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Aerobic Oxidative Mannich Reaction Promoted by Catalytic Amounts of Stable Radical Cation Salt

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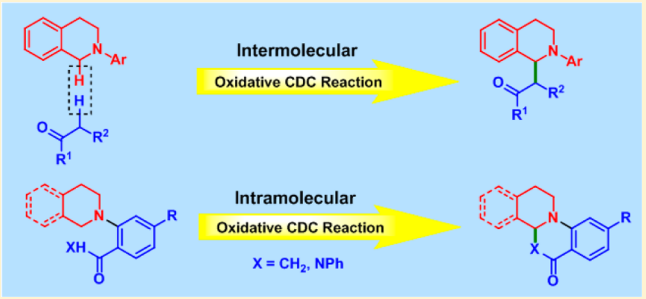
Supporting Information

ABSTRACT: A catalytic amount of triarylaminium salt is demonstrated to be an efficient initiator for oxidative Mannich reaction of tertiary amines and nonactivated ketones under mild neutral conditions. Air is essential for this reaction and acts as a terminal oxidant. Metal catalysts, acid or base additives, and stoichiometric amounts of chemical oxidants are all avoided in this methodology. Six examples of intramolecular cyclized products are also delivered.



Mannich reaction involves the condensation of enolizable aldehydes or ketones with imine or iminium species to afford substituted β-amino carbonyl compounds. It is a fundamentally important carbon−carbon bond construction method in organic synthesis and has been widely utilized in the syntheses of natural products and pharmaceuticals.[1] During the past few years, the oxidative coupling of amines has gained significant attention since the pioneering study of Murahashi[2] and Li.[3] In these reactions, the secondary amines or tertiary amines are oxidized to generate highly reactive imine or iminium intermediates that can be used for further functionalization.[4] Until now, various kinds of nucleophiles have been utilized to intercept the imine or iminium intermediates generated in situ to construct new C−C bonds under Mannich-type processes.[4] However, the utilization of the nonactivated ketones as the nucleophiles to carry out the classic Mannich reaction under oxidizing conditions is relatively scarce.[5] Although a few successful processes have been achieved in this area, these methods generally have some serious drawbacks: (1) Extra Brönsted acids or secondary amines are always required as additives to activate ketones to their enolate form;[5a−c,e−n] (2) light or heating sources are usually needed to run the reactions;[5a,c−o,q] (3) costly and toxic transition metal reagents or photoredox complexes often act as catalysts;[5a−n] (4) stoichiometric amounts of dangerous oxidants[5b,p,q] or pure oxygen are frequently necessary; and (5) no more than three successful ketone examples are reported in most of the so far published papers.[5c,d,f,h,j−q] Therefore, due to the increasing demand for sustainable methods in organic synthesis, the development of a metal free, additive free, chemical oxidant free, and energy source free methodology under aerobic conditions for the oxidative Mannich reaction is highly desirable. Our group has had a long-standing interest in radical cation mediated transformations and their synthetic potential.[6] As part of our ongoing interest in stable radical cation salt initiated aerobic oxidative reactions of amines,[6] herein, we report a catalytic amounts of triarylaminium salt induced sp^3−sp^3 C−C bond formation protocol between tertiary amines and unmodified ketones with air as a sustainable and efficient oxidant under mild conditions. The additional advantage of this method is that it does not require the activation of ketones. Six examples of intramolecular cyclized products are delivered too.

In our preliminary investigation, as shown in Table 1, we chose *N*-phenyl-1,2,3,4-tetrahydroisoquinoline (**1a**) and acetone (**2a**) as model substrates. A 0.5 mmol portion of **1a** was treated with 10 mmol % tris(4-bromophenyl)-aminium hexachloroantimonate[7] ($TBPA^{\bullet+}SbCl_6^-$, a well-known stable radical cation salt; see Table 1 for its structure) in 10 equiv of acetone under an air atmosphere. The reaction was carried out at ambient temperature, and acetone was used as both reactant and solvent. To our delight, the reaction worked smoothly and the desired β-amino ketone **3aa** was isolated in good yield (66%, Table 1, entry 1) after 12 h. We then optimized the reaction conditions by changing initiator loadings. The best yield (92%, Table 1, entry 2) was achieved with 20 mol % $TBPA^{\bullet+}SbCl_6^-$. No appreciable differences of the transformation were observed when pure oxygen gas was used instead of an air atmosphere (Table 1, entry 5). Subsequently, we chose acetophenone (**2k**, 2 equiv) as a high boiling point ketone to screen the solvents. The highest yield (76%, Table 1, entry 6) was observed when acetonitrile was used as solvent. The reaction of **1a** with acetone in the absence of molecular oxygen (in argon atmosphere) afforded no product (Table 1, entry 11), indicating that dioxygen is definitely crucial for the reaction.

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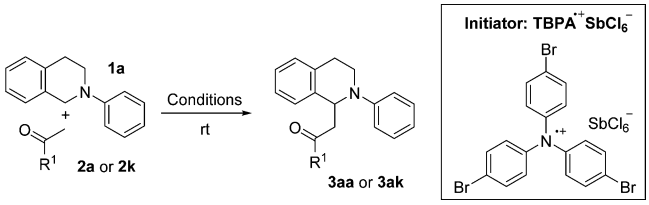
Table 1. Screening of Reaction Conditions



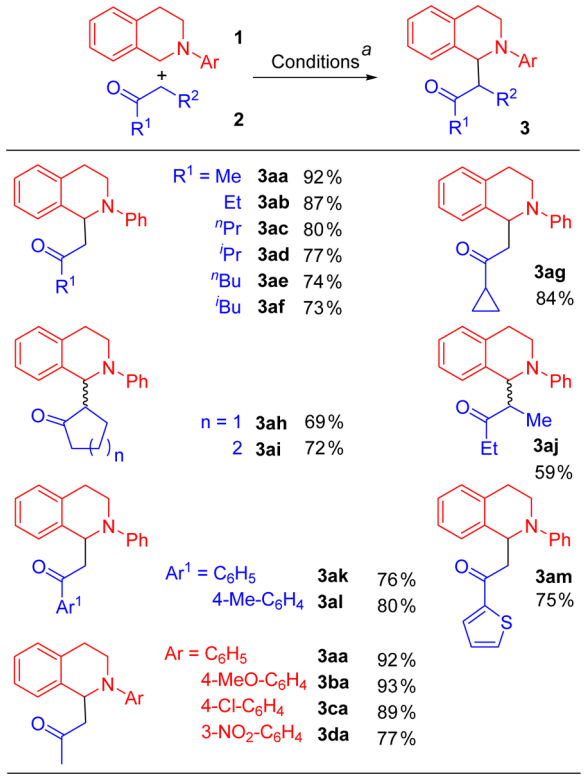
entry	R^1	conditions		yield (%)[a]
1	Me	10 mol % catalyst,	neat, air, rt, 12 h	66
2	Me	20 mol % catalyst,	neat, air, rt, 12 h	92
3	Me	5 mol % catalyst,	neat, air, rt, 12 h	38
4	Me	30 mol % catalyst,	neat, air, rt, 12 h	87
5	Me	20 mol % catalyst,	neat, O_2, rt, 12 h	92
6	Ph	20 mol % catalyst,	MeCN, air, rt, 48 h	76
7	Ph	20 mol % catalyst,	$CHCl_3$, air, rt, 48 h	60
8	Ph	20 mol % catalyst,	CH_2Cl_2, air, rt, 48 h	65
9	Ph	20 mol % catalyst,	$(CHCl)_2$, air, rt, 48 h	48
10	Ph	20 mol % catalyst,	THF, air, rt, 48 h	51
11	Me	20 mol % catalyst,	neat, Ar, rt, 12 h	trace

[a]Isolated yields of the isolated products.

Under the optimized conditions, we probed the generality and scope of both ketones and tetrahydroisoquinolines for this TBPA radical cation induced aerobic oxidative Mannich reaction (Table 2). Initially, we investigated different unmodified ketones. Methyl alkyl ketones gave the corresponding products in high yields (Table 2, **3ab**−**3ag**). The bulky methyl ketones **2e**−**g** still effectively gave good results in this method. Methyl aryl ketones were transformed into the corresponding β-amino products smoothly (Table 2, **3ak**−**3am**). Notably, the methyl heteroaryl ketone **2m** could also be coupled with **1a** to give **3am** in satisfactory yield. Besides the methyl alkyl and aryl ketones, cycloketones and pentan-3-one could also be used to construct sp^3−sp^3 C−C bonds (Table 2, **3ah**−**3aj**). Furthermore, we explored the variety of tetrahydroisoquinolines. For both electron-donating and electron-withdrawing groups, the desired products were achieved in high yields (Table 2, **3ba**−**3da**). The reaction can also be performed successfully in CH_3CN with a significantly reduced amount of ketone (see Table 2, **3ak**−**3am**), but it runs most conveniently in neat ketones if liquid and inexpensive ketones are employed. The reaction of tetrahydroisoquinoline (**1a**) with acetone had been performed on a 10 mmol scale to evaluate the practicability of this protocol, and no loss of yield was observed (Scheme 1). It indicates that our method can be conveniently scaled up. Moreover, as shown in Scheme 1, the TBPA can be efficiently recovered after the reaction by column chromatographic separation and can be recycled back to TBPA$^{\bullet+}$SbCl$_6^-$ easily in perfect yield.

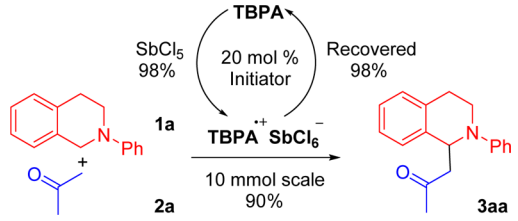
The success of intermolecular aerobic oxidative Mannich reaction of tertiary amines by using catalytic amounts of triarylaminium salt encouraged us to investigate the analogous intramolecular dehydrogenative coupling reaction to deliver ring-fused tetrahydroquinoline derivatives. Ring-fused tetrahydroquinolines are valuable precursors of a lot of bioactive molecules and are widely used building blocks in organic synthesis.[8] As summarized in Table 3, three tetrahydroisoquinoline derivatives were first examined. For both electron-donating and electron-withdrawing groups, the desired products were achieved in high yields (Table 3, **5a**−**5c**). The piperidine derived substrate is applicable to giving product **5d**

Table 2. Scope of TBPA Radical Cation Salt Induced Intermolecular Aerobic Oxidative Mannich Reaction[a,b]



[a]Standard reaction conditions: For aliphatic ketones: tetrahydroisoquinolines **1** (0.5 mmol), ketones **2** (10 equiv), TBPA$^{\bullet+}$SbCl$_6^-$ (0.1 mmol), ambient air, rt. For aromatic ketones: tetrahydroisoquinolines **1** (0.5 mmol), ketones **2** (2 equiv), TBPA$^{\bullet+}$SbCl$_6^-$ (0.1 mmol), MeCN (5 mL), ambient air, rt. [b]Isolated yields of the isolated products.

Scheme 1. Scale-Up Experiment and Recycle of the Initiator



in this method too. The thiophene derived substrate also provided the product **5e** in good yield. To extend the scope of our method, we also presented here an example of a triarylaminium salt promoted intramolecular C−N bond-forming reaction, as shown in Scheme 2.

A plausible mechanism for this catalytic amounts of triarylaminium salt induced aerobic oxidative transformation is illustrated in Scheme 3. In this transformation, the Ar_3N radical cation plays two roles in generating iminium ion **A**: (1) generating the radical cation of substrate **1** as a one electron oxidant and (2) abstracting α-H of substrate **1** as a molecular oxygen activator. The iminium species **A** can then be trapped with nucleophiles such as ketones to afford the desired product **3**.

In conclusion, we have reported a novel triarylaminium salt promoted method that is highly efficient and simple for the oxidative coupling of tertiary amines with various kinds of

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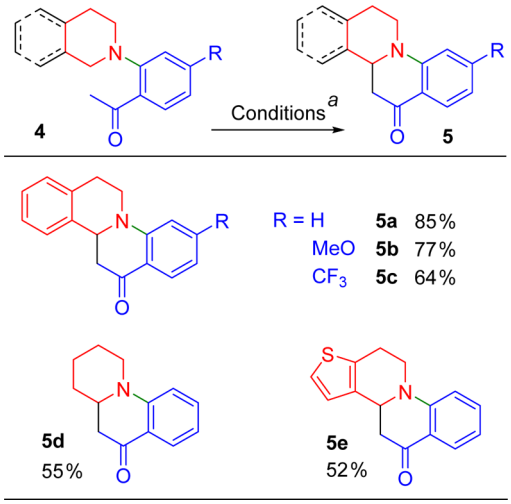
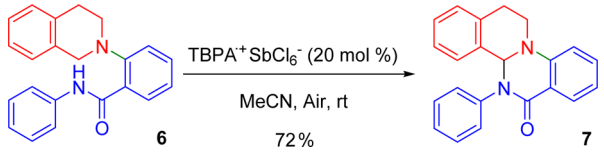
Table 3. Scope of TBPA Radical Cation Salt Induced Intramolecular Aerobic Oxidative Mannich Reaction[a,b]



[a]Standard reaction conditions: tetrahydroisoquinolines **1** (0.5 mmol), $TBPA^{\bullet+}SbCl_6^-$ (0.1 mmol), MeCN (5 mL), ambient air, rt. [b]Isolated yields of the isolated products.

Scheme 2. TBPA Radical Cation Salt Induced Intramolecular C–N Bond-Forming Reaction



unmodified ketones. The highlight of the method is that it requires only catalytic amounts of TBPA radical cation salt as initiator under mild neutral aerobic conditions. The normally used metal catalysts, acid or base additives, and stoichiometric amounts of chemical oxidants are all avoided. Furthermore, six examples of intramolecular cyclized products are delivered too.

EXPERIMENTAL SECTION

General Information. The starting materials, reagents, and solvents, purchased from commercial suppliers, were used without further purification. Analytical TLC was performed with silica gel GF254 plates, and the products were visualized by UV detection. Flash chromatography was carried out using silica gel 200–300. ^{1}HNMR (400 MHz) and ^{13}CNMR (100 MHz) spectra were measured with $CDCl_3$ as solvent. HRMS were carried out on an Orbitrap analyzer.

General Procedure for $TBPA^{\bullet+}SbCl_6^-$ Induced Intermolecular Aerobic Oxidative Mannich Reaction. *Method I.* *N*-Aryl tetrahydroisoquinolines (**1**, 0.5 mmol) were dissolved in ketones (**2**, 5 mmol) at ambient temperature; $TBPA^{\bullet+}SbCl_6^-$ (0.1 mmol) was then added in one portion under stirring. The reactions were performed under an air atmosphere at room temperature and completed as monitored by TLC. The products were separated by silica gel column chromatography using petroleum ether/ethyl acetate (v/v 40:1 to 20:1) to afford the products.

Method II. *N*-Aryl tetrahydroisoquinolines (**1**, 0.5 mmol) and ketones (**2**, 1 mmol) were dissolved in MeCN (5 mL) at ambient temperature; $TBPA^{\bullet+}SbCl_6^-$ (0.1 mmol) was then added in one portion under stirring. The reactions were performed under an air atmosphere at room temperature and completed as monitored by TLC. The products were separated by silica gel column chromatography using petroleum ether/ethyl acetate (v/v 40:1 to 20:1) to afford the products.

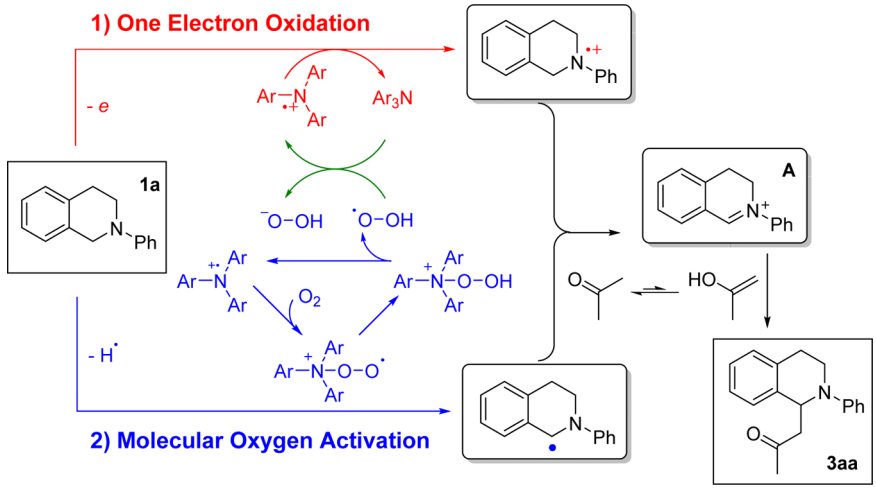
General Procedure for $TBPA^{\bullet+}SbCl_6^-$ Induced Intramolecular Aerobic Oxidative Mannich Reaction. Substrates (**4** or **6**, 0.5 mmol) were dissolved in MeCN (5 mL) at ambient temperature; $TBPA^{\bullet+}SbCl_6^-$ (0.1 mmol) was then added in one portion under stirring. The reactions were performed under an air atmosphere at room temperature and completed as monitored by TLC. The products were separated by silica gel column chromatography using petroleum ether/ethyl acetate (v/v 20:1) to afford the products.

Characterization of the Products. *1-(2-Phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)propan-2-one (**3aa**).*[5a] The desired pure product was obtained in 92% yield (122 mg) as a white solid, mp 82–84 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.24 (t, J = 7.4 Hz, 2H), 7.16 (m, 4H), 6.93 (d, J = 8.1 Hz, 2H), 6.77 (t, J = 7.2 Hz, 1H), 5.40 (t, J = 6.2 Hz, 1H), 3.64–3.46 (m, 2H), 3.11–2.97 (m, 2H), 2.89–2.74 (m, 2H), 2.07 (s, 3H).

*1-(2-Phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)butan-2-one (**3ab**).*[5a] The desired pure product was obtained in 87% yield (121 mg) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26–7.21 (m, 2H), 7.19–7.09 (m, 4H), 6.94 (d, J = 8.2 Hz, 2H), 6.77 (t, J = 7.2 Hz, 1H), 5.42 (t, J = 6.3 Hz, 1H), 3.71–3.47 (m, 2H), 3.11–2.98 (m, 2H), 2.88–2.72 (m, 2H), 2.43–2.19 (m, 2H), 0.98 (t, J = 7.3 Hz, 3H).

*1-(2-Phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)pentan-2-one (**3ac**).*[5a] The desired pure product was obtained in 80% yield (117 mg) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.12 (m, 6H), 7.02–6.92 (m, 2H), 6.79 (t, J = 7.2 Hz, 1H), 5.44 (t, J = 6.2 Hz, 1H), 3.81–3.44 (m, 2H), 3.20–2.98 (m, 2H), 2.94–2.71 (m, 2H), 2.43–2.15 (m, 2H), 1.64–1.47 (m, 2H), 0.86 (t, J = 7.4 Hz, 3H).

Scheme 3. Proposed Reaction Mechanism



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*3-Methyl-1-(2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)butan-2-one (**3ad**).* The desired pure product was obtained in 77% yield (113 mg) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.29−7.20 (m, 2H), 7.19−7.08 (m, 4H), 6.94 (d, J = 8.1 Hz, 2H), 6.75 (t, J = 7.2 Hz, 1H), 5.43 (t, J = 6.2 Hz, 1H), 3.68−3.43 (m, 2H), 3.15−2.99 (m, 2H), 2.91−2.76 (m, 2H), 2.48−2.31 (m, 1H), 1.06−0.88 (m, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 212.8, 148.7, 138.5, 134.3, 129.3, 128.5, 126.8, 126.7, 126.1, 117.9, 114.3, 54.8, 47.0, 42.0, 41.7, 27.4, 17.6, 17.5. HRMS (ESI) exact mass calcd for $C_{20}H_{24}NO$ [M + H] m/z 294.1858, found 294.1853.

*1-(2-Phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)hexan-2-one (**3ae**).*[5a] The desired pure product was obtained in 74% yield (114 mg) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25−7.20 (m, 2H), 7.19−7.09 (m, 4H), 6.94 (d, J = 8.3 Hz, 2H), 6.76 (t, J = 7.2 Hz, 1H), 5.42 (t, J = 6.2 Hz, 1H), 3.71−3.46 (m, 2H), 3.12−2.97 (m, 2H), 2.88−2.72 (m, 2H), 2.38−2.17 (m, 2H), 1.52−1.42 (m, 2H), 1.28−1.16 (m, 2H), 0.84 (t, J = 7.3 Hz, 3H).

*4-Methyl-1-(2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)pentan-2-one (**3af**).*[5b] The desired pure product was obtained in 73% yield (112 mg) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31−7.08 (m, 6H), 6.95 (d, J = 14.4 Hz, 2H), 6.76 (t, J = 7.2 Hz, 1H), 5.43 (t, J = 6.2 Hz, 1H), 3.69−3.46 (m, 1H), 3.17−2.94 (m, 2H), 2.91−2.69 (m, 2H), 2.27−1.98 (m, 3H), 0.85 (d, J = 6.3 Hz, 6H).

*1-Cyclopropyl-2-(2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-ethan-1-one (**3ag**).* The desired pure product was obtained in 84% yield (122 mg) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.23 (m, 2H), 7.23−7.10 (m, 4H), 6.98 (d, J = 8.2 Hz, 2H), 6.80 (t, J = 7.3 Hz, 1H), 5.48 (m, 1H), 3.73−3.53 (m, 2H), 3.25−2.83 (m, 4H), 1.90−1.79 (m, 1H), 1.07−0.97 (m, 2H), 0.89−0.76 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 209.3, 148.8, 138.5, 134.5, 129.4, 128.6, 127.0, 126.8, 126.2, 118.0, 114.5, 54.8, 49.9, 42.0, 27.5, 21.6, 11.1, 11.0. HRMS (ESI) exact mass calcd for $C_{20}H_{22}NO$ [M + H] m/z 292.1701, found 292.1707.

*1-Phenyl-2-(2-phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)ethan-1-one (**3ak**).*[5a] The desired pure product was obtained in 76% yield (124 mg) as a pale yellow solid, mp 105−107 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 7.3 Hz, 2H), 7.57−7.48 (m, 1H), 7.47−7.35 (m, 2H), 7.34−7.19 (m, 4H), 7.19−7.08 (m, 1H), 6.96 (d, J = 7.8 Hz, 2H), 6.82−6.70 (m, 1H), 5.73−5.63 (m, 1H), 3.73−3.51 (m, 3H), 3.47−3.33 (m, 1H), 3.18−3.04 (m, 1H), 3.01−2.86 (m, 1H).

*2-(2-Phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-(p-tolyl)ethan-1-one (**3al**).*[5a] The desired pure product was obtained in 80% yield (136 mg) as a white solid, mp 113−115 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 8.1 Hz, 2H), 7.28−7.17−7.06 (m, 8H), 6.97 (d, J = 8.1 Hz, 2H), 6.74 (t, J = 7.2 Hz, 1H), 5.69−5.60 (m, 1H), 3.75−3.49 (m, 3H), 3.45−3.28 (m, 1H), 3.19−3.01 (m, 1H), 3.01−2.84 (m, 1H), 2.38 (s, 3H).

*2-(2-Phenyl-1,2,3,4-tetrahydroisoquinolin-1-yl)-1-(thiophen-2-yl)-ethan-1-one (**3am**).* The desired pure product was obtained in 75% yield (125 mg) as a yellow solid, mp 131−133 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 4.9 Hz, 1H), 7.57 (d, J = 3.7 Hz, 1H), 7.32−7.01 (m, 9H), 6.79 (t, J = 7.2 Hz, 1H), 5.64 (t, 1H), 3.74−3.52 (m, 3H), 3.31 (dd, J = 15.8, 7.2 Hz, 1H), 3.22−3.08 (m, 1H), 3.00−2.88 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 191.3, 148.7, 144.6, 138.1, 134.5, 134.0, 132.1, 129.4, 128.6, 128.1, 127.2, 126.9, 126.3, 118.0, 114.4, 55.6, 46.0, 42.0, 27.5. HRMS (ESI) exact mass calcd for $C_{21}H_{20}NOS$ [M + H] m/z 334.1266, found 334.1273.

*1-(2-(4-Methoxyphenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)-propan-2-one (**3ba**).*[5e] The desired pure product was obtained in 93% yield (137 mg) as a pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22−7.07 (m, 4H), 6.91 (d, J = 8.9 Hz, 2H), 6.81 (d, J = 8.9 Hz, 2H), 5.24 (t, J = 6.3 Hz, 1H), 3.75 (s, 3H), 3.63−3.38 (m, 2H), 3.09−2.93 (m, 2H), 2.82−2.66 (m, 2H), 2.06 (s, 3H).

*1-(2-(4-Chlorophenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)propan-2-one (**3ca**).*[5e] The desired pure product was obtained in 89% yield (133 mg) as a red oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23−7.11 (m, 6H), 6.85 (d, J = 9.0 Hz, 2H), 5.34 (t, J = 6.2 Hz, 1H), 3.68−3.43 (m, 2H), 3.10−2.96 (m, 2H), 2.90−2.76 (m, 2H), 2.09 (s, 3H).

*1-(2-(3-Nitrophenyl)-1,2,3,4-tetrahydroisoquinolin-1-yl)propan-2-one (**3da**).* The desired pure product was obtained in 77% yield (119 mg) as a red solid, mp 101−102 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (s, 1H), 7.62−7.12 (m, 7H), 5.46 (t, J = 6.2 Hz, 1H), 3.75−3.56 (m, 2H), 3.17−3.01 (m, 2H), 2.99−2.83 (m, 2H), 2.12 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 206.4, 149.5, 149.3, 137.5, 134.0, 129.9, 128.6, 127.2, 126.8, 126.6, 119.4, 112.1, 107.7, 54.6, 50.2, 42.2, 31.1, 27.0. HRMS (ESI) exact mass calcd for $C_{18}H_{19}N_2O_3$ [M + H] m/z 311.1396, found 311.1401.

*6,7,11b,12-Tetrahydro-13H-isoquinolino[2,1-a]quinolin-13-one (**5a**).*[8a] The desired pure product was obtained in 85% yield (106 mg) as a yellow solid, mp 122−124 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 7.8 Hz, 1H), 7.46 (t, J = 7.8 Hz, 1H), 7.31−7.13 (m, 4H), 7.00 (d, J = 8.6 Hz, 1H), 6.82 (t, J = 7.4 Hz, 1H), 4.74 (d, J = 13.7 Hz, 1H), 4.18−4.04 (m, 1H), 3.28−3.02 (m, 3H), 2.99−2.87 (m, 1H), 2.85−2.71 (m, 1H).

*3-Methoxy-6,7,11b,12-tetrahydro-13H-isoquinolino[2,1-a]quinolin-13-one (**5b**).*[8a] The desired pure product was obtained in 77% yield (108 mg) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (d, J = 9.1 Hz, 1H), 7.30−7.06 (m, 4H), 6.49−6.33 (m, 2H), 4.72 (d, J = 13.3 Hz, 1H), 4.11−3.98 (m, 1H), 3.87 (s, 3H), 3.26−2.83 (m, 4H), 2.82−2.67 (m, 1H).

*3-(Trifluoromethyl)-6,7,11b,12-tetrahydro-13H-isoquinolino[2,1-a]quinolin-13-one (**5c**).* The desired pure product was obtained in 64% yield (102 mg) as a yellow solid, mp 150−152 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 7.9 Hz, 1H), 7.33−7.15 (m, 5H), 7.03 (d, J = 7.9 Hz, 1H), 4.80 (d, J = 13.7 Hz, 1H), 4.24−4.04 (m, 1H), 3.32−3.04 (m, 3H), 3.04−2.90 (m, 1H), 2.89−2.74 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.1, 151.9, 134.9, 133.8, 129.3, 128.8, 127.1, 126.9, 125.6, 122.5, 113.9, 113.9, 110.4, 110.4, 57.6, 46.6, 42.7, 29.3. HRMS (ESI) exact mass calcd for $C_{18}H_{15}F_3NO$ [M + H] m/z 318.1106, found 318.1111.

*1,2,3,4,4a,5-Hexahydro-6H-pyrido[1,2-a]quinolin-6-one (**5d**).*[8b] The desired pure product was obtained in 55% yield (55 mg) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, J = 7.3 Hz, 1H), 7.40 (t, J = 7.0 Hz, 1H), 6.94 (d, J = 8.6 Hz, 1H), 6.79 (t, J = 7.4 Hz, 1H), 3.98 (d, J = 11.3 Hz, 1H), 3.30 (m, 1H), 2.76−2.50 (m, 3H), 1.94−1.20 (m, 6H).

*3b,4,11,12-Tetrahydro-5H-thieno[3′,2′:3,4]pyrido[1,2-a]quinolin-5-one (**5e**).* The desired pure product was obtained in 52% yield (66 mg) as a yellow solid, mp 146−148 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, J = 7.7 Hz, 1H), 7.47 (t, J = 7.0 Hz, 1H), 7.18 (d, J = 5.0 Hz, 1H), 7.05 (d, J = 8.4 Hz, 1H), 6.95−6.78 (m, 2H), 4.65 (d, J = 13.2 Hz, 1H), 4.34−4.20 (m, 1H), 3.19−2.94 (m, 4H), 2.82−2.69 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 193.5, 152.2, 135.5, 135.0, 133.5, 128.4, 124.2, 123.8, 121.1, 118.2, 113.6, 57.2, 45.4, 43.3, 24.9. HRMS (ESI) exact mass calcd for $C_{15}H_{14}NOS$ [M + H] m/z 256.0796, found 256.0790.

*5-Phenyl-4b,5,12,13-tetrahydro-6H-isoquinolino[2,1-a]quinazolin-6-one (**7**).*[8c] The desired pure product was obtained in 72% yield (118 mg) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (dd, J = 7.8, 1.5 Hz, 1H), 7.51 (d, J = 7.6 Hz, 2H), 7.44−7.33 (m, 4H), 7.23−7.05 (m, 4H), 7.01 (d, J = 8.2 Hz, 1H), 6.94−6.87 (m, 1H), 6.19 (s, 1H), 4.26 (m, 1H), 3.81−3.69 (m, 1H), 3.32 (m, 1H), 2.88 (m, 1H).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Copies of NMR spectra. 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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REFERENCES

(1) For reviews about Mannich reactions, see: (a) Kleinman, E. D. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, U.K., 1991; Vol. 2, p 893. (b) Arend, M.; Westermann, B.; Risch, N. *Angew. Chem., Int. Ed.* **1998**, *37*, 1044. (c) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069. (d) Ting, A.; Schaus, S. E. *Eur. J. Org. Chem.* **2007**, 5797. (e) Verkade, J. M. M.; van Hemert, L. J. C.; Quaedflieg, P. J. L. M.; Rutjes, F. P. J. T. *Chem. Soc. Rev.* **2008**, *37*, 29−41.

(2) Murahashi, S.; Komiya, N.; Terai, H.; Nakae, T. *J. Am. Chem. Soc.* **2003**, *125*, 15312.

(3) (a) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2004**, *126*, 11810. (b) Li, Z.; Li, C.-J. *Org. Lett.* **2004**, *6*, 4997.

(4) For reviews, see: (a) Murahashi, S.; Zhang, D. *Chem. Soc. Rev.* **2008**, *37*, 1490. (b) Li, C.-J. *Acc. Chem. Res.* **2009**, *42*, 335. (c) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215. (d) Klussmann, M.; Sureshkumar, D. *Synthesis* **2011**, *3*, 353. (e) Girard, S. A.; Knauber, T.; Li, C.-J. *Angew. Chem., Int. Ed.* **2014**, *53*, 74.

(5) (a) Shen, Y.; Li, M.; Wang, S.; Zhan, T.; Tan, Z.; Guo, C. *Chem. Commun.* **2009**, 953. (b) Sud, A.; Sureshkumar, D.; Klussmann, M. *Chem. Commun.* **2009**, 3169. (c) Shu, X.; Yang, Y.; Xia, X.; Ji, K.; Liu, X.; Liang, Y. *Org. Biomol. Chem.* **2010**, *8*, 4077. (d) Zeng, T.; Song, G.; Moores, A.; Li, C. *Synlett.* **2010**, *13*, 2002. (e) Xie, J.; Li, H.; Zhou, J.; Cheng, Y.; Zhu, C. *Angew. Chem., Int. Ed.* **2012**, *51*, 1252. (f) Rueping, M.; Vila, C.; Koenigs, R.; Poscharny, K.; Fabry, D. *Chem. Commun.* **2011**, *47*, 2360. (g) Cherevatskaya, M.; Neumann, M.; Fuldner, S.; Harlander, C.; Kummel, S.; Dankesreiter, S.; Pfitzner, A.; Zeitler, K.; Kçnig, B. *Angew. Chem., Int. Ed.* **2012**, *51*, 4062. (h) Rueping, M.; Zoller, J.; Fabry, D.; Poscharny, K.; Koenigs, M.; Mayer, E. W. *Chem.—Eur. J.* **2012**, *18*, 3478. (i) Xue, Q.; Xie, J.; Jin, H.; Cheng, Y.; Zhu, C. *Org. Biomol. Chem.* **2013**, *11*, 1606. (j) To, W.; Liu, Y.; Lau, T.; Che, C. *Chem.—Eur. J.* **2013**, *19*, 5654. (k) Pan, Y.; Kee, C.; Chen, L.; Tan, C. *Green Chem.* **2011**, *13*, 2682. (l) Liu, Q.; Li, Y.; Zhang, H.; Chen, B.; Tung, C.; Wu, L. *Chem.—Eur. J.* **2012**, *18*, 620. (m) Mohlmann, L.; Baar, M.; Rie, J.; Antonietti, M.; Wang, X.; Blechert, S. *Adv. Synth. Catal.* **2012**, *354*, 1909. (n) Wang, S.; Nai, C.; Jiang, X.; Pan, Y.; Tan, C.; Nesladek, M.; Xu, Q.; Loh, K. P. *J. Phys. Chem. Lett.* **2012**, *3*, 2332. (o) Alagiri, K.; Devadig, P.; Prabhu, R. *Chem.—Eur. J.* **2012**, *18*, 5160. (p) Dhineshkumar, J.; Lamani, M.; Alagiri, K.; Prabhu, R. *Org. Lett.* **2013**, *15*, 1092. (q) Nobuta, T.; Tada, N.; Fujiya, A.; Kariya, A.; Miura, T.; Itoh, A. *Org. Lett.* **2013**, *15*, 574.

(6) (a) Huo, C.; Xu, X.; An, J.; Jia, X.; Wang, X.; Wang, C. *J. Org. Chem.* **2012**, *77*, 8310. (b) Huo, C.; Kang, L.; Xu, X.; Jia, X.; Wang, X.; Yuan, Y.; Xie, H. *Tetrahedron.* **2014**, *70*, 1055. (c) Huo, C.; Wang, C.; Wu, M.; Jia, X.; Xie, H.; Yuan, Y. *Adv. Synth. Catal.* **2014**, *356*, 411. (d) Huo, C.; Wang, C.; Sun, C.; Jia, X.; Wang, X.; Chang, W.; Wu, M. *Adv. Synth. Catal.* **2013**, *355*, 1911. (e) Huo, C.; Wang, C.; Wu, M.; Jia, X.; Wang, X.; Yuan, Y.; Xie, H. *Org. Biomol. Chem.* **2014**, *12*, 3123.

(7) (a) Nelsen, S. F. *Acc. Chem. Res.* **1987**, *20*, 269. (b) Bauld, N. L. *Tetrahedron* **1989**, *45*, 5307. (c) Schmittel, M.; Burghart, A. *Angew. Chem., Int. Ed.* **1997**, *36*, 2550.

(8) (a) Zhang, G.; Wang, S.; Ma, Y.; Kong, W.; Wang, R. *Adv. Synth. Catal.* **2013**, *355*, 874. (b) Nie, S.-Z.; Sun, X.; Wei, W.-T.; Zhang, X.-J.; Yan, M.; Xiao, J.-L. *Org. Lett.* **2013**, *15*, 2394. (c) Neel, A. J.; Hehn, J. P.; Tripet, P. F.; Toste, F. D. *J. Am. Chem. Soc.* **2013**, *135*, 14044. (d) Barton, D. H.; Nakanishi, K.; Meth-Cohn, O. *Comprehensive Natural Chemistry*; Elsevier: Oxford, U.K., 1999; Vols. *1*−*9*.