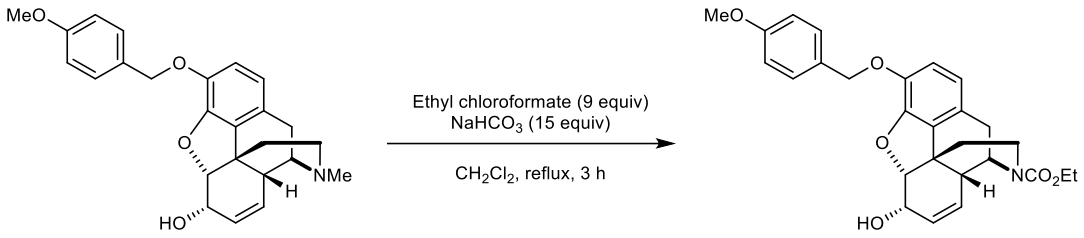
(4*R*,4a*R*,7*S*,7a*R*,12b*S*)-9-[(4-Methoxybenzyl)oxy]-3-methyl-2,3,4,4a,7,7a-hexahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-7-ol (69)



Morphine **1** **69**

To a stirred suspension of morphine (**1**) (500 mg, 1.75 mmol) in EtOH (4.5 mL) was added NaOEt (21 wt. % in ethanol, 0.76 mL, 1.93 mmol) and stirred at room temperature for 20 min under argon. The solution of 4-methoxybenzyl chloride (0.42 mL, 3.06 mmol) in EtOH (0.8 mL) was then added dropwise over 30 min and the resulting mixture stirred for 16 h at room temperature. The reaction mixture was diluted with H_2O (30 mL), extracted with EtOAc (3 × 20 mL), combined organic extracts were washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo*. The crude mixture was purified by column chromatography (0-10% 2M NH_3[MeOH]/CH_2Cl_2 gradient) to give **69** as a white solid (290 mg, 41%). R_f = 0.40 (10% 2M NH_3[MeOH]/CH_2Cl_2); m.p. 146-149 °C (Et_2O); $[\alpha]_D^{20.1}$ −68 (*c* 1.00, $CDCl_3$); IR (ATR) 3546 (OH), 2926, 2799 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (2H, d, *J* = 8.5 Hz, Ar**H**), 6.88 (2H, d, *J* = 8.5 Hz, Ar**H**), 6.71 (1H, d, *J* = 8.2 Hz, Ar**H**), 6.52 (1H, d, *J* = 8.2 Hz, Ar**H**), 5.69-5.64 (1H, m, HOCHC**H**CH), 5.31-5.25 (1H, m, HOCHCHC**H**), 5.08 (1H, d, *J* = 11.4 Hz, ArC**H**$_a$H$_b$O), 5.01 (1H, d, *J* = 11.4 Hz, ArCH$_a$**H**$_b$O), 4.87 (1H, d, *J* = 6.5 Hz, ArOC**H**), 4.15 (1H, dd, *J* = 6.5, 2.8 Hz, C**H**OH), 3.80 (3H, s, ArOC**H**$_3$), 3.35 (1H, dd, *J* = 6.3, 3.2 Hz, C**H**N), 3.03 (1H, d, *J* = 18.6 Hz, ArC**H**$_a$H$_b$CH), 2.73 (1H, br s, O**H**), 2.69-2.65 (1H, m, C**H**CHN), 2.59 (1H, dd, *J* = 12.3, 4.9 Hz, C**H**$_a$H$_b$N), 2.46-2.34 (4H, m, NC**H**$_3$ and CH$_a$**H**$_b$N), 2.29 (1H, dd, *J* = 18.6, 6.3 Hz, ArCH$_a$**H**$_b$CH), 2.06 (1H, td, *J* = 12.4, 5.0 Hz, C**H**$_a$H$_b$CH$_2$N), 1.91-1.83 (1H, m, CH$_a$**H**$_b$CH$_2$N); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.4 (C), 147.0 (C), 141.2 (C), 133.4 (CH), 131.3 (C), 129.3 (2 × CH), 128.3 (CH), 127.7 (2 × C), 119.6 (CH), 115.9 (CH), 113.9 (2 × CH), 91.2 (CH), 71.6 (CH_2), 66.4 (CH), 58.9 (CH), 55.3 (CH_3), 46.5 (CH_2), 43.1 (CH_3), 42.8 (C), 40.7 (CH), 35.8 (CH_2), 20.5 (CH_2); HRMS (ESI) exact mass calculated for $[C_{25}H_{28}NO_4]^+$ $[M+H]^+$: 406.2013, found 406.2011.

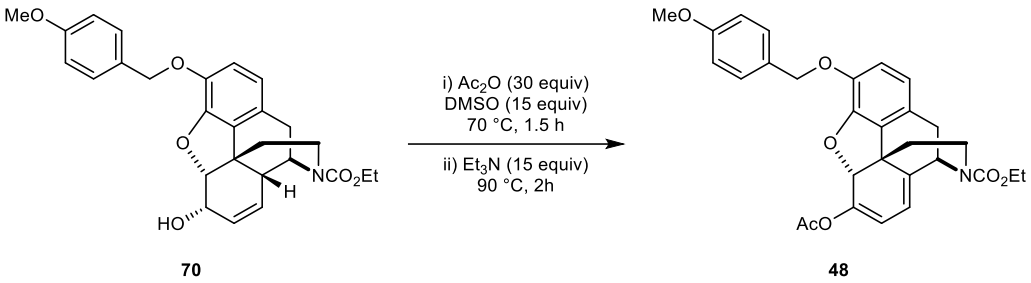
Ethyl (4*R*,4a*R*,7*S*,7a*R*,12b*S*)-7-hydroxy-9-[(4-methoxybenzyl)oxy]-1,2,4,4a,7,7a-hexahydro-3*H*-4,12-methanobenzofuro[3,2-*e*]isoquinoline-3-carboxylate (70)



69 **70**

General Procedure A was followed using amine **69** (200 mg, 0.49 mmol). Purification by column chromatography (0-60% EtOAc/cyclohexane gradient) gave carbamate **70** as a white foam (202 mg, 89%). R_f = 0.21 (50% EtOAc/cyclohexane); m.p. 170-171 °C (Et_2O); $[\alpha]_D^{20.1}$ −108 (*c* 1.00, $CDCl_3$); IR (ATR) 3419 (OH), 2929, 1683 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (2H, d, *J* = 8.4 Hz, Ar**H**), 6.89 (2H, d, *J* = 8.4 Hz, Ar**H**), 6.74 (1H, d, *J* = 8.2 Hz, Ar**H**), 6.53 (1H, d, *J* = 8.2 Hz, Ar**H**), 5.77-5.66 (1H, m, HOCHC**H**CH), 5.32-5.23 (1H, m, HOCHCHC**H**), 5.08 (1H, d, *J* = 11.5 Hz, C$\mathbf{H}_a$$H_b$OAr), 5.01 (1H, d, *J* = 11.5 Hz, C$H_a$$\mathbf{H}_b$OAr), 4.97-4.78 (2H, m, ArOC**H** and C**H**N), 4.25-3.96 (4H, m, $CO_2C\mathbf{H}_2$ and C**H**OH and C$\mathbf{H}_a$$H_b$N), 3.80 (3H, s, ArOC$\mathbf{H}_3$), 3.08-2.91 (1H, m, C$H_a$$\mathbf{H}_b$N), 2.90-2.78 (2H, m, O**H** and ArC$\mathbf{H}_a$$H_b$CH), 2.72 (1H, d, *J* = 18.7 Hz, ArC$\mathbf{H}_a$$H_b$CH), 2.55-2.49 (1H, m, C**H**CHN), 1.99-1.85 (2H, m, C$\mathbf{H}_2$$CH_2$N) 1.34-1.24 (3H, m, $CH_2C\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 159.5 (C), 155.4 (C), 147.1 (C), 141.4 (C), 134.2 (CH), 130.2 (C), 129.3 (2 × CH), 129.2 (C), 127.1 (CH), 126.5 (C), 120.1 (CH), 116.3 (CH), 113.9 (2 × CH), 91.1 (CH), 71.6 (CH_2), 66.1 (CH), 61.6 (CH_2), 55.3 (CH_3), 50.1 (CH), 43.3 (C), 39.6 (CH), 37.4 (CH_2), 35.5 (CH_2), 29.5 (CH_2), 14.7 (CH_3); HRMS (ESI) exact mass calculated for $[C_{27}H_{30}NO_6]^+$ $[M+H]^+$: 464.2068, found 464.2065.

Ethyl (4*R*,7a*R*,12b*S*)-7-acetoxy-9-[(4-methoxybenzyl)oxy]-1,2,4,7a-tetrahydro-3*H*-4,12-methanobenzofuro[3,2-*e*]isoquinoline-3-carboxylate (48)



70 **48**

General Procedure B was followed using secondary alcohol **70** (93 mg, 0.2 mmol). Purification by column chromatography (0-5% EtOAc/CH_2Cl_2 gradient) gave diene **48** as a clear yellow oil (52 mg, 52%). R_f = 0.30 (40% EtOAc/cyclohexane); $[\alpha]_D^{20.1}$ −220 (*c* 1.00, $CDCl_3$); IR (ATR) 2911, 1759 (C=O), 1688 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.35 (2H, d, *J* = 8.5 Hz, Ar**H**), 6.88 (2H, d, *J* = 8.5 Hz, Ar**H**), 6.71 (1H, d, *J* = 8.2 Hz, Ar**H**), 6.54 (1H, d, *J* = 8.2 Hz, Ar**H**), 5.79 (1H, d, *J* = 6.2 Hz, AcOCC**H**CH), 5.66-5.57 (1H, m, AcOCC**H**CH), 5.50 (1H, s, ArOC**H**), 5.28-5.08 (1H, m, C**H**N), 5.07 (2H, s, C$\mathbf{H}_2$OAr), 4.24-3.99 (3H, m, $CO_2C\mathbf{H}_2$ and C$\mathbf{H}_a$H$_b$N), 3.79 (3H, s, ArOC$\mathbf{H}_3$), 3.33-3.09 (2H, m, CH$_a\mathbf{H}_b$N and ArC$\mathbf{H}_a$H$_b$CH), 3.02 (1H, d, *J* = 18.1 Hz, ArCH$_a\mathbf{H}_b$CH), 2.23-2.14 (4H, m, $O_2CC\mathbf{H}_3$ and C$\mathbf{H}_a$H$_b$CH$_2$N), 1.87-1.76 (1H, m, CH$_a\mathbf{H}_b$CH$_2$N), 1.34-1.23 (3H, m, CH$_2$C$\mathbf{H}_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.1 (C), 159.4 (C), 155.1 (C), 145.4 (C), 143.9 (C), 142.2 (C), 136.4 (C), 132.4 (C), 129.4 (C), 129.3 (2 × CH), 127.1 (C), 119.8 (CH), 116.8 (CH), 115.4 (CH), 113.8 (2 × CH), 110.8 (CH), 87.5 (CH), 71.7 (CH_2), 61.6 (CH_2), 55.3 (CH_3), 52.2 (CH), 47.4 (C), 38.2 (CH_2), 37.4 (CH_2), 37.4 (CH_2), 21.2 (CH_3), 14.7 (CH_3); HRMS (ESI) exact mass calculated for $[C_{29}H_{30}NO_7]^+$ $[M+H]^+$: 504.2017, found 504.2010.

Chapter 2: Synthesis of Novel Semi-Synthetic Opiate Derivatives *via* Tungsten Polyoxometalate (POM) Photocatalysis

4. Introduction

4.1. Tungsten-Based POMs in Organic Photocatalysis

In recent years, significant efforts have been made on the part of the synthetic organic community to expand the arsenal of the available tools for selective sp^3 C-H functionalisation.[63] Among these, photocatalytic radical strategies for sp^3 C-H bond cleavage have been actively explored as attractive alternatives to thermal approaches.[64,65] Typically, these approaches involve a photocatalyst (PC), which is activated upon light irradiation. (Figure 28). The resulting excited photocatalyst (PC*) species may abstract a hydrogen atom from sp^3 C-H bonds via a direct hydrogen atom transfer (*d*-HAT) step, to give the corresponding alkyl radical, which in turn can undergo subsequent radical reactions to lead to C-H functionalised products.[66]

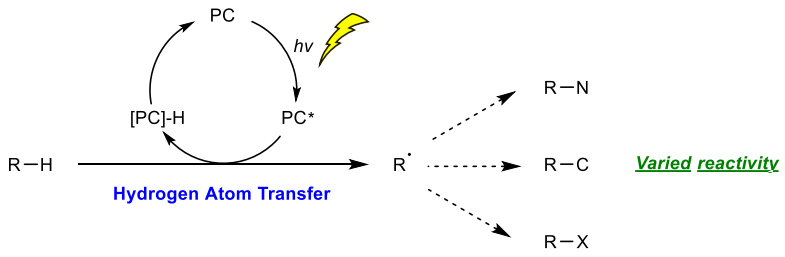


Figure 28. General manifold for direct HAT photocatalytic C-H bond activation

Among the different classes of photocatalysts developed for sp^3 C-H functionalisation, polyoxometalates (POMs) have been identified as a particularly useful class, with the earliest reports describing POM utility dating back to the 1980s.[67–71]

Under irradiation, POMs can be reduced in a reversible fashion to give mixed-valence polyanions, known as heteropoly blues.[72] The distinctive blue colour is a hallmark feature of POMs, associated with the additional electrons on the metal centres, originally present in their highest oxidation state.[73] Monitoring the colour change of the reaction mixture can therefore be a useful qualitative tool for tracking the system evolution.

Tungsten-based POMs, in particular the decatungstate anion $[W_{10}O_{32}]^{4-}$, have been shown to be particularly applicable in the context of HAT catalysis, offering a useful tool for

the elaboration of C-H bonds.[74,75] Hill and co-workers first produced reports describing C-H functionalisation of unactivated alkanes using *tert*-butylammoniumdecatungstate (TBADT, Figure 29) as a HAT photocatalyst in the 1990s, including ethylation, vinylation and carbonylation of cyclohexane.[76–78]

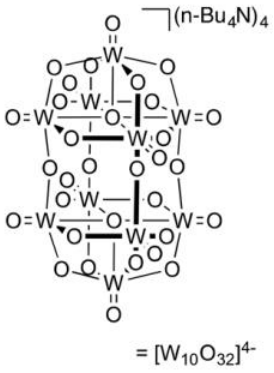


Figure 29. Structure of TBADT catalyst.[79]

Despite these early reports, mechanistic insights into the activation process of organic substrates by the decatungstate anion have only been elucidated recently through computational studies.[80] The absorption spectrum of the decatungstate anion shows a broad band centred at 324 nm, due to an allowed HOMO-LUMO transition with a marked LMCT character, whereby electrons move from oxygen centres to tungsten atoms. The singlet excited state (S_1) initially formed has a short lifetime in the order of a few tens of a picoseconds; it does not interact with organic substrates, but rapidly decays to the actual reactive state (wO).[81] This is a "relaxed" excited state, which is characterised by highly electrophilic oxygen centres with partial radical character.[80] Interaction of wO with an organic substrate in solution can then proceed via a HAT mechanism, leading to a radical organic species and the protonated monoreduced form of decatungstate, $H^+[W_{10}O_{32}]^{5-}$, which on a longer timescale can spontaneously disproportionate, leading to the reduced form $[W_{10}O_{32}]^{6-}$ and the oxidised form of the cluster $[W_{10}O_{32}]^{4-}$.

The following section will provide a detailed overview of the reports describing the use of TBADT as a photocatalyst towards sp^3 C-H bond functionalisation, with a focus on C-C bond formation, and how it can be applied towards the late-stage functionalisation of complex natural products, including semi-synthetic opiate derivatives.

4.2. C-C Bond Formation by Homolytic Cleavage of C-H Bonds with TBADT

4.2.1. From Aldehydes

The formyl group is known to have a relatively weak C−H bond (e.g. approx. 88 kcal/ mol for benzaldehyde)[82], which can be selectively abstracted by TBADT under irradiation to generate acyl radicals.[83] The S_H2 transition state for formyl C−H cleavage by DT anion would be stabilised by partial positive charge on the carbonyl carbon, which provides a beneficial polar effect.[84] Albini and co-workers have reported facile acylation of electrophilic olefins through decatungstate-mediated activation of aldehydes (Figure 30). Using equimolar quantities of heptaldehyde and electron-poor olefins in the presence of TBADT (2 mol%) at room temperature yielded the corresponding functionalised ketones in moderate to good yield. The scope of olefins included α,β-unsaturated esters (**71**), nitriles (**72**) and ketones (**73** and **74**).

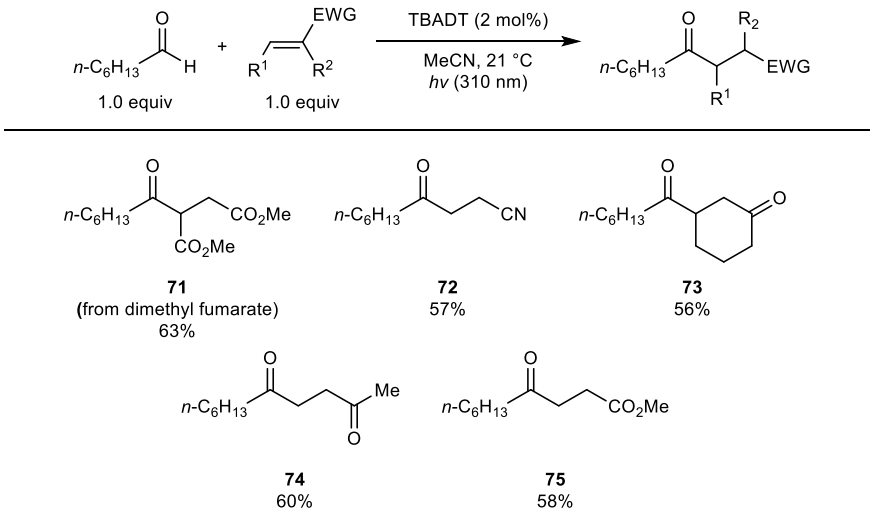


Figure 30. Acylation of electrophilic olefins through TBADT-catalysed activation of aldehydes

The authors proposed that the process is initiated by the excited TBADT species $[W_{10}O_{32}]^{4-*}$, which is able to abstract hydrogen from the aldehyde species to generate the corresponding acyl radical (Figure 31). The resulting radical can then react with the electron-deficient olefin, forming a new C-C bond. The TBADT species $H^+[W_{10}O_{32}]^{5-}$ can then back transfer the hydrogen atom to the adduct radical species, thus generating the final product and turning over the catalytic cycle.

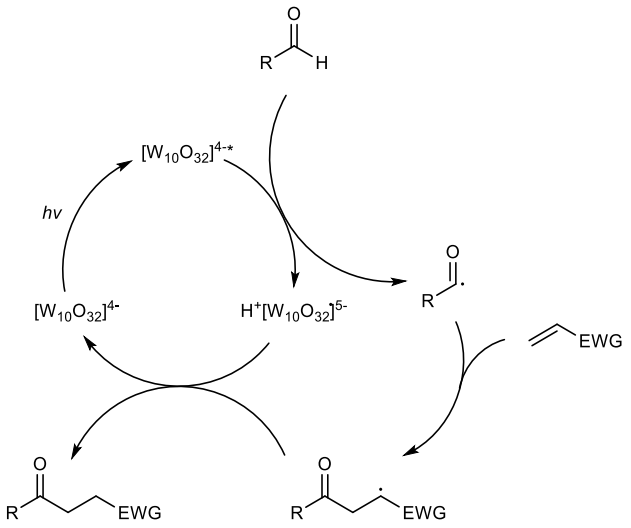


Figure 31. Proposed reaction mechanism for TBADT-catalysed C-C bond formation using aldehydes and electron deficient olefins

Interestingly, the authors also established that in the reaction of secondary and tertiary aldehydes, decarbonylation of the acyl radical intermediates often competes (Figure 32). The undesired side reaction was partially suppressed by performing the reaction at lower temperature or under a CO atmosphere.

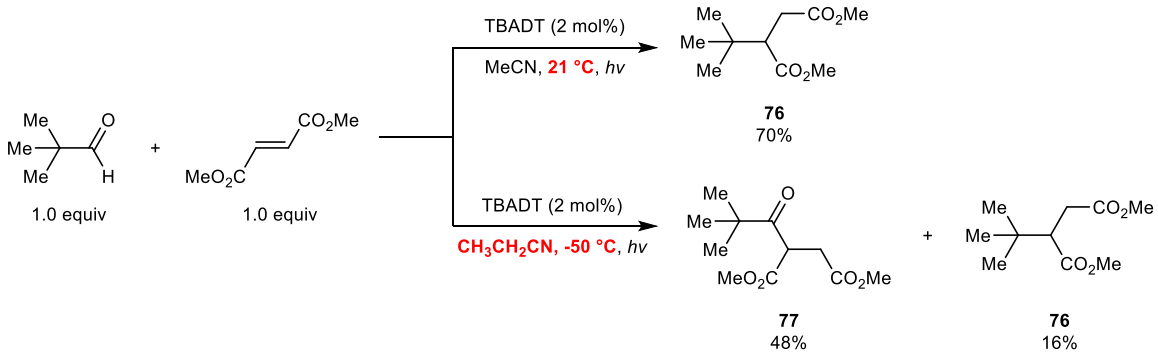


Figure 32. Competing decarbonylation of tertiary acyl radicals

Albini and co-workers later extended the same methodology towards the formyl C–H alkylation of aromatic and heteroaromatic aldehydes (Figure 33).[85] Notably, the method was successfully applied to both electron-rich (**78**) and electron-poor (**85**) heteroaromatic systems. The shortcomings of the method included poor compatibility with free phenols (**81**), which reacted in a sluggish manner, and could not be isolated. Protection of the phenol as a silyl ether remedied the problem affording **82** in 81% yield. Furthermore, when using aromatic aldehydes that had strong absorption at 366 nm, such as 4-nitrobenzaldehyde or naphthaldehyde, no acylation occurred.

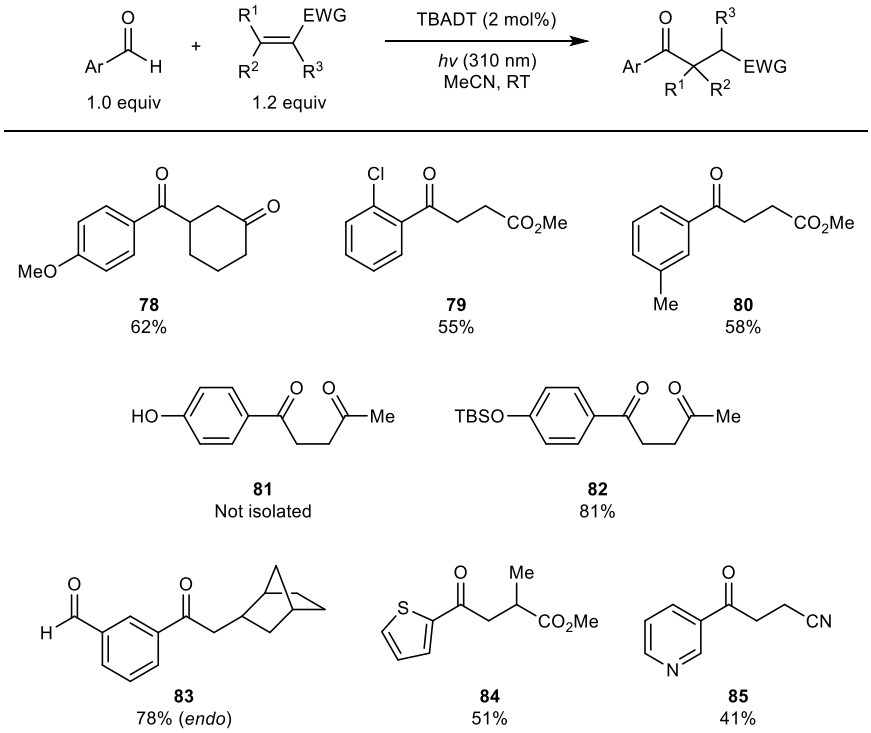


Figure 33. TBADT-catalysed C-C bond formation using aromatic aldehydes

Orfanopoulos and co-workers have demonstrated an interesting application of TBADT catalysis towards acylation of C_{60} fullerene (Figure 34).[86] Notably, the authors had to use a vast excess (~100 equiv.) of the aldehyde species in order to achieve moderate yields of the corresponding products. A mixture of chlorobenzene and acetonitrile was used as a solvent to improve solubility.

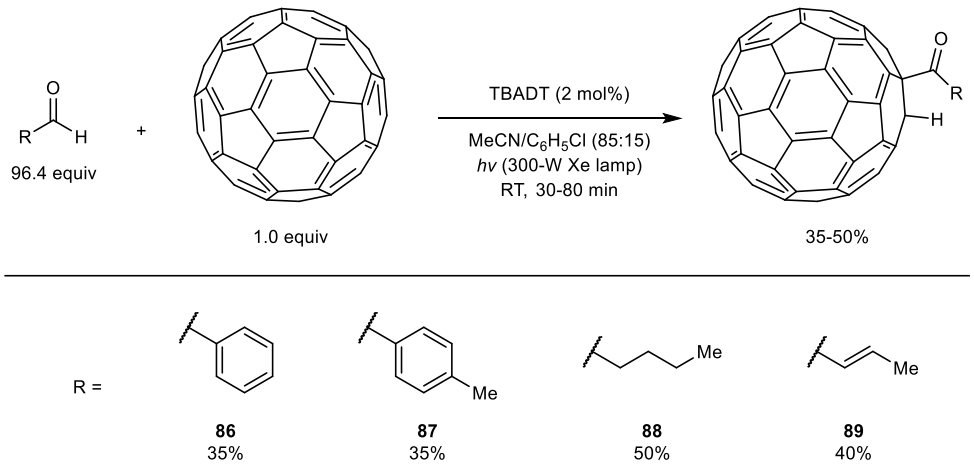


Figure 34. TBADT-catalysed acylation of [60]fullerene

Ryu and co-workers have reported a two-step TBADT-catalysed C-H functionalisation protocol whereby cyclic ketones were used as masked aldehydes in a Norrish Type 1 transformation to achieve a one-pot synthesis of homoallyl ketones (Figure 35).[87]

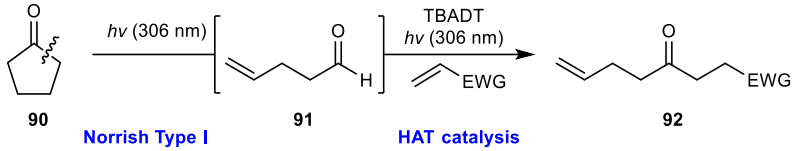


Figure 35. Synthesis of homoallyl ketones via a merger of Norrish Type I reactivity and TBADT catalysis

When cyclopentanone (**90**) was irradiated, in the absence of the TBADT catalyst, 4-pentenal **91** was obtained in 98% yield. Following this first reaction, electron-deficient alkenes and TBADT catalyst were added to the reaction mixture, and the resulting solution was irradiated with the same light source, which gave homoallyl ketones **93** in moderate to good yields (Figure 36). Notably, bicyclic ketone norcamphor also underwent the transformation to give the corresponding cyclopentenone **99** in 54% yield.

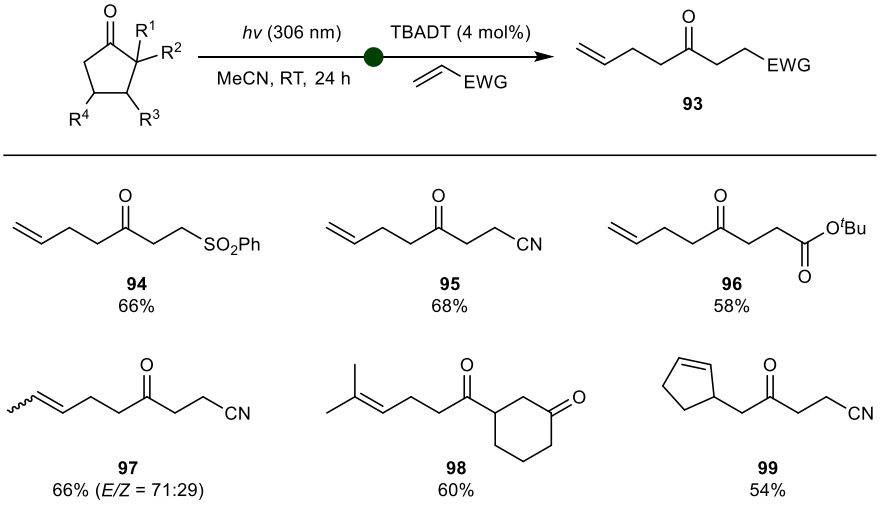


Figure 36. Scope of TBADT-catalysed synthesis of homoallyl ketones from cyclic ketones

Furthermore, while the reaction was proposed to proceed via an enal species containing an allylic C−H bond which could undergo C−H functionalization, no such reactivity was observed. The authors attributed this to the enhanced radical polar effect the S_H2 transition state of formyl proton abstraction (Figure 37).

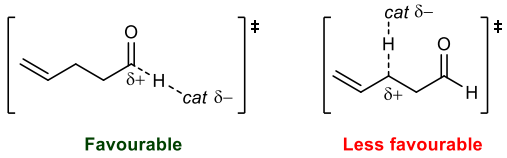


Figure 37. Proposed enhanced radical polar effect in the formyl proton abstraction compared to allylic proton abstraction

4.2.2. From Alkanes

Notably, the photoexcited TBADT species can also abstract protons from non-activated alkanes to generate reactive alkyl radicals (e.g. BDE of cyclohexane approx. 99 kcal/ mol[82]). Albini and co-workers were first to extensively map out the reactivity of TBADT-generated alkyl radicals towards electron-deficient olefins,[88,89] including reactions performed under sunlight in lieu of UV irradiation (Figure 38).[90] Reactions typically required a large excess of the alkane and gave the corresponding adducts only in moderate to good yields, despite full conversion of the starting material. More recently, Fagnoni and co-workers have also described the application of this reactivity in flow.[91]

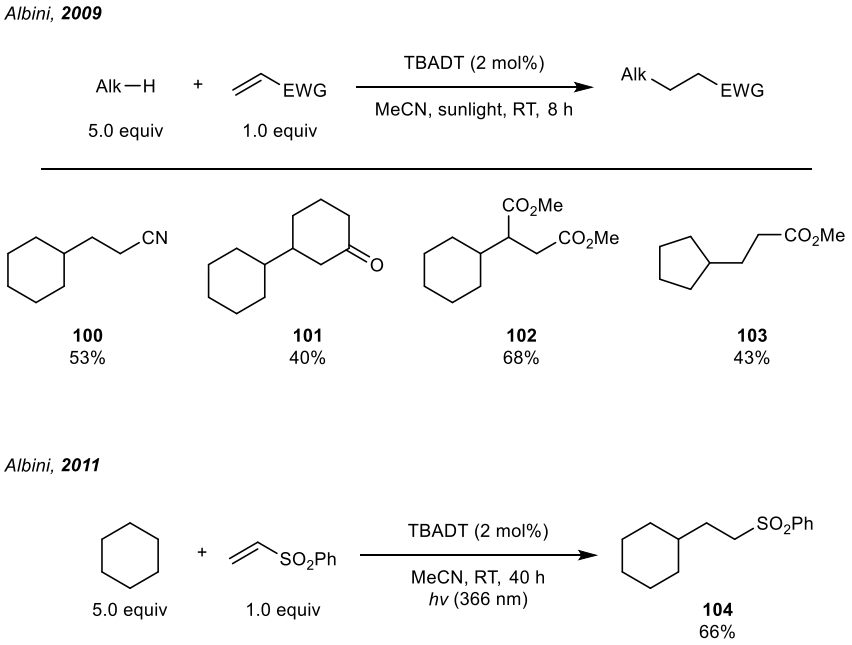


Figure 38. Work by Albini et al demonstrating TBADT-catalysed alkylation of electron-deficient olefins

Albini and co-workers further discovered that if the reaction is pressurised with CO, TBADT-generated alkyl radicals add to CO to give acyl radicals, which subsequently undergo addition to electron-deficient alkenes to provide unsymmetrical ketones (Figure 39).[92] Use of

a large excess of the alkyl coupling partner was found to be imperative in order to obtain satisfactory yields. Likewise, the yield was diminished if the reaction was performed at a lower pressure of CO due to the competing direct reaction between the alkyl radical and the radical acceptor.

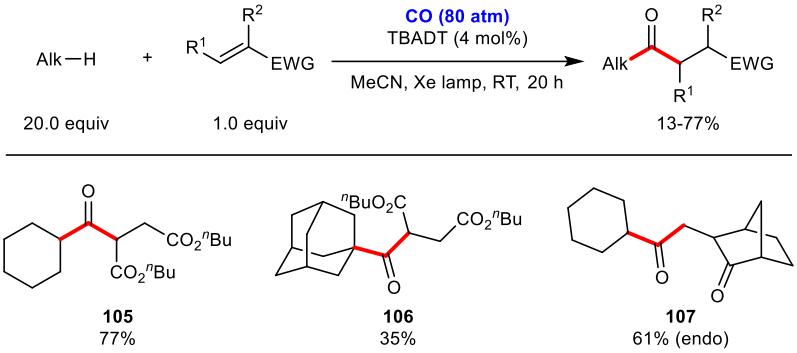


Figure 39. Synthesis of unsymmetrical ketones from TBADT-generated alkyl radicals under CO pressure

Selective C-H activation of alkylaromatics can also be achieved with TBADT. Albini and co-workers demonstrated that the presence of a more labile benzylic hydrogen in alkylaromatics generally drives the selective formation of benzyl radicals (Figure 40).[93] The method was successfully applied to ring-substituted toluenes (**108**-**110**), indane (**112**) and durene (**113**) among other substrates. Interestingly, the authors found that using aqueous $LiClO_4$ in conjunction with MeCN/ H_2O solvent system resulted in improved yields, compared to identical conditions without $LiClO_4$, but offered no explanation for the underlying cause of the observed effect.

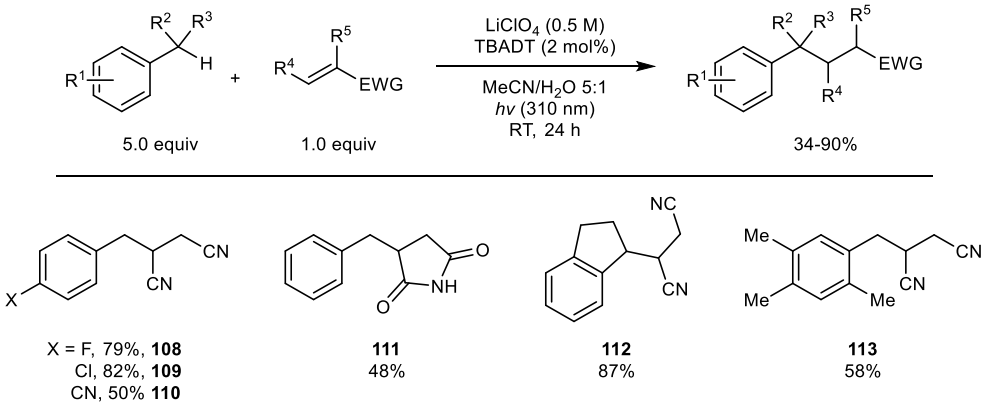


Figure 40. TBADT-catalysed benzylic activation of alkylaromatics

In contrast to the benzylic C-H activation described above, Ryu and co-workers have demonstrated that 2-alkylpyridines are far less amenable to TBADT-catalysed α-C–H

functionalization and instead react exclusively at β- and γ-positions, depending on the nature of the alkyl chain (Figure 41).[94] Using a large excess of 2-isopentylpyridine the authors were able to show reactivity towards a range of electron-deficient olefins in moderate to good yields. The absence of C−H abstraction at the *α*-position was rationalised by an inductive effect of the pyridine ring influencing the S_H2 transition states.

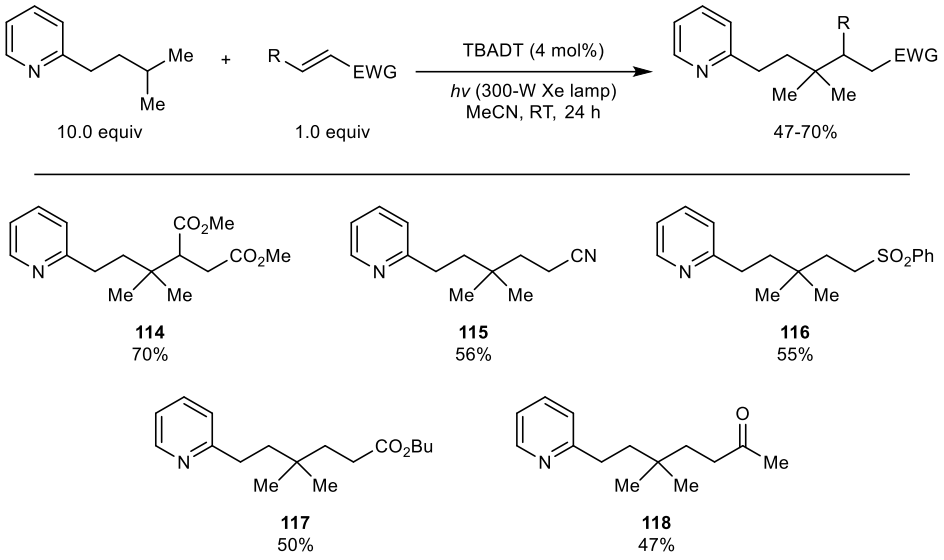


Figure 41. TBADT-catalysed γ-functionalisation of 2-alkylpyridines

More recently, Wang and co-workers have employed TBADT in an asymmetric aliphatic C-H alkylation of exocyclic enones using a chiral proton-transfer shuttle **119** as a cocatalyst (Figure 42).[95] Using a vast excess of the alkane species (20-200 equiv) and a combination of 4 mol% TBADT and 2 mol% phosphoric acid **199** at 30 °C, the authors were able to show a broad scope with moderate to high yields and up to 93% *ee*. With respect to the substrate scope, a range of substituted 1-tetralone derivatives (**120**-**122**) bearing both electron-donating and electron-withdrawing substituents were well tolerated. A heteroaryl-fused enone also reacted smoothly to afford the corresponding product **123**. Exocyclic enones without fused rings could also be tolerated (**124**), while acyclic enones only worked with moderate yield and greatly diminished *ee* (**125**). The authors also explored the scope of hydrocarbons, showing successful application of both aliphatic (**126**) and aromatic (**127**) substrates. Furthermore, an aliphatic aldehyde was successfully employed to give a chiral 1,4-dicarbonyl product **128**, albeit with lower *ee*.

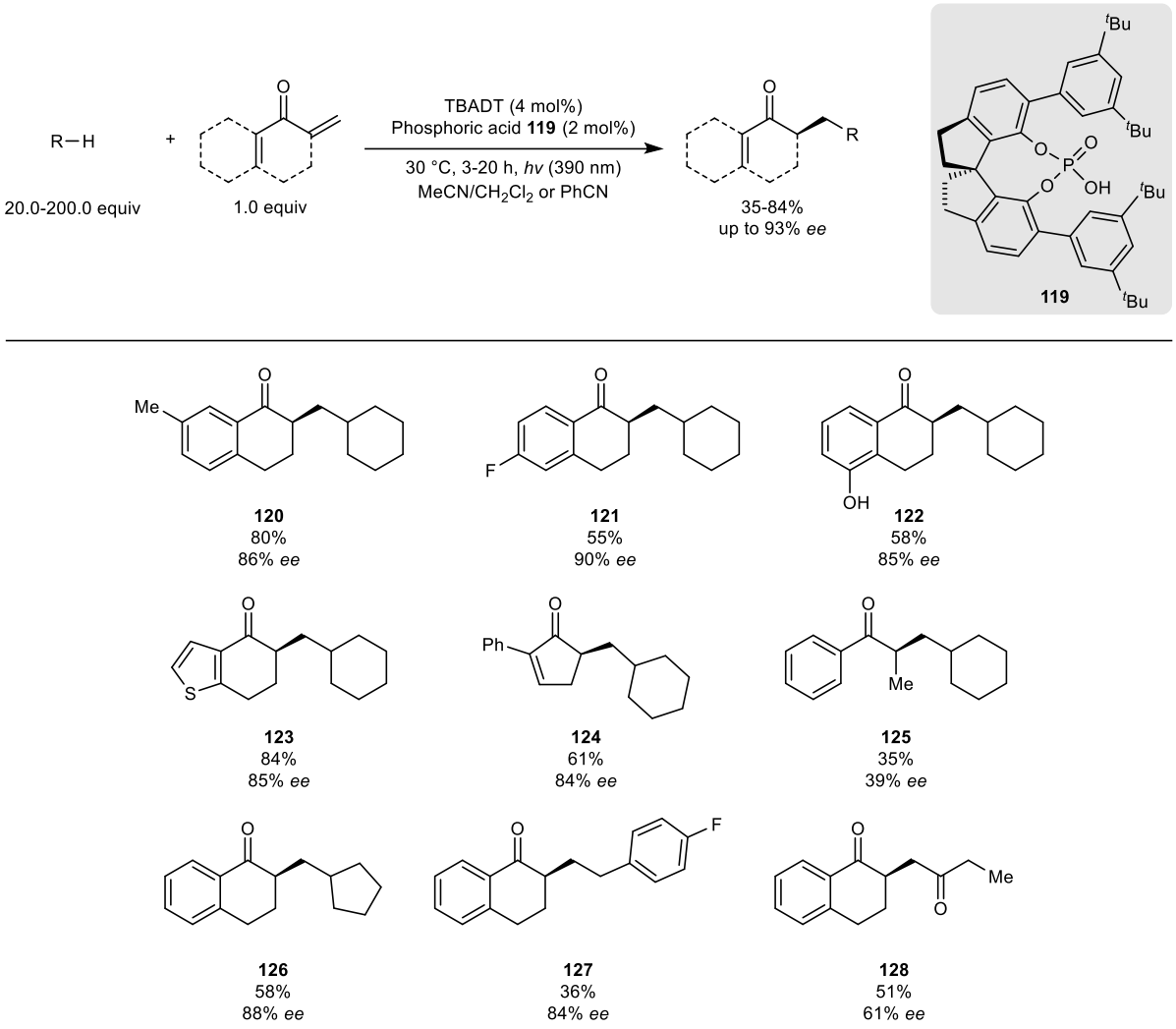


Figure 42. Asymmetric C-H alkylation employing tandem TBADT/ chiral phosphoric acid catalysis

Mechanistically, the authors proposed that an initial photoexcited TBADT-mediated HAT generates alkyl radical **130**, which can undergo conjugate addition to the enone **131**, followed by back-transfer of the hydrogen atom from the reducing TBADT-species to furnish enol **133** (Figure 43). Chiral phosphoric acid co-catalyst **119** can then effect an enantioselective protonation, acting as a chiral proton-transfer shuttle to furnish the desired chiral ketone **134**.

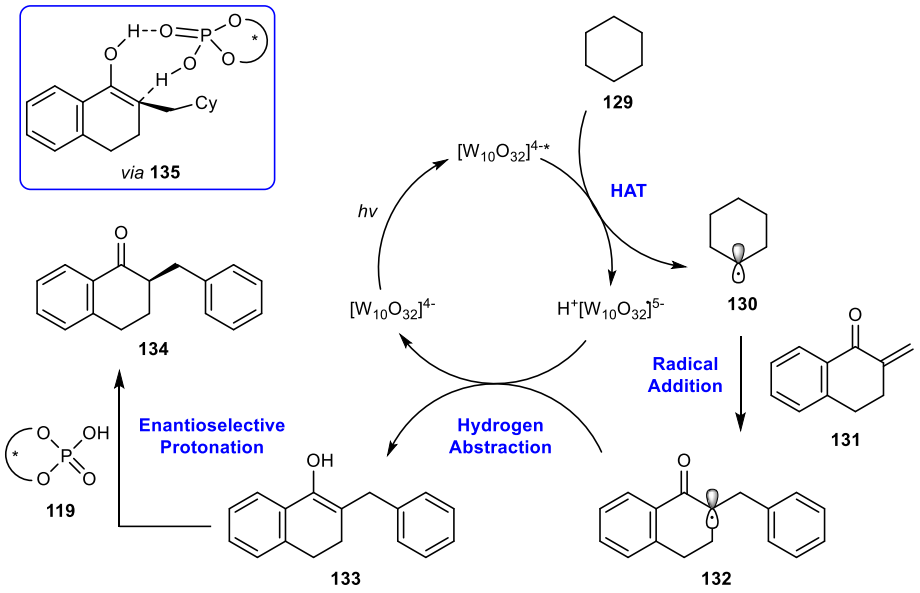


Figure 43. Proposed catalytic cycle for the asymmetric C-H alkylation via TBADT/ chiral phosphoric acid catalysis

4.2.3. From Alcohols and Ethers

TBADT is also capable of abstracting hydrogen atoms from saturated aliphatic alcohols, with cleavage occurring at the more electron-rich C-H bond adjacent to the oxygen atom to form the corresponding α-hydroxyalkyl radical. Albini and co-workers produced an early report on the reaction of excess isopropanol with acrylonitrile under TBADT catalysis to form the corresponding γ-hydroxynitrile in 72% yield (Figure 44).[96]

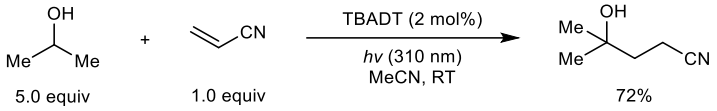


Figure 44. Reaction of isopropanol with acrylonitrile catalysed by TBADT

Fukuyama and co-workers later expanded on a similar methodology, whereby they demonstrated a larger scope of primary (**137**) and secondary (**136** and **139**) alcohols reacting successfully with electron deficient alkenes to furnish the desired products in moderate to good yields (Figure 45).[97] The selectivity for α-abstraction was highlighted with isopentanol derivative **138**, whereby C–H bond cleavage took place site-selectively α to the hydroxyl group, and no functionalization at the methine C–H bond was observed.

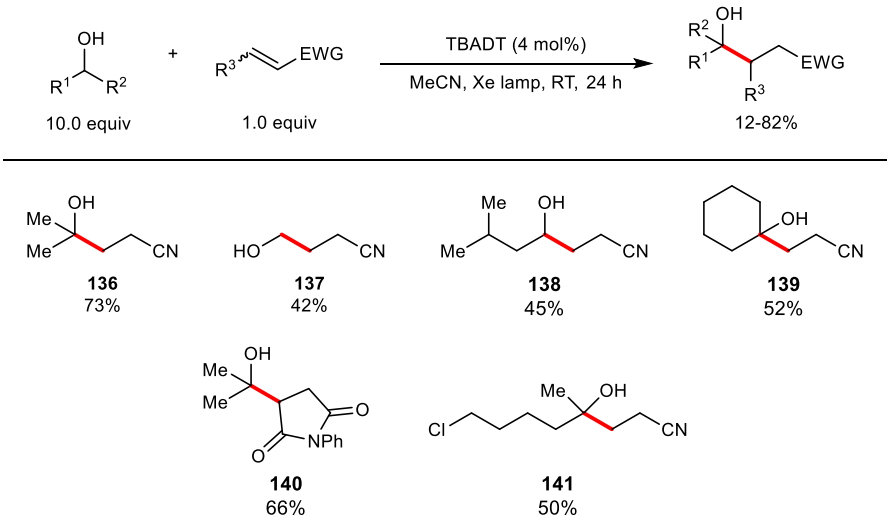


Figure 45. TBADT-catalysed α-alkylation of aliphatic alcohols

Analogous to alcohols, ethers can also undergo TBADT-catalysed hydrogen atom abstraction α to the oxygen atom. The resulting α-oxy radicals have been employed in C–C bond formation, first reported by Dondi and co-workers,[96] and later expanded by Tzirakis *et al* to demonstrate functionalisation of C_{60} fullerene with aryl ethers and crown ethers (Figure 46).[98,99] Notably, in both cases a vast excess of the ether was required in order to achieve moderate yields.

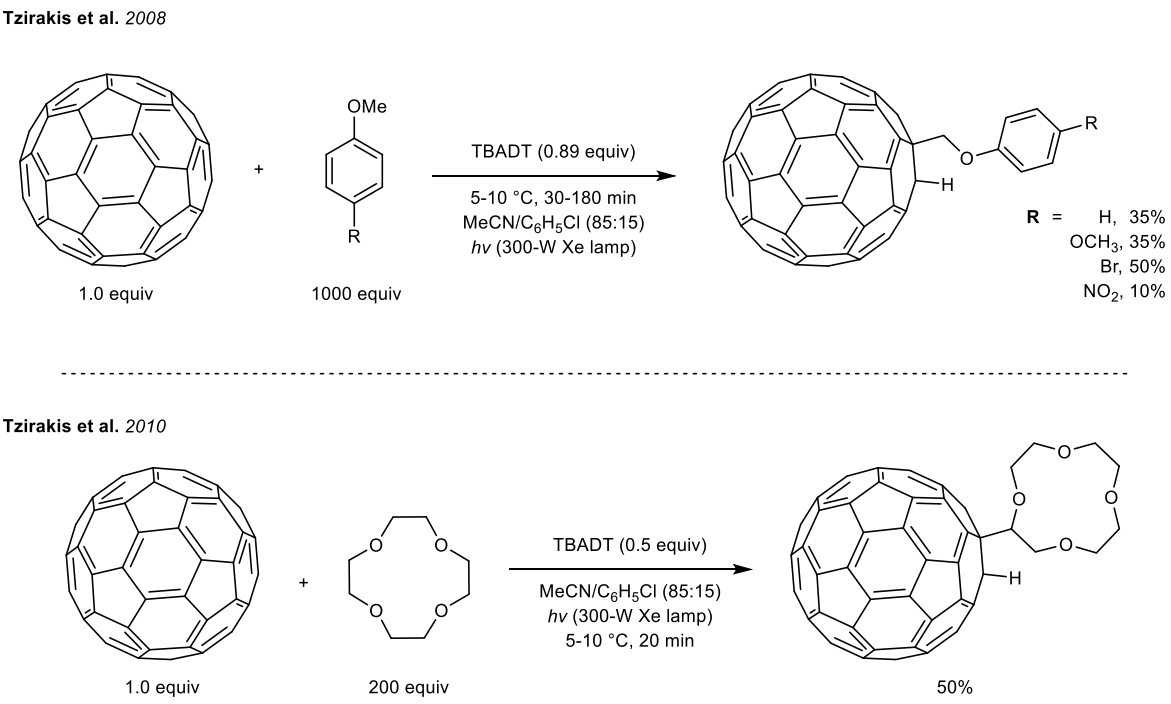


Figure 46. TBADT-catalyst addition of ethers to [60]fullerene

Leveraging the high selectivity of TBADT-catalysed α-activation of ethers, Ravelli and co-workers have reported a robust method for the synthesis of 2-substituted oxetanes (Figure 47).[100] By trapping oxetane-derived *α*-oxy radicals with electron-deficient olefins, the authors were able to generate a range of 2-substituted oxetanes **142**-**145** in modest to good yields.

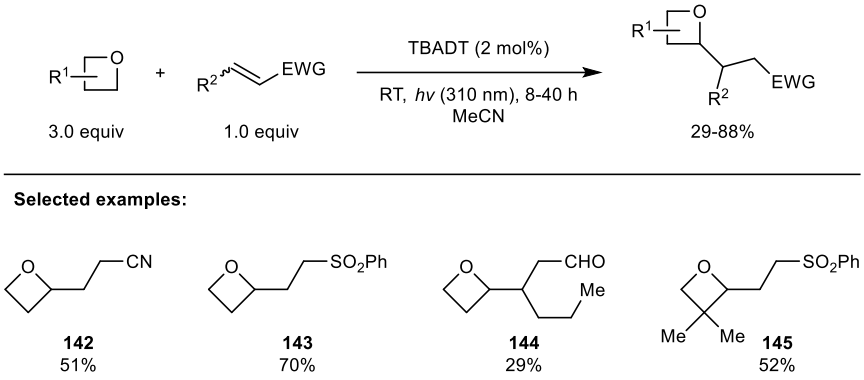


Figure 47. Synthesis of 2-substituted oxetanes through TBADT-catalysed C-H activation

The authors also found that in the case of pre-functionalised 2-substituted oxetane **146**, reaction yielded the 2,4-*trans*-disubstituted oxetane **148** as a major product, with smaller quantities of 2,2-disubstituted **149** as a minor product (Figure 48). This suggested that the presence of a bulky substituent in the 2-position overrides the abstraction of proton from the methine carbon, directing it instead to give the 2,4-*trans* product.

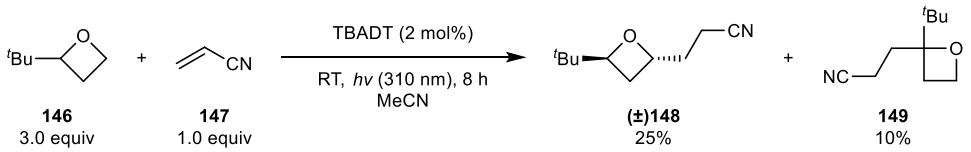


Figure 48. Effect of the substitution pattern on TBADT-catalysed oxetane derivatisation

More recently, in an interesting departure from reports describing functionalisation of electron-deficient olefins, Quattrini and co-workers produced a method for TBADT-catalysed derivatisation of aromatics (Figure 49).[101] Specifically, the authors reported a photocatalytic Minisci reaction using TBADT and persulfate anions, which proceeded with THF, among other substrates, with high selectivity and moderate yield.

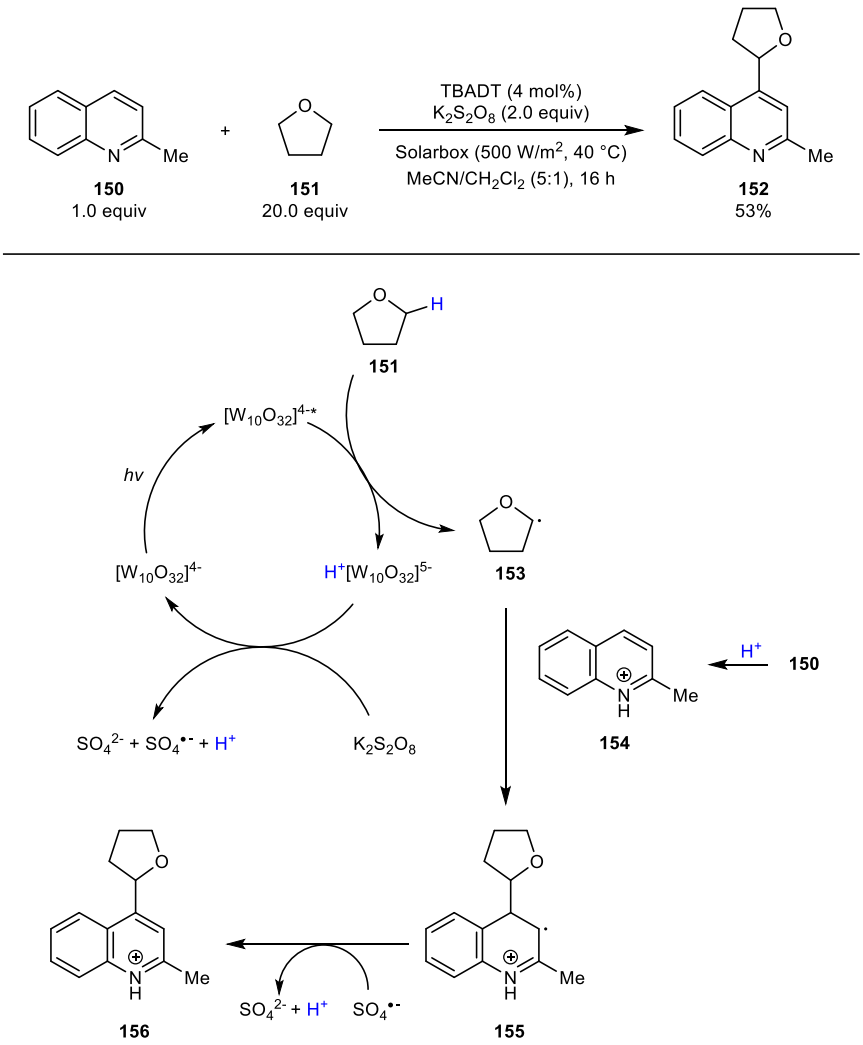


Figure 49. TBADT-catalysed Minisci reaction and proposed mechanism

Mechanistically, the authors proposed that following the HAT step, which produces the nucleophilic radical species **153**, the catalyst is oxidised by $K_2S_2O_8$, liberating an equivalent of acid along with a strong oxidant ($SO_4^{\bullet -}$). The nucleophilic radical species **153** is then trapped by the protonated heterocycle **154**, and the resulting radical adduct **155** is oxidised by ($SO_4^{\bullet -}$) to give the protonated desired product **156**. The authors noted, however, that other minor pathways could be operating simultaneously. For example, minor quantities of the ($SO_4^{\bullet -}$) species could be formed directly from the persulfate via thermal or photoinduced cleavage. The same species could potentially also be involved in hydrogen abstraction of the α-oxy protons from THF. Nonetheless, control experiments demonstrated that the presence of TBADT is crucial for the reaction to proceed.

1,3-Benzodioxoles have also been shown to react effectively with electron-deficient olefins through selective formation of the *α,α*-dioxyalkyl radical by Ravelli and co-workers

(Figure 50).[102] Notably, even in the presence of other reactive moieties on the benzene ring, such as the piperonal derivative **159**, the reaction proceeded exclusively at the methylene C-H. Furthermore, having a small substituent at the CH_2 group was not detrimental to the reactivity, as demonstrated by the methyl derivative **161**.

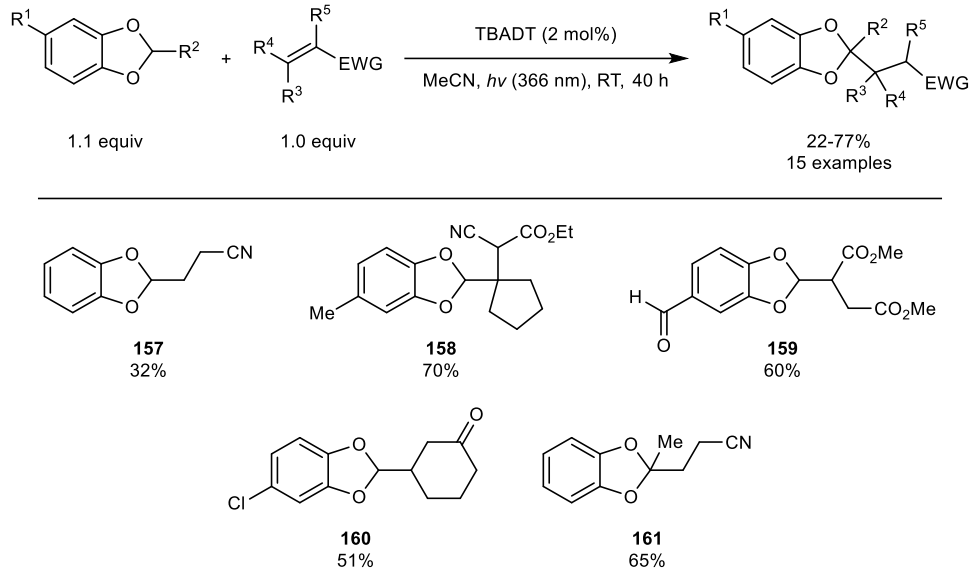


Figure 50. TBADT-catalysed selective functionalisation of 1,3-benzodioxoles

An enantioselective variant of a similar process has been developed by Murphy and co-workers, which relies on iminium ion trapping of radicals to produce β,β-disubstituted cyclic ketones with high *ee* (Figure 51).[103] In this method, chiral organocatalyst **162**, containing a redox-active carbazole moiety, drives the formation of iminium ions and the stereoselective trapping of benzodioxole radicals by means of an electron-relay mechanism.

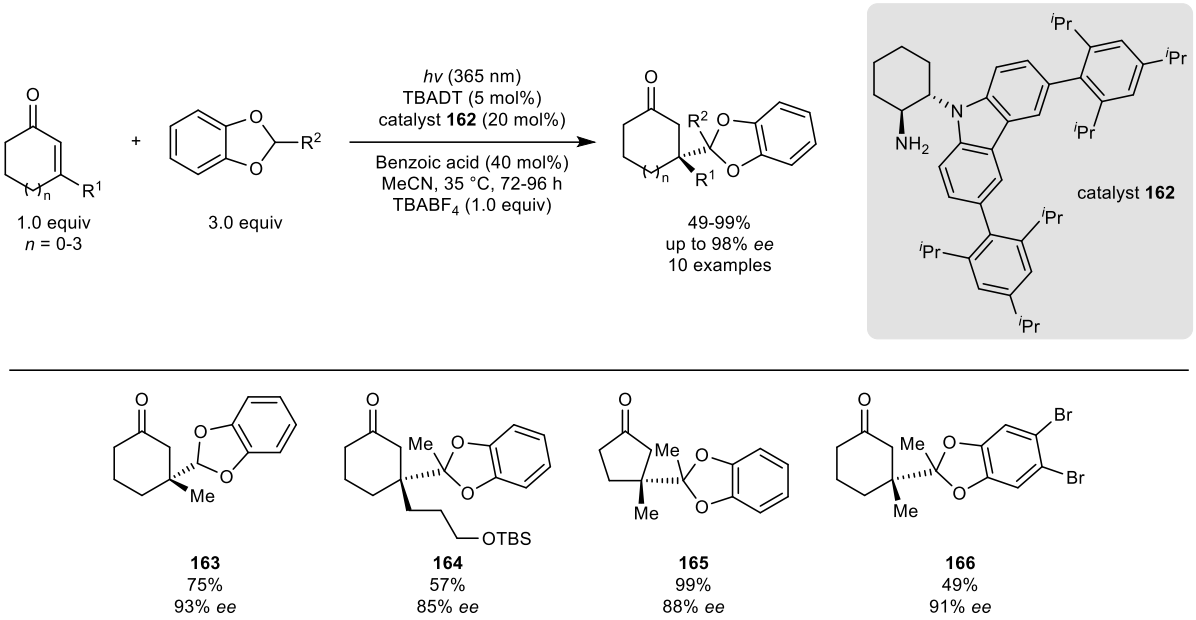


Figure 51. Asymmetric TBADT-catalysed addition of 1,3-benzodioxoles to β-substituted cyclic enones via iminium ion trapping

The proposed mechanism for this transformation is initiated by the condensation of the chiral carbazole-based catalyst **174** and the β-substituted enone **167** to give the chiral iminium ion **168** (Figure 52). The authors suggest that the stability of this ion and the *Z*-configuration of the C=N double bond originate from a stabilising intramolecular charge transfer π-π interaction between the electron-rich carbazole and the electron-deficient iminium ion, bringing the two moieties into proximity. This purportedly governs the stereocontrol of the radical conjugate addition that follows, to give the α-iminyl radical cation **169**, which can undergo a rapid proximity-driven intramolecular reduction via SET. This in turn generates a carbazoliumyl radical cation **170** (dubbed "e^- hole"), which can undergo fast tautomerisation of the secondary enamine to afford the imine **171**. At this point, the radical cation can be reduced by the reducing photocatalytic species $H^+[W_{10}O_{32}]^{5-}$, closing the photoredox cycle. The iminium ion cycle is then terminated through the hydrolysis of imine **172** to regenerate catalyst **174** and liberate product **173**.

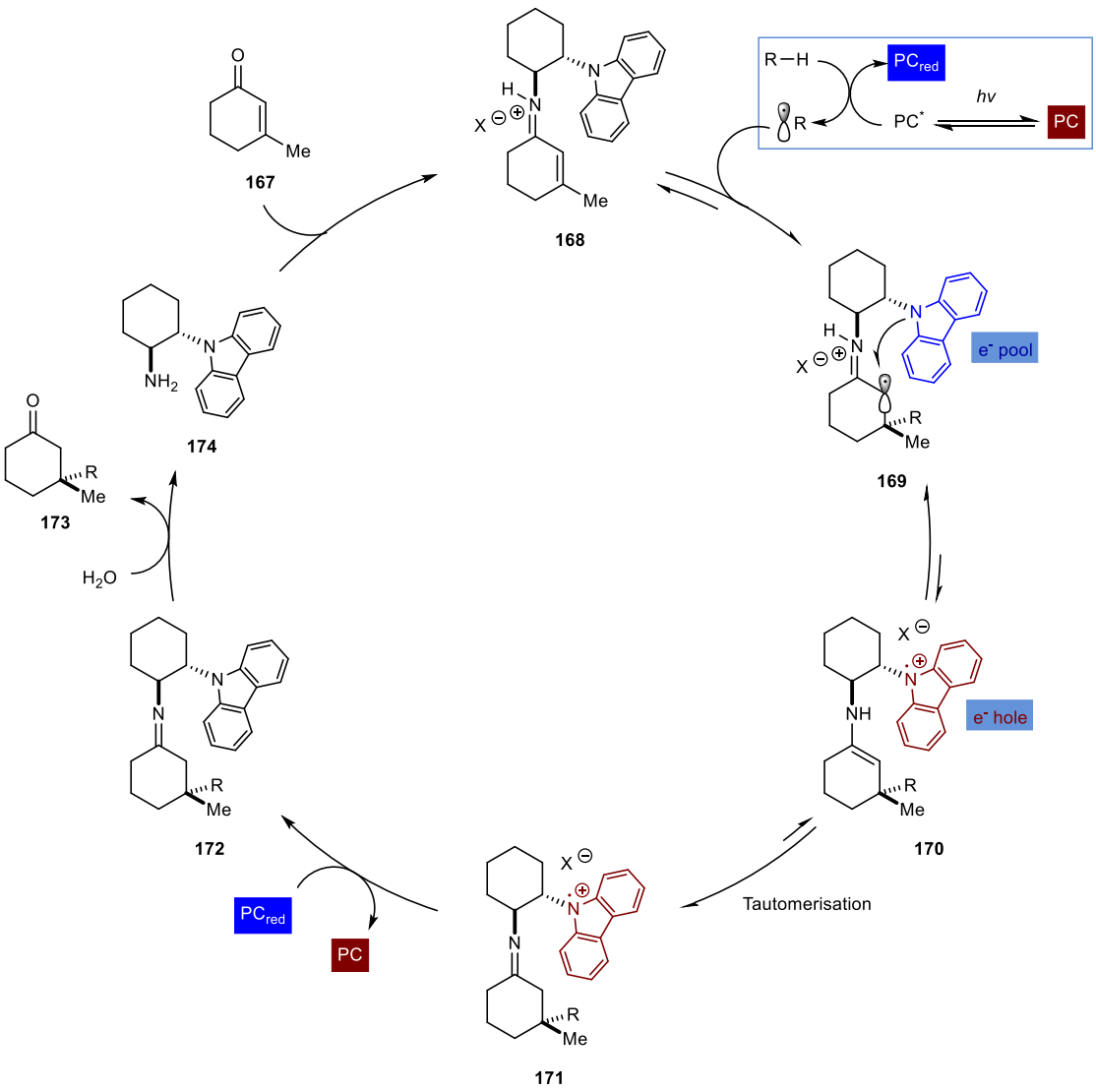


Figure 52. Proposed mechanism for the TBADT-catalysed asymmetric synthesis of quaternary carbon centres

4.2.4. From Amides and Esters

Amides can also be utilised in TBADT-catalysed C-C bond formation. Angioni and co-workers have demonstrated diverse reactivity of primary, secondary and tertiary amides towards electron-deficient olefins, catalysed by TBADT (Figure 53).[104] Formamide was shown to react via the formyl C-H (**175**), while with DMF the reaction proceeded selectively on the *N*-methyl C-H bond (**176**). Similarly, C-H functionalization of *N,N*-dimethylacetamide took place site-selectively at the *N*-methyl group (**177**). The lack of the reactivity *α* to the carbonyl is similar to that observed for ketones (*vide infra*). In the case of *γ*-butyrolactam, the reaction proceeded predominantly via the *N*-methylene C-H (**179**), rather than *N*-methyl in approximately 13:1 ratio.

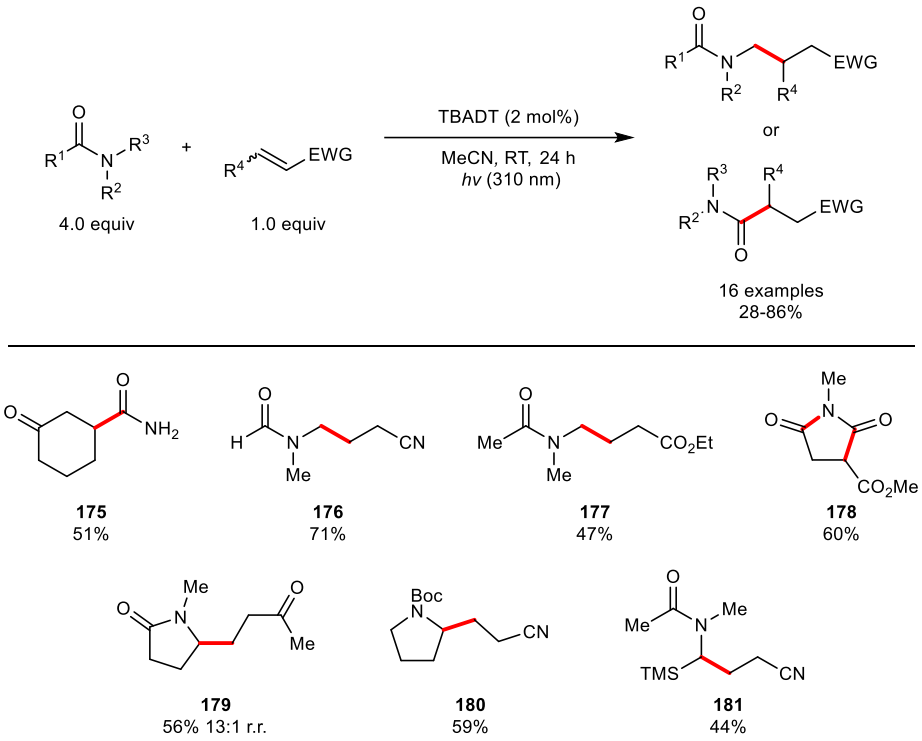


Figure 53. Derivatisation of amides with electron-deficient olefins catalysed by TBADT

Prieto and co-workers have described a TBADT/ disulfide photocatalytic dual system for the hydrocarbamoylation of styrenes (Figure 54).[105] Using bis-(4-methoxyphenyl)-disulfide as a co-catalyst at 10 mol% loading, the authors were able to demonstrate TBADT-catalysed addition of formamide to substituted styrenes (**182** and **183**), as well as pyridinyl derivative **184**. The authors noted that attempts at hydrocarbamoylation of aliphatic vinyl compounds

were unsuccessful. *N*-Substituted formamide derivatives were tolerated under the reaction conditions (**185**), while *N,N*-substituted radical donors were found to be unreactive (**186**).

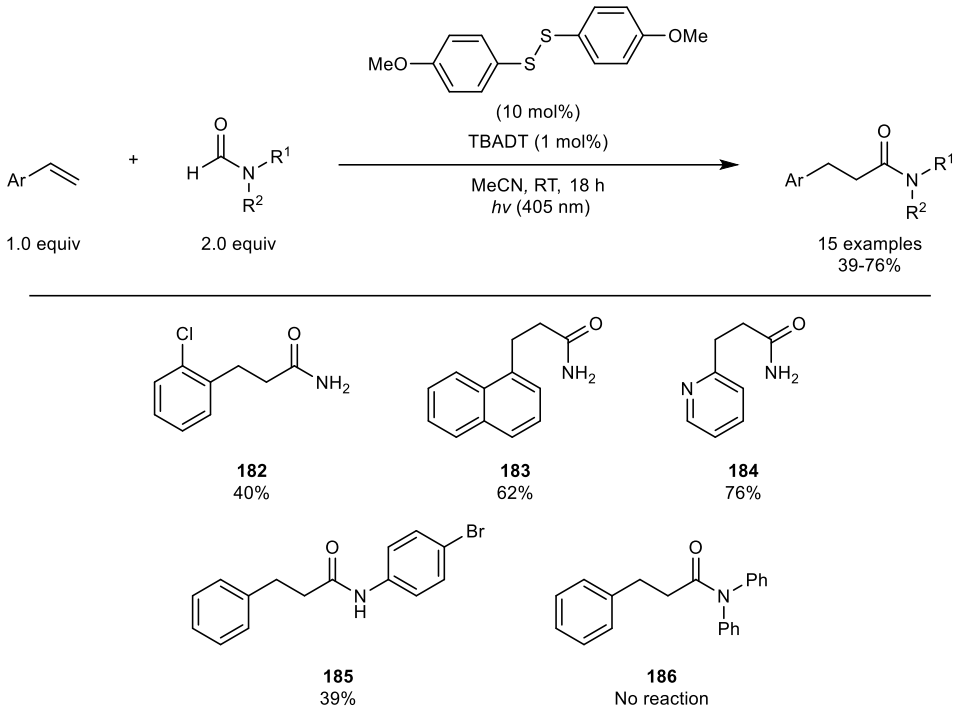


Figure 54. Dual TBADT/ disulfide catalytic system for hydrofunctionalisation of styrenes

The reaction mechanism was proposed to involve the disulfide catalyst as an electron mediator and a hydrogen donor, wherein the disulfide can form the corresponding thiyl radical under light irradiation (Figure 55). This radical species can then be reduced by $H^+[W_{10}O_{32}]^{5-}$, resulting in *in situ* thiol formation, followed by proton donation to liberate the desired product. The authors noted that direct use of thiophenol resulted in significantly diminished yield.

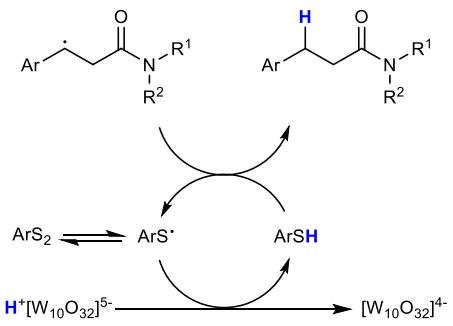


Figure 55. Proposed mechanism for the TBADT/ disulfide catalysed hydrofunctionalisation of styrenes

Esters can also be used as radical precursors under TBADT catalysis. Yamada and co-workers have investigated the polar and steric effects on site-selective photocatalysed C-H

functionalisation of esters and lactones (Figure 56).[106] In the case of *tert*-butyl butyrate **187** the reaction proceeded mainly at the β-methylene group and to a much lesser extent at the γ-methyl group. No α-alkylation was observed at all, consistent with deactivating polar effects being exerted in the S_H2 transition state. On the other hand, alkylation of *γ*-butyrolactone **189** proceeded largely at the γ position, and further introduction of a methyl group at the *γ*-position resulted in selective C−H alkylation at the methine C−H bond.

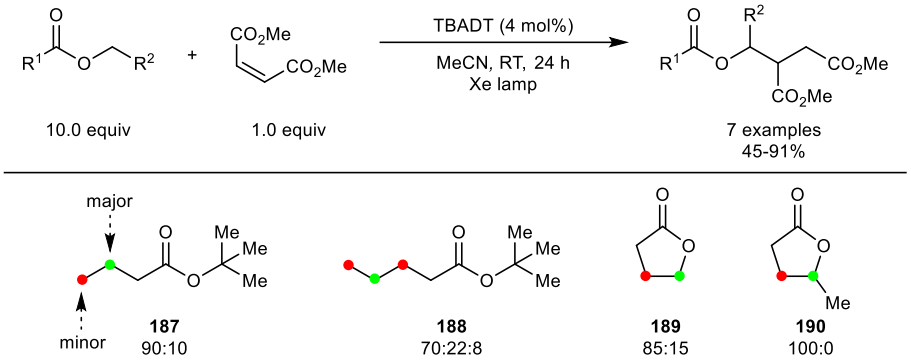


Figure 56. C-H functionalisation of esters via TBADT catalysis

The authors demonstrated that site selectivity in TBADT-catalysed C-H functionalisation of lactones can be achieved through a combination of polar and steric effects (Figure 57). Specifically, when *gem*-dimethyl lactone **191** was subject to the reaction conditions, no reaction took place. The lack of reactivity was attributed to polar effects in the *α*-methylene position and steric effects in the remaining positions. In contrast, when the lactone was modified with an isoamyl tether **193** the methine C-H of the isoamyl chain was selectively functionalised.

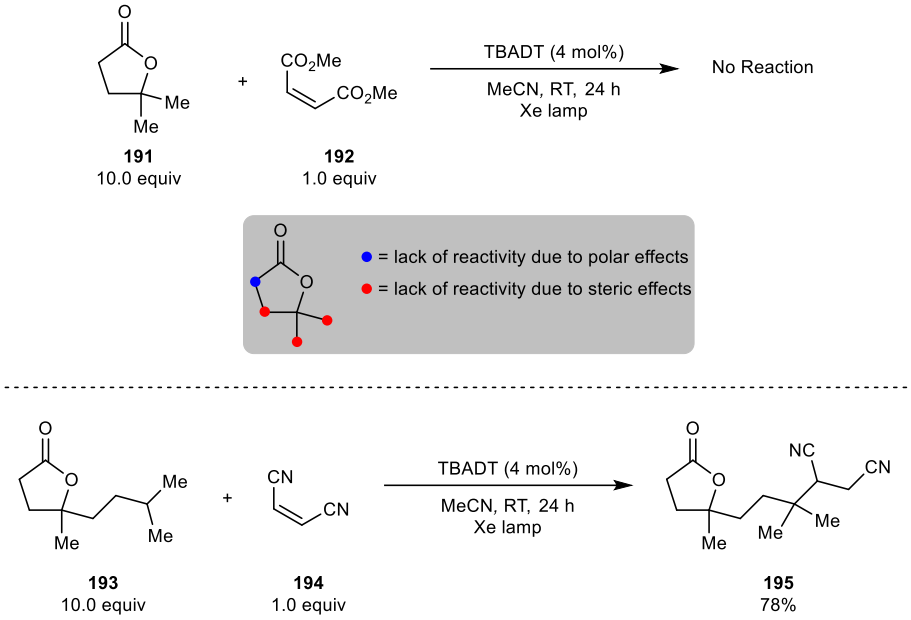


Figure 57. Polar and steric effects in TBADT-catalysed functionalisation of lactones

4.2.5. From Ketones (β-abstraction)

Ketones have also been shown to undergo TBADT-catalysed C-H functionalisation by Okada and co-workers.[107] The group demonstrated photoinduced regioselective β-alkylation of cyclopentanones with electron-deficient alkenes (Figure 58). Using an excess of ketone (5.0 equiv) moderate to good yields could be achieved, with complete regioselectivity for the β-position (**196**-**199**).

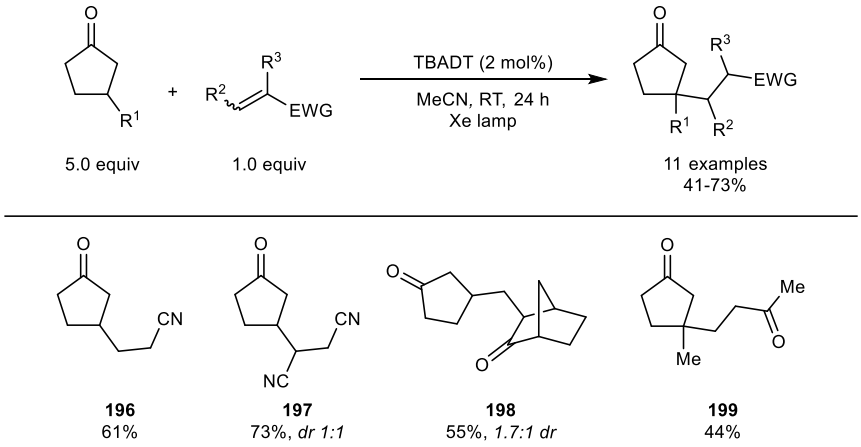


Figure 58. β-alkylation of cyclopentanones under TBADT catalysis

The authors proposed that the regioselectivity arises from the more favourable polar S_H2 transition state in the β-position (Figure 59). The C-H bond cleavage should be promoted

by polar effects, since the oxygen-centred radicals on the photoexcited TBADT species are electronegative in nature, and therefore would be balanced by a positively charged carbon centre. Therefore, **TS-A** would proceed *via* an unstabilised electron-deficient carbon centre in the α-position that can be regarded as an Umpolung type, making it less favourable than C-H bond cleavage in the β-position (**TS-B**).

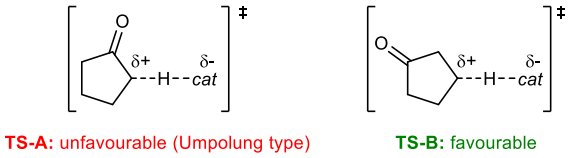


Figure 59. Comparison of the possible transition states in TBADT-catalysed C-H activation of cyclopentanone

Furthermore, carrying out the reaction under CO pressure allowed for β-acylation of cyclopentanone *via* consecutive trapping of the β-keto radical with CO and electron deficient alkenes (Figure 60, **200**-**202**).

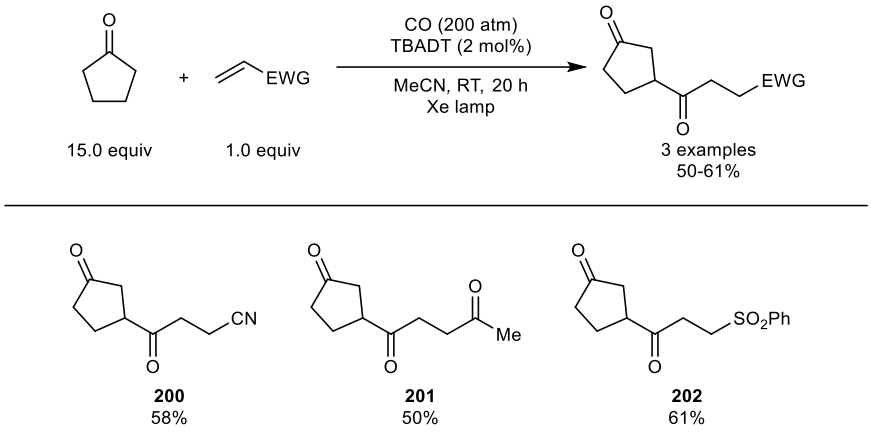


Figure 60. TBADT-catalysed β-acylation of cyclopentanone via a three-component reaction

Similar to esters (*vide supra*), Yamada and co-workers have shown that a high degree of selectivity can be achieved in C-H functionalisation of ketones through a cooperative polar/ steric strategy (Figure 61).[106] This was highlighted by the case of 2-isoamyl-4-tert-butylcyclohexanone **203** bearing five methyl, five methylene, and three methine C−H bonds, whereby only one methine C−H bond in the isoamyl tether was selectively functionalized to exclusively give **204** as a single product.

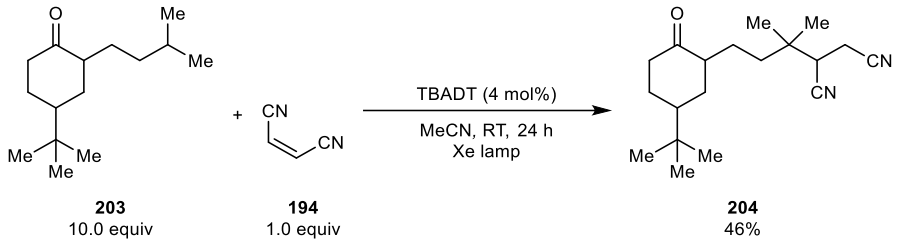


Figure 61. Selective C-H functionalisation of a poly-substituted cyclohexanone

4.3. TBADT in Late-stage Functionalisation of Natural Products

Despite the extensive literature reports on the TBADT-catalysed C-H bond functionalisation of a variety of substrate classes, this methodology has not seen a particularly wide uptake in the efforts towards late-stage functionalisation of natural products. This is surprising, given the mild nature of the transformation and the large variety of functional groups that can be used as reactive handles for C-H bond functionalisation. Only a small number of reports containing such examples can be found in the modern literature and they are outlined in the section below.

Cao and co-workers have described C-H functionalisation of androsterone derivative **205** and lithocholic acid derivative **206** in the context of their dual catalytic strategy employing TBADT and cobalt catalysis for the dehydrogenative coupling between alkanes/ aldehydes and aryl alkenes (Figure 62).[108] The methodology relies on the synergistic combination of TBADT photocatalysis with cobaloxime-mediated hydrogen-evolution cross-coupling. The cobalt catalyst is responsible for intercepting the radical adduct formed upon addition of the photogenerated radical onto the olefin which then undergoes a photoinduced β-hydride elimination, restoring the original double bond.

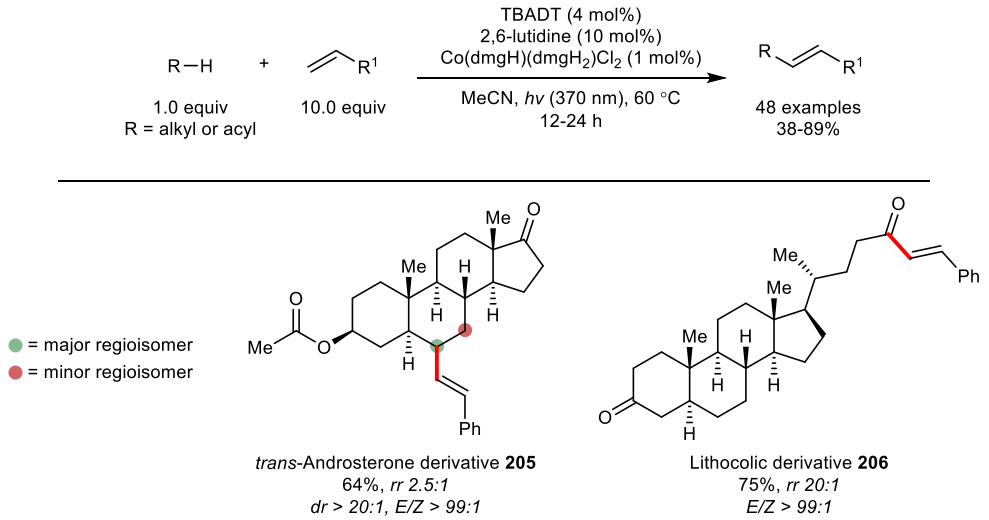


Figure 62. Dual TBADT/ cobalt catalysis employed in natural product derivatisation

A different dual-catalytic approach leveraging TBADT and nickel catalysts has been disclosed by MacMillan and co-workers, demonstrating robust C-H arylation of natural product sclareolide (**220**), using aryl bromides as coupling partners (Figure 63).[109] In this method, the carbon-centred radicals generated with TBADT are able to act as nucleophiles in nickel-mediated cross-coupling with aryl bromides to afford C(sp^3)-C(sp^2) cross-coupled products.

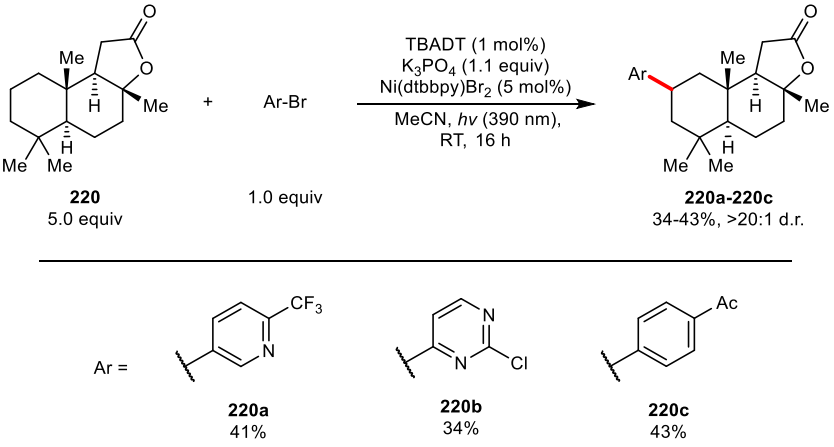


*Figure 63. Dual TBADT/ nickel catalytic approach towards C-H arylation of sclareolide (**220**)*

Zwick and Renata have employed TBADT in the photocatalysed azidation of leucine (**207**) towards the formal synthesis of Manzacidin C (Figure 64).[110] Using an excess of the sulfonyl azide **208** as a radical acceptor, the authors were able to show direct azidation of unprotected leucine on a 2.0 mmol scale as the starting point for their synthesis.

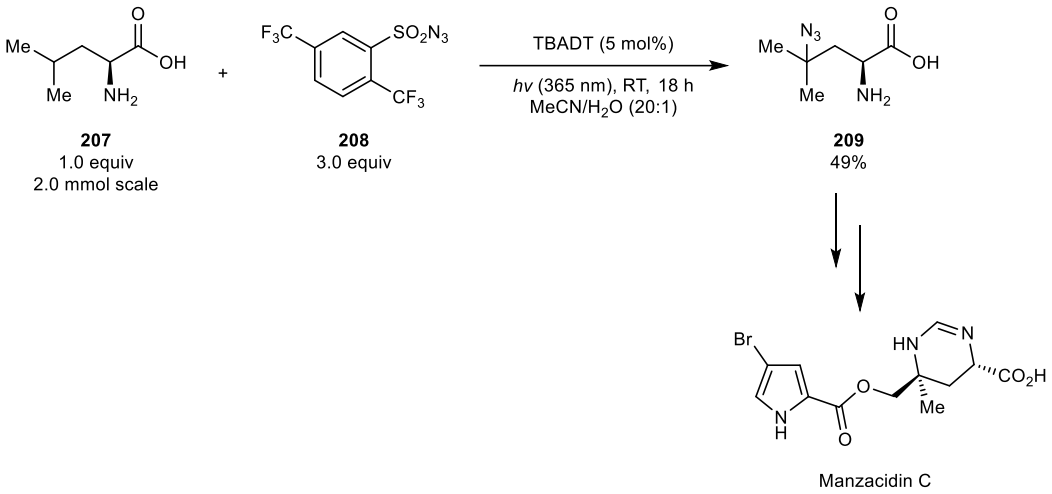


Figure 64. TBADT-catalysed azidation of leucine used in the formal synthesis of Manzacidin C

Wan and co-workers have applied a novel method for the C-N bond formation based on a combination of radical-polar crossover (RPC) and TBADT catalysis to several natural products (Figure 65).[111] More specifically, the authors coupled TBADT catalysis to generate α-radicals from ethers, with a subsequent chemical oxidation of the initially formed C-centred radical with *tert*-butyl hydroperoxide (TBHP) to afford a carbocation. The carbocation could then be trapped with *N*-heteroaryl-based nucleophiles, resulting in a new C-N bond. This methodology was applied to natural product derivatives **210**-**212** to give the corresponding products in moderate to good yields.

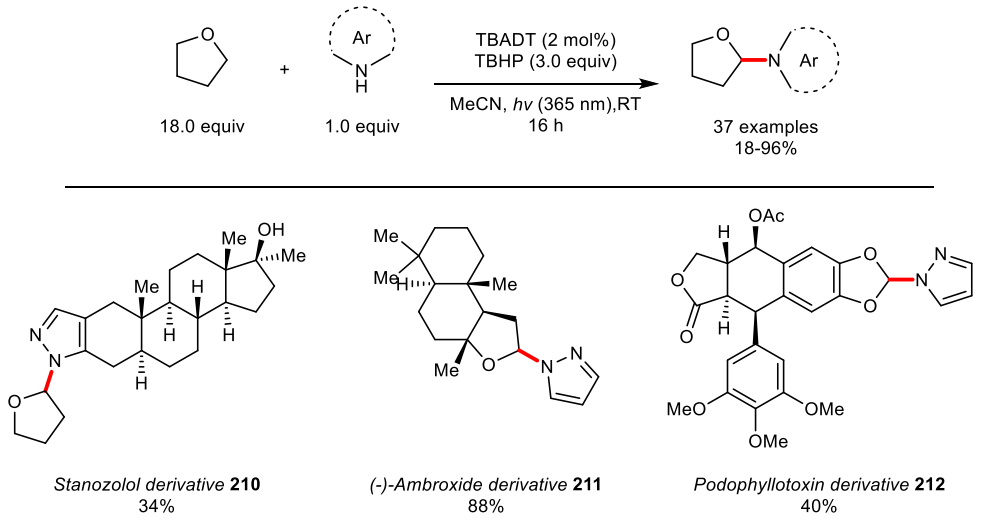


Figure 65. Radical-polar crossover and TBADT catalysis combination used for C-N bond formation in complex natural products

The same group also reported TBADT-catalysed C-H oxidation of natural products under aerobic conditions in flow (Figure 66).[112] Both activated (**213** and **214**) and unactivated (**215**) C-H bonds in complex natural scaffolds could be oxidised using this method, furnishing the

desired products in moderate yields. Of note is the use of HCl in the solvent mixture, which the authors found to significantly enhance the rate of the reaction, as well as the selectivity towards the ketone products over the intermediate alcohol products.

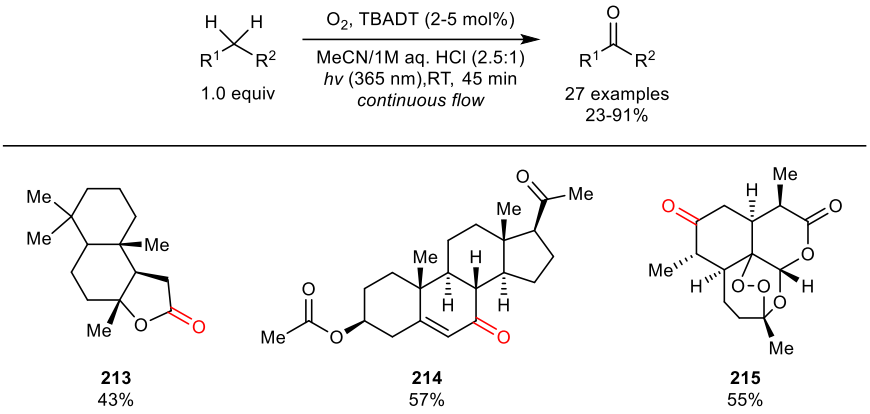


Figure 66. Aerobic oxidation of natural products in flow using TBADT catalysis

Dong and co-workers have demonstrated a procedure for difluoromethylthiolation of aldehydes under TBADT catalysis (Figure 67).[113] Using this methodology, the authors demonstrated difluoromethylthiolation of a number of aromatic-aldehyde-containing natural products, such as L-menthol **217** and dehydrocholic acid derivative **218** in moderate yields.

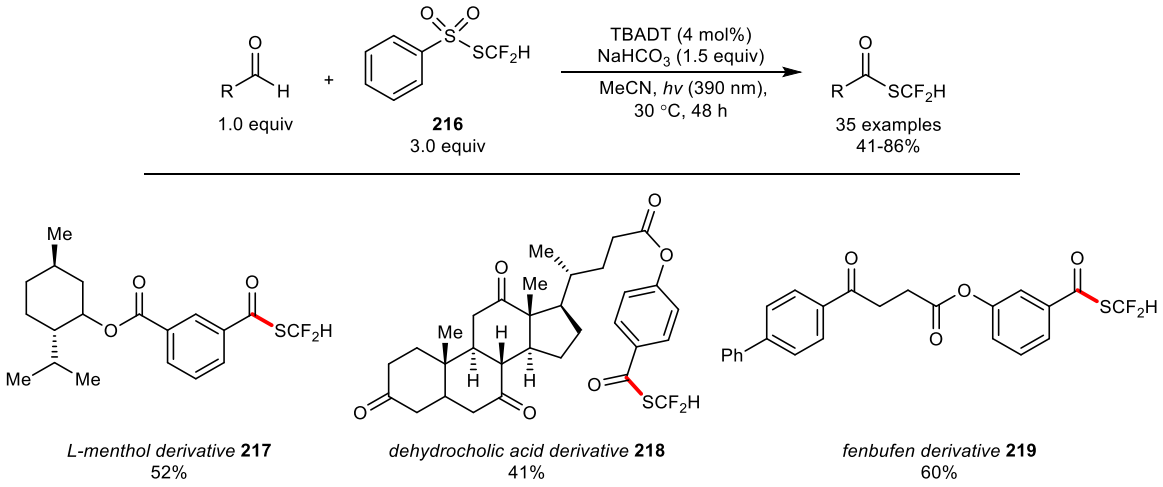


Figure 67. Difluoromethylthiolation of natural products and drug compounds catalysed by TBADT

Trapping alkyl radicals generated by TBADT catalysis with electrophilic fluorinating reagents such as NFSI can lead to selective sp^3 C-H bond fluorination. Halperin and co-workers have applied this approach to the fluorination of natural product sclareolide (Figure 68).[114]

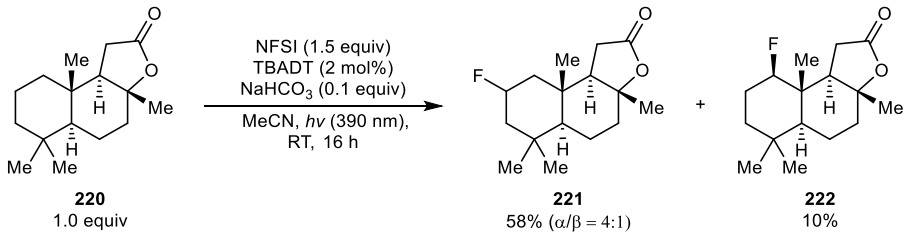


Figure 68. C-H fluorination of sclareolide under TBADT catalysis

Kleoff and co-workers also used sclareolide to demonstrate C-H bond halogenation under TBADT catalysis (Figure 69).[115] Specifically, the authors employed an electrophilic chlorine source **223** to effect a C-H bond chlorination of sclareolide under flow conditions (the epimeric ratio was not reported in this case).

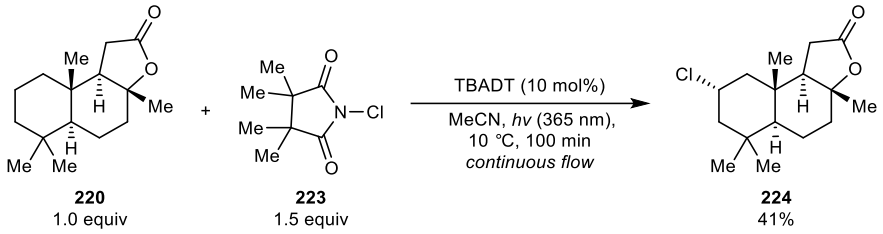


Figure 69. C-H chlorination of sclareolide under TBADT catalysis in flow

Recently, TBADT was used by Lefebvre and co-workers to functionalise levoglucosenone (**225**), a biomass-derived chiral unsaturated enone, as a way to produce value-added chemicals from biomass feedstock (Figure 70).[116] The authors demonstrated that radicals generated under TBADT photocatalysis can add to the electron-deficient double bond of levoglucosenone in a stereoselective fashion.

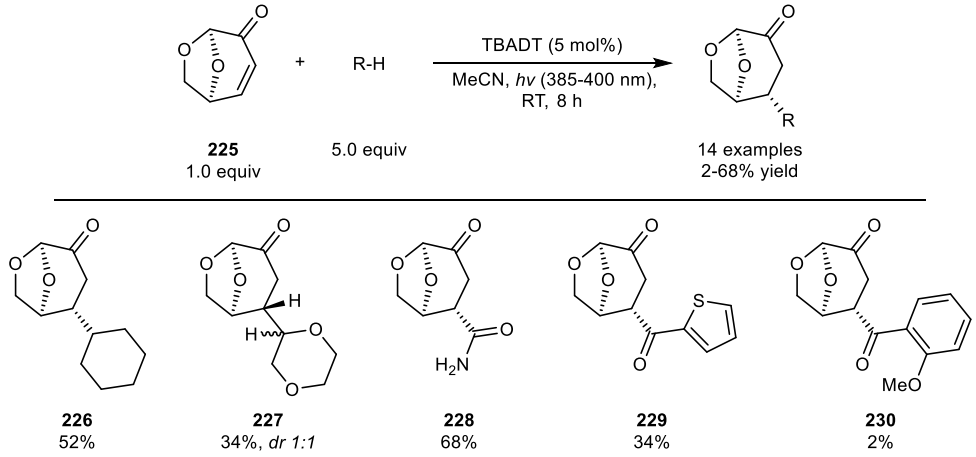


Figure 70. Derivatisation of levoglucosenone via TBADT catalysis

4.4. Conclusion

In conclusion, TBADT has been shown as a versatile photocatalyst for sp^3 C-H bond functionalisation, particularly in enabling the highly coveted C-C bond formation under mild conditions. The mild nature of TBADT catalysis and the high degree of selectivity between multiple C-H bonds that can be achieved with it make it particularly attractive in the context of late-stage functionalisation of complex natural products as well as pharmaceutical compounds. However, only a limited number of reports exist in the literature showcasing the potential of TBADT in the context of late-stage functionalisation. Therefore, there exists a need to demonstrate the applicability of TBADT catalysis towards late-stage functionalisation of complex molecules to increase the awareness of its utility among the synthetic community and further promote the development of this photocatalytic approach.

5. Results and Discussion

5.1. Aims and Objectives

Considering the wealth of C-C bond forming reactions that have been demonstrated using TBADT in the past two decades, it is surprising that this approach has seen relatively little uptake among the synthetic organic community towards late-stage functionalisation of natural products.

Having access to several members of the morphinan family within our lab, we endeavoured to address this gap in the research literature and apply TBADT catalysis towards derivatisation of the morphinan scaffold.

As discussed in Chapter 1, morphine, as well as its semi-synthetic congeners are extremely useful in the clinical setting for the treatment of pain and other disorders. However, opioids are largely plagued with serious side effects that include respiratory depression, addiction and constipation, among others. As a result, concerted efforts within the synthetic and pharmaceutical communities have long been aimed at developing morphine-derived analogues that would be devoid of life-threatening side effects, while maintaining their desirable therapeutic properties. Ongoing efforts in this area have resulted in extensive mapping of the structure-activity relationship (SAR) of the morphinan scaffold.

However, gaps in the morphinan SAR still remain. In particular, only a handful of derivatives substituted at the C8 position have been synthesised and investigated. Kotick and co-workers have reported 1,4-additions of organometallic reagents to the C-ring of codeinone (**60**), producing a small number of analogues **231**-**236** (Figure 71).[46] Some of these analogues displayed moderate potency and a mixed agonist-antagonist action profile.

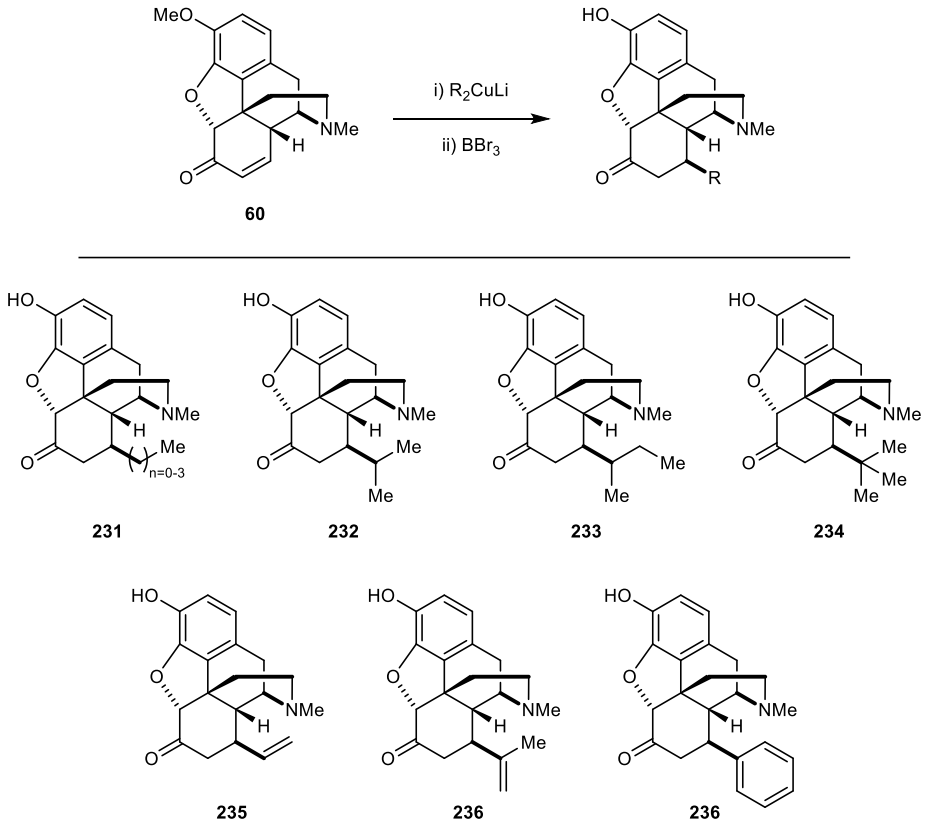


Figure 71. 1,4-addition of organocuprates to codeinone, reported by Kotick et al

The same group also demonstrated cyclopropanation and epoxidation of codeinone **60** to prepare a range of derivatives (Figure 72).[117] The cyclopropane derivative **237** was found to be nine times more potent as an opioid agonist than dihydrocodeinone.

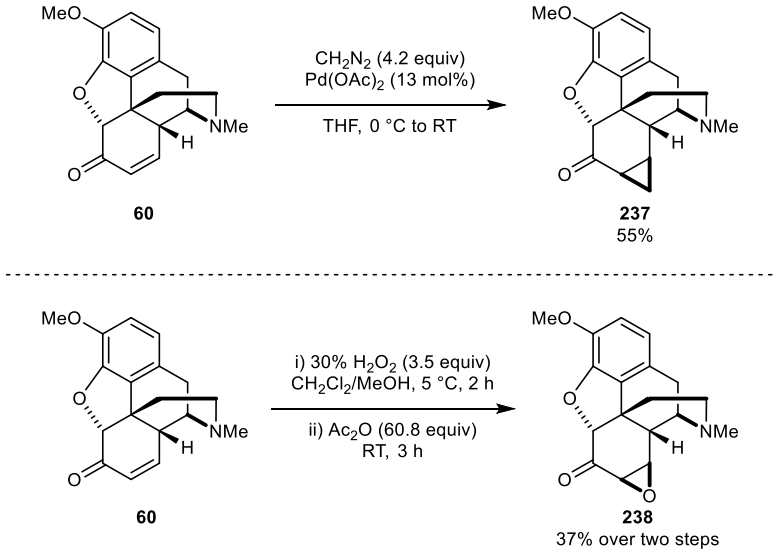


Figure 72. Cyclopropanation and epoxidation of the C-ring of codeinone

In light of this relative scarcity of C8 analogues, our group questioned whether the 1,4-addition of nucleophilic radicals generated using TBADT to morphinan opioids containing an enone in the C-ring would constitute a versatile method to produce C8-substituted derivatives, complementary to those described previously (Figure 73).

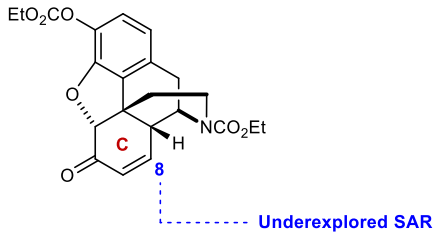


Figure 73: Underexplored morphinan SAR

To our knowledge, no prior study has focused on this approach, with the only related precedent being the 1,4-addition of photochemically generated THF radicals to the morphinan enone **239**, as part of a larger investigation into the photochemistry of structurally modified morphine alkaloids (Figure 74).[118]

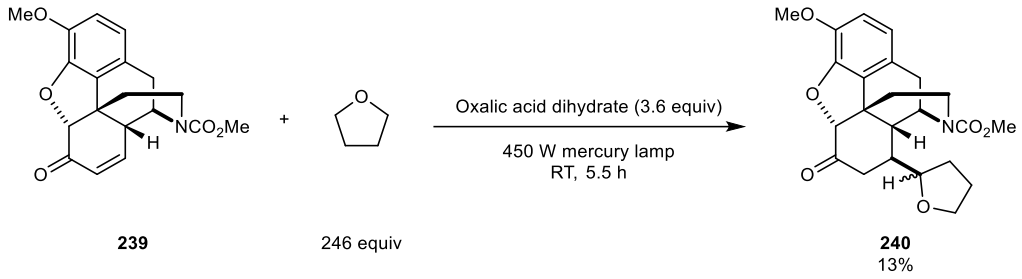


Figure 74. Photochemical addition of THF to a morphinan enone XX

Furthermore, the successful execution of this strategy would represent an advanced utilisation of TBADT catalysis towards complex natural product derivatisation. The use of TBADT as a HAT photocatalyst could represent a formidable challenge when applied to the morphinan scaffold – being able to generate radicals from C-H bonds at benzylic and allylic positions, α- to heteroatoms, and formyl groups, as well as at secondary or tertiary C-H bonds of simple alkyl groups could present chemoselectivity issues (Figure 75). Specifically, potentially reactive sites on the enone **33** include the benzylic C-10 position, the allylic C-14 position, the C-5 position next an ether linkage, as well as the C-16 position α to the carbamate group. Radicals generated in these positions could be oxidised in the presence of adventitious oxygen from the air or otherwise react with another molecule of the enone itself and lead to large quantities of undesired side products. Nevertheless, investigating these

issues of functional group tolerance are exactly the types of studies required to enable greater application of methods for late-stage modification of highly functionalised molecules.

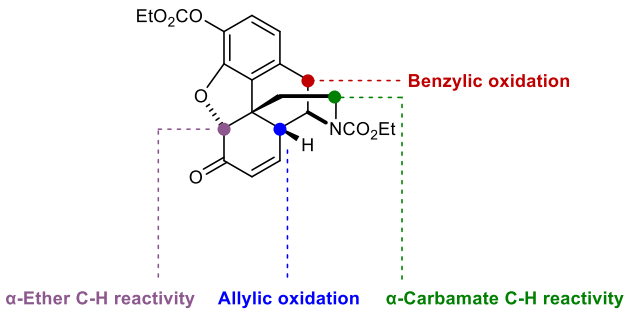


*Figure 75: C-H bonds in morphinan opioid **33** with potential HAT reactivity*

This project therefore had two main goals:

- Firstly, to show the utility of TBADT catalysis in the context of late-stage natural product derivatisation and expand the applicability of TBADT catalysis beyond simple unfunctionalised substrates.
- Secondly, this project was aimed at leveraging the HAT reactivity under the TBADT manifold to catalyse addition of a range of nucleophilic radicals into enone-containing morphinans and thus producing novel morphinan analogues with substituents in the 8-position (Figure 76).

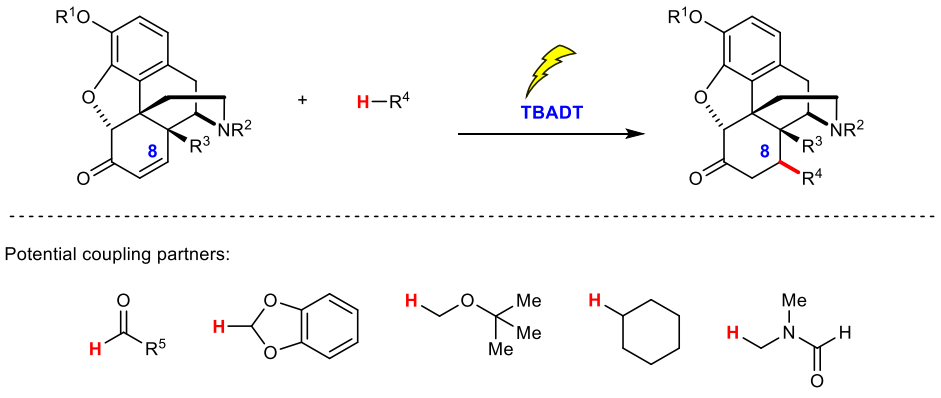


Figure 76. Proposed aims of the project – application of TBADT catalysis to the morphinan scaffold and generation of C8-substituted analogues.

5.2. Initial Results and Reaction Optimisation

The initial discovery of TBADT-catalysed radical addition to enone **33** was made by Elliot Smith, a member of the Lam group. To see whether TBADT-catalysed radical addition into enone **33** was possible, a degassed mixture of **33** and excess radical donor **241** was irradiated with UV light (370 nm) at room temperature in the presence of 5 mol% TBADT in acetonitrile (Figure 77). To our pleasure, after 5 hours of reaction time addition product **242** was formed in 55% yield, as determined by ^{1}H NMR spectroscopy. (N.B. see below for discussion on diastereoselectivity)

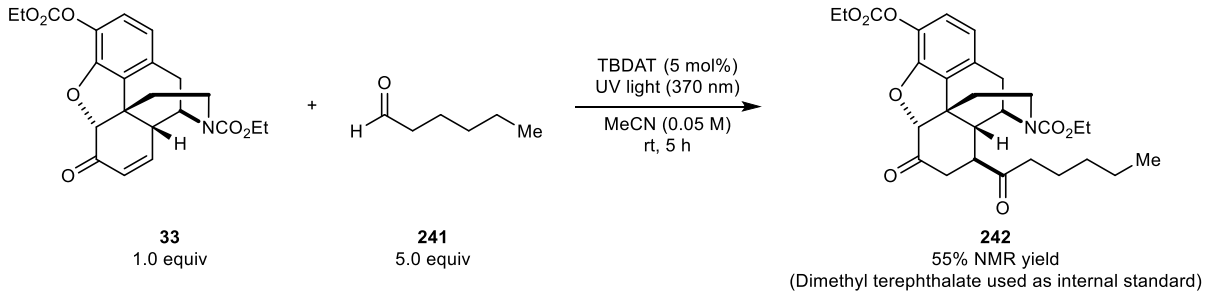
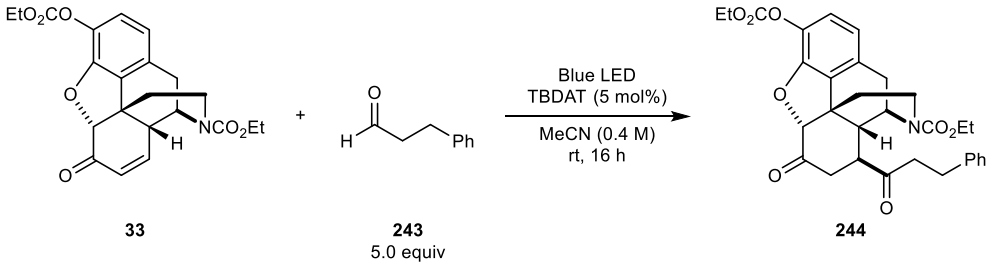


*Figure 77: Initial entry into TBADT-catalysed addition to enone **33**, performed by Elliot Smith, Lam Group*

With this encouraging initial result in hand, reaction conditions were further optimised using 3-phenylpropanal **243** as a model radical donor and enone **33** as a model radical acceptor (Table 3). It was found that irradiation of a solution of enone **33** and 3-phenylpropanal (5.0 equiv) in dry MeCN (0.4 M concentration) in the presence of TBADT (5 mol%) at room temperature under an argon atmosphere for 16 h with blue LEDs gave the 1,4-addition product **244** in a 67% isolated yield (Table 3, Entry 1). The blue LED source used was a 40W Kessil H160 Tuna Flora lamp set to blue at maximum intensity. On the above setting, the lamp has an emission spectrum with a small peak at *ca*. 390 nm (see the Experimental Section for lamp emission spectra). Changing the light source to a UV LED lamp (set at 370 nm) reduced the yield to 54% (Table 3, Entry 2). This might be explained by the higher intensity light leading to increased photochemical decomposition of enone **33**. Reducing the catalyst loading, reaction time or concentration had detrimental effects on the yield (Table 3, Entries 3-5). No reaction was observed in the absence of TBADT (Table 3, Entry 6) and increasing the quantity of 3-phenylpropanal to 10.0 equivalents increased the yield to 74% (Table 3, Entry 7). On the other hand, decreasing the number of equivalents of radical donor **243** to 2.0 led to a significant reduction in yield (Table 3, Entry 8). When the reaction was

conducted under air, it gave near identical results to the reaction conducted under argon (Table 3, Entry 9). This observation was contrary to the expected loss in yield, given that TBADT catalysed C-H oxidations under O_2 atmosphere are established in the literature. However, literature procedures for TBADT-catalysed oxidations routinely use high pressures of O_2 in order to achieve good yields, which might explain why atmospheric pressure of O_2 did not have an impact on the present reaction system. Finally, inclusion of H_2O (10 equiv) had a negative effect on the yield (Table 3, Entry 10).

*Table 3: Reaction optimisation for the radical addition to enone **33***



Entry[a]	Derivation from Conditions	Yield of 244[b]
1	None	67%
2	UV lamp (370 nm)	54%
3	1 mol% TBADT	32%
4	5 h reaction time	28%
5	0.1 M concentration	54%
6	No TBADT	Not detected
7	10.0 Equivalents of 3-phenylpropanal	74%
8	2.0 Equivalents of 3-phenylpropanal	43%
9	In air	69%
10	In presence of H_2O (10 equiv)	42%

[a] Reactions were conducted using 0.30 mmol of **33** in dry MeCN under Argon atmosphere. See the Experimental section for details of the blue LED source used. [b] Yield after isolation by column chromatography.

5.3. Substrate Scope

With the optimised conditions in hand, efforts were next focused on exploring the radical donor substrate scope (Figure 78). The reaction proved to work well using a diverse range of radical precursors. Various aldehydes reacted successfully, including cyclic and acyclic aliphatic aldehydes (**244-247**), heteroatom-containing aldehydes (**246**-**248**), 4-substituted benzaldehydes (**249** and **250**), as well as formamide (**251**), which represents a handle for further substrate derivatisation. Interestingly, when using cyclohexanecarboxaldehyde as a radical precursor, formation of a small quantity of the decarbonylated product **254** was also observed in the NMR spectrum of the unpurified reaction mixture (not isolated), most likely resulting from decarbonylation of the initially formed acyl radical and subsequent addition to the enone. Other radical precursors, such as 1,3-benzodioxole (**252**) and cyclohexane (**254**) could also be employed and gave the corresponding addition products in appreciable yields. DCE was used as a co-solvent in the case of cyclohexane in order to homogenise the reaction mixture, due immiscibility of cyclohexane with acetonitrile. With DMF, C-H functionalisation occurred at one of the methyl groups, in line with the previous literature, to give the corresponding product **253** in 31% yield.

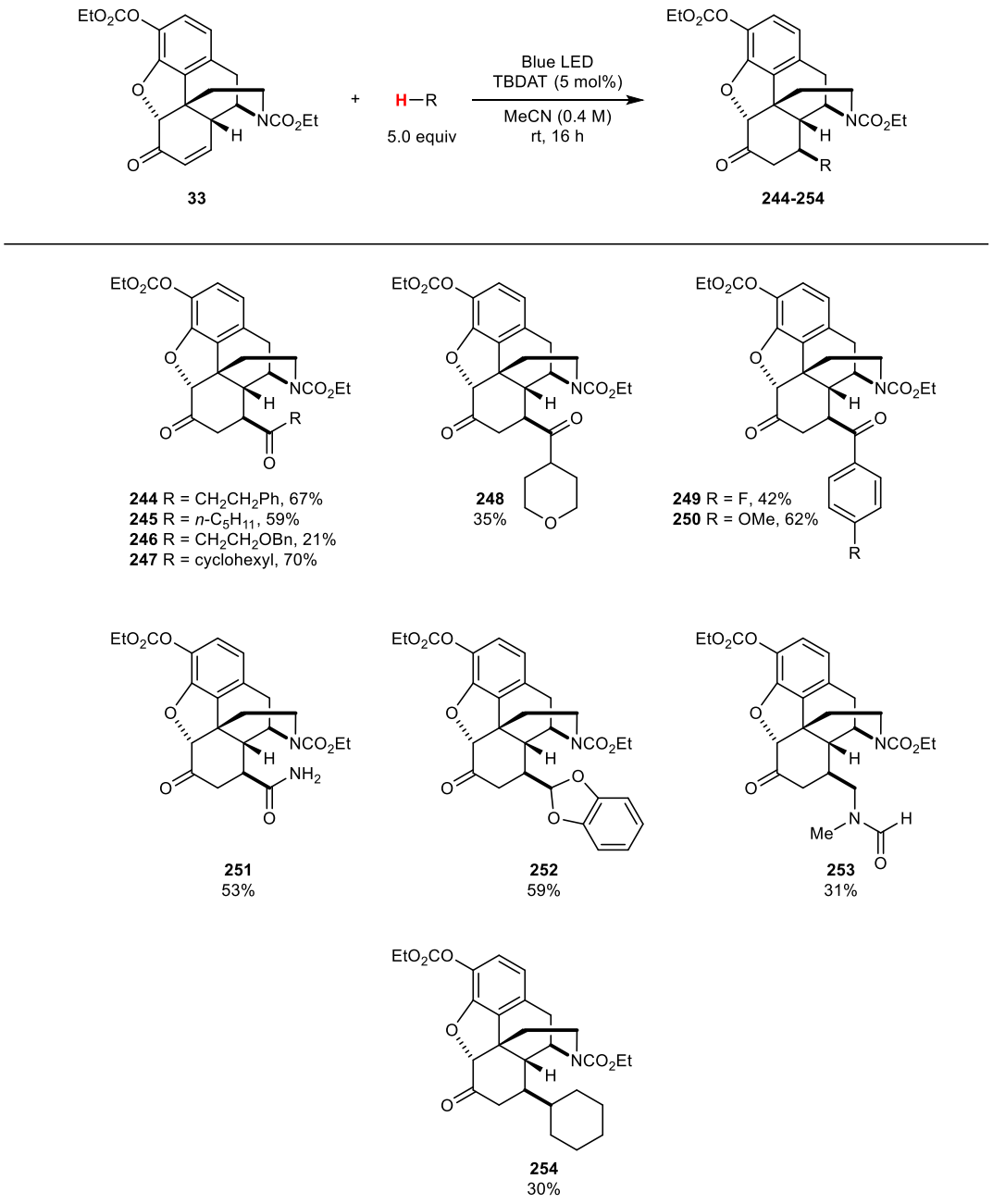


Figure 78. Scope of radical precursors

There was no clear correlation between the different substrate classes and the yields observed. In general, the remaining mass balance in these reactions consisted mostly of unreacted starting materials, with little or no side product formation. Nonetheless, the observed yields were generally in line with previous reports on TBADT-catalysed conjugate addition reactions.

We were also able to establish the absolute stereochemistry of product **244** after obtaining a single crystal X-ray structure (Figure 79). As can be seen, the new acyl fragment sits equatorial in the C ring, thus avoiding a significant steric clash with rings A and B. Thus, the stereochemical outcomes of the other reactions were implied by analogy.

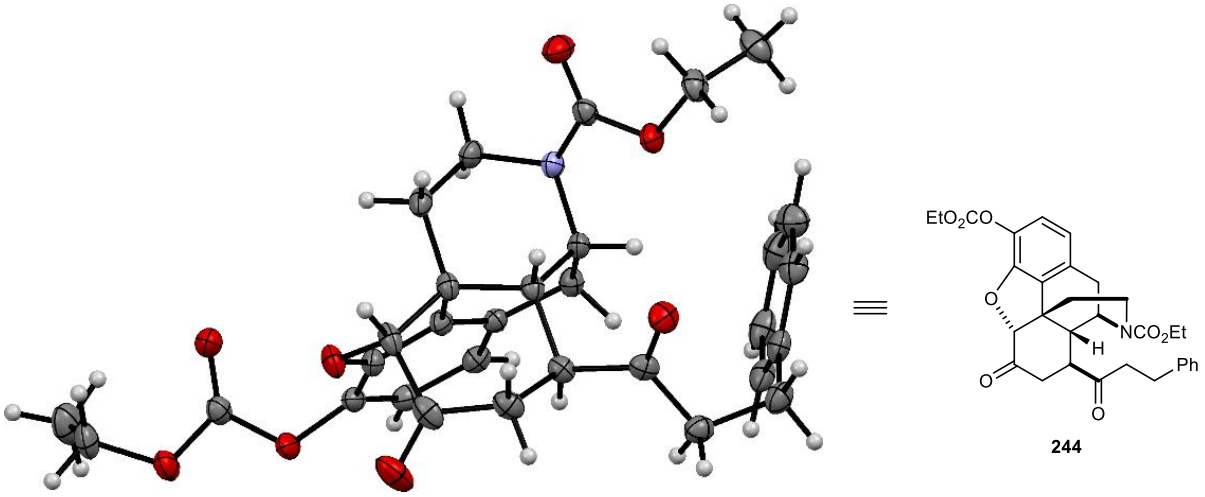


*Figure 79: Crystal structure of **244** showing the newly formed stereocentre (CDC 2149928)*

The stereochemical outcome can also be rationalised by examining the 3D structure of the enone **33** scaffold, frequently referred to as "T-shaped" in the morphinan literature (Figure 80). The radical can approach the alkene either from "above" or "below" the C-ring. If the radical approaches from "below" the C-ring, the path is hindered by rings A and B, which lie perpendicular to rings C and D, thus disfavouring this approach. On the other hand, if the radical approaches from "above" the plane of the prochiral centre, the path is unobstructed, as rings C and D are effectively coplanar.

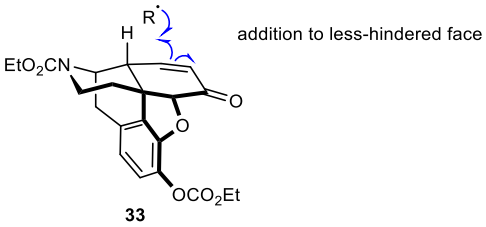


*Figure 80: Stereochemical model for radical nucleophile addition to enone **33***

Despite having achieved successful addition of a variety of radical precursors to enone **33**, a large number of radical precursors that were well precedented in the TBADT literature proved unreactive when applied to enone **33** (Figure 81). Heteroaromatic aldehydes 2-

thiophenecarboxaldehyde **255**, furfural **256** and nicotinaldehyde **257** all gave no conversion to the desired adduct, despite having good literature precedent.[85] 4-Nitrobenzaldehyde **259** equally showed no conversion, however, in this case the lack of reactivity can be rationalised based on strong absorption of this heterocycle at 366 nm, which could prevent C-H abstraction.[85] Poor solubility of certain radical donors such as 4-cyanobenzaldehyde **260** and 4-formylphenylboronic acid **261**, even with the addition of DCE as a co-solvent, appeared to inhibit their reactivity.

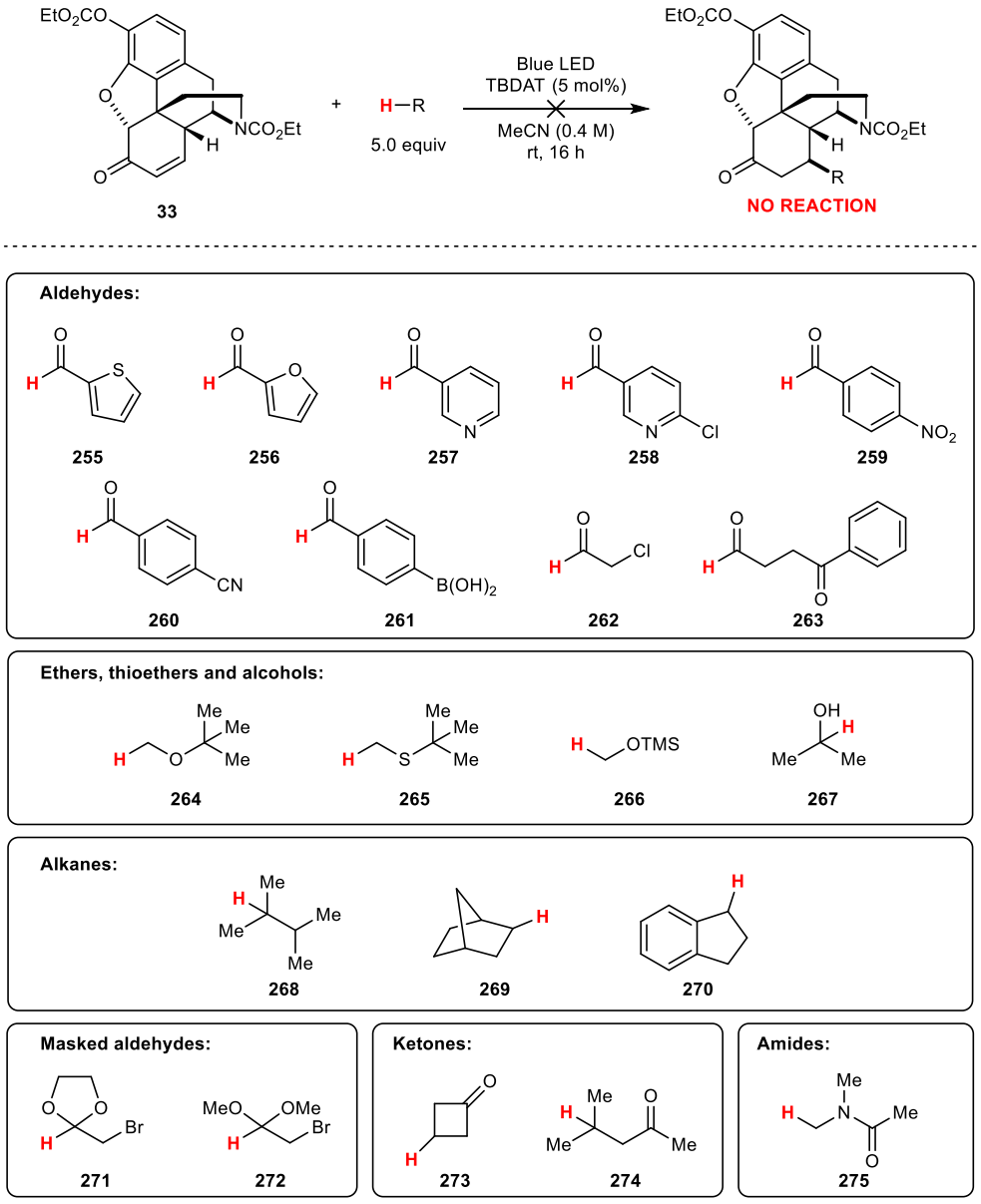


*Figure 81: Radical precursors that did not undergo addition to enone **33***

Reaction with chloroacetaldehyde **262** also did not result in any product formation. However, chloroacetaldehyde was used as a 55 wt% solution in H_2O, and it is possible, that

the reactivity was shut down due to the excess H_2O. This is in line with the observation from the reaction optimisation (*vide supra*) that doping the reaction with 10 equivalent of H_2O reduces the yield considerably. Using neat bromoacetaldehyde ethylene acetal **271** or bromoacetaldehyde dimethyl acetal **272** as masked aldehyde equivalents did not result in any conversion either. This might potentially indicate the detrimental electronic effect of having a halogen atom *α* to the proton that is being abstracted by TBADT, which might create an unfavourable S_H2 transition state. The lack of reactivity of these haloacetaldehyde fragments is unfortunate, as the resulting addition products could provide handles for further derivatisation in Hantzsch pyrrole synthesis-type reactions. Equally, 4-oxo-4-phenylbutanal **263**, which could provide entry to pyrrole derivatives via Paal-Knorr synthesis, did not show any reactivity either.

tert-Butylmethyl ether **264**, as well as tertbutyl methyl sulfide **265** did not show any reactivity under blue LED irradiation. Equally, TMS-protected methanol **266** did not react under the developed conditions, although it is possible that methanol is deprotected by photo-irradiation. Employment of isopropanol **267** also did not show any reactivity. In this case, inadvertent oxidation of isopropanol to acetone that would prevent reactivity is unlikely, since the reactions were carried out under air-free conditions. Interestingly, *N,N*-dimethylacetamide **275** showed no reactivity, despite the successful reaction that was observed using DMF. No conversion was observed with ketones: cyclobutanone **273** and 4-methylpentan-2-one **274** did not undergo conjugate addition to enone **33** under the reaction conditions. Despite the success with cyclohexane, other alkanes did not show reactivity, including 2,3-dimethylbutane **268**, norbornane **269** and indane **270**.

The lack of reactivity of so many radical precursors that have literature precedent might be partially explained by the insufficient electrophilicity of the enone **33**. In almost all cases where the reaction did not work, the reaction mixture still turned the characteristic blue colour, indicating proton abstraction by the excited-state TBADT species. This would suggest that the radical species were generated but were not able to react with the enone. Thus, the reactivity might be limited by the relative electrophilicity of the morphinan enone and the relative nucleophilicity of the various radical donor species.

In an attempt to improve the radical donor scope some of the reactions were repeated under UV lamp irradiation centred at *ca.* 370 nm (see the Experimental Section for lamp emission spectra), instead of a blue LED (Figure 82). Pleasingly, reaction with TBME under UV

irradiation yielded the desired product **276** in 34% yield. It is difficult to rationalise this apparent increase in reactivity compared to blue light irradiation other than potentially being able to generate C-centred radicals by UV irradiation alone (i.e. outside of the TBADT catalytic cycle) and thus having more of the reactive radical species that can react with the enone. However, no other substrates that were reattempted under UV irradiation were successful. *tert*-Butylmethylsulfide, cyclobutanone, 4-methylpentan-2-one and nicotinaldehyde all showed no conversion under UV irradiation.

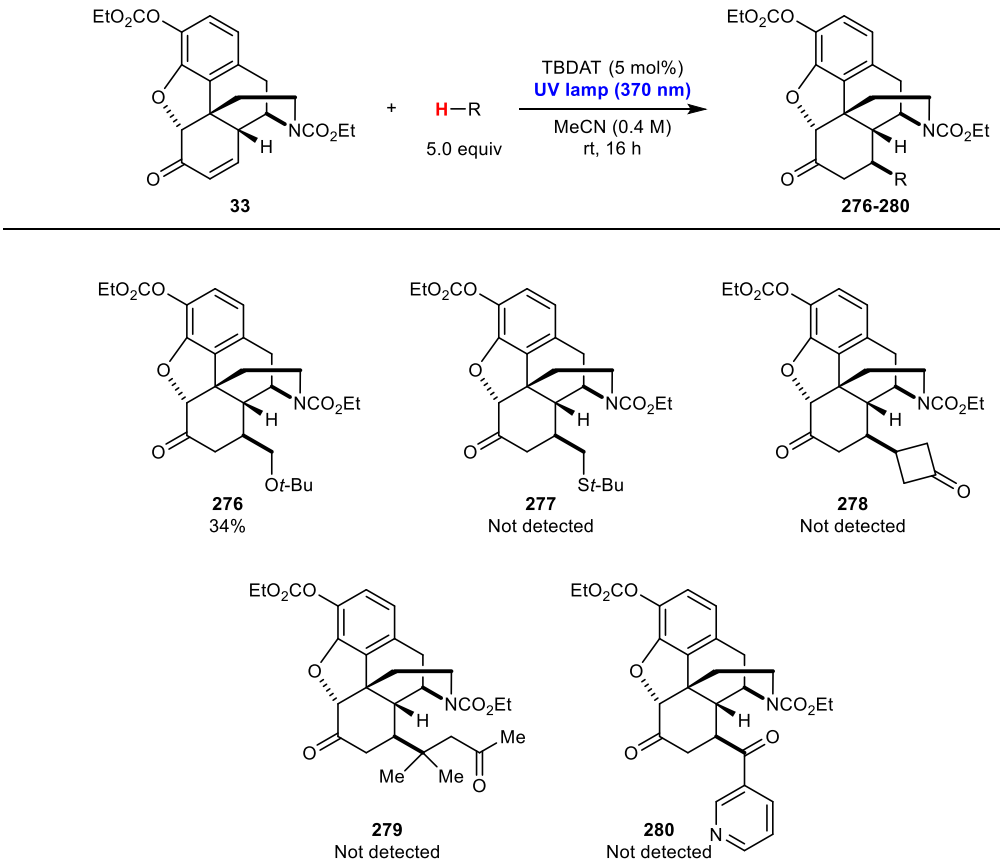


Figure 82: Attempts to improve radical donor scope under UV irradiation

Moving forward, the scope of enone electrophiles was explored by varying the substituents on the morphinan scaffold (Figure 83). It was found that analogues of **33** containing alternative protecting groups on the phenol (TBS **281** or methyl **282**) and/or a cyanomide group on the *N*-17 position (**283**) reacted successfully with 3-phenylpropanal using blue LEDs to give the corresponding products in 36-63% yield.

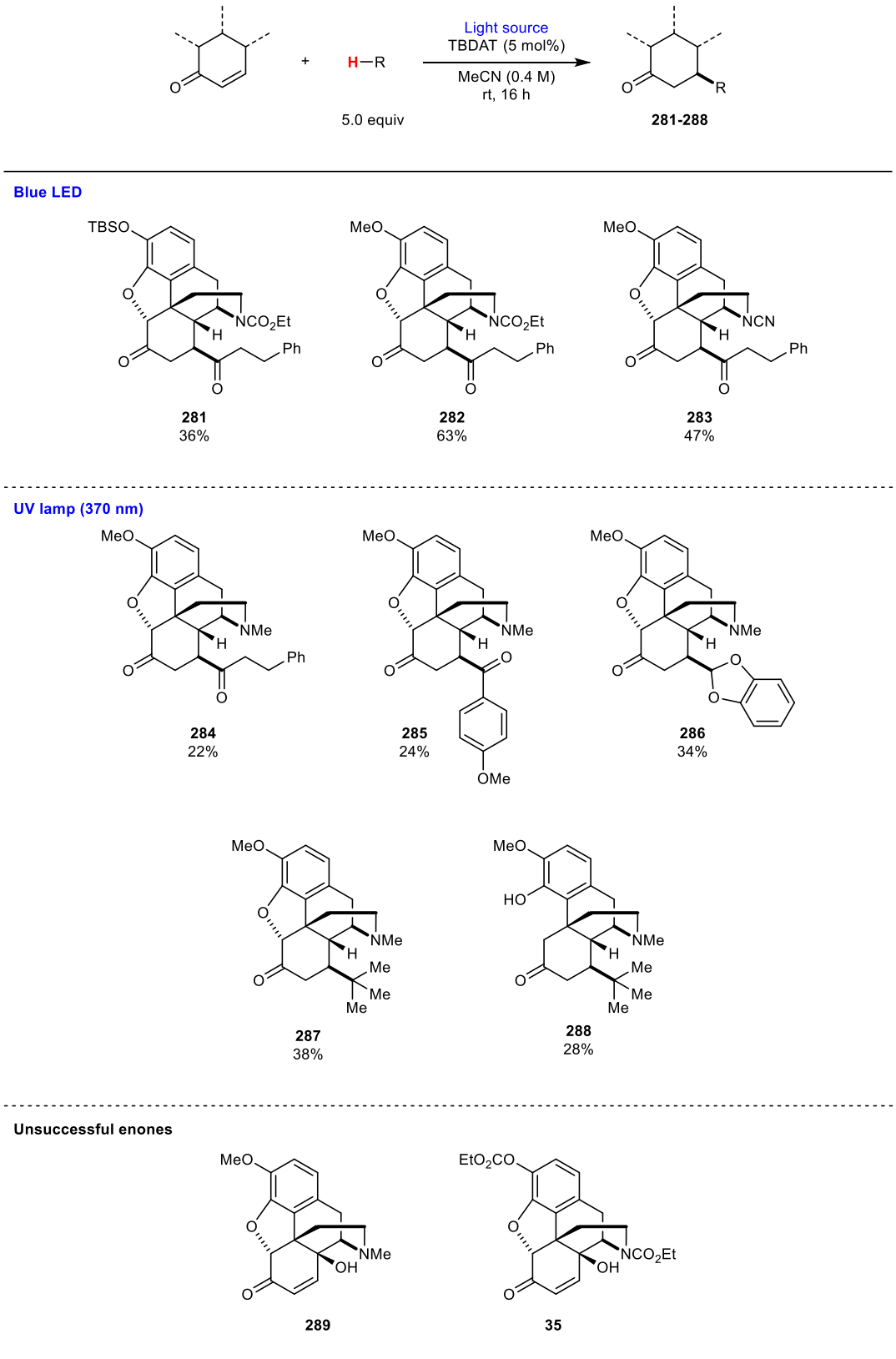


Figure 83. Scope of opioid radical acceptors

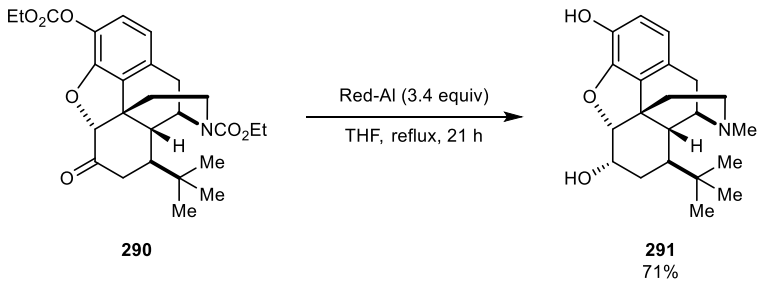
In addition, under UV irradiation, codeinone reacted with 3-phenylpropanal, 4-methoxybenzaldehyde, and 1,3-benzodixole to give the corresponding addition products **284**-**286** in moderate yields. Notably, the use of pivaldehyde as the radical precursor led to

decarbonylation of the initially formed acyl radical to give a *tert*-butyl radical, which added to codeinone to give the corresponding product **287**. When these reactions were performed under blue LED irradiation, the yields were substantially diminished. These results were pleasing as there are relatively few examples in the literature of free tertiary amines undergoing TBADT-catalysed transformations. Furthermore, a ring-opened derivative, containing an additional free phenol group, reacted with pivaldehyde to give the corresponding product **288** in 28% yield. This transformation displays the remarkable tolerance of TBADT towards all of the functional groups present in the starting morphinan enone; the remaining mass balance in this case consisted mostly of unreacted starting materials, with no side products detected.

Unfortunately, attempts to functionalise 14-hydroxycodeinone **289** or enone **35** using either blue LEDs or UV irradiation were not successful, and gave mostly recovered starting materials. This can potentially be rationalised by both steric and electronic effects that the additional hydroxyl group has on the enone.

5.4. Product Derivatization

To demonstrate the removal of the ethoxycarbonyl group present in many of the products and unmask the native functionality present in opiates, **290** was treated with Red-Al (Figure 84). This resulted in a global reduction (deprotection of the carbonate to give the free phenol, conversion of the carbamate to an *N*-methyl group and diastereoselective reduction of the ketone) to give **291** in 71% yield.



290 **291** 71%

*Figure 84. Global deprotection of derivative **290** using Red-Al*

An attempt was also made to carry out a regioselective Fischer indole synthesis on the di-ketone **244**, using the newly installed exocyclic ketone as a reactive handle (Figure 85).

Reacting **244** with 1.2 equivalents of phenylhydrazine **292** and 3.0 equivalents of *p*-toluenesulfonic acid in ethanol at 50 °C for 6 h gave a complex mixture, from which no desired product **293** was isolated.

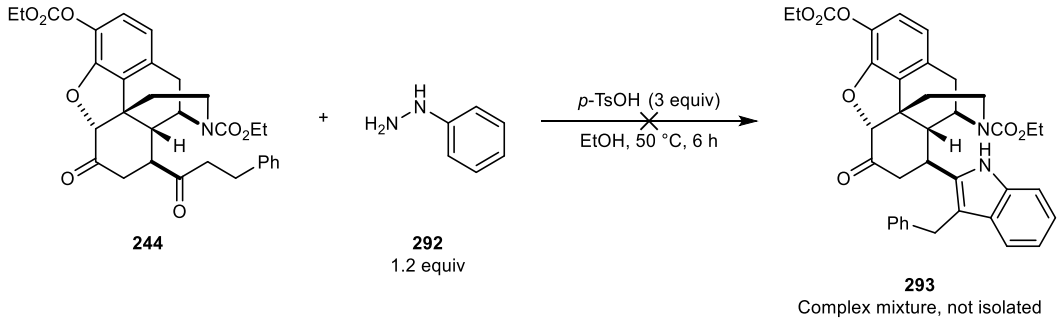


*Figure 85: Attempted Fischer indole synthesis using di-ketone **244***

5.5. Conclusions and Future Work

In conclusion, this work demonstrated the utility and applicability of TBADT catalysis towards late-stage functionalisation of natural products, such as morphine. Specifically, this work demonstrated the ability to forge new sp^3 C-C bonds on complex molecular scaffolds under mild conditions. What is more, this work demonstrated that even in the presence of other reactive handles on the morphinan scaffold, such as C-H bonds in the benzylic, allylic, *α*- to oxygen and *α*- to carbamate positions, the reactions proceeded cleanly to give the desired products in moderate to good yields. In fact, no side product formation was observed in most cases and the remaining mass balance in these reactions consisted mostly of unreacted starting materials, which could be recovered through column chromatography. Thus, it is hoped that this study will inform greater application of this method for late-stage modification of highly functionalised molecules.

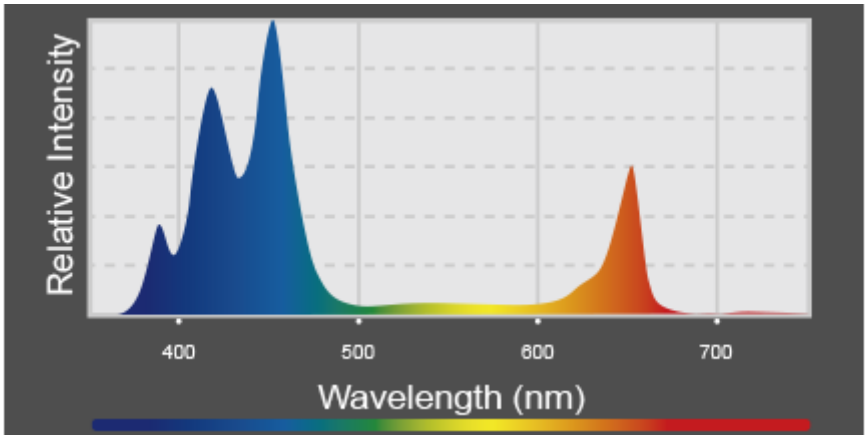
Importantly, this investigation also resulted in the generation of a series of novel morphinan analogues substituted at the 8-position on the C-ring, which is an underexplored area in terms of morphinan SAR. A host of novel functional moieties were introduced in this position, including acyl, amide, alkyl and benzodioxole fragments. Some of these moieties can be used as functional handles for further derivatisation and analogue generation in order to explore new vectors for opioid receptor binding. The compounds generated in this study will

be investigated for their potential biological activity and binding to the opioid receptors as part of the follow-up work.

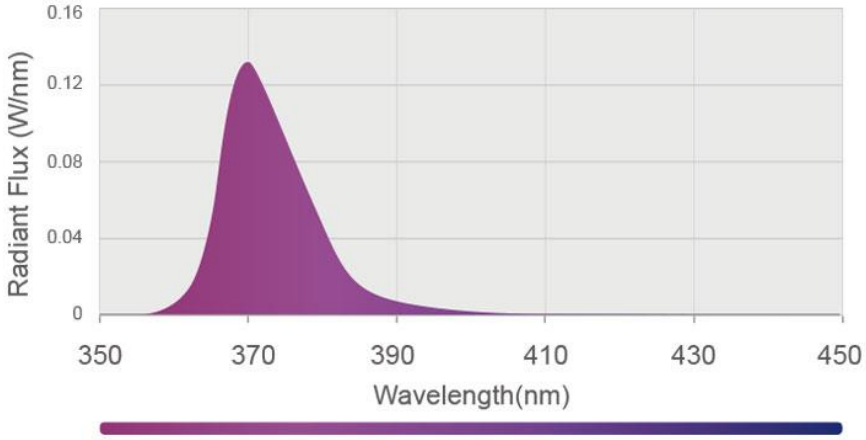
6. Experimental

6.1. General Information

All commercially available reagents were used as received unless otherwise stated. TBADT was prepared according to literature procedure.[109] Petrol refers to Sigma-Aldrich product 24587 (petroleum ether boiling point 40−60 °C). Thin layer chromatography (TLC) was performed on Merck DF-Alufoilien 60F254 0.2 mm precoated plates. Compounds were visualized by exposure to UV light or by dipping the plates into solutions of potassium permanganate or vanillin followed by gentle heating. Flash column chromatography was carried out using silica gel (Fisher Scientific 60 Å particle size 35-70 micron or Fluorochem 60 Å particle size 40-63 micron). Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. The solvent of recrystallization is reported in parentheses. Infrared (IR) spectra were recorded on Bruker platinum alpha FTIR spectrometer on the neat compound using the attenuated total reflectance technique. NMR spectra were acquired on Bruker Ascend 400 or Ascend 500 spectrometers. ^{1}H and ^{13}C NMR spectra were referenced to external tetramethylsilane via the residual protonated solvent (^{1}H) or the solvent itself (^{13}C). ^{19}F NMR spectra were referenced through the solvent lock (^{2}H) signal according to the IUPAC-recommended secondary referencing method following Bruker protocols. All chemical shifts are reported in parts per million (ppm). For $CDCl_3$, the shifts are referenced to 7.26 ppm for ^{1}H NMR spectroscopy and 77.16 ppm for ^{13}C NMR spectroscopy. Coupling constants (*J*) are quoted to the nearest 0.1 Hz. Assignments were made using the DEPT sequence with secondary pulses at 90° and 135°. High resolution mass spectra were recorded using electrospray ionization (ESI) techniques. X-ray diffraction data were collected at 120 K on an Agilent SuperNova diffractometer using CuKα radiation. All photoreactions were performed in a commercially available EvoluChem™ PhotoRedOx Box reactor. Reactions under blue LED irradiation were performed using a 40W Kessil H160 Tuna Flora lamp set to BLUE at maximum intensity. Lamp emission spectrum is shown below (https://kessil.com/aquarium/horticulture_H160.php):



Reactions under UV irradiation were performed using a 40W Kessil PR160L-370nm lamp set to maximum intensity. Lamp emission spectrum is shown below (https://kessil.com/science/PR160L-370.php):

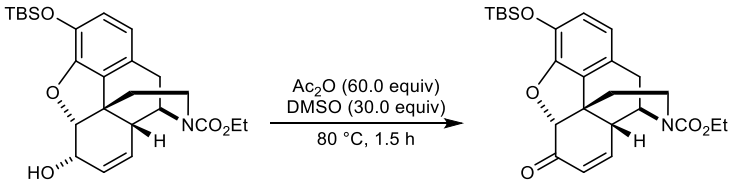


A representative reaction setup is shown below:

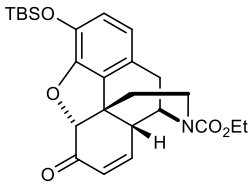

Kessil
PR160L-370nm
EvoluChem
1000
22
heidolph

6.2. Preparation of Substrates for TBADT-Catalyzed Radical Addition

Ethyl (4*R*,4a*R*,7a*R*,12b*S*)-9-[(*tert*-butyldimethylsilyl)oxy]-7-oxo-1,2,4,4a,7,7a-hexahydro-3*H*-4,12-methanobenzofuro[3,2-*e*]isoquinoline-3-carboxylate (294)

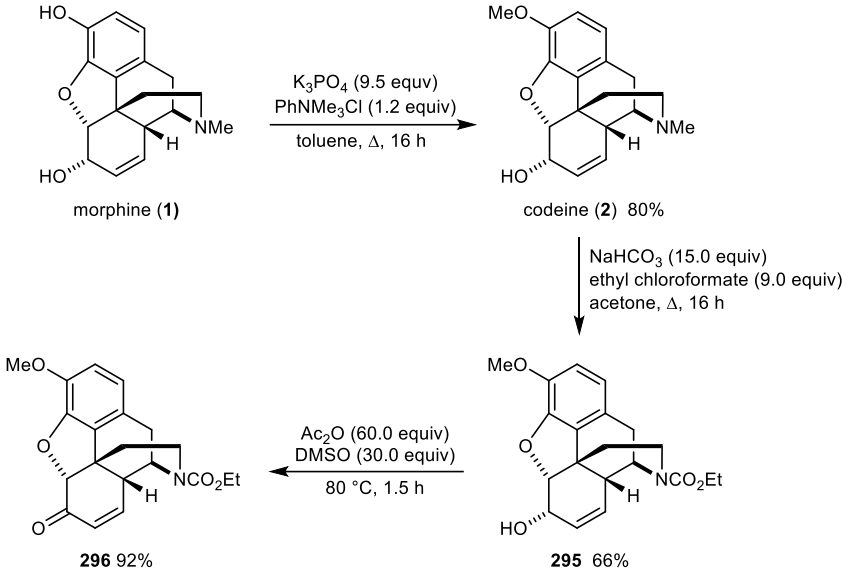


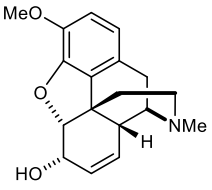
49 **294** 98%



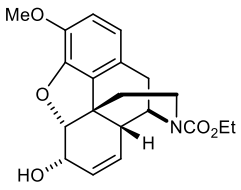
Ethyl (4*R*,4a*R*,7a*R*,12b*S*)-9-[(*tert*-butyldimethylsilyl)oxy]-7-oxo-1,2,4,4a,7,7a-hexahydro-3*H*-4,12-methanobenzofuro[3,2-*e*]isoquinoline-3-carboxylate (294). To a stirred solution of alcohol **49** (91 mg, 0.20 mmol) in Ac_2O (0.60 mL, 6.00 mmol) was added DMSO (0.20 mL, 3.00 mmol) and the resulting mixture was stirred at 70 °C for 1.5 h. The reaction was cooled to room temperature, diluted with H_2O (5 mL), and extracted with Et_2O (3 × 5 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution (3 × 20 mL), brine (20 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give **294** as a white solid (89 mg, 98%) as a pair of rotamers in a 1.5:1 ratio. R_f = 0.24 (50% EtOAc/petrol); m.p. 111-116 °C (Et_2O); $[\alpha]_D^{20.1}$ −130 (*c* 1.00, $CHCl_3$); IR (ATR) 2929, 2857, 1674 (C=O), 1659 (C=O), 1496, 1470, 1417, 1317, 1267, 1230 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.67-6.59 (2H, m, Ar**H** and O=CC**H**=CH), 6.54 (1H, d, *J* = 8.2 Hz, Ar**H**), 6.11 (1H, dd, *J* = 10.2, 2.8 Hz, O=CCH=C**H**), 5.05-5.00 (0.6H, m, C**H**N, rotamer A), 4.90-4.84 (0.4H, m, C**H**N, rotamer B), 4.65 (1H, s, ArOC**H**), 4.27-3.95 (3H, m, C**H**$_2$CH$_3$ and C**H**$_a$H$_b$N), 3.05-2.98 (1H, m, C**H**CHN), 2.95-2.83 (1H, m, CH$_a$**H**$_b$N), 2.83-2.78 (2H, m, ArC**H**$_2$), 2.00-1.82 (2H, m, C**H**$_2$CH$_2$N), 1.36-1.22 (3H, m, CH$_2$C**H**$_3$), 0.96 (9H, s, C(C**H**$_3$)$_3$), 0.18 (3H, s, Si(C**H**$_3$)$_a$), 0.12 (3H, s, Si(C**H**$_3$)$_b$); **Rotamer A (Major)** ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.9 (C), 155.7 (C), 147.4 (C), 147.1 (CH), 138.1 (C), 133.3 (CH), 128.1 (C), 125.4 (C), 122.9 (CH), 120.5 (CH), 87.7 (CH), 61.9 (CH_2), 50.4 (CH), 43.7 (C), 40.5 (CH), 38.1 (CH_2), 33.8 (CH_2), 29.4 (CH_2), 25.8 (3 × CH_3), 18.4 (C), 14.8 (CH_3), −4.5 (CH_3), −4.6 (CH_3); **Rotamer B (Minor)** ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.9 (C), 155.7 (C), 147.4 (C), 147.1 (CH), 138.1 (C), 133.3 (CH), 128.1 (C), 125.4 (C), 122.9 (CH), 120.5 (CH), 87.7 (CH), 61.9 (CH_2), 50.8 (CH), 43.7 (C), 40.5 (CH), 38.1 (CH_2), 33.5 (CH_2), 29.4 (CH_2), 25.8 (3 × CH_3), 18.4 (C), 14.8 (CH_3), −4.5 (CH_3), −4.6 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{25}H_{34}NO_5Si]^+$ $[M+H]^+$: 456.2201, found 456.2202.

Ethyl (4*R*,4a*R*,7a*R*,12b*S*)-9-methoxy-7-oxo-1,2,4,4a,7,7a-hexahydro-3*H*-4,12-methanobenzofuro[3,2-*e*]isoquinoline-3-carboxylate (296)

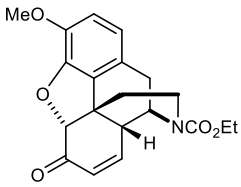




Codeine: (4*R*,4a*R*,7*S*,7a*R*,12b*S*)-9-methoxy-3-methyl-2,3,4,4a,7,7a-hexahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-7-ol (2). A mixture of morphine **1** (2.50 g, 8.75 mmol), K_3PO_4 (17.6 g, 83.1 mmol), trimethylphenylammonium chloride (1.80 g, 10.50 mmol), and toluene (125 mL), was stirred under reflux for 16 h. The reaction was cooled to room temperature, filtered through a short plug of celite, washing through with toluene (50 mL), and concentrated *in vacuo*. Purification of the residue by column chromatography (10% 2 M NH_3[MeOH]/CH_2Cl_2) gave codeine (**2**) as an off-white foam (2.10 g, 80%). The analytical data were consistent with those reported previously.[119] m.p. 155-158 °C (Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.66 (1H, d, *J* = 8.2 Hz), 6.60-6.53 (1H, m), 5.71 (1H, ddt, *J* = 9.9, 3.3, 1.4 Hz), 5.29 (1H, dt, *J* = 9.9, 2.7 Hz), 4.89 (1H, dd, *J* = 6.5, 1.3 Hz), 4.21-4.13 (1H, m), 3.84 (3H, s), 3.35 (1H, dd, *J* = 6.3, 3.3 Hz), 3.04 (1H, d, *J* = 18.6 Hz), 2.67 (1H, p, *J* = 2.9 Hz), 2.59 (1H, ddd, *J* = 12.0, 5.4, 2.3 Hz), 2.46-2.35 (4H, m), 2.30 (1H, dd, *J* = 19.3, 6.3 Hz), 2.07 (1H, td, *J* = 12.4, 5.1 Hz), 1.87 (1H, ddd, *J* = 12.7, 3.7, 1.9 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 146.3, 142.2, 133.4, 131.1, 128.2, 127.0, 119.5, 112.9, 91.3, 66.4, 58.9, 56.3, 46.4, 43.0, 42.9, 40.9, 35.8, 20.4.

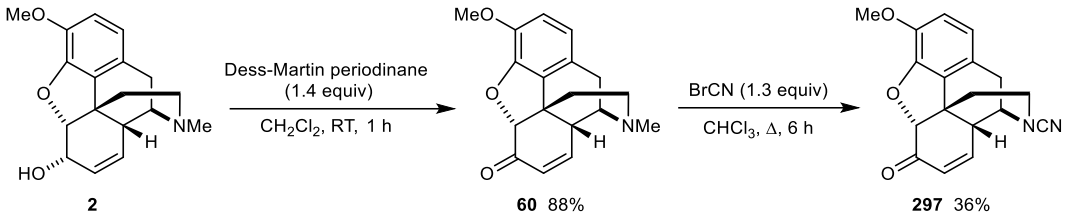


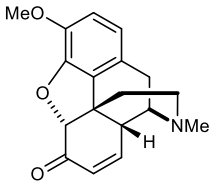
Ethyl (4*R*,4a*R*,7*S*,7a*R*,12b*S*)-7-hydroxy-9-methoxy-1,2,4,4a,7,7a-hexahydro-3*H*-4,12-methanobenzofuro[3,2-*e*]isoquinoline-3-carboxylate (295). To a stirred suspension of codeine (**2**) (641 mg, 2.14 mmol) and $NaHCO_3$ (2.70 g, 32.1 mmol) in acetone (12 mL) was added ethyl chloroformate (1.8 mL, 19.3 mmol) in one portion and the resulting mixture was heated under reflux for 16 h. The reaction was cooled to room temperature, filtered, washing through with acetone (12 mL) and concentrated *in vacuo*. Purification of the residue by column chromatography (40% EtOAc/petrol) gave **295** as a white foam (502 mg, 66%). The analytical data were consistent with those reported previously.[120] m.p. 148-152 °C (Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.68 (1H, d, *J* = 8.3 Hz), 6.57 (1H, d, *J* = 8.2 Hz), 5.80-5.72 (1H, m), 5.33-5.25 (1H, m), 4.99-4.76 (2H, m), 4.24-3.95 (2H, m), 3.84 (3H, s), 3.01-2.49 (5H, m), 1.99-1.86 (2H, m), 1.34-1.22 (3H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ 155.4, 146.4, 142.6, 134.5, 129.9, 127.0, 125.7, 120.0,113.2, 91.2, 66.1, 61.5, 56.4, 50.4, 43.4, 39.7, 37.4, 35.5,29.6, 14.8.



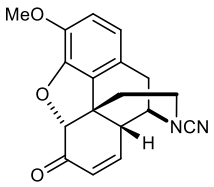
Ethyl (4*R*,4a*R*,7a*R*,12b*S*)-9-methoxy-7-oxo-1,2,4,4a,7,7a-hexahydro-3*H*-4,12-methanobenzofuro[3,2-*e*]isoquinoline-3-carboxylate (296). To a stirred solution of **295** (72 mg, 0.20 mmol) in Ac_2O (0.60 mL, 6.00 mmol) was added DMSO (0.20 mL, 3.00 mmol) and the resulting mixture was stirred at 70 °C for 1.5 h. The reaction was cooled to room temperature, diluted with H_2O (5 mL), and extracted with Et_2O (3 × 5 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ solution (3 × 20 mL), brine (20 mL), dried ($MgSO_4$), and concentrated *in vacuo* to give **296** as a white foam (65 mg, 92%). The analytical data were consistent with those reported previously.[120] m.p. 157-159 °C (Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.69 (1H, d, *J* = 8.3 Hz), 6.67-6.57 (2H, m), 6.11 (1H, dd, *J* = 10.2, 2.9 Hz), 5.06-4.82 (1H, m), 4.68 (1H, s), 4.27-3.91 (3H, m), 3.84 (3H, s), 3.08-3.01 (1H, m), 2.93-2.74 (3H, m), 2.02-1.85 (2H, m), 1.38-1.17 (3H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.1, 155.6, 147.2, 145.0, 142.9, 133.4, 127.9, 124.8, 120.5, 115.0, 87.8, 61.8, 56.8, 50.3, 43.6, 40.4, 38.1, 33.6, 29.4, 14.8.

(4*R*,4a*R*,7a*R*,12b*S*)-9-Methoxy-7-oxo-1,2,4,4a,7,7a-hexahydro-3*H*-4,12-methanobenzofuro[3,2-*e*]isoquinoline-3-carbonitrile (1d)





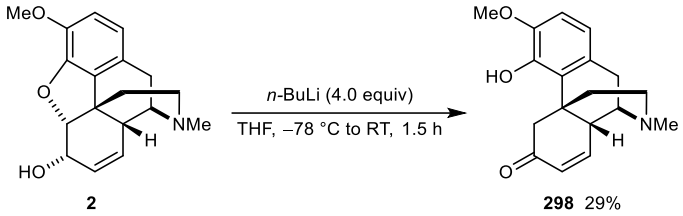
(4*R*,4a*R*,7a*R*,12b*S*)-9-Methoxy-3-methyl-2,3,4,4a-tetrahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-7(7a*H*)-one (60). To a stirred solution of codeine **2** (1.4 g, 4.72 mmol) in CH_2Cl_2 (60 mL) was added Dess-Martin Periodinane (2.80 g, 6.61 mmol) in one portion and the resulting mixture was stirred at room temperature for 1 h. 1 M Aqueous NaOH solution (60 mL) was then added and the mixture was stirred for a further 1 h. The layers were separated, and aqueous layer was extracted with CH_2Cl_2 (60 mL). The combined organic layers were washed with brine (100 mL), dried (Na_2SO_4), and concentrated *in vacuo* to give **60** as an off-white foam (1.12 g, 80%), which was used in the subsequent step without further purification. The analytical data were consistent with those reported previously.[121] m.p. 178-182 °C (Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.70 (1H, d, *J* = 8.2 Hz), 6.68-6.61 (2H, m), 6.11 (1H, dd, *J* = 10.2, 2.9 Hz), 4.72 (1H, s), 3.87 (3H, s), 3.44 (1H, dd, *J* = 5.4, 3.0 Hz), 3.27-3.20 (1H, m), 3.18-3.07 (1H, m), 2.64 (1H, ddd, *J* = 12.3, 4.9, 1.8 Hz), 2.48 (3H, s), 2.39-2.27 (2H, m), 2.10 (1H, td, *J* = 12.2, 5.0 Hz), 1.88 (1H, ddd, *J* = 12.4, 3.9, 1.9 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 194.6, 149.0, 145.0, 142.7, 132.8, 129.1, 126.0, 120.0, 115.0, 88.2, 59.2, 57.0, 47.1, 43.2, 43.0, 41.5, 34.0, 20.6.



(4*R*,4a*R*,7a*R*,12b*S*)-9-Methoxy-7-oxo-1,2,4,4a,7,7a-hexahydro-3*H*-4,12-methanobenzofuro[3,2-*e*]isoquinoline-3-carbonitrile (297). A round-bottom flask was charged with **60** (446 mg, 1.50 mmol), BrCN (207 mg, 1.95 mmol), and $CHCl_3$ (9 mL), and the resulting mixture was stirred under reflux for 6 h. The reaction was cooled to room temperature, diluted with $CHCl_3$ (50 mL), and washed with 1 M aqueous HCl solution (3 × 50 mL), 2 M aqueous NaOH solution (50 mL), H_2O (50 mL), brine (50 mL). The organic solution was dried (Na_2SO_4) and concentrated *in vacuo*. Purification of the residue by column chromatography (60% EtOAc/petrol) gave **297** as an off-white solid

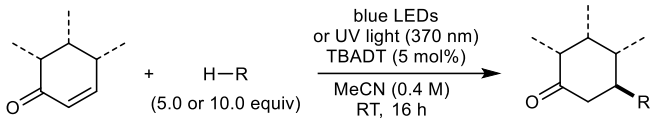
(166 mg, 36%). R_f = 0.25 (60% EtOAc/petrol); m.p. 155-159 °C (Et_2O); $[\alpha]_D^{20.1}$ −212 (*c* 1.00, $CHCl_3$); IR (ATR) 2935, 2836, 2206 (C≡N), 1670 (C=O), 1503, 1438, 1400, 1320, 1304, 1275 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.73 (1H, d, *J* = 8.2 Hz, Ar**H**), 6.67 (1H, d, *J* = 8.2 Hz, Ar**H**), 6.56 (1H, dd, *J* = 10.3, 2.1 Hz, O=CC**H**=CH), 6.14 (1H, dd, *J* = 10.3, 2.9 Hz, O=CCH=C**H**), 4.70 (1H, s, ArOC**H**), 4.11 (1H, ddd, *J* = 5.3, 3.4, 1.4 Hz, C**H**N), 3.84 (3H, s, OC$\mathbf{H}_3$), 3.35-3.28 (2H, m, C**H**CHCN and C$\mathbf{H}_a$H$_b$N), 3.22-3.12 (2H, m, CH$_a$**H**$_b$N and ArC$\mathbf{H}_a$H$_b$), 2.85 (1H, dd, *J* = 18.5, 4.3 Hz, ArCH$_a$**H**$_b$), 2.15 (1H, td, *J* = 12.7, 5.5 Hz, C$\mathbf{H}_a$H$_b$CH$_2$N), 1.94 (1H, ddd, *J* = 13.0, 4.0, 1.5 Hz, CH$_a$**H**$_b$CH$_2$N); ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.4 (C), 145.4 (CH), 145.1 (C), 143.4 (C), 133.7 (CH), 127.2 (C), 123.6 (C), 120.8 (CH), 117.4 (C), 115.6 (CH), 87.5 (CH), 57.2 (CH), 56.9 (CH_3), 43.9 (CH_2), 42.8 (C), 39.8 (CH), 32.7 (CH_2), 28.6 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{18}H_{17}N_2O_3]^+$ $[M+H]^+$: 309.1234, found 309.1232.

(4b*S*,8a*R*,9*R*)-4-Hydroxy-3-methoxy-11-methyl-9,10-dihydro-5*H*-9,4b-(epiminoethano)phenanthren-6(8a*H*)-one (298)

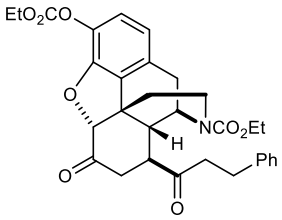


To a stirred solution of **2** (1.70 g, 5.68 mmol) in THF (71 mL) at −78 °C was added *n*-BuLi (2.38 M in hexanes, 9.56 mL, 22.7 mmol) and the resulting mixture was stirred at −78 °C for 1 h. The reaction was warmed to room temperature and stirred for a further 30 min. The reaction was quenched with H_2O (30 mL) and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were washed with brine (30 mL), dried (Na_2SO_4), and concentrated *in vacuo*. Purification of the residue by column chromatography (10% 2 M NH_3[MeOH]/CH_2Cl_2) gave **298** as a beige foam (494 mg, 29%). The analytical data were consistent with those reported previously.[122] m.p. 174-177 °C (Et_2O); ^1H NMR (400 MHz, $CDCl_3$) δ 6.69 (1H, d, *J* = 9.8 Hz), 6.63 (1H, d, *J* = 8.4 Hz), 6.55 (1H, d, *J* = 7.5 Hz), 6.14 (1H, s), 5.88 (1H, d, *J* = 9.9 Hz), 4.26 (1H, d, *J* = 15.6 Hz), 3.80 (3H, s), 3.22 (1H, m), 2.98 (2H, m), 2.51(5H, m), 2.02 (4H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ 199.5, 149.5, 144.9, 144.5, 130.9, 130.1, 122.8, 118.2, 108.8, 56.1, 55.9, 48.9, 47.1, 42.6, 40.5, 36.3, 24.3.

6.3. General Procedure: TBADT-Catalysed Radical Addition to Enones



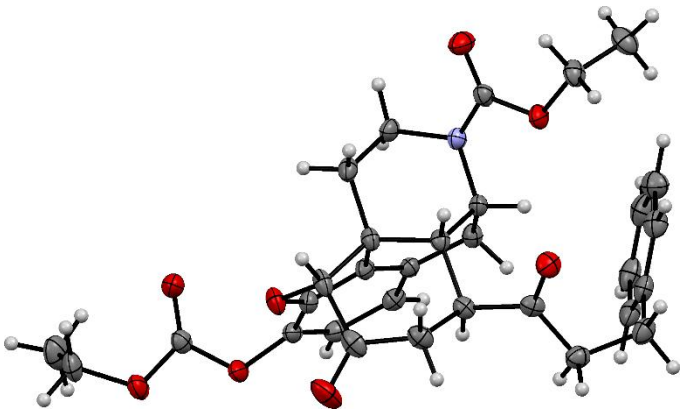
An oven-dried microwave vial fitted with a magnetic stirrer bar was charged with the appropriate enone (0.30 mmol) and TBADT (50.0 mg, 0.015 mmol). The vial was capped with a crimp cap seal and flushed with argon (5 min). Freshly deoxygenated MeCN (0.75 mL) and the appropriate radical donor (1.50 mmol or 3.00 mmol) were added, the cap was sealed with PTFE tape, and the contents were stirred at room temperature for 16 h under blue LED irradiation using a A160WE Kessil Tuna Blue lamp or UV irradiation using a 40W Kessil PR160L-370 nm lamp. The reaction mixture was concentrated *in vacuo* and purified by column chromatography to give the addition product.

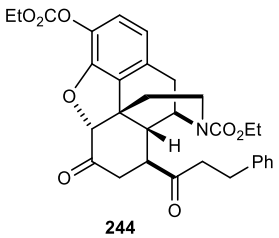


Ethyl (4*R*,4a*R*,5*S*,7a*R*,12b*S*)-9-[(ethoxycarbonyl)oxy]-7-oxo-5-(3-phenylpropanoyl)-1,2,4,4a,5,6,7,7a-octahydro-3*H*-4,12-methanobenzofuro[3,2-*e*]isoquinoline-3-carboxylate (244). Prepared according to the General Procedure using enone **33** (124 mg, 0.30 mmol) and 3-phenylpropanal (0.20 mL, 1.50 mmol) as the radical donor, under blue LED irradiation. Purification by column chromatography (50% EtOAc/petrol) gave **244** (110 mg, 67%) as a white foam, as a *ca*. 1:1 mixture of rotamers. R_f = 0.33 (50% EtOAc/petrol); m.p. 133-138 °C (Et_2O); $[\alpha]_D^{20.1}$ −180 (*c* 1.00, $CHCl_3$); IR (ATR) 2929, 2109, 1760 (C=O), 1732 (C=O), 1687 (C=O), 1624 (C=O), 1495, 1443, 1370, 1316 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.34-7.13 (5H, m, $C_6\mathbf{H}_5$), 6.99 (1H, d, *J* = 8.2 Hz, Ar**H**), 6.71 (1H, d, *J* = 8.2 Hz, Ar**H**), 4.77-4.66 (1.5H, m, ArOC**H** and C**H**N, rotamer A), 4.58-4.53 (0.5H, m, C**H**N, rotamer B), 4.39-4.31 (2H, m, $OCO_2C\mathbf{H}_2$), 4.26-3.94 (3H, m, $NCO_2C\mathbf{H}_2$ and $C\mathbf{H}_aH_bN$), 3.02-2.88 (2H, m, $C\mathbf{H}_2CH_2Ph$), 2.88-2.55 (6H, m, $CH_2C\mathbf{H}_2Ph$ and $ArC\mathbf{H}_2$ and $CH_a\mathbf{H}_bN$ and $O{=}CCH_2C\mathbf{H}$), 2.45-2.26 (3H, m, $O{=}CC\mathbf{H}_2CH$ and C**H**CHN), 2.09-1.97 (1H, m, $C\mathbf{H}_aH_bCH_2N$), 1.96-1.85 (1H, m, $CH_a\mathbf{H}_bCH_2N$), 1.40 (3H, t, *J* = 7.1 Hz, $OCO_2CH_2C\mathbf{H}_3$), 1.37-1.25 (3H, m, $NCO_2CH_2C\mathbf{H}_3$); **Rotamer A** ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.6 (C), 203.9 (C), 176.1 (C), 155.1 (C), 152.9 (C), 147.9 (C), 140.4 (C), 133.5 (C), 130.4 (C), 128.8 (2 × CH), 128.4 (CH), 126.5 (2 × CH), 123.3 (CH), 120.6 (CH), 91.4 (CH), 65.3 (CH_2), 61.9 (CH_2), 48.4 (CH), 48.0 (CH), 46.9 (C), 44.8 (CH_2), 42.6 (CH), 42.0 (CH_2), 37.8 (CH_2), 35.0 (CH_2), 29.5 (CH_2),

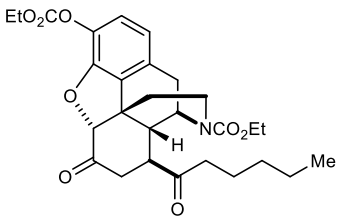
28.8 (CH_2), 14.8 (CH_3), 14.3 (CH_3); **Rotamer B** ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.9 (C), 204.1 (C), 176.1 (C), 155.5 (C), 152.9 (C), 147.9 (C), 140.4 (C), 133.5 (C), 130.7 (C), 128.8 (2 × CH), 128.4 (CH), 126.5 (2 × CH), 123.3 (CH), 120.6 (CH), 91.4 (CH), 65.3 (CH_2), 61.9 (CH_2), 48.5 (CH), 48.2 (CH), 46.9 (C), 44.8 (CH_2), 42.6 (CH), 42.0 (CH_2), 38.0 (CH_2), 35.0 (CH_2), 29.7 (CH_2), 28.8 (CH_2), 14.8 (CH_3), 14.3 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{31}H_{34}NO_8]^+$ $[M+H]^+$: 548.2279, found 548.2270.

Vapor diffusion of Et_2O into a solution of **244** in *t*-BuOH gave crystals that were suitable for X-ray crystallography:



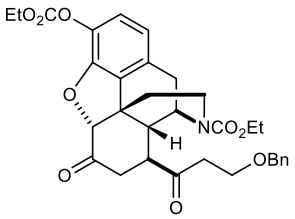


244
CCDC 2149928



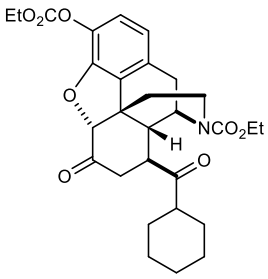
Ethyl (4*R*,4a*R*,5*S*,7a*R*,12b*S*)-9-[(ethoxycarbonyl)oxy]-5-hexanoyl-7-oxo-1,2,4,4a,5,6,7,7a-octahydro-3*H*-4,12-methanobenzofuro[3,2-*e*]isoquinoline-3-carboxylate (245). Prepared according to the General Procedure using enone **33** (124 mg, 0.30 mmol) and hexanal (0.18 mL, 1.50 mmol) as the radical donor, under blue LED irradiation. Purification by column chromatography (50% EtOAc/petrol) gave **245** (91 mg, 59%) as a white foam, as a *ca*. 1:1 mixture of rotamers. R_f = 0.41 (50% EtOAc/petrol); m.p. 181-183 °C (Et_2O); $[\alpha]_D^{20.1}$ −152 (*c* 1.00, $CHCl_3$); IR (ATR) 2928, 1760 (C=O), 1732 (C=O), 1687 (C=O), 1624 (C=O), 1496, 1442, 1423, 1370, 1312 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.98 (1H, d, *J* = 8.3 Hz, Ar**H**), 6.73 (1H, d, *J* = 8.3 Hz, Ar**H**), 4.75 (1H, s, ArOC**H**), 4.70-4.65 (0.5H, m, C**H**N, rotamer A), 4.60-4.53 (0.5H, m, C**H**N, rotamer B), 4.39-4.25 (2H, m, $OCO_2C\mathbf{H}_2$), 4.22-3.91 (3H, m, $NCO_2C\mathbf{H}_2$ and $C\mathbf{H}_aH_bN$), 2.91-2.64 (4H, m, $CH_a\mathbf{H}_bN$ and $ArC\mathbf{H}_2$ and $O{=}CCH_2C\mathbf{H}$), 2.53-2.26 (5H, m, C**H**CHN and $O{=}CC\mathbf{H}_2CH_2$ and $O{=}CC\mathbf{H}_2CH$), 2.02 (1H, td, *J* = 12.4, 5.3 Hz, $C\mathbf{H}_aH_bCH_2N$), 1.92-1.83 (1H, m, $CH_a\mathbf{H}_bCH_2N$), 1.63-1.50 (2H, m, $O{=}CCH_2C\mathbf{H}_2$), 1.38 (3H, t, *J* = 7.1 Hz, $OCO_2CH_2C\mathbf{H}_3$), 1.31-1.22 (7H, m, $NCO_2CH_2C\mathbf{H}_3$ and $C\mathbf{H}_2C\mathbf{H}_2CH_3$), 0.92-0.75 (3H, m, $(CH_2)_4C\mathbf{H}_3$);

Rotamer A ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.6 (C), 204.2 (C), 155.0 (C), 153.0 (C), 148.0 (C), 133.6 (C), 130.4 (C), 127.1 (C), 123.3 (CH), 120.6 (CH), 91.4 (CH), 65.3 (CH_2), 61.9 (CH_2), 48.4 (CH), 47.7 (CH), 46.9 (C), 43.5 (CH_2), 42.9 (CH), 42.4 (CH_2), 37.8 (CH_2), 34.9 (CH_2), 31.3 (CH_2), 29.1 (CH_2), 23.1 (CH_2), 22.5 (CH_2), 14.8 (CH_3), 14.3 (CH_3), 14.0 (CH_3); **Rotamer B** ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.9 (C), 204.4 (C), 155.5 (C), 153.0 (C), 148.0 (C), 133.6 (C), 130.7 (C), 127.1 (C), 123.3 (CH), 120.6 (CH), 91.4 (CH), 65.3 (CH_2), 61.9 (CH_2), 48.6 (CH), 47.7 (CH), 46.9 (C), 43.5 (CH_2), 43.1 (CH), 42.4 (CH_2), 38.1 (CH_2), 35.0 (CH_2), 31.3 (CH_2), 29.1 (CH_2), 23.1 (CH_2), 22.5 (CH_2), 14.8 (CH_3), 14.3 (CH_3), 14.0 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{28}H_{36}NO_8]^+$ $[M+H]^+$: 514.2435, found 514.2430.



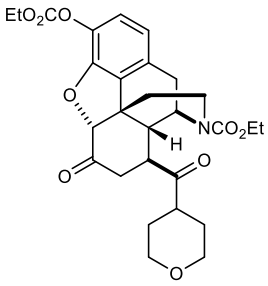
Ethyl (4*R*,4a*R*,5*S*,7a*R*,12b*S*)-5-[3-(benzyloxy)propanoyl]-9-[(ethoxycarbonyl)oxy]-7-oxo-1,2,4,4a,5,6,7,7a-octahydro-3*H*-4,12-methanobenzofuro[3,2-*e*]isoquinoline-3-carboxylate (246). Prepared according to the General Procedure using enone **33** (124 mg, 0.30 mmol) and 3-(benzyloxy)propanal (0.23 mL, 1.50 mmol) as the radical donor, under blue LED irradiation. Purification by column chromatography (50% EtOAc/petrol) gave **246** (36 mg, 21%) as an off-white foam, as a *ca*. 1:1 mixture of rotamers. R_f = 0.21 (50% EtOAc/petrol); m.p. 158-163 °C (Et_2O); $[\alpha]_D^{20.1}$ −165 (*c* 1.00, $CHCl_3$); IR (ATR) 2929, 1762 (C=O), 1685 (C=O), 1623 (C=O), 1495, 1443, 1425, 1370, 1316, 1232 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37-7.23 (5H, m, C_6**H**$_5$), 6.96 (1H, d, *J* = 8.2 Hz, Ar**H**), 6.63 (1H, d, *J* = 8.2 Hz, Ar**H**), 4.78-4.70 (1.5H, m, ArOC**H** and C**H**N, rotamer A), 4.67-4.60 (0.5H, m, C**H**N, rotamer B) 4.50-4.42 (2H, m, OC**H**$_2$Ph), 4.37-4.29 (2H, m, OCO_2C**H**$_2$), 4.22-3.93 (3H, m, NCO_2C**H**$_2$ and C**H**$_a$H$_b$N), 3.78-3.65 (2H, m, C**H**$_2$OBn), 2.84-2.61 (6H, m, CH$_a$**H**$_b$N and O=CC**H**$_2$CH$_2$ and ArC**H**$_2$CH and O=CCH$_2$C**H**), 2.56-2.35 (3H, m, O=CC**H**$_2$CH and C**H**CHN), 2.06-1.96 (1H, m, C**H**$_a$H$_b$CH$_2$N), 1.92-1.84 (1H, m, CH$_a$**H**$_b$CH$_2$N), 1.39 (3H, t, *J* = 7.1 Hz, OCO_2CH_2C**H**$_3$), 1.35-1.17 (3H, m, NCO_2CH_2C**H**$_3$); **Rotamer A** ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.6 (C), 204.1 (C), 155.4 (C), 153.0 (C), 147.9 (C), 137.8 (C), 133.5 (C), 130.9 (C), 128.6 (2 × CH), 128.0 (2 × CH), 127.9 (CH), 127.0 (C), 123.2 (CH), 120.7 (CH), 91.5 (CH), 73.6 (CH_2), 65.7 (CH_2), 65.3 (CH_2), 61.8 (CH_2), 48.5 (CH), 48.4 (CH), 46.9 (C), 42.9 (CH_2), 42.5 (CH), 41.9 (CH_2), 38.1 (CH_2), 35.1 (CH_2), 28.9 (CH_2), 14.8 (CH_3), 14.3 (CH_3); **Rotamer B** ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.4 (C), 203.9 (C), 155.2 (C), 153.0 (C), 147.9 (C), 137.8 (C), 133.5 (C), 130.7 (C), 128.6 (2 × CH), 128.0 (2 × CH), 127.9 (CH), 127.0 (C), 123.2 (CH), 120.7 (CH), 91.5 (CH), 73.6 (CH_2), 65.6 (CH_2), 65.3 (CH_2), 61.8 (CH_2), 48.5 (CH), 48.4 (CH), 46.9

(C), 42.7 (CH_2), 42.5 (CH), 41.9 (CH_2), 37.9 (CH_2), 34.9 (CH_2), 28.8 (CH_2), 14.8 (CH_3), 14.3 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{32}H_{36}NO_9]^+$ $[M+H]^+$: 578.2385, found 578.2382.

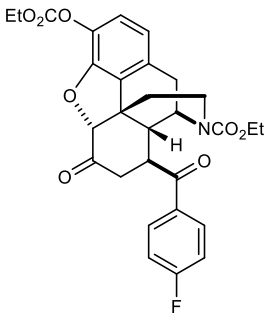


Ethyl (4*R*,4a*R*,5*S*,7a*R*,12b*S*)-5-(cyclohexanecarbonyl)-9-[(ethoxycarbonyl)oxy]-7-oxo-1,2,4,4a,5,6,7,7a-octahydro-3*H*-4,12-methanobenzofuro[3,2-*e*]isoquinoline-3-carboxylate (247). Prepared according to the General Procedure using enone **33** (124 mg, 0.30 mmol) and cyclohexanecarbaldehyde (0.18 mL, 1.50 mmol) as the radical donor, under blue LED irradiation. Purification by column chromatography (50% EtOAc/petrol) gave **247** (109 mg, 70%) as a white foam, as a *ca*. 1:1 mixture of rotamers. R_f = 0.37 (50% EtOAc/petrol); m.p. 150-155 °C (Et_2O); $[\alpha]_D^{20.1}$ −212 (*c* 1.00, $CHCl_3$); IR 2928, 2855, 1762 (C=O), 1733 (C=O), 1690 (C=O), 1624 (C=O), 1496, 1443, 1371, 1313 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.02 (1H, d, *J* = 8.2 Hz, Ar**H**), 6.77 (1H, d, *J* = 8.2 Hz, Ar**H**), 4.79 (1H, s, ArOC**H**), 4.68-4.63 (0.5H, m, C**H**N, rotamer A), 4.57-4.53 (0.5H, m, C**H**N, rotamer B), 4.40-4.32 (2H, m, $OCO_2C\mathbf{H}_2$), 4.23-3.96 (3H, m, $NCO_2C\mathbf{H}_2$ and $C\mathbf{H}_aH_bN$), 2.93-2.68 (4H, m, $CH_a\mathbf{H}_bN$ and $ArC\mathbf{H}_2$ and C**H**CHN), 2.62-2.39 (3H, m, O=CC$\mathbf{H}_2$CH and O=CC**H**$(CH_2)_2$), 2.39-2.28 (1H, m, $O{=}CCH_2C\mathbf{H}$), 2.10-2.01 (1H, m, $C\mathbf{H}_aH_bCH_2N$), 1.95-1.86 (1H, m, $CH_a\mathbf{H}_bCH_2N$), 1.84-1.59 (4H, m, $C\mathbf{H}_2(CH_2)_3C\mathbf{H}_2$), 1.41 (3H, t, *J* = 7.1 Hz, $OCO_2CH_2C\mathbf{H}_3$), 1.35-1.23 (9H, m, $NCO_2CH_2C\mathbf{H}_3$ and $CH_2(C\mathbf{H}_2)_3CH_2$); **Rotamer A (Major)** ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.4 (C), 204.4 (C), 155.4 (C), 153.0 (C), 148.0 (C), 133.6 (C), 130.7 (C), 127.1 (C), 123.3 (CH), 120.6 (CH), 91.5 (CH), 65.4 (CH_2), 61.8 (CH_2), 51.3 (CH), 48.7 (CH), 47.0 (C), 46.5 (CH), 43.2 (CH), 42.8 (CH_2), 38.0 (CH_2), 35.2 (CH_2), 29.8 (CH_2), 28.3 (CH_2), 25.7 (2 × CH_2), 25.5 (2 × CH_2), 14.8 (CH_3), 14.3 (CH_3); **Rotamer B (Minor)** ^{13}C NMR (101 MHz, $CDCl_3$) δ 211.7 (C), 204.3 (C), 155.4 (C), 153.0 (C), 148.0 (C), 133.6 (C), 130.7 (C), 127.1 (C), 123.3 (CH), 120.6 (CH), 91.5 (CH), 65.4 (CH_2), 61.8 (CH_2), 51.0 (CH), 48.5 (CH), 47.0 (C), 46.3 (CH), 43.0 (CH), 42.8 (CH_2), 37.8 (CH_2), 35.0 (CH_2), 29.8 (CH_2), 28.3 (CH_2), 25.7 (2 × CH_2), 25.5 (2 × CH_2), 14.8 (CH_3), 14.3 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{29}H_{36}NO_8]^+$ $[M+H]^+$: 526.2435, found 526.2424.

Ethyl (4*R*,4a*R*,5*S*,7a*R*,12b*S*)-9-[(ethoxycarbonyl)oxy]-7-oxo-5-(tetrahydro-2*H*-pyran-4-carbonyl)-1,2,4,4a,5,6,7,7a-octahydro-3*H*-4,12-methanobenzofuro[3,2-*e*]isoquinoline-3-

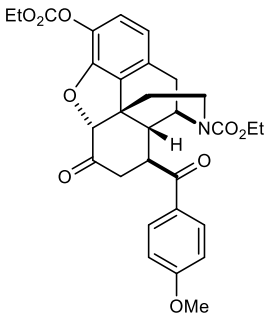


carboxylate (248). Prepared according to the General Procedure using enone **33** (124 mg, 0.30 mmol) and tetrahydro-2*H*-pyran-4-carbaldehyde (0.16 mL, 1.50 mmol) as the radical donor, under blue LED irradiation. Purification by column chromatography (50% EtOAc/petrol) gave **248** (55 mg, 35%) as a yellow foam, as a 1.5:1 mixture of rotamers. R_f = 0.19 (50% EtOAc/petrol); m.p. 161-165 °C (Et_2O); $[\alpha]_D^{20.1}$ −155 (*c* 1.00, $CHCl_3$); IR 2931, 2851, 1762 (C=O), 1732 (C=O), 1689 (C=O), 1624 (C=O), 1495, 1443, 1371, 1314 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.99 (1H, d, *J* = 8.3 Hz, Ar**H**), 6.74 (1H, d, *J* = 8.3 Hz, Ar**H**), 4.77 (1H, s, ArOC**H**), 4.65-4.59 (0.6H, m, C**H**N, rotamer A), 4.54-4.46 (0.4H, m, C**H**N, rotamer B), 4.38-4.27 (2H, m, $OCO_2C\mathbf{H}_2$), 4.21-4.05 (2H, m, $NCO_2C\mathbf{H}_2$), 4.03-3.87 (3H, m, $C\mathbf{H}_aH_bN$ and $(C\mathbf{H}_aH_b)_2O$), 3.47-3.29 (2H, m, $(CH_a\mathbf{H}_b)_2O$), 2.86-2.67 (4H, m, $ArC\mathbf{H}_2$ and $CH_a\mathbf{H}_bN$ and C**H**CHN), 2.61-2.35 (4H, m, $O{=}CC\mathbf{H}_2$ and $O{=}CCH_2C\mathbf{H}$ and $O{=}CC\mathbf{H}(CH_2)_2$), 2.10-1.97 (1H, m, $C\mathbf{H}_aH_bCH_2N$), 1.93-1.83 (1H, m, $CH_a\mathbf{H}_bCH_2N$), 1.70-1.59 (4H, m, $(C\mathbf{H}_aH_b)_2CH_2O$), 1.38 (3H, t, *J* = 7.1 Hz, $OCO_2CH_2C\mathbf{H}_3$), 1.30-1.22 (3H, m, $NCO_2CH_2C\mathbf{H}_3$); **Rotamer A (Major)** ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.5 (C), 204.1 (C), 155.4 (C), 152.9 (C), 148.0 (C), 133.6 (C), 130.4 (C), 127.0 (C), 123.4 (CH), 120.6 (CH), 91.4 (CH), 67.0 (2 × CH_2), 65.4 (CH_2), 61.9 (CH_2), 48.6 (CH), 48.1 (CH), 47.0 (C), 45.9 (CH), 43.0 (CH), 42.7 (CH_2), 38.0 (CH_2), 35.1 (CH_2), 29.0 (CH_2), 27.9 (2 × CH_2), 14.7 (CH_3), 14.3 (CH_3); **Rotamer B (Minor)** ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.5 (C), 203.9 (C), 155.1 (C), 152.9 (C), 148.0 (C), 133.6 (C), 130.2 (C), 127.0 (C), 123.4 (CH), 120.6 (CH), 91.4 (CH), 67.0 (2 × CH_2), 65.4 (CH_2), 61.9 (CH_2), 48.6 (CH), 48.1 (CH), 47.0 (C), 45.9 (CH), 43.0 (CH), 42.7 (CH_2), 37.8 (CH_2), 35.1 (CH_2), 29.2 (CH_2), 27.7 (2 × CH_2), 14.7 (CH_3), 14.3 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{28}H_{34}NO_9]^+$ $[M+H]^+$: 528.2228, found 528.2216.



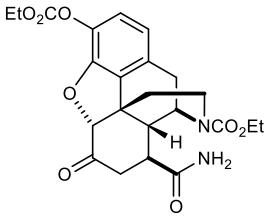
Ethyl (4*R*,4a*R*,5*S*,7a*R*,12b*S*)-9-[(ethoxycarbonyl)oxy]-5-(4-fluorobenzoyl)-7-oxo-1,2,4,4a,5,6,7,7a-octahydro-3*H*-4,12-methanobenzofuro[3,2-*e*]isoquinoline-3-carboxylate (249). Prepared according to the General Procedure using enone **33** (124 mg, 0.30 mmol) and 4-fluorobenzaldehyde (0.16 mL, 1.50 mmol) as the radical donor, under blue LED irradiation. Purification by column chromatography (50% EtOAc/petrol) gave **249** (67 mg, 42%) as a white foam, as a 1.5:1 mixture of rotamers. R_f = 0.33 (50% EtOAc/petrol); m.p. 143-145 °C (Et_2O); $[\alpha]_D^{20.1}$ −206 (*c* 1.00,

$CHCl_3$); IR 2935, 1760 (C=O), 1731 (C=O), 1680 (C=O), 1623 (C=O), 1595, 1496, 1444, 1425, 1371 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.92-7.84 (2H, m, Ar**H**), 7.19-7.08 (2H, m, Ar**H**), 7.01 (1H, d, *J* = 8.2 Hz, Ar**H**), 6.73 (1H, d, *J* = 8.2 Hz, Ar**H**), 4.83 (1H, s, ArOC**H**), 4.66-4.59 (0.6H, m, C**H**N, rotamer A), 4.56-4.49 (0.4H, m, C**H**N, rotamer B), 4.37-4.29 (2H, m, $OCO_2C\mathbf{H}_2$), 4.19-3.93 (3H, m, $NCO_2C\mathbf{H}_2$ and $C\mathbf{H}_aH_bN$), 3.31-3.17 (1H, m, $O{=}CCH_2C\mathbf{H}$), 3.05-2.94 (1H, m, C**H**CHN), 2.81-2.57 (4H, m, $CH_a\mathbf{H}_bN$ and $ArC\mathbf{H}_2$ and $O{=}CC\mathbf{H}_aH_b$), 2.56-2.47 (1H, m, $O{=}CCH_a\mathbf{H}_b$), 2.09 (1H, td, *J* = 12.6, 5.3 Hz, $C\mathbf{H}_aH_bCH_2N$), 1.96-1.86 (1H, m, $CH_a\mathbf{H}_bCH_2N$), 1.39 (3H, t, *J* = 7.1 Hz, $OCO_2CH_2C\mathbf{H}_3$), 1.29-1.22 (3H, m, $NCO_2CH_2C\mathbf{H}_3$); **Rotamer A (Major)** ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.5 (C), 196.7 (C), 166.5 (d, *J* = 257.4 Hz, C), 155.0 (C), 153.0 (C), 148.0 (C), 133.6 (C), 132.1 (C), 131.3 (2 × CH), 130.4 (C), 127.1 (C), 123.4 (CH), 120.64 (CH), 116.5 (d, *J* = 22.0 Hz, 2 × CH), 91.5 (CH), 65.4 (CH_2), 61.8 (CH_2), 48.3 (CH), 47.1 (C), 43.4 (CH), 43.3 (CH_2), 42.2 (CH), 37.9 (CH_2), 35.2 (CH_2), 28.9 (CH_2), 14.7 (CH_3), 14.3 (CH_3); **Rotamer B (Minor)** ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.5 (C), 196.9 (C), 166.5 (d, *J* = 257.4 Hz, C), 155.4 (C), 153.0 (C), 148.0 (C), 133.6 (C), 132.1 (C), 131.3 (2 × CH), 130.7 (C), 127.1 (C), 123.4 (CH), 120.6 (CH), 116.5 (d, *J* = 22.0 Hz, 2 × CH), 91.5 (CH), 65.4 (CH_2), 61.8 (CH_2), 48.5 (CH), 47.1 (C), 43.4 (CH), 43.3 (CH_2), 42.4 (CH), 38.1 (CH_2), 35.2 (CH_2), 29.0 (CH_2), 14.7 (CH_3), 14.3 (CH_3); ^{19}F NMR (276 MHz, $CDCl_3$) δ −102.8; HRMS (ESI) Exact mass calculated for $[C_{29}H_{29}FNO_8]^+$ $[M+H]^+$: 538.1872, found 538.1870.



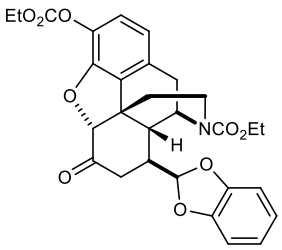
Ethyl (4*R*,4a*R*,5*S*,7a*R*,12b*S*)-9-[(ethoxycarbonyl)oxy]-5-(4-methoxybenzoyl)-7-oxo-1,2,4,4a,5,6,7,7a-octahydro-3*H*-4,12-methanobenzofuro[3,2-*e*]isoquinoline-3-carboxylate (250). Prepared according to the General Procedure using enone **33** (124 mg, 0.30 mmol) and 4-methoxybenzaldehyde (0.18 mL, 1.50 mmol) as the radical donor, under blue LED irradiation. Purification by column chromatography (50% EtOAc/petrol) gave **250** (102 mg, 62%) as a white foam, as a 1.2:1 mixture of rotamers. R_f = 0.25 (50% EtOAc/petrol); m.p. 198-201 °C (Et_2O); $[\alpha]_D^{20.1}$ −175 (*c* 1.00, $CHCl_3$); IR 2923, 2853, 1761 (C=O), 1731 (C=O), 1688 (C=O), 1669 (C=O), 1598, 1573, 1511, 1496 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.85 (2H, d, *J* = 8.9 Hz, Ar**H**), 7.04 (1H, d, *J* = 8.3 Hz, Ar**H**), 6.98-6.90 (2H, m, Ar**H**), 6.76 (1H, d, *J* = 8.3 Hz, Ar**H**), 4.85 (1H, s, ArOC**H**), 4.69-4.62 (0.6H, m, C**H**N, rotamer A), 4.58-4.53 (0.4H, m, C**H**N, rotamer B), 4.37 (2H, q, *J* = 7.1 Hz, $OCO_2C\mathbf{H}_2$), 4.22-3.96 (3H, m, $NCO_2C\mathbf{H}_2$ and $C\mathbf{H}_aH_bN$), 3.89 (3H, s, $OC\mathbf{H}_3$), 3.34-3.21 (1H, m, C**H**CHN), 3.07-

2.98 (1H, m, O=CCH$_2$C**H**), 2.84-2.61 (4H, m, CH$_a$**H**$_b$N and ArC**H**$_2$ and O=CC**H**$_a$H$_b$), 2.58-2.48 (1H, m, O=CCH$_a$**H**$_b$), 2.12 (1H, dt, *J* = 12.7, 6.4 Hz, C**H**$_a$H$_b$CH$_2$N), 1.99-1.90 (1H, m, CH$_a$**H**$_b$CH$_2$N), 1.43 (3H, t, *J* = 7.1 Hz, OCO$_2$CH$_2$C**H**$_3$), 1.34-1.24 (3H, m, NCO$_2$CH$_2$C**H**$_3$); **Rotamer A (Major)** ^{13}C NMR (101 MHz, CDCl$_3$) δ 205.0 (C), 196.6 (C), 164.6 (C), 153.0 (C), 148.1 (C), 133.6 (C), 131.0 (2 × CH), 130.6 (C), 128.7 (C), 127.3 (C), 123.3 (CH), 121.8 (C), 120.6 (CH), 114.4 (2 × CH), 91.6 (CH), 65.4 (CH$_2$), 61.8 (CH$_2$), 55.7 (CH$_3$), 48.4 (CH), 47.1 (C), 43.7 (CH), 43.6 (CH$_2$), 41.8 (CH), 38.1 (CH$_2$), 35.2 (CH$_2$), 29.5 (CH$_2$), 14.8 (CH$_3$), 14.3 (CH$_3$); **Rotamer B (Minor)** ^{13}C NMR (101 MHz, CDCl$_3$) δ 205.0 (C), 196.6 (C), 164.6 (C), 153.0 (C), 148.1 (C), 133.6 (C), 130.9 (2 × CH), 130.6 (C), 128.7 (C), 127.3 (C), 123.3 (CH), 121.8 (C), 120.6 (CH), 114.4 (2 × CH), 91.6 (CH), 65.4 (CH$_2$), 61.8 (CH$_2$), 55.7 (CH$_3$), 48.4 (CH), 47.1 (C), 43.7 (CH), 43.6 (CH$_2$), 41.8 (CH), 37.9 (CH$_2$), 35.2 (CH$_2$), 29.5 (CH$_2$), 14.8 (CH$_3$), 14.3 (CH$_3$); HRMS (ESI) Exact mass calculated for [C$_{30}$H$_{32}$NO$_9$]$^+$ [M+H]$^+$: 550.2072, found 550.2056.



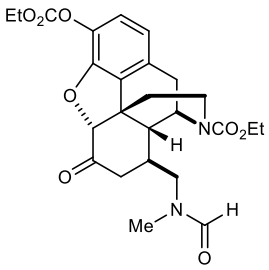
Ethyl (4*R*,4a*R*,5*S*,7a*R*,12b*S*)-5-carbamoyl-9-[(ethoxycarbonyl)oxy]-7-oxo-1,2,4,4a,5,6,7,7a-octahydro-3*H*-4,12-methanobenzofuro[3,2-*e*]isoquinoline-3-carboxylate (251). Prepared according to the General Procedure using enone **33** (124 mg, 0.30 mmol) and formamide (0.06 mL, 1.50 mmol) as the radical donor, under blue LED irradiation. Purification by column chromatography (90% EtOAc/CH$_2$Cl$_2$) gave **251** as a white foam (73 mg, 53%), as a 2.3:1 mixture of rotamers. R$_f$ = 0.16 (90% EtOAc/CH$_2$Cl$_2$); m.p. 182-184 °C (Et$_2$O); $[\alpha]_D^{20.1}$ –149 (*c* 1.00, CHCl$_3$); IR 3350 (NH), 3203 (NH), 2980, 1762 (C=O), 1731 (C=O), 1667 (C=O), 1623 (C=O), 1496, 1442, 1371 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.90 (1H, d, *J* = 8.1 Hz, Ar**H**), 6.78 (0.7H, s, N**H**$_a$H$_b$, rotamer A), 6.65 (1H, d, *J* = 8.1 Hz, Ar**H**), 6.57 (0.3H, s, N**H**$_a$H$_b$, rotamer B), 6.25 (0.7H, s, NH$_a$**H**$_b$, rotamer A), 5.68 (0.3H, s, NH$_a$**H**$_b$, rotamer B), 4.75-4.60 (2H, m, C**H**N and ArOC**H**), 4.34-4.20 (2H, m, OCO$_2$C**H**$_2$), 4.17-4.02 (1H, m, C**H**$_a$H$_b$N), 3.99-3.74 (2H, m, NCO$_2$C**H$_2$**), 3.14-2.84 (1H, m, ArC**H**$_a$H$_b$), 2.80-2.56 (4H, m, ArCH$_a$**H**$_b$ and CH$_a$**H**$_b$N and O=CC**H**$_a$H$_b$ and O=CCH$_2$C**H**), 2.50-2.37 (1H, m, O=CCH$_a$**H**$_b$), 2.18-1.96 (2H, m C**H**CHN and C**H**$_a$H$_b$CH$_2$N), 1.86-1.79 (1H, m, CH$_a$**H**$_b$CH$_2$N), 1.36 (3H, t, *J* = 7.1 Hz, OCO$_2$CH$_2$C**H**$_3$), 1.30-1.09 (3H, m, NCO$_2$CH$_2$C**H**$_3$); **Rotamer A (Major)** ^{13}C NMR (101 MHz, CDCl$_3$) δ 205.7 (C), 173.4 (C), 155.5 (C), 153.0 (C), 147.9 (C), 133.3 (C), 131.0 (C), 127.3 (C), 123.1 (CH), 120.4 (CH), 91.3 (CH), 65.5 (CH$_2$), 62.0 (CH$_2$), 48.7 (CH), 46.7 (C), 43.1 (CH$_2$), 43.0 (CH), 42.5 (CH), 37.9 (CH$_2$), 34.8 (CH$_2$), 28.6 (CH$_2$), 14.6 (CH$_3$), 14.2 (CH$_3$); **Rotamer B (Major)** ^{13}C NMR (101 MHz, CDCl$_3$) δ 205.7 (C),

172.9 (C), 155.2 (C), 153.0 (C), 147.9 (C), 133.3 (C), 131.0 (C), 127.3 (C), 123.1 (CH), 120.4 (CH), 91.3 (CH), 65.5 (CH_2), 61.9 (CH_2), 48.7 (CH), 46.7 (C), 43.1 (CH_2), 43.0 (CH), 42.5 (CH), 37.9 (CH_2), 34.6 (CH_2), 29.0 (CH_2), 14.8 (CH_3), 14.2 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{23}H_{27}N_2O_8]^+$ $[M+H]^+$: 459.1762, found 459.1747.

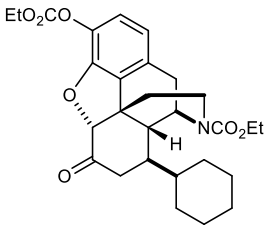


Ethyl (4*R*,4a*R*,5*S*,7a*R*,12b*S*)-5-(benzo[*d*][1,3]dioxol-2-yl)-9-[(ethoxycarbonyl)oxy]-7-oxo-1,2,4,4a,5,6,7,7a-octahydro-3*H*-4,12-methanobenzofuro[3,2-*e*]isoquinoline-3-carboxylate (252). Prepared according to the General Procedure using enone **33** (124 mg, 0.30 mmol) and 1,3-benzodioxole (0.17 mL, 1.50 mmol) as the radical donor, under blue LED irradiation. Purification by column chromatography (50% EtOAc/petrol) gave **252** (95.0 mg, 59%) as a white foam, as a *ca*. 1:1 mixture of rotamers. R_f = 0.27 (50% EtOAc/petrol); m.p. 149-154 °C (Et_2O); $[\alpha]_D^{20.1}$ −199 (*c* 1.00, $CHCl_3$); IR (ATR) 2922, 1761 (C=O), 1733 (C=O), 1684 (C=O), 1625, 1483, 1442, 1371, 1355, 1312 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.97 (1H, d, *J* = 8.3 Hz, Ar**H**), 6.86-6.75 (4H, m, Ar**H**), 6.73 (1H, d, *J* = 8.3 Hz, Ar**H**), 6.25-6.20 (0.5H, m, C**H**O_2, rotamer A), 6.11-6.06 (0.5H, m, C**H**O_2, rotamer B), 5.26-5.21 (0.5H, m, C**H**N, rotamer A), 5.10-5.05 (0.5H, m, C**H**N, rotamer B), 4.74 (1H, s, ArOC**H**), 4.40-4.24 (2H, m, $OCO_2C\mathbf{H}_2$), 4.21-3.97 (3H, m, $NCO_2C\mathbf{H}_2$ and $C\mathbf{H}_aH_bN$), 3.07-2.95 (1H, m, $ArC\mathbf{H}_aH_b$), 2.87-2.72 (2H, m, $ArCH_a\mathbf{H}_b$ and $CH_a\mathbf{H}_bN$), 2.72-2.58 (2H, m, $O{=}CC\mathbf{H}_aH_bCH$ and C**H**CHN), 2.50-2.30 (1H, m, $O{=}CCH_a\mathbf{H}_bCH$), 2.08-1.87 (3H, m, $C\mathbf{H}_2CH_2N$ and $O{=}CCH_2C\mathbf{H}$), 1.37 (3H, t, *J* = 7.1 Hz, $OCO_2CH_2C\mathbf{H}_3$), 1.32-1.10 (3H, m, $NCO_2CH_2C\mathbf{H}_3$); **Rotamer A** ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.5 (C), 155.1 (C), 152.9 (C), 148.0 (C), 147.2 (C), 147.0 (C), 133.5 (C), 130.9 (C), 127.0 (C), 123.3 (CH), 122.1 (2 × CH), 120.7 (CH), 110.8 (CH), 108.8 (2 × CH), 91.6 (CH), 65.3 (CH_2), 61.9 (CH_2), 48.3 (CH), 47.2 (C), 42.0 (CH), 40.3 (CH), 38.7 (CH_2), 37.9 (CH_2), 35.1 (CH_2), 28.9 (CH_2), 14.7 (CH_3), 14.3 (CH_3); **Rotamer B** ^{13}C NMR (101 MHz, $CDCl_3$) δ 204.6 (C), 155.6 (C), 152.9 (C), 148.0 (C), 147.2 (C), 147.0 (C), 133.5 (C), 130.9 (C), 127.0 (C), 123.3 (CH), 122.1 (2 × CH), 120.7 (CH), 110.8 (CH), 108.8 (2 × CH), 91.6 (CH), 65.3 (CH_2), 61.9 (CH_2), 48.6 (CH), 47.2 (C), 42.2 (CH), 40.3 (CH), 39.8 (CH_2), 38.1 (CH_2), 35.2 (CH_2), 29.1 (CH_2), 14.7 (CH_3), 14.3 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{29}H_{30}NO_9]^+$ $[M+H]^+$: 536.1915, found 536.1897.

Ethyl (4*R*,4a*R*,5*S*,7a*R*,12b*S*)-9-[(ethoxycarbonyl)oxy]-5-[(*N*-methylformamido)methyl]-7-oxo-1,2,4,4a,5,6,7,7a-octahydro-3*H*-4,12-methanobenzofuro[3,2-*e*]isoquinoline-3-

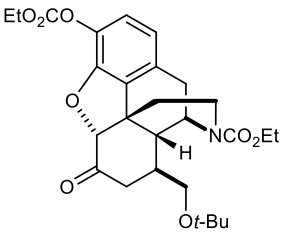


carboxylate (253). Prepared according to the General Procedure using enone **33** (124 mg, 0.30 mmol) and DMF (0.12 mL, 1.50 mmol) as the radical donor, under blue LED irradiation. Purification by column chromatography (10% MeOH/EtOAc) gave **253** (45 mg, 31%) as an off-white solid, as a complex mixture of rotamers. R_f = 0.25 (10% MeOH/EtOAc); m.p. 136-137 °C (Et_2O); $[\alpha]_D^{20.1}$ −159 (*c* 1.00, $CHCl_3$); IR (ATR) 2929, 1762 (C=O), 1730 (C=O), 1667 (C=O), 1625 (C=O), 1495, 1443, 1425, 1371, 1318 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6, 120 °C) δ 8.04 (1H, s, O=C**H**), 6.99 (1H, d, *J* = 8.3 Hz, Ar**H**), 6.78 (1H, d, *J* = 8.3 Hz, Ar**H**), 5.01 (1H, s, ArOC**H**), 4.94 (1H, s, C**H**N), 4.29 (2H, q, *J* = 7.1 Hz, $OCO_2C\mathbf{H}_2$), 4.15 (2H, q, *J* = 7.1 Hz, $NCO_2C\mathbf{H}_2$), 3.96 (1H, dd, *J* = 13.9, 5.3 Hz, $C\mathbf{H}_aH_bNCO_2$), 3.56-3.30 (2H, m, $C\mathbf{H}_2NCH_3$), 3.08-2.82 (4H, m, $ArC\mathbf{H}_aH_b$ and $NC\mathbf{H}_3$), 2.79-2.61 (2H, m, $ArCH_a\mathbf{H}_b$ and $CH_a\mathbf{H}_bNCO_2$), 2.48-2.34 (2H, m, $O{=}CC\mathbf{H}_aH_b$ and C**H**CHN), 2.23-2.03 (2H, m, $O{=}CCH_a\mathbf{H}_b$ and $C\mathbf{H}_aH_bCH_2N$), 1.67 (1H, ddd, *J* = 12.7, 4.0, 1.5 Hz, $CH_a\mathbf{H}_bCH_2N$), 1.61-1.44 (1H, m, C**H**CH_2N), 1.33 (3H, t, *J* = 7.1 Hz, $OCO_2CH_2C\mathbf{H}_3$), 1.26 (3H, t, *J* = 7.1 Hz, $NCO_2CH_2C\mathbf{H}_3$); ^{13}C NMR (101 MHz, DMSO-d_6, 120 °C) δ 204.3 (C), 162.4 (CH), 154.1 (C), 151.4 (C), 146.9 (C), 132.2 (C), 130.5 (C), 127.1 (C), 121.7 (CH), 119.3 (CH), 90.8 (CH), 64.2 (CH_2), 60.3 (CH_2), 50.2 (CH), 47.6 (C), 46.4 (CH_2), 45.9 (CH), 43.6 (CH_2), 42.4 (CH_2), 41.8 (CH_2), 37.3 (CH_3), 33.9 (CH), 27.6 (CH_2), 13.8 (CH_3), 13.2 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{25}H_{31}N_2O_8]^+$ $[M+H]^+$: 487.2075, found 487.2068.



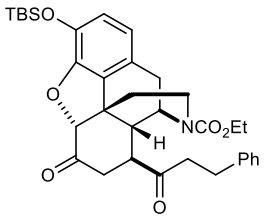
Ethyl (4*R*,4a*R*,5*R*,7a*R*,12b*S*)-5-cyclohexyl-9-[(ethoxycarbonyl)oxy]-7-oxo-1,2,4,4a,5,6,7,7a-octahydro-3*H*-4,12-methanobenzofuro[3,2-*e*]isoquinoline-3-carboxylate (254). Prepared according to a slight modification of General Procedure A using enone **33** (124 mg, 0.30 mmol) and cyclohexane (0.32 mL, 3.00 mmol) as the radical donor under blue LED irradiation, but with the addition of DCE (0.2 mL) to solubilize the reaction mixture. Purification by column chromatography (50% EtOAc/petrol) gave **254** (45 mg, 30%) as a white foam, as a 1.5:1 mixture of rotamers. R_f = 0.31 (50% EtOAc/petrol); m.p. 163-167 °C (Et_2O); $[\alpha]_D^{20.1}$ −184 (*c* 1.00, $CHCl_3$); IR (ATR) 2923, 2852, 1762 (C=O), 1729 (C=O), 1687 (C=O), 1496, 1443, 1371, 1318, 1233 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.97 (1H, d, *J* = 8.2 Hz, Ar**H**), 6.72 (1H, d, *J* = 8.2 Hz, Ar**H**), 5.08-4.98 (0.6H, m, C**H**N, rotamer A), 4.93-4.89 (0.4H, m, C**H**N, rotamer B), 4.73 (1H, s, ArOC**H**), 4.39-4.31 (2H, m, $CO_2C\mathbf{H}_2$), 4.24-3.96 (3H, m, $NCO_2C\mathbf{H}_2$

and C**H**$_a$H$_b$N), 2.92-2.72 (3H, m, CH$_a$**H**$_b$N and ArC**H**$_2$), 2.44-2.29 (2H, m, O=CC**H**$_a$H$_b$ and C**H**CHN), 2.19-2.08 (1H, m, O=CCH$_a$**H**$_b$), 1.98 (1H, td, *J* = 12.4, 5.2 Hz, C**H**$_a$H$_b$CH$_2$N), 1.92-1.87 (1H, m, CH$_a$**H**$_b$CH$_2$N), 1.86-1.50 (2H, m, O=CCH$_2$C**H** and C**H**(CH$_2$)$_2$), 1.40 (3H, t, *J* = 7.1 Hz, OCO$_2$CH$_2$C**H**$_3$), 1.37-1.20 (13H, m, NCO$_2$CH$_2$C**H**$_3$ and CH(C**H**$_2$)$_5$); **Rotamer A (Major)** ^{13}C NMR (101 MHz, CDCl$_3$) δ 206.6 (C), 155.7 (C), 153.1 (C), 148.0 (C), 133.4 (C), 130.8 (C), 127.8 (C), 122.9 (CH), 120.3 (CH), 92.1 (CH), 65.3 (CH$_2$), 61.8 (CH$_2$), 48.1 (CH), 47.5 (C), 43.4 (CH), 41.2 (CH$_2$), 40.8 (CH), 38.1 (CH$_2$), 37.8 (CH), 35.5 (CH$_2$), 29.8 (CH$_2$), 26.9 (CH$_2$), 26.6 (2 × CH), 26.4 (CH$_2$), 14.8 (CH$_3$), 14.3 (CH$_3$); **Rotamer B (Minor)** ^{13}C NMR (101 MHz, CDCl$_3$) δ 206.7 (C), 155.7 (C), 153.1 (C), 148.0 (C), 133.4 (C), 131.1 (C), 127.8 (C), 122.9 (CH), 120.4 (CH), 92.1 (CH), 65.3 (CH$_2$), 61.8 (CH$_2$), 48.1 (CH), 47.5 (C), 44.0 (CH), 41.2 (CH$_2$), 40.8 (CH), 38.4 (CH$_2$), 37.8 (CH), 35.5 (CH$_2$), 29.8 (CH$_2$), 26.9 (CH$_2$), 26.6 (2 × CH), 26.4 (CH$_2$), 14.8 (CH$_3$), 14.3 (CH$_3$); HRMS (ESI) Exact mass calculated for [C$_{28}$H$_{36}$NO$_7$]$^+$ [M+H]$^+$: 498.2486, found 498.2474.

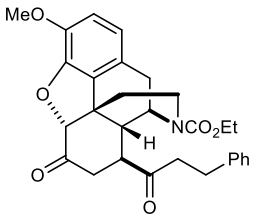


Ethyl (4*R*,4a*R*,5*S*,7a*R*,12b*S*)-5-(*tert*-butoxymethyl)-9-[(ethoxycarbonyl)oxy]-7-oxo-1,2,4,4a,5,6,7,7a-octahydro-3*H*-4,12-methanobenzofuro[3,2-*e*]isoquinoline-3-carboxylate (276). Prepared according to the General Procedure using enone **33** (124 mg, 0.30 mmol) and TBME (0.18 mL, 1.50 mmol) as the radical donor, under UV irradiation. Purification by column chromatography (50% EtOAc/petrol) gave **276** (51 mg, 34%) as an off-white foam, as a *ca.* 1:1 mixture of rotamers. R$_f$ = 0.41 (50% EtOAc/petrol); m.p. 170-175 °C (Et$_2$O); $[\alpha]_D^{20.1}$ −198 (*c* 1.00, CHCl$_3$); IR 2974, 1763 (C=O), 1730 (C=O), 1688 (C=O), 1495, 1443, 1425, 1367, 1317, 1232 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 6.92 (1H, d, *J* = 8.2 Hz, Ar**H**), 6.68 (1H, d, *J* = 8.2 Hz, Ar**H**), 5.12-5.07 (0.5H, m, C**H**N, rotamer A), 5.05-4.99 (0.5H, m, C**H**N, rotamer B), 4.68 (1H, s, ArOC**H**), 4.38-4.23 (2H, m, OCO$_2$C**H**$_2$), 4.23-3.92 (3H, m, NCO$_2$C**H**$_2$ and C**H**$_a$H$_b$N), 3.47-3.20 (2H, m, C**H**$_2$OC(CH$_3$)$_3$), 2.92 (1H, dd, *J* = 18.7, 5.8 Hz, ArC**H**$_a$H$_b$), 2.84-2.66 (2H, m, ArC**H**$_a$H$_b$ and CH$_a$**H**$_b$N), 2.47-2.24 (3H, m, O=CC**H**$_2$ and C**H**CHN), 2.02-1.91 (1H, m, C**H**$_a$H$_b$CH$_2$N), 1.86 (1H, td, *J* = 12.0, 3.7 Hz, CH$_a$**H**$_b$CH$_2$N), 1.53-1.42 (1H, m, C**H**CH$_2$O), 1.36 (3H, t, *J* = 7.2 Hz, OCO$_2$CH$_2$C**H**$_3$), 1.31-1.22 (3H, m, NCO$_2$CH$_2$C**H**$_3$), 1.17 (9H, s, OC(C**H**$_3$)$_3$); **Rotamer A** ^{13}C NMR (101 MHz, CDCl$_3$) δ 206.3 (C), 155.6 (C), 153.0 (C), 148.0 (C), 133.3 (C), 131.4 (C), 127.7 (C), 122.8 (CH), 120.4 (CH), 91.8 (CH), 73.1 (C), 65.2 (CH$_2$), 62.8 (CH$_2$), 61.7 (CH$_2$), 48.7 (CH), 47.2 (C), 44.1 (CH), 43.8 (CH$_2$), 38.2 (CH$_2$), 36.9 (CH), 35.2 (CH$_2$), 29.2 (CH$_2$), 27.5 (3 × CH$_3$), 14.9 (CH$_3$), 14.3 (CH$_3$); **Rotamer B** ^{13}C NMR (101 MHz, CDCl$_3$) δ 206.3

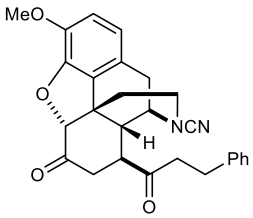
(C), 155.3 (C), 153.0 (C), 148.0 (C), 133.3 (C), 131.2 (C), 127.7 (C), 122.8 (CH), 120.3 (CH), 91.8 (CH), 73.0 (C), 65.2 (CH_2), 62.6 (CH_2), 61.7 (CH_2), 48.5 (CH), 47.2 (C), 44.1 (CH), 43.8 (CH_2), 38.0 (CH_2), 36.7 (CH), 35.0 (CH_2), 28.9 (CH_2), 27.5 (3 × CH_3), 14.8 (CH_3), 14.3 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{27}H_{36}NO_8]^+$ $[M+H]^+$: 502.2435, found 502.2419.



Ethyl (4*R*,4a*R*,5*S*,7a*R*,12b*S*)-9-[(*tert*-butyldimethylsilyl)oxy]-7-oxo-5-(3-phenylpropanoyl)-1,2,4,4a,5,6,7,7a-octahydro-3*H*-4,12-methanobenzofuro[3,2-*e*]isoquinoline-3-carboxylate (281). Prepared according to a slight modification of the General Procedure using enone **294** (59 mg, 0.13 mmol), TBADT (22 mg, 0.0065 mmol), MeCN (0.33 mL) and 3-phenylpropanal (0.09 mL, 0.65 mmol) as the radical donor, under blue LED irradiation. Purification by column chromatography (25% EtOAc/petrol) gave **281** (64 mg, 36%) as a white foam, as a *ca.* 1:1 mixture of rotamers. R_f = 0.37 (50% EtOAc/petrol); m.p. 158-164 °C (Et_2O); $[\alpha]_D^{20.1}$ −201 (*c* 1.00, $CHCl_3$); IR (ATR) 2928, 2856, 1688 (C=O), 1633 (C=O), 1606, 1497, 1470, 1426, 1376, 1315 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29-7.11 (5H, m, $C_6\mathbf{H}_5$), 6.68 (1H, d, *J* = 8.1 Hz, Ar**H**), 6.56 (1H, d, *J* = 8.1 Hz, Ar**H**), 4.69-4.65 (0.5H, m, C**H**N, rotamer A), 4.63 (1H, s, ArOC**H**), 4.53-4.48 (0.5H, m, C**H**N, rotamer B), 4.25-4.10 (2H, m, $CO_2C\mathbf{H}_2$), 4.10-3.90 (1H, m, $C\mathbf{H}_aH_bN$), 2.95-2.87 (2H, m, O=CC$\mathbf{H}_2CH_2$), 2.86-2.60 (6H, m, $C\mathbf{H}_2Ph$ and $CH_a\mathbf{H}_bN$ and $ArC\mathbf{H}_2$ and O=$CCH_2C\mathbf{H}$), 2.43-2.24 (3H, m, O=CC$\mathbf{H}_2CH$ and C**H**CHCN), 1.96 (1H, td, *J* = 12.5, 5.3 Hz, $C\mathbf{H}_aH_bCH_2N$), 1.86-1.76 (1H, m, $CH_a\mathbf{H}_bCH_2N$), 1.31-1.24 (3H, m, $CH_2C\mathbf{H}_3$), 1.01 (9H, s, $C(C\mathbf{H}_3)_3$), 0.29 (3H, s, $Si(C\mathbf{H}_3)_a$), 0.22 (3H, s, $Si(C\mathbf{H}_3)_b$); **Rotamer A (Major)** ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.8 (C), 204.8 (C), 155.5 (C), 147.2 (C), 140.5 (C), 138.6 (C), 128.7 (2 × CH), 128.4 (2 × CH), 126.4 (CH), 125.9 (C), 125.2 (C), 123.1 (CH), 120.5 (CH), 90.6 (CH), 61.8 (CH_2), 48.8 (CH), 48.3 (CH), 47.0 (C), 44.9 (CH_2), 42.9 (CH), 42.2 (CH_2), 38.2 (CH_2), 35.2 (CH_2), 29.5 (CH_2), 28.6 (CH_2), 25.8 (3 × CH_3), 18.4 (C), 14.8 (CH_3), −4.4 (CH_3), −4.6 (CH_3); **Rotamer B (Minor)** ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.8 (C), 204.8 (C), 155.5 (C), 147.2 (C), 140.5 (C), 138.6 (C), 128.7 (2 × CH), 128.4 (2 × CH), 126.4 (CH), 125.9 (C), 125.2 (C), 123.1 (CH), 120.5 (CH), 90.6 (CH), 61.8 (CH_2), 48.6 (CH), 48.3 (CH), 47.0 (C), 44.3 (CH_2), 42.9 (CH), 42.2 (CH_2), 38.1 (CH_2), 35.0 (CH_2), 29.5 (CH_2), 28.6 (CH_2), 25.8 (3 × CH_3), 18.4 (C), 14.8 (CH_3), −4.4 (CH_3), −4.6 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{34}H_{44}NO_6Si]^+$ $[M+H]^+$: 590.2932, found 590.2916.

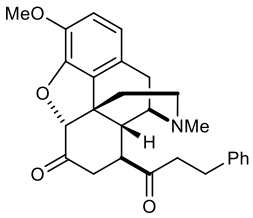


Ethyl (4*R*,4a*R*,5*S*,7a*R*,12b*S*)-9-methoxy-7-oxo-5-(3-phenylpropanoyl)-1,2,4,4a,5,6,7,7a-octahydro-3*H*-4,12-methanobenzofuro[3,2-*e*]isoquinoline-3-carboxylate (282). Prepared according to a slight modification of the General Procedure using enone **295** (60 mg, 0.17 mmol), TBADT (28 mg, 0.0085 mmol), MeCN (0.43 mL) and 3-phenylpropanal (0.11 mL, 0.85 mmol) as the radical donor, under blue LED irradiation. Purification by column chromatography (40% EtOAc/petrol) gave **282** (52 mg, 63%) as a white foam, as a *ca.* 1:1 mixture of rotamers. R_f = 0.40 (50% EtOAc/petrol); m.p. 148-152 °C (Et_2O); $[\alpha]_D^{20.1}$ –186 (*c* 1.00, $CHCl_3$); IR (ATR) 2929, 1684 (C=O), 1601, 1502, 1426, 1375, 1315, 1275, 1259, 1234 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.33-7.12 (5H, m, $C_6\mathbf{H}_5$), 6.76 (1H, d, *J* = 8.2 Hz, Ar**H**), 6.69-6.61 (1H, m, Ar**H**), 4.74-4.65 (1.5H, m ArOC**H** and C**H**N, rotamer A), 4.57-4.49 (0.5H, m, rotamer B), 4.23-4.14 (2H, m, $CO_2C\mathbf{H}_2$), 4.13-3.96 (1H, m, $C\mathbf{H}_aH_bN$), 3.92 (3H, s, $OC\mathbf{H}_3$), 3.00-2.89 (2H, m, $C\mathbf{H}_2CH_2Ph$), 2.85-2.59 (6H, m, $ArC\mathbf{H}_2$ and $CH_2C\mathbf{H}_2Ph$ and $CH_a\mathbf{H}_bN$ and $O{=}CCH_2C\mathbf{H}$), 2.46-2.28 (3H, m, $O{=}CC\mathbf{H}_2CH$ and C**H**CHCN), 2.05-1.97 (1H, m, $C\mathbf{H}_aH_bCH_2N$), 1.92-1.83 (1H, m, $CH_a\mathbf{H}_bCH_2N$), 1.37-1.26 (3H, m, $CH_2C\mathbf{H}_3$); **Rotamer A (Major)** ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.7 (C), 205.2 (C), 155.5 (C), 145.3 (C), 143.4 (C), 140.4 (C), 128.7 (2 × CH), 128.4 (2 × CH), 126.4 (CH), 126.0 (C), 124.8 (C), 120.7 (CH), 115.3 (CH), 91.1 (CH), 61.8 (CH_2), 56.8 (CH_3), 48.6 (CH), 48.3 (CH), 47.0 (C), 44.8 (CH_2), 42.8 (CH), 42.0 (CH_2), 38.2 (CH_2), 35.0 (CH_2), 29.5 (CH_2), 28.5 (CH_2), 14.8 (CH_3); **Rotamer B (Minor)** ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.0 (C), 205.0 (C), 155.2 (C), 145.3 (C), 143.4 (C), 140.4 (C), 128.7 (2 × CH), 128.4 (2 × CH), 126.5 (CH), 126.0 (C), 124.5 (C), 120.7 (CH), 115.3 (CH), 91.1 (CH), 61.8 (CH_2), 56.8 (CH_3), 48.7 (CH), 48.4 (CH), 46.9 (C), 44.2 (CH_2), 42.8 (CH), 42.0 (CH_2), 38.0 (CH_2), 34.8 (CH_2), 29.6 (CH_2), 28.5 (CH_2), 14.8 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{29}H_{32}NO_6]^+$ $[M+H]^+$: 490.2224, found 490.2223.

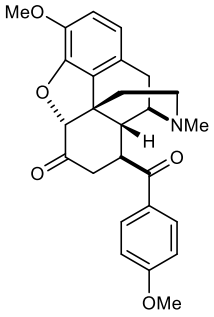


(4*R*,4a*R*,5*S*,7a*R*,12b*S*)-9-Methoxy-7-oxo-5-(3-phenylpropanoyl)-1,2,4,4a,5,6,7,7a-octahydro-3*H*-4,12-methanobenzofuro[3,2-*e*]isoquinoline-3-carbonitrile (283). Prepared according to a slight modification of the General Procedure using enone **297** (93 mg, 0.30 mmol) and 3-phenylpropanal (0.20 mL, 1.50 mmol) as the radical donor, under blue LED irradiation. Purification by column chromatography (50% EtOAc/petrol) gave **283** (62 mg, 47%) as a white foam. R_f = 0.30 (50% EtOAc/petrol); m.p. 177-181 °C (Et_2O); $[\alpha]_D^{20.1}$

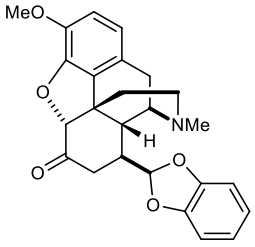
−192 (*c* 1.00, $CHCl_3$); IR (ATR) 2930, 2205 (C≡N), 1730 (C=O), 1711 (C=O), 1636, 1606, 1504, 1439, 1392, 1365 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32-7.10 (5H, m, $C_6\mathbf{H}_5$), 6.77 (1H, d, *J* = 8.3 Hz, Ar**H**), 6.68 (1H, d, *J* = 8.3 Hz, Ar**H**), 4.72 (1H, s, ArOC**H**), 3.90 (3H, s, ArOC$\mathbf{H}_3$), 3.60 (1H, ddd, *J* = 5.8, 3.1, 1.2 Hz, C**H**N), 3.24 (1H, dd, *J* = 12.9, 3.8 Hz, ArC$\mathbf{H}_a\mathrm{H}_b$), 3.05-2.76 (6H, m, Ar$\mathrm{CH}_a\mathbf{H}_b$ and O=CCH_2C**H** and C$\mathbf{H}_a\mathrm{H}_b$N and O=CC$\mathbf{H}_2\mathrm{CH}_2$ and C$\mathbf{H}_a\mathrm{H}_b$Ph), 2.64 (1H, dt, *J* = 17.3, 7.1 Hz, $\mathrm{CH}_a\mathbf{H}_b$Ph), 2.58-2.46 (1H, m, $\mathrm{CH}_a\mathbf{H}_b$N), 2.45-2.34 (2H, m, O=CC$\mathbf{H}_2$CH), 2.33-2.22 (1H, m, C**H**CHN), 2.16 (1H, td, *J* = 12.7, 5.4 Hz, C$\mathbf{H}_a\mathrm{H}_b\mathrm{CH}_2$N), 1.91-1.84 (1H, m, $\mathrm{CH}_a\mathbf{H}_b\mathrm{CH}_2$N); ^{13}C NMR (101 MHz, $CDCl_3$) δ 207.5 (C), 204.2 (C), 145.2 (C), 143.6 (C), 140.2 (C), 128.7 (2 × CH), 128.4 (2 × CH), 126.7 (CH), 125.2 (C), 123.6 (C), 120.8 (CH), 117.3 (C), 115.5 (CH), 90.8 (CH), 56.8 (CH_3), 55.1 (CH), 48.1 (CH), 45.8 (C), 44.0 (CH_2), 43.8 (CH_2), 41.7 (CH_2), 41.6 (CH), 33.9 (CH_2), 29.5 (CH_2), 27.7 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{27}H_{27}N_2O_4]^+$ $[M+H]^+$: 443.1965, found 443.1960.



(4*R*,4a*R*,5*S*,7a*R*,12b*S*)-9-Methoxy-3-methyl-5-(3-phenylpropanoyl)-2,3,4,4a,5,6-hexahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-7(7a*H*)-one (284). Prepared according to a slight modification of **t**he General Procedure using enone **60** (54 mg, 0.18 mmol), TBADT (30 mg, 0.009 mmol), MeCN (0.45 mL) and 3-phenylpropanal (0.24 mL, 1.80 mmol) as the radical donor under UV irradiation. Purification by column chromatography (5% 2 M NH_3[MeOH]/CH_2Cl_2) gave **284** as an off-white solid (17 mg, 22%). R_f = 0.24 (5% 2 M NH_3[MeOH]/CH_2Cl_2); m.p. 130-136 °C (Et_2O); $[\alpha]_D^{20.1}$ −165 (*c* 1.00, $CHCl_3$); IR (ATR) 2921, 2849, 1729 (C=O), 1666 (C=O), 1598, 1573, 1507, 1438, 1377, 1313 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.29-7.24 (2H, m, Ar**H**), 7.22-7.13 (3H, m, Ar**H**), 6.71 (1H, d, *J* = 8.2 Hz, Ar**H**), 6.63 (1H, d, *J* = 8.2 Hz, Ar**H**), 4.68 (1H, s, ArOC**H**), 3.90 (3H, s, OC$\mathbf{H}_3$), 2.98-2.82 (5H, m, O=CC$\mathbf{H}_2\mathrm{CH}_2$ and O=CCH_2C**H** and C**H**N and C$\mathbf{H}_a\mathrm{H}_b$N), 2.76-2.59 (2H, m, C$\mathbf{H}_2$Ph), 2.58-2.42 (2H, m, ArC$\mathbf{H}_a\mathrm{H}_b$ and O=CC$\mathbf{H}_a\mathrm{H}_b$CH), 2.41-2.29 (5H, m, Ar$\mathrm{CH}_a\mathbf{H}_b$ and NC$\mathbf{H}_3$ and C**H**CHN), 2.23-2.07 (3H, m, $\mathrm{CH}_a\mathbf{H}_b$N and O=C$\mathrm{CH}_a\mathbf{H}_b$CH and C$\mathbf{H}_a\mathrm{H}_b\mathrm{CH}_2$N), 1.82-1.75 (1H, m, $\mathrm{CH}_a\mathbf{H}_b\mathrm{CH}_2$N); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.1 (C), 205.2 (C), 145.2 (C), 143.4 (C), 140.6 (C), 128.7 (2 × CH), 128.6 (CH), 126.5 (2 × CH), 120.4 (CH), 115.2 (CH), 91.2 (CH), 57.3 (CH_3), 57.0 (CH), 48.6 (CH), 47.0 (CH_2), 46.5 (C), 43.9 (CH_2), 42.6 (CH_2), 42.3 (CH_3), 34.9 (CH_2), 32.1 (C), 29.9 (CH), 29.4 (CH_2), 27.4 (C), 20.2 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{27}H_{30}NO_4]^+$ $[M+H]^+$: 432.2169, found 432.2163.

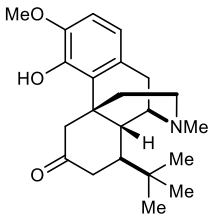


(4*R*,4a*R*,5*S*,7a*R*,12b*S*)-9-Methoxy-5-(4-methoxybenzoyl)-3-methyl-2,3,4,4a,5,6-hexahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-7(7a*H*)-one (285). Prepared according to a slight modification of The General Procedure using enone **60** (54 mg, 0.18 mmol), TBADT (30 mg, 0.009 mmol), MeCN (0.45 mL) and 4-methoxybenzaldehyde (0.22 mL, 1.80 mmol) as the radical donor under UV irradiation. Purification by column chromatography (5% 2 M NH_3[MeOH]/CH_2Cl_2) gave **285** as an off-white solid (19 mg, 24%). R_f = 0.19 (5% 2 M NH_3[MeOH]/CH_2Cl_2); m.p. 143-145 °C (Et_2O); $[\alpha]_D^{20.1}$ −198 (*c* 1.00, $CHCl_3$); IR (ATR) 2921, 2849, 1729 (C=O), 1666 (C=O), 1598, 1573, 1507, 1438, 1377, 1313 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.80 (2H, d, *J* = 9.0 Hz, Ar**H**), 6.90 (2H, d, *J* = 8.9 Hz, Ar**H**), 6.76 (1H, d, *J* = 8.2 Hz, Ar**H**), 6.68 (1H, d, *J* = 8.2 Hz, Ar**H**), 4.78 (1H, s, ArOC**H**), 3.95 (3H, s, OC**H**$_3$), 3.86 (3H, s, OC**H**$_3$), 3.30 (1H, ddd, *J* = 13.3, 11.4, 2.7 Hz, O=CCH$_2$C**H**), 3.17 (1H, dd, *J* = 11.4, 2.7 Hz, C**H**CHN), 3.07-3.02 (1H, m, C**H**N), 2.68 (1H, t, *J* = 13.3 Hz, O=CC**H**$_a$H$_b$), 2.61-2.56 (1H, m, C**H**$_a$H$_b$N), 2.47 (1H, dd, *J* = 13.3, 2.7 Hz, O=CCH$_a$**H**$_b$), 2.35 (3H, s, NC**H**$_3$), 2.25-2.15 (2H, m, CH$_a$**H**$_b$N and ArC**H**$_a$H$_b$), 1.89-1.82 (1H, m, ArCH$_a$**H**$_b$), 1.34-1.27 (2H, m, C**H**$_2$CH$_2$N); ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.5 (C), 197.2 (C), 164.4 (C), 149.8 (C), 145.3 (C), 143.3 (C), 130.9 (2 × CH), 128.9 (C), 120.2 (CH), 116.2 (C), 115.0 (CH), 114.3 (2 × CH), 91.5 (CH), 56.9 (CH_3), 55.9 (CH), 55.7 (CH_3), 53.6 (C), 47.0 (CH_2), 46.9 (CH_2), 43.9 (CH_2), 42.8 (CH_3), 42.0 (CH), 29.8 (CH_2), 22.5 (CH); HRMS (ESI) Exact mass calculated for $[C_{26}H_{28}NO_5]^+$ [M+H]$^+$: 434.1962, found 434.1963.

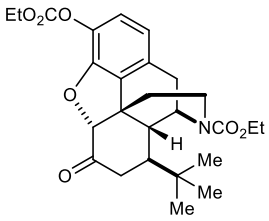


(4*R*,4a*R*,5*S*,7a*R*,12b*S*)-5-(Benzo[*d*][1,3]dioxol-2-yl)-9-methoxy-3-methyl-2,3,4,4a,5,6-hexahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-7(7a*H*)-one (286). Prepared according to a slight modification of the General Procedure using enone **60** (89 mg, 0.30 mmol) and 1,3-benzodioxole (0.34 mL, 3.00 mmol) as the radical donor under UV irradiation. Purification by column chromatography (5% 2 M NH_3[MeOH]/CH_2Cl_2) gave **286** as an off-white solid (43 mg, 34%). R_f = 0.32 (5% 2 M NH_3[MeOH]/CH_2Cl_2); m.p. 143-146 °C (Et_2O); $[\alpha]_D^{20.1}$ −201 (*c* 1.00, $CHCl_3$); IR (ATR) 2915, 1729 (C=O), 1608, 1504, 1483, 1437, 1354, 1277, 1234, 1156 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.83-6.75 (4H, m, Ar**H**), 6.73 (1H, d, *J* = 8.2 Hz, Ar**H**), 6.67 (1H, d, *J* = 8.3 Hz, Ar**H**), 6.15 (1H, d, *J* = 3.5 Hz, C**H**O$_2$), 4.70 (1H, s, ArOC**H**),

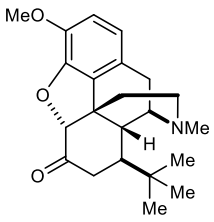
3.92 (3H, s, ArOC**H**$_3$), 3.56 (1H, dd, *J* = 5.5, 2.9 Hz, C**H**N), 3.10 (1H, d, *J* = 18.6 Hz, ArC**H**$_a$H$_b$), 2.82 (1H, dd, *J* = 11.8, 2.9 Hz, C**H**CHN), 2.65 (1H, dd, *J* = 13.4, 2.6 Hz, O=CC**H**$_a$H$_b$), 2.62-2.56 (1H, m, C**H**$_a$H$_b$N), 2.49-2.36 (5H, m, NC**H**$_3$ and O=CCH$_a$**H**$_b$ and ArCH$_a$**H**$_b$), 2.25 (1H, td, *J* = 11.9, 3.3 Hz, CH$_a$**H**$_b$N), 2.14 (1H, td, *J* = 12.0, 4.5 Hz, C**H**$_a$H$_b$CH$_2$N), 2.03-1.93 (1H, m, O=CCH$_2$C**H**), 1.89-1.83 (1H, m, CH$_a$**H**$_b$CH$_2$N); ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.3 (C), 147.3 (C), 147.2 (C), 145.2 (C), 143.0 (C), 127.1 (C), 126.3 (C), 121.9 (CH), 121.9 (CH), 120.2 (CH), 114.9 (CH), 110.5 (CH), 108.7 (CH), 108.6 (CH), 91.6 (CH), 56.9 (CH), 56.9 (CH_3), 47.0 (CH_2), 46.8 (C), 43.5 (CH), 43.2 (CH_3), 40.2 (CH), 39.2 (CH_2), 35.7 (CH_2), 20.0 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{25}H_{26}NO_5]^+$ $[M+H]^+$: 420.1805, found 420.1810.



(4b*S*,8*S*,8a*R*,9*R*)-8-(*tert*-butyl)-4-Hydroxy-3-methoxy-11-methyl-8,8a,9,10-tetrahydro-5*H*-9,4b-(epiminoethano)phenanthren-6(7*H*)-one (288) Prepared according to a slight modification of the General Procedure using enone **298** (90 mg, 0.30 mmol) and pivaldehyde (0.33 mL, 3.00 mmol) as the radical donor under UV irradiation. Purification by column chromatography (7.5% 2 M NH_3[MeOH]/CH_2Cl_2) gave **288** as an off-white solid (30 mg, 28%). R_f = 0.39 (10% 2 M NH_3[MeOH]/CH_2Cl_2); m.p. 193-196 °C (Et_2O); $[\alpha]_D^{20.1}$ −165 (*c* 1.00, $CHCl_3$); IR (ATR) 2934 (OH), 2837, 1702 (C=O), 1605, 1583, 1483, 1438, 1409, 1367, 1334 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74-6.62 (2H, m, Ar**H**), 6.06 (1H, br s, O**H**), 4.12 (1H, d, *J* = 18.4 Hz, O=CC**H**$_a$H$_b$C), 3.83 (3H, s, OC**H**$_3$), 3.15-3.07 (1H, m, C**H**N), 3.02-2.96 (2H, m, ArC**H**$_2$), 2.60-2.51 (1H, m, C**H**$_a$H$_b$N), 2.43 (3H, s, NC**H**$_3$), 2.29 (1H, d, *J* = 17.5 Hz, O=CC**H**$_a$H$_b$CH), 2.16-2.07 (2H, m, CH$_a$**H**$_b$N and O=CCH$_a$**H**$_b$C), 2.01 (1H, dd, *J* = 6.5, 3.1 Hz, C**H**CHN), 1.98-1.87 (2H, m, O=CCH$_a$**H**$_b$CH and C**H**$_a$H$_b$CH$_2$N), 1.82 (1H, dt, *J* = 12.7, 7.0 Hz, CH$_a$**H**$_b$CH$_2$N), 1.61 (1H, dd, *J* = 9.3, 6.4 Hz, C**H**C(CH$_3$)$_3$), 0.92 (9H, s, C(C**H**$_3$)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 214.2 (C), 144.9 (C), 143.4 (C), 131.3 (C), 125.5 (C), 118.8 (CH), 108.8 (CH), 58.9 (CH), 56.1 (CH_3), 50.7 (CH_2), 47.3 (CH_2), 45.4 (CH), 43.4 (CH), 43.2 (CH_3), 40.1 (CH_2), 38.1 (CH_2), 36.8 (C), 35.9 (C), 27.8 (3 × CH_3), 23.1 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{22}H_{32}NO_3]^+$ $[M+H]^+$: 358.2377, found 358.2368.



Ethyl (4*R*,4a*R*,5*S*,7a*R*,12b*S*)-5-(*tert*-butyl)-9-[(ethoxycarbonyl)oxy]-7-oxo-1,2,4,4a,5,6,7,7a-octahydro-3*H*-4,12-methanobenzofuro[3,2-*e*]isoquinoline-3-carboxylate (290). Prepared according to the General Procedure using enone **33** (124 mg, 0.30 mmol) and pivaldehyde (0.16 mL, 1.50 mmol) as the radical donor under blue LED irradiation. Purification by column chromatography (50% EtOAc/petrol) gave **290** (112 mg, 79%) as a white foam, as a 1.5:1 mixture of rotamers. R_f = 0.33 (50% EtOAc/petrol); m.p. 189-192 °C (Et_2O); $[\alpha]_D^{20.1}$ –190 (*c* 1.00, $CHCl_3$); IR (ATR) 2972, 1761 (C=O), 1733 (C=O), 1686 (C=O), 1551, 1484, 1398, 1370, 1317, 1231 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.98 (1H, d, *J* = 8.3 Hz, Ar**H**), 6.74 (1H, d, *J* = 8.2 Hz, Ar**H**), 5.39-5.32 (0.6H, m, C**H**N, rotamer A), 5.25-5.18 (0.4H, m, C**H**N, rotamer B), 4.70 (1H, s, ArOC**H**), 4.41-4.24 (2H, m, $OCO_2C\mathbf{H}_2$), 4.24-3.94 (3H, m, $NCO_2C\mathbf{H}_2$ and $C\mathbf{H}_aH_bN$), 3.13-3.03 (1H, m, $ArC\mathbf{H}_aH_b$), 2.87-2.70 (2H, m, $ArCH_a\mathbf{H}_b$ and $CH_a\mathbf{H}_bN$), 2.53-2.42 (1H, m, $O{=}CC\mathbf{H}_aH_bCH$), 2.38-2.28 (1H, m, C**H**CHN), 2.22-2.11 (1H, m, $O{=}CCH_a\mathbf{H}_bCH$), 2.04-1.94 (1H, m, $C\mathbf{H}_aH_bCH_2N$), 1.93-1.84 (1H, m, $CH_a\mathbf{H}_bCH_2N$), 1.39 (3H, t, *J* = 7.1 Hz, $OCO_2CH_2C\mathbf{H}_3$), 1.34-1.24 (4H, m $NCO_2CH_2C\mathbf{H}_3$ and $C\mathbf{H}C(CH_3)_3$), 1.04 (9H, s, $C(C\mathbf{H}_3)_3$, rotamer **A**), 1.03 (9H, s, $C(C\mathbf{H}_3)_3$, rotamer **B**); **Rotamer A (Major)** ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.7 (C), 155.5 (C), 153.0 (C), 147.8 (C), 133.2 (C), 131.3 (C), 128.1 (C), 123.0 (CH), 120.3 (CH), 92.1 (CH), 65.2 (CH_2), 61.9 (CH_2), 50.0 (CH), 47.9 (C), 45.8 (CH), 45.0 (CH), 41.8 (CH_2), 37.8 (CH_2), 36.6 (CH_2), 34.1 (C), 29.1 (CH_3 × 3), 29.0 (CH_2), 14.8 (CH_3), 14.3 (CH_3); **Rotamer B (Minor)** ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.5 (C), 155.5 (C), 153.0 (C), 147.8 (C), 133.2 (C), 131.0 (C), 128.1 (C), 122.9 (CH), 120.2 (CH), 92.1 (CH), 65.2 (CH_2), 61.8 (CH_2), 49.9 (CH), 47.8 (C), 45.6 (CH), 45.0 (CH), 41.6 (CH_2), 37.6 (CH_2), 36.4 (CH_2), 34.1 (C), 29.1 (3 × CH_3), 28.9 (CH_2), 14.8 (CH_3), 14.3 (CH_3); HRMS (ESI) Exact mass calculated for $[C_{26}H_{34}NO_7]^+$ $[M+H]^+$: 472.2330, found 472.2331.

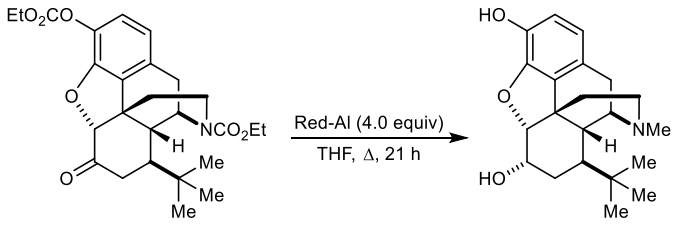


(4*R*,4a*R*,5*S*,7a*R*,12b*S*)-5-(*tert*-Butyl)-9-methoxy-3-methyl-2,3,4,4a,5,6-hexahydro-1*H*-4,12-methanobenzofuro[3,2-*e*]isoquinolin-7(7a*H*)-one (287). Prepared according to a slight modification of the General Procedure using enone **60** (54 mg, 0.18 mmol), TBADT (30 mg, 0.009 mmol), MeCN (0.45 mL) and pivaldehyde (0.20 mL, 1.80 mmol) as the radical donor under UV irradiation. Purification by column chromatography (5% 2 M NH_3[MeOH]/CH_2Cl_2) gave **287** as an off-white solid (24 mg, 38%). R_f = 0.24 (5% 2 M NH_3[MeOH]/CH_2Cl_2); m.p. 157-161 °C (Et_2O); $[\alpha]_D^{20.1}$

−169 (*c* 1.00, $CHCl_3$); IR (ATR) 2912, 2840, 2800, 1726 (C=O), 1610, 1504, 1438, 1398, 1368, 1334 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.73 (1H, d, *J* = 8.2 Hz, Ar**H**), 6.67 (1H, d, *J* = 8.2 Hz, Ar**H**), 4.67 (1H, s, ArOC**H**), 3.92 (3H, s, OC$\mathbf{H}_3$), 3.60 (1H, dd, *J* = 5.7, 2.7 Hz, C**H**N), 3.01 (1H, d, *J* = 18.5 Hz, ArC$\mathbf{H}_a$H$_b$), 2.60-2.42 (7H, m, NC$\mathbf{H}_3$ and ArCH$_a$$\mathbf{H}_b$ and O=CC$\mathbf{H}_a$H$_b$ and C$\mathbf{H}_a$H$_b$N and C**H**CHN), 2.28-2.03 (3H, m, O=CCH$_a$$\mathbf{H}_b$ and CH$_a$$\mathbf{H}_b$N and C$\mathbf{H}_aH_bCH_2$N), 1.84 (1H, ddd, *J* = 12.2, 3.4, 1.7 Hz, CH$_a$$\mathbf{H}_bCH_2$N), 1.31 (1H, td, *J* = 11.3, 3.2 Hz, C**H**C(CH$_3$)$_3$), 0.99 (9H, s, C(C$\mathbf{H}_3$)$_3$); ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.2 (C), 145.0 (C), 142.8 (C), 128.1 (C), 126.8 (C), 119.8 (CH), 114.5 (CH), 92.0 (CH), 59.1 (CH), 56.9 (CH_3), 47.6 (C), 47.0 (CH_2), 46.4 (CH), 45.9 (CH), 43.5 (CH_3), 42.2 (CH_2), 36.9 (CH_2), 34.1 (C), 29.3 (3 × CH_3), 19.8 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{22}H_{30}NO_3]^+$ $[M+H]^+$: 356.2220, found 356.2225.

6.4. Product Derivatisation

(4*R*,4a*R*,5*S*,7*S*,7a*R*,12b*S*)-5-(*tert*-Butyl)-3-methyl-2,3,4,4a,5,6,7,7*a*-octahydro-1*H*-4, 12-methanobenzofuro[3,2-*e*]isoquinoline-7,9-diol (291)



An oven-dried microwave vial fitted with a magnetic stirrer bar was capped with a crimp cap seal and flushed with argon (5 min), then charged with Red-Al (60% wt. in toluene, 0.11 mL, 0.34 mmol). A solution of **290** (46 mg, 0.10 mmol) in dry THF (0.5 mL) was then added slowly and the resulting mixture was heated under reflux for 21 h. The reaction was cooled to room temperature, quenched carefully with saturated aqueous Rochelle's salt solution (3 mL) and extracted with a 3:1 CH_2Cl_2/MeOH mixture (3 × 5 mL). The combined organic extracts were washed with brine (10 mL), dried (Na_2SO_4), concentrated *in vacuo*, and purified by column chromatography (10% 2 M NH_3[MeOH]/CH_2Cl_2) to give **291** as an off-white foam (25 mg, 71%). R_f = 0.16 (10% 2 M NH_3[MeOH]/CH_2Cl_2); m.p. 190-194 °C (Et_2O); $[\alpha]_D^{20.1}$ −133 (*c* 1.00, $CHCl_3$); IR (ATR) 3286 (OH), 2923, 1503, 1456, 1395, 1365, 1335, 1242, 1175, 1151 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.76 (1H, br s, ArO**H**), 6.54 (1H, d, *J* = 8.0 Hz, Ar**H**), 6.42 (1H, d, *J* = 8.0 Hz, Ar**H**), 4.45 (1H, d, *J* = 5.3 Hz, CHO**H**), 4.41 (1H, d, *J* = 3.7 Hz, ArOC**H**), 3.68-3.57 (1H, m, C**H**OH), 3.31-3.28 (1H, m, C**H**N), 2.80 (1H, d, *J* = 18.6 Hz, ArC**H**$_a$H$_b$), 2.43-2.29 (2H, m, ArCH$_a$**H**$_b$ and C**H**$_a$H$_b$N), 2.25 (3H, s, NC**H**$_3$), 2.09 (1H, td, *J* = 12.0, 3.4 Hz, CH$_a$**H**$_b$N), 2.01-1.88 (2H, m, C**H**CHN and C**H**$_a$H$_b$CH$_2$N), 1.49-1.41 (1H, m, CH$_a$**H**$_b$CH$_2$N), 1.22-1.17 (1H, m, HOCHC**H**$_a$H$_b$), 1.01-0.91 (1H, m, HOCHCH$_a$**H**$_b$), 0.89-0.84 (10H, m, C**H**C(CH$_3$)$_3$ and C(C**H**$_3$)$_3$); ^{13}C NMR (101 MHz, DMSO-d_6) δ 145.9 (C), 137.7 (C), 130.7 (C), 125.7 (C), 118.0 (CH), 116.7 (CH), 90.7 (CH), 66.1 (CH), 59.9 (CH), 54.9 (C), 45.5 (CH_2), 43.4 (CH_3), 40.4 (CH), 38.6 (CH), 38.3 (CH_2), 35.4 (C), 28.3 (3 × CH_3), 27.1 (CH_2), 19.4 (CH_2); HRMS (ESI) Exact mass calculated for $[C_{21}H_{30}NO_3]^+$ $[M+H]^+$: 344.2220, found 344.2225.

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