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Lewis Acid-Catalyzed Cyclization of Enaminones with Propargylic Alcohols: Regioselective Synthesis of Multisubstituted 1,2-Dihydropyridines

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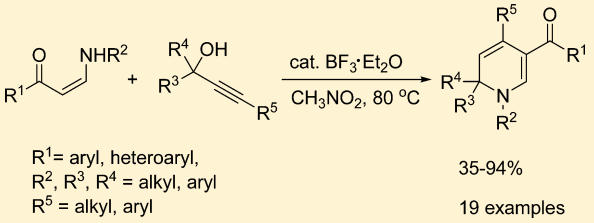
Supporting Information

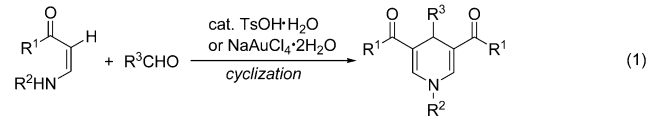
ABSTRACT: A highly efficient $BF_3{\cdot}Et_2O$-catalyzed cascade reaction of enaminones with propargylic alcohols under mild reaction conditions has been developed. This methodology offers regioselective access to multisubstituted 1,2-dihydropyridines in good to excellent yields.



Dihydropyridines are of great value as core structures in biologically active molecules.[1,2] They are also versatile building blocks that provide ready access to a variety of nitrogen-containing heterocycles such as piperidines[3] or pyridines.[4] 1,4-Dihydropyridines have been the most studied,[5] whereas 1,2-dihydropyridines have received relatively little attention. There are several synthetic approaches to 1,2-dihydropyridines reported in the literature, such as nucleophilic addition onto *N*-alkyl or *N*-acylpyridinium salts,[3,6] 6π-electrocyclization of 1-azatrienes,[7] and others.[8] Although these methods are effective for certain substrates, the development of general procedures for the regioselective synthesis of highly functionalized dihydropyridines from readily available starting materials still remains an important task in organic chemistry. As a part of our ongoing studies on the development of heterocycle forming protocols starting from enaminone derivatives,[9] we recently reported a facile acid-catalyzed approach to the synthesis of 1,4-dihydropyridines from the reactions of readily available aldehydes with enaminones (Scheme 1, eq 1).[10] Next, we became interested in the development of new methodologies for the construction of 1,2-dihydropyridines from enaminones. We envisioned that this might be realized by the proper choice of electrophiles and acid catalysts. It was found that when propargylic alcohols were used as electrophiles, an efficient synthesis of 1,2-dihydropyridines could be achieved by a Lewis acid-catalyzed cyclization reaction. Herein, we describe this new synthetic route for the synthesis of functionalized 1,2-dihydropyridines. In addition, these reactions could proceed smoothly without the requirement of inert atmospheres (Scheme 1, eq 2).

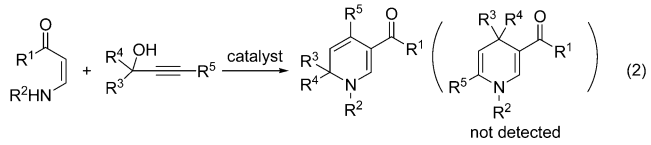
Scheme 1

Previous work



(1)

This work



(2)

We began our investigation with (*Z*)-1-phenyl-3-(phenylamino)prop-2-en-1-one (**1a**), which was readily prepared through conjugate addition of aniline with terminal alkynone.[10] The reaction of **1a** with propargyl alcohol **2a** was selected as the prototypical case to screen the experimental conditions. First, the reaction of **1a** with 2,4-diphenylbut-3-yn-2-ol (**2a**) was carried out using CuI (10 mol %) as the catalyst in nitromethane at 80 °C; however, only trace amounts of the desired dihydropyridine were detected (Table 1, entry 1). Similar results were observed for CuCl (Table 1, entry 2). To our delight, when $Cu(OTf)_2$ was used, the desired dihydropyridine **3a** was produced in 47% yield after 4 h (Table 1, entry 3). Brønsted acids gave good yields of the desired dihydropyridine (Table 1, entries 4−6). It is interesting that $BF_3{\cdot}Et_2O$ in nitromethane afforded **3a** in 88% yield within 1 h (Table 1, entry 9). Other solvents such as 1,4-dioxane, toluene and DCE also produced the desired dihydropyridine in good yields (Table 1, entries 12, 20, 21). However, DMF or DMSO gave only a trace amount of the product (Table 1, entries 10−11). CH_3CN gave a similar result to that of nitromethane (Table 1, entry 22). When the reaction was carried out at 50 °C in nitromethane, the desired product was obtained in 69% yield and required much longer reaction time (Table 1, entry 13).

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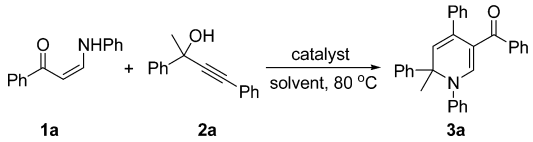
Table 1. Optimization of Reaction Conditions for the Formation of 3a



1a 2a 3a

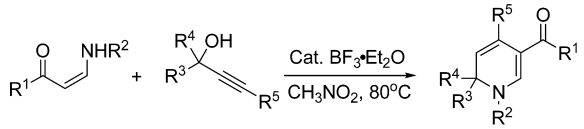
entry	catalyst (mol %)	solvent	time (h)	yield (%)[a,b]
1	CuI (10)	CH_3NO_2	7	trace
2	CuCl (10)	CH_3NO_2	7	trace
3	$Cu(OTf)_2$ (10)	CH_3NO_2	4	47
4	$TsOH·H_2O$ (10)	CH_3NO_2	3	75
5	CF_3COOH (10)	CH_3NO_2	2	74
6	CF_3SO_3H (10)	CH_3NO_2	2	80
7	$FeCl_3·6H_2O$ (10)	CH_3NO_2	3	67
8	$FeCl_3$ (10)	CH_3NO_2	3	77
9	$BF_3·Et_2O$ (10)	CH_3NO_2	1	88
10	$BF_3·Et_2O$ (10)	DMF	12	trace
11	$BF_3·Et_2O$ (10)	DMSO	12	trace
12	$BF_3·Et_2O$ (10)	1,4-dioxane	2	82
13	$BF_3·Et_2O$ (10)	CH_3NO_2	8	69[c]
14	$BF_3·Et_2O$ (10)	CH_3NO_2	18	23[d]
15	$BF_3·Et_2O$ (10)	CH_3NO_2	1	88[e]
16	$BF_3·Et_2O$ (10)	CH_3NO_2	1	83[f]
17	$BF_3·Et_2O$ (5)	CH_3NO_2	1	89
18	$BF_3·Et_2O$ (3)	CH_3NO_2	4	89[g]
19	–	CH_3NO_2	4	–
20	$BF_3·Et_2O$ (5)	toluene	2	81
21	$BF_3·Et_2O$ (5)	DCE	2	80
22	$BF_3·Et_2O$ (5)	CH_3CN	1	89
23	$BF_3·Et_2O$ (5)	THF	3	52
24	$FeCl_2$ (5)	CH_3NO_2	4	75
25	$FeBr_3$ (5)	CH_3NO_2	3	80
26	$AlCl_3$ (5)	CH_3NO_2	5	23

[a]Unless otherwise noted, all reactions were carried out under air in 0.25 mmol scale with the ratio of **1a**:**2a** = 1:1.2. [b]Isolated yield. [c]The reaction was carried out at 50 °C. [d]The reaction was carried out at room temperature. [e]The ratio of **1a**:**2a** = 1:1.3. [f]The ratio of **1a**:**2a** = 1.2:1. [g]0.5 mmol scale.

Reactions conducted at room temperature resulted in much lower yield (Table 1, entry 14). Lowering the catalyst loading to 5 mol % gave 89% yield in 1 h (Table 1, entry 17). Even 3 mol % of $BF_3·Et_2O$ resulted in a high yield of the desired dihydropyridine; however, prolonged reaction time was required (Table 1, entry 18). Other Lewis acids such as $FeCl_3$, $FeCl_2$, $FeBr_3$ also gave good yields of **3a** (Table 1, entries 8, 24, 25). A control experiment showed that no desired product was formed in the absence of $BF_3·Et_2O$ (Table 1, entry 19). The optimized reaction conditions were to use 5 mol % of $BF_3·Et_2O$ as the catalyst and nitromethane as the solvent at 80 °C. One of the advantages of this method to prepare dihydropyridines is that the substituents on the pyridine ring were introduced in a regioselective manner.

With the optimized reaction conditions in hand, we next examined the substrate scope of this catalytic method for the synthesis of 1,2-dihydropyridines using a variety of (*Z*)-enaminones and propargyl alcohols with the results shown in Table 2. We first investigated the electronic effects of the aromatic substituents on carbonyl carbon of enaminones. It was found that an electron-donating (-OMe) aryl group afforded the corresponding product **3b** in 85% yield (Table 2, entry 2).

Table 2. Synthesis of Various of 1,2-Dihydropyridines



1 2 3

entry	**1** (R^1, R^2)	**2** (R^3/R^4/R^5)	time (h)	product	yield (%)[a]
1	**1a** (Ph, Ph)	**2a** (Ph/Me/Ph)	1	**3a**	89
2	**1b** (*p*-$MeOC_6H_4$, Ph)	**2a**	2	**3b**	85
3	**1c** (*p*-ClC_6H_4, Ph)	**2a**	1	**3c**	94
4	**1d** (*o*-BrC_6H_4, Ph)	**2a**	1	**3d**	77
5	**1e** (2-thienyl, Ph)	**2a**	1	**3e**	98
6	**1f** (cyclohexyl, Ph)	**2a**	1	**3f**	85
7	**1g** (Ph, *p*-$MeOC_6H_4$)	**2a**	1	**3g**	90
8	**1h** (Ph, *p*-$NO_2C_6H_4$)	**2a**	1	**3h**	67
9	**1i** (Ph, *m*-ClC_6H_4)	**2a**	1	**3i**	88
10	**1j** (Ph, *o*-CNC_6H_4)	**2a**	1	**3j**	73
11	**1k** (Ph, benzyl)	**2a**	5	**3k**	35
12	**1a**	**2b** (Ph/Ph/Ph)	4	**3l**	82
13	**1a**	**2c** (*p*-ClC_6H_4/Me/Ph)	2	**3m**	89
14	**1a**	**2d** (Ph/cyclopropyl/Ph)	2	**3n**	67
15	**1a**	**2e** (Ph/Me/*p*-FC_6H_4)	1	**3o**	92
16	**1a**	**2f** (Ph/Me/*p*-MeC_6H_4)	2	**3p**	72
17	**1a**	**2g** (Ph/Ph/H)	4		–

[a]Isolated yields.

Electron-withdrawing (-Cl, -Br) aryl groups also gave high yields of **3c** and **3d**, respectively (Table 2, entries 3, 4). A heteroaryl enaminone such as 2-thienylenaminone was also compatible under the reaction conditions, furnishing **3e** in 98% yield (Table 2, entry 5). The substituents on the carbonyl carbon could also be alkyl groups, such as cyclohexyl (**1f**), with the corresponding **3f** obtained in 85% yield (Table 2, entry 6). The electronic effects of the aromatic substituents on nitrogen of enaminones were then examined. An electron-donating (-OMe) aryl group gave much higher yield than that of an electron-withdrawing ($-NO_2$) one (Table 2, entries 7, 8). The reaction also proceeded smoothly with other electron-withdrawing aryl groups, such as *m*-Cl (**1i**), *o*-CN (**1j**), furnishing the desired dihydropyridines **3i**, **3j** in 88 and 73% yields, respectively (Table 2, entries 9, 10). Enaminone **1k** with an alkyl substituent on nitrogen led to the formation of **3k** in moderate yield (Table 2, entry 11). The cyclization reaction has been successfully extended to other propargyl alcohols. Triphenyl substituted alcohol **2b** reacted smoothly with **1a** to give **3l** in 82% yield (Table 2, entry 12). The structure of **3l** was further confirmed by X-ray crystallographic analysis. Compound **2c** with a *p*-Cl aryl group on the propargylic carbon gave the dihydropyridine **3m** in 89% yield (Table 2, entry 13). Incorporation of a cyclopropyl group on the propargylic alcohol in the reaction provided **3n** in a good yield, with the cyclopropyl group well tolerated during the reaction (Table

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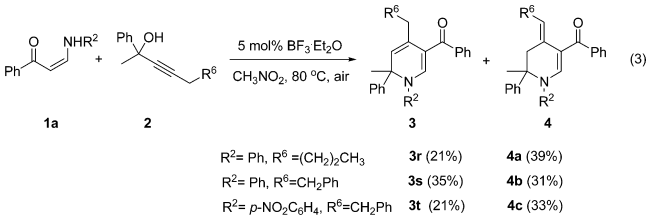
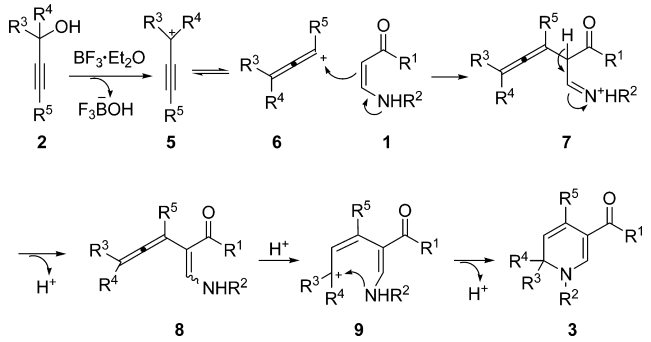
2, entry 14). Both aryl and alkyl groups are tolerated at the alkynyl position. The *p*-F aryl group resulted in 92% of **3o**, while *p*-Me group gave 72% of the corresponding **3p** (Table 2, entries 15, 16). Unfortunately, the terminal propargylic alcohol **2g** provided no product (Table 2, entry 17). It is worthy to note that substrates with alkyl groups on the triple bond resulted in not only the desired 1,2-dihydropyridines **3**, but also its isomers **4** derived from a 1,3-hydrogen shift. In the case of **4c**, the structure was confirmed by X-ray crystallography (eq 3).



(3)

On the basis of the above results and the reported work concerning the reaction of propyargyl alochols,[11] a possible reaction mechanism is proposed in Scheme 2. Initially,

Scheme 2. Proposed Reaction Pathway



propargyl cation **5** or allenyl cation **6**[12,13] is generated in the presence of $BF_3{\cdot}Et_2O$, which is trapped by enaminone **1** to give intermediate **7**. Deprotonation of **7** forms **8**, which then undergoes protonation followed by double bond *E*/*Z* isomerization to produce allylic cation **9**. Intramolecular cyclization leads to product **3**. Alternatively, a formal 1,3-hydrogen migration to allenic moiety might occur after deprotonation at imine nitrogen of **7** to afford a conjugated azatriene, and the final dihydropyridine **3** is formed through a 6π-electrocyclization. To understand the reaction mechanism, the reaction was carried out at lower temperature in order to "observe" intermediate **8**. However, no information about such intermediate could be obtained at the current stage. It seems that the transformation of **8** to the final dihydropyridine is not the rate determining step.

In conclusion, we have shown that multisubstituted 1,2-dihydropyridines are efficiently prepared by the $BF_3{\cdot}Et_2O$-catalyzed cascade reactions using enaminones and propargyl alcohols. Aryl and alkyl substituents on both enaminones and propargyl alcohols are compatible in the cascade reactions, furnishing the desired 1,2-dihydropyridines in good to excellent yields. In this procedure, the regioselective introduction of substituents on the pyridine is determined by the appropriate choice of the enaminone and propargyl alcohol, thereby allowing for considerable versatility.

EXPERIMENTAL SECTION

High-resolution mass spectra were performed on a mass spectrometer with a TOF (for EI or ESI) or FT-ICR (for MALDI) analyzer.

Typical Procedure for the $BF_3{\cdot}Et_2O$-Catalyzed Synthesis of (6-Methyl-1,4,6-triphenyl-1,6-dihydropyridin-3-yl)(phenyl)-methanone (3a). To a solution of (*Z*)-enaminones **1a** (0.25 mmol, 56 mg) and propargyl alcohol **2a** (0.3 mmol, 67 mg) in CH_3NO_2 (2 mL) was added $BF_3{\cdot}Et_2O$ (1.6 uL, 5 mol %). The resulting solution was stirred at 80 °C under air until the reaction was complete as monitored by thin-layer chromatography. The solvent was evaporated under reduced pressure, and the residue was purified by chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 10:1) to afford the 1,2-dihydropyridine derivatives **3a** in 89% (95 mg) isolated yield as a yellow solid: mp 139−140 °C; ^{1}H NMR (400 MHz, $CDCl_3$, Me_4Si) δ 7.60 (d, *J* = 6.4 Hz, 2H), 7.47 (d, *J* = 7.2 Hz, 2H), 7.31−7.27 (m, 4H), 7.25−7.20 (m, 3H), 7.13−7.08 (m, 8H), 6.80−6.78 (m, 2H), 5.11 (s, 1H), 1.74 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, Me_4Si) δ 191.5, 149.8, 146.1, 143.5, 140.2, 140.1, 133.7, 130.8, 129.1, 128.9, 128.6, 128.0, 127.8, 127.7, 127.2, 127.0, 126.7, 126.4, 124.4, 110.6, 64.5, 26.6; HRMS (EI) calcd for $C_{31}H_{26}NO$ $(M + H)^+$ 428.2014, found 428.2020.

(4-Methoxyphenyl)(6-methyl-1,4,6-triphenyl-1,6-dihydropyridin-3-yl)methanone (3b). (The reaction time was 2 h). Column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 5:1) afforded the title product in 85% (97 mg) isolated yield as a yellow solid: mp 127−128 °C; ^{1}H NMR (400 MHz, $CDCl_3$, Me_4Si) δ 7.60 (d, *J* = 8.4 Hz, 2H), 7.48 (d, *J* = 7.4, 2H), 7.31−7.26 (m, 4H), 7.15−7.08 (m, 8H), 6.81 (d, *J* = 7.0 Hz, 2H), 6.73 (d, *J* = 8.4, 2H), 5.10 (s, 1H), 3.69 (s, 3H), 1.75 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, Me_4Si) δ 190.8, 161.9, 148.7, 146.3, 143.6, 140.1, 133.9, 132.6, 131.2, 128.8, 128.6, 127.7, 127.2, 126.8, 126.7, 126.4, 124.2, 113.2, 110.8, 64.4, 55.2, 26.6; HRMS (EI) calcd for $C_{32}H_{28}NO_2$ $(M + H)^+$ 458.2120, found 458.2125.

(4-Chlorophenyl)(6-methyl-1,4,6-triphenyl-1,6-dihydropyridin-3-yl)methanone (3c). Column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 10:1) afforded the title product in 94% (108 mg) isolated yield as a yellow solid: mp 143−144 °C; ^{1}H NMR (400 MHz, $CDCl_3$, Me_4Si) δ 7.51−7.46 (m, 4H), 7.32−7.28 (m, 3H), 7.25−7.22 (m, 1H), 7.18−7.16 (m, 2H), 7.14−7.06 (m, 8H), 6.81 (s, 2H), 5.11 (s, 1H), 1.74 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, Me_4Si) δ 190.2, 149.7, 146.0, 143.4, 140.0, 138.6, 136.8, 133.6, 130.4, 128.96, 128.6, 128.2, 127.9, 127.8, 127.2, 126.9, 126.4, 124.3, 110.4, 64.7, 26.7; HRMS (ESI) calcd for $C_{31}H_{25}ClNO$ $(M + H)^+$ 462.1625, found 462.1619.

(2-Bromophenyl)(6-methyl-1,4,6-triphenyl-1,6-dihydropyridin-3-yl)methanone (3d). Column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 8:1) afforded the title product in 77% (97 mg) isolated yield as a yellow solid: mp 162−163 °C; ^{1}H NMR (300 MHz, $CDCl_3$, Me_4Si) δ 7.54−7.52 (m, 2H), 7.47−7.44 (m, 1H), 7.38−7.33 (m, 5H), 7.30−7.15 (m, 9H), 7.12−7.07 (m, 1H), 6.88−6.85 (m, 2H), 5.18 (s, 1H), 1.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, Me_4Si) δ 189.0, 152.3, 145.5, 143.0, 141.9, 139.9, 132.9, 132.7, 130.0, 129.7, 128.8, 128.5, 127.8, 127.5, 127.4, 127.3, 127.1, 126.6, 126.3, 125.1, 120.0, 110.1, 64.8, 26.8; HRMS (ESI) calcd for $C_{31}H_{24}BrNO$ 505.1041, found 505.1031.

(6-Methyl-1,4,6-triphenyl-1,6-dihydropyridin-3-yl)-(thiophen-2-yl)methanone (3e). Column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 15:1) afforded the title product in 98% (106 mg) isolated yield as a yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$, Me_4Si) δ 7.50−7.47 (m, 3H), 7.38 (d, *J* = 2.8 Hz, 1H), 7.34−7.27 (m, 3H), 7.24−7.20 (m, 1H), 7.14−7.11 (m, 8H), 6.89−6.87 (m, 1H), 6.84−6.82 (m, 2H), 5.10 (s, 1H), 1.74 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, Me_4Si) δ 182.9, 148.4, 146.2, 145.3, 143.5, 139.2, 133.4, 131.0, 130.9, 128.9, 128.6, 127.7, 127.1, 127.0, 126.8, 126.4, 124.4, 110.8, 64.5, 26.6; HRMS (ESI) calcd for $C_{29}H_{23}NOS$ 433.1500, found 433.1504.

Cyclohexyl(6-methyl-1,4,6-triphenyl-1,6-dihydropyridin-3-yl)methanone (3f). Column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 25:1) afforded the title product in 85% (92 mg) isolated yield as a yellow liquid: ^{1}H NMR (400 MHz,

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$CDCl_3$, Me_4Si) δ 7.51 (s, 1H), 7.43−7.41 (m, 2H), 7.30−7.11 (m, 11H), 6.89−6.87 (m, 2H), 4.99 (s, 1H), 2.35 (t, J = 11.2 Hz, 1H), 1.71 (s, 3H), 1.66−1.47 (m, 5H), 1.35−1.26 (m, 2H), 1.07−0.93(m, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, Me_4Si) δ 199.9, 146.1, 146.1, 143.7, 141.3, 134.0, 128.9, 128.5, 127.8, 127.6, 127.1, 126.8, 126.8, 126.3, 124.2, 111.1, 64.1, 45.8, 29.9, 29.2, 26.5, 26.0, 25.8, 25.7; HRMS (ESI) calcd for $C_{31}H_{32}NO$ $(M + H)^+$ 434.2484, found 434.2494.

(1-(4-Methoxyphenyl)-6-methyl-4,6-diphenyl-1,6-dihydropyridin-3-yl)(phenyl)methanone (3g). Column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 5:1) afforded the title product in 90% (103 mg) isolated yield as a yellow solid: mp 132−133 °C; ^{1}H NMR (400 MHz, $CDCl_3$, Me_4Si) δ 7.58 (d, J = 7.2 Hz, 2H), 7.46 (d, J = 7.6 Hz, 2H), 7.31−7.08 (m, 12H), 6.69−6.59 (m, 4H), 5.09 (s, 1H), 3.64 (s, 3H), 1.70 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, Me_4Si) δ 191.3, 158.6, 150.6, 146.0, 140.3, 140.3, 136.2, 133.9, 130.6, 129.1, 128.6, 128.6, 128.0, 127.8, 127.7, 127.2, 126.7, 126.7, 124.0, 113.9, 109.6, 64.6, 55.3, 26.6; HRMS (MALDI/DHB) calcd for $C_{32}H_{28}NO_2$ $(M + H)^+$ 458.2120, found 458.2115.

(6-Methyl-1-(4-nitrophenyl)-4,6-diphenyl-1,6-dihydropyridin-3-yl)(phenyl)methanone (3h). Column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 8:1) afforded the title product in 67% (79 mg) isolated yield as a yellow solid: mp 225−226 °C; ^{1}H NMR (400 MHz, $CDCl_3$, Me_4Si) δ 7.97−7.95 (m, 2H), 7.65−7.63 (m, 2H), 7.47−7.45 (m, 2H), 7.33−7.25 (m, 7H), 7.14−7.05 (m, 5H), 6.99−6.96 (m, 2H), 5.19 (s, 1H), 1.90 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, Me_4Si) δ 192.3, 149.3, 145.5, 145.2, 144.6, 139.3, 139.1, 133.0, 131.6, 129.1, 129.1, 128.2, 128.1, 127.9, 127.2, 127.1, 126.0, 124.5, 124.4, 114.9, 65.1, 25.8; HRMS (ESI) calcd for $C_{31}H_{25}N_2O_3$ $(M + H)^+$ 473.1865, found 473.1860.

(1-(2-Chlorophenyl)-6-methyl-4,6-diphenyl-1,6-dihydropyridin-3-yl)(phenyl)methanone (3i). Column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 10:1) afforded the title product in 88% (101 mg) isolated yield as a yellow solid: mp 185−186 °C; ^{1}H NMR (400 MHz, $CDCl_3$, Me_4Si) δ 7.60−7.50 (m, 2H), 7.46−7.40 (m, 2H), 7.32−7.22 (m, 7H), 7.14−6.99 (m, 7H), 6.82 (s, 1H), 6.68−6.66 (m, 1H), 5.12 (s, 1H), 1.76 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, Me_4Si) δ 191.7, 148.3, 145.7, 144.6, 139.8, 139.8, 134.4, 133.7, 131.0, 129.8, 129.1, 128.7, 128.0, 128.0, 127.7, 127.2, 127.0, 126.8, 126.4, 124.7, 124.6, 111.6, 64.6, 26.4; HRMS (ESI) calcd for $C_{31}H_{24}ClNO$ 461.1546, found 461.1537.

2-(5-Benzoyl-2-methyl-2,4-diphenylpyridin-1(2*H*)-yl)-benzonitrile (3j). Column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 10:1) afforded the title product in 73% (83 mg) isolated yield as a yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$, Me_4Si) δ 7.92−7.90 (m, 2H), 7.64−7.62 (m, 1H), 7.58−7.56 (m, 2H), 7.44−7.35 (m, 5H), 7.33−7.31 (m, 1H), 7.29−7.17 (m, 7H), 7.10−7.06 (m, 1H), 6.64 (s, 1H), 5.31 (s, 1H), 1.86 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, Me_4Si) δ 191.8, 148.0, 145.7, 145.2, 139.6, 139.3, 133.9, 133.7, 132.8, 131.1, 129.3, 128.7, 128.4, 128.1, 128.1, 128.1, 127.7, 127.7, 127.1, 126.8, 126.7, 125.3, 116.5, 112.8, 112.4, 65.1, 26.2; HRMS (ESI) calcd for $C_{32}H_{24}N_2O$ 452.1889, found 452.1881.

Benzyl-6-methyl-4,6-diphenyl-1,6-dihydropyridin-3-yl)-(phenyl)methanone (3k). (The reaction time was 5 h). Column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 10:1) afforded the title product in 35% (39 mg) isolated yield as a yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$, Me_4Si) δ 7.54 (d, J = 7.6 Hz, 2H), 7.42 (d, J = 7.2 Hz, 2H), 7.33−7.36 (m, 2H), 7.26−7.07 (m, 13H), 6.99−6.97 (m, 2H), 4.97 (s, 1H), 3.98 (d, J = 14.8 Hz, 1H), 4.07 (d, J = 14.8 Hz, 1H), 1.77 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, Me_4Si) δ 190.5, 151.4, 145.3, 140.5, 140.2, 136.7, 133.9, 130.3, 129.0, 128.9, 128.6, 128.0, 128.0, 127.9, 127.8, 127.6, 127.2, 127.1, 126.6, 123.7, 108.0, 64.5, 53.3, 25.4; HRMS (ESI) calcd for $C_{32}H_{28}NO$ $(M + H)^+$ 442.2171, found 442.2173.

Phenyl(1,4,6,6-tetraphenyl-1,6-dihydropyridin-3-yl)-methanone (3l). (The reaction time was 4 h). Column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 10:1) afforded the title product in 82% (100 mg) isolated yield as a yellow solid: mp 145−146 °C; ^{1}H NMR (400 MHz, $CDCl_3$, Me_4Si) δ 7.59 (s, 1H), 7.38−7.36 (m, 5H), 7.22−76.99 (m, 15H), 6.97−6.86 (m, 5H), 5.55 (s, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$, Me_4Si) δ 192.4, 146.5, 144.2, 143.1, 140.1, 139.5, 134.6, 130.9, 128.9, 128.8, 128.3, 127.9, 127.8, 127.7, 127.6, 127.4, 126.9, 125.7, 125.6, 124.1, 114.0, 72.6; HRMS (MALDI/DHB) calcd for $C_{36}H_{28}NO$ $(M + H)^+$ 490.2171, found 490.2165.

(6-(4-Chlorophenyl)-6-methyl-1,4-diphenyl-1,6-dihydropyridin-3-yl)(phenyl)methanone (3m). (The reaction time was 2 h). Column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 15:1) afforded the title product in 89% (103 mg) isolated yield as a yellow solid: mp 176−177 °C; ^{1}H NMR (400 MHz, $CDCl_3$, Me_4Si) δ 7.59 (d, J = 7.2 Hz, 2H), 7.40 (d, J = 8.0 Hz, 2H), 7.27−7.21 (m, 6H), 7.16−7.12 (m, 8H), 6.81−6.79 (m, 2H), 5.06 (s, 1H), 1.72 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, Me_4Si) δ 191.6, 149.5, 144.7, 143.2, 140.0, 139.9, 134.2, 133.8, 130.9, 129.1, 129.0, 128.8, 128.1, 127.9, 127.8, 127.3, 127.2, 126.9, 126.8, 123.8, 110.7, 64.1, 26.7; HRMS (ESI) calcd for $C_{31}H_{25}ClNO$ $(M + H)^+$ 462.1625, found 462.1633.

(6-Cyclopropyl-1,4,6-triphenyl-1,6-dihydropyridin-3-yl)-(phenyl)methanone (3n). (The reaction time was 2 h). Column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 10:1) afforded the title product in 67% (76 mg) isolated yield as a yellow solid: mp 241−242 °C; ^{1}H NMR (400 MHz, $CDCl_3$, Me_4Si) δ 7.71−7.67 (m, 4H), 7.39−7.27 (m, 7H), 7.21−7.12 (m, 8H), 6.91−6.89 (m, 2H), 4.68 (s, 1H), 1.43−1.38 (m, 1H), 0.95−0.89 (m, 1H), 0.78 −0.70 (m, 2H), 0.59−0.55 (m, 1H); ^{13}C NMR (100.6 MHz, $CDCl_3$, Me_4Si)) δ 191.2, 150.4, 147.2, 143.7, 140.4, 140.1, 135.9, 130.7, 129.1, 128.7, 128.4, 127.9, 127.7, 127.6, 127.3, 127.28, 127.1, 127.0, 126.6, 117.2, 108.9, 69.1, 18.4, 2.5, 1.7; HRMS (ESI) calcd for $C_{33}H_{27}NO$ 453.2093, found 453.2084.

(4-(4-Fluorophenyl)-1,6,6-triphenyl-1,6-dihydropyridin-3-yl)(phenyl)methanone (3o). Column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 10:1) afforded the title product in 92% (103 mg) isolated yield as a yellow solid: mp 144−145 °C; ^{1}H NMR (400 MHz, $CDCl_3$, Me_4Si) δ 7.69−7.67 (m, 2H), 7.55−7.53 (m, 2H), 7.38−7.29 (m, 7H), 7.20−7.14 (m, 5H), 6.91−6.85 (m, 4H), 5.15 (s, 1H), 1.81 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, Me_4Si) δ 191.2, 161.7 (d, $^1J_{C-F}$ = 245.1 Hz), 150.0, 145.9, 143.2, 139.9, 136.0 (d, $^4J_{C-F}$ = 3.5 Hz), 132.6, 130.8, 128.9, 128.8, 128.6 (d, $^3J_{C-F}$ = 8.0 Hz), 128.6, 128.0, 127.8, 127.0, 126.6, 126.2, 124.4, 114.4 (d, $^2J_{C-F}$ = 21.4 Hz), 110.1, 64.5, 26.7; HRMS (ESI) calcd for $C_{31}H_{24}FNO$ 445.1842, found 445.1833.

(6-Methyl-1,6-diphenyl-4-(*p*-tolyl)-1,6-dihydropyridin-3-yl)-(phenyl)methanone (3p). (The reaction time was 2 h). Column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 10:1) afforded the title product in 72% (80 mg) isolated yield as a yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$, Me_4Si) δ 7.71−7.69 (m, 2H), 7.55−7.52 (m, 2H), 7.37−7.28 (m, 8H), 7.16−7.11 (m, 4H), 7.03−7.01 (m, 2H), 6.87−6.84 (m, 2H), 5.18 (s, 1H), 2.26 (s, 3H), 1.81 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, Me_4Si) δ 191.4, 149.8, 146.0, 143.3, 139.9, 137.0, 136.2, 133.4, 130.7, 129.0, 128.8, 128.5, 128.3, 127.9, 127.6, 126.9, 126.9, 126.6, 126.3, 124.1, 110.6, 64.5, 26.7, 21.1; HRMS (ESI) calcd for $C_{32}H_{27}NO$ 441.2093, found 441.2081.

(4-Butyl-6-methyl-1,6-diphenyl-1,6-dihydropyridin-3-yl)-(phenyl)methanone (3r). (The reaction time was 3 h). Column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 30:1) afforded the title product in 21% (22 mg) isolated yield as a yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$, Me_4Si) δ 7.65−7.63 (m, 2H), 7.49−7.47 (m, 2H), 7.39−7.34 (m, 5H), 7.31−7.27 (m, 1H), 7.14−7.11 (m, 3H), 7.08 (s, 1H), 6.75−6.72 (m, 2H), 4.94 (s, 1H), 2.67−2.56 (m, 2H), 1.71 (s, 3H), 1.47−1.34 (m, 4H), 0.90 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, Me_4Si) δ 192.9, 151.2, 146.7, 143.5, 141.1, 132.3, 130.3, 128.9, 128.7, 128.4, 128.0, 127.6, 126.9, 126.7, 126.4, 121.9, 110.0, 64.2, 33.0, 31.7, 26.8, 22.6, 14.1; HRMS (ESI) calcd for $C_{29}H_{29}NO$ 407.2249, found 407.2243.

(*E*)-(4-Butylidene-6-methyl-1,6-diphenyl-1,4,5,6-tetrahydropyridin-3-yl)(phenyl)methanone (4a). (The reaction time was 3 h). Column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 30:1) afforded the title product in 39% (40 mg) isolated yield as a yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$, Me_4Si) δ 7.63−7.61 (m, 2H), 7.41−7.30 (m, 8H), 7.26−7.23 (m, 1H), 7.17−7.13 (m, 2H), 7.09−7.05 (m, 1H), 6.92−6.89 (m, 2H), 6.20 (t, J = 7.6

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Hz, 1H), 2.98 (d, J = 14.0 Hz, 1H), 2.57 (d, J = 14.0 Hz, 1H), 1.96−1.90 (m, 1H), 1.85−1.77 (m, 1H), 1.69 (s, 3H), 1.15−1.08 (m, 1H), 0.99−0.94 (m, 1H), 0.68 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, Me_4Si) δ 194.3, 149.1, 144.2, 144.0, 141.3, 130.1, 128.8, 128.7, 128.3, 128.1, 127.9, 127.0, 125.6, 125.5, 124.7, 124.6, 113.2, 63.2, 41.9, 29.6, 26.4, 22.8, 13.7; HRMS (ESI) calcd for $C_{29}H_{29}NO$ 407.2249, found 407.2243.

(6-Methyl-4-phenethyl-1,6-diphenyl-1,6-dihydropyridin-3-yl)(phenyl)methanone (3s). (The reaction time was 2 h). Column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 15:1) afforded the title product in 35% (40 mg) isolated yield as a yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$, Me_4Si) δ 7.67−7.64 (m, 2H), 7.41−7.31 (m, 7H), 7.29−7.23 (m, 5H), 7.18−7.14 (m, 1H), 7.12−7.07 (m, 4H), 6.72−7.69 (m, 2H), 4.82 (s, 1H), 2.98−2.92 (m, 2H), 2.84−2.80 (m, 2H), 1.61 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, Me_4Si) δ 192.8, 151.7, 146.2, 143.3, 142.4, 141.1, 131.0, 130.2, 128.9, 128.8, 128.7, 128.4, 128.1, 128.0, 127.5, 127.0, 126.8, 126.6, 125.4, 123.0, 109.6, 64.2, 35.9, 35.6, 26.5; HRMS (ESI) calcd for $C_{33}H_{29}NO$ 455.2249, found 455.2239.

(*E*)-(6-Methyl-1,6-diphenyl-4-(2-phenylethylidene)-1,4,5,6-tetrahydropyridin-3-yl)(phenyl)methanone (4b). (The reaction time was 2 h). Column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 15:1) afforded the title product in 31% (35 mg) isolated yield as a yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$, Me_4Si) δ 7.62−7.59 (m, 2H), 7.46 (s, 1H), 7.35−7.28 (m, 8H), 7.17−7.03 (m, 6H), 6.93−6.91 (m, 2H), 6.70−6.68 (m, 2H), 6.37 (t, J = 7.6 Hz, 1H), 3.26 (d, J = 8.0 Hz, 2H), 3.12 (d, J = 13.6 Hz, 1H), 2.66 (d, J = 14.0 Hz, 1H), 1.70 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, Me_4Si) δ 194.0, 149.4, 143.9, 143.8, 141.1, 140.6, 130.0, 128.7, 128.6, 128.5, 128.24, 127.9, 127.8, 127.0, 125.8, 125.6, 125.5, 125.3, 125.1, 124.6, 112.7, 63.0, 41.7, 33.5, 26.6; HRMS (ESI) calcd for $C_{33}H_{29}NO$ 455.2249, found 455.2239.

(6-Methyl-1-(4-nitrophenyl)-4-phenethyl-6-phenyl-1,6-dihydropyridin-3-yl)(phenyl)methanone (3t). (The reaction time was 2 h). Column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 10:1) afforded the title product in 21% (26 mg) isolated yield as a yellow liquid: ^{1}H NMR (400 MHz, $CDCl_3$, Me_4Si) δ 7.97−7.95 (m, 2H), 7.74−7.71 (m, 2H), 7.50−7.43 (m, 3H), 7.34−7.10 (m, 11H), 6.88−6.85 (m, 2H), 4.88 (s, 1H), 2.87−2.85 (m, 2H), 2.77−2.75 (m, 2H), 1.75 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, Me_4Si) δ 193.4, 149.2, 147.4, 145.4, 144.5, 141.9, 140.2, 131.2, 130.2, 128.9, 128.8, 128.8, 128.3, 128.1, 127.9, 126.1, 125.6, 125.1, 124.5, 124.4, 113.7, 64.7, 35.6, 34.8, 25.7; HRMS (ESI) calcd for $C_{33}H_{28}N_2O_3$ 500.2100, found 500.2091.

(*E*)-(6-Methyl-1-(4-nitrophenyl)-6-phenyl-4-(2-phenylethylidene)-1,4,5,6-tetrahydropyridin-3-yl)(phenyl)methanone (4c). (The reaction time was 2 h). Column chromatography on silica gel (eluent: petroleum ether/ethyl acetate = 10:1) afforded the title product in 33% (42 mg) isolated yield as a yellow solid: mp 152−153 °C; ^{1}H NMR (400 MHz, $CDCl_3$, Me_4Si) δ 8.00−7.99 (m, 2H), 7.66−7.64 (m, 2H), 7.45−7.30 (m, 9H), 7.15−7.09 (m, 3H), 6.96−6.94 (m, 2H), 6.76−6.74 (m, 2H), 6.25 (t, J = 7.6 Hz, 1H), 3.29 (d, J = 7.6 Hz, 2H), 3.06 (d, J = 14.0 Hz, 1H), 2.78 (d, J = 13.6 Hz, 1H), 1.82 (s, 3H); ^{13}C NMR (100.6 MHz, $CDCl_3$, Me_4Si) δ 194.7, 149.3, 145.0, 143.6, 142.9, 140.3, 140.2, 131.1, 129.0, 128.9, 128.3, 128.2, 128.1, 127.6, 127.4, 125.7, 125.5, 125.2, 124.5, 122.9, 116.1, 63.4, 42.6, 33.6, 25.5; HRMS (ESI) calcd for $C_{33}H_{28}N_2O_3$ 500.2100, found 500.2091.

■ ASSOCIATED CONTENT

Supporting Information

Experimental details, spectroscopic characterization of all new compounds, and X-ray crystallography of compound **3l** and **4c**. 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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