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Cross-Coupling of Nonactivated Primary and Secondary Alkyl Halides with Aryl Grignard Reagents Catalyzed by Chiral Iron Pincer Complexes

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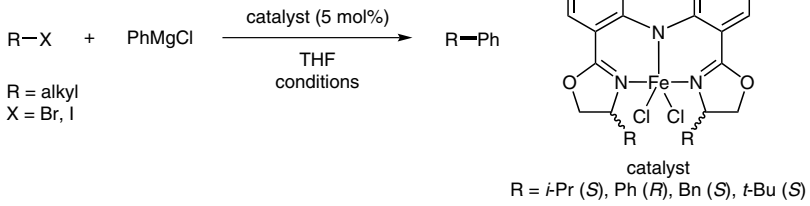

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Abstract Iron(III) bisoxazolinylphenylamido (bopa) pincer complexes are efficient precatalysts for the cross-coupling of nonactivated primary and secondary alkyl halides with phenyl Grignard reagents. The reactions proceed at room temperature in moderate to excellent yields. A variety of functional groups can be tolerated. The enantioselectivity of the coupling of secondary alkyl halides is low.

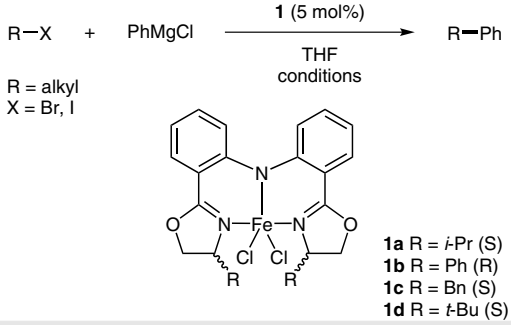
Key words Kumada coupling, iron pincer complex, alkyl halide, aryl Grignard reagent, enantioselectivity

Carbon–carbon cross-coupling reactions are amongst the most ubiquitous synthetic methods in organic chemistry. Although many advances in C–C coupling have been made, the use of alkyl electrophiles as the coupling partners is still challenging, due to the comparatively high barrier for the oxidative addition of alkyl electrophile to the metal center, and the competing β-hydrogen elimination of the metal–alkyl intermediate.[1] Reaction protocols involving Pd and Ni catalysts have been well established and broadly used.[2] In recent years, iron catalysts have been increasingly applied in the field of C–C coupling reactions[3] thanks to its low cost, low toxicity, and high abundance, as well as the high functional group tolerance and high reactivity of iron-catalyzed reactions.[4–7]

In 2004, Nakamura et al. reported the iron-catalyzed Kumada cross-coupling of secondary alkyl halides with aryl Grignard reagents.[5] Simple iron(III) chloride salts in the presence of tetramethylethylenediamine (TMEDA) in tetrahydrofuran at –78 to 0 °C were utilized to generate alkylarene products in 45–99% yields; the reactions required a slow addition of Grignard reagents and TMEDA. Hayashi et al. were able to couple primary and secondary alkyl halides with aryl Grignard reagents in the presence of $Fe(acac)_3$ in refluxing diethyl ether. The yields were slightly lower than in Nakamura's case, yet a slow addition of Grignard reagents was not necessary.[6] By slightly modifying the reaction conditions of Nakamura's system, Bedford et al. was able to expand the iron catalysis. By precoordiantion of iron(III) chloride with various amine, phosphine, phosphite, arsine, and carbene ligands, they were able to reduce the amount of ligands used from excess to stoichiometric amount (with respect to the catalyst).[8] Bedford et al. also showed that well-defined iron(III) salen complex are active towards the Kumada coupling of alkyl halides with aryl Grignard reagents without additives.[9] In these salen systems, the color turns black upon addition of Grignard reagents, suggesting the formation of iron nanoparticles. In a further study, preformed and in situ generated nanoparticles proved to be equally active.[10] Fürstner et al. applied an $[Fe(C_2H_4)_4][Li(tmeda)]_2$ in the cross coupling of various primary and secondary alkyl halides.[7] The reaction was carried out at –20 °C in a tetrahydrofuran solution. This reaction shows a remarkable chemoselectivity in the presence of various functional groups. Following these pioneering studies, many reports of iron-catalyzed alkyl–aryl Kumada coupling appeared. However, to the best of our knowledge, there was no precedent for iron-catalyzed enantioselective alkyl–aryl coupling.

To achieve enantioselective cross coupling, a strong and modular chiral ligand framework is required. This is challenging for iron as previous studies suggested that some iron complexes decomposed during cross coupling to give iron nanoparticles, which were the catalytically active species.[9,10] We chose the tridentate bisoxazolinylphenylamido (bopa) pincer ligand for iron. We thought that the chelating pincer ligand should stabilize iron ion in different oxidation states and prevent the formation of iron nanoparticles. Furthermore, the ligand system is module and modification of the chiral oxazoline units can be easily done. Herein, we re-

port that these iron–bopa complexes are indeed very active catalyst for the coupling of both secondary and primary alkyl halides with phenyl Grignard reagents at ambient temperature (Scheme 1). In contrast to most previous reports, the coupling proceeds smoothly without any additives. Furthermore, the chelating bopa ligand remains on the iron center during catalysis. The synthetic utility of this catalyst system is demonstrated by the coupling of a large number of functionalized substrates. We also describe preliminary attempts towards enantioselective alkyl–aryl coupling using these chiral complexes.

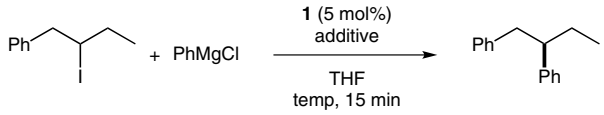


Scheme 1

We commenced our investigations on the cross-coupling of 2-iodo-1-phenylbutane with phenylmagnesium chloride (1.1 equiv) in tetrahydrofuran using DMA (dimethylacetamide) as additive at room temperature in the presence of 5 mol% iron catalyst (Table 1). All complexes **1a**–**c** showed similar activity, giving yields of about 50%. Complex **1c** was taken for further screening because it was the best catalyst among the three. Complex **1d** was not included in the screening as it was introduced only in a later stage of this work.

The effect of additive was investigated next. The amount of DMA was lowered from 16 mol% (Table 1, entries 1–3) to 5 mol% (1 equiv to catalyst, entry 4), and the yield remained the same. Changing to different additives such as TMEDA, *O*-TMEDA, and NMP (entries 5–7) did not significantly change the yields. To our surprise, a higher yield (69%) was obtained without any additive (entry 8). Lowering the temperature (entries 9–11) further increased the yield; at –40 °C, the yield was 95%. Changing the solvent from tetrahydrofuran to diethyl ether (entry 12) lowered the yield to 28% at room temperature. Although the highest yield was

Table 1 Optimization of Reaction Conditions[a]



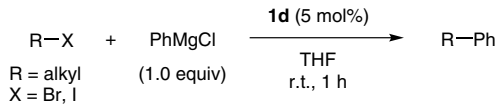
Entry	Cat., additive (mol%)	Temp (°C)	Yield (%)[b]
1	**1a**, DMA (16)	r.t.	47
2	**1b**, DMA (16)	r.t.	53
3	**1c**, DMA (16)	r.t.	56
4	**1c**, DMA (5)	r.t.	57
5	**1c**, TMEDA (5)	r.t.	60
6	**1c**, *O*-TMEDA (5)[c]	r.t.	50
7	**1c**, NMP (5)	r.t.	47
8	**1c**, –	r.t.	69
9	**1c**, –	0	78
10	**1c**, –	–20	89
11	**1c**, –	–40	95
12	**1c**, –[d]	r.t.	28

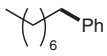
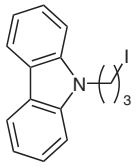
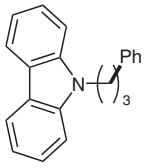
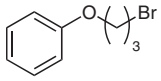
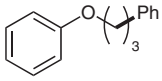
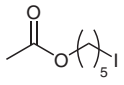
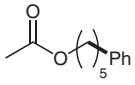
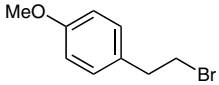
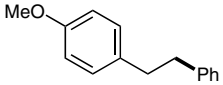
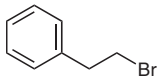
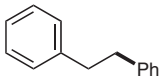
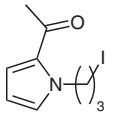
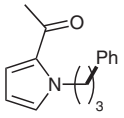
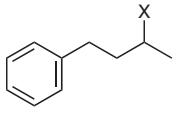
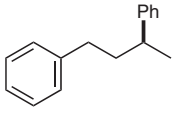
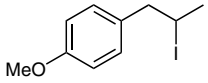
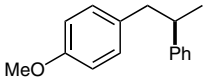
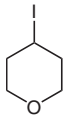
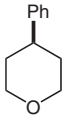
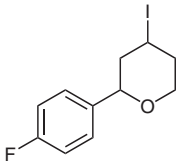
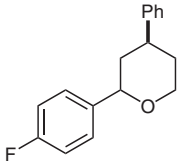
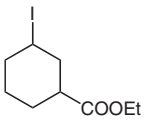
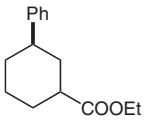
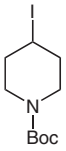
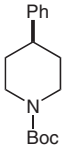
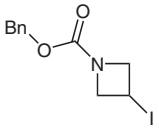
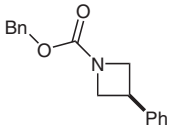
[a] Conditions: 2-iodo-1-phenylbutane (0.5 mmol), PhMgCl (0.55 mmol), catalyst (5 mol%), dodecane (as internal standard) in THF (4.0 mL).
[b] Yields were determined by GC (dodecane as internal standard; 100% conversion).
[c] Bis[2-(*N*,*N*-dimethylamino)ethyl] ether.
[d] Et_2O was used as a solvent.

obtained at –40 °C, it was decided to investigate the scope of the coupling at room temperature for the convenience of experiments.

The optimized coupling conditions at room temperature were applied for the coupling of various primary alkyl halides (Table 2, entries 1–7) as well as cyclic and acyclic secondary alkyl halides (entries 8–14). Both alkyl iodides and bromides reacted smoothly to give the corresponding products in generally high to excellent yields. The protocol tolerates a range of functional groups, including ethers (entries 3, 5, and 9), carbamates (entry 14), N-heterocycles (entries 2 and 7), Boc-protected piperidine (entry 13), and tetrahydropyran (entries 10, 11). Base-sensitive ester- (entries 4 and 12) and ketone- (entry 7) containing compounds were coupled with a high chemoselectivity despite the use of Grignard reagent. Natural-product-derived compounds, including 3-iodocholestene, cholestenyl-6-iodohexanoate, and menthyl-6-iodohexanoate (Table 3, entries 1–3), were also coupled in moderate to good yields.

Table 2 Cross-Coupling Reaction of Alkyl Halides with Phenyl Grignard

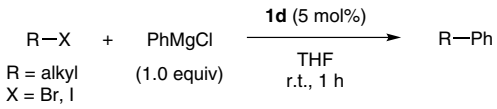


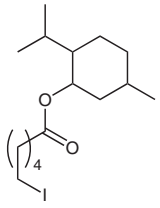
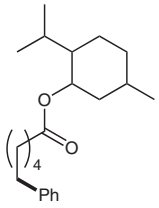
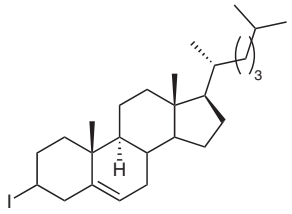
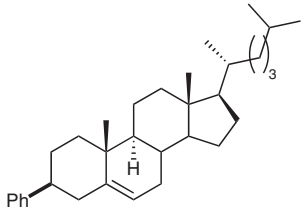
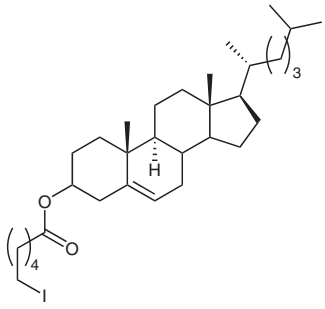
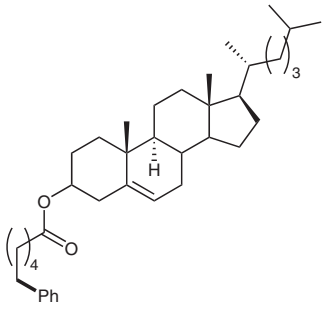
Entry	Halide	Product	Yield (%)[a]
1			92[b,c] 82[c]
2			83
3			68
4			83
5			98
6			57
7			57 (25)[d]
8			95[b,c] (X = I) 88[c] (X = I) 93[c] (X = Br)
9			90
10			75
11			92[e]
12			71[f]
13			88
14			65

[a] Isolated yields at 100% conversion.
[b] Reaction at –40 °C.
[c] Catalyst **1b** was used.
[d] Starting material recovered: 25%.
[e] Mixture of diastereoisomers: 66:34 (dr for RX = 91:9).
[f] Mixture of diastereoisomers: 52:48 (dr for RX = 81:19).

Having demonstrated the catalytic efficiency of this iron-pincer system, the enantioselective C–C coupling reactions were studied. Three different substrates were chosen (Table 4) and the reaction was performed at the previously optimized conditions using the chiral iron precatalysts. These substrates were chosen because the two enantiomers of the products could be readily separated by chiral HPLC, and because previous report showed that the phenyl group could be an effective directing group in nickel-catalyzed enantioselective alkyl–alkyl coupling.[11] When the phenyl group is at the β-position of the alkyl iodide, nearly no enantioselectivity was obtained for all four iron catalysts (Table 4, entries 1–4). More encouraging results were obtained for substrates with a phenyl group at the α-position of the alkyl halide. The *tert*-butyl-substituted bopa ligand gave the highest enantiomeric excess (ee), in the range of 15–20%. Although only low enantiomeric excesses were obtained in these experiments, the results demonstrate that a bopa-based ligand system is capable of inducing enantioselectivity. They also confirm the homogenous nature of the iron catalysis.

Table 3 Cross-Coupling of Natural-Product-Derived Compounds with Phenyl Grignard



Entry	Halide	Product	Yield (%)[a]
1			83
2			53
3			85

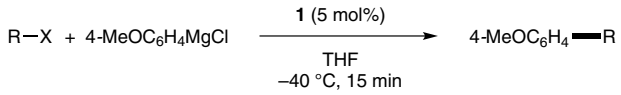
[a] Isolated yields at 100% conversion.
[b] Mixture of stereoisomers: 81:19 (dr for RX = 100:0).

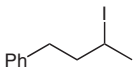
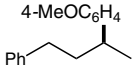
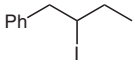
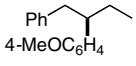
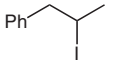
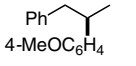
To conclude, we have found an iron-complex system that allows the coupling of nonactivated and functionalized alkyl halides with phenyl Grignard reagents. The coupling is rapid and tolerates a wide range of different functional groups. Naturally derived compounds could be coupled in high chemoselectivity. Enantioselectivity, albeit low, is demonstrated.

All manipulations were carried out under an inert N_2 atmosphere using standard Schlenk or glove box techniques. The solvents were purified and dried using a two column solid-state purification system (Innovative Technology, NJ, USA). They were transferred to the glove box in a Strauss-flask without exposure to air. The solvents were stored over molecular sieves (3 Å). $CDCl_3$ was purchased from Armar Chemicals, and was degassed and stored over dried and activated molecular sieves (3 Å). (*S*)-2-Amino-3,3-dimethylbutan-1-ol (L-*tert*-leucinol) was purchased from TCI. The following chemicals were synthesized: 2,2′-iminodibenzoic acid,[12] (*S*)-(+)-2-amino-3-methylbutan-1-ol (L-valinol),[13] (*R*)-(−)-phenylglycinol,[13] L-(−)-2-amino-3-phenylpropan-1-ol (L-phenylalaninol),[13] 2,2′-iminodibenzoyl chloride,[14] Bopa-R (R = *i*-Pr, Ph, Bn, *t*-Bu),[14] and [Fe(Bopa-R)Cl_2] (R = *i*-Pr, Ph, Bn, *t*-Bu),[14,15] All known primary and secondary halides were either commercially available or prepared according to the literature procedures.[4,16]

NMR spectra were recorded on a Bruker Avance 400 spectrometer. ^{1}H NMR chemical shifts were referenced to TMS (δ = 0) or the residual solvent peak (abbreviation ovrlp: overlapping signals). GC measurements were conducted on a PerkinElmer Clarus 400 GC equipped with an FI-detector. GC-MS measurements were conducted on an Agilent 7980A GC equipped with Agilent 5975C MS and an FI-detector.

Table 4 Enantiomeric Excess in the Cross-Coupling of Alkyl Iodides with Phenyl Grignard in the Presence of 5 mol% **1**



Entry	Substrate	Product	Catalyst	Yield (%)[a]	ee (%)
1			**1a**	83	0
2			**1b**	>95	1
3			**1c**	73	1
4			**1d**	77	3
5			**1a**	84	7
6			**1b**	92	3
7			**1c**	94	5
8			**1d**	>95	19
9			**1a**	88	8
10			**1b**	86	13
11			**1c**	86	8
12			**1d**	71	16

[a] Yields were determined by GC (dodecane as internal standard; conversion 100%).

The Grignard reagents were titrated prior to every use following the literature procedure.[17]

Primary Alkyl Iodides (Table 3, Entries 1 and 2); General Procedure

A 250 mL conical flask equipped with a Teflon-coated magnetic stirrer was charged with 6-bromohexanoic acid (1.0 equiv), natural product alcohol (1.1 equiv), *N*,*N*′-dicyclohexylcarbodiimide (DCC, 1.0 equiv), 4-dimethylaminopyridine (DMAP, 2 mol%), and CH_2Cl_2 (100 mL). The reaction mixture was stirred at r.t. overnight. The mixture was then filtered, and the filtrate was washed with aq ~1 M HCl (~100 mL). The organic fraction was dried in vacuo to give a crude alkyl bromide, which was introduced into a 250 mL round-bottomed flask equipped with a Teflon-coated magnetic stirrer, followed by the addition of NaI (5 equiv), acetone (50 mL), and H_2O (5 mL). The reaction mixture was then heated at 60 °C until all alkyl bromide was consumed as determined by GC analysis. After cooling to r.t., the mixture was concentrated in vacuo, and the residue was partitioned between CH_2Cl_2 (50 mL) and H_2O (100 mL). The aqueous solution was extracted with CH_2Cl_2 (2 × 50 mL). The combined organic fractions were concentrated in vacuo, and the residue was purified by flash chromatography on silica gel using a mixture of hexanes and EtOAc as an eluent to afford the respective alkyl iodide.

2-Isopropyl-4-methylcyclohexyl 6-Iodohexanoate (Table 3, Entry 1)

Following the general procedure, 6-bromohexanoic acid (2.54 g, 13 mmol), (±)-menthol (2.24 g, 14.3 mmol), DCC (2.68 g, 13 mmol), DMAP (32 mg, 0.20 mmol), and NaI (9.74 g, 65 mmol) were used to prepare the title product; yield: 2.43 g 6.39 mmol, 49%); yellow liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.64–4.58 (m, 1 H), 3.11 (t, *J* = 7.0 Hz, 2 H), 2.23 (t, *J* = 7.5 Hz, 2 H), 1.94–1.88 (m, 1 H), 1.84–1.74 (ovrlp, 3 H), 1.63–1.54 (ovrlp, 4 H), 1.47–1.33 (ovrlp, 4 H), 1.04–0.78 (ovrlp, 9 H), 0.69 (d, *J* = 6.8 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.7, 73.8, 46.9, 40.9, 34.3, 34.2, 33.1, 31.3, 29.9, 26.2, 23.9, 23.3, 22.0, 20.7, 16.3, 6.4.

(3*S*,8*S*,9*S*,10*R*,13*R*,14*S*,17*R*)-10,13-Dimethyl-17-[(*R*)-6-methylheptan-2-yl]-2,3,4,7,8,9,10,11,12,13,14,15,16,17-tetradecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl 6-Iodohexanoate (Table 3, Entry 3)

Following the general procedure, 6-bromohexanoic acid (1.95 g, 10 mmol), cholesterol (4.25 g, 11 mmol), DCC (2.06 g, 10 mmol), DMAP (24 mg, 0.20 mmol), and NaI (7.50 g, 50 mmol) were used to prepare the title product; yield: 4.28 g (7.01 mmol, 70%); white powder.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 5.37 (d, *J* = 4.7 Hz, 1 H), 4.66–4.57 (m, 1 H), 3.19 (t, *J* = 7.0 Hz, 2 H), 2.32–2.27 (ovrlp, 4 H), 2.04–1.93 (ovrlp, 2 H), 1.90–1.81 (ovrlp, 5 H), 1.68–1.24 (m, 16 H), 1.19–0.94 (ovrlp, 12 H), 0.91 (d, *J* = 6.5 Hz, 3 H), 0.87–0.85 (ovrlp, 6 H), 0.68 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.9, 139.7, 122.7, 74.0, 56.8, 56.2, 50.1, 42.4, 39.8, 39.6, 38.3, 37.1, 36.7, 36.3, 35.9, 34.5, 33.2, 32.01, 31.95, 30.0, 28.3, 28.1, 27.9, 24.4, 24.1, 23.9, 23.0, 22.7, 21.1, 19.4, 18.8, 12.0, 6.7.

Screening of Coupling Reactions (Tables 1 and 4); General Procedure

Alkyl halide (0.5 mmol) and dodecane (60 µL) were dissolved in THF (3.0 mL) and a stock solution of [Fe(Bopa-R)Cl_2] **1** (25 mM, 1.0 mL) was added. The solution was brought to the corresponding temperature and PhMgCl (1.85 M in THF, 0.3 mL) was added over a time period of 5 min. The reaction mixture stirred for another 10 min and was quenched with H_2O (20 mL). The solution was acidified with aq 1 M HCl and extracted with CH_2Cl_2 (3 × 20 mL). The crude extract was dried (Na_2SO_4) and analyzed by GC. The solvent was then further evaporated and the product was purified for HPLC measurement by chromatography on silica gel (0 to 1% EtOAc in hexanes).

Substrate Scope of Coupling Reactions (Tables 2 and 3); General Procedure

Alkyl halide (Method A: 0.5 mmol, Method B: 0.25 mmol) was dissolved in THF [3.0 mL (A)/1.5 mL (B)] and a stock solution (25 mM) of [Fe(Bopa-*t*Bu)Cl_2] (**1d**) [1.0 mL (A)/0.5 mL (B)] was added. Afterwards PhMgCl (1.00 M) [0.5 mL (A)/0.25 mL (B)] was added over a time period of 15 min. The solution was stirred for another 45 min. Method A: The reaction was then quenched with H_2O (20 mL), acidified with aq 1 M HCl, and extracted with CH_2Cl_2 (3 × 20 mL). The crude extract was dried (Na_2SO_4) and further purified by chromatography on silica gel (eluent: 1% to 45% EtOAc in hexanes). Method B: The reaction was quenched by adding EtOH (0.5 mL). The reaction mixture was transferred on a preparative TLC plate and then further separated (eluent: EtOAc–hexanes).

1-Phenyloctane (Table 2, Entry 1)[18]

Method A: yield at r.t.: 78 mg (82%), at –40 °C: 87 mg (92%); colorless liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.28 (m, 2 H), 7.23–7.17 (m, 3 H), 2.63 (t, *J* = 7.8 Hz, 2 H), 1.64 (quint, *J* = 6.0 Hz, 2 H), 1.39–1.29 (m, 10 H), 0.91 (t, *J* = 6.9 Hz, 3 H).

9-(3-Phenylpropyl)-9*H*-carbazole (Table 2, Entry 2)[16]

Method A: yield: 118 mg (83%); white solid; mp 110–112 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.10 (d, *J* = 7.7 Hz, 2 H), 7.63–7.38 (m, 3 H), 7.38–7.11 (m, 10 H), 4.33 (t, *J* = 7.3 Hz, 2 H), 2.72 (t, *J* = 7.7 Hz, 2 H), 2.23 (quint, *J* = 7.5 Hz, 2 H).

(3-Phenoxypropyl)benzene (Table 2, Entry 3)[16]

Method B: yield: 36 mg (68%); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.12 (m, 7 H), 6.95–6.85 (m, 3 H), 3.97 (t, *J* = 6.1 Hz, 2 H), 2.82 (t, *J* = 7.5 Hz, 2 H), 2.13 (quint, *J* = 6.9 Hz, 2 H).

5-Phenylpentyl Acetate (Table 2, Entry 4)[19]

Method A: yield: 86 mg (83%); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.24 (m, 2 H), 7.15–7.21 (m, 3 H), 4.05 (t, *J* = 6.7 Hz, 2 H), 2.62 (t, *J* = 7.7 Hz, 2 H), 2.03 (s, 3 H), 1.45 (quint, *J* = 7.5 Hz, 4 H), 1.40 (quint, *J* = 7.6 Hz, 2 H).

1-Methoxy-4-(2-phenethyl)benzene (Table 2, Entry 5)[20]

Method A: yield: 104 mg (98%); white solid; mp 58–60 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.26 (m, 2 H), 7.22–7.15 (m, 3 H), 7.11–7.06 (m, 2 H), 6.85–6.78 (m, 2 H), 3.79 (s, 3 H), 2.92–2.82 (m, 4 H).

1,2-Diphenylethane (Table 2, Entry 6)[21]

Method A: yield: 52 mg (57%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.29 (m, 4 H), 7.27–7.19 (m, 6 H), 2.95 (s, 4 H).

1-[1-(3-Phenylpropyl)-1*H*-pyrrol-2-yl]ethanone (Table 2, Entry 7)[21]

Method B: yield: 32 mg (57%); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.28 (m, 2 H), 7.24–7.16 (m, 3 H), 6.99 (dd, *J* = 4.1, 1.7 Hz, 1 H), 6.85 (dd, *J* = 2.4, 1.8 Hz, 1 H), 6.15 (dd, *J* = 4.1, 2.5 Hz, 1 H), 4.36 (t, *J* = 7.2 Hz, 2 H), 2.69–2.61 (t, *J* = 7.8 Hz, 2 H), 2.46 (s, 3 H), 2.10 (quint, *J* = 7.5 Hz, 2 H).

1,3-Diphenylbutane (Table 2, Entry 8)[22]

Method A: for X = Br, yield at r.t.: 98 mg (93%); for X = I, yield at r.t.: 86 mg (88%), at –40 °C: 100 mg (95%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.13 (m, 10 H), 2.75 (hext, *J* = 7.1 Hz, 1 H), 2.61–2.47 (m, 2 H), 2.02–1.86 (m, 2 H), 1.31 (d, *J* = 7.0 Hz, 3 H).

1-Methoxy-4-(2-phenylpropyl)benzene (Table 2, Entry 9)[22]

Method A: yield: 102 mg (90%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.23 (m, 2 H), 7.23–7.11 (m, 3 H), 6.98 (d, *J* = 8.7 Hz, 2 H), 6.77 (d, *J* = 8.7 Hz, 2 H), 3.77 (s, 3 H), 3.01–2.83 (m, 2 H), 2.71 (dd, *J* = 13.3, 8.1 Hz, 1 H), 1.23 (d, *J* = 6.8 Hz, 3 H).

4-Phenyltetrahydro-2*H*-pyran (Table 2, Entry 10)[23]

Method A: yield: 61 mg (75%); white solid; mp 42–44 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.20 (m, 5 H), 4.15–4.07 (m, 2 H), 3.56 (td, *J* = 11.5, 2.7 Hz, 2 H), 2.78 (tt, *J* = 11.5, 4.4 Hz, 1 H), 1.94–1.75 (m, 4 H).

2-(4-Fluorophenyl)-4-phenyltetrahydro-2*H*-pyran (Table 2, Entry 11)[24]

Method A: yield: 118 mg (92%); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ (mixture of stereoisomers) = 7.4 –7.31 (m, 14 H), 7.27–7.14 (m, 11 H), 7.11–6.95 (m, 7 H), 4.91 (t, *J* = 5.0 Hz, 1 H), 4.47 (dd, *J* = 11.2, 2.0 Hz, 2 H), 4.34–4.25 (m, 2 H), 3.89–3.71 (m, 5 H), 3.11–3.02 (m, 1 H), 2.96 (ddd, *J* = 16.0, 10.2, 3.9 Hz, 2 H), 2.39–2.23 (m, 3 H), 2.06–2.02 (m, 2 H), 1.97–1.81 (m, 5 H), 1.80–1.67 (m, 2 H), 1.28–1.20 (m, 2 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (mixture of stereoisomers) =128.59, 128.57, 128.09 (d, *J* = 8.0 Hz), 127.48 (d, *J* = 8.0 Hz), 127.15, 126.73, 126.45, 126.23, 115.30 (d, *J* = 21.2 Hz), 115.13 (d, *J* = 21.3 Hz), 79.29, 73.45, 68.71, 62.81, 42.07, 41.52, 35.93, 35.46, 33.26, 32.12.

Ethyl 3-Phenylcyclohexanecarboxylate (Table 2, Entry 12)

Method A: yield: 82 mg (71%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ (mixture of *cis*- and *trans*-isomers) = 7.43–7.12 (m, 5 H), 4.34–4.03 (m, 2 H), 2.85–1.40 (m, 10 H), 1.38–1.23 (m, 3 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ (mixture of *cis*- and *trans*-isomers) = 175.72, 175.12, 146.90, 146.65, 128.40, 128.33, 126.86, 126.80, 126.15, 125.94, 60.21, 60.19, 43.86, 43.67, 39.90, 39.75, 36.45, 34.86, 33.49, 33.26, 28.57, 27.20, 25.87, 23.02, 14.34, 14.24.

HRMS (APCI): *m*/*z* [M + H]$^+$ calcd for $[C_{15}H_{21}O_2]^+$: 233.1542; found: 233.1544.

***tert*-Butyl 4-Phenylpiperidine-1-carboxylate (Table 2, Entry 13)**[21]

Method A: yield: 115 mg (88%); yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30 (m, 2 H), 7.25–7.16 (m, 3 H), 4.24 (dd, *J* = 9.6, 8.0 Hz, 2 H), 2.80 (t, *J* = 12.1 Hz, 2 H), 2.64 (tt, *J* = 12.1, 3.5 Hz, 1 H), 1.82 (m, 2 H), 1.64 (m, 2 H), 1.48 (s, 9 H).

Benzyl 3-Phenylazetidine-1-carboxylate (Table 2, Entry 14)

Method A: yield: 87 mg (65%); light yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.26 (m, 10 H), 5.15 (d, *J* = 13.9 Hz, 2 H), 4.44 (t, *J* = 8.8 Hz, 2 H), 4.10 (dd, *J* = 8.8, 6.1 Hz, 2 H), 3.82 (ddt, *J* = 12.3, 8.8, 6.1 Hz, 1 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 142.17, 137.01, 129.09, 128.79, 128.35, 128.30, 127.41, 127.03, 66.99, 34.24, 0.31.

HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $[C_{17}H_{17}NO_2 + Na]^+$: 290.1157; found: 290.1170.

Menthyl 6-Phenylhexanoate (Table 3, Entry 1)

Method B: yield: 66 mg (83%); colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.05 (m, 5 H), 4.67 (td, *J* = 10.9, 4.3 Hz, 1 H), 2.72–2.50 (m, 2 H), 2.28 (t, *J* = 7.5 Hz, 2 H), 2.03–1.81 (m, 2 H), 1.67–1.24 (m, 10 H), 0.86 (ddd, *J* = 56.1, 27.3, 7.2 Hz, 12 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.37, 142.55, 128.39, 128.28, 125.68, 73.93, 47.03, 40.96, 35.80, 34.67, 34.29, 31.39, 31.14, 28.79, 26.27, 25.01, 23.42, 22.06, 20.79, 16.31.

HRMS (APCI): *m*/*z* [M + Na]$^+$ calcd for $[C_{22}H_{34}O_2 + Na]^+$: 353.2457; found: 353.2447.

3-Phenylcholest-5-ene (Table 3, Entry 2)[25]

Method B: yield: 59 mg (53%); white solid; mp 126–129 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.12 (m, 5 H), 5.45 (s, 0.2 H), 5.35 (d, *J* = 4.7 Hz, 0.8 H), 2.52–2.52 (m, 2 H), 2.06–1.94 (m, 3 H), 1.87–1.70 (m, 4 H), 1.61–1.34 (m, 12 H), 1.17–1.00 (m, 14 H), 0.94–0.90 (m, 3 H), 0.87 (dd, *J* = 6.5, 1.7 Hz, 6 H), 0.69 (d, *J* = 8.6 Hz, 3 H).

HRMS (APCI): *m*/*z* [M + H]$^+$ calcd for $[C_{33}H_{51}]^+$: 447.3985; found: 447.3988.

3-Cholest-5-enyl 6-Phenylhexanoate (Table 3, Entry 3)

Method B: yield: 119 mg (85%); yellowish oil.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.20 (m, 2 H), 7.11–7.18 (m, 3 H), 5.30 (m, 1 H), 4.64–4.57 (dt, *J* = 15.5, 7.5 Hz, 1 H), 2.60 (t, *J* = 7.6 Hz, 2 H), 2.27 (dd, *J* = 15.1, 7.7 Hz, 4 H), 2.02–1.95 (t, *J* = 15.7 Hz, 2 H), 1.89–1.78 (m, 3 H), 1.69–1.43 (m, 12 H), 1.39–1.25 (m, 8 H), 1.17–1.06 (m, 6 H), 1.01 (s, 3 H), 0.92 (d, *J* = 6.1 Hz, 3 H), 0.89–0.82 (m, 6 H), 0.66 (s, 4 H).

^{13}C NMR (101 MHz, $CDCl_3$): δ = 173.25, 142.60, 139.77, 128.48, 128.36, 125.75, 122.70, 73.81, 56.79, 56.24, 50.12, 42.42, 39.84, 39.64, 38.26, 37.11, 36.70, 36.30, 35.92, 35.85, 34.71, 32.02, 31.97, 31.22, 28.82, 28.36, 28.14, 27.91, 25.03, 24.41, 23.96, 22.96, 22.70, 21.15, 19.45, 18.84, 11.98.

HRMS (ESI): *m*/*z* $[M + K]^+$ calcd for $[C_{39}H_{60}O_2 + K]^+$: 599.4230; found: 599.4226

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0034-1380136.

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