Synthetic approaches to *N*- and 4-substitued 1,4-dihydro-3(2H)-isoquinolinone derivatives

Michael J. O' Sullivan, Richard J.D. Hatley, Christopher R. Wellaway, Sean P. Bew, Christopher J. Richards

PII: S0040-4020(21)00727-4

DOI: https://doi.org/10.1016/j.tet.2021.132455

Reference: TET 132455

To appear in: *Tetrahedron*

Received Date: 14 August 2021

Revised Date: 16 September 2021

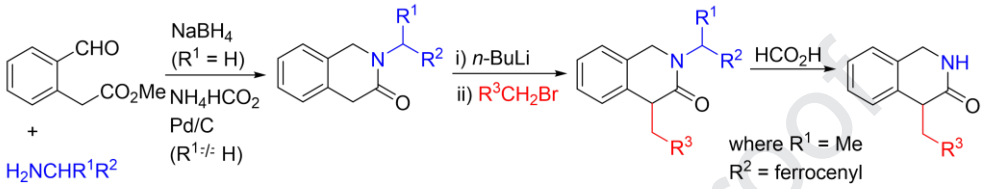
Accepted Date: 17 September 2021

Please cite this article as: O' Sullivan MJ, Hatley RJD, Wellaway CR, Bew SP, Richards CJ, Synthetic approaches to *N*- and 4-substitued 1,4-dihydro-3(2H)-isoquinolinone derivatives, *Tetrahedron* (2021), doi: https://doi.org/10.1016/j.tet.2021.132455.

Graphical Abstract

Synthetic approaches to *N*- and 4-substituted 1,4-dihydro-3(2H)-isoquinolinone derivatives

Michael J. O'Sullivan, Richard J. D. Hatley, Christopher R. Wellaway, Sean P. Bew and Christopher J. Richards
School of Chemistry, University of East Anglia, Norwich, NR4 7TJ, U.K. and GlaxoSmithKline, Stevenage, SG1 2NY, U.K.



Tetrahedron
journal homepage: www.elsevier.com

Synthetic approaches to *N*- and 4-substitued 1,4-dihydro-3(2H)-isoquinolinone derivatives

Michael J. O' Sullivan[a], Richard J. D. Hatley[b], Christopher R. Wellaway[b], Sean P. Bew[a] and Christopher J. Richards[a]*

[a]*School of Chemistry, University of East Anglia, Norwich Research Park, Norwich, NR4 7TJ, U.K.*
[b]*GlaxoSmithKline, Gunnels Wood Road, Stevenage, SG1 2NY, U.K.*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

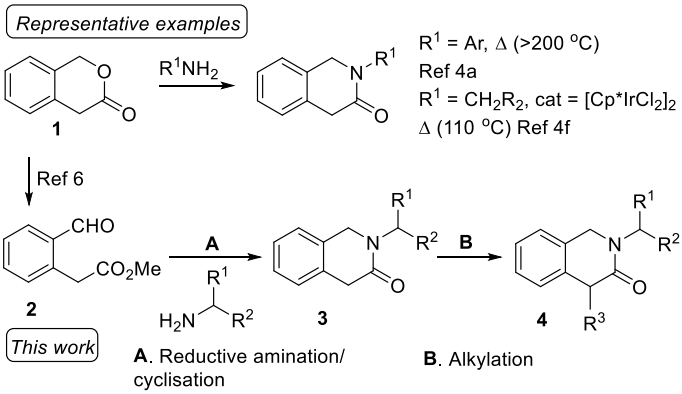
Keywords:
isoquinolinone
reductive amination
α-alkylation
deprotection
ferrocenyl

ABSTRACT

Reaction of methyl-2-(2-formylphenyl)acetate with primary amines in a reductive amination/cyclisation process resulted in *N*-substituted 1,4-dihydro-3(2H)-isoquinolinones. With H_2NCH_2R sodium borohyride is a suitable reductant (11 examples), but $H_2NCHR^1R^2$ required a transfer hydrogenation using ammonium formate catalysed by palladium on carbon (9 examples). 4-Substituted-1,4-dihydro-3(2H)-isoquinolinones were synthesised by deprotonation (*n*-butyllithium) and addition of R^3CH_2Br (12 examples with R^3 = alkyl, Ar, $CH{=}CH_2$, C≡CH). Modest diastereoselectivity was achieved with 1,4-dihydro-3(2H)-isoquinolinones derived from $H_2NCHMeR^2$ [R^2 = (η^5-C_5H_4)Co(η^4-C_4Ph_4) - max. dr = 1.9 : 1], but use of $H_2NCHMeFc$ (Fc = ferrocenyl) provided a new method of 1,4-dihydro-3(2H)-isoquinolinone *N*-deprotection with formic acid.

1. Introduction

1,4-Dihydro-3(2H)-isoquinolinones are a compound class of interest in medicinal chemistry[1] due to these heterocycles displaying a combination of aromaticity and saturation, an amide functionality, and several points of derivatisation, some of which can also lead to chiral variants. Furthermore, amide reduction generates tetrahydroisoquinolines,[2] a related compound class forming the core structure of many bioactive alkaloid derivatives.[3] Although numerous synthetic routes to 1,4-dihydroisoquinolinones are known,[4] including methods for the asymmetric synthesis of 1- and, to a lesser extent, 4-substituted derivatives,[5] these are limited by the lack of simplicity and generality required for the synthesis of multiple derivatives. For example, the reaction of 3-isochromanone **1** with mostly aromatic amines requires prolonged heating at high temperature (200-250 °C),[4a] and although a lower temperature (*ca.* 110 °C) iridium catalysed variant of this reaction has been developed,[4f] this is limited to aliphatic amines of structure RCH_2NH_2 (Scheme 1). Furthermore, existing methods for the synthesis of 4-substitued dihydroisoquinolinones utilise simultaneous ring-formation.[4c,g,h,i] Introduction of a 4-substiuent on a preformed dihydroisoquinolinone appears to have been little studied. To these ends we were attracted to the possibility of employing methyl-2-(2-formylphenyl)acetate **2** as the starting material, itself available from 3-isochromanone,[6] and also available commercially, for a simple yet potentially versatile reductive amination/cyclisation method for the synthesis of *N*-substituted derivatives **3**. Subsequent α-carbonyl alkylation offered a potentially stereoselective route to 4-substituted derivatives **4**, and by the use of suitable R^1/R^2 nitrogen substituents deprotection is also an option. The results of this investigation are reported in this paper.



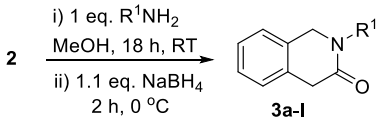
Scheme 1. Approaches to the synthesis of 1,4-dihydro-3(2H)-isoquinolinone derivatives.

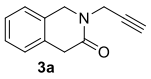
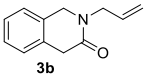
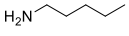
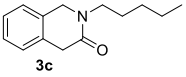
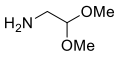
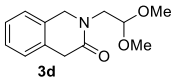
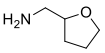
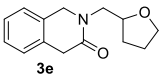
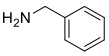
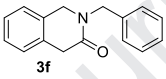
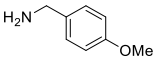
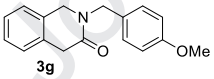
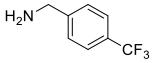
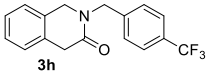
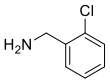
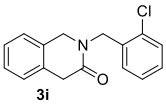
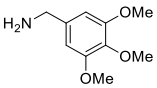
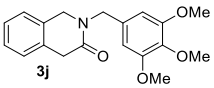
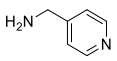
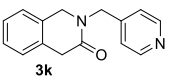
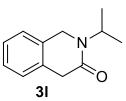
2. Results and Discussion

Combining **2** with propargylamine in methanol at room temperature gave *in situ* imine generation such that subsequent reduction of an ice bath cooled reaction mixture with sodium

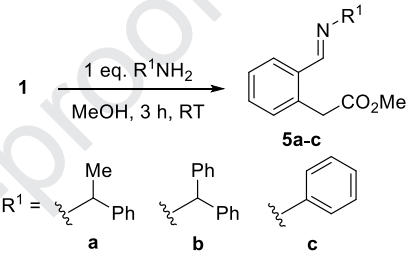
borohydride, followed by cyclisation, resulted in a good yield of the new *N*-propargyl derivative **3a** (Table 1, entry 1).

Table 1. Synthesis of 1,4-dihydro-3(2H)-isoquinolinones **3a-l**.



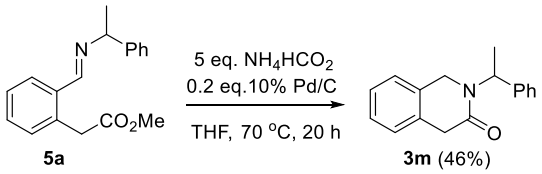
Entry	Amine	Product	Yield(%)
1		 **3a**	78
2		 **3b**	84
3		 **3c**	63
4		 **3d**	85
5		 **3e**	91
6		 **3f**	96
7		 **3g**	63
8		 **3h**	50
9		 **3i**	98
10		 **3j**	98
11		 **3k**	69
12		 **3l**	38

This methodology was extended successfully to a range of unbranched primary amines (allyl, alkyl and benzyl) to give **3b-k** in generally good yield (entries 2-11). The use of benzylamines with both electron-donating and electron-withdrawing substituents worked well, and the mild reaction conditions employed are compatible with the acid-sensitive dimethylacetal functionality (entry 4). However, the use of isopropylamine resulted in a reduced yield (entry 12), and other α-branched primary amines such as α-methylbenzylamine and diphenylmethylamine gave no product, as was the case with aniline. Imine formation with benzylamine was examined in more detail, with ^{1}H NMR spectroscopy revealing the complete formation of essentially a single isomer after *ca*. 3 hours, as revealed by the new signal at 8.60 ppm. In addition, imines **5a-c** were similarly generated readily (Scheme 2), revealing reduction as the problematic step with respect to overall reductive amination.



Scheme 2. Synthesis of imines **5a-c**.

Initial attempts at chemoselective reduction of the imine functionality of **5a** were unsuccessful. No reaction was observed with $NaBH_4$ (as expected), $NaBH(OAc)_3$, picoline borane and DIBAL-H. Use of $LiAlH_4$ resulted in selective ester reduction. Hydrogenation with an H-cube using Pd/C at 40 °C and 1 atm H_2 was partially successful, resulting in a 10% yield of cyclised product **3m**. This led to an attempted transfer hydrogenation with ammonium formate with 0.2 equivalents of 10% Pd/C as catalyst. A trace of **3m** was observed with ethanol as solvent at 70 °C, and changing to THF gave this product in an encouraging 46% yield (Scheme 3).

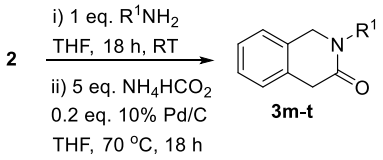


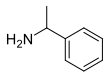
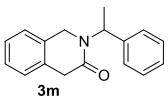
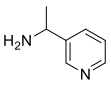
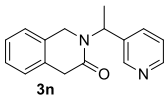
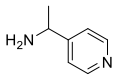
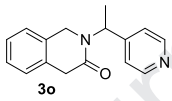
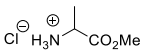
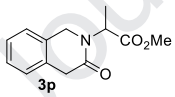
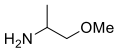
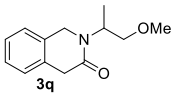
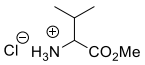
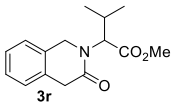
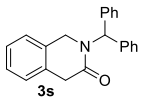
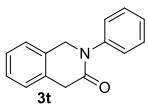
Scheme 3. Synthesis of 1,4-dihydro-3(2H)-isoquinolinone **3m**.

This procedure was then extended to the use of **2** in a one-pot reductive amination/cyclisation sequence employing α-branched primary amines. Initial imine formation in THF was followed by heating at 70 °C with ammonium formate and 0.2 equivalents of 10% Pd/C to give a series of new 1,4-dihydroisoquinolinone derivatives (Table 2). In this way α-methylbenzylamine derivative **3m** was generated in good yield (entry 1), and this methodology is applicable to pyridinyl (entries 2 and 3), amino ester (entries 4 and 6) and ether (entry 5) derivatives. Significantly, primary amines with an α-substituent larger than

methyl are viable reactants (entries 6 and 7), although use of an aromatic amine, aniline, was less successful (entry 8). This is a limiting example with respect to the reduction of the intermediate and less reactive imine (**5c**). The modest yield obtained in some cases is ascribed to the reactivity of the additional functionality in the starting amine rather than a consequence of sterics. In support of this view is the relative success of the reaction with benzhydrylamine (entry 7).

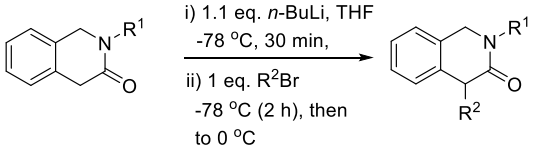
Table 2. Synthesis of 1,4-dihydro-3(2H)-isoquinolinones **3m-3t** derived from α-branched primary amines and aniline

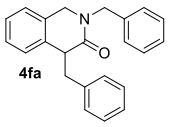
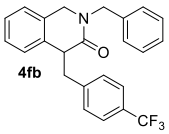
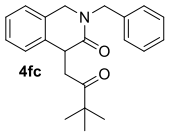
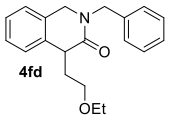
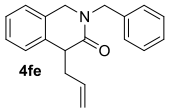
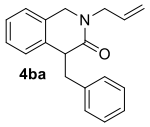
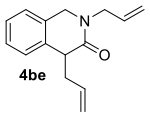
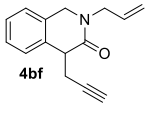


Entry	Amine	Product	Yield(%)
1			80
2			48
3			22
4			32
5			26
6			44
7			54
8			3

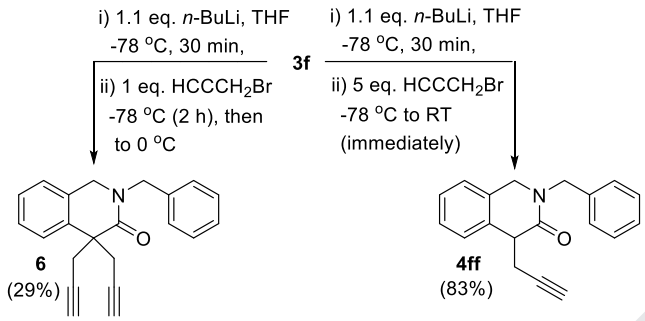
Alkylation of *N*-substituted 1,4-dihydroisoquinolinones appears to be a little studied reaction despite the apparent simplicity of this process for the synthesis of more complex derivtives. This was achieved readily with *N*-benzyl and *N*-allyl substrates **3f** and **3b** by deprotonation with *n*-butyllithium followed by addition of RCH_2Br as electrophile. Use of benzyl, allyl, propargyl, alkyl and α-keto reactants resulted in a range of derivatives **4** in generally good yield (Table 3).

Table 3. Alkylation of 1,4-dihydro-3(2H)-isoquinolinones to give **4fa-4fe**, **4ba**, **4be** and **4bf**.



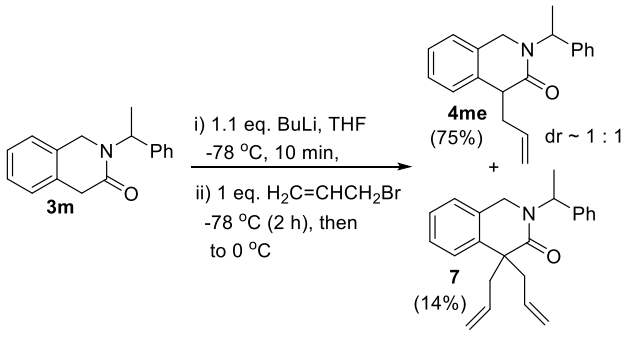
Entry	Substrate	R^2Br	Product	Yield(%)
1	**3f**	$PhCH_2Br$		95
2	**3f**	*p*-$CF_3C_6H_4$-CH_2Br		40
3	**3f**	*t*-$BuCOCH_2Br$		81
4	**3f**	$EtOCH_2CH_2Br$		58
5	**3f**	$CH_2{=}CHCH_2Br$		58
6	**3b**	$PhCH_2Br$		42
7	**3b**	$CH_2{=}CHCH_2Br$		98
8	**3b**	$CH{\equiv}CCH_2Br$		79

In contrast to the expected single alkylation product arising from the use of 1.1 equivalents of base and 1 equivalent of electrophile, use of propargyl bromide with **3f** under these conditions resulted in the formation only of di-propargyl derivative **6** (29% w.r.t. **3f** - Scheme 4). On further investigation of this reaction it was found that the mono-propargyl derivative **4ff** was formed almost exclusively following the addition at -78 °C of 5 equivalents of propargyl bromide to the initially formed lithium enolate, and immediate warming of the reaction mixture to room temperature. As propargylation of *N*-allyl substrate **3b** proceeded readily without this complication (Table 3, entry 8), as otherwise did the alkylation of **3f** (entries 1-5), it is the specific combination of *N*-benzyl and C(4)-propargyl substituents that promote the formation of **6**. This can be accounted for by the greater stability of the enolate derived from **4ff**, although the synergistic influence of the substituents that results in this effect is not clear.



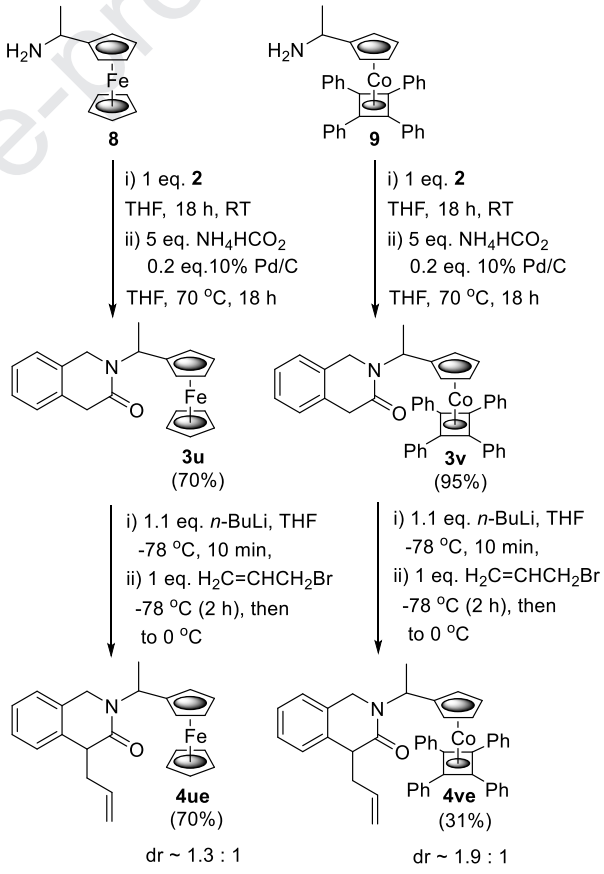
Scheme 4. Mono and di-propargylation of **3f**.

The success of this alkylation chemistry prompted us to investigate the diastereoselectivity of this process using chiral 1,4-dihydroisoquinolinone derivative **3m** (Scheme 5). Use of allyl bromide as electrophile resulted predominantly in mono-allylation product **4me** together with **7** resulting from di-allylation. That the former was formed as an essentially 1 : 1 mixture of diastereoisomers was revealed clearly by integration of the two methyl doublets for **4me** in the ^{1}H NMR spectrum at 1.54 and 1.60 ppm.



Scheme 5. Allylation of chiral substrate **3m**.

We reasoned that replacement of the phenyl group in **3m** by a larger substituent may induce stereoselectivity in this reaction, and to this end investigated the use as auxiliaries of ferrocene and bulky cobalt-sandwich complex derived amines **8** and **9**. Although in this preliminary study both were used as racemates, they may obtained readily as single enantiomers by asymmetric synthesis.[7,8] In addition, and to fulfil the role of a chiral auxiliary, they also had the potential to be removed readily from an alkylated 1,4-dihydroisoquinolinone product (*vide infra*). The methodology described above for reductive amination/cyclisation with α-substituted primary amines worked well with these organometallic substates to give **3u** and **3v** in good yield (Scheme 6). Deprotonation and allylation of the former gave almost exclusively **4ue**, with just *ca.* 5% of the di-allylation product. The modest diastereoselectivity (1.3 : 1) was improved a little on application of this chemistry to **3v** to give **4ve** (1.9 : 1). The basis of this approach is outlined in Figure 1. Good diastereoselectivity requires conformational control of the N-C(α) bond (with the smallest substituent of the stereogenic centre, hydrogen, oriented towards oxygen), and blocking by Ar of one face of the enolate. Although achieved to a modest extent, even with the cobalt sandwich-complex containing a very bulky tetraphenylcyclobutadiene moiety, this model can be used to predict, tentatively, the relative configuration of the major diastereoisomer obtained.



Scheme 6. Synthesis and allylation of 1,4-dihydroisoquinolinones containing ferrocene and cobalt-sandwich complex-based auxiliaries.

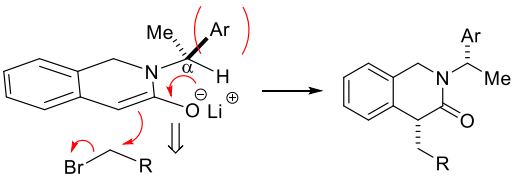
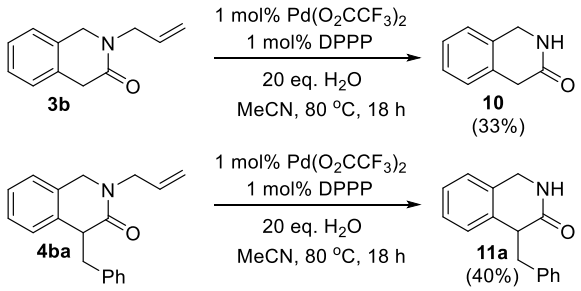


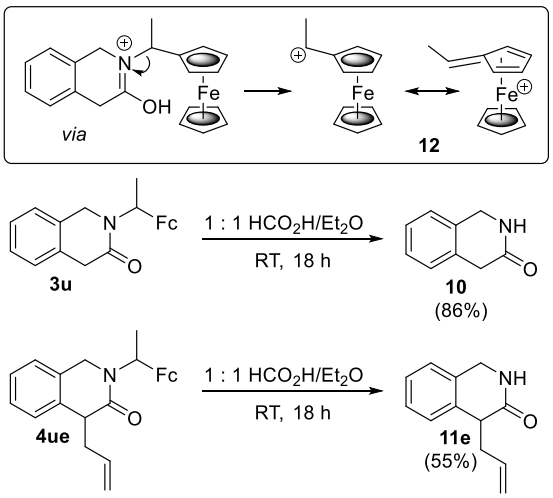
Figure 1. Model of the basis of diastereoselectivity.

Removal of a nitrogen substituent to generate the core 1,4-dihydroisoquinolinone structure **10** was investigated first with *N*-allyl derivative **3b**. Application of the conditions developed for the deprotection of *N*-allyl amides by palladium-catalysed hydrolytic deallylation[9] resulted in a modest yield of the required product **10** (Scheme 7). Application of this method to benzyl derivative **4ba** gave **11a**, but this reaction was not successful with the allyl and propargyl congeners **4be** and **4bf**.



Scheme 7. Allyl deprotection of **3b** and **4ba**.

As an alternative to allyl removal, we initially carried out preliminary experiments on the oxidative deprotection of PMB-related derivative **3j**. As these were not successful we then considered the viability of deprotecting ferrocene derivative **3u** *via* the generation of an α-ferrocenyl carbenium ion **12** under acidic conditions (Scheme 8). Stabilised significantly by charge delocalisation, **12** is akin to the trityl cation,[10] but the ferrocene-containing precursor is introduced readily and has the advantage of colour, significantly aiding the isolation by flash column chromatography of compounds such as **3u**. It also contains a stereogenic centre, but as already discussed, in the context of this work its viability as a chiral auxiliary is limited. Investigation of a number of acidic conditions for the deprotection of **3u** revealed success with a 1 : 1 mixture of HCO_2H and Et_2O to give **10** (Scheme 9). Application to allylated derivative **4ue** resulted in the successful formation of **11e**.



Scheme 8. Ferrocenyl deprotection of **3u** and **4ue**.

In conclusion, methyl-2-(2-formylphenyl)acetate **2** may be transformed readily into a wide range of *N*-substituted 1,4-dihydro-3(2H)-isoquinolinone derivatives by a reductive amination/cyclisation pathway. Intermediate imines derived from primary amines of structure $H_2NCH_2R^1$ are reduced readily with sodium borohydride prior to cyclisation. In contrast, imines derived from primary amines of structure $H_2NCHR^1R^2$ are mostly inert to reduction by sodium borohydride, and a range of other reducing agents. In this instance 1,4-dihydroisoquinolinones resulted following transfer hydrogenation with ammonium formate catalysed by palladium on carbon. Mono-substitution of the 4-position was achieved readily by deprotonation followed by alkylation. Although the diastereoselectivity of this process was at best modest, with 1,4-dihydroisoquinolinones derived from chiral primary amines of structure $H_2NCHMeR^1$, the use of R^1 = ferrocenyl permitted a novel acid-catalysed deprotection strategy for the release of the N-H moiety.

3. Experimental

THF was dried over sodium benzophenone ketyl. Silica gel (40 – 63 μm) was used for chromatography unless otherwise stated. *n*-BuLi was used as a 2.5 M solution in hexanes. Methyl-2-(2-formylphenyl)acetate 26 was obtained commercially (CAS no. 63969-83-5).

General Procedure A for the synthesis of *N*-substituted 1,4-dihydro-3(2H)-isoquinolinones 3 obtained from $H_2NCH_2R^1$. To a solution of methyl-2-(2-formylphenyl)acetate **2** (20 mg, 0.11 mmol) in methanol (0.2 mL) was added an equimolar amount of RNH_2 and the mixture stirred for 18 hours at room temperature in a sealed tube. After cooling to 0 °C, 1.1 equivalents of $NaBH_4$ was added while stirring. After 2 hours, distilled water (2 mL) was added to quench the reaction which was then diluted with ethyl acetate (5 mL). The organic layer was washed with distilled water (5 mL) and brine (5 mL) before being dried ($MgSO_4$) and filtered. The solvent was removed *in vacuo* and the resulting product purified by column chromatography (4:1 CH_2Cl_2: EtOAc) unless otherwise stated.

2-(Prop-2-yn-1-yl)-1,4-dihydroisoquinolin-3(2H)-one 3a: Compound was synthesised according to general procedure A. RNH_2 = propargylamine. R_f = 0.46. **3a** was isolated as an oil (78% yield). IR (thin film) cm^{-1}: 3297, 3232, 2964, 2923, 2852, 2117, 1738, 1665, 1481, 1459, 1440. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29 – 7.23 (m, 2H, H^{Ar}), 7.23 – 7.20 (m, 1H, H^{Ar}), 7.18 – 7.15 (m, 1H, H^{Ar}), 4.61 (s, 2H, CH_2), 4.40 (d, J = 2.5 Hz, 2H, CH_2), 3.65 (s, 2H, CH_2), 2.26 (t, J = 2.5 Hz, 1H, CH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.6, 132.0, 131.0, 127.8, 127.5, 126.8, 125.4, 78.3, 72.6, 50.1, 37.3, 35.5. HRMS (ESI) *m/z*: [M + Na]$^+$ calcd for $C_{12}H_{11}N_1O_1Na_1$, 208.0733; found, 208.0726.

2-Allyl-1,4-dihydroisoquinolin-3(2H)-one 3b: Compound was synthesised according to general procedure A. RNH_2 = allylamine. R_f = 0.59. **3b** was isolated as an oil (84% yield). IR (thin film) cm^{-1}: 3051, 1640, 1482, 1459, 1441, 1416. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25-7.18 (m, 2H, H^{Ar}), 7.15 – 7.11 (m, 2H, H^{Ar}), 5.77 (ddt, J = 16.5, 10.6, 5.9 Hz, 1H, =CH), 5.20 – 5.18 (m,

1H, =CH_2), 5.16 (dq, J = 8.9, 1.3 Hz, 1H, =CH_2), 4.40 (s, 2H, CH_2), 4.13 (dt, J = 5.9, 1.3 Hz, 2H, CH_2), 3.61 (s, 2H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6, 132.5, 132.3, 131.4, 127.5, 127.2, 126.6, 125.1, 117.8, 50.1, 49.0, 37.4. HRMS (ESI) *m/z*: [M + Na]+ calcd for $C_{12}H_{13}N_1O_1Na_1$, 210.0889; found, 210.0887.

2-Pentyl-1,4-dihydroisoquinolin-3(2H)-one 3c: Compound was synthesised according to general procedure A. RNH_2 = amylamine. R_f = 0.32. **3c** was isolated as an oil (63% yield). IR (thin film) cm^{-1}: 2957, 2922, 2859, 1652, 1486, 1458, 1432. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28 – 7.21 (m, 2H, H^{Ar}), 7.17 (t, J = 6.4 Hz, 2H, H^{Ar}), 4.46 (s, 2H, CH_2), 3.61 (s, 2H, CH_2), 3.53 – 3.49 (m, 2H, CH_2) 1.64 – 1.57 (m, 2H, CH_2), 1.38 – 1.27 (m, 4H, CH_2), 0.89 (t, J = 7.1 Hz, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.9, 132.7, 131.7, 127.7, 127.4, 126.7, 125.2, 51.0, 47.1, 37.7, 29.2, 27.2, 22.6, 14.1. HRMS (ESI) *m/z*: [M + H]$^+$ calcd for $C_{14}H_{20}N_1O_1$, 218.1545; found, 218.1551.

2-(2,2-Dimethoxyethyl)-1,4-dihydroisoquinolin-3(2H)-one 3d: Compound was synthesised according to general procedure A. RNH_2 = aminoacetaldehyde dimethyl acetal. R_f = 0.19. **3d** was isolated as a yellow oil (85% yield). IR (thin film) cm^{-1}: 3463, 2937, 2835, 1653, 1483, 1458. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 – 7.20 (m, 2H, H^{Ar}), 7.18 – 7.14 (m, 2H, H^{Ar}), 4.58 (s, 2H, CH_2), 4.53 (t, J = 5.5 Hz, 1H, CH), 3.62 (s, 2H, CH_2), 3.61 (d, J = 5.5 Hz, 2H, CH_2), 3.40 (s, 6H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.5, 132.4, 132.1, 127.6, 127.3, 126.7, 125.2, 103.5, 55.2, 52.9, 49.6, 37.8. No mass ion in HRMS obtainable.

2-((Tetrahydrofuran-2-yl) methyl)-1,4-dihydroisoquinolin-3(2H)-one 3e: Compound was synthesised according to general procedure A. RNH_2 = tetrahydrofurfurylamine. R_f = 0.20. **3e** was isolated as a yellow oil (91% yield). IR (thin film) cm^{-1}: 3435, 2075, 1637, 1489. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25 – 7.20 (m, 2H, H^{Ar}), 7.19 – 7.12 (m, 2H, H^{Ar}), 4.71 (d, J = 15.7 Hz, 1H, CH_2), 4.55 (d, J = 15.7 Hz, 1H, CH_2), 4.13 (qd, J = 7.1, 3.2 Hz, 1H, CH), 3.90 (dd, J = 14.1, 3.2 Hz, 1H, CH_2), 3.88 – 3.83 (m, 1H, CH_2), 3.87 – 3.83 (m, 1H, CH_2), 3.74 (dd, J = 14.2, 7.2 Hz, 1H, CH_2), 3.62 (s, 2H, CH_2), 3.35 (dd, J = 14.2, 7.2 Hz, 1H, CH_2), 2.04 – 1.96 (m, 1H, CH_2), 1.89 – 1.82 (m, 2H, CH_2), 1.61 – 1.52 (m, 1H, CH). ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.7, 132.4, 132.2, 127.6, 127.3, 126.7, 125.2, 78.5, 68.3, 52.7, 50.9, 37.8, 29.2, 25.8. HRMS (ESI) *m/z*: [M + Na]$^+$ calcd for $C_{14}H_{17}N_1O_2Na_1$, 254.1151; found, 254.1144.

2-Benzyl-1,4-dihydroisoquinolin-3(2H)-one 3f: Compound was synthesised according to general procedure A. RNH_2 = benzylamine. R_f = 0.45. **3f** was isolated as a yellow solid (96% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35 – 7.30 (m, 2H, H^{Ar}), 7.30 – 7.24 (m, 4H, H^{Ar}), 7.21-7.17 (m, 2H, H^{Ar}), 7.07 (d, J = 7.3 Hz, 1H, H^{Ar}), 4.76 (s, 2H, CH_2), 4.38 (s, 2H, CH_2), 3.73 (s, 2H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.1, 136.8, 132.3, 131.3, 128.9, 128.1, 127.7, 127.7, 127.4, 126.7, 125.3, 50.4, 50.1, 37.5. The spectral data were consistent with that reported in the literature.[12]

2-(4-Methoxybenzyl)-1,4-dihydroisoquinolin-3(2H)-one 3g: Compound was synthesised according to general procedure A. RNH_2 = *p*-methoxybenzylamine. R_f = 0.43. **3g** was isolated as a yellow oil (63% yield). IR (thin film) cm^{-1}: 2998, 2957, 2931, 2836, 1651, 1611, 1513, 1485, 1458, 1441. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 – 7.15 (m, 5H, H^{Ar}), 7.07 (d, J = 7.5 Hz, 1H, H^{Ar}), 6.87-6.83 (m, 2H, H^{Ar}), 4.69 (s, 2H, CH_2), 4.36 (s, 2H, CH_2), 3.79 (s, 3H, CH_3), 3.69 (s, 2H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.0, 159.2, 132.3, 131.4, 129.5, 128.8, 127.6, 127.4, 126.7, 125.3, 114.3, 55.4, 50.1, 49.5, 37.6. HRMS (ESI) *m/z*: [M + Na]$^+$ calcd for $C_{17}H_{17}N_1O_2Na_1$, 290.1151; found, 290.1143. The spectral data were consistent with that reported in the literature.[4f]

2-(4-(Trifluoromethyl)benzyl)-1,4-dihydroisoquinolin-3(2H)-one 3h: Compound was synthesised according to general procedure A. RNH_2 = 4-(trifluoromethyl)benzylamine. Purified on a Combiflash Companion using a 0-100% gradient of cyclohexane:EtOAc. **3h** was isolated as a yellow oil (50% yield). IR (thin film) cm^{-1}: 2911, 1648, 1637, 1617, 1487, 1460, 1438, 1419, 1411. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.60 (d, J = 8.1 Hz, 2H, H^{Ar}), 7.41 (d, J = 8.1 Hz, 2H, H^{Ar}), 7.20 - 7.32 (m, 3H, H^{Ar}), 7.11 (d, J = 6.6 Hz, 1H, H^{Ar}), 4.83 (s, 2H, CH_2), 4.43 (s, 2H, CH_2), 3.75 (s, 2H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.2, 140.9, 132.1, 130.9, 129.9 (q, J = 32.8 Hz), 128.1, 127.8, 127.4, 126.7, 125.7 (q, J = 3.7 Hz), 125.2, 124.1 (br q, J = 272.2 Hz), 50.6, 49.7, 37.4. HRMS (ESI) *m/z*: [M + H]$^+$ calcd for $C_{17}H_{15}F_3N_1O_1$, 306.1106; found, 306.1106. The spectral data were consistent with that reported in the literature.[4f]

2-(2-Chlorobenzyl)-1,4-dihydroisoquinolin-3(2H)-one 3i: Compound was synthesised according to general procedure A. RNH_2 = 2-chlorobenzylamine. R_f = 0.56. **3i** was isolated as a yellow oil (98% yield). IR (thin film) cm^{-1}: 2922, 1655, 1475, 1443. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40 – 7.37 (m, 1H, H^{Ar}), 7.28 (d, J = 6.1 Hz, 1H, H^{Ar}), 7.24 – 7.18 (m, 5H, H^{Ar}), 7.12 (d, J = 7.5 Hz, 1H, H^{Ar}), 4.90 (s, 2H, CH_2), 4.45 (s, 2H, CH_2), 3.73 (s, 2H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.4, 134.2, 133.8, 132.3, 131.3, 129.8, 129.1, 128.9, 127.8, 127.5, 127.4, 126.8, 125.4, 50.9, 47.5, 37.6. HRMS (ESI) *m/z*: [M + H]$^+$ calcd for $C_{16}H_{15}Cl_1N_1O_1$, 272.0842; found, 272.0844.

2-(3,4,5-Trimethoxybenzyl)-1,4-dihydroisoquinolin-3(2H)-one 3j: Compound was synthesised according to general procedure A. RNH_2 = 3,4,5-trimethoxybenzylamine. R_f = 0.34. **3j** was isolated as a yellow oil (98% yield). IR (thin film) cm^{-1}: 3472, 2939, 2839, 1651, 1592, 1506, 1458, 1421. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28 – 7.18 (m, 3H, H^{Ar}), 7.10 (d, J = 7.4 Hz, 1H, H^{Ar}), 6.45 (s, 2H, H^{Ar}), 4.69 (s, 2H, CH_2), 4.39 (s, 2H, CH_2), 3.82 (s, 3H, CH_3), 3.77 (s, 6H, CH_3), 3.70 (s, 2H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.3, 153.6, 137.5, 132.5, 132.4, 131.6, 127.8, 127.4, 126.8, 125.23, 105.0, 61.0, 56.2, 50.3, 50.2, 37.8. HRMS (ESI) *m/z*: [M + Na]$^+$ calcd for $C_{19}H_{21}N_1O_4Na_1$, 350.1363; found, 350.1356.

2-(Pyridine-4-ylmethyl)-1,4-dihydroisoquinolin-3(2H)-one 3k: Compound was synthesised according to general procedure A. RNH_2 = 4-(aminomethyl)pyridine. R_f = 0.0 (flushed from column with 10% MeOH in EtOAc) **3k** was isolated as a green oil (69% yield). IR (thin film) cm^{-1}: 3435, 2075, 1638, 1418. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.55 (brs, 2H, H^{Ar}), 7.31 – 7.14 (m, 5H, H^{Ar}), 7.10 (d, J = 7.4 Hz, 1H, H^{Ar}), 4.76 (s, 2H, CH_2), 4.42 (s, 2H, CH_2), 3.73 (s, 2H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.5, 150.3, 145.9, 132.1, 130.9, 128.0, 127.5, 127.0, 125.3, 122.7, 50.9, 49.3, 37.5. HRMS (ESI) *m/z*: [M + Na]$^+$ calcd for $C_{15}H_{14}N_2O_1Na_1$, 261.1004; found, 261.0999.

2-Isopropyl-1,4-dihydroisoquinolin-3(2H)-one 3l: Compound was synthesised according to general procedure A. RNH_2 = isopropylamine. R_f = 0.39. **3l** was isolated as a yellow oil (38% yield). IR (thin film) cm^{-1}: 2970, 1725, 1638, 1475, 1457, 1434. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 – 7.18 (m, 3H, H^{Ar}), 7.15 (d, J = 6.9 Hz, 1H, H^{Ar}), 4.97 (hept, J = 6.9 Hz, 1H, CH), 4.30 (s, 2H, CH_2), 3.58 (s, 2H, CH_2), 1.17 (d, J = 6.9 Hz, 6H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.6, 132.9, 132.3, 127.6, 127.1, 126.6, 125.1, 43.9, 43.8, 38.5, 19.6. HRMS (ESI) *m/z*: [M + H]$^+$ calcd for $C_{12}H_{16}N_1O_1$, 190.1232; found, 190.1233.

General Procedure B for the synthesis of imines 5. To a solution of methyl-2-(2-formylphenyl) acetate **2** (20 mg, 0.11 mmol) in methanol (0.2 mL) was added an equimolar amount of RNH_2 and the reaction mixture stirred for 3 hours at room temperature in a sealed tube followed by removal of the solvent *in vacuo* to afford the product.

(*E*)-Methyl 2-(2-(((1-phenylethyl)imino)methyl)phenyl) acetate 5a: Compound was synthesised according to general procedure B. RNH_2 = (*rac*)-α-methylbenzylamine. IR (thin film) cm^{-1}: 2970, 2840, 1734, 1643, 1601, 1575, 1492, 1450, 1435, 1406. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.57 (s, 1H, =C*H*), 7.72-7.68 (m, 1H, H^{Ar}), 7.47 - (dd, *J* = 8.2, 1.0 Hz, 2H, H^{Ar}), 7.41 – 7.36 (m, 4H, H^{Ar}), 7.29 – 7.24 (m, 2H, H^{Ar}), 4.52 (q, *J* = 6.6 Hz, 1H, C*H*), 4.10 (d, *J* = 16.3 Hz, 1H, CH_2), 4.01 (d, *J* = 16.3 Hz, 1H, CH_2), 3.62 (s, 3H, OCH_3), 1.61 (d, *J* = 6.6 Hz, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.2, 159.5, 145.1, 134.5, 133.7, 131.9, 130.9, 130.0, 128.4, 127.5, 126.8, 126.6, 70.9, 51.8, 50.2, 40.0, 25.1. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{18}H_{20}N_1O_2$, 282.1489; found, 282.1498.

(*E*)-Methyl 2-(2-((benzhydrylimino)methyl)phenyl) acetate 5b: Compound was synthesised according to general procedure B. RNH_2 = benzhydrylamine. IR (thin film) cm^{-1}: 3025, 2950, 2841, 1734, 1639, 1599, 1575, 1492, 1452, 1435, 1406. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.64 (s, 1H, =C*H*), 7.77 – 7.72 (m, 1H, H^{Ar}), 7.45 – 7.36 (m, 10H, H^{Ar}), 7.29 – 7.22 (m, 2H, H^{Ar}), 5.56 (s, 1H, C*H*), 4.11 (s, 2H, CH_2), 3.50 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.1, 161.3, 143.8, 134.4, 134.1, 132.1, 131.7, 130.3, 128.5, 127.7, 127.6, 127.0, 79.6, 51.8, 50.5, 40.2. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{23}H_{22}N_1O_2$, 344.1645; found, 344.1652.

(*E*)-Methyl 2-(2-((phenylimino)methyl)phenyl) acetate 5c: Compound was synthesised according to general procedure B. RNH_2 = aniline. IR (thin film) cm^{-1}: 3022, 2950, 1733, 1698, 1625, 1590, 1572, 1486, 1450, 1434, 1406. ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.68 (s, 1H, =C*H*), 7.96 – 7.92 (m, 1H, H^{Ar}), 7.46 – 7.40 (m, 4H, H^{Ar}), 7.33 – 7.31 (m, 1H, H^{Ar}), 7.28 – 7.21 (m, 3H, H^{Ar}), 4.08 (s, 2H, CH_2), 3.70 (s, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.0, 159.8, 152.0, 134.6, 134.5, 132.0, 130.9, 130.9, 129.2, 127.8, 126.1, 120.9, 52.1, 39.8. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{16}N_1O_2$, 254.1176; found, 254.1178.

General Procedure C for the synthesis of *N*-substituted 1,4-dihydro-3(2H)-isoquinolinones obtained from $H_2NCHR^1R^2$. To a sample of methyl 2-(2-formylphenyl)acetate **2** (1 eq.) under a nitrogen atmosphere was added an equimolar amount of amine (RNH_2) followed by dry tetrahydrofuran (THF). The reaction was stirred at room temperature for 18 hours. After this time, ammonium formate (5 eq.) and 10% palladium on carbon (0.2 eq.) were added to the reaction under a nitrogen atmosphere. The reaction vessel was fitted with a reflux condenser and heated to 70 °C for 18 hours. After cooling to room temperature the reaction mixture was poured onto a 5% sodium metabisulfite solution before extraction with EtOAc. The organic phase was washed with brine, passed through an Isolute Phase Separator and the solvent removed *in vacuo*. The sample was loaded in CH_2Cl_2 and purified *via* Combiflash (silica - 80g) using a 0-100% ethyl acetate-cyclohexane mix over 30 mins. The appropriate fractions were combined and evaporated *in vacuo* to give the product.

2-(1-Phenylethyl)-1,4-dihydroisoquinolin-3(2H)-one 3m: Compound was synthesised according to general procedure C (**2** 2.00 g, THF (20 mL). RNH_2 = (*rac*)-α-methylbenzylamine. **3m** was isolated as an off-yellow solid (80% yield) IR (thin film) cm^{-1}: 3029, 2972, 2879, 1636, 1604, 1494, 1468, 1451, 1432. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 - 7.29 (m, 5H, H^{Ar}), 7.27 - 7.24 (m, 1H, H^{Ar}), 7.22 - 7.17 (m, 2H, H^{Ar}), 7.04 (d, *J* = 6.9 Hz, 1H, H^{Ar}), 6.19 (q, *J* = 7.1 Hz, 1H, C*H*), 4.27 (d, *J* = 15.4 Hz, 1H, CH_2), 3.98 (d, *J* = 15.4 Hz, 1H, CH_2), 3.71 (s, 2H, CH_2), 1.61 (d, *J* = 7.1 Hz, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.0, 140.0, 132.6, 132.1, 128.6, 127.5, 127.4, 127.2, 127.0, 126.5, 125.1, 50.2, 44.9, 38.3, 15.8. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{17}H_{18}N_1O_1$, 252.1388; found, 252.1386. The spectral data were consistent with that reported in the literature.[4e]

2-(1-(Pyridin-3-yl)ethyl)-1,4-dihydroisoquinolin-3(2H)-one 3n: Compound was synthesised according to general procedure C. (**2** 0.050 g, THF 1 mL) RNH_2 = (*rac*)-α-methyl-3-pyridinemethanamine. **3n** was isolated as an oil (48% yield). IR (thin film) cm^{-1}: 2977, 1714, 1646, 1478, 1457, 1424. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.57 - 8.60 (m, 1H, H^{Ar}), 8.53 (dd, *J* = 4.8, 1.1 Hz, 1H, H^{Ar}), 7.50-7.56 (m, 1H, H^{Ar}), 7.29 - 7.16 (m, 4H, H^{Ar}), 7.03 (d, *J* = 7.3 Hz, 1H, H^{Ar}), 6.19 (q, *J* = 7.1 Hz, 1H, C*H*), 4.33 (d, *J* = 15.2 Hz, 1H CH_2), 3.98 (d, *J* = 15.2 Hz, 1H, CH_2), 3.69 (s, 2 H), 1.64 (d, *J* = 7.1 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.2, 148.9, 148.7, 135.6, 135.0, 132.4, 131.6, 127.7, 127.1, 126.7, 125.1, 123.4, 48.5, 45.0, 38.7, 15.6. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{17}N_2O_1$, 253.1341; found, 253.1336.

2-(1-(Pyridin-4-yl)ethyl)-1,4-dihydroisoquinolin-3(2H)-one 3o: Compound was synthesised according to general procedure C. (**2** 0.050 g, THF 1 mL) RNH_2 = (*rac*)-α-methyl-4-pyridinemethanamine. **3o** was isolated as an oil (22% yield). IR (thin film) cm^{-1}: 3035, 2980, 2940, 1714, 1667, 1599, 1556, 1458, 1414. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.57 - 8.54 (m, 2H, H^{Ar}), 7.32 - 7.26 (m, 1H, H^{Ar}), 7.24 - 7.16 (m, 4H, H^{Ar}), 7.05 (d, *J* = 7.3 Hz, 1H, H^{Ar}), 6.13 (q, *J* = 7.3 Hz, 1H, C*H*), 4.33 (d, *J* = 15.4 Hz, 1H, CH_2), 3.97 (d, *J* = 15.4 Hz, 1H, CH_2), 3.72 (s, 2H, CH_2), 1.62 (d, *J* = 7.3 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.4, 150.1, 149.4, 132.4, 131.6, 127.8, 127.2, 126.8, 125.0, 122.0, 49.5, 45.3, 38.3, 15.5. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{17}N_2O_1$, 253.1341; found, 253.1340.

Methyl 2-(3-oxo-3,4-dihydroisoquinolin-2(1H)-yl)propanoate 3p: Compound was synthesised according to general procedure C. (**2** 0.050 g, THF 1 mL) RNH_2 = L-alanine methyl ester hydrochloride with 1 eq. Et_3N added to generate free base. **3p** was isolated as an oil (32% yield). IR (thin film) cm^{-1}: 3037, 2850, 2925, 1655, 1594, 1497, 1460, 1407. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31 - 7.18 (m, 4H, H^{Ar}), 5.38 (q, *J* = 7.3 Hz, 1H, C*H*), 4.41 - 4.55 (m, 2H, CH_2), 3.73 (s, 3H, OCH_3), 3.67 (br s, 2H, CH_2), 1.50 (d, *J* = 7.3 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.1, 169.5, 132.9, 131.8, 127.7, 127.2, 126.7, 125.1, 52.3, 51.5, 47.0, 37.8, 14.5. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{13}H_{16}N_1O_3$, 234.1130; found, 234.1131.

2-(1-Methoxypropan-2-yl)-1,4-dihydroisoquinolin-3(2H)-one 3q: Compound was synthesised according to general procedure C. (**2** 0.050 g, THF 1 mL) RNH_2 = (*rac*)-1-methoxy-2-propanamine. **3q** was isolated as an oil (26% yield). IR (thin film) cm^{-1}: 2987, 2931, 1713, 1668, 1605, 1463. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 - 7.17 (m, 4H, H^{Ar}), 5.00-4.93 (m, 1H, C*H*), 4.36 - 4.48 (m, 2H, CH_2), 3.62 - 3.65 (m, 2H, CH_2), 3.54 (dd, *J* = 10.3, 7.1 Hz, 1H, CH_2), 3.44 (dd, *J* = 10.3, 4.9 Hz, 1H, CH_2), 3.34 (s, 3H, OCH_3), 1.22 (d, *J* = 7.1 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.3, 132.8, 132.4, 127.5, 127.0, 126.5, 125.0, 74.2, 58.9, 47.7, 45.6, 38.4, 14.1. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{13}H_{18}N_1O_2$, 220.1338; found, 220.1334.

Methyl 3-methyl-2-(3-oxo-3,4-dihydroisoquinolin-2(1H)-yl)butanoate 3r: Compound was synthesised according to general procedure C. (**2** 0.050 g, THF 1 mL) RNH_2 = L-valine methyl ester hydrochloride with 1 eq. Et_3N added to generate free base. **3r** was isolated as an oil (44% yield). IR (thin film) cm^{-1}: 2966, 1749, 1718, 1678. ^1H NMR (400 MHz, $CDCl_3$): δ 7.31 - 7.17 (m, 4H, H^{Ar}), 5.04 (d, *J* = 10.5 Hz, 1H, C*H*), 4.60 (dd, *J* = 15.7, 1.00 Hz, 1H, CH_2), 4.43 (d, *J* = 15.7 Hz, 1H, CH_2), 3.71 (s, 3H, OCH_3), 3.66 (s, 2H, CH_2), 2.41 - 2.27 (m, 1H, CH_2), 1.04 (d, *J* = 6.7 Hz, 3H, CH_3), 0.84 (d, *J* = 6.7 Hz, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.5, 170.1, 132.5, 132.4, 127.7, 127.0, 126.7, 125.1, 60.8, 51.9, 46.7, 38.5, 27.8, 19.6, 18.9. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{20}N_1O_3$, 262.1443; found, 262.1439.

2-(Diphenylmethyl)-1,4-dihydroisoquinolin-3(2H)-one 3s: Compound was synthesised according to general procedure C. (**2** 0.100 g, THF 10 mL) RNH_2 = Benzhydrylamine. **3s** was isolated as a yellow crystalline solid (54% yield). Mp: 159-160 °C, IR (thin film) cm^{-1}: 3019, 2915, 1740, 1650, 1601, 1583, 1493, 1468, 1451, 1422. ^1H NMR (500 MHz, $CDCl_3$): δ 7.37 – 7.27 (m, 8H, H^{Ar}), 7.25 – 7.20 (m, 6H, H^{Ar}), 7.07 (d, *J* = 8.0 Hz, 1H), 4.18 (s, 2H, CH_2), 3.73 (s, 2H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.7, 138.7, 132.8, 132.4, 128.8, 128.7, 127.8, 127.7, 127.2, 126.8, 125.3, 59.9, 47.4, 38.7. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{22}H_{20}N_1O_1$, 314.1545; found, 314.1541.

2-Phenyl-1,4-dihydroisoquinolin-3(2H)-one 3t: Compound was synthesised according to general procedure C. (**2** 0.080 g, THF 2 mL) RNH_2 = aniline. **3t** was isolated as an oil (2 mg, 3% yield). ^1H NMR (400 MHz, DMSO-d_6): δ 7.45 - 7.20 (m, 9 H, H^{AR}), 4.88 (s, 2H, CH_2), 3.73 (s, 2H, CH_2). The spectral data were consistent with that reported in the literature.[4j]

General Procedure D for the alkylation of *N*-substituted 1,4-dihydro-3(2H)-isoquinolinones. Either **3f** (0.28mmol) or **3b** (0.53mmol) was dissolved in dry THF (0.4 mL or 0.6 mL respectively), placed under an N_2 atmosphere and cooled with stirring to -78 °C. To this was added 1.1 equivalents of *n*-BuLi and the reaction stirred for a further 10 minutes at -78 °C. Then one equivalent of RBr was added and the solution stirred for a further 2 hours at -78 °C before being allowed to warm to 0 °C. The reaction was quenched by the slow addition of distilled water. Extraction with EtOAc was followed by washing of the organic layer with distilled water and then brine. After drying over $MgSO_4$ the solvent was removed *via* evaporation and the resulting product purified by column chromatography.

2,4-Dibenzyl-1,4-dihydroisoquinolin-3(2H)-one 4fa: Compound was synthesised according to general procedure D. RBr = benzyl bromide. R_f = 0.18 (4:1 PE:EtOAc). **4fa** was isolated as a yellow oil (95% yield). IR (thin film) cm^{-1}: 3435, 2075, 1643, 1496, 1454. ^1H NMR (500 MHz, $CDCl_3$): δ 7.32 – 7.24 (m, 3H, H^{Ar}), 7.24 – 7.19 (m, 3H, H^{Ar}), 7.18 – 7.10 (m, 2H, H^{Ar}), 7.02 (s, 3H, H^{Ar}), 6.90 (d, *J* = 7.1 Hz, 1H, H^{Ar}), 6.73 (d, *J* = 7.1 Hz, 2H, H^{Ar}), 4.76 (d, *J* = 14.7 Hz, 1H, CH_2), 4.47 (d, *J* = 14.7 Hz, 1H, CH_2), 3.99 (t, *J* = 5.5 Hz, 1H, C*H*), 3.87 (d, *J* = 15.5 Hz, 1H, CH_2), 3.46 (d, *J* = 15.5 Hz, 1H, CH_2), 3.34-3.28 (m, 1H, CH_2), 3.17-3.11 (m, 1H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 137.2, 136.6, 135.2, 131.6, 129.8, 128.7, 128.4, 128.0, 127.9, 127.6, 127.4, 126.7, 125.0, 50.3, 49.6, 48.8, 41.5 (*C*=O not observed). HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{23}H_{21}N_1O_1Na_1$, 350.1515; found, 350.1515. The spectral data were consistent with that reported in the literature.[4h,i]

2-Benzyl-4-(4-(trifluoromethyl)benzyl)-1,4-dihydroisoquinolin-3(2H)-one 4fb: Compound was synthesised according to general procedure D. RBr = 4-(trifluoromethyl)benzyl bromide. R_f = 0.68 (4:1 CH_2Cl_2:EtOAc). **4fb** was isolated as a yellow oil (40% yield). IR (thin film) cm^{-1}: 3032, 2928, 1649, 1486, 1455. ^1H NMR (500 MHz, $CDCl_3$): δ 7.34 – 7.28 (m, 3H, H^{Ar}), 7.27 – 7.17 (m, 6H, H^{Ar}), 7.02 (d, *J* = 7.5 Hz, 1H, H^{Ar}), 6.95 (d, *J* = 7.5 Hz, 1H, H^{Ar}), 6.81 (d, *J* = 8.0 Hz, 2H, H^{Ar}), 4.68 (d, *J* = 14.5 Hz, 1H, CH_2), 4.56 (d, *J* = 14.5 Hz, 1H, CH_2), 4.02 – 3.93 (m, 2H, C*H*,CH_2), 3.51 (d, *J* = 15.8 Hz, 1H, CH_2), 3.38 (dd, *J* = 13.0, 5.6 Hz, 1H, CH_2), 3.18 (dd, *J* = 13.0, 5.6 Hz, 1H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.4, 141.4, 136.3, 134.5, 131.4, 130.0, 128.8, 128.6, 127.8, 127.8, 127.7, 127.0, 125.4, 125.2, 124.8 (q, *J* = 30 Hz), 123.2, 50.5, 49.7, 48.1, 41.1. HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{24}H_{20}F_3N_1O_1Na_1$, 418.1395; found, 418.1394.

2-Benzyl-4-(3,3-dimethyl-2-oxobutyl)-1,4-dihydroisoquinolin-3(2H)-one 4fc: Compound was synthesised according to general procedure D. RBr = 1-bromopinacolone. R_f = 0.74 (4:1 CH_2Cl_2:EtOAc). **4fc** was isolated as a yellow oil (81% yield). IR (thin film) cm^{-1}: 3466, 2970, 2870, 2037, 1702, 1645, 1495, 1478, 1453. ^1H NMR (500 MHz, $CDCl_3$): δ 7.34 – 7.29 (m, 2H, H^{Ar}), 7.28 – 7.23 (m, 3H, H^{Ar}), 7.22 (d, *J* = 7.5 Hz, 1H, H^{Ar}), 7.17 (t, *J* = 7.5 Hz, 1H, H^{Ar}), 7.08 (d, *J* = 7.5 Hz, 1H, H^{Ar}), 7.05 (d, *J* = 7.5 Hz, 1H, H^{Ar}), 4.84 (d, *J* = 15.0 Hz, 1H, CH_2), 4.68 (d, *J* = 15.0 Hz, 1H, CH_2), 4.47 (d, *J* = 15.5 Hz, 1H, CH_2), 4.39 (d, *J* = 15.5 Hz, 1H, CH_2), 4.08 (t, *J* = 5.5 Hz, 1H, C*H*), 3.43 (dd, *J* = 17.8, 5.5 Hz, 1H, CH_2), 3.27 (dd, *J* = 17.8, 5.5 Hz, 1H, CH_2), 1.15 (s, 9H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 213.2, 171.2, 136.8, 135.5, 131.9, 128.8, 128.0, 127.6, 127.5, 126.6, 125.7, 125.3, 50.5, 50.0, 44.2, 41.2, 38.0, 26.6. HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{22}H_{25}N_1O_2Na_1$, 358.1777; found, 358.1775.

2-Benzyl-4-(2-ethoxyethyl)-1,4-dihydroisoquinolin-3(2H)-one 4fd: Compound was synthesised according to general procedure D. RBr = 2-bromoethyl ethyl ether. R_f = 0.41 (4:1 CH_2Cl_2:EtOAc). **4fd** was isolated as a yellow oil (58% yield). IR (thin film) cm^{-1}: 3500, 2079, 1642, 1485, 1453. ^1H NMR (500 MHz, $CDCl_3$): δ 7.34 – 7.30 (m, 2H, H^{Ar}), 7.29 – 7.24 (m, 4H, H^{Ar}), 7.22 – 7.16 (m, 2H, H^{Ar}), 7.07 (d, *J* = 7.4 Hz, 1H, H^{Ar}), 4.79 (d, *J* = 14.8 Hz, 1H, CH_2), 4.69 (d, *J* = 14.8 Hz, 1H, CH_2), 4.51 (d, *J* = 15.8 Hz, 1H, CH_2), 4.19 (d, *J* = 15.8 Hz, 1H, CH_2), 3.79 (t, *J* = 7.1 Hz, 1H, C*H*), 3.48 – 3.40 (m, 4H, CH_2), 2.23 – 2.13 (m, 1H, CH_2), 2.04 - 1.95 (m, 1H, CH_2), 1.17 (t, *J* = 7.0 Hz, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.9, 137.0, 136.2, 131.3, 128.8, 128.1, 127.6, 126.7, 125.5, 67.5, 66.2, 50.3, 49.8, 44.7, 33.2, 15.4. HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{20}H_{23}N_1O_2Na_1$, 332.1626; found, 332.1619.

4-Allyl-2-benzyl-1,4-dihydroisoquinolin-3(2H)-one 4fe: Compound was synthesised according to general procedure D. RBr = allyl bromide. R_f = 0.33 (4:1 PE:EtOAc). **4fe** was isolated as a yellow oil (58% yield). IR (thin film) cm^{-1}: 3435, 2075, 1634, 1497, 1453. ^1H NMR (500 MHz, $CDCl_3$): δ 7.30-7.20 (m, 6H, H^{Ar}), 7.22 – 7.15 (m, 2H, H^{Ar}), 7.06 (d, *J* = 7.5 Hz, 1H, H^{Ar}), 5.75 – 5.66 (m, 1H), 5.01 – 4.95 (m, 2H, CH_2), 4.89 (d, *J* = 14.7 Hz, 1H, CH_2), 4.63 (d, *J* = 14.7 Hz, 1H, CH_2), 4.51 (d, *J* = 15.9 Hz, 1H, CH_2), 4.20 (d, *J* = 15.9 Hz, 1H, CH_2), 3.72 (t, *J* = 6.4 Hz, 1H, C*H*), 2.69 – 2.63 (m, 2H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.3, 136.9, 135.8, 134.4, 131.1, 128.8, 128.2, 127.7, 127.7, 127.5, 126.7, 125.3, 118.0, 50.3, 50.0, 47.5, 38.7. HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{19}H_{19}N_1O_1Na_1$, 300.1359; found, 300.1352. The spectral data were consistent with that reported in the literature.[4i]

2-Allyl-4-benzyl-1,4-dihydroisoquinolin-3(2H)-one 4ba: Compound was synthesised according to general procedure D. RBr = Benzyl bromide. R_f = 0.75 (4:1 CH_2Cl_2:EtOAc). **4ba** was isolated as a clear oil (42% yield). IR (thin film) cm^{-1}: 3029, 2925, 1634, 1487, 1454, 1417. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24 – 7.14 (m, 3H, H^{Ar}), 7.14-7.06 (m, 2H, H^{Ar}), 7.01 – 6.95 (m, 2H, H^{Ar}), 6.77 – 6.74 (m, 2H, H^{Ar}), 5.69 (ddt, *J* = 16.4, 10.2, 6.1 Hz, 1H, =C*H*), 5.16 – 5.09 (m, 2H, =CH_2), 4.16 (ddt, *J* = 15.0, 5.9, 1.3 Hz, 1H, CH_2), 3.94 – 3.87 (m, 3H, C*H* and CH_2), 3.45 (d, *J* = 15.7 Hz, 1H, CH_2), 3.30 (dd, *J* = 13.0, 6.6 Hz, 1H, CH_2), 3.10 (dd, *J* = 13.0, 4.5 Hz, 1H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.7, 137.3, 135.3, 132.6, 131.7, 129.8, 128.0, 127.9, 127.5, 126.7, 124.9, 118.0, 49.4, 49.3, 48.8, 41.4. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{20}N_1O_1$, 278.1545; found, 278.1546.

2,4-Diallyl-1,4-dihydroisoquinolin-3(2H)-one 4be: Compound was synthesised according to general procedure D. RBr = Allyl bromide. R_f = 0.81 (4:1 CH_2Cl_2:EtOAc). **4be** was isolated as a yellow oil (98% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29 – 7.20 (m, 2H, H^{Ar}), 7.15 (d, *J* = 7.4 Hz, 2H, H^{Ar}), 5.85-5.76 (m, 1H, C*H*), 5.73 – 5.65 (m, 1H, C*H*), 5.26 – 5.15 (m, 2H, CH_2), 5.01 – 4.93 (m, 2H, CH_2), 4.59 (d, *J* = 15.8 Hz, 1H, CH_2), 4.24 (d, *J* = 15.8 Hz, 1H, CH_2), 4.21 – 4.09 (m, 2H, CH_2), 3.64 (t, *J* = 6.3 Hz, 1H, C*H*), 2.62 (t, *J* = 7.1 Hz, 2H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$): δ 171.0, 135.9, 134.4, 132.8, 131.3, 127.8, 127.5, 126.7, 125.3, 118.0, 117.9, 49.9, 49.4, 47.7, 38.5. The spectral data were consistent with that reported in the literature.[4g]

2-Allyl-4-(prop-2-ynyl)-1,4-dihydroisoquinolin-3(2H)-one 4bf: Compound was synthesised according to general procedure D. RBr = Propargyl bromide. R_f = 0.7 (4:1 CH_2Cl_2:EtOAc). **4bf** was isolated as a clear oil (79% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33 – 7.26 (m, 3H, H^{Ar}), 7.17 (d, *J* = 7.3 Hz, 1H, H^{Ar}), 5.87-5.75 (m, 1H, =C*H*), 5.25 – 5.19 (m, 2H, =CH_2), 4.66 (d, *J* = 15.8 Hz, 1H, CH_2), 4.31 (d, *J* = 15.8 Hz, 1H, CH_2), 4.25-4.15 (m, 2H, CH_2), 3.71 – 3.67 (m, 1H), 2.94 – 2.83 (m, 2H, CH_2), 1.91 (t, *J* = 2.7 Hz, 1H, C*H*). ^{13}C NMR (125 MHz, $CDCl_3$): δ 169.8, 134.6, 132.6, 131.6, 127.7, 127.5, 127.2, 125.3, 118.0, 81.1, 70.8, 50.1, 49.6, 45.3, 23.5. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{15}H_{16}N_1O_1$, 226.1232; found, 226.1230.

2-Benzyl-4,4-di(prop-2-ynyl)-1,4-dihydroisoquinolin-3(2H)-one 6: Compound was synthesised according to general procedure D. RBr = propargyl bromide. R_f = 0.92 (4:1 CH_2Cl_2:EtOAc). **6** was isolated as a yellow oil (29% yield). IR (thin film) cm^{-1}: 3449, 3293, 2925, 2855, 2119, 1644, 1495, 1451, 1430. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44 (d, *J* = 8.0 Hz, 1H, H^{Ar}), 7.39 – 7.25 (m, 7H, H^{Ar}), 7.07 (d, *J* = 7.6 Hz, 1H, H^{Ar}), 4.86 (s, 2H, CH_2), 4.47 (s, 2H, CH_2), 3.11 (d, *J* = 16.4, 2H, CH_2), 2.77 (d, *J* = 16.4, Hz, 2H, CH_2), 1.82 (t, *J* = 2.5 Hz, 2H, C*H*). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.3, 136.6, 135.2, 131.1, 128.7, 128.3, 127.7, 127.3, 126.4, 125.4, 80.2, 71.1, 50.9, 49.8, 49.4, 29.4. HRMS (ESI) *m/z*: $[M + Na]^+$ calcd for $C_{22}H_{19}N_1O_1Na_1$, 336.1359; found, 336.1358.

2-Benzyl-4-(prop-2-ynyl)-1,4-dihydroisoquinolin-3(2H)-one 4ff: 3f (0.020 g, 0.08 mmol) was dissolved in dry THF (0.4 mL), placed under an N_2 atmosphere and cooled to -78 °C with stirring. To this was added 1.1 equivalents of *n*-BuLi and the reaction stirred for a further 10 minutes followed by the addition of propargyl bromide (0.050 g, 0.42 mmol - 5 equivalents) and immediately removal from the cooling bath. When at room temperature the reaction mixture was quenched by the slow addition of distilled water (1 mL) followed by extraction with EtOAc (5 mL). The organic layer was washed with distilled water (5 mL) and brine (5 mL), dried ($MgSO_4$), filtered and the solvent removed *in vacuo*, and the product purified by column chromatography. R_f = 0.75 (4:1 CH_2Cl_2:EtOAc). **4ff** was isolated as a yellow oil (83% yield). IR (thin film) cm^{-1}: 3289, 2920, 2850, 1638, 1496, 1454. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35 – 7.22 (m, 8H, H^{Ar}), 7.09 (d, *J* = 7.5 Hz, 1H, H^{Ar}), 4.90 (d, *J* = 14.8 Hz, 1H, CH_2), 4.68 (d, *J* = 14.8 Hz, 1H, CH_2), 4.58 (d, *J* = 15.8 Hz, 1H, CH_2), 4.26 (d, *J* = 15.8 Hz, 1H, CH_2), 3.79 – 3.73 (m, 1H, C*H*), 2.97 (ddd, *J* = 16.7, 6.8, 2.6 Hz, 1H, CH_2), 2.88 (ddd, *J* = 16.7, 4.7, 2.7 Hz, 1H, CH_2), 1.87 (t, *J* = 2.6 Hz, 1H, C*H*). ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.1, 136.7, 134.5, 131.5, 128.8 (2C), 128.3 (2C), 127.7, 127.5, 127.2, 125.4, 81.0, 70.9, 50.5, 50.2, 45.3, 29.9, 23.9. The spectral data were consistent with that reported in the literature.[4i]

2-(1-Phenylethyl)-4-(prop-2-en-1-yl)-1,4-dihydroisoquinolin-3(2H)-one 4me and 2-(1-phenylethyl)-4,4-di(prop-2-en-1-yl)-1,4-dihydroisoquinolin-3(2H)-one 7: 3m (100 mg, 0.40 mmol) was dissolved in dry THF (0.6 mL) under an N_2 atmosphere and cooled to -78 °C with stirring. *n*-BuLi (0.41 mmol) was added and the reaction stirred for 10 minutes prior to the addition of allyl bromide (48 mg, 0.40 mmol). After stirring for a further 2 hours at -78 °C the reaction mixture was removed from cooling bath and allowed warm to room temperature before quenching with distilled water (5 mL) and extracted with EtOAc (10 mL). The organic layer was washed with distilled water (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered, and the solvent removed *in vacuo*, and the product purified by column chromatography (2:1 hexane:EtOAc). The ratio of diastereoisomers (1 : 1) was determined by ^{1}H NMR spectroscopy prior to chromatography.

4me R_f = 0.25 (87 mg, 75% yield, yellow oil). ^{1}H NMR data is of both diastereomers of **4me.** 1H NMR (500 MHz, $CDCl_3$) δ 7.38-7.14 (m, 16H, H^{Ar}), 7.06 (d, *J* = 7.5 Hz, 1H, H^{Ar}), 6.96 (d, *J* = 7.4 Hz, 1H, H^{Ar}), 6.18 (q, *J* = 7.1 Hz, 2H, C*H*), 5.79 – 5.66 (m, 2H, =C*H*), 5.05 – 4.96 (m, 4H, =CH_2), 4.41 (d, *J* = 15.6 Hz, 1H, CH_2), 4.04 (d, *J* = 16.0 Hz, 1H, CH_2), 3.95 (d, *J* = 16.0 Hz, 1H, CH_2), 3.90 (d, *J* = 15.6 Hz, 1H, CH_2), 3.74 – 3.67 (m, 2H, C*H*), 2.69 – 2.62 (m, 3H, CH_2), 2.62 – 2.55 (m, 1H, CH_2), 1.60 (d, *J* = 7.1 Hz, 3H, CH_3), 1.54 (d, *J* = 7.1 Hz, 3H, CH_3). HRMS (ESI) *m/z*: $[M + H]+$ calcd for $C_{20}H_{22}NO$, 292.1701; found, 292.1699.

7 R_f = 0.41 (19 mg, 14% yield, yellow oil) ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.27 (m, 7H, H^{Ar}), 7.17 – 7.13 (m, 1H, H^{Ar}), 6.95 (d, J = 7.5 Hz, 1H, H^{Ar}), 6.32 (q, *J* = 7.1 Hz, 1H, C*H*), 5.42 (dddt, *J* = 17.2, 15.6, 10.2, 7.2 Hz, 2H, =C*H*), 5.00 (dddt, *J* = 17.0, 10.1, 2.3, 1.2 Hz, 2H, =CH_2), 4.92 – 4.86 (m, 2H, =CH_2), 4.26 (d, *J* = 16.1 Hz, 1H, CH_2), 3.87 (d, *J* = 16.1 Hz, 1H, CH_2), 3.08 (dd, *J* = 13.7, 7.3 Hz, 1H, CH_2), 2.99 (dd, *J* = 13.5, 7.5 Hz, 1H, CH_2), 2.57 (dd, *J* = 13.7, 6.9 Hz, 1H, CH_2), 2.51 (dd, *J* = 13.5, 7.0 Hz, 1H, CH_2), 1.57 (d, *J* = 7.1 Hz, 3H, CH_3). HRMS (ESI) *m/z*: [M + H]+ calcd for $C_{23}H_{26}NO$, 332.2014; found, 332.2013.

2-(1-Ethylferrocene)-1,4-dihydroisoquinolin-3(2H)-one 3u: Compound was synthesised according to general procedure C. (**2** 0.073 g, THF 10 mL) RNH_2 = (*rac*)-1-(aminoethyl)ferrocene **8**. **3u** was isolated as an orange oil (70% yield). IR (thin film) cm^{-1}: 3082, 2978, 2893, 1739, 1632, 1499, 1471, 1455, 1435. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.21 (dd, *J* = 8.9, 5.5 Hz, 1H, H^{Ar}), 7.18-7.14 (m, 2H, H^{Ar}), 7.03 (d, *J* = 7.4 Hz, 1H, H^{Ar}), 5.92 (q, *J* = 7.0 Hz, 1H, C*H*), 4.27 – 4.24 (m, 1H, CH_2), 4.18 – 4.10 (m, 9H, Cp*H*), 3.98 (d, *J* = 15.6 Hz, 1H, CH_2), 3.60 (s, 2H, CH_2), 1.50 (d, *J* = 7.0 Hz, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$): δ 168.4, 132.7, 132.3, 127.5, 127.1, 126.6, 125.3, 87.7, 69.1, 66.8, 67.5, 66.7, 47.9, 44.5, 38.4, 16.5. HRMS (ESI) *m/z*: $[M]^+$ calcd for $C_{21}H_{21}N_1O_1Fe_1$, 357.1019; found, 357.1014.

2-(1-Ethylcyclopentadienyltetraphenylcyclobutadienecobalt)-1,4-dihydroisoquinolin-3(2H)-one 3v: Compound was synthesised according to general procedure C. (**2** 0.017 g, THF 10 mL) RNH_2 = 1-aminoethyl(η^5-cyclopentadienyl)(η^4-tetraphenylcyclobutadiene)cobalt **9**. **3v** was isolated as a dark orange oil (95 % yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 – 7.44 (m, 8H, H^{Ar}), 7.26 – 7.21 (m, 12H, H^{Ar}), 7.20 – 7.16 (m, 1H, H^{Ar}), 7.14-7.09 (m, 2H, H^{Ar}), 6.98 (d, *J* = 7.4 Hz, 1H, H^{Ar}), 5.49 (q, *J* = 6.9 Hz, 1H, C*H*), 4.74 – 4.72 (m, 1H, Cp*H*), 4.64 (dd, *J* = 4.1, 2.5 Hz, 1H, Cp*H*), 4.60 (dt, *J* = 2.7, 1.5 Hz, 1H, Cp*H*), 4.52 (td, *J* = 2.7, 1.5 Hz, 1H, Cp*H*), 4.08 (d, *J* = 15.6 Hz, 1H, CH_2), 3.90 (d, *J* = 15.6 Hz, 1H, CH_2), 3.53 (s, 2H, CH_2), 0.85 (d, *J* = 6.9 Hz, 3H, CH_3). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.1, 136.1, 132.7, 132.3, 128.9, 128.2, 127.4, 127.1, 126.6, 126.5, 125.2, 98.4, 83.9, 82.9, 82.7, 81.6, 75.3, 45.6, 44.6, 38.3, 15.3. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{44}H_{37}Co_1N_1O_1$, 654.2207; found, 654.2210.

2-(1-Ethylferrocene)-4-(prop-2-en-1-yl)-1,4-dihydroisoquinolin-3(2H)-one 4ue: 3u (0.030 g, 0.084 mmol) was dissolved in dry THF (0.6 mL) under an N_2 atmosphere and cooled to -78 °C. To this was added one equivalent of *n*-BuLi and the reaction stirred for 15 minutes prior to the addition of allyl bromide (0.10 g, 0.08 mmol). After stirring for a further 2 hours at -78 °C the reaction mixture was removed from cooling bath and allowed warm to room temperature before quenching with distilled water (2 mL) and extracted with EtOAc (5 mL). The organic layer was washed with distilled water (5 mL) and brine (5 mL), dried ($MgSO_4$), filtered, and the solvent removed *in vacuo*, and the product purified by column chromatography (4:1 CH_2Cl_2:EtOAc) to yield **4ue** as a yellow solid (23 mg, 70% yield) R_f=0.85. The ratio of diastereoisomers (1.3 : 1) was obtained by ^{1}H NMR spectroscopy prior to chromatography. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (t, *J* = 7.4 Hz, 2H, H^{Ar}), 7.19 – 7.09 (m, 4H, H^{Ar}), 7.05 (d, *J* = 7.4 Hz, 1H, H^{Ar}), 6.97 (d, *J* = 7.5 Hz, 1H, H^{Ar}), 6.00-5.88 (m, 2H, C*H*), 5.75 – 5.60 (m, 2H, =C*H*), 5.02 – 4.91 (m, 4H, =CH_2), 4.28-4.22 (m, 3H, CH_2 and Cp*H*), 4.21 – 4.06 (m, 16H, Cp*H*), 4.01 – 3.95 (m, 2H, C*H* and CH_2), 3.91 (d, *J* = 16.1 Hz, 2H, CH_2), 3.61 (t, *J* = 6.5 Hz, 2H, C*H*), 2.63 – 2.58 (m, 2H, CH_2), 2.53 (dd, *J* = 13.9, 6.7 Hz, 2H, CH_2), 1.51 (d, *J* = 7.1 Hz, 3H, C*H*), 1.48 (d, *J* = 7.0 Hz, 3H, CH_3 - major diastereoisomer). HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{24}H_{25}N_1O_1Fe_1$, 397.1332; found, 397.1324.

2-(1-Ethylcyclopentadienyltetraphenylcyclobutadienecobalt)-4-(prop-2-en-1-yl)-1,4-dihydroisoquinolin-3(2H)-one 4ve*:* 3v (0.033 g, 0.05 mmol) was dissolved in dry THF (0.6 mL) under an N_2 atmosphere and cooled to - 78°C. To this was added one equivalent of *n*-BuLi and the reaction stirred for 10 minutes prior to the addition of allyl bromide (6 mg, 0.05 mmol). After stirring for a further 2 hours at -78 °C the reaction mixture was removed from cooling bath and allowed warm to room temperature before quenching with distilled water (5 mL) and extracted with EtOAc (10 mL). The organic layer was washed with distilled water (10 mL) and brine (10 mL), dried ($MgSO_4$), filtered, and the solvent removed *in vacuo*, and the product purified by column chromatography (2:1 Hexane:EtOAc) to yield **4ve** as an orange solid (11 mg, 31% yield). The ratio of diastereoisomers (1.7 : 1) was obtained by ^{1}H NMR spectroscopy prior to chromatography. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 – 7.37 (m, 16H, H^{Ar}), 7.28-7.24 (m, 24H, H^{Ar}), 7.10 – 6.70 (m. 8H, H^{Ar}), 5.69 – 5.44 (m, 2H, =C*H*), 4.95-4.85 (m, 4H, =CH_2), 4.59 – 4.52 (m, 4H, Cp*H*), 4.49 – 4.42 (m, 2H, Cp*H*), 4.39 – 4.34 (m, 2H Cp*H*), 4.18 (dd, *J* = 14.1, 7.6 Hz, 1H, CH_2), 3.91 (t, *J* = 9.7 Hz, 2H, CH_2), 3.83 (d, *J* = 15.7 Hz, 1H, CH_2), 3.75 (t, *J* = 7.9 Hz, 1H, C*H*), 3.56 – 3.52 (m, 1H, C*H*), 2.60 – 2.44 (m, 4H, CH_2), 0.85 (d, *J* = 7.0 Hz, 3H, CH_3), 0.79 (d, *J* = 6.9 Hz, 3H, CH_3 - major diastereoisomer).

1,4-Dihydroisoquinolin-3(2H)-one 10 by allyl deprotection: **3b** (50 mg, 0.27 mmol) was dissolved in MeCN (0.5 mL) and to this added $Pd(OCOCF_3)_2$ (1 mg, 1 mol%), DPPP (1 mg, 1 mol%) and H_2O (97 μL). The reaction mixture was heated to 80 °C for 18 hours. After cooling it was diluted with EtOAc (5 mL) and washed with satd. sodium bicarb. solution (2 x 5 mL) and brine (2 x 5 mL). The organic layer was dried ($MgSO_4$), filtered, the solvent removed *in vacuo*, and the residue purified by column chromatography (4:1 CH_2Cl_2:EtOAc to remove impurities before flushing with eluent containing an additional 10% MeOH to give **10** a brown solid (13 mg, 33%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.22 (m, 2H, H^{Ar}), 7.20 – 7.14 (m, 2H, H^{Ar}), 7.01 (s, br, 1H, N*H*), 4.50 (s, 2H, CH_2), 3.59 (s, 2H, CH_2). The spectral data were consistent with that reported in the literature.[13]

1,4-Dihydroisoquinolin-3(2H)-one 10 by α-ferrocenyl deprotection: 3u (0.011 g, 0.03 mmol) was dissolved in 2:1 formic acid/diethyl ether (0.9 mL) and stirred at room temperature for 24 hours. The solvent was removed and the residue purified by column chromatography (4:1 CH_2Cl_2:EtOAc to remove impurities before flushing with eluent containing an additional 10% MeOH to give **10** a brown solid (4 mg, 86%).

4-Benzyl-1,4-dihydroisoquinolin-3(2H)-one 11a*:* 4ba (98 mg, 0.35 mmol), $Pd(OCOCF_3)_2$ (4.7 mg, 0.014 mmol), DPPP (5.8 mg, 0.014 mmol) and H_2O (0.13 mL, 7 mmol) were suspended in MeCN (1 mL) and then heated with stirring at 80 °C for 18 hours. After cooling the reaction mixture was diluted with EtOAc (20 mL) and washed with saturated sodium bicarbonate solution (20 mL) and brine (~20 mL). The organic layer was passed through an isolute phase separator and the solvent removed *in vacuo* to give an orange oil. The sample was loaded in dichloromethane and purified on Companion 5 NP 6G silica (Si) 12 g using 0-50% ethyl acetate-cyclohexane over 30 mins. The column was flushed with 3:1 EtOAc:EtOH and the solvent removed *in vacuo* to yield 62 mg of a yellow/white material. Attemped recrystallisation from MeOH/pentane gave a precipitate which was filtered and further purifued on the arrays team MDAP (HpH Method B) to give **11a** as a yellow solid (34 mg, 40%). IR (thin film) cm^{-1}: 3182, 3027, 2923, 1667, 1483, 1456, 1415. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 - 7.11 (m, 5H, H^{Ar}), 7.05 - 7.01 (m, 1H, H^{Ar}), 6.87 - 6.82 (m, 3H, H^{Ar}), 4.08 (dd, *J* = 15.7, 4.2 Hz, 1H, CH_2), 3.84 (t, *J* = 6.3 Hz, 1H, C*H*), 3.71 (d, *J* = 15.7 Hz, 1H, CH_2), 3.28 (dd, *J* = 13.1, 6.8 Hz, 1H, CH_2), 3.17 (dd, *J* = 13.0, 4.8 Hz, 1H, CH_2). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 137.2, 134.8, 131.4, 129.7, 128.2, 128.0, 127.2, 126.7, 126.6, 125.1, 48.4, 44.7, 40.8. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{16}N_1O_1$, 238.1232; found, 238.1232.[14]

4-Allyl-1,4-dihydroisoquinolin-3(2H)-one 11e: 4ue (23 mg, 58 μmol) was dissolved in 2:1 formic acid/diethyl ether (0.9 mL) and stirred at room temperature for 24 hours. The solvent was removed and the residue purified by column chromatography (4:1 CH_2Cl_2:EtOAc to remove impurities before flushing with eluent containing an additional 10% MeOH to give **11e** as a brown solid (6 mg, 55%).^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.22 (m, 2H, H^{Ar}), 7.16 (t, *J* = 8.0 Hz, 2H, H^{Ar}), 6.41 (br, s, 1H, N*H*), 5.73 (ddt, *J* = 16.1, 10.9, 7.2 Hz, 1H, C*H*), 5.03 – 4.97 (m, 2H, CH_2), 4.63 (d, *J* = 15.6 Hz, 1H, CH_2), 4.36 (dd, *J* = 15.6, 3.8 Hz, 1H, CH_2), 3.58 (t, *J* = 6.5 Hz, 1H, C*H*), 2.67 – 2.63 (m, 2H, CH_2). ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.0, 135.5, 134.2, 131.0, 128.2, 127.6, 126.9, 125.6, 118.2, 45.2, 38.4, 29.9. HRMS (ESI) *m/z*: $[M + H]^+$ calcd for $C_{12}H_{14}N_1O_1$, 188.1075; found, 188.1069.

Acknowledgments

We thank the University of East Anglia and GlaxoSmithKline for financial support (studentship for MJOS).

References and notes

1. Holzer, P.; Masuya, K.; Furet, P.; Kallen, J.; Valat-Stachyra, T.; Ferretti, S.; Berghausen, J.; Bouisset-Leonard, M.; Buschmann, N.; Pissot-Soldermann, C.; Rynn, C.; Ruetz, S.; Stutz, S.; Chène, P.; Jeay, S.; Gessier, F. *J. Med. Chem.* **2015**, *58*, 6348-6358.
2. Finkelstein, J.; Brossi, A. *J. Heterocycl. Chem.* **1967**, *4*, 315-318.
3. (a) Menachery, M. D.; Lavanier, G. L.; Wetherly, M. L.; Guinaudeau, H.; Shamma, M. *J. Nat. Prod*. **1986**, 49, 745-778. (b) Scott, J. D.; Williams, R. M. *Chem. Rev*. **2002**, *102*, 1669-1730. (c) Chrzanowska, M.; Rozwadowska, M. D. *Chem. Rev*. **2004**, *104*, 3341-3370.
4. (a) Shvo, Y.; Taylor, E. C.; Mislow, K.; Raban, M. *J. Am. Chem. Soc*. **1967**, *89*, 4910-4917. (b) Kamochi, Y.; Watanabe, Y. *Hetereocycles* **1987**, *26*, 2385-2391. (c) Suzuki, H.; Abe, H.; Thiruvikraman, S. V. *J. Org. Chem*. **1994**, *59*, 6116-6118. (d) Koltunov, K. Y.; Prakash, G. K. S.; Rasul, G.; Olah, G. A. *J. Org. Chem*. **2002**, *67*, 8943-8951. (e) Dolle, R. E.; MacLeod, C.; Martinez-Teipel, B.; Barker, W.; Seida, P. R.; Herbertz, T. *Angew. Chem. Int. Ed*. **2005**, *44*, 5830-5833. (f) Kim, K.; Hong, S. H. *J. Org. Chem*. **2015**, *80*, 4152-4156. (g) Padmanaban, M.; Carvalho, L. C. R.; Petkova, D.; Lee, J.-W.; Santos, A. S.; Marques, M. M. B.; Maulide, N. *Tetrahedron* **2015**, *71*, 5994-6005. (h) Hu, Y.; Shen, Z.; Huang, H. *ACS Catal*. **2016**, *6*, 6785-6789. (i) Kaiser, D.; de la Torre, A.; Shaaban, S.; Maulide, N. *Angew. Chem. Int. Ed*. **2017**, *56*, 5921-5925. (j) Huang, Y.; Yi, W.; Sun, Q. ; Zhang, L.; Yi, F. *RSC Adv*. **2018**, *8*, 74-79. (k) Li, Z.; Chen, J.; Wu. L.; Lu, A. R. P.; Wang, Y. *Org. Lett*. **2020**, *22*, 26-30.
5. 1-Substituted examples: (a) Kurihara, K.; Yamamoto, Y.; Miyaura, N. *Adv. Synth. Catal*. **2009**, *351*, 260-270. (b) Amat, M.; Elias, V.; Llor, N.; Subrizi, F.; Molins, E.; Bosch, J. *Eur. J. Org. Chem*. **2010**, 4017-4026. (c) Zhou, W.; Zhang, Y.-X.; Nie, X.-D.; Si, C.-M.; Sun, X.; Wei, B.G. *J. Org. Chem*. **2018**, *83*, 9879-9889. 4-Substituted examples: (d) Hong, S. K.; Park, W.; Park, Y. S. *Tetrahedron* **2020**, *76*, 130841.
6. Kowalkowska, A. ; Jończyk, A. *Synth. Commun*. **2011**, *41*, 3308-3317.
7. Vicennati, P.; Cozzi, P. G. *Eur. J. Org. Chem*. **2007**, 2248-2253.
8. Arthurs, R. A.; Horton, P. N.; Coles, S. J.; Richards, C. J. *Chem. Eur. J*. **2018**, *24*, 4310-4319.
9. Ohmura, N.; Nakamura, A.; Hamasaki, A.; Tokunaga, M. *Eur. J. Org. Chem*. **2008**, 5042–5045.
10. Goodman, H.; Mei, L.; Gianetti, M. *Front. Chem*. **2019**, *7*, 365.
11. Hatano, M.; Suzuki, S.; Ishihara, K. *J. Am. Chem. Soc*. **2006**, *128*, 9998–9999.
12. Bouaucheau, C.; Parlier, A.; Rudler, H. *J. Org. Chem.* **1997**, *62*, 7247-7259.
13. Tamura, Y.; Uenishi, J.; Maeda, H.; Choi, H.; Ishibashi, H. *Synthesis* **1981**, 534-537.
14. Bowman, W. R.; Heaney, H.; Jordan, B. M. *Tetrahedron Lett*. **1988**, *29*, 6657-6660.

Supplementary Material

Copies of the ^{1}H and ^{13}C NMR spectra for the compounds reported.

Declaration of interests

☐The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

C. J. Richards reports financial support was provided by University of East Anglia.