Cobalt-Catalyzed Chelation-Assisted Alkylation of Arenes with Primary and Secondary Alkyl Halides

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Abstract: Cobalt–N-heterocyclic carbene catalytic systems have been developed for chelation-assisted ortho-alkylation of aromatic compounds with alkyl halides. Aryl imines can be selectively monoalkylated using various primary and secondary alkyl chlorides and bromides at room temperature. The catalytic system is also applicable to 2-arylpyridine derivatives, which, without steric hindrance, are amenable to dialkylation using an excess amount of alkyl halide. Mechanistic experiments including reactions of stereochemical probes and radical clocks indicate that the reaction involves single-electron transfer from the cobalt center to the alkyl halide to form the corresponding alkyl radical, which has a finite lifetime before it undergoes C–C bond formation.

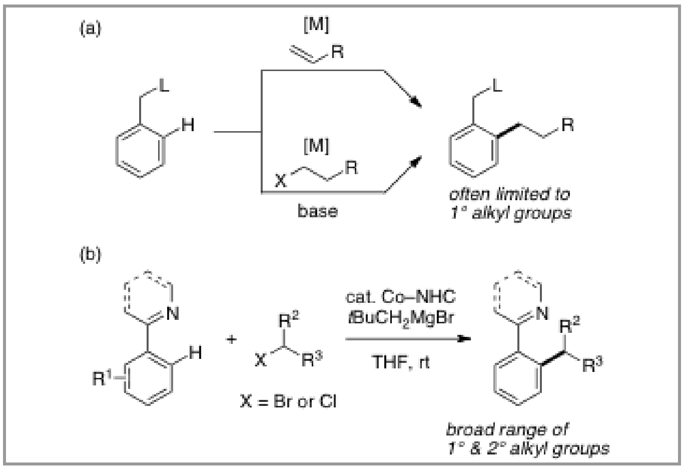
Key words: C–H functionalization; cobalt; alkylation; alkyl halides; radical reaction

Introduction

Alkylation of aromatic compounds is among the most important C–C bond-forming transformations in organic synthesis. Since the discovery of ruthenium-catalyzed ortho alkylation of aromatic ketones with olefins by Murai et al.,[1] transition metal-catalyzed, chelation-assisted alkene hydroarylation has evolved into a versatile approach that complements the classical Friedel–Crafts alkylation.[2,3] However, unlike the Friedel–Crafts chemistry, this approach has met with limited success in the introduction of secondary alkyl groups because of several reasons such as anti-Markovnikov selectivity with terminal alkenes,[4,5] low reactivity of internal alkenes, and isomerization of alkenes bearing allylic hydrogens. In addition, some alkenes (e.g., cyclobutene) are not readily available from commercial sources regardless of their potential utility.

Recently, ortho alkylation using alkyl halides as alkylating agents has attracted significant attention as an alternative to the aforementioned hydroarylation approach.[6,7] Nevertheless, this approach has also met with limited success in the introduction of secondary alkyl groups with some exceptions.[7h] Only handful examples of alkylation with secondary alkyl halides have been reported in the literature,[8-10] presumably due to their low reactivity toward transition metal catalysts and propensity of secondary alkyl–metal complexes for β-hydride elimination.

Over the past several years, we have been interested in cobalt catalysis for C–H bond functionalizations, including those involving chelation-assisted C–H activation.[11] As a part of this research program, we recently found that a cobalt–N-heterocyclic carbene (NHC) catalyst, in combination with a neopentyl Grignard reagent, efficiently promotes ortho-alkylation of aromatic ketimines with alkyl chlorides and bromides.[12] The reaction allows introduction of a variety of primary and secondary alkyl groups under mild conditions. In this article, we report on the full details of this reaction along with expanded substrate scope and mechanistic investigation.



Scheme 1 Cobalt-catalyzed ortho-alkylation of arenes with alkyl halides

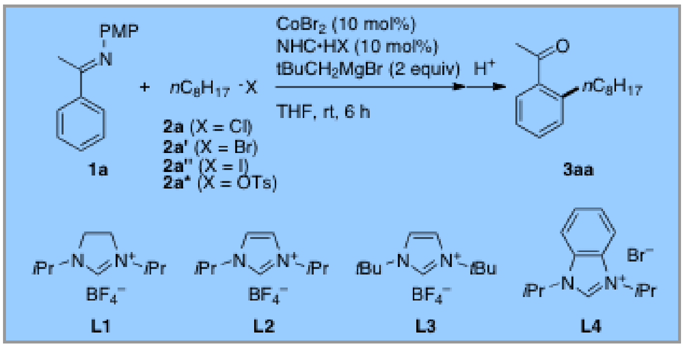
Ortho-Alkylation of Aryl Imines

Prior to this study, we developed cobalt–NHC catalytic systems for the ortho C–H functionalization using an aryl aldimine or an aryl chloride as the electrophile. Thus, cobalt catalysts generated from cobalt salt, imidazolium salt, and neopentylmagnesium bromide promote addition of 2-arylpyridines to aryl aldimines[13] and ortho-arylation of aryl ketimines with aryl chlorides.[14] Ackermann and coworkers also developed cobalt–NHC systems for ortho-arylation of 2-arylpyridines and *N*-pyridylindoles with aryl sulfamates and carbamates,[15] which were later extended to ortho-arylation and -alkylation of the same substrates with the corresponding chlorides.[16] Thus, we envisioned that a similar catalytic system would also allow ortho C–H alkylation with an alkyl halide as the electrophile.

To test this hypothesis, we chose acetophenone imine **1a** and *n*-octyl chloride **2a** as model reactants and screened reaction conditions (Table 1). The catalytic system consisting of $CoBr_2$ (10 mol%), IMes•HCl (10 mol%), and tBuCH$_2$MgBr (2 equiv), which was effective for ortho arylation, promoted the reaction to afford the alkylation product **3aa** in a moderate yield of 38% (entry 1). Other typical NHC preligands such as IPr•HCl and SIMes•HCl were less effective (entries 2 and 3). Further screening led us to find that *N*,*N'*-diisopropylimidazolinium tetrafluoroborate **L1** gave rise to a higher catalytic activity, thus improving the yield to 64% (entry 4). Whereas the unsaturated analogue **L2** and the *tert*-butyl analogue **L3** gave poorer results (entries 5 and 6), the benzo-fused analogue **L4** further improved the yield to 82% (entry 7). As was observed in our previous studies,[13,14] tBuCH$_2$MgBr was the Grignard reagent of choice among other primary and secondary Grignard reagents, which caused ortho neopentylation to only a small extent (< 2% for most cases).

With **L1** and **L4** as preligands, we next examined the effect the leaving group. While the reaction of *n*-octyl bromide **2a'** proceeded smoothly using both **L1** and **L4** (entries 8 and 9), *n*-octyl iodide **2a''** afforded the product **3aa** in only low yields (entries 10 and 11) because of an undesirable side reaction, that is, dehydrohalogenation. *n*-Octyl tosylate **2a*** took part in the reaction at an elevated temperature of 60 °C, affording **3aa** in moderate yields (entries 12 and 13). However, we found that, by simply mixing **2a*** and tBuCH$_2$MgBr, substantial displacement of the tosyloxy group with the bromide anion occurs even at room temperature. This observation suggests that the alkylation with **2a*** involves prior conversion of **2a*** to **2a'**.

Table 1 Screening of NHC Preligands and Leaving Groups[a]



Entry	nC_8H_{17}–X	NHC•HX	Yield (%)[b]
1	**2a**	IMes•HCl	38
2	**2a**	IPr•HCl	13
3	**2a**	SIMes•HCl	20
4	**2a**	**L1**	64
5	**2a**	**L2**	38
6	**2a**	**L3**	14
7	**2a**	**L4**	82[c]
8	**2a'**	**L1**	79[c]
9	**2a'**	**L4**	57
10	**2a''**	**L1**	14
11	**2a''**	**L4**	6
12	**2a***	**L1**	64[c]
13	**2a***	**L4**	49[c]

[a] The reaction was performed on a 0.3 mmol scale using 1.2–1.5 equiv of *n*-octyl halide. PMP = *p*-methoxyphenyl.

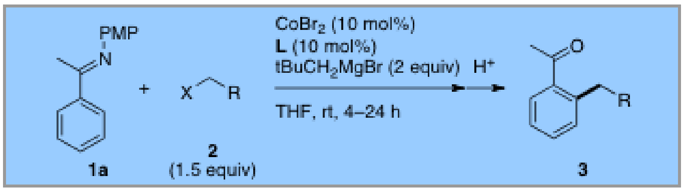
[b] Determined by GC using *n*-tridecane as an internal standard.

[c] Isolated yield.

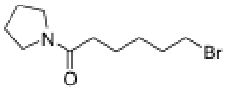
[d] The reaction was performed at 60 °C.

We next explored the scope of the Co–**L1** and Co–**L4** catalytic systems for the alkylation of **1a** with a variety of primary alkyl chlorides and bromides (Table 2). The reaction of *n*-hexyl bromide on a 10 mmol scale afforded the product **3ab** in 77% yield (entry 1). 5-Bromo-1-pentene afforded the expected alkylation product **3ad** as the major product, which was accompanied by a small amount of the isomer **3ad'** arising from olefin isomerization (entry 4). Chemoselective C–Br bond cleavage/alkylation was achieved for 1-bromo-4-fluorobutane and 1-bromo-4-chlorobutane (entries 5 and 6). On the other hand, 6-bromohexyl tosylate afforded the expected product **3ag** along with a minor product **3ag'** bearing 6-bromohexyl group (entry 7). The latter product appears to have formed through OTs/Br exchange between the major product **3ag** and tBuCH$_2$MgBr (vide supra). Dihalogenated substrates having alkyl–Cl and aryl–X (X = F or Cl) moieties underwent chemoselective activation of the former, affording the products **3ah** and **3ai** in good yields (entries 8 and 9). Alkyl halides hindered at the β-position, such as neopentyl bromide, trimethylsilylmethyl chloride, and cyclopentylmethyl bromide, smoothly participated in the reaction (entries 10–12). Alkyl bromides bearing acetal or secondary amide moiety could be tolerated (entries 13 and 14). An alkyl chloride containing a pyridine ring reacted rather sluggishly, presumably due to coordination of the pyridine nitrogen atom to the catalyst (entry 15).

Table 2 Alkylation of **1a** with Primary Alkyl Halides[a]



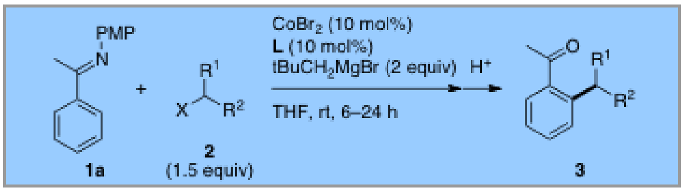
Entry	**2**/**L**/Time (h)	Product(s)	Yield (%)[b]
1[c]	 **2b'**/**L1**/6	**3ab**	77
2	 **2c**/**L4**/24	**3ac**	73
3	 **2c'**/**L1**/24	**3ac**	82
4	 **2d'**/**L1**/6	**3ad** (R = -(CH$_2$)$_3$CH=CH$_2$) **3ad'** (R = -(CH$_2$)$_2$CH=CHCH$_3$)	66[d] 6[d]
5	 **2e'**/**L1**/24	**3ae** (R = -(CH$_2$)$_4$F)	73
6	 **2f'**/**L1**/24	**3af** (R = -(CH$_2$)$_4$Cl)	80
7	 **2g'**/**L1**/4	**3ag** (R = -(CH$_2$)$_6$OTs) **3ag'** (R = -(CH$_2$)$_6$Br)	71 18
8	 **2h** (X = F)/**L4**/24	**3ah**	77

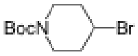
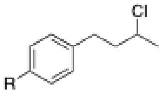
9	**2i** (X = Cl)/**L4**/24	**3ai**	61
10	 **2j'**/**L1**/13	**3aj**	86
11	 **2k**/**L1**/24	**3ak**	65
12	 **2l'**/**L1**/14	**3al**	87
13	 **2m'**/**L4**/24	**3am** (R = -$(CH_2)_3C(=O)CH_3$)	69
14[e]	 **2n'**/**L1**/24	**3an**	41[f]
15	 **2o**/**L4**/24	**3ao**	19[g]

[a] Unless otherwise noted, the reaction was performed on a 0.3 mmol scale.
[b] Isolated yield.
[c] 10 mmol scale.
[d] Obtained as a mixture. The ratio was determined by ^1H NMR.
[e] 2 equiv of **2n'** was used, and an additional 1 equiv of tBuCH$_2$MgBr was added at a reaction time of 2 h.
[f] Obtained as a mixture with **2n'** and its β-elimination product.
[g] Obtained as a mixture with *p*-anisidine.

The present catalytic system also allowed alkylation of **1a** with a broad range of secondary alkyl chlorides and bromides, as summarized in Table 3. Four-to-twelve-membered cycloalkyl halides participated in the reaction to afford the corresponding products **3ap**–**3at** in moderate to good yields (entries 1–7). Boc-protected 4-bromopiperidine also furnished the product **3au** albeit in a moderate yield (entry 8). With the Co–**L1** catalyst, acyclic secondary alkyl halides such as isopropyl chloride/bromide and *sec*-butyl bromide afforded the alkylation products **3av** and **3aw** in moderate yields with high ratios of the secondary and primary isomers (*i*:*n* up to 99:1; entries 9–11). For these cases, the Co–**L4** catalyst improved the product yields by ca. 10–20% but deteriorated the secondary-to-primary ratios (*i*:*n* = 8:2 to 7:3). Exclusive formation of the 3-pentylation product **3ax** was observed with 3-bromopentane as the substrate (entry 12). Secondary alkyl chlorides containing aromatic moieties, including one bearing *para*-chlorophenyl group, were also amenable to the present reaction (entries 13–15). The reaction of *exo*-2-chloronorbornane resulted in predominant formation of the *exo*-arylation product (entry 16).

Table 3 Alkylation of **1a** with Secondary Alkyl Halides[a]



En-try	2	L	Time (h)	Product	Yield (%)[b]
1	cC_4H_7Cl (**2p**)	**L4**	24	**3ap**	51
2	cC_4H_7Br (**2p'**)	**L1**	24	**3ap**	75
3[c]	cC_5H_9Cl (**2q**)	**L1**	24	**3aq**	78
4	$cC_6H_{11}Cl$ (**2r**)	**L4**	12	**3ar**	73
5	$cC_6H_{11}Br$ (**2r'**)	**L1**	6	**3ar**	90
6	$cC_7H_{13}Cl$ (**2s**)	**L4**	24	**3as**	84
7[c,d]	$cC_{12}H_{23}Cl$ (**2t**)	**L1**	24	**3at**	65
8[c,d]	 **2u**	**L1**	24	**3au**	42
9	iC_3H_7Cl (**2v**)	**L1**	6	**3av** (i:n = 99:1)[e]	65
10	iC_3H_7Br (**2v'**)	**L1**	6	**3av** (i:n = 93:7)[e]	68
11	*sec*-C_4H_9Br (**2w'**)	**L1**	6	**3aw** (i:n = 94:6)[e]	56
12	 **2x'**	**L1**	24	**3ax**	63
					
13	**2y** (R = H)	**L1**	24	**3ay** (i:n = 94:6)[e]	76
14	**2z** (R = OMe)	**L1**	24	**3az** (i:n = 94:6)[e]	61
15	**2aa** (R = Cl)	**L1**	12	**3aaa** (i:n = 86:14)[e]	75
16	 **2ab**	**L1**	24	**3aab** (*exo*:*endo* = 90:10)	82

[a] The reaction was performed on a 0.3 mmol scale.
[b] Isolated yields.
[c] An additional 1 equiv of tBuCH$_2$MgBr was added at a reaction time of 2 h or 5 h.
[d] 2 equiv of alkyl halide was used.
[e] The ratio of the secondary and primary alkylation products.

The scope of aromatic imines was then explored using randomly chosen cycloalkyl halides as the reaction partners (Figure 1). Imines derived from para-substituted (methoxy, fluoro, chloro, and phenyl) acetophenones afforded the products **3br**, **3co**, **3dq**, and **3eq** in moderate to good yields, while *p*-bromoacetophenone imine gave a complex mixture of products arising from ortho alkylation and cross-coupling on the C–Br bond. Alkylation of *m*-tolyl, 2-naphthyl, and 3-fluorenyl groups occurred at the less hindered position with exclusive regioselectivity (see the products **3fq**, **3gq**, and **3ho**). On the other hand, a methylenedioxy group exhibited a directing effect so that alkylation took place on its proximity, thus affording the product **3ip** and its regioisomer in a ratio of 84:16. Tetralone- and propiophenone-derived imines also smoothly participated in the reaction (see the products **3jr** and **3kq**). The C2 positions of thiophene and indole were also amenable to the present alkylation, affording the corresponding cyclohexylated products **3lo** and **3mq** in modest yields.

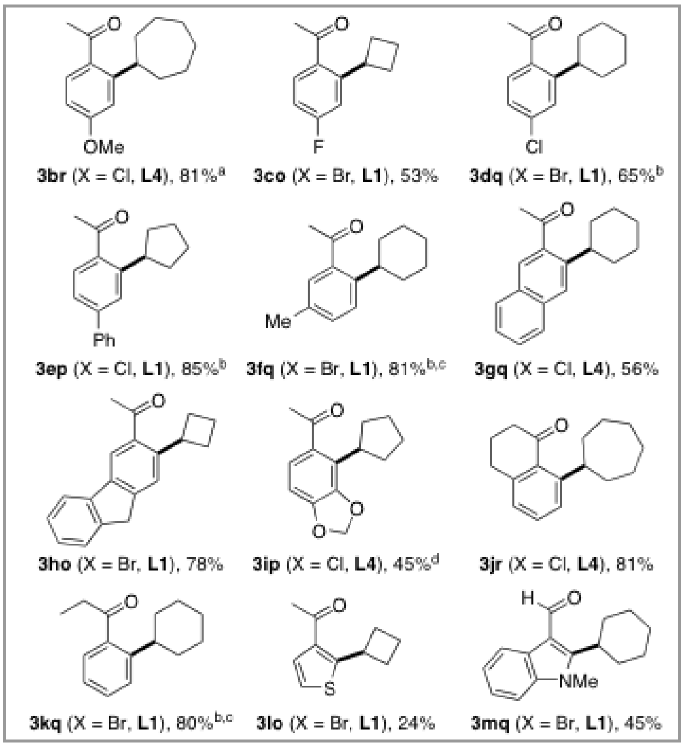
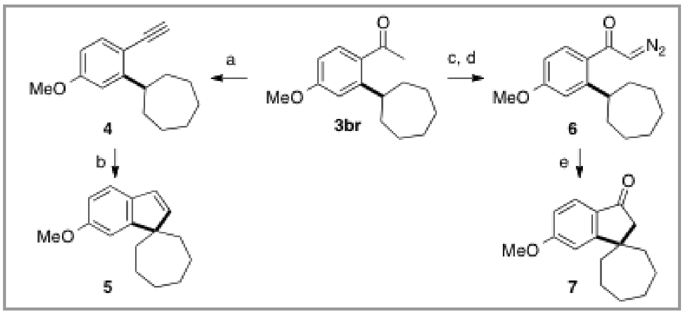


Figure 1 Products of cycloalkylation of various aryl imines (0.3 mmol scale, reaction time = 24 h). [a] Reaction time was 6 h. [b] An additional tBuCH$_2$MgBr (1 equiv) was added at a reaction time of 2, 4, or 5 h. [c] 2 equiv of alkyl halide was used. [d] Obtained as a mixture with its regioisomer in a ratio of 84:16.

The present cycloalkylation products can be transformed into unique benzo-fused spirocycles through manipulation of the acetyl and cycloalkyl groups (Scheme 2). Conversion of the acetyl group of **3br** to an ethynyl group is followed by platinum-catalyzed carbocyclization[17] to afford indene **5** in a moderate yield. Alternatively, diazo transfer to the acetyl group of **3br** and subsequent rhodium-catalyzed intramolecular C–H insertion gave indenone **7** in 27% overall yield (unoptimized).



Scheme 2 Transformations of cycloalkylation product **3br** to benzo-fused spirocycles. Reaction conditions: a) LDA, ClP(O)(OEt)$_2$, THF, –78 °C to rt, then LDA, –78 °C to rt, 56%; b) PtCl$_2$, CuBr, toluene, 100 °C, 77%; c) LiHMDS, THF, –78 °C, then CF$_3$CO$_2$CH$_2$CF$_3$, –78 °C to rt; d) 4-acetamidobenzenesulfonyl azide, H$_2$O, Et$_3$N, MeCN, rt, 75% (two steps); e) Rh$_2$(OAc)$_4$, CH$_2$Cl$_2$, rt, 36%.

Ortho-Alkylation of 2-Arylpyridines

The present catalytic system is also applicable to ortho-alkylation of 2-arylpyridine derivatives with primary and secondary alkyl chlorides and bromides (Figure 2). The reaction of 2-phenylpyridine **8a** and *n*-octyl chloride **2a** (1.5 equiv) using the Co–**L1** catalytic system afforded a monoalkylation product **9aa** in 71% yield, which was accompanied by a dialkylation product **10aa** in 16% yield. A similar result was obtained in the reaction of **8a** with neopentyl bromide (see **9aj**). The formation of **10aa** was notable because the reaction of aryl imines did not produce any dialkylation products (vide supra), and also because the Ackermann's catalytic system (Co(acac)$_3$, IMes•HCl, CyMgBr in DMPU) did not cause dialkylation of the same substrate.[16] When the reaction was performed using increased amounts of **2a** (2.5 equiv) and tBuCH$_2$MgBr (3 equiv), **10aa** was obtained as the dominant product in 76% yield. Ortho-dialkylation was also feasible using secondary alkyl halides as the alkylating agents. Thus, para-substituted 2-arylpyridine derivatives participated in the reaction with 2.5 equiv of isopropyl chloride, cyclobutyl bromide, or cyclohexyl chloride to afford dialkylation products **10bv**, **10cp**, and **10dr** in moderate to good yields, accompanied by a small amount of the corresponding monoalkylation products. Exclusive monoalkylation was achieved using 2-arylpyridine derivatives bearing a meta-substituent on the aryl moiety or a 3-substituent on the pyridine ring (see **10ep**, **10fr**, and **10gp**). Of note was the substrate bearing meta-chlorophenyl group, which underwent cyclohexylation at the more hindered ortho position (**10fr**), presumably because of secondary directing effect of the lone pair of the chlorine atom.[18] Similar secondary directing effects have also been observed in Ackermann's cobalt-catalyzed ortho-arylation of 2-arylpyridines with meta-alkoxy and -fluoro substituents.[15,16] Arylpyridine derivatives having only one reactive site also participated in the reaction with secondary alkyl halides (see **10hv**, **10iq**, and **10jq**).

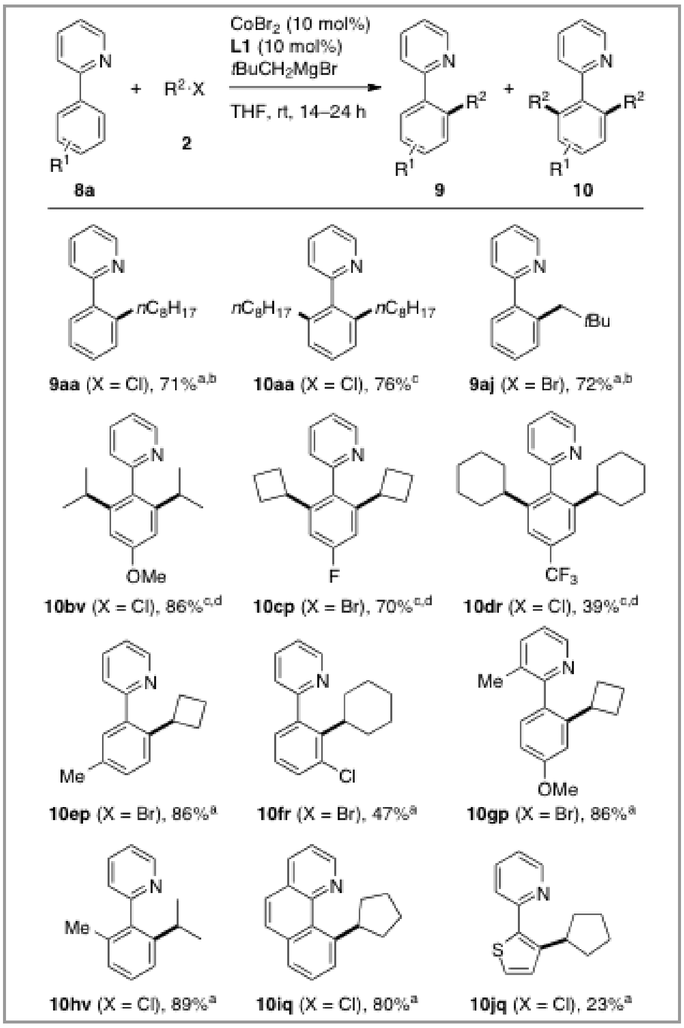
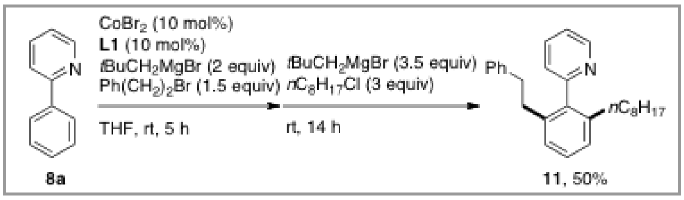


Figure 2 Ortho-alkylation of 2-arylpyridines with alkyl halides. [a] 1.5 equiv of alkyl halide and 2 equiv of tBuCH$_2$MgBr were used. [b] Dialkylation products were obtained as byproducts (< 20% yield). [c] 2.5 equiv of alkyl halide and 3 equiv of tBuCH$_2$MgBr were used. [d] Monoalkylation products were obtained as byproducts (< 10% yield).

The high catalytic activity of the present system allowed sequential introduction of different alkyl groups onto 2-phenylpyridine in a one-pot operation (Scheme 3). Thus, the reaction of **8a** and 2-phenylethyl bromide (1.5 equiv) was performed under the standard monoalkylation conditions, followed by addition of excess amounts of *n*-octyl chloride (3.0 equiv) and tBuCH$_2$MgBr (3.5 equiv) to afford the unsymmetrically substituted dialkylation products **11** in 50% isolated yield, along with symmetric dialkylation products derived from *n*-octyl chloride and 2-phenylethyl bromide as byproducts (19% and 4% GC yields, respectively).[19]



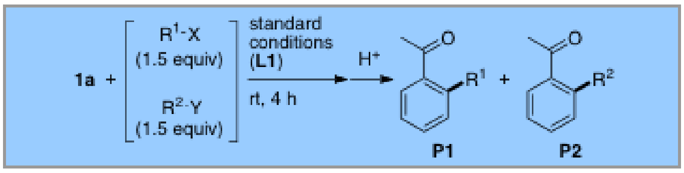
Scheme 3 Sequential ortho alkylation with different alkyl halides

Mechanistic Investigations

Having established the synthetic scope of the ortho alkylation reaction, we turned our attention to its mechanistic aspects. The present reaction appears to have some relevance to the cobalt-catalyzed cross-coupling reactions of alkyl halides and aryl Grignard reagents developed by Yorimitsu/Oshima and Cahiez.[20,21] However, the scopes of alkyl halides for these reactions and the present reaction do not completely overlap. The cross-coupling reaction is applicable to primary and secondary alkyl iodides and bromides but not to chlorides. Thus, we became particularly interested in the carbon–halogen bond activation step of the present reaction. Below we describe a series of experiments that we performed to gain insight into this step.

Chemoselective activation of the alkyl bromide moiety over the alkyl chloride moiety in the reaction of 1-bromo-4-chlorobutane prompted us to systematically investigate the chemoselectivity of the reaction by intermolecular competition experiments (Table 4). Not unexpectedly, a competition of nC$_{10}$H$_{21}$Br and nC$_8$H$_{17}$Cl in the reaction with **1a** resulted in predominant formation of the alkylation product of the former (entry 1). In a similar fashion, the reaction using a mixture of isopropyl bromide-d_7 and isopropyl chloride resulted in predominant incorporation of the deuterated isopropyl group (entry 2). Interestingly, primary and secondary alkyl bromides (nC$_{10}$H$_{21}$Br and cC$_6$H$_{11}$Br) exhibited a similar reactivity and thus produced the corresponding products in ca. 1:1 ratio (entry 3). We also examined the effect of the ring size of cycloalkyl halide on its relative reactivity. Thus, cyclohexyl chloride reacted in preference to cyclobutyl chloride (entry 4), while it lost the competition with cyclopentyl chloride or cycloheptyl chloride (entries 5 and 6).

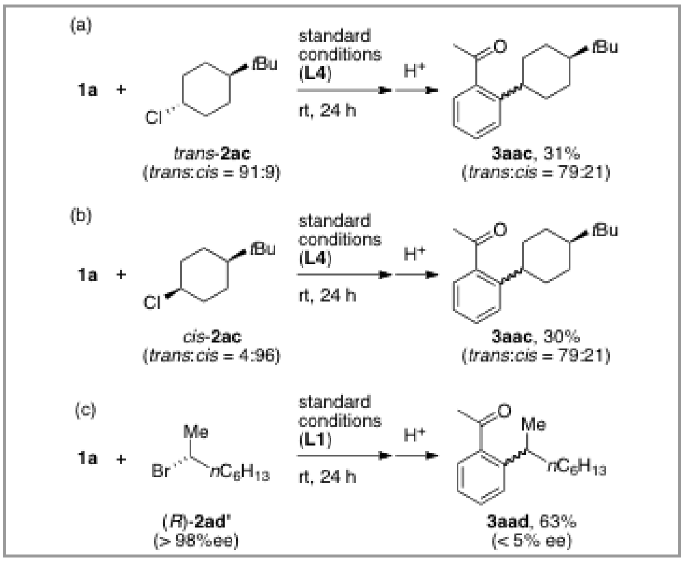
Table 4 Intermolecular Competition of Two Alkyl Halides[a]



Entry	R^1–X	R^2–Y	Yield (%)[b]	
			P1	**P2**
1	nC$_{10}$H$_{21}$Br	nC$_8$H$_{17}$Cl	64	2
2	iC$_3$D$_7$Br	iC$_3$H$_7$Cl	74	6
3	nC$_{10}$H$_{21}$Br	cC$_6$H$_{11}$Br	36	33
4	cC$_6$H$_{11}$Cl	cC$_4$H$_7$Cl	35	12
5	cC$_6$H$_{11}$Cl	cC$_5$H$_{11}$Cl	10	58
6	cC$_6$H$_{11}$Cl	cC$_7$H$_{13}$Cl	11	64

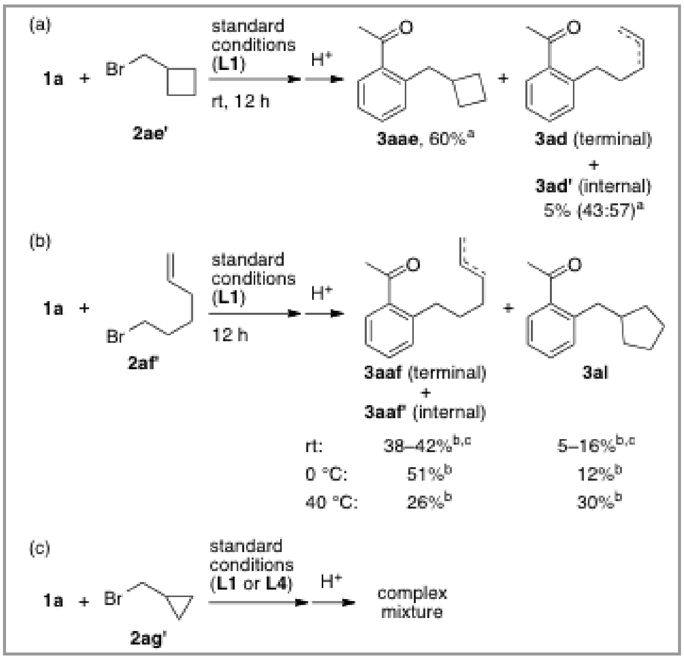
a The reaction was performed on a 0.3 mmol scale.
b Estimated by GC using *n*-tridecane as an internal standard.

The *exo*/*endo* selectivity of 90:10 in the reaction of *exo*-2-chloronorbornane (Table 3, entry 16) shows that the reaction is not stereospecific. Given this result, we looked into the stereochemical course of the reaction using a few probes (Scheme 4). Reactions of **1a** with both the trans and cis isomers of 1-chloro-4-*tert*-butylcyclohexane **2ac** resulted in the formation of the corresponding alkylation product **3aac** with the same trans/cis ratio of ca. 8:2 (Scheme 4a, b). Thus, the diastereochemical information in the starting materials was completely lost during the reaction. Furthermore, the reaction of **1a** with (*R*)-2-bromooctane **2ad** (> 98% ee) afforded the product **3aad** as a virtually racemic mixture, clearly showing involvement of a stereochemical mutation process (Scheme 4c).



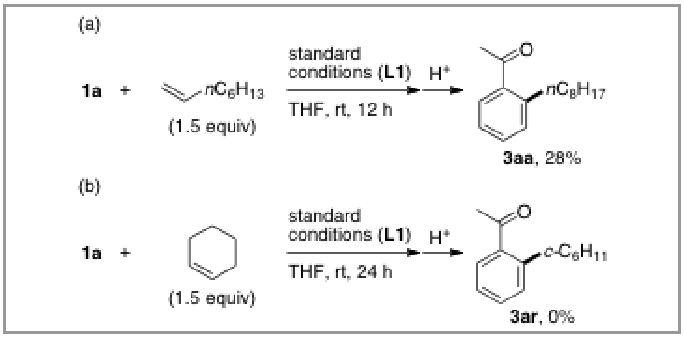
Scheme 4 Reactions with stereochemistry probes.

The above results are indicative of a radical process in the present reaction. To further probe this possibility, radical clock experiments were performed (Scheme 5). The reaction of **1a** with cyclobutylmethyl bromide **2ae'** under the standard conditions afforded a direct alkylation product **3aae** in 60% yield along with ring-opening alkylation byproducts **3ad** and **3ad'** (Scheme 5a). Note that the identity of the byproducts was confirmed by comparison with the authentic samples reported in Table 2, entry 4. The formation of **3ad** and **3ad'** suggests that the reaction involves cyclobutylmethyl radical, which can undergo ring-opening to give 4-pentenyl radical at a rate of 5 x 10^{3} s^{-1}.[22] Another probe substrate, 6-bromo-1-hexene **2af'**, showed somewhat puzzling behavior (Scheme 5b). For three runs performed under the standard conditions at room temperature, direct alkylation products **3aaf**/**3aaf'** were obtained in modest overall yield of ca. 40%, which were accompanied by a varying amount (5–16%) of a ring-closing alkylation product **3al** (the identity confirmed by comparison with the authentic sample reported in Table 2, entry 12).[23] We observed a certain correlation between the reaction temperature and the fate of **2af'**. Thus, while formation of the direct alkylation products is favored at a low temperature (0 °C), at a higher temperature (40 °C), the ring-closing alkylation even overrides the direct alkylation. While we have not figured out the factors behind the irreproducibility and the varying yield, these observations support the formation of 5-hexenyl radical and its cyclization to cyclopentylmethyl radical (rate constant = 2.3 x 10^{5} s^{-1})[22] in the cobalt catalysis. Note that, for unknown reasons, the reaction using cyclopropylmethyl bromide **2ag'** led to the formation of a complex mixture, in which we could not detect either a direct alkylation product or a ring-opening alkylation product (Scheme 5c).



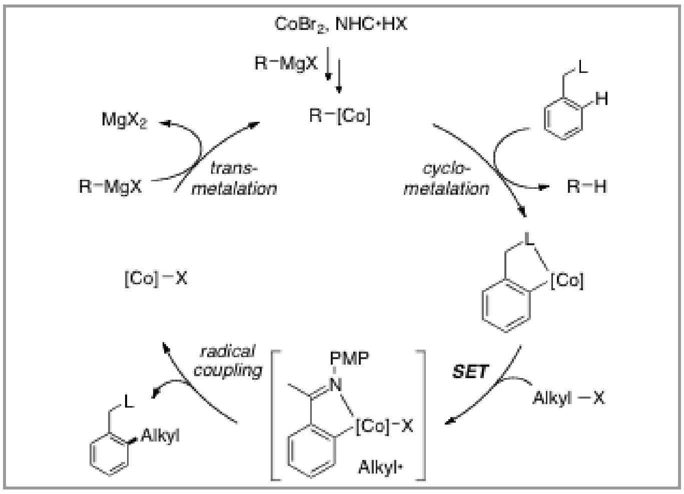
Scheme 5 Radical clock experiments. [a] Isolated yield. [b] Determined by GC using *n*-tridecane as an internal standard. [c] Results obtained by three runs.

Finally, control experiments using alkenes instead of alkyl halides were performed (Scheme 6). The reaction of **1a** with 1-octene afforded the ortho-octylation product **3aa** in 28% yield (Scheme 6a), which was significantly lower than that obtained using *n*-octyl bromide (Table 1, entry 8). Furthermore, cyclohexene failed to give the corresponding cyclohexylated product **3ar** (Scheme 6b). These observations indicate that the major productive pathway of the present reaction does not involve formation of alkene via dehydrohalogenation of alkyl halide.



Scheme 6 Control experiments using olefins as reaction partners

While further experiments are necessary not only on the C–X cleavage step but also on the C–H activation step to completely unravel the reaction mechanism, we propose a catalytic cycle outlined in Scheme 7, assuming that the first step is cyclometalation of aryl imine or 2-arylpyridine with an organocobalt species.[24] The resulting cobaltacycle intermediate undergoes single-electron transfer to the alkyl halide,[25] which results in formation of the corresponding alkyl radical and one-electron oxidation of the cobalt center. The alkyl radical would then undergo radical coupling with the aryl group on the cobalt center to afford the ortho-alkylation product. Transmetalation of the resulting cobalt halide and the Grignard reagent regenerates the alkylcobalt species. Judging from the radical clock experiments, the radical coupling process should occur at a relatively fast rate.



Scheme 7 Proposed catalytic cycle

In conclusion, we developed cobalt-based catalytic systems for imine- and pyridine-directed ortho-alkylation of aromatic compounds with alkyl chlorides and bromides. The reaction features mild reaction temperatures, broad scope of primary and secondary alkyl halides, and useful chemoselectivity. Mechanistic experiments indicate that the reaction involves a unique combination of cobalt-mediated cyclometalation and single-electron transfer processes. Exploration of other electrophilic reaction partners for cobalt-catalyzed ortho C–H functionalization is currently ongoing.

All reactions dealing with air- and moisture-sensitive compounds were performed by standard Schlenk techniques in oven-dried reaction vessels under nitrogen atmosphere. Analytical thin-layer chromatography (TLC) was performed on Merck 60 F254 silica gel plates. Flash chromatography was performed using 40-63 µm silica gel (Si 60, Merck). ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on JEOL ECA-400 (400 MHz) or Bruker AV-400 (400 MHz) spectrometers. ^{1}H and ^{13}C NMR spectra are reported in parts per million (ppm) downfield from an internal standard, tetramethylsilane (0 ppm) and $CHCl_3$ (77.0 ppm), respectively. Gas chromatographic (GC) analysis was performed on a Shimadzu GC-2010 system equipped with an FID detector and a capillary column, DB-5 (Agilent J&W, 0.25 mm i.d. x 30 m, 0.25 µm film thickness). High-performance liquid chromatograph (HPLC) analysis was performed using Shimadzu LC-20 AD system equipped with Shimadzu SPD-20A UV/vis detector and Daicel Chiralpak IC column. High-resolution mass spectra (HRMS) were obtained with a Waters Q-Tof Premier LC HR mass spectrometer. Unless otherwise noted, reagents were purchased from Aldrich, Alfa Aesar, or other commercial suppliers and were used as received. THF was distilled over Na/benzophenone. 1,3-Diisopropylbenzimidazolium bromide (**L4**) was synthesized according to the literature procedure.[26] Neopentylmagnesium bromide was prepared from neopentyl bromide and magnesium turnings in anhydrous THF and titrated before use. Aryl imines and 2-arylpyridines were synthesized according to the literature procedures.[27,28] Alkyl halides **2h**,[12] **2i**,[12] **2n'**,[12] **2o**,[12] **2t**,[29] **2y**,[30] **2z**,[30] **2aa**,[30] *trans*/*cis*-**2ac**,[31] and (*R*)-**2ad'**[32] were synthesized according to the literature procedures. The characterization data for **2z** and **2aa** are given in the Supporting Information.

1-(2-Octylphenyl)ethanone (3aa): Typical Procedure for Cobalt-Catalyzed Ortho-Alkylation

In a 10 mL Schlenk tube were placed $CoBr_2$ (6.6 mg, 0.03 mmol), 1,3-diisopropylbenzimidazolium bromide (**L4**, 8.5 mg, 0.03 mmol), (*E*)-4-methoxy-*N*-(1-phenylethylidene)aniline (**1a**, 67.6 mg, 0.30 mmol), 1-chlorooctane (**2a**, 76.5 µL, 0.45 mmol), and THF (0.69 mL). To the mixture was added a THF solution of tBuCH$_2$MgBr (1.92 M, 0.31 mL, 0.60 mmol) dropwise at 0 °C. The reaction mixture was stirred at room temperature for 6 h, and then quenched by the addition of 3 N HCl (1.0 mL). The resulting mixture was stirred at room temperature for 1 h, and then extracted with ethyl acetate (3 x 10 mL). The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (eluent: hexane/EtOAc = 40/1) to afford **3aa** as a light yellow oil (57.3 mg, 82%).

1-(2-Octylphenyl)ethanone (3aa)

Light yellow oil; yield: 57.3 mg (82%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.87 (t, J = 7.2 Hz, 3H), 1.26-1.35 (m, 10H), 1.53-1.59 (m, 2H), 2.57 (s, 3H), 2.83 (t, J = 8.0 Hz, 2H), 7.22-7.26 (m, 2H), 7.36-7.40 (m, 1H), 7.60-7.62 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 22.6, 29.3, 29.4, 29.7, 29.9, 31.9 (two signals overlapping), 34.0, 125.5, 128.9, 131.1, 131.2, 138.0, 142.9, 202.3.

HRMS (ESI) m/z $[M + H]^+$ calcd for $C_{16}H_{25}O$: 233.1905; found: 233.1903.

1-(2-Hexylphenyl)ethanone (3ab)

The reaction was performed on a 10 mmol scale using a 100-mL 2-necked flask as a reaction vessel.

Light yellow oil; yield: 1.58 g (77%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 0.88 (t, *J* = 6.8 Hz, 3H), 1.28-1.38 (m, 6H), 1.54-1.58 (m, 2H), 2.57 (s, 3H), 2.83 (t, *J* = 8.0 Hz, 2H), 7.22-7.26 (m, 2H), 7.35-7.39 (m, 1H), 7.60-7.62 (m, 1H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 14.0, 22.6, 29.4, 29.9, 31.7, 31.8, 34.0, 125.5, 128.9, 131.1, 131.2, 138.1, 142.8, 202.3.

HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{21}O$: 205.1592; found: 205.1594.

1-(2-Phenethylphenyl)ethanone (3ac)[33]

Light yellow oil; yield: 48.9 mg (73%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 2.58 (s, 3H), 2.96 (t, *J* = 8.0 Hz, 2H), 3.22 (t, *J* = 8.0 Hz, 2H), 7.24-7.35 (m, 7H), 7.44 (td, *J* = 7.5 Hz, 1.3 Hz, 1H), 7.72 (dd, *J* = 7.7 Hz, 1.0 Hz, 1H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 29.6, 36.3, 38.2, 125.8, 125.9 (two signals overlapping), 128.2, 128.6, 129.2, 131.42, 131.45, 137.8, 141.9, 201.9.

1-(2-(Pent-4-en-1-yl)phenyl)ethanone (3ad)

Obtained as a mixture with (*E*)-1-(2-(pent-3-en-1-yl)phenyl)ethanone (**3ad'**); light yellow oil; yield: 40.9 mg (72%, **3ad**:**3ad'** = 92:8).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.64-1.71 (m, 2H), 2.10-2.15 (m, 2H), 2.57 (s, 3H), 2.86 (t, *J* = 6.0 Hz, 2H), 4.97 (ddt, *J* = 10.2 Hz, 2.0 Hz, 1.1 Hz, 1H), 5.02 (ddt, *J* = 17.1 Hz, 1.7 Hz, 1.6 Hz, 1H), 5.85 (ddt, *J* = 17.0 Hz, 10.3 Hz, 6.6 Hz, 1H), 7.24-7.28 (m, 2H), 7.39 (td, *J* = 7.4 Hz, 1.2 Hz, 1H), 7.64 (dd, *J* = 8.4 Hz, 1.2 Hz, 1H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 29.9, 30.9, 33.5, 33.7, 114.6, 125.7, 129.1, 131.2, 131.3, 137.9, 138.6, 142.5, 202.1.

HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{13}H_{17}O$: 189.1279; found: 189.1280.

1-(2-(4-Fluorobutyl)phenyl)ethanone (3ae)

Light yellow oil; yield: 42.5 mg (73%)

^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.67-1.82 (m, 4H), 2.58 (s, 3H), 2.89 (t, *J* = 7.6 Hz, 2H), 4.46 (dt, $^{1}J_{\mathrm{C–F}}$ = 47.2 Hz, *J* = 5.6 Hz, 2H), 7.25-7.29 (m, 2H), 7.40 (td, *J* = 7.4 Hz, *J* = 1.2 Hz, 1H), 7.66 (d, *J* = 7.6 Hz, 1H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 27.3 (d, $^{3}J_{\mathrm{C–F}}$ = 5.2 Hz), 29.8, 30.3 (d, $^{2}J_{\mathrm{C–F}}$ = 19.2 Hz), 33.5, 84.0 (d, $^{1}J_{\mathrm{C–F}}$ = 163 Hz), 125.9, 129.3, 131.2, 131.4, 137.7, 142.3, 201.9.

HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{16}FO$: 195.1185; found: 195.1185.

1-(2-(4-Chlorobutyl)phenyl)ethanone (3af)

Light yellow oil; yield: 50.4 mg (80%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.70-1.75 (m, 2H), 1.81-1.86 (m, 2H), 2.58 (s, 3H), 2.87 (t, *J* = 7.6 Hz, 2H), 3.55 (t, *J* = 6.8 Hz, 2H), 7.25-7.29 (m, 2H), 7.39 (t, *J* = 7.6 Hz, 1H), 7.66 (d, *J* = 8.0 Hz, 1H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 28.9, 29.8, 32.5, 33.2, 44.8, 125.9, 129.3, 131.2, 131.5, 137.6, 142.1, 201.9.

HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{12}H_{16}ClO$: 211.0890; found: 211.0887.

6-(2-Acetylphenyl)hexyl 4-methylbenzenesulfonate (3ag)

Brown oil; yield: 80.4 mg (71%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.31-1.40 (m, 4H), 1.50-1.53 (m, 2H), 1.62-1.66 (m, 2H), 2.44 (s, 3H), 2.57 (s, 3H), 2.79 (t, *J* = 7.6 Hz, 2H), 4.01 (t, *J* = 6.4 Hz, 2H), 7.21-7.27 (m, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.37 (td, *J* = 7.2 Hz, *J* = 1.2 Hz, 1H), 7.64 (dd, *J* = 8.0 Hz, *J* = 1.2 Hz, 1H), 7.79 (d, *J* = 8.4 Hz, 2H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 21.6, 25.1, 28.7, 28.9, 29.9, 31.5, 33.8, 70.6, 125.7, 127.8, 129.1, 129.8, 131.1, 131.4, 133.2, 137.7, 142.6, 144.6, 202.1.

HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{27}O_4S$: 375.1630; found: 375.1632.

1-(2-(6-Bromohexyl)phenyl)ethanone (3ag')

Light yellow oil; yield: 15.0 mg (18%).

^{1}H NMR (400 MHz, CDCl$_3$): δ 1.41-1.49 (m, 4H), 1.54-1.63 (m, 2H), 1.83-1.90 (m, 2H), 2.84 (s, 3H), 2.84 (t, *J* = 7.6 Hz, 2H), 3.40 (t, *J* = 6.8 Hz, 2H), 7.24-7.27 (m, 2H), 7.39 (td, *J* = 7.6 Hz, *J* = 1.2 Hz, 1H), 7.64 (d, *J* = 7.6 Hz, 1H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 28.0, 28.8, 29.9, 31.5, 32.7, 33.89, 33.93, 125.7, 129.1, 131.1, 131.3, 137.8, 142.7, 202.1.

HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{20}BrO$: 283.0698; found: 283.0697.

1-(2-(3-(4-Fluorophenyl)propyl)phenyl)ethanone (3ah)

Light yellow oil; yield: 59.2 mg (77%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.85-1.93 (m, 2H), 2.57 (s, 3H), 2.67 (t, *J* = 7.6 Hz, 2H), 2.89 (t, *J* = 7.6 Hz, 2H), 6.96 (t, *J* = 8.4 Hz, 2H), 7.13 -7.17 (m, 2H), 7.23-7.29 (m, 2H), 7.40 (t, *J* = 7.6 Hz, 1H), 7.66 (d, *J* = 7.6 Hz, 1H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 29.8, 33.4, 33.7, 35.0, 118.9 (d, $^{2}J_{\mathrm{C–F}}$ = 21 Hz), 125.8, 129.2, 129.6 (d, $^{3}J_{\mathrm{C–F}}$ = 8 Hz), 131.1, 131.4, 137.7, 137.9 (d, $^{4}J_{\mathrm{C–F}}$ = 4 Hz), 142.3, 161.1 (d, $^{1}J_{\mathrm{C–F}}$ = 241 Hz), 202.0.

HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{17}H_{18}FO$: 257.1338; found: 257.1342.

1-(2-(3-(4-Chlorophenyl)propyl)phenyl)ethanone (3ai)

Light yellow oil; yield: 49.9 mg (61%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.82-1.93 (m, 2H), 2.57 (s, 3H), 2.66 (t, *J* = 7.6 Hz, 2H), 2.88 (t, *J* = 7.6 Hz, 2H), 7.13 (d, *J* = 8.4 Hz, 2H), 7.22 -7.29 (m, 4H), 7.39 (td, *J* = 7.6 Hz, 1.2 Hz, 1H), 7.66 (dd, *J* = 7.6 Hz, 1.2 Hz, 1H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 29.8, 33.2, 33.7, 35.2, 125.9, 128.3, 129.3, 129.8, 131.2, 131.4, 131.5, 137.7, 140.8, 142.3, 202.0.

HRMS (ESI) *m/z* [M + H]$^+$ calcd for $C_{17}H_{18}ClO$: 273.1045; found: 273.1046.

1-(2-Neopentylphenyl)ethanone (3aj)

Light yellow oil; yield: 49.3 mg (86%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 0.84 (s, 9H), 2.56 (s, 3H), 2.94 (s, 2H), 7.19 (d, *J* = 7.6 Hz, 1H), 7.23-7.27 (m, 1H), 7.35 (td, *J* = 7.6 Hz, *J* = 1.2 Hz, 1H), 7.54 (dd, *J* = 7.6 Hz, *J* = 0.8 Hz, 1H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 29.4, 30.2, 32.6, 44.4, 125.7, 127.9, 130.0, 133.3, 138.5, 140.4, 203.6.

HRMS (ESI) *m/z* [M + H]$^+$ calcd for $C_{13}H_{19}O$: 191.1436; found: 191.1431.

1-(2-((Trimethylsilyl)methyl)phenyl)ethanone (3ak)

Light yellow oil; yield: 40.4 mg (65%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = -0.05 (s, 9H), 2.56 (s, 3H), 2.62 (s, 2H), 7.06 (d, *J* = 7.6 Hz, 1H), 7.14 (t, *J* = 6.8 Hz, 1H), 7.30 (td, *J* = 7.2 Hz, *J* = 1.2 Hz, 1H), 7.69 (dd, *J* = 7.6 Hz, *J* = 0.8 Hz, 1H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = -1.6, 25.2, 29.5, 123.7, 130.0, 131.0, 131.3, 135.5, 142.3, 201.4.

HRMS (ESI) *m/z* [M + H]$^+$ calcd for $C_{12}H_{19}OSi$: 207.1205; found: 207.1201.

1-(2-(Cyclopentylmethyl)phenyl)ethanone (3al)

Yellow oil; yield: 52.7 mg (87%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.13-1.21 (m, 2H), 1.47-1.54 (m, 2H), 1.57-1.69 (m, 4H), 2.00-2.08 (m, 1H), 2.57 (s, 3H), 2.89 (d, *J* = 7.3 Hz, 2H), 7.22-7.26 (m, 2H), 7.37 (t, *J* = 7.8 Hz, 1H), 7.60 (d, *J* = 7.3 Hz, 1H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 25.0, 30.3, 32.7, 39.5, 42.1, 125.8, 129.0, 131.2, 131.7, 138.5, 142.3, 202.8.

HRMS (ESI) *m/z* [M + H]$^+$ calcd for $C_{14}H_{19}O$: 203.1436; found: 203.1436.

5-(2-Acetylphenyl)pentan-2-one (3am)

Orange oil; yield: 42.1 mg (69%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.83-1.89 (m, 2H), 2.12 (s, 3H), 2.47 (t, *J* = 7.6 Hz, 2H), 2.56 (s, 3H), 2.82 (t, *J* = 7.6 Hz, 2H), 7.24-7.28 (m, 2H), 7.37 (td, *J* = 7.6 Hz, *J* = 1.2 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 25.6, 29.7, 29.8, 33.1, 43.3, 125.9, 129.3, 131.2, 131.5, 137.6, 141.9, 201.9, 208.9.

HRMS (ESI) *m/z* [M + H]$^+$ calcd for $C_{13}H_{17}O_2$: 205.1229; found: 205.1224.

6-(2-Acetylphenyl)-1-(pyrrolidin-1-yl)hexan-1-one (3an)

Obtained as a mixture with 6-bromo-1-(pyrrolidin-1-yl)hexan-1-one and (*E*)-1-(pyrrolidin-1-yl)hex-4-en-1-one (41% yield as determined by weight and ^{1}H NMR analysis).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.38-1.45 (m, 2H), 1.55-1.70 (m, 4H), 1.82-1.87 (m, 2H), 1.90-1.95 (m, 2H), 2.26 (t, *J* = 8.0 Hz, 2H), 2.56 (s, 3H), 2.83 (t, *J* = 8.0 Hz, 2H), 3.40 (t, *J* = 6.8 Hz, 2H), 3.45 (t, *J* = 6.8 Hz, 2H), 7.23-7.25 (m, 2H), 7.38 (t, *J* = 7.6 Hz, 1H), 7.61 (d, *J* = 7.2 Hz, 1H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 24.4, 24.8, 26.1, 29.5, 29.9, 31.5, 33.9, 34.7, 45.6, 46.6, 125.6, 129.0, 131.2, 131.3, 137.9, 142.6, 171.9, 202.2.

HRMS (ESI) *m/z* [M + H]$^+$ calcd for $C_{18}H_{26}NO_2$: 288.1964; found: 288.1965.

1-(2-(3-(Pyridin-3-yl)propyl)phenyl)ethanone (3ao)

Obtained as a mixture with *p*-anisidine; yield (19% yield as determined by weight and ^{1}H NMR analysis).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.89-1.95 (m, 2H), 2.57 (s, 3H), 2.69 (t, *J* = 8.0 Hz, 2H), 2.90 (t, *J* = 8.0 Hz, 2H), 7.18-7.30 (m, 3H), 7.40 (td, *J* = 7.6 Hz, 1.2 Hz, 1H), 7.51 (dd, *J* = 7.6 Hz, 1.0 Hz, 1H), 7.68 (dd, *J* = 7.6 Hz, 1.2 Hz, 1H), 8.43 (d, *J* = 4.0 Hz, 1H), 8.45 (s, 1H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 29.7, 33.0 (two signals overlapping), 33.8, 123.2, 126.0, 129.4, 131.2, 131.5, 135.8, 137.5, 139.9, 147.2, 149.9, 152.8, 201.8.

HRMS (ESI) *m/z* [M + H]$^+$ calcd for $C_{16}H_{18}NO$: 240.1388; found: 240.1386.

1-(2-Cyclobutylphenyl)ethanone (3ap)

Light yellow oil; yield: 26.5 mg (51%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.69-1.82 (m, 1H), 1.96-2.17 (m, 3H), 2.32-2.38 (m, 2H), 2.54 (s, 3H), 4.02 (m, 1H), 7.21-7.25 (m, 1H), 7.40-7.46 (m, 2H), 7.51 (d, *J* = 7.6 Hz, 1H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 18.1, 29.4, 30.0, 38.1, 125.4, 127.2, 127.8, 131.0, 138.2, 144.9, 203.0.

HRMS (ESI) *m/z* [M + H]$^+$ calcd for $C_{12}H_{15}O$: 175.1123; found: 175.1125.

1-(2-Cyclopentylphenyl)ethanone (3aq)[34]

Light yellow oil; yield: 35.7 mg (63%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.54-1.62 (m, 2H), 1.66-1.71 (m, 2H), 1.78-1.83 (m, 2H), 2.03-2.09 (m, 2H), 2.57 (s, 3H), 3.43-3.48 (m, 1H), 7.19-7.23 (m, 1H), 7.39-7.41 (m, 2H), 7.45 (d, *J* = 7.6 Hz, 1H).

^{13}C NMR (100 MHz, CDCl$_3$): δ 25.8, 30.7, 35.1, 41.5, 125.2, 127.1, 127.3, 130.9, 139.9, 145.2, 204.0.

1-(2-Cyclohexylphenyl)ethanone (3ar)[34]

Light yellow oil; yield: 44.2 mg (73%).

^{1}H NMR (400 MHz, CDCl$_3$): δ = 1.15-1.21 (m, 1H), 1.39-1.44 (m, 4H), 1.73-1.85 (m, 5H), 2.57 (s, 3H), 3.00-3.07 (m, 1H), 7.20-7.24 (m, 1H), 7.37-7.40 (m, 2H), 7.47 (d, *J* = 7.2 Hz, 1H).

^{13}C NMR (100 MHz, CDCl$_3$): δ = 26.2, 26.9, 30.8, 34.5, 40.0, 125.3, 127.1, 127.6, 130.9, 139.1, 146.6, 203.8.

1-(2-Cycloheptylphenyl)ethanone (3as)

Light yellow oil; yield: 54.6 mg (84%).

^1H NMR (400 MHz, $CDCl_3$): δ = 1.53-1.71 (m, 8H), 1.76-1.80 (m, 2H), 1.87-1.92 (m, 2H), 2.57 (s, 3H), 3.15-3.20 (m, 1H), 7.17-7.22 (m, 1H), 7.35-7.41 (m, 2H), 7.45 (d, J = 7.6 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.4, 27.7, 30.7, 36.9, 41.6, 125.0, 127.37, 127.42, 131.0, 138.2, 148.7, 203.6.

HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{15}H_{21}O$: 217.1592; found: 217.1593.

1-(2-Cyclododecylphenyl)ethanone (3at)

Light yellow oil; yield: 55.9 mg (65%).

^1H NMR (400 MHz, $CDCl_3$): δ = 1.36-1.75 (m, 20H), 1.75-1.82 (m, 2H), 2.56 (s, 3H), 3.39-3.42 (m, 1H), 7.18-7.22 (m, 1H), 7.38-7.43 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.9, 23.0, 23.2, 24.0 (two signals overlapping), 30.8, 31.8, 34.1, 125.1, 126.9, 128.0, 130.6, 140.3, 146.1, 204.2.

HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{20}H_{31}O$: 287.2375; found: 287.2377.

tert-Butyl 4-(2-acetylphenyl)piperidine-1-carboxylate (3au)

Brown oil; yield: 38.4 mg (42%).

^1H NMR (400 MHz, $CDCl_3$): δ = 1.47 (s, 9H), 1.58-1.63 (m, 2H), 1.77-1.80 (m, 2H), 2.57 (s, 3H), 2.73-2.84 (m, 2H), 3.29 (tt, J = 12.0 Hz, 3.3 Hz, 1H), 4.18-4.23 (brs, 2H), 7.26 (t, J = 7.4 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.41 (t, J = 7.2 Hz, 1H), 7.57 (d, J = 7.6 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.5, 30.4, 33.2, 38.0, 44.5, 79.4, 125.8, 127.2, 128.4, 131.4, 138.4, 145.0, 154.9, 203.0.

HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{18}H_{26}NO_3$: 304.1913; found: 304.1916.

1-(2-Isopropylphenyl)ethanone (3av)[35]

Light yellow oil; yield: 31.5 mg (65%).

^1H NMR (400 MHz, $CDCl_3$): δ = 1.24 (d, J = 6.8 Hz, 6H), 2.57 (s, 3H), 3.47 (septet, J = 6.8 Hz, 1H), 7.22-7.25 (m, 1H), 7.41-7.43 (m, 2H), 7.48 (d, J = 7.6 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.1, 29.2, 30.7, 125.3, 126.5, 127.6, 131.0, 138.9, 147.6, 203.7.

1-(2-(*sec*-Butyl)phenyl)ethanone (3aw)

Light yellow oil; yield: 29.6 mg (56%).

^1H NMR (400 MHz, $CDCl_3$): δ = 0.81 (t, J = 7.6 Hz, 3H), 1.23 (d, J = 6.8 Hz, 3H), 1.53-1.67 (m, 2H), 2.56 (s, 3H), 3.17 (app. sextet, J = 7.0 Hz, 1H), 7.22 (td, J = 7.6 Hz, J = 1.6 Hz, 1H), 7.35 (d, J = 7.6 Hz, 1H), 7.39-7.46 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 12.2, 22.0, 30.8, 31.1, 36.2, 125.3, 126.8, 127.3, 130.8, 139.8, 146.4, 203.9.

HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{12}H_{17}O$: 177.1279; found: 177.1274.

1-(2-(Pentan-3-yl)phenyl)ethanone (3ax)

Light yellow oil; yield: 36.1 mg (63%).

^1H NMR (400 MHz, $CDCl_3$): δ = 0.77 (t, J = 7.4 Hz, 6H), 1.52-1.61 (m, 2H), 1.63-1.72 (m, 2H), 2.54 (s, 3H), 2.94-3.02 (m, 1H), 7.22 (td, J = 7.6 Hz, J = 1.2 Hz, 1H), 7.31 (d, J = 7.6 Hz, 1H), 7.38-7.44 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 12.0, 29.3, 31.1, 43.2, 125.2, 126.9, 127.0, 130.6, 141.2, 144.4, 204.1.

HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{13}H_{19}O$: 191.1436; found: 191.1438.

1-(2-(4-Phenylbutan-2-yl)phenyl)ethanone (3ay)

Light yellow oil; yield: 57.8 mg (76%).

^1H NMR (400 MHz, $CDCl_3$): δ = 1.31 (d, J = 6.8 Hz, 3H), 1.86-2.02 (m, 2H), 2.46-2.52 (m, 1H), 2.53 (s, 3H), 2.57-2.62 (m, 1H), 3.33-3.89 (m, 1H), 7.12-7.14 (m, 2H), 7.17 (d, J = 7.6 Hz, 1H), 7.24-7.28 (m, 3H), 7.42-7.45 (m, 2H), 7.50 (d, J = 7.6 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.5, 30.6, 34.0, 34.3, 40.0, 125.5, 125.6, 126.8, 127.5, 128.2 (two signals overlapping), 131.0, 139.6, 142.4, 146.1, 203.5.

HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{18}H_{21}O$: 253.1592; found: 253.1594.

1-(2-(4-(4-Methoxyphenyl)butan-2-yl)phenyl)ethanone (3az)

Light yellow oil; yield: 51.4 mg (61%).

^1H NMR (400 MHz, $CDCl_3$): δ = 1.29 (d, J = 6.8 Hz, 3H), 1.87-1.95 (m, 2H), 2.37-2.45 (m, 1H), 2.48-2.56 (m, 4H), 3.30-3.36 (m, 1H), 3.78 (s, 3H), 6.80 (d, J = 8.4 Hz, 2H), 7.03 (d, J = 8.4 Hz, 2H), 7.25-7.27 (m, 1H), 7.42-7.44 (m, 2H), 7.49 (d, J = 7.6 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.6, 30.7, 33.2, 34.4, 40.3, 55.3, 113.7, 125.5, 126.9, 127.6, 129.2, 131.1, 134.6, 139.7, 146.2, 157.7, 203.7.

HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{18}H_{21}O$: 283.1698; found: 283.1703.

1-(2-(4-(4-Chlorophenyl)butan-2-yl)phenyl)ethanone (3aaa)

Light yellow oil; yield: 64.5 mg (75%).

^1H NMR (400 MHz, $CDCl_3$): δ = 1.29 (d, J = 6.8 Hz, 3H), 1.83-1.95 (m, 2H), 2.39-2.47 (m, 1H), 2.51-2.59 (m, 4H), 3.33-3.38 (m, 1H), 7.04 (d, J = 8.4 Hz, 2H), 7.10 (d, J = 8.4 Hz, 2H), 7.23-7.27 (m, 1H), 7.39-7.47 (m, 2H), 7.50 (dd, J = 1.2 Hz, 7.6 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.5, 30.6, 33.4, 34.2, 39.9, 125.5, 126.7, 127.7, 128.3, 129.6, 131.1, 131.3, 139.4, 140.9, 146.0, 203.4.

HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{18}H_{20}ClO$: 287.1203; found: 287.1203.

exo-1-(2-(Bicyclo[2.2.1]heptan-2-yl)phenyl)ethanone (3aab)[3c]

Light yellow oil; yield: 52.6 mg (82%).

^1H NMR (400 MHz, $CDCl_3$): δ = 1.21-1.32 (m, 2H), 1.37-1.43 (m, 1H), 1.47-1.51 (m, 1H), 1.53-1.61 (m, 3H), 1.68-1.86 (m, 1H), 2.35 (d, J = 18.4 Hz, 2H), 2.56

(s, 3H), 3.19 (dd, J = 8.9 Hz, 6.0 Hz, 1H), 7.20 (td, J = 8.0 Hz, J = 1.6 Hz, 1H), 7.36-7.42 (m, 2H), 7.49 (d, J = 7.2 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ 28.7, 30.4, 30.6, 36.6, 37.0, 40.2, 42.6, 43.4, 125.0, 126.4, 128.0, 130.7, 139.3, 146.2, 203.7.

1-(2-Cycloheptyl-4-methoxyphenyl)ethanone (3br)

The reaction was performed on a 10 mmol scale.

Light yellow oil; yield: 2.10 g (85%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.56-1.63 (m, 6H), 1.69-1.78 (m, 4H), 1.87-1.92 (m, 2H), 2.54 (s, 3H), 3.45-3.50 (m, 1H), 3.83 (s, 3H), 6.70 (dd, J = 8.8 Hz, J = 2.8 Hz, 1H), 6.88 (d, J = 2.8 Hz, 1H), 7.59 (d, J = 8.8 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.5, 27.7, 30.0, 36.9, 41.1, 55.2, 109.6, 113.3, 129.9, 131.2, 153.0, 161.9, 201.0.

HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{16}H_{23}O_2$: 247.1698; found: 247.1693.

1-(2-Cyclobutyl-4-fluorophenyl)ethanone (3co)

Light yellow oil; yield: 30.4 mg (53%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.77-1.80 (m, 1H), 1.80-1.81 (m, 3H), 1.98-2.39 (m, 2H), 2.53 (s, 3H), 4.04-4.08 (m, 1H), 6.90 (td, J = 8.0 Hz, J = 2.4 Hz, 1H), 7.09 (dd, J = 10.8 Hz, J = 2.4 Hz, 1H), 7.57 (dd, J = 8.8 Hz, J = 6.0 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.9, 29.3, 29.8, 38.1, 112.1 (d, $^2J_{C–F}$ = 21 Hz), 114.6 (d, $^2J_{C–F}$ = 21 Hz), 130.9 (d, $^3J_{C–F}$ = 9 Hz), 134.0, 149.2 (d, $^3J_{C–F}$ = 8 Hz), 164.4 (d, $^1J_{C–F}$ = 250 Hz), 200.9.

HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{12}H_{14}FO$: 193.1029; found: 193.1032.

1-(4-Chloro-2-cyclohexylphenyl)ethanone (3dq)

Orange oil; yield: 45.9 mg (65%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.23-1.29 (m, 1H), 1.36-1.43 (m, 4H), 1.73-1.83 (m, 5H), 2.55 (s, 3H), 3.08-3.11 (m, 1H), 7.20 (dd, J = 8.4 Hz, 2.0 Hz, 1H), 7.35 (d, J = 2.0 Hz, 1H), 7.44 (d, J = 8.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.1, 26.7, 30.6, 34.4, 39.8, 125.5, 127.6, 129.3, 137.0, 137.1, 149.1, 202.2.

HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{14}H_{18}ClO$: 237.1046; found: 237.1041.

1-(3-Cyclopentyl-[1,1'-biphenyl]-4-yl)ethanone (3ep)

Yellow solid; yield: 67.6 mg (85%); mp 78.5–79.6 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.65-1.75 (m, 4H), 1.84-1.87 (m, 2H), 2.13-2.15 (m, 2H), 2.62 (s, 3H), 3.07-3.63 (m, 1H), 7.39 (t, J = 7.6 Hz, 1H), 7.44-7.49 (m, 3H), 7.58-7.65 (m, 3H), 7.60 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.8, 30.5, 35.1, 41.5, 124.0, 126.0, 127.2, 127.8, 128.3, 128.8, 138.3, 140.5, 143.8, 146.2, 203.2.

HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{19}H_{21}O$: 265.1592; found: 265.1591.

1-(2-Cyclohexyl-5-methylphenyl)ethanone (3fq)

Light yellow oil; yield: 38.1 mg (53%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.22-1.29 (m, 1H), 1.34-1.45 (m, 4H), 1.73-1.83 (m, 5H), 2.34 (s, 3H), 2.55 (s, 3H), 2.97-3.01 (m, 1H), 7.21 (d, J = 8.0 Hz, 1H), 7.26 (s, 1H), 7.27 (d, J = 8.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.8, 26.2, 26.9, 30.7, 34.6, 39.6, 127.0, 128.1, 131.6, 134.8, 139.1, 143.5, 203.9.

HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{15}H_{21}O$: 217.1592; found: 217.1593.

1-(3-Cyclohexylnaphthalen-2-yl)ethanone (3gq)

Yellow oil; yield: 42.6 mg (56%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26-1.35 (m, 1H), 1.42-1.55 (m, 4H), 1.78-1.98 (m, 5H), 2.70 (s, 3H), 3.21-3.27 (m, 1H), 7.46 (td, J = 8.0 Hz, J = 1.2 Hz, 1H), 7.53 (td, J = 8.0 Hz, J = 1.2 Hz, 1H), 7.78 (s, 1H), 7.83 (t, J = 8.0 Hz, 2H), 8.03 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.3, 27.0, 30.6, 34.9, 39.6, 125.7, 125.9, 127.4, 127.6, 128.2, 128.6, 130.6, 134.5, 137.9, 143.7, 203.2.

HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{18}H_{21}O$: 253.1592; found: 253.1591.

1-(2-Cyclobutyl-9*H*-fluoren-3-yl)ethanone (3ho)

Light yellow oil; yield: 59.2 mg (75%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.85-1.90 (m, 1H), 2.02-2.19 (m, 1H), 2.14-2.19 (m, 2H), 2.41-2.48 (m, 2H), 2.61 (s, 3H), 3.88 (s, 2H), 4.13-4.18 (m, 1H), 7.35 (t, J = 6.8 Hz, 1H), 7.42 (t, J = 7.2 Hz, 1H), 7.56 (d, J = 7.6 Hz, 1H), 7.71 (s, 1H), 7.80 (s, 1H), 7.86 (d, J = 7.6 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.1, 29.6, 29.9, 36.5, 38.4, 118.4, 120.4, 124.8, 125.1, 126.8, 127.5, 136.5, 139.9, 140.8, 144.30, 144.33, 144.4, 202.6.

HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{19}H_{19}O$: 263.1436; found: 263.1435.

1-(4-Cyclopentylbenzo[*d*][1,3]dioxol-5-yl)ethanonene (3ip)

Pale yellow solid; obtained partially in a pure form (17.2 mg, 25%) and partially as a mixture with its regioisomer (13.9 mg, 20%, ratio = 64:36); mp 65.8–66.9 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.60-1.64 (m, 2H), 1.80-1.93 (m, 6H), 2.53 (s, 3H), 3.45-3.54 (m, 1H), 5.98 (s, 2H), 6.68 (d, J = 8.0 Hz, 1H), 7.12 (d, J = 8.0 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.4, 30.4, 31.9, 38.6, 101.0, 105.3, 123.5, 128.4, 134.6, 146.4, 149.7, 201.7.

HRMS (ESI) m/z [M + H]$^+$ calcd for $C_{14}H_{17}O_3$: 233.1178; found: 233.1178.

8-Cycloheptyl-3,4-dihydronaphthalen-1(2*H*)-one (3jr)

Orange oil; yield: 59.4 mg (81%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.55-1.65 (m, 6H), 1.70-1.82 (m, 4H), 1.88-1.91 (m, 2H), 2.03-2.10 (m, 2H), 2.66 (t, *J* = 6.8 Hz, 2H), 2.92 (t, *J* = 6.0 Hz, 2H), 3.84-3.89 (m, 1H), 7.04 (d, *J* = 7.6 Hz, 1H), 7.27 (d, *J* = 6.4 Hz, 1H), 7.34 (t, *J* = 6.0 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.9, 27.7, 27.8, 31.2, 37.0, 40.8, 41.3, 125.8, 125.9, 130.3, 132.2, 145.1, 153.2, 200.6.

HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{17}H_{23}O$: 243.1749; found: 243.1750.

1-(2-Cyclohexylphenyl)propan-1-one (3kq)

Light yellow oil; yield: 51.8 mg (80%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.20 (t, *J* = 7.2 Hz, 3H), 1.22-1.30 (m, 1H), 1.37-1.44 (m, 4H), 1.73-1.84 (m, 5H), 2.86 (q, *J* = 7.2 Hz, 2H), 2.83-2.89 (m, 1H), 7.19-7.23 (m, 1H), 7.37-7.39 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 8.4, 26.2, 26.8, 34.6, 36.3, 40.2, 125.3, 126.7, 127.0, 130.4, 139.6, 146.0, 207.3.

HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{15}H_{21}O$: 217.1592; found: 217.1595.

1-(2-Cyclobutylthiophen-3-yl)ethanone (3lo)

Light yellow oil; yield: 15.1 mg (24%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.84-1.90 (m, 1H), 1.98-2.12 (m, 3H), 2.48 (s, 3H), 2.49-2.53 (m, 2H), 4.34-4.40 (m, 1H), 7.06 (d, *J* = 5.6 Hz, 1H), 7.35 (d, *J* = 5.6 Hz, 1H)

^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.1, 29.8, 31.2, 36.0, 121.1, 129.4, 134.6, 160.3, 193.5.

HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{10}H_{13}OS$: 181.0687; found: 181.0692.

2-Cyclohexyl-1-methyl-1*H*-indole-3-carbaldehyde (3mq)

Brown oil; yield: 32.4 mg (45%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26-1.47 (m, 3H), 1.84-2.05(m, 7H), 3.20-3.26 (m, 1H), 3.80 (s, 3H), 7.28-7.29 (m, 3H), 8.36-8.38 (m, 1H), 10.4 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.8, 27.0, 30.9, 32.9, 37.4, 109.3, 114.0, 121.7, 122.9, 123.2, 126.1, 136.9, 155.2, 184.8.

HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{16}H_{20}NO$: 242.1545; found: 242.1545.

(2-Ethynyl-5-methoxyphenyl)cycloheptane (4)

To a solution of LDA prepared at 0 °C from diisopropylamine (148.7 mg, 1.47 mmol) and *n*-butyllithium in hexane (1.6 M, 1.30 mL, 1.47 mmol) in THF (10 mL) was added dropwise a solution of **3br** (350 mg, 1.4 mmol) in THF (5 mL) at –78 ˚C. The resulting mixture was stirred for 1 h, followed by the addition of diethyl chlorophosphate (265.7 mg, 1.54 mmol). The reaction mixture was gradually warmed to room temperature, and was added dropwise to a solution of LDA in THF (3.15 mmol, prepared as above) at –78 °C. The resulting mixture was warmed to room temperature over 3 h, quenched with water, and then extracted with hexane (3 x 10 mL). The extract was washed with 1 N HCl (10 mL), water (10 mL), and aqueous $NaHCO_3$ (10 mL). The organic solution was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (eluent: hexane/EtOAc = 10/1) to afford **4** as a yellow oil (181.7 mg, 56 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.60-1.66 (m, 6H), 1.70-1.74 (m, 2H), 1.78-1.84 (m, 2H), 1.91-1.96 (m, 2H), 3.18 (s, 1H), 3.20-3.25 (m, 1H), 3.80 (s, 3H), 6.66 (dd, *J* = 8.4 Hz, 2.4 Hz, 1H), 6.77 (d, *J* = 2.4 Hz, 1H), 7.40 (d, *J* = 8.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.5, 27.8, 35.8, 43.8, 55.2, 79.2, 82.6, 110.4, 111.9, 112.8, 134.2, 154.1, 160.1.

HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{16}H_{21}O$: 229.1592; found: 229.1593.

6'-Methoxyspiro[cycloheptane-1,1'-indene] (5)

A solution of **4** (68.5 mg, 0.30 mmol), CuBr (86.1 mg, 0.60 mmol), and $PtCl_2$ (8.0 mg, 0.03 mmol) in toluene (3 mL) was stirred at 100 °C for 24 h. After completion of the reaction, a dark solid in the reaction mixture was removed by filtration through a pad of Celite, followed by washing of the Celite bed with diethyl ether (3 x 5 mL). The combined filtrate was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (eluent: hexane/EtOAc = 10/1 – 5/1) to afford **5** as a yellow oil (53.0 mg, 77 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.55-1.60 (m, 2H), 1.67-1.79 (m, 6H), 1.81-1.85 (m, 4H), 3.83 (s, 3H), 6.51 (d, *J* = 5.6 Hz, 1H), 6.59 (d, *J* = 5.6 Hz, 1H), 6.75 (dd, *J* = 8.0 Hz, 2.4 Hz, 1H), 6.96 (d, *J* = 2.0 Hz, 1H), 7.16 (d, *J* = 8.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.5, 29.9, 36.9, 55.5, 56.8, 108.8, 110.9, 121.3, 127.6, 135.4, 143.8, 156.9, 158.0.

HRMS (ESI) *m/z* $[M + H]^+$ calcd for $C_{16}H_{21}O$: 229.1592; found: 229.1592.

1-(2-Cycloheptyl-4-methoxyphenyl)-2-diazoethanone (6)

To a solution of LiHMDS (1.0 M, 1.30 mL) in 10 mL THF was added **3br** (289 mg, 1.2 mmol) in THF (5 mL) over 1 min at –78 ˚C. The resulting mixture was stirred for 30 min, followed by the addition of trifluoroethyl trifluoroacetate (282.3 mg, 1.44 mmol) over 2-3 min. After additional stirring for 3 h, the reaction mixture was allowed to room temperature and then poured into a separatory funnel together with Et_2O (10 mL) and 5% aq. HCl (20 mL). The aqueous layer was extracted with Et_2O (30 mL). The combined organics were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure to afford a yellow oil. The oil was placed in a dry 50 mL 3-necked round bottom flask under a nitrogen atmosphere and dissolved in acetonitrile (10 mL). To this solution was added water (0.02 mL) and NEt_3 (0.25 mL), followed by the dropwise addition of *p*-acetamidobenzenesulfonyl azide (432.4 mg, 1.8 mmol) in acetonitrile (10 mL). The resulting solution was stirred at ambient temperature for 8 h, and then poured into a separatory funnel with Et_2O (20 mL). The organic layer was washed with 5% NaOH aqueous solution (3 x 20 mL), water (3 x 20 mL), and brine. The combined organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by silica gel chromatography (eluent: hexane/EtOAc = 30/1 - 5/1) to afford **6** as a yellow oil (240.9 mg, 75 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.53-1.61 (m, 6H), 1.63-1.70 (m, 2H), 1.72-1.77 (m, 2H), 1.87-2.00 (m, 2H), 3.24-3.37 (m, 1H), 3.77 (s, 3H), 5.52 (s, 1H), 6.64 (dd, *J* = 2.4 Hz, 8.4 Hz, 1H), 6.84 (d, *J* = 2.4 Hz, 1H), 7.24 (d, *J* = 8.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.2, 27.6, 36.7, 41.3, 55.0, 56.1, 109.8, 113.0, 128.8, 129.1, 151.2, 161.4, 189.6.

HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{21}N_2O_2$: 273.1602; found: 273.1603.

6'-Methoxyspiro[cycloheptane-1,1'-inden]-3'(2'*H*)-one (7)

A solution of **6** (81.7 mg, 0.30 mmol) in dichloromethane (22.5 mL) was added dropwise to a suspension of $Rh_2(OAc)_4$ (2.7 mg, 6 μmol) in dichloromethane (7.5 mL) at room temperature over a period of 6 h using a syringe pump. The resulting mixture was stirred for additional 3 h and then concentrated under reduced pressure. The crude product was purified by silica gel chromatography (eluent: hexane/EtOAc = 10/1) to afford **7** as a yellow oil (26.2 mg, 36 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.56-1.62 (m, 2H), 1.65-1.72 (m, 6H), 1.75-1.79 (m, 2H), 1.90 (t, *J* = 12.0 Hz, 2H), 2.60 (s, 2H), 3.89 (s, 3H), 6.87 (dd, *J* = 8.0 Hz, 2.4 Hz, 1H), 6.93 (d, *J* = 2.4 Hz, 1H), 7.62 (d, *J* = 8.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.6, 28.5, 41.9, 45.8, 50.3, 55.6, 107.6, 114.7, 125.1, 128.2, 165.4, 168.2, 204.4.

HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{21}O_2$: 245.1542; found: 245.1544.

2-(2-Octylphenyl)pyridine (9aa)[36]

Yellow oil; yield: 57.3 mg (71 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86 (t, *J* = 7.2 Hz, 3H), 1.17-1.26 (m, 10H), 1.43-1.47 (m, 2H), 2.70 (t, *J* = 8.0 Hz, 2H), 7.23-7.39 (m, 6H), 7.71-7.76 (m, 1H), 8.69 (d, *J* = 4.8 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 22.6, 29.1, 29.2, 29.4, 31.2, 31.8, 32.9, 121.5, 124.1, 125.7, 128.2, 129.66, 129.68, 136.0, 140.3, 140.8, 149.1, 160.3.

2-(2,6-Dioctylphenyl)pyridine (10aa)

Obtained as a mixture with 2-(2-neopentyl-6-phenethylphenyl)pyridine; 76% yield as determined by weight and ^{1}H NMR analysis.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.85 (t, *J* = 7.3 Hz, 6H), 1.11-1.16 (m, 16H), 1.21-1.25 (m, 4H), 1.37-1.42 (m, 4H), 2.29 (t, *J* = 7.8 Hz, 4H), 7.11 (d, *J* = 7.8 Hz, 2H), 7.22-7.26 (m, 3H), 8.69-8.71 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2, 22.8, 29.3, 29.4, 29.7, 31.3, 32.0, 33.8, 121.7, 125.2, 126.7, 128.1, 135.9, 140.1, 149.5, 159.9.

HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{27}H_{42}N$: 380.3317; found: 380.3316.

2-(2-Neopentylphenyl)pyridine (9aj)[7a]

Colorless oil; yield: 48.4 mg (72 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.64 (s, 9H), 2.88 (s, 2), 7.19-7.39 (m, 6H), 7.71 (td, *J* = 7.8 Hz, 1.8 Hz, 1H), 8.66-8.68 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.7, 33.0, 45.1, 121.6, 125.0, 126.2, 127.6, 130.3, 132.6, 136.2, 137.7, 141.7, 149.1, 161.5.

2-(2,6-Diisopropyl-4-methoxyphenyl)pyridineaniline (10bv)

Light yellow solid; yield: 69.3 mg (86 %); mp 81.6–82.5 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.07 (d, *J* = 6.8 Hz, 6H), 1.11 (d, *J* = 6.8 Hz, 6H), 2.47-2.54 (m, 2H), 3.85 (s, 3H), 6.75 (s, 2H), 7.24 (t, *J* = 7.6 Hz, 2H), 7.68-7.73 (m, 1H), 8.69-8.71 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.7, 24.0, 55.1, 108.1, 121.4, 125.4, 131.7, 135.6, 148.1, 149.3, 159.6, 159.9.

HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{18}H_{24}NO$: 270.1858; found: 270.1859.

2-(2,6-Dicyclobutyl-4-fluorophenyl)pyridineaniline (10cp)

Yellow solid; yield: 59.2 mg (70 %); mp 62.3–63.6 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.63-1.69 (m, 3H), 1.71-1.82 (m, 5H), 1.91 (t, *J* = 9.2 Hz, 2H), 1.97-2.06 (m, 2H), 3.26-3.33 (m, 2H), 6.93 (d, $J_{H\text{-}F}$ = 10.0 Hz, 2H), 7.15 (d, *J* = 7.6 Hz, 1H), 7.23-7.26 (m, 1H), 7.68-7.72 (m, 1H), 8.68 (d, *J* = 5.2 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.9, 29.2, 29.8, 38.4 (d, $^4J_{C\text{-}F}$ = 1 Hz), 110.3 (d, $^2J_{C\text{-}F}$ = 21 Hz), 121.7, 125.3, 134.1, 135.7, 146.1 (d, $^3J_{C\text{-}F}$ = 8 Hz), 149.3, 158.8, 163.0 (d, $^1J_{C\text{-}F}$ = 243 Hz).

HRMS (ESI) *m*/*z* [M + H]$^+$ calcd for $C_{19}H_{21}FN$: 282.1658; found: 282.1657.

2-(2,6-Dicyclohexyl-4-(trifluoromethyl)phenyl)pyridine (10dr)

White solid; yield: 45.4 mg (39%); mp 140.8–142.2 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.94-1.06 (m, 4H), 1.12-1.23 (m, 2H), 1.31-1.43 (m, 4H), 1.58-1.70 (m, 8H), 1.82 (d, *J* = 12.4 Hz, 2H), 2.08 (tt, *J* = 3.0 Hz, 11.6 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 1H), 7.29-7.32 (m, 1H), 7.38-7.46 (m, 2H), 7.72-7.78 (m, 1H), 8.71 (d, *J* = 4.8 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.9, 26.6, 26.7, 33.8, 34.3, 41.2, 120.3 (q, $^3J_{C\text{-}F}$ = 4 Hz), 122.0, 124.4, 127.0 (q, $^1J_{C\text{-}F}$ = 248 Hz), 130.3 (q, $^2J_{C\text{-}F}$ = 31 Hz), 135.8, 142.3, 146.6, 149.4, 158.7.

HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{24}H_{29}F_3N$: 388.2252; found: 388.2255.

2-(2-Cyclobutyl-5-methylphenyl)pyridine (10ep)

Yellow oil; yield: 57.9 mg (86%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.71-1.73 (m, 1H), 1.82-1.87 (m, 1H), 1.98-2.06 (m, 4H), 2.37 (s, 3H), 3.76-3.81 (m, 1H), 7.17 (s, 1H), 7.19-7.25 (m, 2H), 7.32-7.35 (m, 2H), 7.68-7.73 (m, 1H), 8.67-8.69 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.2, 20.9, 30.0, 37.7, 121.5, 124.1, 126.5, 129.0, 130.1, 135.1, 135.8, 139.6, 140.7, 149.2, 160.4.

HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{18}N$: 224.1439; found: 224.1441.

2-(3-Chloro-2-cyclohexylphenyl)pyridine (10fr)

Light yellow oil; yield: 38.3 mg (47%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.13-1.23 (m, 3H), 1.35-1.44 (m, 2H), 1.65-1.80 (m, 5H), 2.70 (tt, *J* = 2.8 Hz, 11.6 Hz, 1H), 7.26-7.29 (m, 1H), 7.30-7.34 (m, 4H), 7.73-7.77 (m, 1H), 8.69-8.70 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.1, 26.7, 34.3, 39.5, 122.0, 124.1, 127.9, 128.4, 129.6, 131.1, 136.1, 141.5, 144.1, 149.4, 158.9.

HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{19}ClN$: 272.1206; found: 272.1205.

2-(2-Cyclobutyl-4-methoxyphenyl)-3-methylpyridine (10gp)

Light yellow oil; yield: 57.9 mg (86%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.65-1.78 (m, 3H), 1.82-2.09 (m, 3H), 2.09 (s, 3H), 3.38-3.47 (m, 1H), 3.85 (s, 3H), 6.77 (dd, *J* = 2.4 Hz, 8.4 Hz, 1H), 6.94 (d, *J* = 2.4 Hz, 1H), 7.04 (d, *J* = 8.4 Hz, 1H), 7.15 (dd, *J* = 4.8 Hz, 7.6 Hz, 1H), 7.53 (d, *J* = 6.8 Hz, 1H), 8.46-8.48 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.0, 19.3, 29.3, 38.1, 55.2, 110.3, 112.3, 121.9, 129.6, 131.8, 131.9, 137.4, 145.2, 146.4, 159.3, 159.5.

HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{17}H_{20}NO$: 254.1545; found: 254.1541.

2-(2-Isopropyl-6-methylphenyl)pyridine (10hv)

Obtained as a mixture with 2-(*o*-tolyl)pyridine (**8h**). (89% yield as determined by weight and ^{1}H NMR analysis).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.12 (d, *J* = 4.8 Hz, 3H), 1.13 (d, *J* = 4.8 Hz, 3H), 2.00 (s, 3H), 2.57-2.64 (m, 1H), 7.10 (d, *J* = 7.2 Hz, 1H), 7.11-7.31 (m, 4H), 7.72-7.77 (m, 1H), 8.72-8.73 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.4, 23.91, 23.94, 30.1, 121.5, 122.7, 124.5, 127.2, 128.2, 135.6, 136.0, 139.5, 146.4, 149.5, 159.9.

HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{18}N$: 212.1439; found: 212.1440.

10-Cyclopentylbenzo[*h*]quinoline (10iq)

Light yellow oil; yield: 59.5 mg (80%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.74-1.81 (m, 2H), 1.86-1.96 (m, 4H), 2.37-2.43 (m, 2H), 5.71-5.75 (m, 1H), 7.47 (dd, *J* = 4.4 Hz, 8.0 Hz, 1H), 7.62-7.67 (m, 2H), 7.79 (t, *J* = 8.4 Hz, 2H), 7.85 (d, *J* = 7.6 Hz, 1H), 8.14 (dd, *J* = 2.0 Hz, 8.0 Hz, 1H), 9.02-9.03 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.7, 34.7, 43.5, 120.5, 125.3, 126.0, 127.4, 127.6, 129.1, 129.4, 135.3, 135.4, 146.9, 147.2, 148.7.

HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{18}N$: 248.1439; found: 248.1437.

2-(3-Cyclopentylthiophen-2-yl)pyridine (10jq)

Brown oil; yield: 15.7 mg (23%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.63-1.70 (m, 4H), 1.82-1.83 (m, 2H), 2.03-2.09 (m, 2H), 3.49-3.53 (m, 1H), 7.06 (d, *J* = 5.6 Hz, 1H), 7.16-7.19 (m, 1H), 7.32 (d, *J* = 5.6 Hz, 1H), 7.50 (d, *J* = 8.0 Hz, 1H), 7.69-7.23 (m, 1H), 8.64-8.65 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.7, 34.9, 39.3, 121.4, 122.6, 126.0, 127.6, 136.3, 137.6, 144.8, 149.7, 153.7.

HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{16}NS$: 230.1003; found: 230.1004.

2-(2-Octyl-6-phenethylphenyl)pyridine (11)

Colorless oil; yield: 55.6 mg (50%)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86 (t, *J* = 7.2 Hz, 3H), 1.13-1.16 (m, 8H), 1.20-1.25 (m, 2H), 1.40-1.41 (m, 2H), 2.28-2.34 (m, 2H), 2.57-2.76 (m, 4H), 6.91 (d, *J* = 7.0 Hz, 2H), 7.09-7.19 (m, 6H), 7.27 (t, *J* = 7.5 Hz, 2H), 7.71 (td, *J* = 7.7 H, 1.8 Hz, 1H), 8.73 (d, *J* = 4.4 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.3, 22.8, 29.3, 29.4, 29.7, 31.3, 32.0, 33.7, 36.3, 38.0, 121.9, 125.2, 125.9, 126.8, 127.1, 128.3, 128.38, 128.44, 136.0, 139.8, 140.2, 141.1, 142.3, 149.6, 159.7.

HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{27}H_{34}N$: 372.2691; found: 372.2689.

1-(2-(4-(*tert*-Butyl)cyclohexyl)phenyl)ethanone (3aac)

Light yellow oil; yield: 23.8 mg (31%, trans:cis = 79:21).

^{1}H NMR (400 MHz, $CDCl_3$, *trans* isomer): δ = 0.88 (s, 9H), 1.08-1.22 (m, 3H), 1.35-1.48 (m, 2H), 1.79-1.93 (m, 4H), 2.57 (s, 3H), 2.98 (tt, *J* = 12 Hz, 3.2 Hz, 1H), 7.20-7.24 (m, 1H), 7.37-7.40 (m, 2H), 7.47-7.48 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$, *trans* isomer): δ = 27.6, 27.7, 30.8, 32.5, 34.8, 40.0, 47.9, 125.3, 127.0, 127.7, 130.9, 139.3, 146.4, 203.8.

HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{27}O$: 259.2062; found: 259.2057.

1-(2-(Octan-2-yl)phenyl)ethanone (3aad)

Obtained as a mixture with the linear isomer **3aa**, and the ortho-neopentylation product **3aj** (63% yield as determined by weight and ^{1}H NMR analysis). See the Supporting Information for the determination of the enantiomeric excess.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.83-0.85 (m, 3H), 1.09-1.26 (m, 11H), 1.46-1.66 (m, 2H), 2.52 (s, 3H), 3.23 (sextet, J = 7.3 Hz, 1H), 7.18-7.23 (m, 1H), 7.34-7.45 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.3, 22.7, 22.8, 27.9, 29.6, 31.0, 32.0, 32.1, 34.7, 38.6, 125.5, 127.1, 127.5, 131.1, 139.9, 146.9, 204.1

HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{16}H_{25}O$: 233.1905; found: 233.1908.

1-(2-(Cyclobutylmethyl)phenyl)ethanone (3aae)

Obtained as a mixture with the ring-opening alkylation products **3ad** and **3ad'** (60% yield as determined by weight and ^{1}H NMR analysis).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.67-1.74 (m, 2H), 1.77-1.85 (m, 2H), 1.95-2.02 (m, 2H), 2.52-2.60 (m, 4H), 2.97 (d, J = 7.6 Hz, 2H), 7.21 (d, J = 7.6 Hz, 1H), 7.25 (d, J = 7.6 Hz, 1H), 7.34-7.38 (m, 1H), 7.60 (d, J = 7.6 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.3, 28.3, 30.0, 37.1, 40.3, 125.6, 128.8, 130.9, 131.0, 138.2, 140.8, 202.5.

HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{13}H_{17}O$: 189.1279; found: 189.1274.

1-(2-(Hex-5-en-1-yl)phenyl)ethanone (3aaf)

Obtained as a mixture with (*E*)-1-(2-(hex-4-en-1-yl)phenyl)ethanone (**3aaf'**) (88:12); yellow oil; yield: 58.6 mg (97%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.44-1.50 (m, 2H), 1.55-1.61 (m, 2H), 2.06-2.11 (m, 2H), 2.58 (s, 3H), 2.85 (t, J = 7.6 Hz, 2H), 4.94 (ddt, J = 10.2 Hz, 2.0 Hz, 1.1 Hz, 1H), 5.00 (ddt, J = 17.1 Hz, 1.9 Hz, 1.6 Hz, 1H), 5.81 (ddt, J = 17.0 Hz, 10.2 Hz, 6.7 Hz, 1H), 7.24-7.27 (m, 2H), 7.39 (td, J = 7.6 Hz, 1.2 Hz, 1H), 7.63 (dd, J = 7.6 Hz, 1.2 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.9, 29.9, 31.3, 33.6, 33.8, 114.3, 125.6, 129.0, 131.1, 131.2, 137.9, 138.9, 142.7, 202.2.

HRMS (ESI) *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{19}O$: 203.1436; found: 203.1437.

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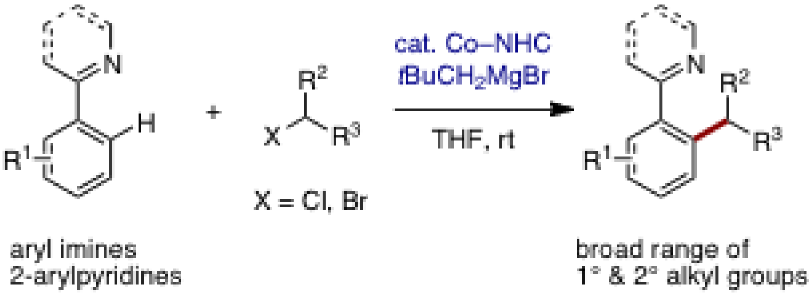
Graphical abstract:



Short title: Cobalt-Catalyzed Alkylation of Arenes

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