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Low-Valent Niobium-Catalyzed Intermolecular [2 + 2 + 2] Cycloaddition of *tert*-Butylacetylene and Arylnitriles to Form 2,3,6-Trisubstituted Pyridine Derivatives

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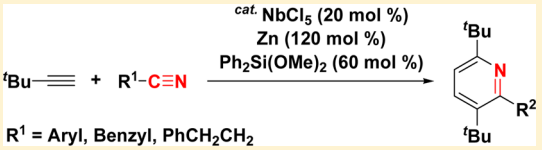
Supporting Information

ABSTRACT: A catalytic system based on low-valent niobium has been developed, consisting of $NbCl_5$, Zn, and an alkoxysilane. This combination has been shown to be an efficient catalyst for the synthesis of pyridine derivatives from the intermolecular cycloaddition of alkynes and nitriles via a niobacyclopentadiene intermediate.



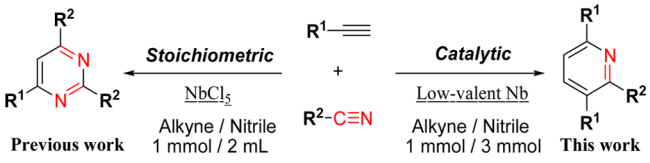
Pyridines are an important class of azaheterocyclic compounds and include natural products, biologically active substances,[1] functional materials[2] and ligands.[3] By way of example, niacin and vitamin B_6 are both well-known pyridine derivatives. Neutral pyridine-based pillaring ligands are also employed in the construction of metal−organic frameworks (MOFs), since they can be fully exchanged with different pyridine-based ligands to enable "stepwise" MOF synthesis.[4]

Among the methods available for the preparation of pyridines, the transition-metal-catalyzed cycloaddition reaction of alkynes with nitriles is of particular importance, since this methodology is capable of introducing various substituent groups onto the pyridine ring.[5−11] Many of the reported cycloaddition reactions have been intramolecular reactions using α,ω-diynes or cyanoalkynes. For instance, Takeuchi and co-workers reported that pyridines could be produced from the Ir-catalyzed [2 + 2 + 2] cycloaddition of α,ω-diynes with nitriles.[8]

Alternatively, the transition-metal-catalyzed intermolecular [2 + 2 + 2] cross-cycloaddition reaction between two alkyne molecules and one nitrile is one of the simplest and most atom-economical methods for preparing pyridines. However, little work has been reported in this field because of the difficulty in controlling the chemo- and regioselectivity of the reaction. Wakatsuki and Yamazaki reported a Co-catalyzed reaction that was the first example of the synthesis of pyridines via the [2 + 2 + 2] intermolecular cycloaddition reactions of alkynes with nitriles.[6a] These intra- and intermolecular cycloaddition reactions typically employ late transition metals as catalysts, such as Co,[6] Rh,[7] Ir,[8] Ni,[9] Ru[10] and Fe.[11]

The synthesis of pyridines in this manner has not yet been achieved using early transition metals as catalysts. Some stoichiometric reactions employing early transition metals have, however, been reported, such as the synthesis of pyridines from two alkynes, a nitrile and $Ti(OiPr)_2$,[12] the Zr/Ni-mediated cyclotrimerization of alkynes and nitriles to give pentasubstituted pyridines[13] and the preparation of tetrasubstituted pyridines from the reaction of Ta-alkyne complexes with alkynenitriles.[14] In addition, our research group has reported the $NbCl_5$-mediated intermolecular cycloaddition reaction of alkynes with benzonitriles.[15] This reaction did not produce pyridines, though, and instead gave pyrimidines when using a stoichiometric amount of $NbCl_5$ (Scheme 1, "Previous work").

Scheme 1. Transition-Metal-Catalyzed [2 + 2 + 2] Cycloaddition of Alkynes with Nitriles



Recently, we reported that the $NbCl_3(DME)$[16] is a useful catalyst for the selective synthesis of 1,3-cyclohexadienes from the reaction of alkynes with alkenes.[17] We additionally determined that the $NbCl_5$/hydrosilane system serves as an efficient low-valent Nb catalyst for the selective cycloaddition of alkynes and alkenes to form 1,3-cyclohexadienes.[17c]

In this paper, we report the intermolecular [2 + 2 + 2] cycloaddition of terminal alkynes and nitriles, catalyzed by low-valent Nb (generated in situ from $NbCl_5$, Zn and $Ph_2Si(OMe)_2$), leading to 2,3,6-trisubstituted pyridines in high yields (Scheme 1, "This work").

Initially, *tert*-butylacetylene (**1a**) and benzonitrile (**2a**) were used as model substrates for the optimization of the cycloaddition reaction conditions, with the results presented in Table 1. We investigated various low-valent niobium species. When **1a** (1 mmol) was reacted with **2a** (3 mmol) in the presence of $NbCl_3(DME)$ (0.2 mmol) in toluene (2 mL) at 80 °C for 16 h, the reaction produced trisubstituted pyridine (**3a**) in 11% yield as well as **4a** in 36% yield (entry 1). Previously, we

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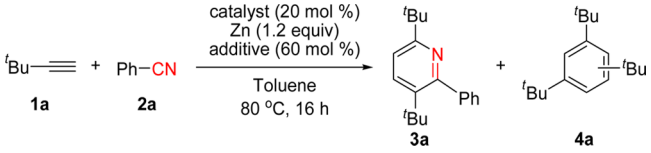
Table 1. $NbCl_5/Zn/Ph_2Si(OMe)_2$ Catalyzed Reaction of *tert*-Butylacetylene (1a) with Benzonitrile (2a) under Various Conditions[a]



1a 2a 3a 4a

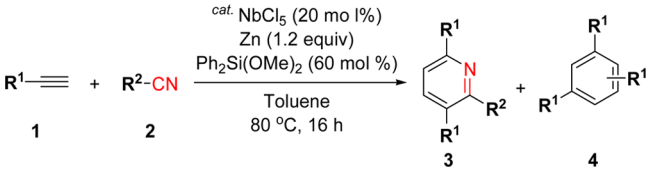
entry	catalyst	additive	yield (%)[b] 3a	4a
1[c]	$NbCl_3$(DME)	none	11(95)	36
2[c]	$NbCl_5$	none	n.d.[g]	n.d.[g]
3	$NbCl_5$	none	26(77)	41
4	$NbCl_5$	$PhSiMe_3$	33(88)	43
5	$NbCl_5$	$PhSi(OMe)_3$	70(97)	17
6	$NbCl_5$	$MeSi(OMe)_3$	72(98)	18
7	$NbCl_5$	$Ph_2Si(OMe)_2$	82[74](98)	10
8[d]	$NbCl_5$	$Ph_2Si(OMe)_2$	64(98)	27
9[e]	$NbCl_5$	$Ph_2Si(OMe)_2$	38(96)	15
10[f]	$NbCl_5$	$Ph_2Si(OMe)_2$	27(96)	7
11	$NbCl_3$(DME)	$Ph_2Si(OMe)_2$	47(71)	15
12	$TaCl_5$	$Ph_2Si(OMe)_2$	trace	8
13	$ZrCl_4$	$Ph_2Si(OMe)_2$	n.d.[g]	n.d.[g]

[a]Reaction conditions: **1a** (1 mmol), **2a** (3 mmol), catalyst (0.2 mmol), Zn (1.2 mmol) and additive (0.6 mmol) in toluene (2 mL) at 80 °C for 16 h under Ar. [b]Yields were determined by GC on the basis of the quantity of **1a** used. All are GC yields except the value in the square brackets. The numbers in parentheses show the selectivity (%) of the 2,3,6-substituted adduct. [c]Without Zn. [d]**1a** (1 mmol) and **2a** (0.5 mmol) were used. [e]Zn (0.2 mmol) was used. [f]$NbCl_5$ (0.1 mmol), Zn (1.1 mmol), $Ph_2Si(OMe)_2$ (0.3 mmol) were used. [g]Not detected by GC.

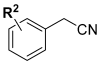
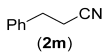
reported that $NbCl_5$ is an effective agent for the activation of nitriles.[15] We therefore applied $NbCl_5$ to this reaction; however, the result was that neither **3a** nor **4a**[18] were observed in the products (entry 2). When low-valent Nb species were instead generated by $NbCl_5$ in conjunction with Zn,[19] **3a** was obtained in 26% yield with good regioselectivity (entry 3). The data related to subsequent screening of silane compounds as additives are shown in entries 4−7 and reveal that alkoxysilanes are effective for this reaction. Between the two alkoxysilanes tested, $Ph_2Si(OMe)_2$ demonstrated the most pronounced influence on reactivity, producing **3a** in the best yield with excellent regioselectivity. However, other additives ($AgSbF_6$, 1,1-bis(diphenyldiphosphino)methane), and biacetyl-bis-(phenylimine)) exhibited no activity in the formation of pyridine derivatives. On the basis of the results of these experiments, the presence of alkoxy substituents on the silyl group is useful for the cycloaddition of alkynes and nitriles (entry 4 vs entry 5). Interestingly, even when **1a** and **2a** were allowed to react in a stoichiometric molar ratio (**1a**:**2a** = 2:1), the yield of the product was still acceptable at 64% (entry 8). As the catalyst precursor for this reaction, the Nb(V) complex $NbCl_5$ appears to be highly efficient. While $NbCl_3$(DME) was used as catalyst under these conditions, **3a** was obtained in moderate yield (entry 11). When early transtion-metal analogues, $TaCl_5$ and $ZrCl_4$, were used as the catalyst, even though **1a** was evidently converted during the course of the reaction, almost none of the desired pyridine derivative was observed (entries 12 and 13).

Using the optimized conditions shown in Table 1, entry 7, the reactions of various nitriles (**2**) were examined (Table 2).

Table 2. $NbCl_5/Zn/Ph_2Si(OMe)_2$ Catalyzed Reactions of Acetylenes (1) and Nitriles (2) Leading to 2,3,6-Trisubstituted Pyridines[a]



1 2 3 4

entry	1 (R^1)	2 (R^2)	yield (%) 3[b]	4[c]
				
1	tBu (**1a**)	H (**2a**)	74 (**3a**)	10 (**4a**)
2	**1a**	4-Me (**2b**)	74 (**3b**)	15 (**4a**)
3	**1a**	4-Cl (**2c**)	82 (**3c**)	15 (**4a**)
4	**1a**	4-CF_3 (**2d**)	51 (**3d**)	11 (**4a**)
5	**1a**	4-CO_2Me (**2e**)	53 (**3e**)	11 (**4a**)
6	**1a**	3-Me (**2f**)	71 (**3f**)	12 (**4a**)
7	**1a**	2-Me (**2g**)	48 (**3g**)	23 (**4a**)
				
8	**1a**	H (**2h**)	87 (**3h**)	8 (**4a**)
9	**1a**	4-Me (**2i**)	85 (**3i**)	7 (**4a**)
10	**1a**	4-Cl (**2j**)	89 (**3j**)	8 (**4a**)
11	**1a**	4-OMe (**2k**)	66 (**3k**)	trace
12	**1a**	3,4-dichloro (**2l**)	75 (**3l**)	15 (**4a**)
13	**1a**	 (**2m**)	71 (**3m**)	9 (**4a**)
14	TES[d] (**1b**)	**2a**	trace	trace
15	Ph (**1c**)	**2a**	trace	39 (**4b**)

[a]Reaction conditions: See optimized conditions (Table 1, entry 7). [b]2,3,6-Trisubstituted pyridines were all obtained with >96% regioselectivity. [c]Yields were determined by GC on the basis of the quantity of **1** used. [d]TES = triethylsilyl.

1a was reacted with various benzonitriles with substituents on the benzene ring (**2a**−**2g**) under the optimized conditions (entries 1−7). The benzonitrile derivatives 4-tolunitrile (**2b**), 4-chlorobenzonitrile (**2c**), 4-(trifluoromethyl)benzonitrile (**2d**), 4-cyanobenzoate (**2e**) and 3-tolunitrile (**2f**) participated in the reaction, and the corresponding 2,3,6-trisubstituted pyridines (**3b**−**3f**) were obtained in 51−82% yields with high chemoselectivities and excellent regioselectivities. When 2-tolunitrile (**2g**) was applied to this reaction, the desired pyridines (**3g**) were obtained in 48% yield with excellent regioselectivity, although substituted benzenes from the cyclotrimerization of **1a** were also obtained in 23% yield.

We next investigated the scope of the reaction using various benzylnitriles (entries 8−12). Phenylacetonitrile (**2h**) and its derivatives 4-methylphenylacetonitrile (**2i**), 4-chlorophenylacetonitrile (**2j**), 4-methoxyphenylacetonitrile (**2k**) and 3,4-dichlorophenylacetonitrile (**2l**) all underwent reaction, and the corresponding pyridines (**3h**−**3l**) were obtained in 66−89% yields. The reaction of 3-phenylpropanenitrile (**2m**) with **1a** afforded the corresponding 2,3,6-trisubstituted pyridine in 71% yield with 98% regioselectivity (entry 13). The reaction was

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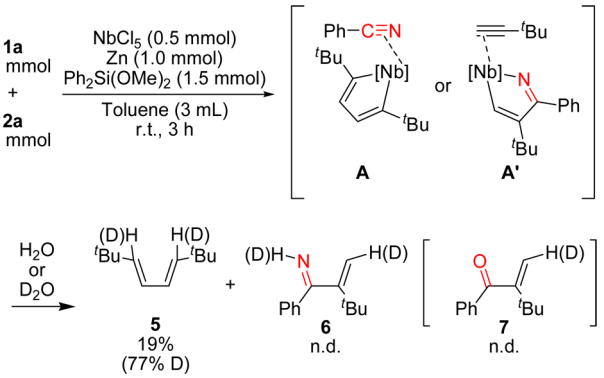
sluggish with aliphatic nitriles such as octanenitrile, trimethylsilyl cyanide, and ethyl cyanoformate and did not afford desired pyridines under these conditions. The use of *tert*-butylacetylene (**1a**) was a suitable substrate in the present reaction. However, when triethylsilylacetylene (**1b**) was used in the reaction, it underwent conversion to a moderate extent, and a negligible amount of the formation of the desired pyridine was detected (entry 14). The reaction with methyl propiolate did not give any corresponding product. The reaction of certain terminal alkynes with **2a** was observed to preferentially result in cyclotrimerization of the alkyne rather than cross-cyclotrimerization of the alkyne and nitrile. As an example, when phenylacetylene (**1c**) was used in the reaction, trace amount of the desired pyridine derivative was detected, whereas **4c** was obtained in 39% yield (entry 15). In case of the reaction of dynes or internal alkynes with **2a**, alkynes were converted, but any products were not obtained.

In general, the results detailed above are notable since they demonstrate the preparation of pyridine derivatives via reactions involving catalysis by a low-valent early transition metal.

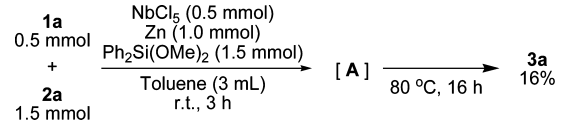
The synthesis of pyridines via the transition-metal-catalyzed cycloaddition reactions of alkynes with nitriles, as demonstrated in this work, may proceed via two possible transition metal intermediates.[20] These two intermediates are presented in Scheme 2. Depending on the path, the key intermediate in the

Scheme 2. Investigation of the Formation of Niobacyclic Intermediates



reaction is either niobacyclopentadiene (**A**) or aza-niobacyclopentadiene (**A′**). To determine which of these two intermediates is the most plausible, we performed experiments to assess the formation of either compound (Scheme 2). We first examined the stoichiometric reaction of **1a** with **2a** under optimized condition (Scheme 2). The reaction mixture was stirred at room temperature for 3 h, after which it was quenched with either H_2O or D_2O to hydrolyze or deuteriolyze whichever key intermediate had formed (**A** or **A′**). The results of GC analysis of the products showed that the diene (**5**) derived from the niobacyclopentadiene complex (**A**)[18] was obtained in 19% (77% D incorporated after deuteriolysis) yield, while the aza-diene (**6**) or hydrolysis product (**7**) derived from **A′** was not observed. After the in situ formation of this niobacyclopentadiene complex, the reaction mixture was stirred at 80 °C for 16 h (i.e., standard conditions), and the corresponding pyridine derivative (**3a**) was obtained in 16% yield (Scheme 3). Furthermore, to get more insights of reaction mechanism, we performed intermolecular competition experiments between differently substituted phenylacetoniriles (Figures S2–S4 in Supporting Information). On the basis of these competition experiments, substantial electronic effect on aryl ring relevant to the coordination of Nb center was not observed. On the basis of these results, our proposed reaction mechanism is shown in Figure 1. In this reaction pathway, the

Scheme 3. Reaction of 1a and 2a via the Formation of A



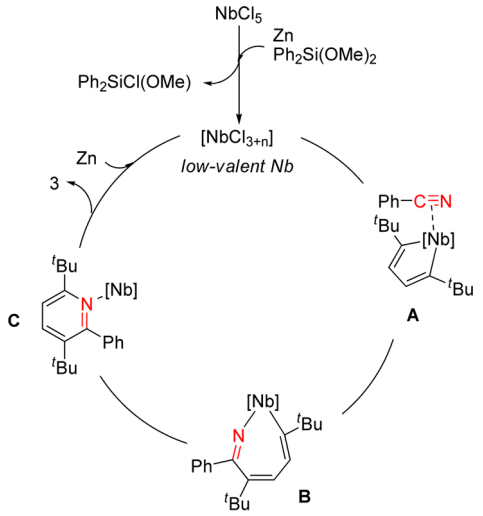


Figure 1. Proposed reaction mechanisms for the formation of pyridine derivatives.

initial step is the generation of the low-valent niobium species from $NbCl_5$, in which Zn[19] acts as a reducing agent. It should be noted that this active low-valent Nb species might also be stabilized by the alkoxysilane, and generated chloro(methoxy)-diphenylsilane.[21] Subsequently, the oxidative cycloaddition of two alkyne molecules to low-valent [Nb] takes place and forms the niobacyclopentadiene intermediate (**A**).[18] Migratory insertion of the nitrile into **A** produces the aza-niobaheptatriene intermediate (**B**), and **B** forms the corresponding pyridine derivative (**3**) via **C**. All attempts to isolate or fully characterize the 5-membered niobacyclic intermediates (**A**) and their corresponding 7-membered niobacyclic intermediates (**B**) have been unsuccessful because of the instability of these niobium species.

In conclusion, we have developed a low-valent niobium catalyzed [2 + 2 + 2] intermolecular cycloaddition reaction between terminal alkynes and nitriles to form 2,3,6-trisubstituted pyridine derivatives. This catalytic system is the first example of the synthesis of pyridines from the reaction of alkynes with nitriles using an early transition metal.

EXPERIMENTAL PROCEDURE

General Methods. GLC analysis was performed with a flame ionization detector using a 0.22 mm × 25 m capillary column (BP-5). ^1H 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 ^1H NMR, ^{13}C NMR, HMQC and HMBC. Compounds **4a**,[23] **4b**,[18] and **5**[24] are known compounds, which have previously been reported.

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Typical Reaction Procedure for the Preparation of 3a (Entry 7, Table 1). A mixture of *tert*-butylacetylene (**1a**) (82 mg, 1 mmol), benzonitrile (**2a**) (309 mg, 3 mmol), $NbCl_5$ (54 mg, 0.2 mmol), Zn (78 mg, 1.2 mmol), $Ph_2Si(OMe)_2$ (146 mg, 0.6 mmol) and toluene (2 mL) was stirred for 16 h at 80 °C under Ar. The yields of the products were estimated from the peak areas on the basis of the internal standard technique using GC, and **3a** was obtained in 82% yield. The products **3a** were isolated by silica gel column chromatography (*n*-hexane:EtOAc = 100:0 to 50:1 as eluent) in 74% yield 99 mg) as yellow liquid.

Typical Reaction Procedure for the Preparation of 5 (Scheme 2). A mixture of *tert*-butylacetylene (**1a**) (49 mg, 0.5 mmol), benzonitrile (**2a**) (154 mg, 1.5 mmol), $NbCl_5$ (135 mg, 0.5 mmol), Zn (65 mg, 1.0 mmol), $Ph_2Si(OMe)_2$ (365 mg, 1.5 mmol) and toluene (3 mL) was stirred for 3 h at room tempreture under Ar. Thereafter, the formation of Nb-cyclopentadiene complex (**A**) was verified by hydrolysis or deuteriolysis of the reaction mixture affording **5**. The yields of the products were estimated from the peak areas on the basis of the internal standard technique using GC, and **5** was obtained in 19% yield.

Typical Reaction Procedure for the Preparation of 3a (Scheme 3). A mixture of *tert*-butylacetylene (**1a**) (49 mg, 0.5 mmol), benzonitrile (**2a**) (154 mg, 1.5 mmol), $NbCl_5$ (135 mg, 0.5 mmol), Zn (65 mg, 1.0 mmol), $Ph_2Si(OMe)_2$ (365 mg, 1.5 mmol) and toluene (3 mL) was stirred for 3 h at room tempreture under Ar. Subsequently, the reaction mixture was stirred at 80 °C for 16 h. The yields of the products were estimated from the peak areas on the basis of the internal standard technique using GC, and **3a** was obtained in 16% yield.

Typical Reaction Procedure for Figure S2 (Supporting Information). A mixture of *tert*-butylacetylene (**1a**) (82 mg, 1 mmol), phenylacetonitrile (**2h**) (177 mg, 1.5 mmol), 4-methylphenylacetonitrile (**2i**) (197 mg, 1.5 mmol) $NbCl_5$ (54 mg, 0.2 mmol), Zn (78 mg, 1.2 mmol), $Ph_2Si(OMe)_2$ (146 mg, 0.6 mmol) and toluene (2 mL) was stirred for 16 h at 80 °C under Ar. The yields of the products were estimated from the peak areas on the basis of the internal standard technique using GC, and **3h**, **3i**, and **4a** were obtained respectively in 26, 29, and 10% yields.

Typical Reaction Procedure for Figure S3 (Supporting Information). A mixture of *tert*-butylacetylene (**1a**) (82 mg, 1 mmol), 4-methylphenylacetonitrile (**2i**) (197 mg, 1.5 mmol), 4-chlorophenylacetonitrile (**2j**) (227 mg, 1.5 mmol) $NbCl_5$ (54 mg, 0.2 mmol), Zn (78 mg, 1.2 mmol), $Ph_2Si(OMe)_2$ (146 mg, 0.6 mmol) and toluene (2 mL) was stirred for 16 h at 80 °C under Ar. The yields of the products were estimated from the peak areas on the basis of the internal standard technique using GC, and **3h**, **3j**, and **4a** were obtained respectively in 19, 17, and 11% yields.

Typical Reaction Procedure for Figure S4 (Supporting Information). A mixture of *tert*-butylacetylene (**1a**) (82 mg, 1 mmol), phenylacetonitrile (**2i**) (177 mg, 1.5 mmol), 4-chlorophenylacetonitrile (**2j**) (227 mg, 1.5 mmol) $NbCl_5$ (54 mg, 0.2 mmol), Zn (78 mg, 1.2 mmol), $Ph_2Si(OMe)_2$ (146 mg, 0.6 mmol) and toluene (2 mL) was stirred for 16 h at 80 °C under Ar. The yields of the products were estimated from the peak areas on the basis of the internal standard technique using GC, and **3i**, **3j**, and **4a** were obtained respectively in 11, 14, and 15% yields.

3a: yield 74% (99 mg), yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (s, 9H), 1.43 (s, 9H), 7.27−8.09 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ30.4 (CH_3), 30.8 (CH_3), 35.0 (C), 37.8 (C), 114.2 (CH), 114.24 (CH), 127.0 (2CH), 128.4 (2CH), 128.5 (CH), 140.6 (C), 155.4 (C), 160.4 (C), 168.8 (C); IR (neat, cm^{-1}) 2962, 2868, 1597, 1301; GC−MS (EI) *m*/*z* (relative intensity) 267 (62) [M$^+$], 252 (100), 211 (19), 154 (2), 79 (1), 77 (4), 57(57); HRMS (EI-TOF) *m*/*z* calcd for $C_{19}H_{25}N$ [M]$^+$ 267.1987, found 267.1975.

3b: yield 74% (104 mg), yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (s, 9H), 1.34 (s, 9H), 2.29 (s, 3H), 7.10−7.89 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2 (CH_3), 30.4 (CH_3), 30.8 (CH_3), 34.9 (C), 37.8 (C), 113.9 (CH), 114.0 (CH), 126.9 (2CH), 129.2 (2CH), 137.8 (C), 138.2 (C), 155.5 (C), 160.3 (C), 168.7 (C); IR (neat, cm^{-1}) 2962, 2868, 1597, 1477, 1394; GC−MS (EI) *m*/*z* (relative intensity) 281 (61) [M$^+$], 266 (100), 225 (20), 191 (1), 167 (2), 91 (4), 77 (2), 57(2); HRMS (EI-TOF) *m*/*z* calcd for $C_{20}H_{27}N$ [M]$^+$ 281.2144, found 281.2137.

3c: yield 82% (123 mg), yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (s, 9H), 1.01 (s, 9H), 6.84−7.62 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.4 (CH_3), 30.8 (CH_3), 35.0 (C), 37.8(C), 114.0 (CH), 114.5 (CH), 128.2 (2CH), 128.6 (2CH), 134.4 (C), 139.0 (C), 154.2 (C), 160.7 (C), 169.0 (C); IR (neat, cm^{-1}) 2976, 2872, 1598, 1496; GC−MS (EI) *m*/*z* (relative intensity) 301 (54) [M$^+$], 286 (100), 245 (18), 111 (1), 77 (3), 57(4); HRMS (EI-TOF) *m*/*z* calcd for $C_{19}H_{24}ClN$ [M]$^+$ 301.1597, found 301.1593.

3d: yield 51% (85 mg), yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28 (s, 9H), 1.34 (s, 9H), 7.25−8.11 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.3 (CH_3), 30.8 (CH_3), 35.0 (C), 37.8 (C), 114.6 (CH), 116.1 (CH), 124.0 (C), 125.42 (2CH), 127.2 (2CH), 130.2 (C), 143.9 (C), 154.0 (C), 160.9 (C), 169.2 (C); ^{19}F NMR (400 MHz, $CDCl_3$) δ = −62.4 (s, CF_3); IR (neat, cm^{-1})2968, 2872, 1620, 1411; GC−MS (EI) *m*/*z* (relative intensity) 335 (48) [M$^+$], 334 (47), 320 (100), 305 (12), 279 (14), 222 (1), 77 (1), 57 (3); HRMS (EI-TOF) *m*/*z* calcd for $C_{20}H_{24}F_3N$ [M]$^+$ 335.1861, found 335.1868.

3e: yield 53% (86 mg), yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (s, 9H), 1.32 (s, 9H), 3.8 (s, 3H), 7.21 (s, 1H), 7.49 (s, 1H), 8.07 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.3 (CH_3), 30.8 (CH_3), 34.9 (C), 37.7 (C), 114.7 (CH), 114.9 (CH), 126.7 (2CH), 129.7 (C), 129.8 (2CH), 144.6(C), 154.1 (C), 160.6 (C), 166.9 (C), 169.0 (C); IR (neat, cm^{-1}) 2978, 2870, 1730, 1394, 1112; GC−MS (EI) *m*/*z* (relative intensity) 325 (52) [M$^+$], 310 (100), 269 (18), 2 67(3), 190 (5), 79(1), 77 (2), 57 (3); HRMS (EI-TOF) *m*/*z* calcd for $C_{21}H_{27}NO_2$ [M]$^+$ 325.2042, found 325.2029.

3f: yield 71% (100 mg), yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (s, 9H), 1.34 (s, 9H), 2.33 (s, 3H), 7.07−7.77 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6 (CH_3), 30.4 (CH_3), 30.8 (CH_3), 34.9 (C), 37.8 (C), 114.0 (CH), 114.4 (CH), 124.2 (CH), 127.7 (CH), 128.4 (CH), 129.1 (CH), 138.0 (C), 140.6 (C), 155.7 (C), 160.3 (C), 168.7 (C); IR (neat, cm^{-1}) 2963, 2868, 1597, 1249; GC−MS (EI) *m*/*z* (relative intensity) 281 (64) [M$^+$], 266 (100), 225 (17), 210 (6), 169 (1), 91 (4), 77 (1), 57(1); HRMS (EI-TOF) *m*/*z* calcd for $C_{20}H_{27}N$ [M]$^+$ 281.2144, found 281.2137.

3g: yield 48% (67 mg), yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26 (s, 9H), 1.32 (s, 9H), 2.35 (s, 3H), 7.12−7.37 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8 (CH_3), 30.4 (CH_3), 30.8 (CH_3), 34.9 (C), 37.8 (C), 113.3 (CH), 118.1 (CH), 125.7 (CH), 127.8 (CH), 129.8 (CH), 130.9 (CH), 136.4 (C), 141.5 (C), 158.4 (C), 159.9 (C), 168.2 (C); IR (neat, cm^{-1}) 2964, 2904, 1701, 1595, 1404; GC−MS (EI) *m*/*z* (relative intensity) 281 (92) [M$^+$], 266 (99), 225 (18), 210 (5), 169 (2), 91 (6), 77 (2), 57(3); HRMS (EI-TOF) *m*/*z* calcd for $C_{20}H_{27}N$ [M]$^+$ 281.2143, found 281.2137.

3h: yield 87% (122 mg), yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.24 (s, 9H), 1.36 (s, 9H), 4.10 (s, 2H), 6.88−7.33 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.3 (CH_3), 30.7 (CH_3), 34.7 (C), 37.5 (C), 45.0 (CH_2), 113.0 (CH), 116.7 (CH), 125.9 (2CH), 128.2 (2CH), 129.1 (CH), 140.5(C), 159.0 (C), 160.1 (C), 168.5 (C); IR (neat, cm^{-1}) 2965, 2868, 1685, 1598, 1558; GC−MS (EI) *m*/*z* (relative intensity) 281 (80) [M$^+$], 266 (100), 225 (19), 168 (2), 91 (11), 79 (2), 77 (3), 57(2); HRMS (EI-TOF) *m*/*z* calcd for $C_{20}H_{27}N$ [M]$^+$ 281.2144, found 281.2144.

3i: yield 85% (125 mg), yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (s, 9H), 1.27 (s, 9H), 3.96 (s, 2H), 6.79−7.17 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.3 (CH_3), 30.7 (CH_3), 34.7 (C), 37.5 (C), 44.3 (CH_2), 113.1 (CH), 116.6 (CH), 128.3 (2CH), 130.4 (2CH), 131.7 (C), 138.9 (C), 158.5 (C), 160.3 (C), 168.6 (C); IR (neat, cm^{-1}) 2958, 2868, 1706, 1598, 1514; GC−MS (EI) *m*/*z* (relative intensity) 295 (100) [M$^+$], 280 (46), 266 (3), 166 (2), 77 (2), 57(5); HRMS (EI-TOF) *m*/*z* calcd for $C_{21}H_{29}N$ [M]$^+$ 295.2300, found 295.2297.

3j: yield 89% (140 mg), yellow liquid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (s, 9H), 1.28 (s, 9H), 2.23 (s, 3H), 3.98 (s, 2H), 6.80−7.16 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.0 (CH_3), 30.3 (CH_3), 30.7 (CH_3), 34.7 (C), 37.5 (C), 44.6 (CH_2), 112.9 (CH), 116.6 (CH), 128.93 (2CH), 128.94 (2CH), 135.3 (C), 137.4.5(C), 159.3 (C),

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160.0 (C), 168.4 (C); IR (neat, cm^{-1}) 2972, 2906, 1706, 1598, 1404, 1361; GC−MS (EI) *m*/*z* (relative intensity) 315 (58) [M^+], 300 (100), 243 (2), 125 (5), 91 (4), 79 (1), 77 (2), 57(4); HRMS (EI-TOF) *m*/*z* calcd for $C_{20}H_{26}ClN$ [$M]^+$ 315.1754, found 315.1751.

3k: yield 66% (103 mg), yellow liquid; ^1H NMR (400 MHz, $CDCl_3$) δ 1.20 (s, 9H), 1.30 (s, 9H), 3.65 (s, 3H), 3.99 (s,2H), 6.72−7.18 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.3 (CH_3), 30.6 (CH_3), 34.7 (C), 37.4 (C), 43.8 (CH_2), 55.1 (CH_3), 113.6 (CH), 116.7 (CH), 127.8 (2CH), 130.0 (2CH), 132.3 (C), 134.5 (C), 157.9 (C), 159.4, 168.1 (C); IR (neat, cm^{-1}) 2970, 2904, 1598, 1361, 1176; GC−MS (EI) *m*/*z* (relative intensity) 311 (100), 297 (56), 281 (1), 253 (19), 194 (1), 148 (1), 92 (2), 77 (2); HRMS (EI-TOF) *m*/*z* calcd for $C_{21}H_{29}NO$, [$M]^+$ 311.2249, found 311.2256.

3l: yield 75% (131 mg), yellow liquid; ^1H NMR (400 MHz, $CDCl_3$) δ 1.18 (s, 9H), 1.27 (s, 9H), 3.94 (s, 2H), 6.81−7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.3 (CH_3), 30.3 (CH_3), 30.7 (CH_3), 34.8 (C), 37.5 (C), 43.9 (CH_2), 113.4 (CH), 116.7 (CH), 127.8 (CH), 128.6 (CH), 130.0 (CH), 131.1 (C), 131.9 (C), 140.6 (C), 157.6 (C), 160.5 (C), 168.8 (C); IR (neat, cm^{-1}) 2966, 2868, 1598, 1548, 1471, 1215; GC−MS (EI) *m*/*z* (relative intensity) 349 (49) [M^+], 334 (100), 2314 (1), 307 (84), 292 (14), 204 (1), 158 (7), 144 (2), 77 (2), 91 (4), 57(1); HRMS (EI-TOF) *m*/*z* calcd for $C_{20}H_{25}{}^{35}Cl^{37}ClN$ [$M]^+$ 351.1335, found 351.1136; HRMS (EI-TOF) *m*/*z* calcd for $C_{20}H_{25}Cl_2N$ [$M]^+$ 349.1364, found 349.1342.

3m: yield 71% (105 mg), yellow liquid; ^1H NMR (400 MHz, $CDCl_3$) δ 1.17 (s, 9H), 1.31 (s, 9H), 3.00 (s, 4H), 6.73−7.19 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 30.3 (CH_3), 30.7 (CH_3), 34.7 (C), 35.8 (CH_2), 37.8 (C), 40.0 (CH_2), 112.9 (CH), 116.9 (CH), 125.6 (2CH), 128.1 (2CH), 128.5 (CH), 134.5 (C), 142.1 (C), 149.2 (C), 168.1 (C); IR (neat, cm^{-1}) 2962, 2904, 1598, 1409, 1361; GC−MS (EI) *m*/*z* (relative intensity) 295 (100) [M^+], 238 (5), 218 (37), 191 (13), 105 (2), 77 (2), 57(3); HRMS (EI-TOF) *m*/*z* calcd for $C_{21}H_{29}N$ [$M]^+$ 295.2300, found 295.2306.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Figures S1−S4, Tables S1−S3, experimental, characterization and original NMR spectra for products **3**. 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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