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Iridium-Catalyzed Alkylation of Methylquinolines with Alcohols

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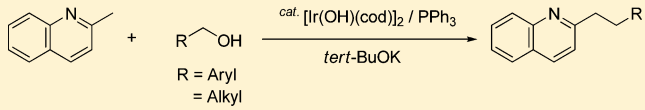
Supporting Information

ABSTRACT: Iridium-catalyzed alkylation of methylquinolines at the methyl substituent was achieved using alcohols as alkylating agents. The reaction proceeded through a transfer hydrogenation pathway from the alcohol to the Ir complex, affording an aldehyde and Ir−H species, followed by base-assisted aldol condensation and hydrogenation. This method provides an atom-economical and convenient route to alkylquinolines from easily accessible methylquinolines.



Quinolines and their derivatives are important motifs in pharmaceutical and agricultural chemistry and are used as building blocks in total syntheses of natural products.[1] Various methods for synthesizing quinolines and quinoline-based natural products have therefore been developed.[2] In particular, the introduction of alkyl-chain moieties into benzoquinones is an important chemical transformation.[3] Conventionally, methylquinolines have been chosen as the starting materials for the preparation of alkylated quinoline derivatives because they are easily accessible.[3] The reaction of a methylquinoline with *n*-BuLi followed by reaction with an alkyl halide is the classic method of synthesizing alkylquinolines.[3] However, since a prerequisite of the conventional reaction is the use of aryl halides as substrates, this method suffers from formation of undesired stoichiometric amounts of waste salts generated from alkyl halides and bases. The development of an improved reaction that is environmentally benign and uses easily accessible starting materials for the introduction of alkyl groups on methylquinolines is therefore highly desirable.

It is well-known that Ir and Ru complexes serve as efficient catalysts for transfer hydrogenation (also known as hydrogen borrowing) from alcohols to aldehydes and ketones.[4] Much research has focused on both α-alkylation and β-alkylation reactions using alcohols as alkylating agents.[5] Our group has focused on Ir-catalyzed α-alkylations of methyl ketones, methyl esters, and active methylene compounds, and Guerbet-type dimerizations of alcohols.[6] We achieved Ir-catalyzed alcohol transformations to esters,[7] and reactions of alcohols with alkynes or enones led to homoallylic alcohols,[8] enones,[9] and 1,3-diketones.[10]

During the course of our investigations, we became aware of the development of methyl alkylation of methylquinolines by a transfer hydrogenation method using alcohols as alkylating agents. This is a convenient method for obtaining synthetically useful quinoline derivatives and also for achieving high-yield direct alkylation of less acidic methyl substituents on the aromatic compound using a simple Ir catalyst system. Recently, Kempe and co-workers reported the alkylations of methylpyrimidines and picolines using Ir complexes bearing P,N-type ligands such as $py_2NP(iPr)_2$.[11] Reflecting on these related studies, we realized the importance of the necessity of investigating efficient synthetic methods for obtaining alkylquinolines from easily accessible methylquinolines using simple catalytic systems. Here we report a simple and versatile method for the preparation of various alkylquinolines from methylquinolines and alcohols in the presence of an $[Ir(OH)(cod)]_2$ catalyst combined with a PPh_3 ligand and a base.

To determine the optimum reaction conditions, the reaction of 2-methylquinoline (**1a**) with benzyl alcohol (**2a**) was chosen as a model reaction and carried out under various reaction conditions. The results for the alkylation reactions are shown in Table 1. For example, the reaction of **1a** (3 mmol) with **2a** (1 mmol) was performed in the presence of $[Ir(OH)(cod)]_2$ (0.05 mmol, 5 mol %) combined with PPh_3 (0.20 mmol, 20 mol %) and *t*-BuOK (0.5 mmol, 50 mol %) in 1,4-dioxane (1 mL) at 130 °C for 24 h, giving **3a** in quantitative yield (Table 1, entry 1). With regard to the Ir complex, $[Ir(OMe)(cod)]_2$, $[IrCl(cod)]_2$, and $[Cp^*IrCl_2]_2$ gave comparable good yields (Table 1, entries 2−4). However, when $IrCl_3{\cdot}3H_2O$ and an Rh analogue, $[RhCl(cod)]_2$, were used, the reactions were sluggish (Table 1, entries 5 and 6). As the base added in the reaction, *t*-BuOK gave the best result, and strong bases such as KOH gave the product in good yield, but weak bases such as Na_2CO_3 resulted in total inactivity under these conditions (Table 1, entries 1, 7, and 8). It was found that the addition of a phosphine ligand was necessary to obtain higher yields from the reaction; the reaction was sluggish if a diphosphine was used, or if the reaction was performed in the absence of a phosphine ligand (Table 1, entries 9−12). In this reaction, high yield formation of **3a** was achieved by using excess (3 equiv to **2a**) amount of **1a** (Table 1, entry 1). However, the conversion of **1a** was 35% and most of unreacted **1a** was recovered (59%) by distillation after the reaction. On the other hand, the equimolar reaction of **1a** with **2a** resulted in decrease in the yield of **3a** (Table 1, entry 13) because **1a** possesses a less acidic methyl

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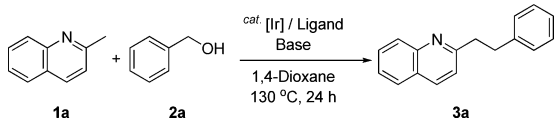
Table 1. Ir-Catalyzed Reactions of 2-Methylquinoline (1a) with Benzyl Alcohol (2a) under Various Conditions[a]



entry	Ir catalyst	base	ligand	yield 3a (%)[b]
1	$[Ir(OH)(cod)]_2$	*t*-BuOK	PPh_3	quant (92)
2	$[Ir(OMe)(cod)]_2$	*t*-BuOK	PPh_3	86
3	$[IrCl(cod)]_2$	*t*-BuOK	PPh_3	81
4	$[Cp^*IrCl_2]_2$	*t*-BuOK	PPh_3	64
5	$IrCl_3 \cdot 3H_2O$	*t*-BuOK	PPh_3	1[c]
6	$[RhCl(cod)]_2$	*t*-BuOK	PPh_3	7
7	$[Ir(OH)(cod)]_2$	KOH	PPh_3	58
8	$[Ir(OH)(cod)]_2$	Na_2CO_3	PPh_3	n.d.[d]
9	$[Ir(OH)(cod)]_2$	*t*-BuOK	PCy_3	59
10	$[Ir(OH)(cod)]_2$	*t*-BuOK	$P(n\text{-Oct})_3$	40
11[e]	$[Ir(OH)(cod)]_2$	*t*-BuOK	dppp	12
12	$[Ir(OH)(cod)]_2$	*t*-BuOK	None	10
13[f]	$[Ir(OH)(cod)]_2$	*t*-BuOK	PPh_3	41[g]

[a]Conditions: **1a** (3 mmol) was allowed to react with **2a** (1 mmol) in the presence of Ir catalyst (0.05 mmol), ligand (0.20 mmol), and base (0.50 mmol) in 1,4-dioxane (1 mL) at 130 °C for 24 h. [b]GC yields based on **2a** except the value in the parentheses. [c]28% of 2-stylquinoline was observed. [d]Not detected by GC. [e]dppp (0.10 mmol) was used. [f]2-Methylquinoline (1 mmol) was used. [g]Conversions of **1a** and **2a** were 14% and 46%.

group and shows low reactivity in the reaction. No reaction took place in the absence of an Ir complex.

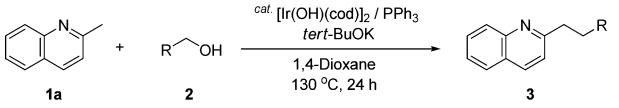
1,4-Dioxane is the most suitable solvent for the reactions (Table 1, entry 1). The use of other selected solvents under these conditions gave the following results: *p*-xylene (43%), diglyme (85%), 1,2-dichlorobenzene (34%), and octane (50%).

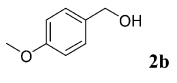
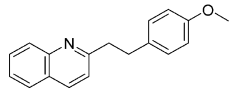
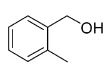
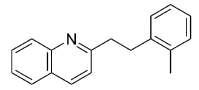
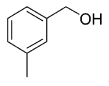
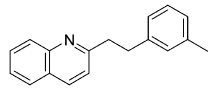
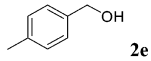
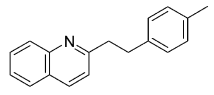
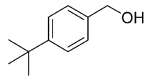
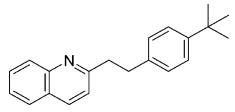
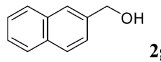
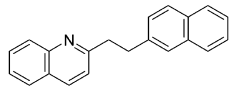
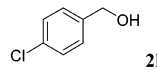
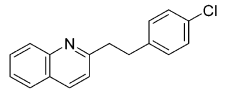
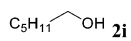
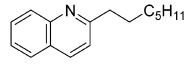
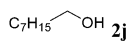
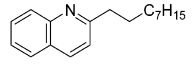
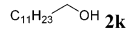
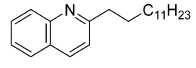
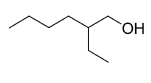
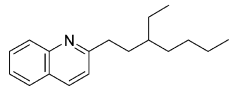
The methyl alkylation of 2-methylquinoline proceeded smoothly using various substituted benzyl alcohols bearing electron-donating/-withdrawing groups (Table 2, entries 1−7), as well as using aliphatic alcohols (Table 2, entries 8−11), giving the corresponding products (**3b**−**3l**) in good to excellent yields under the same condition as for entry 1 in Table 1; the results are shown in Table 2. Although this reaction tolerated various primary alcohols as alkylating agents, unfortunately, the use of secondary alcohols such as benzhydrol was sluggish under these conditions.

The present catalytic system was successfully extended to reactions of various heteroaromatic compounds, and the results are shown in Table 3. 4-Methylquinoline gave the corresponding product in good yield (Table 3, entry 1), but 3- and 6-methylquinoline were totally inactive (Table 3, entries 2 and 3). The use of 2-methylquinoxaline and 2-methylbenzoxazole gave the desired methyl-alkylated products (**3n** and **3o**) in high to excellent yields (Table 3, entries 4 and 5). In contrast, the use of 2-methylpyridine gave the corresponding alkylated pyridine (**3p**) in only 21% yield (Table 3, entry 6).

These results suggest that the use of methylquinolines with benzo substituents on the methylpyridine scaffold is a prerequisite for the reaction to proceed efficiently and in good yield. Furthermore, the use of 2- or 4-methylquinoline efficiently increases the acidity of the methyl protons for the deprotonation step on addition of a base in the catalytic system (pK_a values are 25 for 2-methylquinoline, 25 for 4-methylquinoline, 32 for 3-methylquinoline, and 29.5 for 2-methylpyridine).[12]

Table 2. Ir-Catalyzed Reactions of 2-Methylquinoline (1a) with Primary Alcohols 2[a]



Entry	Alcohol (2)	Product (3)	Yield (%)
1	 2b	 3b	88
2	 2c	 3c	78
3	 2d	 3d	76
4	 2e	 3e	75
5	 2f	 3f	89
6	 2g	 3g	82
7	 2h	 3h	36
8[b,c]	 2i	 3i	64
9[b,c]	 2j	 3j	67
10[b,c]	 2k	 3k	74
11[b,c]	 2l	 3l	78

[a]Conditions: **1a** (3 mmol) was allowed to react with **2** (1 mmol) in the presence of Ir catalyst (0.05 mmol), ligand (0.20 mmol), and base (0.50 mmol) in 1,4-dioxane (1 mL) at 130 °C for 24 h. [b]*t*-BuOK (0.70 mmol) was used. [c]2-Methylquinoline (10 mmol) was used.

A similar enhancement of the reaction by a benzo-substituent effect was observed in our study of Ir-catalyzed reactions of 1-naphthylamine and diols, giving benzo[*h*]quinolines and benzoindoles.[13]

To obtain further insights into the present reaction, the time course of the reaction of **1a** and **2a** was monitored (Figure 1). In the early stage of the reaction, the formation of 2-

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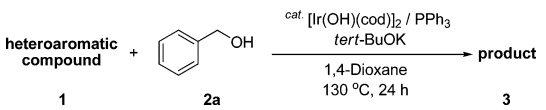
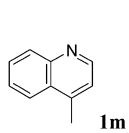
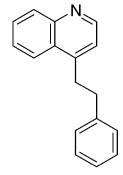
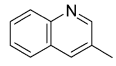
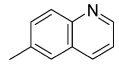
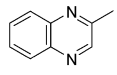
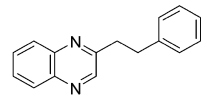
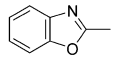
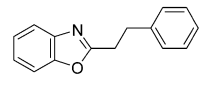
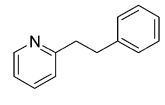
Table 3. Ir-Catalyzed Reactions of Heteroaromatic Compounds 1 with Benzyl Alcohol (2a)[a]



Entry	Heteroaromatic compound (1)	Product (3)	Yield (%)
1[b,c]	 1m	 3m	56
2		--- ---	n.d.[d]
3		--- ---	n.d.[d]
4	 1n	 3n	90
5[c,e]	 1o	 3o	72
6	 1p	 3p	21

[a]Conditions: **1** (3 mmol) was allowed to react **2a** with (1 mmol) in the presence of Ir catalyst (0.05 mmol), ligand (0.20 mmol), and base (0.50 mmol) in 1,4-dioxane (1 mL) at 130 °C for 24 h. [b]*t*-BuOK (0.70 mmol) was used. [c]**1** (5 mmol) was used. [d]Not detected by GC. [e]*t*-BuOK (1 mmol) was used.

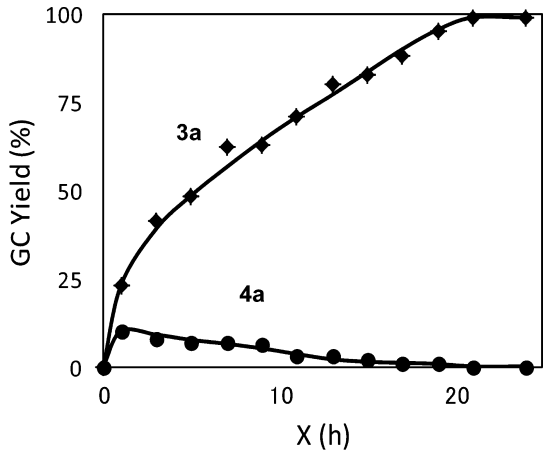


Figure 1. Time-course monitoring of reaction of **1a** with **2a**.

phenylethenylquinoline (**4a**) was detected, which showed that **4a** was an intermediate in the reaction. We interrupted the reaction course at 1 h, and the conversions of **1a** and **2a** were 10% and 41%, respectively. Products **3a** and **4a** were isolated during the course of the reaction. The results, shown in Figure 1 and Scheme 1, clearly indicate that **4a** was an intermediate in the reaction.

The above alkylation reaction is therefore thought to proceed through the following sequential reactions, involving three key steps, as proposed in previous reviews (Figure 2):[4] (i) hydrogen transfer from alcohol **2** to an Ir complex, giving aldehyde **A** and an Ir hydride intermediate **B**; (ii) base-catalyzed aldol condensation by a coupling reaction of **A** and **1a** to form alkenylquinoline **4**;[1c,14] and (iii) selective hydrogenation of **4** by the Ir hydride complex generated during the course of the reaction, leading to alkylated quinoline **3**.

In conclusion, an efficient and selective alkylation of methylquinolines was successfully developed using an Ir complex combined with a phosphine ligand and a base. The reaction provides a simple and atom-economical direct route to alkylquinolines, as the exclusive products, in good to excellent yields.

EXPERIMENTAL SECTION

General. GC analysis was performed with a flame ionization detector using a 0.22 mm × 25 m capillary column (BP-5). ^{1}H and ^{13}C NMR were measured at 400 and 100 MHz, respectively, in $CDCl_3$ with Me_4Si as the internal standard. The products were characterized by ^{1}H NMR, ^{13}C NMR, and GC–MS. The yields of products were estimated from the peak areas based on the internal standard technique using GC.

Compounds **3a**,[15a] **3b**,[15b] **3c**,[15c] **3e**,[15d] **3i**,[15e] **3j**,[15e] **3k**,[15e] **3m**,[15f] **3n**,[15g] **3o**,[15h] **3p**,[15i] and **4a**[1c] were reported previously.

Typical Reaction (Table 1, entry 1). A mixture of [Ir(OH)(cod)]$_2$ (32 mg, 0.05 mmol), PPh_3 (52 mg, 0.20 mmol), *t*-BuOK (56 mg, 0.5 mmol), **1a** (0.43 g, 3 mmol), and **2a** (0.1 g, 1 mmol) in 1,4-dioxane (1 mL) was stirred at 130 °C for 24 h under Ar. The conversions and yields of products were estimated from peak areas based on an internal standard using GC, and the product **3a** was obtained in quantitative yield. The product **3a** was isolated by column chromatography (230–400 mesh silica gel, *n*-hexane/ethyl acetate = 10/1) and Kugelrohr distillation (100 °C (pot)/0.3 mmHg, 1 h) in 92% yield (215 mg) as yellow liquid. After the reaction, unreacted **1a** (1.77 mmol, 253 mg, 59%) was recovered by Kugelrohr distillation (95 °C (pot)/0.3 mmHg, 1 h).

Compound 3b. Yield 88% (232 mg), yellow solid, mp 56–57 °C (lit.[15b] mp 58–59 °C)

Compound 3m. Yield 56% (131 mg), yellow solid, mp 99–100 °C (lit.[15f] mp 96–97 °C)

Compound 3o. Yield 72% (161 mg), white solid, mp 53–54 °C (lit.[15h] mp 53–54 °C)

Compound 3d. Yield 76% (188 mg), yellow liquid; ^{1}H NMR δ 8.09–7.00 (m, 10H), 3.29–3.25 (m, 2H), 3.13–3.09 (m, 2H), 2.312 (s, 3H); ^{13}C NMR δ 161.9 (C), 148.0 (C), 139.7 (C), 136.2 (CH), 136.0 (C), 130.2 (CH), 129.4 (CH), 128.9 (CH), 128.8 (CH), 127.5 (CH), 126.8 (C), 126.1 (CH), 126.0 (CH), 125.8 (CH), 121.5 (CH), 39.7 (CH_2), 33.2 (CH_2), 19.3 (CH_3); IR (neat, cm^{-1}) 3053, 2920, 1599, 1504, 1427, 827, 785, 745; GC–MS (EI) *m*/*z* (relative intensity) 247 (89) [M]$^+$, 246 (100), 156 (56), 142 (2), 128 (14), 105 (11), 91 (3), 77(14); HRMS (EI-TOF) *m*/*z* calcd for $C_{18}H_{17}N$ [M]$^+$ 247.1361, found 247.1357.

Compound 3f. Yield 89% (258 mg), yellow solid, mp 66–67 °C; ^{1}H NMR δ 8.09–7.20 (m, 10H), 3.31–3.27 (m, 2H), 3.14–3.10 (m, 2H), 1.31 (s, 9H); ^{13}C NMR δ 162.0 (C), 148.8 (C), 148.0 (C), 138.5 (C), 136.2 (CH), 129.3 (CH), 128.9 (CH), 128.1 (CH), 127.5 (CH), 126.8 (C), 125.7 (CH), 125.3 (CH), 121.5 (CH), 41.0 (CH_2), 35.4 (CH_2), 34.4 (C), 31.4 (CH_3); IR (neat, cm^{-1}) 2959, 1599, 1500, 1425, 827, 752; GC–MS (EI) *m*/*z* (relative intensity) 289 (94) [M]$^+$, 288 (100), 274 (27), 258 (2), 244 (1), 232 (15), 156 (34), 147 (8), 142 (4), 132 (6), 128 (11), 119 (3), 118 (2), 117 (18), 105 (5), 104 (2), 103 (3), 91 (10), 89 (3), 77 (4), 57 (3); HRMS (EI-TOF) *m*/*z* calcd for $C_{21}H_{23}N$ [M]$^+$ 289.1830, found 289.1840.

Compound 3g. Yield 82% (232 mg), yellow solid, mp 125–126 °C; ^{1}H NMR δ 8.10–7.17 (m, 13H), 3.39–3.28 (m, 4H), 3.13–3.09 (m, 2H); ^{13}C NMR δ 161.7 (C), 148.0 (C), 139.0 (C), 136.2 (CH),

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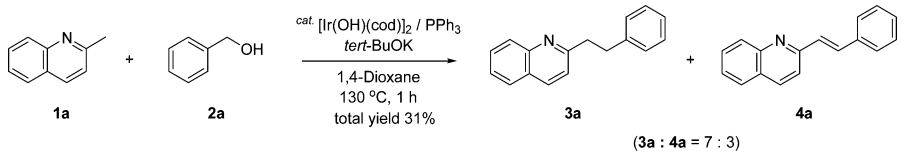
Scheme 1. Observed Reaction Intermediate 4a in the Reaction of 1a with 2a



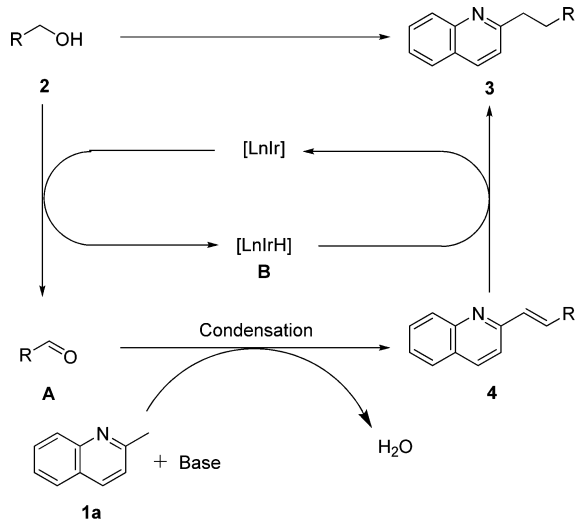


Figure 2. Plausible reaction pathway.

133.6 (C), 132.0 (C), 129.4 (CH), 128.9 (CH), 127.9 (CH), 127.6 (CH), 127.5 (CH), 127.5 (CH), 127.3 (CH), 126.8 (C), 126.6 (CH), 125.9 (CH), 125.8 (CH), 125.2 (CH), 121.6 (CH), 40.9 (CH_2), 36.0 (CH_2); IR (neat, cm^{-1}) 2916, 1597, 1501, 1425, 1126, 858, 829, 746; GC–MS (EI) *m*/*z* (relative intensity) 283 (88) $[M]^+$, 282 (100), 156 (35), 155 (4), 142 (9), 141 (44), 128 (17), 127 (4). Anal. Calcd for $C_{21}H_{17}N$: C, 89.01; H, 6.05; N, 4.94. Found: C, 89.01; H, 5.97; N, 4.93.

Compound 3h. Yield 36% (96 mg), yellow solid, mp 56–57 °C; ^1H NMR δ 8.07–7.12 (m, 10H), 3.26–3.22 (m, 2H), 3.14–3.10 (m, 2H); ^{13}C NMR δ 161.2 (C), 147.9 (C), 139.9 (C), 136.2 (CH), 131.6 (C), 129.8 (CH), 129.4 (CH), 128.8 (CH), 128.4 (CH), 127.5 (CH), 126.7 (C), 125.8 (CH), 121.4 (CH), 40.6 (CH_2), 35.0 (CH_2); IR (neat, cm^{-1}) 3057, 2924, 1600, 1501, 1427, 1090, 1013, 827, 762; GC–MS (EI) *m*/*z* (relative intensity) 267 (89) $[M]^+$, 266 (100), 232 (7), 156 (70), 142 (4), 128 (22), 125 (19), 91(1), 77(9); HRMS (EI-TOF) *m*/*z* calcd for $C_{17}H_{14}NCl$ $[M]^+$ 267.0815, found 267.0820.

Compound 3l. Yield 78% (199 mg), yellow liquid; ^1H NMR δ 7.98–7.18 (m, 6H), 2.90–2.86 (m, 2H), 1.70–1.67 (m, 2H), 1.33–1.21 (m, 9H), 0.83–0.80 (t, *J* = 7.2 Hz 3H), 0.83–0.79 (t, *J* = 7.2, Hz 3H); ^{13}C NMR δ 163.47 (C), 147.9 (C), 136.1 (CH), 129.2 (CH), 128.8 (CH), 127.4 (CH), 126.7 (C), 125.6 (C), 121.3 (CH), 38.9 (CH), 36.8 (CH_2), 33.5 (CH_2), 32.7 (CH_2), 28.9 (CH_2), 25.7 (CH_2), 23.1 (CH_2), 14.1 (CH_3), 10.8 (CH_3); IR (neat, cm^{-1}) 2956, 2926, 2859, 1601, 1504, 1458, 1425, 826, 752; GC–MS (EI) *m*/*z* (relative intensity) 255 (1) $[M]^+$, 226 (6), 198 (5), 184 (2), 170 (1), 156 (39), 143 (100), 142 (4), 128 (6), 57 (2), 43 (2), 29 (4); HRMS (EI-TOF) *m*/*z* calcd for $C_{18}H_{25}N$ $[M]^+$ 255.1987, found 255.1993.

■ ASSOCIATED CONTENT

Supporting Information

^1H, and ^{13}C NMR spectra for products. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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