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Selective Synthesis of Isoquinolin-3-one Derivatives Combining Pd-Catalysed Aromatic Alkylation/Vinylation with Addition Reactions: The Beneficial Effect of Water

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The three-component, palladium/norbornene-catalysed reaction of **1**, haloamides **2** and properly substituted olefins **3** performed in DMF/water at 80 °C selectively gave **5** and **6** through three- and four-bond-forming reactions, respectively. The presence of water was crucial to obtain products in fair to good yields.

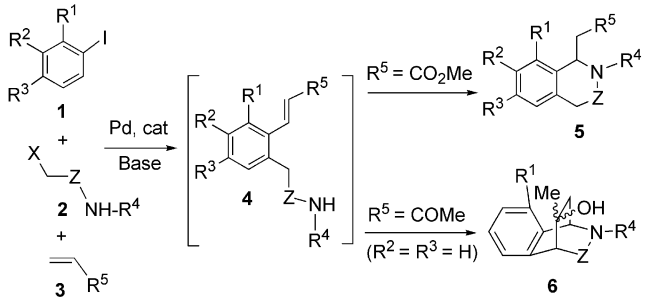
Introduction

The rapid creation of molecular complexity in a regio- and stereodefined manner from simple substrates, combining economical and environmental aspects, represents a great challenge in modern organic chemistry.[1] In this field, multicomponent reactions (MCRs) involving a metal – in particular palladium-catalysed sequential processes – have emerged as powerful tools in diversity-oriented synthesis.[2] They have found multiple applications in the discovery of new bioactive small molecules. Of special interest are heterocyclic compounds containing a ring system found in natural products and drug-like molecules.[3]

As recently reported in the literature, a three-component reaction combining the Catellani reaction[4] and aza-Michael addition led to tetrahydroisoquinoline derivatives **5** (Z = CH_2, CH-alkyl; R^4 = Cbz) in a single synthetic operation producing three sequential bonds (Scheme 1).[5] The reaction of *o*-iodotoluene **1**, **2**-Br and olefin **3** in the presence of $Pd(OAc)_2$/2-trifurylphosphane (TFP) and norbornene as catalysts, Cs_2CO_3 as a base, and in DMF at 80 °C gave **4** as the intermediate, which subsequently underwent an intramolecular aza-Michael addition under the reaction conditions.

Considering the great interest in the 1,2,3,4-tetrahydroisoquinoline nucleus as the structural motif of many alkaloids, we further explored the potential of this reaction, which provides a straightforward entry to the heterocyclic ring commonly synthesised through Pictet–Spengler-type cyclisations.[6]

Here, we evaluated the use of readily accessible haloamides **2** [Z = CO; X = Br, Cl; R^4 = H, PMB, Ph, (±)-α-methylbenzyl, allyl] as the starting alkyl halides in the MCR outlined in Scheme 1. Interestingly, the reaction could selectively lead to structurally diverse isoquinolin-3-ones **5** and **6**. Such compounds are attractive synthetic targets both as precursors and analogues of bioactive compounds.[7]



Scheme 1. Proposed synthesis of isoquinolinones **5** and **6** (Z = CO).

Results and Discussion

We initially found that the reaction of *o*-iodotoluene **1**, haloamides **2** and alkenes **3** under the above-mentioned conditions gave quite a complex mixture, which included no trace of the expected product. An NMR analysis of the crude mixture[8] showed that it mainly consisted of byproducts deriving from undesired transformations of **2**, which was rapidly consumed under the reaction conditions (ca. 20 min at 80 °C by TLC analysis). Control experiments proved that byproduct formation took place in the presence of base. Amides bearing a leaving-group (X) in the α position can undergo base-promoted self-condensation reactions.[9]

We then examined the model reaction of **1** (R^1 = Me), **2**-Cl (R^4 = PMB) and **3** (R^5 = CO_2Me) using different bases and solvents (Table 1).[10]

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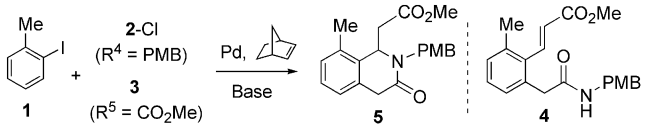
Table 1. Optimisation of reaction conditions.[a]



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Entry	Solvent	Base	Time [h]	**5**/**4**[b]	% Isolated yield
1	DMF	Cs_2CO_3	6	–	–[c]
2	DMF	K_2CO_3	10	100:0	25
3	DMF	$KHCO_3$	10	–	–[c]
4	DMF	K_2HPO_4	18	0:100	15[d]
5	DMF	K_3PO_4	10	traces/–	traces
6	MeCN	Cs_2CO_3	6	–	–[c]
7	DME	Cs_2CO_3	6	100:0	26
8	1,4-dioxane	Cs_2CO_3	22	73:27	44
9	THF	Cs_2CO_3	10	100:0	43
10	DMF/water	Cs_2CO_3	6	100:0	62[e]
11	DMF/water	Cs_2CO_3	6	100:0	76[f]
12	DMF/water	Cs_2CO_3	12	72:28	45[g]
13	DMF/water	K_2CO_3	23	100:0	70[f]
14	DMF/water	K_3PO_4	23	20:80	47[f]
15	MeCN/water	Cs_2CO_3	22	100:0	32[f]
16	THF/water	Cs_2CO_3	26	24:76	46[f]

[a] Conditions: **1** (1 equiv., 0.05 M), **2** (2 equiv.), **3** (2 equiv.), $Pd(OAc)_2$ (10 mol-%), TFP (20 mol-%), norbornene (2.2 equiv.), base (2 equiv.), 80 °C. [b] ^1H NMR analysis of the crude. [c] No trace of **5** was observed. [d] 3 equiv. of K_2HPO_4 were used. [e] 5% water (v/v). [f] 10% water (v/v). [g] 20% water (v/v).

The reaction performed in the presence of K_2CO_3 or K_2HPO_4 gave 25% of **5** and 15% of **4**, respectively (Table 1, Entries 2 and 4). We observed no product or just traces of it with $KHCO_3$ and K_3PO_4 (Table 1, Entries 3 and 5). Carrying out the reaction in less coordinating solvents such as DME, THF and 1,4-dioxane with Cs_2CO_3[11] led to **5** in 26–44% yield (Table 1, Entries 7–9). The reaction in MeCN did not give the expected product (Table 1, Entry 6).

We achieved a significant improvement when we carried out the reaction in a homogeneous solution of DMF and 10% (v/v) water in the presence of Cs_2CO_3 or K_2CO_3. Unexpectedly, under these conditions, we isolated **5** in 76–70% yield (Table 1, Entries 11 and 13).[12,13] Also, the overall reaction yield improved with K_3PO_4 in the presence of water (47%), even if the reaction was less selective, affording a mixture of **5** and **4** (**5**/**4**, 20:80, Table 1, Entry 14).

The amount of water added to DMF appeared to be critical for the selectivity of the reaction. As reported above, we obtained the best result using a DMF/water mixture containing 10% (v/v) water. A lower (5%, v/v) and a higher (20%, v/v) water content produced lower yields of product in both cases (Table 1, Entries 10 and 12). In the last one, the base-catalysed conversion of **4** was slower (Table 1, Entry 12).

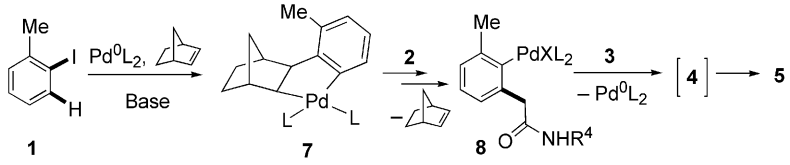
Comparing data obtained in anhydrous and aqueous conditions showed that water exerted a beneficial effect on selectivity when added to polar, coordinating solvents (Table 1, Entries 1, 11, 6 and 15). On the contrary, the overall reaction yields obtained in anhydrous and aqueous THF remained almost unchanged (Table 1, Entries 9 and 16). Under the conditions in the final entry of Table 1, we observed that the base-catalysed conversion to **5** remained incomplete even after prolonged heating.

A few palladium-catalysed transformations (e.g., Heck, Suzuki, and Buchwald–Hartwig reactions) have been reported to proceed more efficiently in aqueous organic solvents than in anhydrous conditions.[14] As previously reported,[5] our reaction occurred through an ordered sequence of steps (Scheme 2, L = TFP): (a) Sequential C–I and C–H bond activation[4,15] of **1** through the formation of palladacycle **7**, (b) $Pd^{II/IV}$-catalysed aromatic alkylation, followed by norbornene expulsion leading to Pd^{II} complex **8**, (c) Vinylation of **8** to give the intermediate **4**, thus completing the catalytic cycle and (d) Intramolecular aza-Michael addition delivering **5**.

While the base-promoted cyclisation of **4** proved to be slower in aqueous DMF (water = 10%, v/v),[16] we verified that palladium-catalysed aromatic alkylation/vinylation occurred rapidly under the same conditions. After heating at 80 °C for 10 min, the reaction gave **4** in 49% yield, and we recovered the unreacted **2**-Cl in 37% yield. In addition to a stabilising effect on the substrate, water could exert a positive effect on the rate of the catalytic cycle (rate acceleration of the terminating Heck reaction[14a] or catalyst activation[14]).

We used optimised conditions (Table 1, entries 11 and 13) to study the scope of the reaction with respect to haloamides, *o*-substituted iodoarenes and olefins. We obtained the best results, in terms of selectivity, by carrying out the reactions in the presence of Cs_2CO_3 (Table 2).

The reaction of *o*-iodotoluene, methyl acrylate and primary or secondary amides **2** (X = Br, Cl) bearing aliphatic and aromatic substituents, afforded **5** in fair to good yields. When we used less reactive **2**-Cl (Table 2, entries 1–5), we obtained at least two-fold higher yields than those with the corresponding **2**-Br (Table 2, entries 2–5). We rationalised these results in terms of different substrate stability. Under the reaction conditions, **2**-Br derivatives could undergo decomposition faster, a bromine atom being recognised as a better leaving group than a chlorine. The use of a chiral



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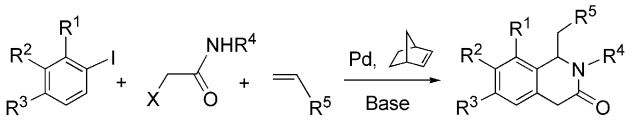
Scheme 2. Proposed reaction mechanism.

Table 2. Scope of the reaction leading to **5**.[a]



1 **2** **3** **5**

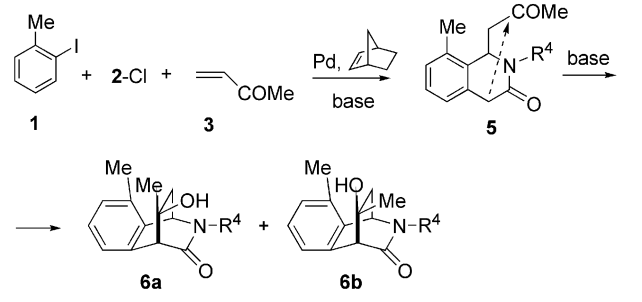
Entry	R^1	R^2	R^3	X	R^4	R^5	% Yield of **5**[b]
1	Me	H	H	Cl	H	CO_2Me	46
2	Me	H	H	Cl(Br)	PMB	CO_2Me	76(35)
3	Me	H	H	Cl(Br)	Ph	CO_2Me	52(18)
4	Me	H	H	Cl(Br)	(±)-α-methylbenzyl	CO_2Me	73(36)[c]
5	Me	H	H	Cl(Br)	allyl	CO_2Me	32(16)
6	MeO	H	H	Cl	PMB	CO_2Me	62
7	2,3-benzo		H	Cl	PMB	CO_2Me	64[d]
8	Me	H	Me	Cl	PMB	CO_2Me	60
9	Me	H	H	Cl	PMB	CN	58
10	Me	H	H	Cl	PMB	COMe	–[e]

[a] Conditions: **1** (1 equiv., 0.05 M), **2** (2 equiv.), **3**, (2 equiv.), $Pd(OAc)_2$ (10 mol-%), TFP (20 mol-%), norbornene (2.2 equiv.), Cs_2CO_3 (2 equiv.), DMF/water (water = 10% v/v), 80 °C, 6 h; PMB = 4-$MeOC_6H_4CH_2$. [b] Isolated yields. [c] 12 h; *dr* = 70:30 (^{1}H NMR analysis of the crude). [d] 4 equiv. of norbornene were used. [e] No trace of **5** was observed in the crude (NMR analysis).

amide containing the (±)-phenylethylamine unit gave a mixture (ca. 70:30) of two diastereomers (Table 2, Entry 4). With R^4 = allyl, we obtained **5** in only moderate yield; the decomposition of **2** was a competing side reaction (Table 2, Entry 5).

We found a good tolerance towards a variety of electron-rich iodoarenes (Table 2, entries 2 and 6–8), while we observed low selectivity (less than 20% yield) with iodoarenes *ortho*-substituted by electron-withdrawing groups (e.g., CF_3, Cl).

Surprisingly, we observed a change in product selectivity upon varying the substituent (R^5) of olefin **3**. As shown in Table 2, the use of methyl acrylate or acrylonitrile (Table 2, Entry 9) as the Heck acceptor gave the corresponding isoquinolin-3-one derivative, whereas we observed no trace of **5** using methyl vinyl ketone (Table 2, Entry 10). The reaction of **1**, secondary **2**-Cl and **3** (R^5 = COMe) delivered diastereomeric mixtures of 1,4-ethanoisoquinolin-3-ones **6** (Scheme 3, Table 3, entries 1–3). This reaction generates four new bonds and two new rings in a single operation, giving access to an interesting class of bridged heterocycles.[7c–7d]



Scheme 3. Synthesis of 1,4-ethanoisoquinolin-3-ones **6**.

Table 3. Scope of the reaction leading to **6** with respect to chloroamides **2**.[a]

Entry	R^4	% Yield of **5**	% Yield of **6**[c]	*dr*[b]
1	PMB	–[d]	55	65:35
2	Ph	–[d]	61	70:30
3	(±)-α-methylbenzyl	–[d]	53	53:27:12:8
4	H	50	traces	–

[a] Conditions: **1** (1 equiv., 0.05 M), **2** (2 equiv.), **3**, (2 equiv.), $Pd(OAc)_2$ (10 mol-%), TFP (20 mol-%), norbornene (2.2 equiv.), Cs_2CO_3 (2 equiv.), DMF/water (10% water, v/v), 80 °C, 4 h. [b] ^{1}H NMR analysis of the crude. [c] Isolated yields. [d] No evidence of the formation of **5** (NMR analysis of the crude).

The reaction likely proceeded through the same mechanism as that which led to **5**. Subsequently, a base-catalysed, intramolecular addition of the C-4 to C-1 substituent occurred, generating the fourth C–C bond and the second ring (Scheme 3). Apparently, the COMe group possessed the requisite properties to favour the cyclisation from the electronic and steric point of view.

The use of a primary amide appeared to prevent the formation of **6**. The reaction with chloroacetamide led to **5** (R^4 = H) as the almost exclusive product (Table 3, Entry 4), as the corresponding aza-anion was stable under the reaction conditions.

We confirmed the structure assigned (by NMR analysis) to the major diastereomer by the X-ray analysis of **6a** (R^4 = PMB, Figure 1).

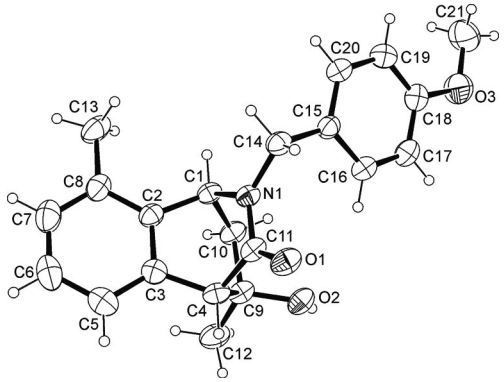


Figure 1. ORTEP plot of **6a** (R^4 = PMB) with atom-numbering scheme. Displacement ellipsoids are drawn at the 30% probability.

Conclusions

Structurally different isoquinolinon-3-ones were selectively obtained through the three-component, palladium/norbornene-catalysed reaction of **1**, **2** (Z = CO) and **3**. Interestingly, using haloamides as the starting halides allowed us to incorporate functionality that promoted in situ, sequential cyclisations, leading to products with increased molecular complexity. We found an important beneficial ef-

fect of water as co-solvent, which led to the development of conditions for successfully performing the reaction.

Experimental Section

General: The palladium-catalysed reactions were performed under nitrogen using standard Schlenk and vacuum line techniques. ^{1}H and ^{13}C NMR spectra were recorded at room temperature in $CDCl_3$ with a 300-AMX spectrometer at 300 and 75 MHz, respectively. Chemical shifts are reported in ppm. High-resolution mass spectra were obtained with an FT-ICR mass spectrometer. Infrared spectra were recorded with an FT-IR spectrophotometer. Melting points are uncorrected.

General Procedure for the Synthesis of Tetrahydroisoquinolin-3-ones (5) and 1,4-Dihydro-1,4-ethanoisoquinolin-3(2*H*)-ones (6): A Schlenk-type flask was charged under nitrogen with Cs_2CO_3 (108.0 mg, 0.33 mmol), $Pd(OAc)_2$ (3.6 mg, 0.0165 mmol), TFP (7.7 mg, 0.033 mmol) and norbornene (34.0 mg, 0.36 mmol) in DMF (1.0 mL). The mixture was stirred at room temp. for 10 min and then treated with **2** (0.33 mmol), **1** (0.165 mmol), **3** (0.33 mmol), DMF (1.97 mL) and water (0.33 mL). The homogeneous solution was heated at 80 °C whilst stirring for the time reported (Table 2 and Table 3) and then cooled to room temp. Saturated aqueous nBu$_4$NCl (40 mL) was added, the mixture was extracted with AcOEt (2 × 20 mL), the combined organic phases were dried (Na_2SO_4), and the solvent was evaporated under vacuum. The residue was purified by flash chromatography on silica gel (eluent: hexane/AcOEt). The isolated **6** [31 mg, 55%, R^4 = PMB; 29.5 mg, 61%, R^4 = Ph; 28 mg, 53%, R^4 = (*rac*)-α-methylbenzyl] turned out to be mixtures of diastereomers (by NMR analysis). In the case of R^4 = PMB or Ph, the major one (**6a**) could be isolated as a diastereomerically pure compound by crystallisation (AcOEt).

Methyl (8-Methyl-3-oxo-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (5, R^1 = Me; R^2 = R^3 = R^4 = H; R^5 = CO_2Me): 18 mg, 46% as a white solid, m.p. 140–141 °C (AcOEt). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 2.35 (s, 3 H), 2.60–2.73 (m, 2 H), 3.57 (d, J = 19.5 Hz, 1 H), 3.65 (d, J = 19.5 Hz, 1 H), 3.79 (s, 3 H), 5.04 (m, 1 H), 6.06 (br. s, 1 H), 7.05 (d, J = 7.4 Hz, 1 H), 7.12 (d, J = 7.2 Hz, 1 H), 7.23 (t, J = 7.5 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 18.6, 36.5, 40.3, 50.3, 52.1, 126.2, 128.1, 129.1, 131.9, 133.2, 171.1, 171.3 ppm. IR (nujol): $\tilde{\nu}$ = 3182, 2926, 1731, 1676 cm^{-1}. HRMS (ESI): m/z [M + Na]$^+$ calcd. for $C_{13}H_{15}NNaO_3$: 256.09441; found 256.09472.

Methyl [2-(4-Methoxybenzyl)-8-methyl-3-oxo-1,2,3,4-tetrahydroisoquinolin-1-yl]acetate (5, R^1 = Me; R^2 = R^3 = H; R^4 = PMB; R^5 = CO_2Me): 44 mg, 76%; pale yellow, viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 2.04 (s, 3 H), 2.52 (dd, J = 15.3, 4.5 Hz, 1 H), 2.73 (dd, J = 15.3, 9.0 Hz, 1 H), 3.59–3.76 (m, 2 H overlapped with two singlets at δ = 3.68 and 3.74), 3.68 (s, 3 H), 3.74 (s, 3 H), 3.98 (d, J = 12.0 Hz, 1 H), 5.04 (dd, J = 4.5, 9.0 Hz, 1 H), 5.42 (d, J = 12.0 Hz, 1 H), 6.77 (d, J = 8.7 Hz, 2 H), 6.99 (t, J = 6.9 Hz, 2 H), 7.07–7.15 (m, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 18.3, 38.0, 39.0, 48.0, 52.1, 53.6, 55.2, 114.0, 125.5, 127.8, 128.7, 128.7, 129.3, 132.4, 132.5, 134.3, 159.0, 169.8, 171.2 ppm. IR (neat): $\tilde{\nu}$ = 2994, 2952, 2838, 1733, 1658, 1513 cm^{-1}. HRMS (ESI): m/z [M + Na]$^+$ calcd. for $C_{21}H_{23}NNaO_4$: 376.15193; found 376.15228.

Methyl (8-Methyl-3-oxo-2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)acetate (5, R^1 = Me; R^2 = R^3 = H; R^4 = Ph; R^5 = CO_2Me): 27.5 mg, 54%; yellow, viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 2.43 (s, 3 H), 2.70 (dd, J = 14.7, 4.2 Hz, 1 H), 2.90 (dd, J = 14.7, 8.7 Hz, 1 H), 3.43 (s, 3 H), 3.75 (d, J = 18.9 Hz, 1 H), 3.95 (d, J = 18.9 Hz, 1 H), 5.56 (dd, J = 8.7, 4.2 Hz, 1 H), 7.11–7.49 (m, 8 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 18.6, 38.3, 39.5, 51.7, 60.1, 125.7, 127.3, 128.2, 129.0, 129.2, 132.5, 132.8, 133.4, 141.5, 169.1, 170.2 ppm. IR (neat): $\tilde{\nu}$ = 2951, 2924, 2852, 1733, 1667, 1599 cm^{-1}. HRMS (ESI): m/z [M + Na]$^+$ calcd. for $C_{19}H_{19}NNaO_3$: 332.12571; found 332.12547.

***rac*-Methyl [8-Methyl-3-oxo-2-(1-phenylethyl)-1,2,3,4-tetrahydroisoquinolin-1-yl]acetate [5, R^1 = Me; R^2 = R^3 = H; R^4 = (*rac*) α-Methylbenzyl; R^5 = CO_2Me, major diastereomer]:** 41 mg, 73%; pale yellow, viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.72 (d, J = 7.5 Hz, 3 H), 1.74 (s, 3 H), 2.71 (dd, J = 15.0, 7.5 Hz, 1 H), 2.87 (d, J = 15.0, 5.1 Hz, 1 H), 3.64 (s, 3 H), 3.64–3.84 (m, 2 H), 4.87 (dd, J = 7.5, 5.1 Hz, 1 H), 6.04 (quartet, J = 7.5 Hz, 1 H), 6.90–7.29 (m, 8 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 16.9, 17.8, 39.0, 41.1, 50.4, 51.7, 51.8, 125.4, 127.3, 127.4, 127.6, 128.4, 128.5, 132.5, 135.8, 139.7, 170.3, 170.9 ppm. IR (neat): $\tilde{\nu}$ = 2950, 1734, 1656, 1538 cm^{-1}. HRMS (ESI): m/z. [M + Na]$^+$ calcd. for $C_{21}H_{23}NNaO_3$: 360.15701; found 360.15744.

Methyl [2-Allyl-8-methyl-3-oxo-1,2,3,4-tetrahydroisoquinolin-1-yl]-acetate (5, R^1 = Me; R^2 = R^3 = H; R^4 = Allyl; R^5 = CO_2Me): 14 mg, 32%; colourless oil. ^{1}H NMR ($CDCl_3$, 25 °C): δ = 2.35 (s, 3 H), 2.62 (dd, J = 15.0, 4.2 Hz, 1 H), 2.79 (dd, J = 15.0, 8.7 Hz, 1 H), 3.58–3.8 (m, 3 H overlapped with a singlet at δ = 3.74), 3.74 (s, 3 H), 4.79–4.86 (m, 1 H), 5.10–5.18 (m, 3 H), 5.68–5.80 (m, 1 H), 7.04–7.23 (m, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 18.5, 37.9, 39.2, 48.1, 52.1, 54.5, 117.3, 125.6, 127.9, 128.9, 132.5, 132.6, 132.8, 134.2, 169.6, 171.1 ppm. IR (neat): $\tilde{\nu}$ = 2947, 2926, 1735, 1659, 1599 cm^{-1}. HRMS (ESI): m/z [M + Na]$^+$ calcd. for $C_{16}H_{19}NNaO_3$: 296.12571; found 296.12587.

Methyl [8-Methoxy-2-(4-methoxybenzyl)-3-oxo-1,2,3,4-tetrahydroisoquinolin-1-yl]acetate (5, R^1 = MeO; R^2 = R^3 = H; R^4 = PMB; R^5 = CO_2Me): 38 mg, 62%; yellow, viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 2.69 (dd, J = 14.4, 5.6 Hz, 1 H), 2.78 (dd, J = 14.5, 5.6 Hz, 1 H), 3.65 (s, 3 H), 3.67 (d, J = 19.0 Hz, 1 H), 3.76–3.82 (m, 1 H), 3.77 (s, 3 H), 3.79 (s, 3 H), 4.20 (d, J = 14.7 Hz, 1 H), 5.18 (t, J = 5.6 Hz, 1 H), 5.32 (d, J = 14.7 Hz, 1 H), 6.73–6.85 (m, 4 H), 7.19–7.30 (m, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 37.0, 38.6, 47.8, 51.7, 52.4, 55.2, 55.4, 108.3, 113.9, 119.6, 123.1, 128.8, 129.2, 133.8, 154.4, 158.9, 169.4, 170.9 ppm. IR (neat): $\tilde{\nu}$ = 2951, 2838, 1735, 1650, 1600, 1513 cm^{-1}. HRMS (ESI): m/z [M + Na]$^+$ calcd. for $C_{21}H_{23}NNaO_5$: 392.14684; found 392.14769.

Methyl [2-(4-Methoxybenzyl)-3-oxo-1,2,3,4-tetrahydrobenzo[*h*]isoquinolin-1-yl]acetate (5, R^1 = R^2 = benzo; R^3 = H; R^4 = PMB; R^5 = CO_2Me): 41 mg, 64%; colourless, viscous oil. ^{1}H NMR ($CDCl_3$, 25 °C): δ = 2.72 (dd, J = 15.3, 4.6 Hz, 1 H), 2.84 (dd, J = 15.3, 7.3 Hz, 1 H), 3.63 (s, 3 H), 3.72 (s, 3 H), 3.8 (d, J = 19.5 Hz, 1 H), 3.9 (d, J = 19.5 Hz, 1 H), 4.15 (d, J = 14.9 Hz, 1 H), 5.45 (d, J = 14.9 Hz, 1 H), 5.68 (dd, J = 7.3, 4.6 Hz, 1 H), 6.75 (d, J = 8.7 Hz, 2 H), 7.18 (d, J = 8.6 Hz, 2 H), 7.27 (m, 1 H), 7.43–7.51 (m, 2 H), 7.70–7.85 (m, 3 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 37.7, 40.0, 48.1, 52.1, 53.6, 55.2, 114.1, 121.7, 125.6, 125.7, 127.1, 128.3, 128.6, 128.8, 129.0, 129.2, 130.0, 130.2, 132.6 ppm. IR (nujol): $\tilde{\nu}$ = 1732, 1651, 1513 cm^{-1}. HRMS (ESI): m/z [M + Na]$^+$ calcd. for $C_{24}H_{23}NNaO_4$: 412.15193; found 412.15187.

Methyl [2-(4-Methoxybenzyl)-6,8-dimethyl-3-oxo-1,2,3,4-tetrahydroisoquinolin-1-yl]acetate (5, R^1 = R^3 = Me; R^2 = H; R^4 = PMB; R^5 = CO_2Me): 36 mg, 60%; colourless, viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 2.01 (s, 3 H), 2.26 (s, 3 H), 2.52 (dd, J = 15.2, 4.3 Hz, 1 H), 2.72 (dd, J = 15.2, 8.6 Hz, 1 H), 3.59 (d, J = 19.2 Hz,

1 H), 3.69 (s, 3 H), 3.75 (s, 3 H), 3.69–3.75 (m, 1 H overlapped with two singlets at δ = 3.69 and 3.75), 3.97 (d, J = 14.8 Hz, 1 H), 4.99 (dd, J = 8.5, 4.3 Hz, 1 H), 5.42 (d, J = 14.8 Hz, 1 H), 6.78 (d, J = 8.2 Hz, 2 H), 6.80 (s, 1 H), 6.82 (s, 1 H), 7.09 (d, J = 8.2 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 18.2, 20.9, 37.9, 39.1, 47.9, 52.0, 53.5, 55.2, 113.9, 126.1, 128.8, 129.2, 129.5, 131.3, 132.3, 137.5, 158.9, 169.9, 171.2 ppm. IR (nujol): $\tilde{\nu}$ = 1733, 1656, 1614 cm^{-1}. HRMS (ESI): m/z [M + Na]$^+$ calcd. for $C_{22}H_{25}NNaO_4$: 390.16758; found 390.16736.

[2-(4-Methoxybenzyl)-8-methyl-3-oxo-1,2,3,4-tetrahydroisoquinolin-1-yl]acetonitrile (5, R^1 = Me; R^2 = R^3 = H; R^4 = PMB, R^5 = CN): 31 mg, 58%; pale yellow, viscous oil. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 2.18 (s, 3 H), 2.67–2.69 (m, 2 H), 3.73 (d, J = 19.4 Hz, 1 H), 3.83 (s, 3 H), 3.98 (d, J = 19.4 Hz, 1 H), 4.45 (d, J = 15.0 Hz, 1 H), 4.87 (t, J = 6.0 Hz, 1 H), 5.33 (d, J = 15.0 Hz, 1 H), 6.88 (d, J = 8.5 Hz, 2 H), 7.10 (d, J = 7.6 Hz, 2 H), 7.20 (d, J = 8.5 Hz, 2 H), 7.26 (t, J = 7.6 Hz, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 18.6, 22.5, 37.6, 48.3, 53.5, 55.2, 114.3, 116.9, 126.1, 128.1, 128.7, 129.2, 129.3, 131.4, 132.6, 132.9, 159.3, 169.4 ppm. IR (neat): $\tilde{\nu}$ = 2952, 2932, 2837, 2248, 1731, 1658, 1613 cm^{-1}. HRMS (ESI): m/z [M + Na]$^+$ calcd. for $C_{20}H_{20}N_2NaO_2$: 343.14170; found 343.14210.

***rac*-(1*R**,4*R**,9*S**)-1,4-Dihydro-9-hydroxy-2-(4-methoxybenzyl)-8,9-dimethyl-1,4-ethanoisoquinolin-3(2*H*)-one (6a, R^1 = Me; R^2 = R^3 = H; R^4 = PMB):** Major diastereomer; white solid, m.p. 202–203 °C (AcOEt). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.17 (s, 3 H), 1.55 (dd, J = 13.2, 1.5 Hz, 1 H), 1.96 (s, 3 H), 2.23 (dd, J = 13.2, 3.6 Hz, 1 H), 3.23 (br. s, 1 H), 3.81 (s, 3 H), 3.92 (s, 1 H), 4.44 (d, J = 14.8 Hz, 1 H), 4.64 (dd, J = 3.6, 1.5 Hz, 1 H), 4.80 (d, J = 14.8 Hz, 1 H), 6.83 (d, J = 8.3 Hz, 2 H), 6.96 (d, J = 7.4 Hz, 1 H), 7.05 (d, J = 8.4 Hz, 2 H), 7.08–7.19 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 17.4, 29.1, 43.2, 47.2, 53.5, 55.3, 62.0, 73.3, 113.9, 123.6, 127.1, 128.2, 128.5, 129.5, 129.9, 136.5, 138.0, 159.0, 173.2 ppm. IR (nujol): $\tilde{\nu}$ = 3245, 1644, 1599, 1512 cm^{-1}. HRMS (ESI): m/z [M + Na]$^+$ calcd. for $C_{21}H_{23}NNaO_3$: 360.15701; found 360.15697.

***rac*-(1*R**,4*R**,9*S**)-1,4-Dihydro-9-hydroxy-8,9-dimethyl-2-phenyl-1,4-ethanoisoquinolin-3(2*H*)-one (6a, R^1 = Me; R^2 = R^3 = H; R^4 = Ph):** Major diastereomer; white solid; m.p. 216–217 °C (AcOEt). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.18 (s, 3 H), 1.72 (dd, J = 13.9, 1.0 Hz, 1 H), 2.39 (s, 3 H), 2.49 (dd, J = 13.9, 3.9 Hz, 1 H), 3.96 (s, 1 H), 4.35 (br. s, 1 H), 5.26 (m, 1 H), 7.03–7.22 (m, 4 H), 7.28–7.36 (m, 4 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 18.0, 29.2, 43.6, 58.5, 62.6, 73.0, 124.0, 124.4, 126.2, 127.6, 128.8, 129.1, 130.0, 136.4, 137.4, 140.2, 172.4 ppm. IR (nujol): $\tilde{\nu}$ = 3304, 1660, 1594 cm^{-1}. HRMS (ESI): m/z [M + Na]$^+$ calcd. for $C_{19}H_{19}NNaO_2$: 316.13080; found 316.13066.

***rac*-1,4-Dihydro-9-hydroxy-8,9-dimethyl-2-(1-phenylethyl)-1,4-ethanoisoquinolin-3(2*H*)-one [6, R^1 = Me; R^2 = R^3 = H; R^4 = (*rac*)-α-methylbenzyl]:** 1:1 Mixture of the two major diastereomers; white solid. ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.17 (s, 3 H), 1.54 (s, 6 H), 1.57–1.61 (m, 2 H overlapped with a singlet at δ = 1.63), 1.63 (s, 3 H), 1.64 (d, J = 6.9 Hz, 3 H), 1.74 (d, J = 6.9 Hz, 3 H), 2.18–2.25 (m, 2 H), 2.3–2.8 (br. s, 2 H), 3.85 (s, 1 H), 3.89 (s, 1 H), 4.48–4.50 (m, 1 H), 4.54–4.57 (m, 1 H), 5.73 (quartet, J = 6.9 Hz, 1 H), 5.80 (quartet, J = 6.9 Hz, 1 H), 6.88–6.93 (m, 2 H), 6.99–7.30 (m, 14 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 16.2, 16.5, 16.8, 29.2, 44.6, 46.1, 49.3, 49.5, 49.6, 49.9, 62.3, 72.1, 73.5, 123.4, 124.5, 126.9, 127.2, 127.3, 127.4, 128.1, 128.3, 128.4, 128.5, 130.0, 130.5, 134.8, 136.2, 137.8, 138.1, 139.0, 139.6, 171.1, 172.0 ppm. IR (nujol): $\tilde{\nu}$ = 3400, 3243, 1650, 1600 cm^{-1}. HRMS (ESI): m/z [M + Na]$^+$ calcd. for $C_{21}H_{23}NNaO_2$: 344.16210; found 344.16257.

8-Methyl-1-(2-oxopropyl)-1,4-dihydroisoquinolin-3(2*H*)-one (5, R^1 = Me; R^2 = R^3 = R^4 = H; R^5 = COMe): 18 mg, 50%; white solid; m.p. 177–178 °C (AcOEt). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 2.02 (s, 3 H), 2.10 (s, 3 H), 2.60 (dd, J = 18.6, 2.7 Hz, 1 H), 2.71 (dd, J = 18.6, 10.2 Hz, 1 H), 3.37, (d, J = 18.0 Hz, 1 H), 3.50 (d, J = 18.0 Hz, 1 H), 4.94 (dt, J = 10.5, 3.3 Hz, 1 H), 6.63 (br. s, 1 H), 6.87 (d, J = 7.5 Hz, 1 H), 6.96 (d, J = 7.2 Hz, 1 H), 7.05 (t, J = 7.5 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 25 °C): δ = 18.6, 30.1, 36.2, 49.1, 49.2, 126.0, 127.9, 129.1, 131.6, 132.0, 133.0, 171.2, 206.2 ppm. IR (nujol): $\tilde{\nu}$ = 3323, 3295, 1710, 1677, 1595 cm^{-1}. HRMS (ESI): m/z [M + Na]$^+$ calcd. for $C_{13}H_{15}NNaO_2$: 240.09950; found 240.09969.

General Procedure for the Synthesis of 2: The preparation is modified from a reported procedure.[17] A solution of amine (8.25 mmol) and dry Et_3N (9.05 mmol) dissolved in dry dichloromethane (12 mL) was cooled to –5 °C with an ice bath. Chloroacetyl chloride (or bromoacetyl bromide, 8.25 mmol) dissolved in dichloromethane (3 mL) was added dropwise to the stirred solution, and the temperature was maintained between –2 °C and –5 °C. The reaction mixture was stirred for 30 min at 0 °C and then allowed to return to room temperature and stirred for an additional 30 min. During this time, a precipitate formed in the case of **2** [X = Cl, Br; R^4 = Ph, PMB, (*rac*)-α-methylbenzyl]. The precipitate was then filtered and washed with dichloromethane. The filtrate was washed with HCl (2 N, 1 × 5 mL) and brine (1 × 15 mL). The organic phase was separated and dried (Na_2SO_4), and the solvent was evaporated under vacuum. The solid residue was crystallised from an appropriate solvent. In the case of **2** (X = Cl; R^4 = allyl) an orange oil was obtained, which was used without further purification. Data for **2**-Cl and **2**-Br (R^4 = PMB) are not reported in the literature.

2-Chloro-*N*-phenylacetamide (2-Cl): 1.24 g, 76%; beige solid; m.p. 123–124 °C (lit.[18] 122–125 °C).

2-Bromo-*N*-phenylacetamide (2-Br): 1.09 g, 62%; beige solid; m.p. 130–131 °C (isopropyl ether) (lit.[19] 129–131 °C).

***N*-Allyl-2-chloroacetamide (2-Cl):** 0.90 g, 82%; yellow-orange oil. Spectroscopic data are consistent with those reported in the literature.[20]

***N*-Allyl-2-bromoacetamide (2-Br):** 1.0 g, 69%; white solid; m.p. 28–29 °C (isopropyl ether/hexane) (lit.[17] 27 °C).

***rac*-2-Bromo-*N*-(α-methylbenzyl)acetamide (2-Br):** 1.7 g, 85%; white solid; m.p. 90–91 °C (isopropyl ether). Spectroscopic data are consistent with those reported in the literature.[21]

***rac*-2-Chloro-*N*-(α-methylbenzyl)acetamide (2-Cl):** 1.47 g, 90%; white solid; m.p. 76–77 °C (isopropyl ether). Spectroscopic data are consistent with those reported in the literature.[22]

2-Chloro-*N*-(4-methoxybenzyl)acetamide (2-Cl): 1.42 g, 81%; light brown solid; m.p. 104–105 °C (isopropyl ether). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.74 (s, 3 H), 4.01 (s, 2 H), 4.35 (d, J = 5.5 Hz, 2 H), 6.72 (br. s, 1 H), 6.82 (d, J = 8.5 Hz, 2 H), 7.15 (d, J = 8.5 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 42.5, 43.3, 55.2, 114.2, 129.2, 129.3, 159.2, 165.5 ppm. IR (nujol): $\tilde{\nu}$ = 3281, 1656, 1617 cm^{-1}. $C_{10}H_{12}ClNO_2$ (213.66): calcd. C 56.21, H 5.66, N 6.56; found C 56.30, H 5.77, N 6.54.

2-Bromo-*N*-(4-methoxybenzyl)acetamide (2-Br): 1.51 g, 71%; pale yellow solid; m.p. 120–121 °C (AcOEt). ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 3.84 (s, 3 H), 3.94 (s, 2 H), 4.44 (d, J = 5.5 Hz, 2 H), 6.73 (br. s, 1 H); 6.91 (d, J = 8.4 Hz, 2 H), 7.25 (d, J = 8.4 Hz, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 29.0, 43.6, 55.2,

113.9, 129.0, 129.4, 159.1, 165.3 ppm. IR (nujol): $\tilde{\nu}$ = 3281, 1649, 1613 cm^{-1}. $C_{10}H_{12}BrNO_2$ (258.11): calcd. C 46.53, H 4.69, N 5.43; found C 46.59, H 4.71, N 5.40.

CCDC-718016 contains the supplementary crystallographic data for **6a**, R^4 = PMB. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): Copies of ^1H and ^{13}C spectra for new **2**, **5**, and **6**.

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