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One-Pot Cascade Synthesis of Quinazolin-4(3*H*)-ones via Nickel-Catalyzed Dehydrogenative Coupling of *o*-Aminobenzamides with Alcohols

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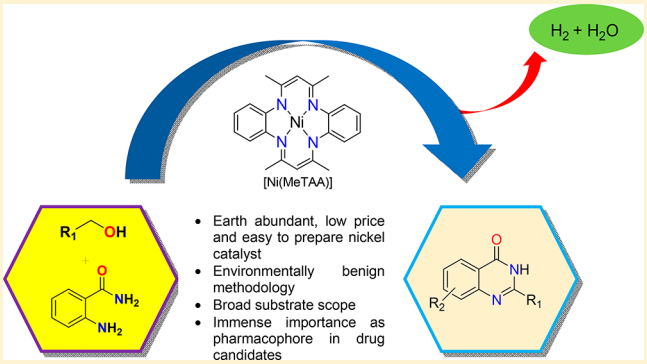
Supporting Information

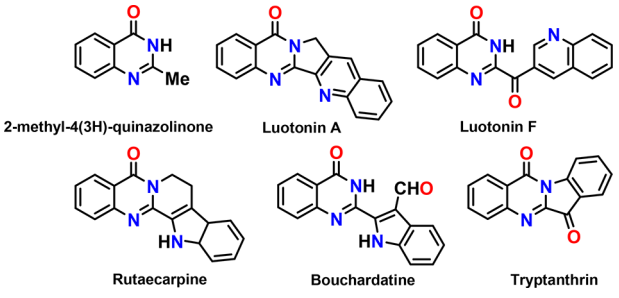
ABSTRACT: In this paper, we report a general, efficient, and environmentally benign method for the one-pot cascade synthesis of quinazolin-4(3*H*)-ones via acceptorless dehydrogenative coupling of *o*-aminobenzamide with alcohols catalyzed by a simple Ni(II) catalyst, [Ni(MeTAA)], featuring a tetraaza macrocyclic ligand (tetramethyltetraaza[14]annulene (MeTAA)). A wide variety of substituted quinazolin-4(3*H*)-ones were synthesized in high yields starting from readily available benzyl alcohols and *o*-aminobenzamides. Several controlled reactions along with deuterium labeling studies were carried out to establish the acceptorless dehydrogenative nature of the reactions.



INTRODUCTION

Quinazolin-4(3*H*)-ones are fundamental building blocks in nature and part of the backbone of more than 150 naturally occurring alkaloids and several biologically active compounds such as 2-methyl-4(3*H*)-quinazolinone, luotonin A, luotonin F, rutaecarpine, bouchardatine, tryptanthrin, etc. (Scheme 1).[1]

Scheme 1. Selected Examples of Quinazolin-4(3*H*)-one Skeleton Containing Natural Products



They are the crucial substructure of a wide variety of known pharmaceutical agents and drug candidates with antimicrobial,[2] anti-inflammatory,[3] anticonvulsant,[4] antihypertensive,[5] hypolipidemic,[6] sedative,[7] antitubercular,[8] antiviral,[9] antimalarial,[10] and anticancer[11] activities. Due to the immense importance as a pharmacophore in drug candidates, the quinazolin-4(3H)-one skeleton is assigned as privileged structure.[12]

Consequently, considerable efforts have been made over the years for their synthesis. Synthetic methods developed so far include fusion of anthranilic acid with amides, amidation of 2-aminobenzoic acids, and cascade reaction of aldehydes with *o*-aminobenzamide involving condensation followed by oxidation of the aminal intermediate.[13] All these synthetic routes involve multistep reaction sequences, and many of them require stoichiometric or excess amounts of strong oxidants such as DDQ,[14a] $CuCl_2$,[14b] MnO_2,[14c] $KMnO_4$,[14d] I_2,[14e] and *t*-BuOOH,[14f−h] and in most of the cases, the reactions are carried out at high temperature.[14] Another limitation associated with these methodologies is the use of relatively unstable aldehydes which are synthesized from readily available alcohols via oxidation with different toxic oxidants. Substituted 2-nitrobenzamides were also used as the starting precursor for cascade synthesis of quinazolin-4(3*H*)-ones.[15] Initial reduction of the nitro group followed by condensation with suitable coupling partners affords the desired quinazolin-4(3*H*)-ones. Other synthetic routes involve Cu-catalyzed N-arylation of 2-halobenzoic acid or its derivatives with ammonia, benzylamines, amidines, amino acids, and amides.[16] A few reports are also available on the Pd-catalyzed carbonylative synthesis of quinazolin-4(3*H*)-ones using gaseous CO.[17] Direct synthesis of carboxylic acids and their derivatives via palladium-catalyzed carbonylation of aryl halides and C−H bonds followed by intramolecular or intermolecular carboxamidation indeed represents a direct and convenient synthetic strategy for quinazolin-4(3*H*)-ones. Other synthetic routes include condensation of *o*-aminobenzamide with aryl methyl ketones[18] and keto alkynes.[19]

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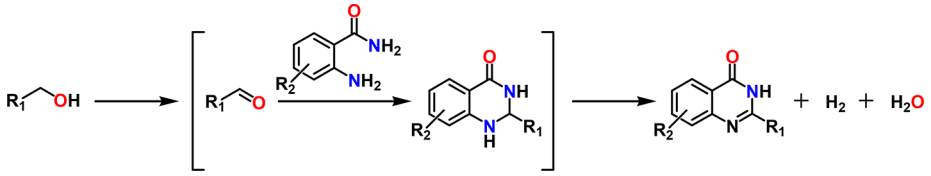
Scheme 2. Cascade Synthesis of Quinazolin-4(3*H*)-ones via Acceptorless Dehydrogenative Coupling of Alcohols and *o*-Aminobenzamides



An environmentally friendly and comparatively mild approach for the synthesis of quinazolin-4(3*H*)-ones is via acceptorless dehydrogenative cyclization of *o*-aminobenzamide or its derivatives with alcohols (Scheme 2).[20] Only hydrogen gas and H_2O are generated as chemical waste. Moreover, this method eliminates the use of preformed aldehydes which are relatively unstable at the reaction conditions, and the use of toxic strong oxidants can also be avoided. In recent years, a few groups used this concept to synthesize quinazolin-4(3*H*)-ones; however, in all cases, expensive heavy metals such as Ir,[20b−d] Pt,[20e] and Pd[20f] were used as catalysts. In 2011, Zhou and co-workers reported a one-pot oxidative cyclization of primary alcohols with *o*-aminobenzamides to quinazolin-4(3*H*)-ones catalyzed by iridium under hydrogen transfer conditions.[20b] In 2015, Li and co-workers reported the acceptorless dehydrogenative condensation of *o*-aminobenzamides with aldehydes to quinazolin-4(3*H*)-ones in water catalyzed by a water-soluble iridium catalyst.[20c] In 2016, using a different iridium catalyst, Li and co-workers also reported the synthesis of quinazolin-4(3*H*)-ones via acceptorless dehydrogenative coupling of *o*-aminobenzamides with the activation of methanol as a C1 source.[20d] Herein we report the one-pot synthesis of quinazolin-4(3*H*)-ones via acceptorless dehydrogenative coupling of *o*-aminobenzamides with benzyl alcohols catalyzed by a square planar Ni(II) complex ([Ni(MeTAA)]) featuring a tetraaza macrocyclic ligand (Figure 1).

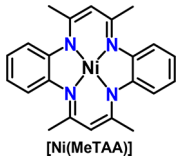


Figure 1. Catalyst used in this study.

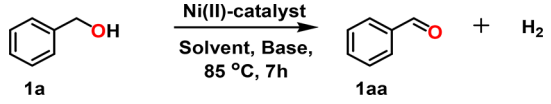
RESULTS AND DISCUSSION

The Ni(II)−macrocycle complex [Ni(MeTAA)] is the nickel(II) complex of the (tetramethyltetraaza[14]annulene (MeTAA)) ligand. It was synthesized following a known literature method.[21] The reaction of 2.0 equiv of 1,2-phenylenediamine, 2.0 equiv of 2,4-pentanedione, and excess nickel(II) acetate tetrahydrate in methanol under refluxing conditions for 48 h resulted in the formation of green-colored nickel(II) macrocyclic complex [Ni(MeTAA)] in almost quantitative yield. Characterization data of the Ni(II) complex thus obtained matched exactly with those reported previously.

The cascade synthesis of quinazolin-4(3*H*)-ones via acceptorless dehydrogenative cyclization of *o*-aminobenzamide or its derivatives with alcohols is believed to proceed through the initial dehydrogenative formation of aldehyde followed by condensation with *o*-aminobenzamide to form the cyclic aminal intermediate, which upon further dehydrogenation affords the desired quinazolin-4(3*H*)-ones (Scheme 2).[20] Therefore, our initial studies were focused on finding the optimal conditions for the acceptorless dehydrogenation of alcohols[22−24] using [Ni(MeTAA)] as the catalyst.

Optimization of the reaction conditions using benzyl alcohol as the model substrate revealed that the reaction proceeded most efficiently in nonpolar solvents such as toluene and xylene, whereas reactions in solvents of high polarities such as MeCN, dioxane, methanol, and DMF afforded poor yields (Table 1, entries 1−7). Among the series of bases examined,

Table 1. Optimization of the Reaction Conditions for the Dehydrogenation of Benzyl Alcohol (1a) Catalyzed by [Ni(MeTAA)][a]



entry	Ni(II) catalyst (concn, mol %)	solvent	base	yield[b] (%)
1	[Ni(MeTAA)] (3)	xylene	KO^{t}Bu	85
2	[Ni(MeTAA)] (3)	xylene	NaO^{t}Bu	93
3	[Ni(MeTAA)] (3)	toluene	NaO^{t}Bu	89
4	[Ni(MeTAA)] (3)	acetonitrile	NaO^{t}Bu	trace
5	[Ni(MeTAA)] (3)	methanol	NaO^{t}Bu	NR
6	[Ni(MeTAA)] (3)	ethanol	NaO^{t}Bu	NR
7	[Ni(MeTAA)] (3)	THF	NaO^{t}Bu	74
8	[Ni(MeTAA)] (3)	xylene	K_2CO_3	45
9	[Ni(MeTAA)] (3)	xylene	K_3PO_4	52
10	[Ni(MeTAA)] (3)	xylene	NaH	58
11	[Ni(MeTAA)] (3)	xylene	NaOH	82
12	[Ni(MeTAA)] (3)	xylene	Na_2CO_3	30
13	[Ni(MeTAA)] (3)	xylene	$NaHCO_3$	trace
14		xylene	NaO^{t}Bu	NR
15	[Ni(MeTAA)] (3)	xylene		NR
16	[Ni(MeTAA)] (2)	xylene	NaO^{t}Bu	87
17	$NiCl_2$ (10)	xylene	NaO^{t}Bu	NR
18	$Ni(OAc)_2$ (10)	xylene	NaO^{t}Bu	trace

[a]Stoichiometry: benzyl alcohol (1.0 mmol), catalyst (0.03 mmol), base (1.5 mmol, 1.5 equiv). [b]Isolated yields after column chromatography. NR = no reaction.

such as K_3PO_4, K_2CO_3, Na_2CO_3, $NaHCO_3$, NaH, NaO^{t}Bu, KO^{t}Bu, NaOMe, and NaOH, the best results were obtained with NaO^{t}Bu (Table 1, entries 1−13). The highest conversion of benzyl alcohol to benzaldehyde was achieved when the reaction was carried out at 85 °C in xylene for 7 h in the presence of NaO^{t}Bu using 3.0 mol % catalyst (Table 1, entry 2). Lowering the temperature or catalyst loading below 3.0 mol % leads to poor conversion of the alcohols to the corresponding aldehydes or ketones.

The stability of the catalytic system was checked in aerial conditions. The catalyst [Ni(MeTAA)] itself is air stable, and

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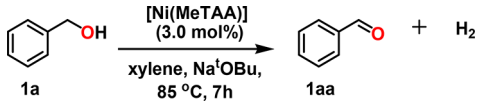
excellent conversion of alcohol to aldehyde was achieved when the reaction was carried out in the presence of air. However, the yield of the corresponding aldehyde or ketones decreased significantly when the reaction was carried out in a closed Schlenk tube (Table 2). This experimental observation is in

Table 2. Dehydrogenation of Benzyl Alcohol (1a) in Open/Closed Systems[a]



entry	open/closed	atmosphere	yield[b] (%)
1	open	Ar	93
2	open	air	80
3	closed	air/Ar	45

[a]Stoichiometry: benzyl alcohol (1.0 mmol), catalyst (0.03 mmol), base (1.5 mmol, 1.5 equiv). [b]Isolated yields after column chromatography.

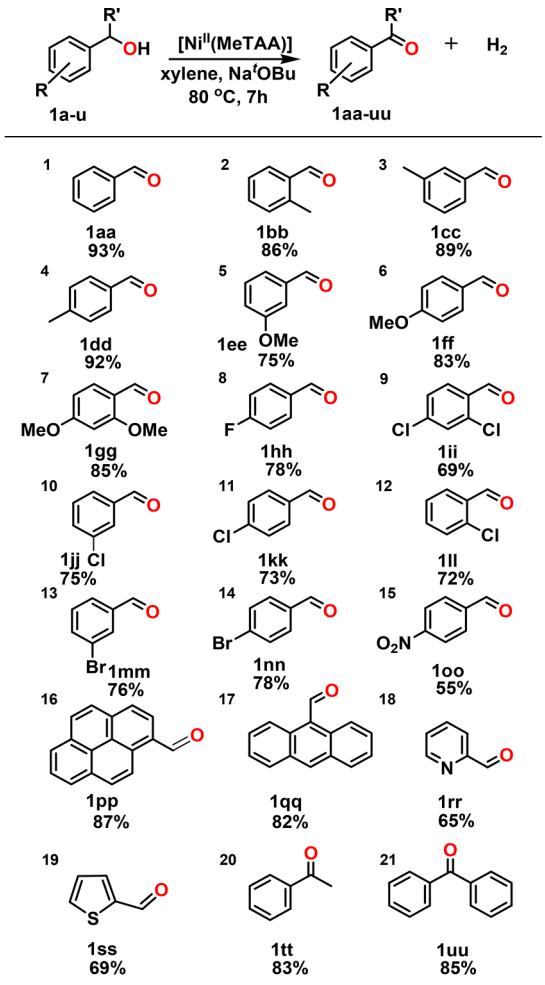
agreement with those for the other reported dehydrogenation reactions where the removal of H_2 from the reaction mixture is essential for the progress of the reaction.[23]

Controlled experiments showed that no product was obtained in the presence of only macrocyclic ligand and base, while other nickel(II) sources such as $NiCl_2$ and $Ni(OAc)_2$ (Table 1, entries 17 and 18) only afforded the corresponding aldehydes in trace amounts (<10%).

Various substituted alcohols with different electronic properties and functional groups were tested under the optimized reaction conditions. As shown in Table 3, excellent yields were obtained with alcohols containing electron-donating groups. Benzyl alcohols having −Me or −OMe groups at the *ortho*-, *para*-, or *meta*-positions afforded the corresponding aldehydes in high yield (Table 3, entries 2−7). Reactions also proceeded with electron-withdrawing groups at the *ortho*-, *para*-, or *meta*-positions of benzyl alcohols, albeit leading to lower yields (Table 3, entries 8−15). For example, 4-nitrobenzyl alcohol (**1o**) produces the corresponding aldehyde (**1oo**) in a moderate yield (55%) (Table 3, entry 15). 1-Pyrenecarboxaldehyde (**1pp**) and 9-anthracenecarboxaldehyde (**1qq**) were also isolated in high yields of 87% and 82%, respectively, from their corresponding alcohols (Table 3, entries 16 and 17). Heterocyclic alcohols were also found to produce the corresponding aldehydes (Table 3, entries 18 and 19). For example, 2-pyridinecarboxaldehyde (**1rr**) was obtained in 65% yield from 2-pyridinemethanol under the optimized reaction conditions. Secondary alcohols also undergo dehydrogenation to produce the corresponding ketones under the same optimized reaction conditions. 1-Phenylethanol or diphenylmethanol afforded acetophenone (**1tt**) and benzophenone (**1uu**) in high yields of 83 and 85%, respectively (Table 3, entries 20 and 21).

Once we had the results of alcohol dehydrogenation reactions in hand, we set out to study the acceptorless dehydrogenative coupling of *o*-aminobenzamide or its derivatives with alcohols to construct the quinazolin-4(3*H*)-one moiety using our nickel catalyst [Ni(MeTAA)]. As expected, the reaction of benzyl alcohol (**1a**) with *o*-aminobenzamide (**2a**) under the preoptimized reaction conditions (optimal conditions for alcohol dehydrogenation) produces 2-phenylquinazolin-4(3*H*)-one (**3aa**) in 40% isolated yield (Table 4, entry 1). Further optimization of the reaction conditions using

Table 3. Dehydrogenation of Various Alcohols Catalyzed by [Ni(MeTAA)][a,b]



[a]Stoichiometry: alcohol (1.0 mmol), catalyst (0.03 mmol), base (1.5 mmol, 1.5 equiv). [b]Isolated yields after column chromatography.

benzyl alcohol (**1a**) and *o*-aminobenzamide (**2a**) as model substrates revealed that the reaction proceeded most efficiently in xylene in the presence of NaO^tBu as the base at 100 °C. A longer reaction time is required for higher conversion, and increasing the catalyst loading from 3.0 to 5.0 mol % further increases the yield (Table 4, entry 11). Similar to the dehydrogenation of alcohols, a high yield of quinazolin-4(3*H*)-one was obtained when the reaction was carried out in the presence of argon under open conditions, and the yield decreased significantly when the reaction was carried out in a closed Schlenk tube (Table 5). Controlled reactions using other nickel(II) sources such as $NiCl_2$ and $Ni(OAc)_2$, however, failed to produce quinazolin-4(3*H*)-one under the optimized conditions (Table 4, entries 14 and 15). In all further catalytic syntheses of quinazolin-4(3*H*)-ones via acceptorless dehydrogenative coupling of *o*-aminobenzamide or its derivatives with alcohols, we therefore focused on reactions with [Ni(MeTAA)] (5 mol %) in xylene at 100 °C (Table 4, entry 11).

With the optimal conditions in hand (Table 4, entry 11), we explored the substrate scope and versatility of the developed [Ni(MeTAA)]-catalyzed cascade reaction. Coupling of *o*-aminobenzamide (**2a**) with various substituted benzyl alcohols was investigated under the optimal reaction conditions, and the

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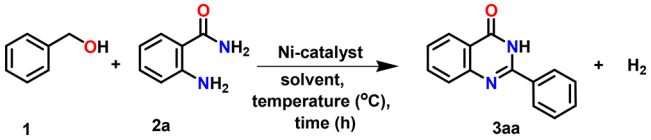
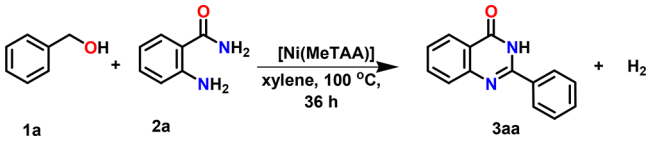
Table 4. Optimization of Reaction Conditions for the Dehydrogenative Coupling of Benzyl Alcohol (1a) and *o*-Aminobenzamide (2a) Catalyzed by [Ni(MeTAA)][a]



entry	Ni(II) catalyst (concn, mol %)	solvent	temp (°C)	time (h)	base	yield[b] (%)
1	[Ni(MeTAA)] (3)	xylene	85	7	NaO^{t}Bu	40
2	[Ni(MeTAA)] (3)	xylene	100	7	NaO^{t}Bu	45
3	[Ni(MeTAA)] (3)	xylene	100	36	NaO^{t}Bu	74
4	[Ni(MeTAA)] (3)	xylene	100	36	KO^{t}Bu	68
5	[Ni(MeTAA)] (3)	xylene	100	36	K_2CO_3	36
6	[Ni(MeTAA)] (3)	xylene	100	36	K_3PO_4	40
7	[Ni(MeTAA)] (3)	xylene	100	36	NaOH	65
8	[Ni(MeTAA)] (3)	xylene	100	36	Na_2CO_3	20
9	[Ni(MeTAA)] (3)	xylene	100	36	$NaHCO_3$	trace
10	[Ni(MeTAA)] (3)	xylene	100	36	NaH	56
11	[Ni(MeTAA)] (5)	xylene	100	36	NaO^{t}Bu	86
12		xylene	100	36	NaO^{t}Bu	NR
13	[Ni(MeTAA)] (5)	xylene	100	36		NR
14	$NiCl_2$ (10)	xylene	100	36	NaO^{t}Bu	NR
15	$Ni(OAc)_2$ (10)	xylene	100	36	NaO^{t}Bu	trace

[a]Stoichiometry: benzyl alcohol (**1a**) (1.1 mmol), *o*-aminobenzamide (**2a**) (1.0 mmol), base (1.5 mmol, 1.5 equiv). [b]Isolated yields after column chromatography. NR = no reaction.

Table 5. Dehydrogenative Coupling of Benzyl Alcohol (1a) and *o*-Aminobenzamide (2a) in Open/Closed Systems[a]



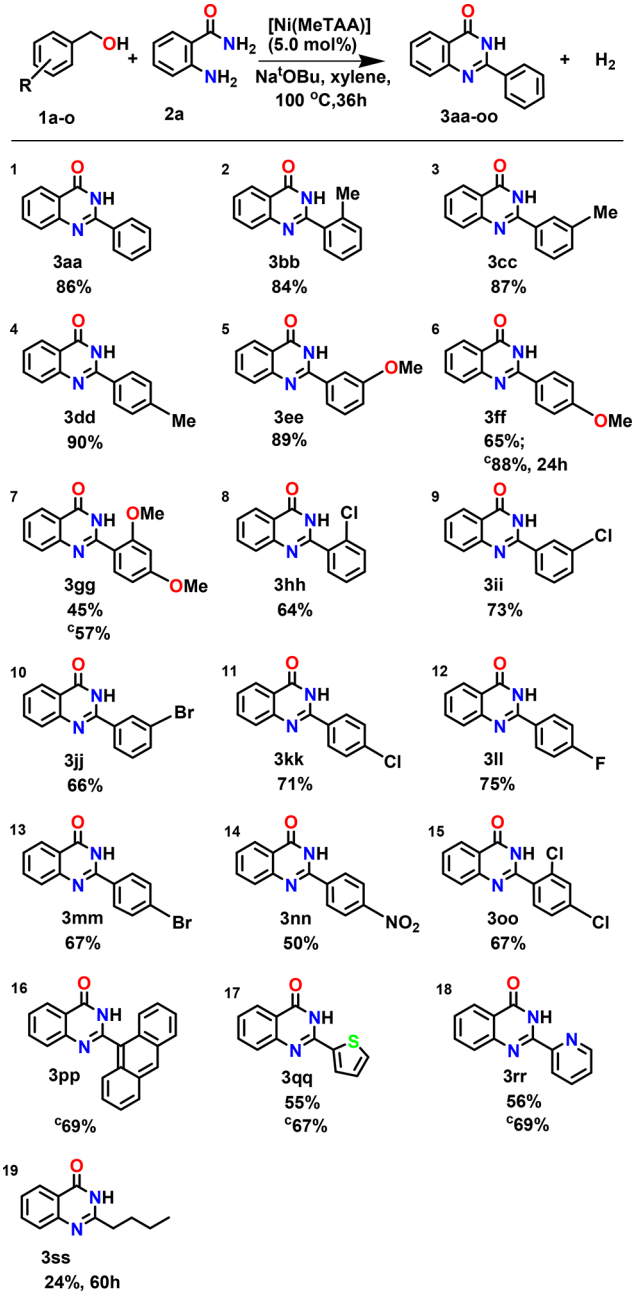
entry	open/closed	atmosphere	yield[b] (%)
1	open	Ar	86
2	open	air	74
3	closed	air/Ar	50

[a]Stoichiometry: benzyl alcohol (**1a**) (1.1 mmol), *o*-aminobenzamide (**2a**) (1.0 mmol), base (1.5 mmol, 1.5 equiv). [b]Isolated yields after column chromatography.

results are summarized in Table 6. Excellent yields of quinazolin-4(3*H*)-ones were obtained with alcohols containing electron-donating groups. Benzyl alcohols having methyl substituents at *ortho*-, *meta*-, or *para*-positions (Table 6, entries 2−4) produced the corresponding quinazolin-4(3*H*)-ones in 84%, 87%, and 90% isolated yields, respectively. The presence of the electron-donating −OMe group in the benzyl alcohols further increases the yield (Table 6, entry 5). Reaction of 3-methoxybenzyl alcohol with *o*-aminobenzamide was found to produce the corresponding quinazolin-4(3*H*)-one in 89% isolated yield (Table 6, entry 5). However, starting from 4-methoxybenzyl alcohol, only a 65% yield of 2-(4-methoxyphenyl)quinazolin-4(3*H*)-one (**3ff**) was isolated. Addition of styrene as a sacrificial hydrogen acceptor,[20b] however, improves the yield of 2-(4-methoxyphenyl)quinazolin-4(3*H*)-one to 88%.

Reactions also proceeded with electron-withdrawing groups at the *ortho*-, *meta*-, or *para*-positions of benzyl alcohols, albeit

Table 6. Dehydrogenative Coupling of *o*-Aminobenzamide with Various Benzyl Alcohols Catalyzed by [Ni(MeTAA)][a−c]



[a]Stoichiometry: benzyl alcohol (1.1 mmol), *o*-aminobenzamide (1.0 mmol), base (1.5 mmol, 1.5 equiv). [b]Isolated yields after column chromatography. [c]Styrene was added as an additive.

leading to lower yields and requiring a longer reaction time (Table 6, entries 7−12). For example, the coupling of *o*-aminobenzamide (**2a**) with 4-nitrobenzyl alcohol (**1o**) afforded the corresponding quinazolin-4(3*H*)-one in a moderate yield (Table 6, entry 14). This may be attributed to the lower reactivity of benzyl alcohols with electron-withdrawing groups to form the corresponding aldehydes via [Ni(MeTAA)]-catalyzed acceptorless dehydrogenation as observed earlier (Table 3, entry 15). 9-Anthracenemethanol was also found to be a suitable coupling partner; the desired quinazolin-4(3*H*)-

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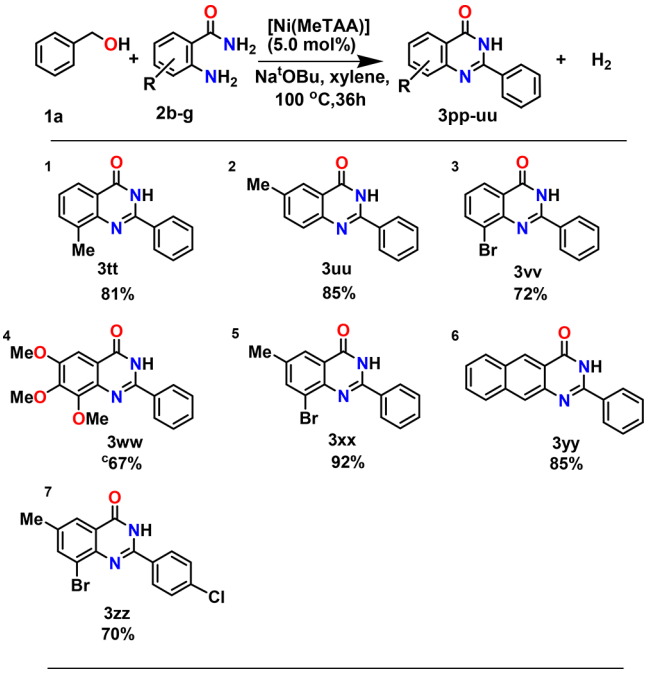
one (**3pp**) was isolated in 69% yield in the presence of styrene as the sacrificial hydrogen abstractor (Table 6, entry 16). Starting from heterocyclic alcohols, such as 2-thiophenemethanol or 2-pyridinemethanol, the corresponding quinazolin-4(3*H*)-ones were obtained in 67% and 69% isolated yields in the presence of styrene as the sacrificial hydrogen abstractor (Table 6, entries 17 and 18). Aliphatic alcohols were also found to be suitable coupling partners, albeit leading to lower yields and requiring a longer reaction time. Reaction of 1-pentanol with *o*-aminobenzamide (**2a**) afforded the corresponding quinazolin-4(3*H*)-one (**3ss**) in 24% isolated yield (Table 6, entry 19) in 60 h.

To further expand the substrate scope, various substituted *o*-aminobenzamides were employed as substrates to test the catalytic formation of quinazolin-4(3*H*)-ones using benzyl alcohol (**1a**) as the reaction partner. As shown in Table 7, *o*-

Table 7. Dehydrogenative Coupling of Various *o*-Aminobenzamides with Benzyl Alcohol Catalyzed by [Ni(MeTAA)][a–c]



[a]Stoichiometry: benzyl alcohol (1.1 mmol), *o*-aminobenzamide (1.0 mmol), base (1.5 mmol, 1.5 equiv). [b]Isolated yields after column chromatography. [c]Styrene was added as an additive.

aminobenzamides with either electron-donating or electron-withdrawing groups were all effective, affording the corresponding quinazolin-4(3*H*)-ones in good yields (Table 7, entries 1–3). *o*-Aminobenzamide bearing multiple electron-donating groups, such as trimethoxy, produced the corresponding quinazolin-4(3*H*)-one (**3ww**) in 67% yield (Table 7, entry 4). Reactions also proceeded with *o*-aminobenzamide bearing both electron-donating and electron-withdrawing groups, and the corresponding quinazolin-4(3*H*)-one (**3xx**) was isolated in 92% yield (Table 7, entry 5). 3-Aminonaphthalene-2-carboxamide was also found to be a suitable coupling partner, affording the 2-phenylbenzo[*g*]quinazolin-4(3*H*)-one (**3yy**) in 85% yield.

To explore the reaction mechanism, to check the dehydrogenative nature of the catalytic reactions, and to confirm H_2 evolution during the cascade synthesis of quinazolin-4(3*H*)-ones, several controlled reactions were carried out. Initial experiments were focused on the [Ni(MeTAA)]-catalyzed dehydrogenation of alcohols.

Intermolecular hydrogen transfer experiments were carried out to make use of the H_2 liberated during dehydrogenation of alcohols to reduce easily reducible substrates (Scheme 3). When the dehydrogenation of diphenylmethanol (**1u**) was carried out separately in the presence of 2,4-dimethoxybenzaldehyde (**1gg**) in a closed system, benzophenone (**1uu**) was obtained in 40% yield and 2,4-dimethoxybenzyl alcohol (**1g**) was obtained as the hydrogenated product of 2,4-dimethoxybenzaldehyde. However, when the reaction was carried out in an open condition under an argon atmosphere, the hydrogen transfer reactions were found to be slowed by some extent. A total of 65% of H_2 was found to be transferred to the corresponding aldehyde when the reaction was carried out in a closed condition, whereas transfer of only 40% of H_2 occurred when the reaction was carried out in an open condition under an argon atmosphere.

To further confirm the H_2 evolution, hydrogenation of styrene was carried out using Pd/C catalyst using the H_2 liberated during dehydrogenation of diphenylmethanol (**1u**) catalyzed by [Ni(MeTAA)]. In a typical experiment, the dehydrogenation reactions were carried out in a flask connected through a rubber tube with a second flask containing styrene and a catalytic amount of Pd/C in THF. The H_2 gas liberated in the first flask during the dehydrogenation of diphenylmethanol (**1u**) was found to reduce styrene present in the second flask (S69). These experimental results along with the available literature data indeed conclusively support the acceptorless dehydrogenation of alcohols catalyzed by [Ni(MeTAA)].[22−24]

To further confirm the H_2 evolution, intermolecular transfer hydrogenation reactions were carried out with deuterium-labeled compound **1u**-d_2 (Scheme 3). When the dehydrogenation of deuterated diphenylmethanol (**1u**-d_2) was carried out in the presence of 2,4-dimethoxybenzaldehyde (**1gg**) in a closed system, benzophenone was obtained, and deuterium exchange was observed in 2,4-dimethoxybenzyl alcohol (**1g**-d_2), the deuterated product of 2,4-dimethoxybenzaldehyde (**1g**).

Once the acceptorless dehydrogenative nature of alcohol oxidation is confirmed, we synthesized the cyclic aminal 2,3-dihydro-2-phenylquinazolin-4(1*H*)-one (**4**) via direct condensation of *o*-aminobenzamide and benzaldehyde (Scheme 4). Interestingly, 2,3-dihydro-2-phenylquinazolin-4(1*H*)-one (**4**), when heated in the presence of NaᵗBuO and [Ni(MeTAA)] under the optimized catalytic conditions, afforded the desired 2-phenylquinazolin-4(3*H*)-one (**3aa**) in 90% isolated yield.

To confirm the H_2 evolution during the [Ni(MeTAA)]-catalyzed dehydrogenative transformation of the cyclic aminal, 2,3-dihydro-2-phenylquinazolin-4(1*H*)-one (**4**) to 2-phenylquinazolin-4(3*H*)-one (**3aa**), this catalytic transformation was carried out in the presence of a sacrificial hydrogen abstractor such as 2,4-dimethoxybenzaldehyde (**1gg**). To our desire, as observed earlier during the dehydrogenation of alcohols, 2,4-dimethoxybenzyl alcohol (**1g**) was isolated as the hydrogenated product of 2,4-dimethoxybenzaldehyde (**1gg**) (Scheme 5). Deuterium labeling experiments were also carried out starting from the deuterium-labeled cyclic aminal **4**-*d*, synthesized from the direct coupling of benzaldehyde-α-d_1 with *o*-aminobenzamide. Deuterium exchange was observed when the cyclic aminal **4**-*d* was heated in the presence of the catalyst [Ni(MeTAA)] and 2,4-dimethoxybenzaldehyde, under the optimized reaction conditions (Scheme 5).

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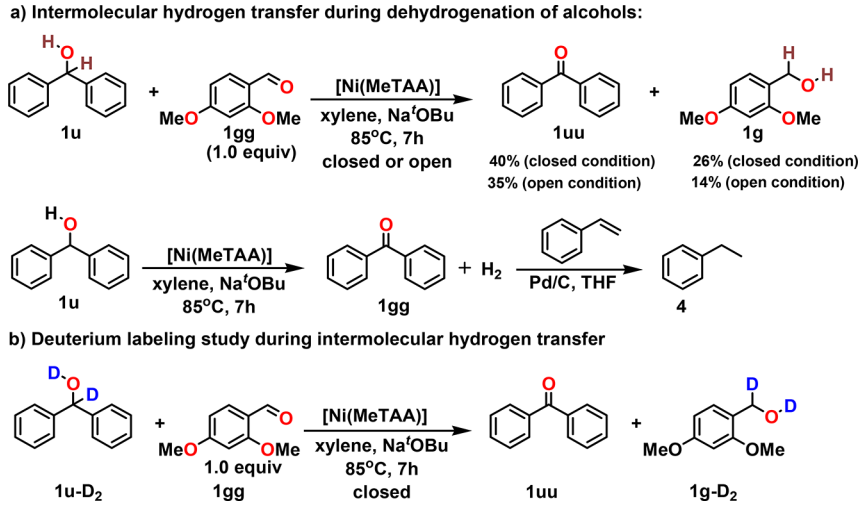
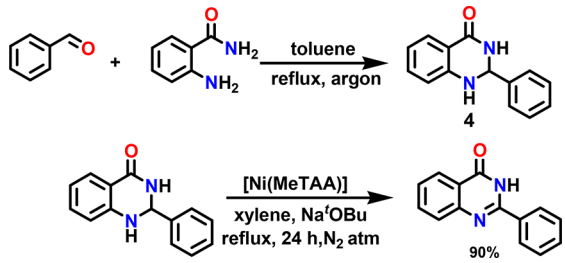
Scheme 3. Controlled Experiments during Dehydrogenation of Alcohols



Scheme 4. [Ni(MeTAA)]-Catalyzed Dehydrogenation of Aminal



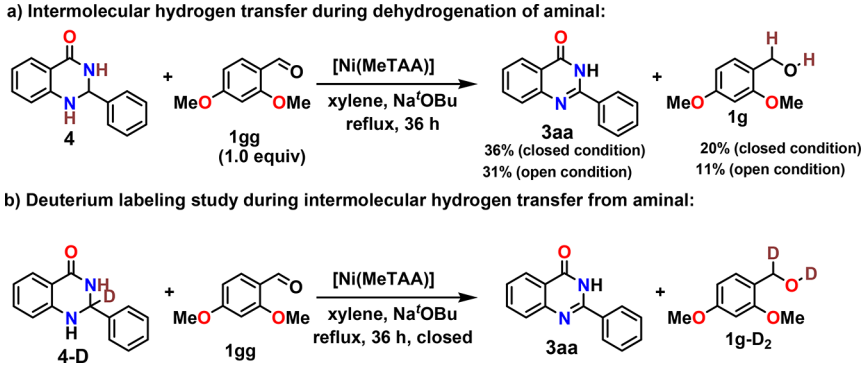
Attempts were also made to quantify the liberated hydrogen during both dehydrogenation of alcohol and dehydrogenative coupling of *o*-aminobenzamide and alcohols using a gas burette. After repeated experiments, a nearly 67% theoretical yield of hydrogen was measured in our experimental conditions during dehydrogenation of diphenylmethanol (**1u**) and a 70% theoretical yield of hydrogen was measured during dehydrogenative coupling of *o*-aminobenzamide (**2a**) and benzyl alcohol (**1a**) (see the Experimental Section for details).

On the basis of the above experimental results along with the available literature,[20] a plausible mechanism for the present [Ni(MeTAA)]-catalyzed acceptorless dehydrogenative coupling of *o*-aminobenzamide or its derivatives with alcohols for the construction of quinazolin-4(3*H*)-ones is depicted in Scheme 6. The reaction is believed to proceed via the formation of an alkoxynickel species (**A**), which undergoes *β*-H elimination to afford a nickel hydride species (**B**) and aldehyde. The nickel hydride species (**B**) releases gaseous hydrogen upon reaction with a second molecule of alcohol with the regeneration of the nickel alkoxide (**A**). The aldehyde, generated in situ, then undergoes condensation with *o*-aminobenzamide to produce the cyclic aminal (**C**). In cycle II, the cyclic aminal (**C**) thus generated affords an aminonickel species (**D**), which upon *β*-H elimination produces quinazolin-4(3*H*)-ones with the liberation of H_2.[20]

CONCLUSION

In summary, we have reported a general and efficient method for the one-pot cascade synthesis of quinazolin-4(3*H*)-ones via acceptorless dehydrogenative coupling of *o*-aminobenzamides with alcohols catalyzed by a cheap and earth-abundant simple Ni(II) catalyst, [Ni(MeTAA)]. This straightforward methodology is economical and practical and has a broad substrate scope. A wide variety of desired quinazolin-4(3*H*)-ones were obtained in high yields starting from readily available starting materials. These results indeed open up an opportunity for the construction of diverse and useful organic molecules of biomedicinal importance using similar cheap and earth-abundant nickel catalysts.

Scheme 5. Controlled Experiments during Dehydrogenation of Aminal



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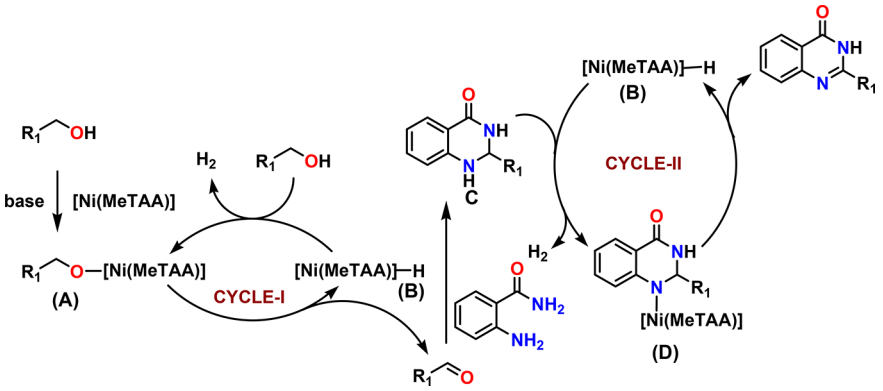
Scheme 6. Proposed Reaction Mechanism



EXPERIMENTAL SECTION

General Information. All reactions were carried out using standard Schlenk techniques under an argon atmosphere. Tetrahydrofuran (THF), toluene, xylene, and 1,4-dioxane were refluxed over sodium/benzophenone, distilled under an argon atmosphere, and stored over 4 Å molecular sieves. All other chemicals were purchased from commercial suppliers and used as received without further purification. Analytical TLC was performed on a Merck 60 F254 silica gel plate (0.25 mm thickness), and column chromatography was performed on Merck 60 silica gel (60−120 mesh). During purification of the reaction mixture of some of the controlled experiments, preparative TLC was used. ^{1}H NMR spectra were recorded on Bruker DPX-300 (300 MHz), Bruker DPX-400 (400 MHz), and Bruker DPX-500 (500 MHz) spectrometers. TMS (tetramethylsilane) was used as the internal standard. ESI mass spectra were recorded on a Micromass Q-TOF mass spectrometer (serial no. YA 263). A PerkinElmer 240C elemental analyzer was used to collect microanalytical data (C, H, N). GC analysis was performed on a 7980A GC system from Agilent Technologies equipped with an FID detector and a J&W HP-5 column.

Synthesis of Ni(II) Catalyst [Ni(MeTAA)]. [Ni(MeTAA)] was synthesized following a known literature method.[21] Reaction of 2.0 equiv of 1,2-phenylenediamine, 2.0 equiv of 2,4-pentanedione, and excess nickel(II) acetate tetrahydrate in methanol under refluxing conditions for 48 h resulted in the formation of green-colored [Ni(MeTAA)] in nearly quantitative yield.

General Procedure for Dehydrogenation of Alcohols. Under an argon atmosphere, a mixture of [Ni(MeTAA)] (0.03 mmol) and NaO^{t}Bu (1.5 mmol) was added to a flame-dried Schlenk tube. The tube was capped with a Teflon screw cap, evacuated, and backfilled with argon. The screw cap was replaced with a rubber septum, and a balloon filled with argon was inserted using a long-neck needle. Alcohol (1.0 mmol) dissolved in 5 mL of xylene was added to the Schlenk tube via a syringe. The Schlenk tube was then placed in an oil bath and heated at 85 °C for a set period. Once the reaction was finished, the resulting mixture was concentrated, volatiles were removed in vacuum, and the residue was purified by column chromatography using silica.

General Procedure for Dehydrogenative Coupling of Alcohols and *o*-Aminobenzamides. Under an argon atmosphere, a mixture of [Ni(MeTAA)] (0.05 mmol), NaO^{t}Bu (1.5 mmol), and *o*-aminobenzamide (1.0 mmol) was added to a flame-dried Schlenk tube. Alcohol (1.10 mmol) dissolved in 10 mL of xylene was added to the Schlenk tube once via a syringe. A balloon filled with argon was inserted into the Schlenk tube using a long-neck needle. The Schlenk tube was then placed in an oil bath and heated at 100 °C for a set period. After the reaction was finished, the resulting mixture was concentrated and the residue was purified by flash chromatography (silica gel).

Hydrogenation of Styrene by Evolved Hydrogen during Alcohol Oxidation. Under an argon atmosphere, a mixture of [Ni(MeTAA)] (0.03 mmol) and NaO^{t}Bu (1.5 mmol) was added to a flame-dried Schlenk tube connected through a rubber tube to another Schlenk tube in which styrene (1.0 mmol) and Pd/C (0.5 g) were placed in THF with a magnetic stirrer. The tube was capped with a Teflon screw cap, evacuated, and backfilled with argon. The screw cap was replaced with a rubber septum. Alcohol (1.0 mmol) dissolved in 5 mL of xylene was added to the first Schlenk tube via a syringe. The Schlenk tube was then placed in an oil bath and heated at 100 °C for 36 h. GC analysis of the reaction mixture present in the second Schlenk containing styrene revealed the conversion of styrene to ethylbenzene.

Volumetric Estimation of Evolved Hydrogen. *During [Ni(MeTAA)]-Catalyzed Dehydrogenation of Alcohol.* Diphenylmethanol (**1u**) (1.0 mmol), [Ni(MeTAA)] (0.03 mmol), and NaO^{t}Bu (1.5 mmol) in 5 mL of xylene were placed in an oven-dried 25 mL Schlenk tube connected to a gas burette. The Schlenk tube was then placed in an oil bath preheated at 85 °C. The reaction was continued until evolution of gas ceased. The experiment was repeated multiple times to get consistent readings. The volume of water displaced was found to be 17.5 mL. The number of moles of hydrogen evolved was calculated by taking into account the vapor pressure of water at 304 K (33.7 Torr), the volume of water displaced (17.5 mL), the atmospheric pressure (761.3126 Torr), and R = 62.3635 L Torr K^{-1} mol^{-1}: $n(H_2) = [(P_{atm} - P_{water})V]/RT$ = 0.000672 mol, expected value 0.001 mol.[24]

During [Ni(MeTAA)]-Catalyzed Dehydrogenative Coupling of Alcohols and o-Aminobenzamide. Benzyl alcohol (**1a**) (1.10 mmol), *o*-aminobenzamide (**2a**) (1.0 mmol), [Ni(MeTAA)] (0.05 mmol), and NaO^{t}Bu (1.5 mmol) in 5 mL of xylene were placed in an oven-dried 25 mL Schlenk tube connected to a gas burette. The Schlenck tube was then placed in an oil bath preheated at 100 °C. The reaction was continued for 36 h. The experiment was repeated multiple times to get consistent readings. The volume of water displaced was found to be 38 mL. The number of moles of hydrogen evolved was calculated by taking into account the vapor pressure of water at 304 K (33.7 Torr), the volume of water displaced (38 mL), the atmospheric pressure (761.3126 Torr), and R = 62.3635 L Torr K^{-1} mol^{-1}: $n(H_2) = [(P_{atm} - P_{water})V]/RT$ = 0.001475 mol, expected value 0.0021 mol.[24]

Characterization Data of the Isolated Compounds. *Characterization Data for the Carbonyl Compounds. Benzaldehyde (**1aa**).*[25] Eluent: petroleum ether/dichloromethane (4:1). Colorless liquid (98 mg, 93%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 10.06 (s, 1H), 7.92 (d, J = 8.0 Hz, 2H), 7.67 (t, J = 8.0 Hz, 1H), 7.57 (t, J = 8.0 Hz, 2H).

*2-Methylbenzaldehyde (**1bb**).*[25e,f] Eluent: petroleum ether/dichloromethane (4:1). Colorless liquid (103 mg, 86%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 10.28 (s, 1H), 7.80 (d, J = 12 Hz, 1H), 7.47 (t, J = 8.0 Hz, 1H), 7.36 (t, J = 8.0 Hz, 1H), 7.24 (d, J = 8.0 Hz, 1H), 2.68 (s, 3H).

*3-Methylbenzaldehyde (**1cc**).*[25c,e] Eluent: petroleum ether/dichloromethane (4:1). Colorless liquid (107 mg, 89%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 9.97 (s, 1H), 7.66 (d, J = 4.0 Hz, 2H), 7.38 (t, J = 8.0 Hz, 2H), 2.41 (s, 3H).

*4-Methylbenzaldehyde (**1dd**).*[25c,e,f] Eluent: petroleum ether/dichloromethane (4:1). Colorless liquid (111 mg, 92%). ^{1}H NMR

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(400 MHz, $CDCl_3$): δ (ppm) = 9.89 (s, 1H), 7.75 (d, J = 8.0 Hz, 2H), 7.29 (d, J = 8.0 Hz, 2H), 2.38 (s, 3H).

3-Methoxybenzaldehyde (**1ee**).[25a,c,e] Eluent: petroleum ether/dichloromethane (4:1). Yellow liquid (92 mg, 75%). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 9.86 (t, J = 5.0 Hz, 1H), 7.26−7.35 (m, 3H), 7.06−7.07 (m, 1H), 3.74 (t, J = 5.5 Hz, 3H).

4-Methoxybenzaldehyde (**1ff**).[25a−c] Eluent: petroleum ether/dichloromethane (4:1). Yellow liquid (113 mg, 83%). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 9.84 (s, 1H), 7.80 (d, J = 8.7 Hz, 2H), 6.97 (d, J = 8.6 Hz, 2H), 3.85 (s, 3H).

2,4-Dimethoxybenzaldehyde (**1gg**).[25b−d] Eluent: petroleum ether/dichloromethane (4:1). White solid (141 mg, 85%). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 10.28 (s, 1H), 7.80 (d, J = 8.7 Hz, 1H), 6.52 (t, J = 8.7 Hz, 2H), 3.88 (d, J = 7.71 Hz, 6H).

4-Fluorobenzaldehyde (**1hh**).[25a] Eluent: petroleum ether/dichloromethane (4:1). Yellow liquid (96 mg, 78%). ^{1}H NMR (500 MHz, CDCl3): δ (ppm) = 9.96 (s, 1H), 7.89−7.93 (m, 2H),7.19−7.24 (m, 2H).

2,4-Dichlorobenzaldehyde(**1ii**).[25h] Eluent: petroleum ether/dichloromethane (4:1). Light yellow crystalline powder (121 mg, 69%). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 10.41 (s, 1H), 7.87 (d, J = 8.37 Hz, 1H), 7.48 (d, J = 8.20 Hz, 1H), 7.38 (d, J = 8.37 Hz, 1H).

3-Chlorobenzaldehyde (**1jj**).[25g] Eluent: petroleum ether/dichloromethane (4:1). Light yellow liquid (105 mg, 75%). ^{1}H NMR (500 MHz, CDCl3): δ (ppm) = 9.97 (s, 1H), 7.83 (t, J = 1.7 Hz, 1H), 7.75−7.79 (m, 1H), 7.56−7.60 (m, 1H), 7.46 (t, J = 7.7 Hz, 1H).

4-Chlorobenzaldehyde (**1kk**).[25c−e] Eluent: petroleum ether/dichloromethane (4:1). White solid (103 mg, 73%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 9.98 (s, 1H), 7.81−7.84 (m, 2H), 7.52 (d, J = 8.4 Hz, 2H).

2-Chlorobenzaldehyde (**1ll**).[25d] Eluent: petroleum ether/dichloromethane (4:1). Brown liquid (101 mg, 72%). ^{1}H NMR (4 00 MHz, $CDCl_3$): δ (ppm) = 10.50 (s, 1H), 7.53 (d, J = 8.19 Hz, 1H), 7.26 (s, 2H), 7.08 (d, J = 8.0 Hz, 1H).

3-Bromobenzaldehyde (**1mm**).[25f] Eluent: petroleum ether/dichloromethane (4:1). Yellow liquid (141 mg, 76%)^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 9.95 (s, 1H), 7.98 (d, J = 0.4 Hz, 1H), 7.82−7.72 (m, 2H), 7.44−7.40 (m, 1H).

4-Bromobenzaldehyde (**1nn**).[25a] Eluent: petroleum ether/dichloromethane (4:1). White crystalline solid (144 mg, 78%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 9.95 (s, 1H), 7.51−7.94 (m, 4H).

4-Nitrobenzaldehyde (**1oo**).[25] Eluent: petroleum ether/dichloromethane (4:1). Slightly yellow crystalline powder (83 mg, 55%). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 10.10 (s, 1H), 8.34 (d, J = 8.1 Hz, 2H), 8.02 (d, J = 9.3 Hz, 2H).

Pyrene 1-aldehyde (**1pp**).[22e] Eluent: petroleum ether/dichloromethane (4:1). Dark yellow solid (200 mg, 87%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 10.80 (s, 1H), 9.45 (d, J = 8.0 Hz, 1H), 8.47 (d, J = 8.0 Hz, 1H), 8.24−8.35 (m, 5H), 8.12 (d, J = 10.0, 2H).

Anthracene-9-carbaldehyde (**1qq**).[25c] Eluent: petroleum ether/dichloromethane (4:1). Yellow solid (169 mg, 82%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 11.43 (s, 1H), 8.91 (d, J = 7.2 Hz, 2H), 8.56 (s, 1H), 7.97 (d, J = 6.4 Hz, 2H), 7.60−7.63 (m, 2H), 7.49 (t, J = 6.0, 1H).

Pyridine-2-carbaldehyde (**1rr**).[25a,b] Eluent: petroleum ether/dichloromethane (4:1). Yellow liquid (70 mg, 65%). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 10.05 (s, 1H), 8.77 (d, J = 3.6 Hz, 1H), 7.83−7.95 (m, 2H), 7.51 (t, J = 5.0 Hz, 1H).

Thiophene-2-carbaldehyde (**1ss**).[25a−c] Eluent: petroleum ether/dichloromethane (4:1). Light brown liquid (77 mg, 69%). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 9.93 (s, 1H), 7.77−7.80 (m, 2H), 7.19 (d, J = 2.7 Hz, 1H).

Acetophenone (**1tt**).[23a] Eluent: petroleum ether/dichloromethane (4:1). Colorless liquid (100 mg, 83%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.85 (t, J = 7.6 Hz, 2H), 7.43−7.47 (m, 1H), 7.35 (t, J = 7.6 Hz, 2H), 2.48 (d, J = 1.2 Hz, 3H).

Benzophenone (**1uu**).[23a,25f] Eluent: petroleum ether/dichloromethane (4:1). White solid (155 mg, 85%). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) = 7.80 (t, J = 7.2 Hz, 4H), 7.58 (t, J = 6.4 Hz, 2H), 7.48 (t, J = 6.0 Hz, 4H).

Characterization Data for the Quinazolin-4-(3H)-ones. 2-Phenylquinazolin-4(3H)-one (**3aa**).[16a,20b] Eluent: petroleum ether/ethyl acetate (3:1). White solid (191 mg, 86%). Mp: 239−241 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 12.53 (s, 1H), 8.15−8.20 (m, 3H), 7.81−7.85 (m, 1H), 7.74 (d, J = 7.89 Hz, 1H), 7.50−7.61 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 162.1, 152.2, 148.6, 134.5, 132.6, 131.3, 128.5, 127.7, 125.8, 127.4, 126.5, 125.8, 120.9.

2-(o-Tolyl)quinazolin-4(3H)-one (**3bb**).[19] Eluent: petroleum ether/ethyl acetate (3:1). White solid (198 mg, 84%). Mp: 223−224 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 12.43 (s, 1H), 8.18 (dd, J = 7.9, 1.03 Hz, 1H), 7.81−7.85 (m, 1H), 7.69 (d, J = 8.07 Hz, 1H), 7.50−7.56 (m, 2H), 7.43 (td, J = 7.68, 1.1 Hz, 1H), 7.31−7.36 (m, 2H), 2.39 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 161.7, 154.3, 148.6, 136.0, 134.3, 134.1, 130.4, 129.8, 129.0, 127.3, 126.5, 125.7, 125.6, 120.9, 19.5.

2-m-Tolylquinazolin-4(3H)-one (**3cc**).[14g,20b] Eluent: petroleum ether/ethyl acetate (3:1). White solid (206 mg, 87%). Mp: 210−212 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 12.46 (s, 1H), 8.15 (dd, J = 7.83, 1.06 Hz, 1H), 8.03 (s, 1H), 7.97 (d, J = 8.0 Hz, 1H), 7.85−7.81 (m, 1H), 7.74 (d, J = 8.0 Hz, 1H), 7.49−7.53 (m, 1H), 7.39−7.45 (m, 2H), 2.40 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 162.1, 152.3, 148.7, 137.8, 134.5, 132.5, 131.9, 128.4, 128.2, 127.4,126.4, 125.7, 124.8, 120.9, 20.9.

2-(p-Tolyl)quinazolin-4(3H)-one (**3dd**).[19,20b] Eluent: petroleum ether/ethyl acetate (3:1). White solid (213 mg, 90%). Mp: 245−246 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 12.45 (s, 1H), 8.16 (dd, J = 7.84, 1.1 Hz, 1H), 8.1 (d, J = 8.2 Hz, 2H), 7.80−7.84 (m, 1H), 7.72 (d, J = 7.84 Hz, 1H), 7.48−7.52 (m,1H), 7.34 (d, J = 8.17 Hz, 2H), 2.38 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 162.2, 152.2, 148.7, 141.4, 134.4, 129.8, 129.1, 127.6, 127.2, 126.3, 125.8, 120.8, 20.9.

2-(3-Methoxyphenyl)quinazolin-4(3H)-one (**3ee**).[14g,20b] Eluent: petroleum ether/ethyl acetate (3:1). White solid (225 mg, 89%). Mp: 210−211 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 12.51 (s, 1H), 8.16 (dd, J = 7.92, 1.09 Hz, 1H), 7.78−7.86 (m, 2H), 7.75−7.74 (m, 2H), 7.43−7.54 (m, 2H), 7.15 (dd, J = 8.03, 2.13 Hz, 1H), 3.87 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 162.9, 159.8, 152.2, 149.1, 147.6, 135.1, 134.5, 130.2, 127.1, 126.3, 121.5, 120.6, 118.1, 113.0, 55.9.

2-(4-Methoxyphenyl)quinazolin-4(3H)-one (**3ff**).[14g,20b,19] Eluent: petroleum ether/ethyl acetate (3:1). White solid (222 mg, 88%). Mp: 240−241 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 12.39 (s. 1H), 8.21−8.17 (m, 2H), 8.13 (dd, J = 7.9, 1.6 Hz, 1H), 7.79−7.83 (m, 1H), 7.69−7.71 (m, 1H), 7.46−7.50 (m, 1H), 7.07−7.11 (m, 2H), 3.85 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 162.2, 161.8, 151.8, 148.7, 134.4, 129.4, 127.2, 126.0, 125.7, 124.7, 120.6, 113.9, 55.4.

2-(2,4-Dimethoxyphenyl)quinazolin-4(3H)-one (**3gg**).[19b] Eluent: petroleum ether/ethyl acetate (3:1). White solid (161 mg, 57%). Mp: 205−206 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 8.16 (d, J = 9.0 Hz, 1H), 7.81 (d, J = 8.9 Hz, 1H), 7.64 (d, J = 10.4 Hz, 1H), 7.55 (d, J = 9.5 Hz, 1H), 7.36 (d, J = 10.9 Hz, 1H), 6.69 (t, J = 8.8 Hz, 1H), 3.84 (s, 3H), 3.79 (s, 3H).

2-(2-Chlorophenyl)quinazolin-4(3H)-one (**3hh**).[14g,20b] Eluent: petroleum ether/ethyl acetate (3:1). White solid (164 mg, 64%). Mp: 195−196 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) = 12.53 (s, 1H), 8.16 (t, J = 6.81 Hz, 3H), 7.83 (t, J = 7.2 Hz, 1H), 7.73 (d, J = 8.1 Hz, 1H), 7.49−7.38 (m, 3H).

2-(3-Chlorophenyl)quinazolin-4(3H)-one (**3ii**).[19b,20b] Eluent: petroleum ether/ethyl acetate (3:1). White solid (187 mg, 73%). Mp: 295−296 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 12.61 (s, 1H), 8.23 (s,1H), 8.15 (d, J = 9.6 Hz, 2H), 7.83 (d, J = 9.08 Hz, 1H), 7.76 (d, J = 10.4 Hz, 1H), 7.54−7.64 (m, 3H).

2-(3-Bromophenyl)quinazolin-4(3H)-one (**3jj**).[20b] Eluent: petroleum ether/ethyl acetate (3:1). White solid (199 mg, 66%). Mp: 296−297 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) = 8.37 (s, 1H), 8.17 (t, J = 7.62 Hz, 2H), 7.76−7.83 (m, 3H), 7.51 (d, J = 6.38 Hz, 2H).

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2-(4-Chlorophenyl)quinazolin-4(3H)-one (**3kk**).[14g,19,20b] Eluent: petroleum ether/ethyl acetate (3:1). White solid (182 mg, 71%). Mp: 298−299 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 12.44 (s, 1H), 8.11−8.19 (m, 3H), 7.92 (br s, 1H), 7.61 (br s, 1H), 7.58 (d, J = 8.5 Hz, 1H), 7.48−7.54 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 162.1, 151.4, 148.5, 136.2, 135.8, 134.4, 132.7, 131.1, 129.5, 128.5, 127.5, 120.6.

2-(4-Fluorophenyl)quinazolin-4(3H)-one (**3ll**).[19a] Eluent: petroleum ether/ethyl acetate (3:1). White solid (180 mg, 75%). Mp: 257−259 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 12.55 (s, 1H), 8.23−8.27 (m, 2H), 8.15 (dd, J = 7.83, 1.15 Hz, 1H), 7.81−7.85 (m, 1H), 7.73 (d, J = 7.96 Hz, 1H), 7.50−7.54 (m, 1H), 7.36−7.41 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 165.2, 162.7, 151.3, 148.5, 134.5, 130.3 (d, J = 9.02 Hz), 129.1, 127.3, 126.5, 125.8, 120.8, 115.5 (d, J = 21.9 Hz).

2-(4-Bromophenyl)quinazolin-4(3H)-one (**3mm**).[14g,19b,20b] Eluent: petroleum ether/ethyl acetate (3:1). White solid (202 mg, 67%). Mp: >300 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 12.56 (s, 1H), 8.12−8.19 (m, 3H), 7.84 (t, J = 7.42 Hz, 1H), 7.73−7.77 (m, 2H), 7.50−7.59 (m, 2H) ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 162.1, 151.4, 148.4, 134.5, 131.5, 131.3, 129.7, 127.7, 126.5, 125.8, 125.1, 120.9.

2-(4-Nitrophenyl)quinazolin-4(3H)-one (**3nn**).[20b] Eluent: petroleum ether/ethyl acetate (3:1). Brown solid (134 mg, 50%). Mp: >300 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) = 12.83 (br s, 1H), 8.37−8.43 (m, 4H), 8.18 (d, J = 8.2 Hz, 1H), 7.88 (t, J = 7.9 Hz, 1H), 7.67 (d, J = 7.2 Hz, 1H), 7.58 (t, J = 8.0 Hz, 1H).

2-(2,4-Dichlorophenyl)quinazolin-4(3H)-one (**3oo**).[20b] Eluent: petroleum ether/ethyl acetate (3:1). White solid (195 mg, 67%). Mp: 225−226 °C. ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) = 12.65 (s, 1H), 8.14−8.21 (m, 1H), 7.81−7.87 (m, 2H), 7.72 (t, J = 8.13 Hz, 2H), 7.53−7.69 (m, 2H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 162.1, 152.2, 148.6, 134.5, 132.6, 131.3, 128.5, 127.7, 127.4, 126.5, 125.7, 120.9.

2-(Anthracen-10-yl)quinazolin-4(3H)-one (**3pp**).[20c] Eluent: petroleum ether/ethyl acetate (3:1). White solid (222 mg, 69%). Mp: 157−158 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 12.77 (s, 1H), 8.79 (s, 1H), 8.26 (d, J = 7.86 Hz, 1H), 8.18 (d, J = 8.29 Hz, 2H), 7.91 (t, J = 7.86 Hz, 1H), 7.74−7.81 (m, 3H), 7.65 (t, J = 7.58 Hz, 1H), 7.51−7.61 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 162.2, 153.6, 149.4, 135.1, 131.1, 129.5, 129.2, 129.0, 128.0, 127.5, 126.5, 126.2, 125.5, 122.2.

2-(Thiophene-2-yl)quinazolin-4(3H)-one (**3qq**).[20b,19a] Eluent: petroleum ether/ethyl acetate (3:1). Yellow solid (153 mg, 67%). Mp: 271−272 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 12.61 (s, 1H), 8.24 (d, J = 3.79 Hz, 1H), 8.12 (d, J = 7.9 Hz, 1H), 7.86 (d, J = 5.07 Hz, 1H), 7.77−7.82 (m, 1H), 7.65 (d, J = 8.09 Hz, 1H), 7.48 (t, J = 7.88 Hz, 1H), 7.23 (t, J = 3.9 Hz, 1H).

2-(Pyridin-2-yl)quinazolin-4(3H)-one (**3rr**).[14g] Eluent: petroleum ether/ethyl acetate (3:1). Yellow solid (154 mg, 69%). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 11.78 (s, 1H), 8.76 (d, J = 4.46 Hz, 1H), 8.45 (d, J = 7.9 Hz, 1H), 8.18 (d, J = 7.84 Hz, 1H), 8.10 (td, J = 7.9, 1.5 Hz, 1H), 7.87 (t, J = 7.72 Hz, 1H), 7.80 (d, J = 8.03 Hz, 1H), 7.64−7.67 (m, 1H), 7.57 (t, J = 7.45, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 160.6, 149.8, 148.8, 148.5, 148.3, 137.9, 134.6, 127.5, 127.1, 126.4, 126.0, 122.0, 121.9.

2-Butylquinazolin-4(3H)-one (**3ss**).[14g] Eluent: petroleum ether/ethyl acetate (3:1). White solid (49 mg, 24%). Mp: 108−109 °C. ^{1}H NMR (DMSO-d_6, 300 MHz): δ (ppm) = 8.16 (s, 1H), 7.79 (d, J = 8.0 Hz, 1H), 7.57 (s, 1H), 7.36 (d, J = 7.6 Hz, 1H), 7.25 (s, 1H), 2.07 (t, J = 7.8 Hz, 2H), 1.25−1.28 (m, 2H), 1.18−1.22 (m, 2H), 0.84 (t, J = 8.4 Hz, 3H).

8-Methyl-2-phenylquinazolin-4(3H)-one (**3tt**).[17i] Eluent: petroleum ether/ethyl acetate (3:1). White solid (191 mg, 81%). Mp: 247−248 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 12.51 (s, 1H), 8.23 (d, J = 6.7 Hz, 2H), 7.99 (d, J = 7.9 Hz, 1H), 7.69 (d, J = 7.3 Hz, 1H), 7.53−7.61 (m, 3H), 7.39 (t, J = 7.6 Hz, 1H), 2.62 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 162.4, 150.9, 147.0, 135.5, 134.8, 132.9, 131.2, 128.5, 127.6, 125.9, 123.4, 120.8, 17.0.

6-Methyl-2-phenylquinazolin-4(3H)-one (**3uu**).[14h,19a] Eluent: petroleum ether/ethyl acetate (3:1). White solid (201 mg, 85%). Mp: 265−268 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 12.44 (s, 1H), 8.18−8.16 (m, 2H), 7.95 (s, 1H), 7.64 (t, J = 9.8 Hz, 2H), 7.51−7.59 (m, 3H), 2.46 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 162.2, 151.5, 146.6, 136.1, 135.7, 132.8, 131.1, 128.5, 127.5, 127.2, 120.6, 20.7.

8-Bromo-2-phenylquinazolin-4(3H)-one (**3vv**).[14h] Eluent: petroleum ether/ethyl acetate (3:1). White solid (217 mg, 72%). Mp: 218−220 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 12.75 (s, 1H), 8.25−8.27 (m, 2H), 8.15 (d, J = 7.9 Hz, 2H), 7.55−7.64 (m, 3H), 7.41 (t, J = 7.8 Hz, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 161.8, 152.8, 146.0, 137.8, 132.3, 131.7, 128.6, 127.9, 127.2, 125.6, 122.6, 122.1.

6,7,8-Trimethoxy-2-phenylquinazolin-4(3H)-one (**3ww**). Eluent: petroleum ether/ethyl acetate (3:1). White solid (209 mg, 67%). Mp: 274−275 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 12.48 (s, 1H), 8.20 (d, J = 7.4 Hz, 1H), 8.19 (d, J = 7.9 Hz, 1H), 7.52−7.58 (m, 3H), 7.38 (s, 1H), 4.07 (s, 3H), 3.92 (s, 3H), 3.89 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 161.6, 152.1, 149.5, 147.8, 138.3, 132.8, 131.0, 128.5, 127.3, 117.0, 101.1, 62.0, 60.8, 55.9. HRMS (ESI, positive ions): m/z calcd for $C_{17}H_{16}N_2O_4^+$ [M + H$^+$] 313.1188, found 313.1195.

8-Bromo-6-methyl-2-phenylquinazolin-4(3H)-one (**3xx**). Eluent: petroleum ether/ethyl acetate (3:1). White solid (290 mg, 92%). Mp: >300 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 12.62 (s, 1H), 8.20−8.22 (m, 2H), 7.97 (s, 1H), 7.91 (s, 1H), 7.51−7.59 (m, 3H), 2.41 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 161.7, 151.9, 143.9, 138.8, 137.4, 132.4, 131.5, 128.5, 127.7, 125.2, 122.1, 121.8, 20.3. HRMS (ESI, positive ions): m/z calcd for $C_{15}H_{11}BrN_2O^+$ [M + Na$^+$] 336.9952, found 336.9961.

2-Phenylbenzo[g]quinazolin-4(3H)-one (**3yy**). Eluent: petroleum ether/ethyl acetate (3:1). White solid (231 mg, 85%). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 12.36 (s, 1H), 8.87 (s, 1H), 8.32 (s, 1H), 8.20−8.25 (m, 3H), 8.11 (d, J = 8.3 Hz, 1H), 7.65−7.69 (m, 1H), 7.61−7.55 (m, 4H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 162.6, 151.2, 144.0, 136.3, 132.8, 131.2, 130.8, 129.2, 128.5, 128.4, 127.7, 127.6, 127.2, 126.2, 124.9, 120.0 HRMS (ESI, positive ions): m/z calcd for $C_{18}H_{12}N_2O^+$ [M + Na$^+$] 295.0847, found 295.0839.

8-Bromo-2-(4-chlorophenyl)-6-methylquinazolin-4(3H)-one (**3zz**). Eluent: petroleum ether/ethyl acetate (3:1). White solid (212 mg, 85%). Mp: >300 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 12.72 (s, 1H), 8.25 (d, J = 8.6 Hz, 2H), 8.02 (s, 1H), 7.95 (s,1H),7.65 (d, J = 8.6 Hz, 2H), 2.45 (s,3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 161.6, 151.0, 143.8, 138.8, 137.6, 136.4, 131.2, 129.5, 128.6, 125.2, 122.1, 121.8, 20.3. HRMS (ESI, positive ions): m/z calcd for $C_{15}H_{10}BrClN_2O^+$ [M + Na$^+$] 370.9563, found 370.9569.

Characterization Data for Some New Substituted Benzamides. 2-Amino-5-methylbenzamide (**2b**).[26] A solution of 2-amino-5-methylbenzoic acid (151 mg, 1 mmol) and 1,1′-carbonyldiimidazole (180 mg, 90%, 1 mmol) in anhydrous THF (15 mL) was stirred at room temperature under argon for 2 h. Ammonia (5 mL, 25%, 73 mmol) was added to it, and the whole solution was stirred vigorously for 6 h. Then THF was removed under vacuum, and the residue was extracted with ethyl acetate three times. The combined organic solvent was dried over Na_2SO_4 and concentrated. The residue was purified by silica gel chromatography with ethyl acetate as the eluent to give the 2-amino-5-methylbenzamide (108 mg, 72%). Eluent: petroleum ether/ethyl acetate (3:1). White solid (108 mg, 72%). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 7.64 (s, 1H), 7.34 (t, J = 4.0 Hz, 1H), 6.94−6.97 (m, 2H), 6.58 (d, J = 8.0 Hz, 1H), 6.30 (s, 2H), 2.14 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 171.2, 147.7, 132.6, 128.5, 122.6, 116.4, 113.7, 19.9.

2-Amino-3-bromo-5-methylbenzamide (**2c**). **2c** was prepared following the same procedure as described above for **2b**. Eluent: petroleum ether/ethyl acetate (3:1). White solid (158 mg, 69%). Mp: 178−180 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 7.86 (s, 1H), 7.43 (s, 1H), 7.38 (s, 1H), 7.27 (s, 1H), 6.40 (s, 2H), 2.17 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 170.4, 144.1, 135.4,

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128.6, 124.5, 115.9, 109.6, 19.4. Anal. Calcd for $C_8H_9BrN_2O$: C, 41.95; H, 3.96; N, 12.23. Found: C, 41.90; H, 4.04; N, 12.27.

*2-Amino-3,4,5-trimethoxybenzamide (**2d**).* **2d** was prepared following the same procedure as described above for **2b**. Eluent: petroleum ether/ethyl acetate (3:1). White solid (131 mg, 58%). ^{1}H NMR (400 MHz, DMSO-d_6): δ (ppm) = 7.70 (s, 1H), 7.01 (s, 2H), 6.06 (s, 1H), 3.79 (s, 3H), 3.72 (s, 3H), 3.71 (s, 3H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 170.6, 145.4, 142.2, 140.0, 139.4, 108.2, 108.2, 60.3, 59.8, 56.5. Anal. Calcd for $C_{10}H_{14}N_2O_4$: C, 53.09; H, 6.24; N, 12.38. Found: C, 53.14; H, 6.30; N, 12.33.

*3-Aminonaphthalene-2-carboxamide (**2e**).* **2e** was prepared following the same procedure as described above for **2b**. Eluent: petroleum ether/ethyl acetate (3:1). Orange solid (93 mg, 50%). Mp: 170−172 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) = 8.23 (s, 1H), 7.97 (s, 1H), 7.67 (s, 1H), 7.54 (s, 1H), 7.41 (s, 1H), 7.26 (s, 1H), 7.01 (s, 1H), 5.35 (s, 2H), 4.20 (s, 1H). ^{13}C NMR (100 MHz, DMSO-d_6): δ (ppm) = 170.3, 145.0, 133.4, 129.4, 129.0, 128.5, 128.0, 125.1, 124.9, 122.5, 109.4. Anal. Calcd for $C_{11}H_{10}N_2O$: C, 70.95; H, 5.41; N, 15.04. Found: C, 70.90; H, 5.47; N, 15.09.

*Characterization Data for 2,3-dihydro-2-phenylquinazolin-(1H)-one (**4**).*[20b] Under an argon atmosphere, a mixture of *o*-aminobenzamide (1.0 mmol) and benzaldehyde (1.0 mmol) in toluene was added to a flame-dried Schlenk tube. The Schlenk tube was then placed in an oil bath, and the reaction mixture was refluxed for 8 h. After the reaction was finished, the resulting mixture was cooled to room temperature and concentrated. Then the residue was purified by silica gel chromatography. Eluent: petroleum ether/ethyl acetate (3:1). White solid (191 mg, 85%). ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) = 8.35 (s, 1H), 7.30−7.41 (m, 3H), 7.25 (d, J = 4.8 Hz, 2H), 6.24 (t, J = 6.3 Hz, 1H), 5.81 (d, J = 6.6 Hz, 1H), 4.92−5.02 (m, 2H), 4.44 (d, J = 3.6 Hz, 1H).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00643.

^{1}H and ^{13}C NMR spectral data (PDF)

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Notes

The authors declare no competing financial interest.

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