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A Transition Metal-Free Minisci Reaction: Acylation of Isoquinolines, Quinolines, and Quinoxaline

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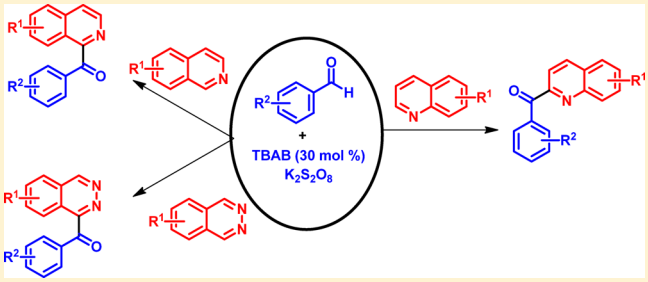
Supporting Information

ABSTRACT: Transition metal-free acylation of isoquinoline, quinoline, and quinoxaline derivatives has been developed employing a cross dehydrogenative coupling (CDC) reaction with aldehydes using substoichiometric amount of TBAB (tetrabutylammonium bromide, 30 mol %) and $K_2S_2O_8$ as an oxidant. This intermolecular acylation of electron-deficient heteroarenes provides an easy access and a novel acylation method of heterocyclic compounds. The application of this CDC strategy for acylation strategy has been illustrated in synthesizing isoquinoline-derived natural products.



INTRODUCTION

Cross dehydrogenative coupling reactions (CDC) for functionalization of organic compounds is a rapidly expanding field as it offers atom economical shorter routes for the synthesis of a variety of useful natural products.[1−3] Metal-free reaction for functionalization of C−H bonds to access C−C and C−heteroatom bonds is a fast emerging area.[2] The acyl derivatives of heterocyclic compounds are present in a variety of drugs that are important in pharmacological studies.[1,2a] Acylation of electron-deficient heteroarenes is a challenging task,[2a−c] whereas acylation of electron-rich arenes is facile.[2d−j] Therefore, synthesis of electron-deficient heteroarenes using atom economical shorter routes is well sought. The Minisci reaction, which provides a facile route to generate radical, offers an alternate method of acylation of heteroarenes.[1a,4] Although the Minisci reaction is useful in coupling nitrogen-containing heterocyclic compounds with aldehydes, it is associated with a few limitations.[5] Recently, Matcha and Antonchick reported a metal-free CDC (cross- dehydrogenative coupling) reaction of heterocycles with aldehydes using $PhI(OCOCF_3)_2$ and $TMSN_3$.[2a] Besides this report, the acylation of electron-deficient heterocyclic compounds was carried out using $FeSO_4$, in the presence of H_2O_2 or TBHP.[2b,c] Shi and Glorius reported intramolecular dehydrogenative arylation of 2-aryl benzaldehydes to obtain fluorenones using quaternary ammonium salts and oxidants.[2j] However, this method[2j] has not been applied to intermolecular version of acylation of heteroarenes, which would provide a novel acylation method of heterocyclic compounds. In this perspective and in continuation of our quest for developing CDC reactions,[6] herein we report a Minisci reaction of coupling aldehydes with heterocycles such as isoquinolines, quinolines, and quinoxaline using TBAB and $K_2S_2O_8$ (Scheme 1).

RESULTS AND DISCUSSION

Optimization Studies. Optimization studies (Table 1) were carried out using 4-phenylisoquinoline (**1a**) and 4-methylbenzaldehyde (**2a**) as model substrates. The solvent screening studies indicated that the solvents such as dioxane, CH_3CN, DMF, toluene, or DMSO are not suited for the reaction (entries 1−5, Table 1), whereas DCE is the most suitable solvent, as the reaction of **1a** with **2a** in the presence of TBAB (30 mol %) and $K_2S_2O_8$ (2 equiv) in DCE furnished **3a** in 81% yield (entry 6, Table 1). Under the similar reaction conditions, TBAI (30 mol %) failed to promote the reaction (entry 7, Table 1). Although the reaction proceeded in the presence of NBS or NCS, the formation of **3a** was not observed with NIS or molecular iodine (entries 8−11, Table 1). The reaction did not proceed with oxidants such as aq TBHP, $(NH_4)_2S_2O_8$, oxone, $NaBO_3$, *m*-CPBA (entries 11−16, Table 1). Decreasing the amount of aldehyde, or TBAB, or oxidant led to lower yield of **3a** (entries 17−21, Table 1). In the absence of TBAB, the reaction yielded **3a** in 20% yield (entry 22, Table 1), whereas the reaction did not proceed in the absence of $K_2S_2O_8$ (entry 23, Table 1). With these screening studies, the optimal condition was established using aldehyde (4 equiv), TBAB (30 mol %), and $K_2S_2O_8$ (2 equiv) in DCE (entry 6, Table 1).[7]

Under optimized reaction conditions, using aldehyde (4 equiv), TBAB (30 mol %), and $K_2S_2O_8$ (2 equiv) in DCE, a variety of isoquinolines were acylated with aromatic or aliphatic aldehydes (Table 2). 4-Phenylisoquinoline (**1a**) underwent a smooth coupling reaction with 4-methoxy benzaldehyde (**2b**), 3,4-dimethoxybenzaldehyde (**2c**), and 4-(benzyloxy)-benzaldehyde (**2d**) to afford the corresponding coupled acylated products **3b**, **3c**, **3d** in good yields (entries 1−3, Table 2). Similarly, aliphatic aldehydes such as 3-methylbutanal (**2e**), butanal (**2f**), and hexanal (**2g**) underwent a smooth reaction with 4-phenylisoquinoline (**1a**) to furnish the coupled products, **3e**, **3f**, and **3g** in good to moderate yields (entries 4−6, Table 2).

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Scheme 1

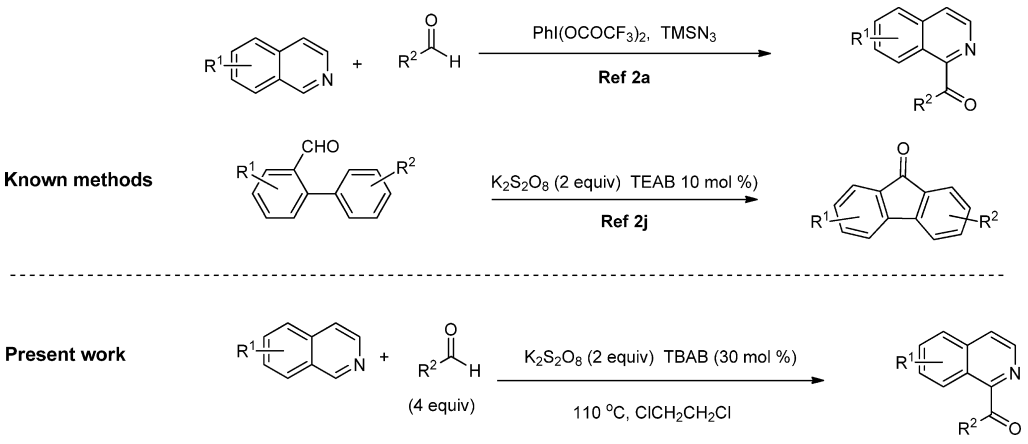
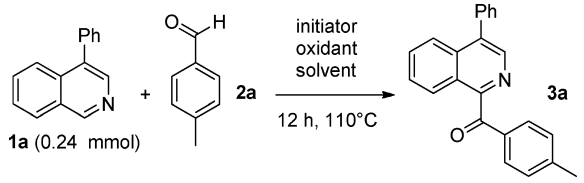


Table 1. Optimization Studies[a]



entry	initiator (mol %)	oxidant (equiv)	solvent	yield (%)[b]
1	TBAB (30)	$K_2S_2O_8$ (2)	dioxane	NR
2	TBAB (30)	$K_2S_2O_8$ (2)	CH_3CN	NR
3	TBAB (30)	$K_2S_2O_8$ (2)	DMF	NR
4	TBAB (30)	$K_2S_2O_8$ (2)	toluene	NR
5	TBAB (30)	$K_2S_2O_8$ (2)	DMSO	NR
6	**TBAB (30)**	**$K_2S_2O_8$ (2)**	**DCE**	**81**
7	TBAI (30)	$K_2S_2O_8$ (2)	DCE	NR
8	NCS (30)	$K_2S_2O_8$ (2)	DCE	63
9	NBS (30)	$K_2S_2O_8$ (2)	DCE	70
10	NIS (30)	$K_2S_2O_8$ (2)	DCE	NR
11	I_2 (30)	aq TBHP (4)	DCE	NR
12	TBAB (30)	aq TBHP (4)	H_2O	NR
13	TBAB (30)	$NH_4S_2O_8$ (2)	DCE	NR
14	TBAB (30)	Oxone (2)	DCE	NR
15	TBAB (30)	$NaBO_3$ (2)	DCE	NR
16	TBAB (30)	*m*-CPBA (2)	DCE	NR
17	TBAB (30)	$K_2S_2O_8$ (2)	DCE	76[c]
18	TBAB (30)	$K_2S_2O_8$ (2)	DCE	55[d]
19	TBAB (20)	$K_2S_2O_8$ (2)	DCE	74
20	TBAB (10)	$K_2S_2O_8$ (2)	DCE	58
21	TBAB (30)	$K_2S_2O_8$ ()	DCE	65
22	none	$K_2S_2O_8$ (2)	DCE	20
23	TBAB (30)	none	DCE	NR

[a]Reaction conditions: **1a** (0.24 mmol), **2a** (0.97 mmol), oxidant (0.49 mmol), initiator (0.073 mmol) in solvent (2.0 mL). [b]Isolated yield. [c]3 equiv of **2a**. [d]2 equiv of **2a**. NR = no reaction, TBAB = tetra-*n*-butylammonium bromide, TBAI = tetra-*n*-butylammonium iodide, NIS = *N*-iodosuccinimide, NBS = *N*-bromosuccinimide, NCS = *N*-chlorosuccinimide.

Further, it was found that the reaction of isoquinoline (**1b**) with 4-methylbenzaldehyde (**2a**) and 4-methoxybenzaldehyde (**2b**) resulted in the formation of coupled products **3h** and **3i** in 55 and 64% yields, respectively (entries 7−8, Table 2). Although isoquinoline (**1b**) reacted well with 3,4-dimethoxybenzaldehyde (**2c**), 2,3,4-trimethoxybenzaldehyde (**2h**), 3,4,5-trimethoxybenzaldehyde (**2i**), and 4-benzyloxybenzaldehyde (**2d**), the corresponding CDC products **3j**, **3k**, **3l**, and **3m** were obtained in moderate to poor yields (entries 9−12, Table 2). Similarly, the reaction of isoquinoline (**1b**) with 4-bromobenzladehyde (**2j**) furnished the coupled product **3n** in 40% yield (entry 12, Table 2), whereas isoquinoline (**1b**) in a reaction with aliphatic aldehydes such as butanal (**2f**) and 3-methylbutanal (**2e**) furnished the coupled products **3o** and **3p** in 52 and 61% yields, respectively (entries 14−15, Table 2). This coupling reaction was found to proceed well with electron rich and sterically unhindered aldehydes such as aliphatic aldehydes. This limitation of obtaining moderate to poor yields could be attributed to decomposition of quinoline and isoquinoline under the reaction conditions.[7]

To expand the scope of this coupling reaction, a variety of isoquinoline derivatives were coupled with a number of aldehydes (Table 3). As can be seen, 4-(4-methoxyphenyl)-isoquinoline (**1c**) underwent coupling under optimal reaction conditions with 4-methylbenzaldehyde (**2a**), 4-methoxybenzaldehyde (**2b**), 3,4-dimethoxybenzaldehyde (**2c**), 3,4,5-trimethoxybenzaldehyde (**2i**), and 4-benzyloxybenzaldehyde (**2d**) to afford the coupled products **3q**, **3r**, **3s**, **3t**, and **3u** in good to moderate yields (entries 1−5, Table 3). Under the optimal conditions, thiophene-2-carbaldehyde (**2k**) also underwent a facile coupling to afford the product **3v** in 41% yield (entry 6, Table 3). To find the generality of this coupling reaction, 4-(4-methoxyphenyl)isoquinoline (**1c**) was further subjected to coupling with aliphatic aldehydes. As can be seen, the coupling of 3-methylbutanal (**2e**) proceeded well to furnish **3w** in 68% yield (entry 7, Table 3). However, the reaction of aldehydes such as butanal (**2f**), hexanal (**2g**), and heptanal (**2l**) with 4-(4-methoxyphenyl)isoquinoline (**1c**) furnished the coupled products **3x**, **3y**, and **3z** in moderate yields (entries 8−10, Table 3). Further, the scope of the strategy has been studied with 5,6,7-trimethoxyisoquinoline (**1d**) as it is an integral part of several bioactive natural products.[1b,c,2a] Therefore, 5,6,7-trimethoxyisoquinoline (**1d**) was reacted with 4-methyl benzaldehyde (**2a**) and 3-methylbutanal (**2e**) to obtain the coupled products **3aa** and **3ab** in moderate yields (46 and 52%, respectively, entries 11−12, Table 3). 4-Bromoisoquinoline (**1e**) was found to react well with 3-methylbutanal (**2e**) to furnish the coupled product **3ac** in good yield (77%, Table 3, entry 13). Under the optimum conditions, quinoxaline (**1f**) found to react with 4-methoxybenzaldehyde (**2b**) and 4-methylbenzaldehyde (**2a**) to furnish the acylated products **4a** and **4b** in 66 and 44% yield, respectively (entries 14−15, Table 3).

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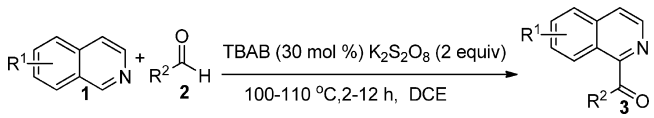
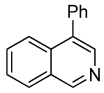
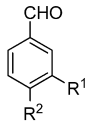
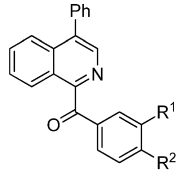
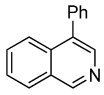
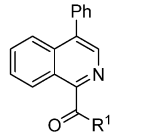
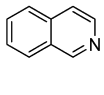
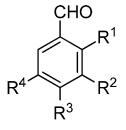
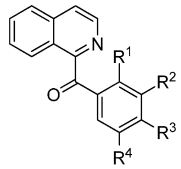
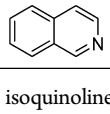
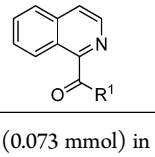
Table 2. Substrate Scope[a,b]



entry	substrates			time (h)	temp (°C)	products		yield (%)
1		1a		**2b**, R^1 = H, R^2 = OMe	12	110		**3b**	78
2		1a		**2c**, R^1 = OMe, R^2 = OMe	12	110		**3c**	70
3		1a		**2d**, R^1 = H, R^2 = OBn	12	110		**3d**	72
4		1a		**2e**: R^1= $CH_2CH(CH_3)_2$	2	100		**3e**	78
5		1a		**2f**: R^1= propyl	2	100		**3f**	60
6		1a	R^1-CHO	**2g**: R^1= pentyl	2	100		**3g**	54
7		1b		**2a**: R^1=R^2= R^4= H, R^3 = Me	12	110		**3h**	55
8		1b		**2b**: R^1= R^2= R^4= H, R^3 = OMe	12	110		**3i**	64
9		1b		**2c**: R^1=R^4= H, R^2 =R^3=OMe	12	110		**3j**	40
10		1b		**2h**: R^1= R^2 =R^3 =OMe, R^4 = H	12	110		**3k**	32
11		1b		**2i**: R^1=H, R^2 =R^3 =R^4=OMe	12	110		**3l**	41
12		1b		**2d**: R^1= R^2 = R^4=H, R^3= OBn	12	110		**3m**	41
13		1b		**2j**: R^1= R^2 = R^4=H, R^3= Br	12	110		**3n**	40
14		1b		**2f**: R^1= propyl	2	100		**3o**	52
15		1b	R^1-CHO	**2e**: R^1= $CH_2CH(CH_3)_2$	2	100		**3p**	61

[a]Reaction conditions: isoquinoline (0.24 mmol), aldehyde (0.97 mmol), $K_2S_2O_8$ (0.49 mmol), TBAB (0.073 mmol) in DCE (2.0 mL). [b]Isolated yield.

The acylation strategy of electron-deficient heterocyclic compounds was further evaluated by reaction of 4-phenylisoquinoline (**1a**) with the secondary and tertiary aldehydes such as cyclohexyl carbaldehyde (**2k**) and pivalaldehyde (**2l**). The reaction of cyclohexyl carbaldehyde (**2k**) with **1a** under the optimal conditions furnished the mixture of alkylated (**6a**) and acylated (**6b**) isoquinoline compounds as an inseparable mixture in a ratio of 23:77 (Scheme 2), whereas the similar reaction of **1a** with pivalaldehyde (**2l**) resulted in the formation of corresponding alkylated derivative of isoquinoline **7**, and the corresponding acylated product was not observed. These two experiments suggest that the stability of acyl radical and alkyl radical is crucial in the formation of prodcuts.[8a]

The application of this CDC strategy for acylation of isoquinoline is illustrated in synthesizing isoquinoline-derived natural products (Scheme 2).[1b−d,2a] As can be seen, 5,6,7-trimethoxyisoquinoline (**1d**) reacted well with 4-methoxybenzaldehyde (**2b**) under optimal reaction conditions to furnish the corresponding acylated product **3ad** in 50% isolated yield. The compound **3ad** (thalimicrinone)[1d,2a] is a natural alkaloid isolated from a *thalictrum* species. Traditionally, thalimicrinone (**3ad**) is synthesized using multistep reaction sequence.[9] Similarly, 6,7-dimethoxyisoquinoline (**1g**) in a CDC reaction with 4-methoxybenzaldehyde (**2b**) furnished the coupled product **3ae** in 29%. Compound **3ae** can be easily reduced to *O*,*O*-dimethylannocherin,[1d,2a] which is another biologically active isoquinoline alkaloid (Scheme 3).

In further demonstration of the utility and applicability of the acylation method, we performed a scaling-up experiment of acylayion of isoquinole (**1b**) with 4-methoxybenzaldehyde (**2b**). As can be seen from Scheme 4, the scaling-up reaction proceeded well to form the corresponding acylated product (**3i**) in 67% yield.

As the coupling reaction of aldehydes was working well with isoquinoline, we thought that it would be relevant to subject quinoline to similar reaction conditions. As can be seen in Scheme 5, quinoline (**1h**) was subjected to the similar coupling reaction with 4-methylbenzaldehyde (**2a**) to find the mixture of 2-acylated as well as 2,4-diacylated products **5a** and **5b** in 69% isolated yields in a ratio of 1.2:1 (Scheme 4). Similarly, 4-benzyloxybenzaldehyde (**2d**) furnished diacylated product **5c** in poor yield (24%). The reaction of quinoline with butanal (**2f**) furnished the mixture of 1-(quinolin-2-yl)butan-1-one **5d** and 1,1′-(quinoline-2,4-diyl)bis(butan-1-one) **5e** in 40% yield in a ratio of 1.2:1 (Scheme 5).

Mechanistic Considerations. On the basis of the literature precedence,[2d,j,10] we believe that the reaction is proceeding through a radical mechanism as shown in Scheme 6. Potassium persulfate ($K_2S_2O_8$) is known to form the sulfate radical **I**. Radical **I** thus generated then undergoes H-abstraction from the aldehyde to form the acyl radical (**II**). Further addition of acyl radical to the heteroarene provides the corresponding amidyl radical **III**. As the α-proton in this amidyl radical is extremely acidic because of the neighboring carbonyl group, deprotonation with the sulfate anion will lead to a radical anion (**IV**), which in turn transfers a single electron (SET) to the persulfate giving the product and radical **I** along with the sulfate anion to sustain the chain.[2d,8b,10b]

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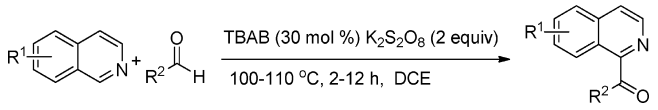
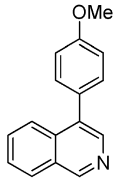
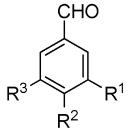
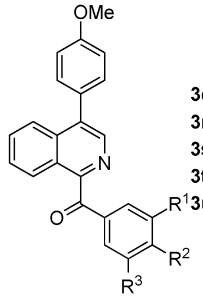
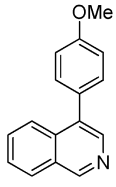
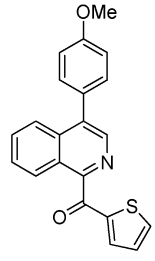
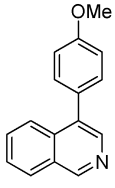
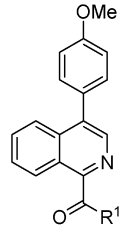
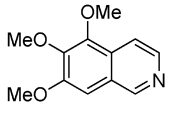
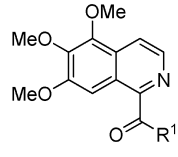
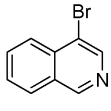
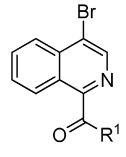
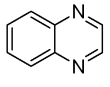
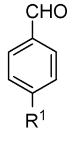
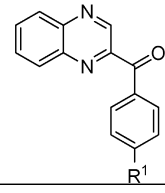
Table 3. Acylation of Isoquinoline Derivatives[a,b]



entry	substrates		time (h)	temp (°C)	products	yield (%)
1	 **1c**	 **2a:** R^1=R^3= H, R^2 = Me	12	110	 **3q**	67
2	**1c**	**2b:** R^1= R^3= H, R^2 = OMe	12	110	**3r**	68
3	**1c**	**2c:** R^1=R^2 =OMe, R^3= H	12	110	**3s**	59
4	**1c**	**2i:** R^1= R^2 =R^3 =OMe	12	110	**3t**	51
5	**1c**	**2d:** R^1=R^3 =H, R^2=OBn	12	110	**3u**	55
6	 **1c**	 **2k**	12	100	 **3v**	41
7	 **1c**	**2e:** R^1= $CH_2CH(CH_3)_2$	2	100	 **3w**	68
8	**1c**	**2f:** R^1= propyl	2	100	**3x**	38
9	**1c**	**2g:** R^1= pentyl	2	100	**3y**	46
10	**1c**	**2l:** R^1= hexyl	2	100	**3z**	42
11	 **1d**	R^1-CHO **2a:** R^1= 4-Me-Ph	12	110	 **3aa**	46
12	**1d**	**2e:** R^1= $CH_2CH(CH_3)_2$	4	100	**3ab**	52
13	 **1e**	R^1-CHO **2e:** R^1= $CH_2CH(CH_3)_2$	2	100	 **3ac**	77
14	 **1f**	 **2b:** R^1= -OMe	8	110	 **4a**	66
15	**1f**	**2a:** R^1= Me	8	110	**4b**	44

[a]Reaction conditions: isoquinoline or quinoxaline (0.24 mmol), aldehyde (0.97 mmol), $K_2S_2O_8$ (0.49 mmol), TBAB (0.073 mmol) in DCE (2.0 mL). [b]Isolated yield.

CONCLUSION

In summary, intermolecular acylation of isoquinolines and quinolines to synthesize useful heterocyclic molecules under transition metal-free conditions has been presented. This Minisci reaction of acylation of electron-deficient aromatic compounds using a substoichiometric amount of TBAB with $K_2S_2O_8$ has been shown to be useful in synthesizing isoquinoline-derived natural product. Further study is underway in our laboratory to explore the further utility and application of this methodology.

EXPERIMENTAL SECTION

Typical Experimental Procedure for Minisci Reaction of Quinoline, Isoquinoline, and Quinoxaline with Aldehyde. Quinoline or isoquinoline or quinoxaline (50 mg, 0.24 mmol), aldehyde (0.97 mmol,

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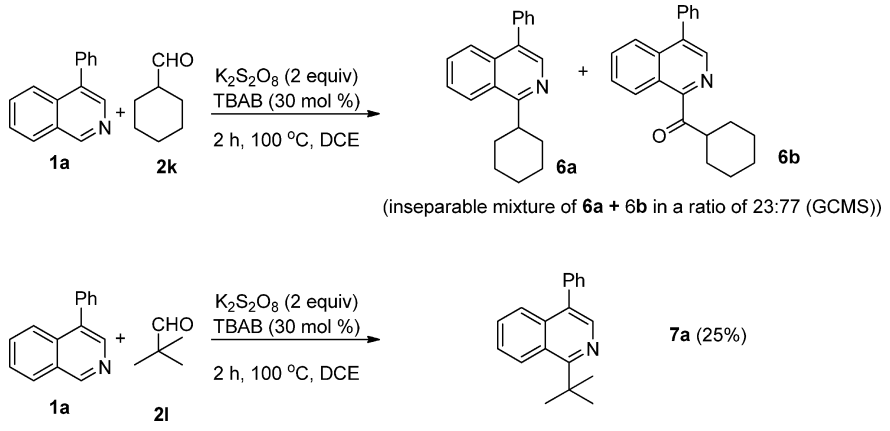
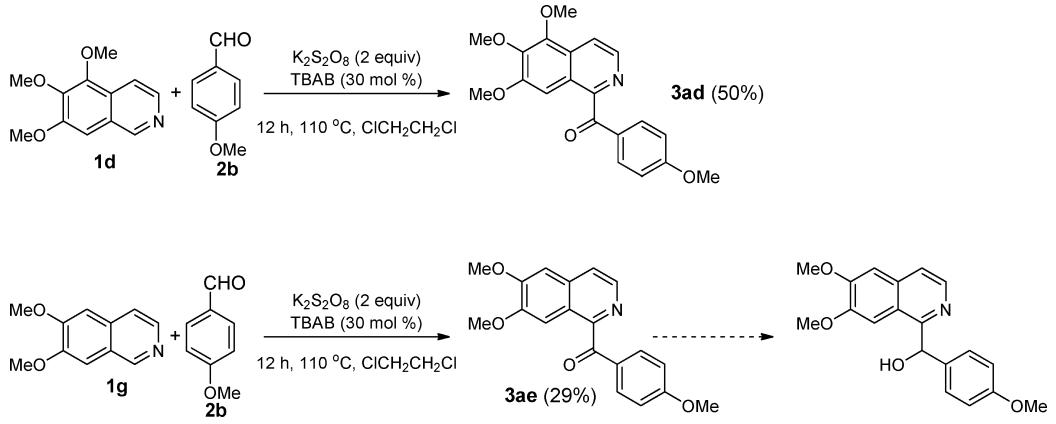
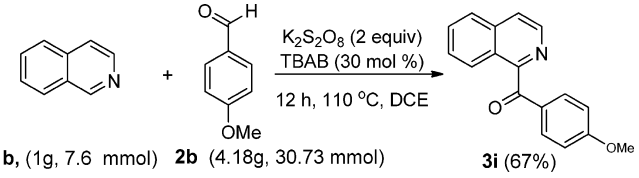
Scheme 2. Reaction of 4-Phenylisoquinoline with the Secondary and Tertiary Aldehydes



Scheme 3. Synthesis of Isoquinoline-Derived Natural Products

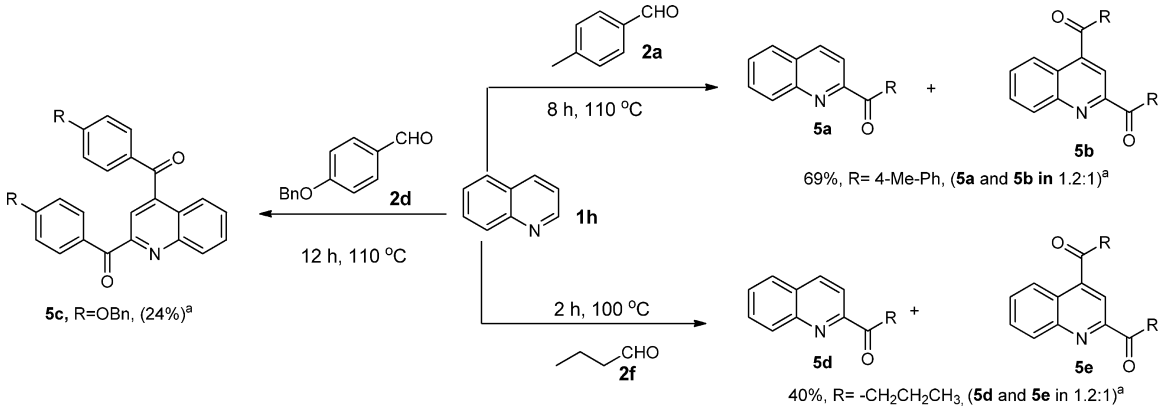


Scheme 4. Scaling-Up Experiment



4 equiv), TBAB (0.073, 0.3 equiv), and $K_2S_2O_8$ (0.49 mmol, 2 equiv) in DCE (2 mL) were stirred at 110 °C (12−24 h for aromatic aldehydes) and 100 °C (2−5 h, for aliphatic aldehydes). After the completion of the reaction (monitored by TLC), the solvent was removed under a vacuum, saturated bicarbonate solution (10 mL) was added, and solvent was extracted with EtOAc (3 × 10 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified on a silica gel column using hexane/EtOAc to get the pure product.

Scheme 5. Acylation of Quinoline[a,b]



[a]Isolated yields. [b]Reaction conditions: quinoline (0.24 mmol), aldehyde (0.97 mmol), $K_2S_2O_8$ (0.49 mmol), TBAB (0.073 mmol) in DCE (2.0 mL), 100−110 °C, 2−12 h.

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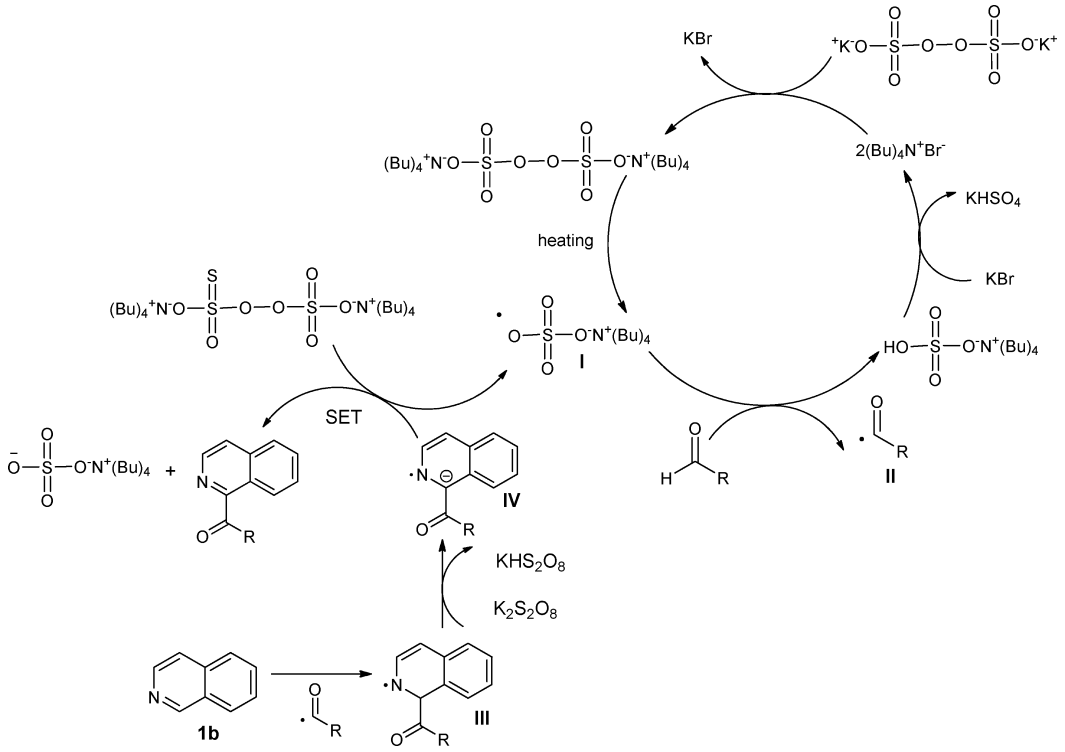
Scheme 6. Tentative Reaction Mechanism



Characterization Data. *(4-Phenylisoquinolin-1-yl)(p-tolyl)-methanone (**3a**).* White soild; Yield 81%; mp 126 °C; R_f (10% EtOAc/Hexane) 0.3. Prepared as shown in general experimental procedure (Reaction completion time 12 h at 110 °C): IR (Neat, cm^{-1}) 3031, 2924, 2855, 1971, 1664, 1605, 1407, 1268, 1251; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.55 (s, 1H), 8.26 (d, J = 8.4 Hz, 1H), 8.00 (d, J = 8.8 Hz, 1H), 7.91 (d, J = 8.0 Hz, 2H), 7.71−7.67 (m, 1H), 7.62−7.51 (m, 1H), 7.56−7.53 (m, 4H), 7.52−7.48 (m, 1H), 7.29 (d, J = 8.0 Hz, 2H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 194.6, 156.1, 144.7, 141.0, 136.6, 135.1, 135.1, 134.2, 130.9, 130.7, 130.1, 129.2, 128.7, 128.2, 128.0, 126.4, 126.2, 125.3, 21.8; HRESI-MS (m/z) Calculated for $C_{23}H_{17}NO$ (M^+ + Na) 346.1208, found (M^+ + Na) 346.1209.

*(4-Methoxyphenyl)(4-phenylisoquinolin-1-yl)methanone (**3b**).* White solid; Yield 78%; mp 145 °C; R_f (10% EtOAc/Hexane) 0.3. Prepared as shown in general experimental procedure (Reaction completion time 12 h at 110 °C): IR (Neat, cm^{-1}) 2925, 2853, 1600, 1426, 1259, 1156; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.54 (s, 1H), 8.24 (d, J = 8.4 Hz, 1H), 8.00 (t, J = 7.6 Hz, 3H), 7.69 (t, J = 8.4 Hz, 1H), 7.61 (t, J = 8.0 Hz, 1H), 7.56−7.55 (m, 4H), 7.53−7.51 (m, 1H), 6.97 (d, J = 8.0 Hz, 2H), 3.89 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 193.4, 164.1, 156.4, 141.0, 136.7, 135.1, 134.9, 133.2, 130.7, 130.1, 129.6, 128.7, 128.2, 127.9, 126.5, 126.1, 125.3, 113.8, 55.5; HRESI-MS (m/z) Calculated for $C_{23}H_{17}NO_2$ (M^+ + H) 340.1338, found (M^+ + H) 340.1339.

*(3,4-Dimethoxyphenyl)(4-phenylisoquinolin-1-yl)methanone (**3c**).* Pale yellow oily liquid; Yield 70%; R_f (10% EtOAc/Hexane) 0.1. Prepared as shown in general experimental procedure (Reaction completion time 12 h at 110 °C): IR (Neat, cm^{-1}) 2930, 2846, 1654, 1593, 1511, 1420, 1268; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.55 (s, 1H), 8.23 (d, J = 8.4 Hz, 1H), 8.01 (d, J = 8.4 Hz, 1H), 7.78 (s, 1H), 7.70 (t, J = 7.6 Hz, 1H), 7.62 (t, J = 7.6 Hz, 1H), 7.57−7.56 (m, 4H), 7.53−7.50 (m, 1H), 7.46- 7.43 (dd, J_1 = 8.4, J_2 = 2.0 Hz, 1H), 6.87 (d, J = 8.4 Hz, 1H), 3.98 (s, 3H), 3.95 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 193.6, 156.4, 154.1, 149.2, 141.0, 136.6, 135.1, 135.0, 130.7, 130.1, 129.7, 128.7, 128.3, 128.0, 127.1, 126.5, 126.2, 125.3, 111.6, 110.0, 56.2, 56.1; HRESI-MS (m/z) Calculated for $C_{24}H_{19}NO_3$ (M^+ + H) 370.1443, found (M^+ + H) 370.1443.

*(4-(Benzyloxy)phenyl)(4-phenylisoquinolin-1-yl)methanone (**3d**).* Pale yellow oily liquid; Yield 72%; R_f (10% EtOAc/Hexane) 0.3. Prepared as shown in general experimental procedure (Reaction completion time 12 h at 110 °C): IR (Neat, cm^{-1}) 2926, 1716, 1523, 1398, 1248, 1052, 1027; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.53 (s, 1H), 8.24 (d, J = 8.4 Hz, 1H), 8.01−7.97 (m, 3H), 7.67 (t, J = 7.2 Hz, 1H), 7.61−7.47 (m, 6H), 7.42−7.24 (m, 5H), 7.03 (d, J = 8.8 Hz, 2H), 5.14 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 193.4, 163.3, 156.4, 141.0, 136.7, 136.1, 135.1, 135.0, 133.2, 130.7, 130.1, 129.8, 128.7, 128.2, 127.9, 127.4, 126.5, 126.1, 125.3, 114.7, 70.2; HRESI-MS (m/z) Calculated for $C_{29}H_{21}NO_2$ (M^+ + Na) 438.1470, found (M^+ + Na) 438.1469.

*3-Methyl-1-(4-phenylisoquinolin-1-yl)butan-1-one (**3e**).* Pale yellow oily liquid; Yield 78%; R_f (10% EtOAc/Hexane) 0.7. Prepared as shown in general experimental procedure (Reaction completion time 2 h at 100 °C): IR (Neat, cm^{-1}) 3058, 3033, 2956, 2929, 2870, 1954, 1693, 1567, 1546; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.92−8.90 (m, 1H), 8.52 (s, 1H), 7.94−7.92 (m, 1H), 7.69−7.63 (m, 2H), 7.56−7.49 (m, 5H), 3.24 (d, J = 6.8 Hz, 2H), 2.42−2.32 (m, 1H), 1.05 (d, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 204.6, 153.1, 140.9, 136.7, 135.3, 130.3, 130.0, 128.6, 128.6, 128.3, 126.8, 125.5, 125.2, 49.2, 25.0, 22.8; HRESI-MS (m/z) Calculated for $C_{20}H_{19}NO$ (M^+ + Na) 312.1364, found (M^+ + Na) 312.1361.

*1-(4-Phenylisoquinolin-1-yl)butan-1-one (**3f**).* Pale yellow oily liquid; Yield 60%; R_f (5% EtOAc/Hexane) 0.7. Prepared as shown in general experimental procedure (Reaction completion time 2 h at 100 °C): IR (Neat, cm^{-1}) 3030, 2959, 2918, 2850, 2872, 2088, 1695, 1540, 1017, 758; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.93−8.91 (m, 1H), 8.52 (s, 1H), 7.94−7.92 (m, 1H), 7.68−7.63 (m, 2H), 7.56−7.49 (m, 5H), 3.34 (t, J = 7.6 Hz, 2H), 1.89−1.80 (m, 2H), 1.06 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 204.8, 152.8, 140.9, 136.7, 136.7, 135.3, 130.3, 130.0, 128.6, 128.6, 128.3, 126.8, 125.5, 125.2, 42.3, 17.7, 13.9; HRESI-MS (m/z) Calculated for $C_{19}H_{17}NO$ (M^+ + Na) 298.1208, found (M^+ + Na) 298.1207.

*1-(4-Phenylisoquinolin-1-yl)hexan-1-one (**3g**).* Pale yellow oily liquid; Yield 54%; R_f (5% EtOAc/Hexane) 0.7. Prepared as shown in general experimental procedure (Reaction completion time 2 h at 100 °C): IR (Neat, cm^{-1}) 3030, 2956, 2920, 2851, 2089, 1696, 1540, 1216, 1017, 757; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.93−8.90 (m, 1H), 8.52

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(s, 1H), 7.95−7.92 (m, 1H), 7.69−7.64 (m, 2H), 7.56−7.48 (m, 5H), 3.35 (t, J = 7.6 Hz, 2H), 1.85−1.77 (quintet, 2H), 1.47−1.35 (m, 4H), 0.92 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 204.9, 152.9, 141.0, 136.7, 136.7, 135.3, 130.3, 130.0, 128.6, 128.6, 128.3, 126.8, 125.5, 125.2, 40.4, 31.5, 24.0, 22.6, 14.0; HRESI-MS (m/z) Calculated for $C_{21}H_{21}NO$ (M^+ + Na) 326.1521, found (M^+ + Na) 326.1520.

*Isoquinolin-1-yl(p-tolyl)methanone (**3h**).*[2a] Pale yellow oily liquid; Yield 55%; R_f (10% EtOAc/Hexane) 0.5. Prepared as shown in general experimental procedure (Reaction completion time 12 h at 110 °C): IR (Neat, cm^{-1}) 3903, 3054, 2918, 2850, 1661, 1604, 1583, 1249; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.58 (d, J = 5.6 Hz, 1H), 8.18 (d, J = 8.8 Hz, 1H), 7.90 (d, J = 8.0 Hz, 1H), 7.84 (d, J = 8.0 Hz, 2H), 7.78 (d, J = 5.6 Hz, 1H), 7.72 (t, J = 7.2 Hz, 1H), 7.59 (t, J = 7.2 Hz, 1H), 7.26 (d, J = 8.0 Hz, 2H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 194.5, 156.8, 144.7, 141.2, 136.6, 134.1, 130.8, 130.6, 129.2, 128.2, 127.0, 126.3, 126.2, 122.3, 21.8; HRESI-MS (m/z) Calculated for $C_{17}H_{13}NO$ (M^+ + Na) 270.0895, found (M^+ + Na) 270.0895.

*Isoquinolin-1-yl(4-methoxyphenyl)methanone (**3i**).*[2a,11] Pale yellow oily liquid; Yield 64%; R_f (20% EtOAc/Hexane) 0.4. Prepared as shown in general experimental procedure (Reaction completion time 12 h at 110 °C): IR (Neat, cm^{-1}) 3055, 2931, 2840, 1663, 1597, 1251, 1152; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.59 (d, J = 5.6 Hz, 1H), 8.17 (d, J = 8.4 Hz, 1H), 7.96−7.89 (m, 3H), 7.78 (d, J = 5.6 Hz, 1H), 7.75−7.70 (m, 1H), 7.61−7.57 (m, 1H), 6.94 (d, J = 8.8 Hz, 2H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 193.4, 164.1, 157.1, 141.2, 136.6, 133.1, 130.6, 129.5, 128.1, 127.0, 126.3, 126.3, 122.2, 113.8, 55.5; HRESI-MS (m/z) Calculated for $C_{17}H_{13}NO_2$ (M^+ + Na) 286.0844, found (M^+ + Na) 286.0843.

*(3,4-Dimethoxyphenyl)(isoquinolin-1-yl)methanone (**3j**).*[2a,12] Yellow solid; Yield 40%; mp 140−142 °C (reported 145−146); R_f (30% EtOAc/Hexane) 0.2. Prepared as shown in general experimental procedure (Reaction completion time 12 h at 110 °C): IR (Neat, cm^{-1}) 3056, 3007, 2935, 2839, 1660, 1583, 1513, 1463, 1420, 1263; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.59 (d, J = 5.6 Hz, 1H), 8.15 (d, J = 8.4 Hz, 1H), 7.91 (d, J = 8.4 Hz, 1H), 7.79 (d, J = 5.6 Hz, 1H), 7.75−7.71 (m, 2H), 7.604 (t, J = 7.6 Hz, 1H), 7.37−7.35 (dd, J_1 = 8.40, J_2 = 1.6 Hz, 1H), 6.83 (d, J = 8.4 Hz, 1H), 3.96 (s, 3H), 3.93 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 193.4, 156.9, 153.9, 149.1, 141.1, 136.5, 130.6, 129.5, 128.0, 127.0, 126.9, 126.2, 126.1, 122.2, 111.4, 109.9, 56.0, 55.9; HRESI-MS (m/z) Calculated for $C_{18}H_{15}NO_3$ (M^+ + Na) 316.0950, found (M^+ + Na) 316.0952.

*Isoquinolin-1-yl(2,3,4-trimethoxyphenyl)methanone (**3k**).*[2a] Brown viscous liquid; Yield 32%; R_f (30% EtOAc/Hexane) 0.2. Prepared as shown in general experimental procedure (Reaction completion time 12 h at 110 °C): IR (Neat, cm^{-1}) 2956, 2928, 2874, 1736, 1595, 1435, 1251; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.50 (d, J = 5.6 Hz, 1H), 8.28 (d, J = 8.4 Hz, 1H), 7.89 (d, J = 8.4 Hz, 1H), 7.75−7.71 (m, 2H), 7.77 (d, J = 8.8 Hz, 1H), 7.64 (t, J = 8.0 Hz, 1H), 6.81 (d, J = 8.8 Hz, 1H), 3.93 (s, 3H), 3.76 (s, 3H), 3.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 194.8, 158.9, 158.3, 154.3, 141.7, 141.0, 136.6, 130.4, 128.0, 126.9, 126.6, 126.3, 125.7, 125.4, 122.0, 107.2, 60.8, 60.6, 56.2; HRESI-MS (m/z) Calculated for $C_{19}H_{17}NO_4$ (M^+ + Na) 346.1055, found (M^+ + Na) 346.1057.

*Isoquinolin-1-yl(3,4,5-trimethoxyphenyl)methanone (**3l**).*[2a] White solid; Yield 41%; mp 115−117 °C; R_f (30% EtOAc/Hexane) 0.2. Prepared as shown in general experimental procedure (Reaction completion time 12 h at 110 °C): IR (Neat, cm^{-1}) 2926, 2856, 1637, 1460, 1312, 1226; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.60 (d, J = 5.6 Hz, 1H), 8.21 (d, J = 8.8 Hz, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7.81 (d, J = 5.6 Hz, 1H), 7.75 (t, J = 7.2 Hz, 1H), 7.63 (t, J = 7.6 Hz, 1H), 7.23 (s, 2H), 3.83 (s, 3H), 3.93 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 193.5, 156.4, 152.9, 143.3, 141.0, 136.7, 131.6, 130.7, 128.3, 127.1, 126.4, 126.1, 122.6, 108.3, 60.9, 56.2; HRESI-MS (m/z) Calculated for $C_{19}H_{17}NO_4$ (M^+ + Na) 346.1055, found (M^+ + Na) 346.1055.

*(4-(Benzyloxy)phenyl)(isoquinolin-1-yl)methanone (**3m**).*[2a] White solid; Yield 41%; mp 124−127 °C; R_f (20% EtOAc/Hexane) 0.7. Prepared as shown in general experimental procedure (Reaction completion time 12 h at 110 °C): IR (Neat, cm^{-1}) 3049, 2924, 2854, 1645, 1602, 1281, 1259; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.57 (d, J = 5.6 Hz, 1H), 8.16 (d, J = 8.8 Hz, 1H), 7.94−7.87 (m, 3H), 7.76 (d, J = 5.2 Hz, 1H), 7.71 (t, J = 7.2 Hz, 1H), 7.58 (t, J = 7.6 Hz, 1H), 7.41−7.33 (m, 5H), 7.0 (d, J = 8.8 Hz, 2H), 5.12 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 193.3, 163.3, 157.0, 141.1, 136.6, 136.1, 133.2, 130.7, 129.7, 128.7, 128.2, 128.2, 127.4, 127.0, 126.3, 122.3, 114.7, 70.2; HRESI-MS (m/z) Calculated for $C_{23}H_{17}NO_2$ (M^+ + Na) 362.1157, found (M^+ + Na) 362.1151.

*(4-Bromophenyl)(isoquinolin-1-yl)methanone (**3n**).*[13] White solid; Yield 40%; mp 88−90 °C (reported 95−98 °C); R_f (10% EtOAc/Hexane) 0.3. Prepared as shown in general experimental procedure (Reaction completion time 12 h at 110 °C): IR (Neat, cm^{-1}) 3053, 2959, 2931, 2102, 1735, 1653, 1437, 1265; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.59 (d, J = 5.6 Hz, 1H), 8.25 (d, J = 8.4 Hz, 1H), 7.92 (d, J = 8.0 Hz, 1H), 7.84−7.81 (m, 3H), 7.75 (t, J = 7.6 Hz, 1H), 7.66−7.60 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 193.5, 155.5, 141.1, 136.8, 135.4, 132.2, 131.7, 130.8, 129.0, 128.5, 127.1, 126.4, 126.0, 123.0; HRESI-MS (m/z) Calculated for $C_{16}H_{10}NOBr$(M^+ + Na) 333.9843, found (M^+ + Na) 333.9844.

*1-(Isoquinolin-1-yl)butan-1-one (**3o**).*[14] Pale yellow oily liquid; Yield 52%; R_f (10% EtOAc/Hexane) 0.7. Prepared as shown in general experimental procedure (Reaction completion time 2 h at 100 °C): IR (Neat, cm^{-1}) 2960, 2931, 2874, 1734, 1435, 1261, 1164, 1018; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.83 (d, J = 8.4 Hz, 1H), 8.56 (d, J = 5.6 Hz, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.79 (d, J = 5.6 Hz, 1H), 7.72−7.64 (m, 2H), 3.30 (t, J = 7.6 Hz, 2H), 1.86−1.77 (m, 2H), 1.05 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 204.80, 153.54, 140.98, 136.95, 130.26, 128.86, 126.91, 126.66, 125.65, 124.14, 42.22, 17.58, 13.84; HRESI-MS (m/z) Calculated for $C_{13}H_{13}NO$(M^+ + H) 200.1075, found (M^+ + H) 200.1074.

*1-(Isoquinolin-1-yl)-3-methylbutan-1-one (**3p**).* Pale yellow oily liquid; Yield 61%; R_f (10% EtOAc/Hexane) 0.7. Prepared as shown in general experimental procedure (Reaction completion time 2 h at 100 °C): IR (Neat, cm^{-1}) 3055, 2957, 2928, 2871, 1697, 1581, 1456, 1363,1288; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.82 (d, J = 8.0 Hz, 1H), 8.56 (d, J = 5.6 Hz, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.78 (d, J = 5.6 Hz, 1H), 7.72−7.64 (m, 2H), 3.20 (d, J = 6.8 Hz, 2H), 2.38−2.28 (m, 1H), 1.03 (d, J = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 204.63, 153.83, 140.99, 136.98, 130.28, 128.87, 126.96, 126.63, 125.64, 124.10, 49.12, 24.96, 22.75; HRESI-MS (m/z) Calculated for $C_{14}H_{15}NO$(M^+ + Na) 236.1051, found (M^+ + Na) 236.1047.

*(4-(4-Methoxyphenyl)isoquinolin-1-yl)(p-tolyl)methanone (**3q**).* Pale yellow solid; Yield 67%; mp 92−94 °C; R_f (10% EtOAc/Hexane) 0.3. Prepared as shown in general experimental procedure (Reaction completion time 12 h at 110 °C): IR (Neat, cm^{-1}) 2924, 2836, 1655, 1605, 1516, 1268, 1246, 1178; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.53 (s, 1H), 8.26 (d, J = 8.4 Hz, 1H), 8.02 (d, J = 8.4 Hz, 1H), 7.90 (d, J = 8.0 Hz, 2H), 7.68 (t, J = 7.2 Hz, 1H), 7.60 (t, J = 7.6 Hz, 1H), 7.48 (d, J = 8.4 Hz, 2H), 7.27 (d, J = 8.0 Hz, 2H), 7.09 (d, J = 8.4 Hz, 2H), 3.90 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 194.6, 159.7, 155.7, 144.7, 141.0, 135.2, 134.9, 134.2, 131.3, 130.9, 130.6, 129.2, 128.8, 127.9, 126.4, 126.2, 125.4, 114.2, 55.4, 21.8; HRESI-MS (m/z) Calculated for $C_{24}H_{19}NO_2$ (M^+ + Na) 376.1313, found (M^+ + Na) 376.1317.

*(4-Methoxyphenyl)(4-(4-methoxyphenyl)isoquinolin-1-yl)-methanone (**3r**).* Yellow solid; Yield 68%; mp 118−120 °C; R_f (10% EtOAc/Hexane) 0.2. Prepared as shown in general experimental procedure (Reaction completion time 12 h at 110 °C): IR (Neat, cm^{-1}) 2931, 1716, 2553, 1716, 1522, 1418, 1248, 1054; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.52 (s, 1H), 8.23 (d, J = 8.4 Hz, 1H), 7.99−8.02 (m, 3H), 7.67 (t, J = 7.2 Hz, 1H), 7.59 (t, J = 7.2 Hz, 1H), 7.48 (d, J = 8.8 Hz, 2H), 7.09 (d, J = 8.4 Hz, 2H), 6.96 (d, J = 8.8 Hz, 2H), 3.90 (s, 3H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 193.5, 164.1, 159.7, 156.0, 141.0, 135.2, 134.7, 133.2, 131.3, 130.6, 129.7, 128.9, 127.8, 126.5, 126.2, 125.4, 114.2, 113.8, 55.5, 55.4; HRESI-MS (m/z) Calculated for $C_{24}H_{19}NO_3$ (M^+ + Na) 392.1263, found (M^+ + Na) 392.1263.

*(3,4-Dimethoxyphenyl)(4-(4-methoxyphenyl)isoquinolin-1-yl)-methanone (**3s**).* Yellow solid; Yield 59%; mp 104−107 °C; R_f (20% EtOAc/Hexane) 0.2. Prepared as shown in general experimental procedure (Reaction completion time 12 h at 110 °C): IR (Neat, cm^{-1}) 3078, 2930, 2838, 1659, 1592, 1515, 1463, 1421, 1269, 1247; ^{1}H NMR

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(400 MHz, $CDCl_3$) δ (ppm) 8.53 (s, 1H), 8.23 (d, J = 8.4 Hz, 1H), 8.03 (d, J = 8.8 Hz, 1H), 7.78 (s, 1H), 7.70 (t, J = 7.2 Hz, 1H), 7.61 (t, J = 7.6 Hz, 1H), 7.49 (d, J = 8.0 Hz, 2H), 7.44 (d, J = 8.4 Hz, 1H), 7.10 (d, J = 8.4 Hz, 2H), 6.86 (d, J = 8.4 Hz, 1H), 3.98 (s, 3H), 3.94 (s, 3H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 193.6, 159.7, 155.9, 154.0, 149.2, 140.9, 135.2, 134.7, 131.3, 130.6, 129.7, 128.8, 127.9, 127.1, 126.4, 126.2, 125.4, 114.2, 111.6, 109.9, 56.1, 56.1, 55.4; HRESI-MS (m/z) Calculated for $C_{25}H_{21}NO_4$ (M^+ + Na) 422.1368, found (M^+ + Na) 422.1365.

*(4-(4-Methoxyphenyl)isoquinolin-1-yl)(3,4,5-trimethoxyphenyl)-methanone (**3t**).* Pale yellow solid; Yield 51%; mp 130−132 °C; R_f (20% EtOAc/Hexane) 0.2. Prepared as shown in general experimental procedure (Reaction completion time 12 h at 110 °C): IR (Neat, cm^{-1}) 2935, 2836, 1663, 1579, 1498, 1413, 1323, 1229, 1127; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.54 (s, 1H), 8.29 (d, J = 8.4 Hz, 1H), 8.05 (d, J = 8.4 Hz, 1H), 7.72 (t, J = 7.2 Hz, 1H), 7.64 (t, J = 7.6 Hz, 1H), 7.50 (d, J = 8.4 Hz, 2H), 7.29 (s, 2H), 7.10 (d, J = 8.4 Hz, 2H), 3.94 (s, 3H), 3.92 (s, 3H), 3.86 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 193.6, 159.8, 155.2, 153.0, 143.3, 140.8, 135.3, 135.1, 131.8, 131.3, 130.7, 128.7, 128.0, 126.4, 125.5, 114.2, 108.5, 60.9, 56.3, 55.4; HRESI-MS (m/z) Calculated for $C_{26}H_{23}NO_5$ (M^+ + Na) 452.1474, found (M^+ + Na) 452.1478.

*(4-(Benzyloxy)phenyl)(4-(4-methoxyphenyl)isoquinolin-1-yl)-methanone (**3u**).* Pale yellow solid; Yield 55%; mp 108−110 °C; R_f (20% EtOAc/Hexane) 0.4. Prepared as shown in general experimental procedure (Reaction completion time 12 h at 110 °C): IR (Neat, cm^{-1}) 3403, 3035, 2927, 1654, 1597, 1247, 1171, 1152; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.51 (s, 1H), 8.23 (d, J = 8.4 Hz, 1H), 8.0−7.98 (m, 3H), 7.68 (t, J = 7.2 Hz, 1H), 7.59 (t, J = 7.6 Hz, 1H), 7.48 (d, J = 8.4 Hz, 2H), 7.42−7.34 (m, 4H), 7.33−7.31 (m, 1H), 7.09 (d, J = 8.8 Hz, 2H), 7.03(d, J = 8.8 Hz, 2H), 5.14 (s, 2H), 3.90 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 193.5, 163.3, 159.7, 155.9, 141.0, 136.1, 135.2, 134.7, 133.2, 131.3, 130.6,129.8, 128.9, 128.7, 128.2, 127.9, 127.4, 126.5, 126.2, 125.4, 70.2, 55.4; HRESI-MS (m/z) Calculated for $C_{30}H_{23}NO_3$ (M^+ + Na) 468.1576, found (M + Na) 468.1578.

*(4-(4-Methoxyphenyl)isoquinolin-1-yl)(thiophen-2-yl)methanone (**3v**).* Pale yellow oily liquid; Yield 41%; *Rf* (10% EtOAc/Hexane) 0.3. Prepared as shown in general experimental procedure (Reaction completion time 12 h at 110 °C): IR (Neat, cm^{-1}) 2927,2852, 1638, 1609, 1508, 1410, 1351, 1247; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.63 (d, J = 8.4 Hz, 1H), 8.56 (s, 1H), 8.02 (d, J = 8.0 Hz, 1H), 7.96 (d, J = 3.6 Hz, 1H), 7.78 (d, J = 4.8 Hz, 1H), 7.72−7.64 (m, 2H), 7.48 (d, J = 8.8 Hz, 2H), 7.17 (t, J = 4.4 Hz, 1H), 7.09 (d, J = 8.8 Hz, 2H), 3.91 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 186.1, 159.8, 153.5, 142.7, 140.7, 136.6, 136.0, 135.9, 135.4, 131.3, 130.6, 128.7, 128.3, 128.1, 126.6, 126.2, 125.4, 114.2, 55.4; HRESI-MS (m/z) Calculated for $C_{21}H_{15}NO_2S$ (M^+ + Na) 368.0721, found (M^+ + Na) 368.0720.

*1-(4-(4-Methoxyphenyl)isoquinolin-1-yl)-3-methylbutan-1-one (**3w**).* Pale yellow oily liquid; Yield 68%; R_f (5% EtOAc/Hexane) 0.7. Prepared as shown in general experimental procedure (Reaction completion time 2 h at 100 °C): IR (Neat, cm^{-1}) 2956, 2919, 2851, 1605, 1262, 1017; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.92−8.90 (m, 1H), 8.50 (s, 1H), 7.98−7.96 (m, 1H), 7.67−7.65 (m, 2H), 7.44 (d, J = 8.4 Hz, 2H), 7.08 (d, J = 8.4 Hz, 2H), 3.906 (s, 3H), 3.24 (d, J = 6.8 Hz, 2H), 2.42−2.31 (m, 1H), 1.05 (d, J = 6.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 204.6, 159.8, 152.7, 141.0, 136.4, 135.4, 131.2, 130.2, 128.9, 128.5, 126.8, 125.6, 125.3, 114.2, 55.4, 49.1, 25.1, 22.8; HRESI-MS (m/z) Calculated for $C_{21}H_{21}NO_2$ (M^+ + Na) 342.1470, found (M^+ + Na) 342.1470.

*1-(4-(4-Methoxyphenyl)isoquinolin-1-yl)butan-1-one (**3x**).* Pale yellow oily liquid; Yield 38%; R_f (5% EtOAc/Hexane) 0.7. Prepared as shown in general experimental procedure (Reaction completion time 2 h at 100 °C): IR (Neat, cm^{-1}) 2960, 2920, 2851, 1683, 1608, 1516, 1248, 1018; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.93−8.91 (m, 1H), 8.50 (s, 1H), 7.98−7.95 (m, 1H), 7.67−7.65 (m, 2H), 7.44 (d, J = 8.4 Hz, 2H), 7.08 (d, J = 8.4 Hz, 2H), 3.90 (s, 3H), 3.33 (t, J = 7.2 Hz, 2H), 1.88−1.79 (m, 2H), 1.06 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 204.8, 159.8, 152.4, 141.0, 136.5, 135.4, 131.2, 130.2, 128.9, 128.6, 126.8, 125.6, 125.3, 114.2, 55.4, 42.3, 17.7, 13.9; HRESI-MS (m/z) Calculated for $C_{20}H_{19}NO_2$ (M^+ + Na) 328.1313, found (M^+ + Na) 328.1313.

*1-(4-(4-Methoxyphenyl)isoquinolin-1-yl)hexan-1-one (**3y**).* Pale yellow oily liquid; Yield 46%; R_f (5% EtOAc/Hexane) 0.4. Prepared as shown in general experimental procedure (Reaction completion time 2 h at 100 °C): IR (Neat, cm^{-1}) 2955, 2929, 2852, 1683, 1696, 1609, 1516, 1248, 1017; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.93−8.90 (m, 1H), 8.504 (s, 1H), 7.98- 7.95 (m, 1H), 7.68−7.65 (m, 2H), 7.44 (d, J = 8.4 Hz, 2H), 7.08 (d, J = 8.4 Hz, 2H), 3.910 (s, 3H), 3.346 (t, J = 7.2 Hz, 2H), 1.84−1.77 (m, 2H), 1.44−1.37 (m, 4H), 0.92 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 204.9, 159.8, 152.5, 141.0, 136.5, 135.4, 131.2, 130.2, 128.9, 128.5, 126.8, 125.6, 125.3, 114.2, 55.4, 40.3, 31.5, 23.9, 22.5, 14.0; HRESI-MS (m/z) Calculated for $C_{22}H_{23}NO_2$ (M^+ + Na) 356.1626, found (M^+ + Na) 356.1625.

*1-(4-(4-Methoxyphenyl)isoquinolin-1-yl)heptan-1-one (**3z**).* Pale yellow oily liquid; Yield 42%; R_f (5% EtOAc/Hexane) 0.4. Prepared as shown in general experimental procedure (Reaction completion time 2 h at 100 °C): IR (Neat, cm^{-1})2955, 2928, 2853, 2065, 1668, 1609, 1496, 1247, 1177; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.93−8.90 (m, 1H), 8.50 (s, 1H), 7.98−7.95 (m, 1H), 7.67−7.65 (m, 2H), 7.44 (d, J = 8.4 Hz, 2H), 7.08 (d, J = 8.8 Hz, 2H), 3.90 (s, 3H), 3.34 (t, J = 7.6 Hz, 2H), 1.83−1.76 (m, 2H), 1.46−1.41 (m, 2H), 1.36−1.33 (m, 4H), 0.89 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 204.9, 159.8, 152.5, 141.0, 136.5, 135.4, 131.2, 130.2, 128.9, 128.5, 126.8, 125.6, 125.3, 114.2, 55.4, 40.4, 31.7, 29.0, 24.2, 22.5, 14.0; HRESI-MS (m/z) Calculated for $C_{23}H_{25}NO_2$ (M^+ + H) 348.1964, found (M^+ + H) 348.1966.

*p-Tolyl(5,6,7-trimethoxyisoquinolin-1-yl)methanone (**3aa**).* Pale yellow solid; Yield 46%; mp 102−105 °C; R_f (20% EtOAc/Hexane) 0.5. Prepared as shown in general experimental procedure (Reaction completion time 12 h at 110 °C): IR (KBr, cm^{-1}) 2942, 2851, 2837, 1654, 1607, 1489, 1406, 1275, 1124; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.48 (d, J = 5.6 Hz, 1H), 7.99 (d, J = 5.6 Hz, 1H), 7.85 (d, J = 8.0 Hz, 2H), 7.40 (s, 1H), 7.27 (d, J = 8.0 Hz, 2H), 4.07 (s, 3H), 4.02 (s, 3H), 3.93 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 194.9, 154.6, 153.7, 146.7, 144.5, 144.2, 139.6, 134.4, 130.9, 129.2, 129.1, 123.8, 116.7, 100.3, 61.6, 61.2, 56.0, 21.7; HRESI-MS (m/z) Calculated for $C_{20}H_{19}NO_4$ (M^+ + Na) 360.1212, found (M^+ + H) 360.1212.

*3-Methyl-1-(5,6,7-trimethoxyisoquinolin-1-yl)butan-1-one (**3ab**).* Yellow solid; Yield 52%; mp 65 °C; R_f (5% EtOAc/Hexane) 0.3. Prepared as shown in general experimental procedure (Reaction completion time 4h at 100 °C): IR (Neat, cm^{-1}) 2953, 2918, 2850, 2121, 1687, 1608, 1579, 1473, 1427, 1403; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.47 (d, J = 5.6 Hz, 1H), 8.23 (s, 1H), 8.03 (d, J = 5.6 Hz, 1H), 4.04- 4.02 (m, 9H), 3.22 (d, J = 6.8 Hz, 2H), 2.38−2.28 (m, 1H), 1.03 (d, J = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 205.2, 155.3, 150.4, 146.4, 143.8, 139.6, 129.7, 123.3, 118.4, 100.9, 61.6, 61.1, 56.1, 48.9, 25.0, 22.8; HRESI-MS (m/z) Calculated for $C_{17}H_{21}NO_4$ (M^+ + H) 304.1549, found (M^+ + H) 304.1549.

*1-(4-Bromoisoquinolin-1-yl)-3-methylbutan-1-one (**3ac**).* Pale yellow oily liquid; Yield 77%; R_f (5% EtOAc/Hexane) 0.7. Prepared as shown in general experimental procedure (Reaction completion time 2 h at 100 °C): IR (Neat, cm^{-1}) 2955, 2926, 2870, 1695, 1652, 1558, 1488, 1398; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.83 (d, J = 8.4 Hz, 1H), 8.74 (s, 1H), 8.21 (d, J = 8.4 Hz, 1H), 7.80 (t, J = 8.0 Hz, 1H), 7.71 (t, J = 7.6 Hz, 1H), 3.16 (d, J = 7.2 Hz, 2H), 2.35−2.24 (m, 1H), 1.01 (d, J = 6.4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 204.0, 152.8, 142.9, 135.6, 131.5, 129.8, 127.1, 126.8, 126.2, 123.4, 49.1, 25.0, 22.7; HRESI-MS (m/z) Calculated for $C_{14}H_{14}BrNO$ (M^+ + Na) 314.0156, found (M^+ + Na) 314.0158.

*(4-Methoxyphenyl)(5,6,7-trimethoxyisoquinolin-1-yl)methanone (**3ad**).*[2a,9] White solid; Yield 50%; mp 142−145 °C (reported 146−148 °C) (lit.[2a,8] mp 146−148); R_f (50% EtOAc/Hexane) 0.75. Prepared as shown in general experimental procedure (Reaction completion time 12 h at 110 °C): IR (Neat, cm^{-1}) 2944, 2838, 1651, 1601, 1585, 1478, 1280, 1255; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.47 (d, J = 6.0 Hz, 1H), 7.99−7.94 (m, 3H), 7.36 (s, 1H), 6.95 (d, J = 8.8 Hz, 2H), 4.07 (s, 3H), 4.02 (s, 3H), 3.93 (s, 3H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 193.8, 164.0, 154.5, 154.0, 146.7, 144.2, 139.5, 133.2, 129.7, 129.1, 123.7, 116.5, 113.7, 100.3, 61.6, 61.2, 56.1, 55.5; HRESI-MS

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(m/z) Calculated for $C_{20}H_{19}NO_5$ ($M^+ + H$) 354.1341, found ($M^+ + H$) 354.1341.

*(6,7-Dimethoxyisoquinolin-1-yl)(4-methoxyphenyl)methanone (**3ae**).*[2a,9,15] Yellow solid; Yield 29%; mp 145−148 °C (lit.[2a,8] mp 150−152); R_f (50% EtOAc/Hexane) 0.4. Prepared as shown in general experimental procedure (Reaction completion time 12 h at 110 °C): IR (Neat, cm^{-1}) 2940, 2837, 1648, 1607, 1509, 1442, 1338, 1264; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.46 (d, J = 5.6 Hz, 1H), 7.95 (d, J = 8.8 Hz, 2H), 7.64 (d, J = 5.6 Hz, 1H), 7.56 (s, 1H), 7.31 (s, 1H), 6.95 (d, J = 8.8 Hz, 2H), 4.0 (s, 3H), 3.95 (s, 3H), 3.87 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 193.9, 163.9, 153.7, 153.2, 151.0, 140.0, 134.0, 133.3, 129.8, 122.8, 121.2, 113.7, 104.8, 104.1, 56.1, 56.0, 55.5; HRESI-MS (m/z) Calculated for $C_{19}H_{17}NO_4$ ($M^+ + H$) 324.1236, found ($M^+ + H$) 324.1235.

*(4-Methoxyphenyl)(quinoxalin-2-yl)methanone (**4a**).*[16] Yellow solid; Yield 66%; mp 112−114 °C (reported 112−114 °C) ; R_f (20% EtOAc/Hexane) 0.3. Prepared as shown in general experimental procedure(Reaction completion time 8 h at 110 °C): IR (KBR, cm^{-1}) 3448, 3055, 3007, 2937, 2842, 1642, 1598, 1510, 1466, 1343, 1329; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.46 (s, 1H), 8.29 (d, J = 8.8 Hz, 2H), 8.21 (d, J = 7.9 Hz, 2H), 7.94−7.77 (m, 2H), 7.02 (d, J = 8.8 Hz, 2H), 3.92 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 190.56, 164.10, 149.23, 145.39, 142.95, 140.29, 133.73, 131.75, 130.70, 130.29, 129.33, 128.28, 113.72, 55.53; HRESI-MS (m/z) Calculated for $C_{16}H_{12}N_2O_2Na$ ($M^+ + Na$) 287.0796, found ($M^+ + Na$) 287.0796.

*Quinoxalin-2-yl(p-tolyl)methanone (**4b**).*[2a,16] Yellow solid; Yield − 44%; mp 100−102 °C (reported 100−102 °C); R_f (10% EtOAc/Hexane) 0.4. Prepared as shown in general experimental procedure (Reaction completion time 8 h at 110 °C): IR (KBR, cm^{-1}) 3435, 2925, 2852, 1654, 1604, 1323, 1307, 1229; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 9.47 (s, 1H), 8.20 (d, J = 8.2 Hz, 2H), 8.15 (d, J = 7.9 Hz, 2H), 7.94−7.78 (m, 2H), 7.34 (d, J = 7.8 Hz, 2H), 2.47 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 192.0, 148.9, 145.3, 144.8, 143.1, 140.4, 132.9, 131.9, 131.4, 130.7, 130.4, 129.4, 129.2, 21.9; HRESI-MS (m/z) Calculated for $C_{16}H_{12}N_2O$ ($M^+ + Na$) 271.0847, found ($M^+ + Na$) 271.0847.

*Quinolin-2-yl(p-tolyl)methanone (**5a**).* White solid; Yield 37%; mp 63−65 °C; R_f (5% EtOAc/Hexane) 0.4. Prepared as shown in general experimental procedure (Reaction completion time 8 h at 110 °C): IR (Neat, cm^{-1}) 3061, 2921, 1656, 1606, 1560, 1501, 1461, 1318; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.31 (d, J = 8.4 Hz, 1H), 8.19 (d, J = 8.8 Hz, 1H), 8.14 (d, J = 8.0 Hz, 2H), 8.06 (d, J = 8.4 Hz, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.76 (t, J = 8.0 Hz, 1H), 7.63 (t, J = 8.0 Hz, 1H), 7.3 (d, J = 7.6 Hz, 2H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 193.5, 155.0, 146.7, 144.0, 137.0, 133.5, 131.6, 130.5, 130.0, 128.9, 128.8, 128.3, 127.6, 120.8, 21.8; HRESI-MS (m/z) Calculated for $C_{17}H_{13}NO$ ($M^+ + Na$) 270.0895, found ($M^+ + Na$) 270.0892.

*Quinoline-2,4-diylbis(p-tolylmethanone) (**5b**).* Pale yellow oily liquid; Yield 32%; R_f (5% EtOAc/Hexane) 0.2. Prepared as shown in general experimental procedure (Reaction completion time 8 h at 110 °C): IR (Neat, cm^{-1}) 3065, 1661, 1605, 1505, 1458, 1353, 1260; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.28 (d, J = 8.4 Hz, 1H), 8.17 (d, J = 8.0 Hz, 2H), 8.0 (s, 1H), 7.94 (d, J = 8.4 Hz, 1H), 7.83−7.78 (m, 3H), 7.62 (t, J = 7.6 Hz, 1H), 7.30 (d, J = 8 Hz, 2H), 7.26 (d, J = 8.0 Hz, 2H), 2.45 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 195.3, 192.7, 154.2, 147.2, 145.7, 145.6, 144.3, 133.9, 133.2, 131.6, 131.0, 130.5, 130.5, 129.6, 129.3, 129.0, 125.7, 125.4, 119.3, 21.83, 21.80; HRESI-MS (m/z) Calculated for $C_{25}H_{19}NO_2$ ($M^+ + Na$) 388.1313, found ($M^+ + Na$) 388.1319.

*Quinoline-2,4-diylbis((4-(benzyloxy)phenyl)methanone) (**5c**).* White solid; Yield 24%; mp 147−149 °C; R_f (20% EtOAc/Hexane) 0.45. Prepared as shown in general experimental procedure (Reaction completion time 12 h at 110 °C): IR (Neat, cm^{-1}) 3063, 2921, 2623, 2113, 1651, 1597, 1574, 1252; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.29 (t, J = 8.8 Hz, 3H), 8.05 (s, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7.86 (d, J = 8.8 Hz, 2H), 7.81 (t, J = 7.6 Hz, 1H), 7.62 (t, J = 7.6 Hz, 1H), 7.45−7.33 (m, 10H), 7.08 (d, J = 8.8 Hz, 2H), 7.02 (d, J = 8.8 Hz, 2H), 5.17 (s, 2H), 5.14 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 194.1, 191.5, 163.7, 163.0, 154.5, 147.1, 146.0, 136.2, 135.8, 134.0, 132.9, 130.9, 130.5, 129.5, 129.2, 128.8, 128.7, 128.7, 128.4, 128.2, 127.5, 125.6, 125.4, 119.2, 115.0, 114.5, 70.3, 70.2; HRESI-MS (m/z) Calculated for $C_{37}H_{27}NO_4$ ($M^+ + Na$) 572.1838, found ($M^+ + Na$) 572.1836.

*1-(Quinolin-2-yl)butan-1-one (**5d**).* Pale yellow oily liquid; Yield 22%; R_f (5% EtOAc/Hexane) 0.3. Prepared as shown in general experimental procedure (Reaction completion time 2 h at 100 °C): IR (Neat, cm^{-1}) 3063, 2962, 2933, 2874, 1697, 1594, 1505, 1458, 1374; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.25 (d, J = 8.4 Hz, 1H), 8.19 (d, J = 8.4 Hz, 1H), 8.12 (d, J = 8.8 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.79−7.75 (m, 1H), 7.637 (t, J = 7.2 Hz, 1H), 3.39−3.36 (t, J = 7.6 Hz, 2H), 1.87−1.78 (sex, 2H), 1.07−1.04 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 202.6, 153.2, 147.2, 136.8, 130.5, 129.9, 129.5, 128.4, 127.6, 118.1, 39.4, 17.6, 13.9; HRESI-MS (m/z) Calculated for $C_{13}H_{13}NO$ ($M^+ + Na$) 222.0895, found ($M^+ + Na$) 222.0899.

*1,1′-(Quinoline-2,4-diyl)bis(butan-1-one) (**5e**).* Pale yellow oily liquid; Yield 18%; R_f (2% EtOAc/Hexane) 0.2. Prepared as shown in general experimental procedure (Reaction completion time 2 h at 100 °C): IR (Neat, cm^{-1}) 3069, 2962, 2933, 2875, 1697, 1654, 1506, 1458, 1361; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.38 (d, J = 8.4 Hz, 1H), 8.29 (s, 1H), 8.24 (d, J = 8.4 Hz, 1H), 7.83−7.80 (m, 1H), 7.73−7.69 (m, 1H), 3.387 (t, J = 7.2 Hz, 2H), 3.069 (t, J = 7.2 Hz, 2H), 1.89−1.77 (m, 4H), 1.08−1.02 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 204.0, 202.1, 152.5, 148.2, 144.2, 131.0, 130.2, 130.0, 125.4, 125.2, 116.2, 44.2, 39.3, 17.6, 17.5, 13.9, 13.7; HRESI-MS (m/z) Calculated for $C_{17}H_{19}NO_2$ ($M^+ + Na$) 292.1313, found ($M^+ + Na$)292.1313.

*Reaction of 4-Phenylisoquinoline (**1a**) with Cyclohexylcarboxaladehyde (**2l**).* 4-Phenyl isoquinoline (**1a**, 50 mg, 0.24 mmol), cyclohexylcarboxaladehyde (**2l**, 0.97 mmol, 4 equiv), TBAB (0.073, 0.3 equiv), and $K_2S_2O_8$ (0.49 mmol, 2 equiv) in DCE (2 mL) were stirred at 100 °C (2 h). After the completion of the reaction (monitored by TLC), the solvent was removed under a vacuum, saturated bicarbonate solution (10 mL) was added, and the solvent was extracted with EtOAc (3 × 10 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to get the crude product, which was purified on a silica gel column using hexane/EtOAc to furnish an inseparable mixure (68 mg) of 1-cyclohexyl-4-phenylisoquinoline (**6a**) and cyclohexyl(4-phenylisoquinolin-1-yl)methanone **6b**. This mixture was subjected to GC−MS analysis (see Supporting Information).

*Reaction of 4-Phenylisoquinoline (**1a**) with Pivaladehyde (**2l**).* 4-Phenyl isoquinoline (**1a**, 50 mg, 0.24 mmol), pivaladehyde (**2k**, 0.97 mmol, 4 equiv), TBAB (0.073, 0.3 equiv), and $K_2S_2O_8$ (0.49 mmol, 2 equiv) in DCE (2 mL) were stirred at 100 °C (2 h). After the completion of the reaction (monitored by TLC), the solvent was removed under a vacuum, saturated bicarbonate solution (10 mL) was added, and the solvent was extracted with EtOAc (3 × 10 mL). The combined organic layer was dried over anhy. Na_2SO_4 and concentrated under reduced pressure. The crude product was purified on a silica gel column using hexane/EtOAc to get the pure 1-(*tert*-butyl)-4-phenylisoquinoline(**7a**).

Pale yellow liquid: Yield 25%; R_f (5% EtOAc/Hexane) 0.6; IR (Neat, cm^{-1}) 3416, 3032, 2966, 2929, 2871, 2645, 2108, 1834; ^1H NMR (400 MHz, $CDCl_3$) δ (ppm) 8.63- 8.60 (m, 1H), 8.39 (s, 1H), 7.93−7.90 (m, 1H), 7.59−7.56 (m, 2H), 7.51−7.45 (m, 5H), 1.72 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 166.74, 140.43, 137.60, 135.70, 131.90, 130.23, 128.85, 128.45, 127.61, 127.35, 126.32, 125.75, 125.46, 39.84, 31.33; HRESI-MS (m/z) Calculated for $C_{19}H_{19}NH$ ($M^+ + H$) 262.1596, found ($M^+ + H$) 262.1596.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^1H and ^{13}C spectra and spectral data are available for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(8) (a) Authors thank anonymous referees' for suggesting these experiments. The reaction of cyclohexylcarbaldehyde with 4-phenylisoquinoline has resulted in an inseparable mixture of alkylated (**6a**) and acylated (**6b**) products, which was characterized by GC−MS analysis (see Supporting Information for the GC−MS spectra). (b) Authors thank anonymous referees' for suggestions.

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