

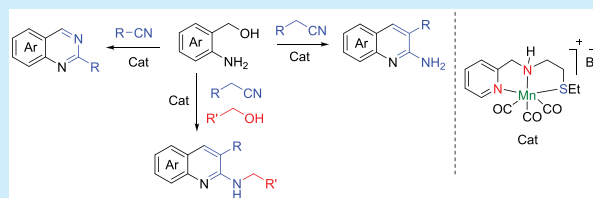
Sustainable Synthesis of Quinazoline and 2-Aminoquinoline via Dehydrogenative Coupling of 2-Aminobenzyl Alcohol and Nitrile Catalyzed by Phosphine-Free Manganese Pincer Complex

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S Supporting Information

ABSTRACT: A sustainable synthesis of quinazoline and 2-aminoquinoline via acceptorless dehydrogenative annulation is presented. The reaction is catalyzed by earth-abundant well-defined manganese complexes bearing NNS ligands. Furthermore, a one-pot synthetic strategy for the synthesis of 2-alkylaminoquinolines through sequential dehydrogenative annulation and N-alkylation reaction has also been demonstrated.



The use of global resources in a sustainable manner is a challenge of the utmost urgency. For chemistry, the development of useful building blocks from renewable starting materials is highly desirable.¹ Alcohols can be obtained renewably from biomass, lignocellulose via fermentation, or catalytic conversion.² Thus, the selective conversion of alcohols to different valuable classes of chemical compounds offers a useful contribution toward the conservation of the finite fossil carbon resources.³ In this regard, acceptorless dehydrogenative coupling (ADC) reaction⁴ became a useful tool for the sustainable synthesis of valuable organic molecules, as this does not require any hydrogen acceptors, oxidant, or prefunctionalization of substrates.

The construction of N-containing compounds has attracted much attention of the pharmaceutical and agrochemical industries due to the important interaction of these types of compounds with the living organisms. Among them, aromatic N-heterocyclic compounds are particularly important, as found in many natural product and bioactive molecules.⁵ Moreover, N-heterocyclic compounds are of great importance due to their wide range of applications as drugs,⁶ agrochemicals,⁷ dyes,⁸ vitamins,⁹ and flavors.¹⁰ Therefore, there is a high demand for new atom-economical and sustainable synthetic protocols that allow the preparation of diversely functionalized N-heterocycles. Indeed, in recent times, an explosive growth in the noble metal-catalyzed dehydrogenative synthesis of N-heteroaromatic molecules has been observed.¹¹

The replacement of expensive noble metal catalysts by earth-abundant, nontoxic first-row transition metals is extremely advantageous with regard to cost effectiveness and sustainability. In addition, the 3d metal-based catalysts could introduce a new selectivity pattern, which enables significant enhancement of the general applicability of these reactions. Despite of the significant progress in de(hydrogenative) reactions by 3d transition metals¹² in recent years, the synthesis of N-heterocycles is still in the nascent stage.¹³ Manganese is the third most abundant transition metal in the

earth's crust, but surprisingly, its applicability toward acceptorless dehydrogenation and hydrogenation reaction was unexplored until 2016.¹⁴ The pioneering work by the groups of Milstein,^{14a} Beller,^{14b,d} Kempe,^{14c} and Kirchner^{14e} triggered rapid growth in the area of manganese-catalyzed ADC reactions.¹⁵ However, the N-heterocycle synthesis via the Mn-catalyzed ADC reaction is in the budding phase.^{14c,e,16} Herein, we report the first Mn-catalyzed (Figure 1) synthesis of quinazoline and 2-aminoquinoline through the dehydrogenative condensation of 2-aminobenzyl alcohol and nitriles. In addition, synthesis of 2-alkylaminoquinolines has also been demonstrated via ADC reaction followed by N-alkylation process.

Intrigued by the sustainable synthesis of pyrimidines from amidine and alcohol reported by the group of Kirchner^{14e} and Kempe,^{14c} we envisioned that quinazoline could be synthesized by the dehydrogenation and condensation reaction between 2-aminobenzyl alcohols and nitriles via an amidine (Figure 2) type intermediate.¹⁷ Thus, initially we investigated the scope of the reaction by our NNS–Mn(I) complexes^{16c,d} (Figure 1) using 2-aminobenzyl alcohol and benzonitrile as model substrates. Therefore, when a xylene solution containing an equimolar mixture 2-aminobenzyl alcohol and benzonitrile was refluxed in the presence of 5 mol % of cat. **1** and 0.5 mmol of tBuOK, 68% desired quinazoline was isolated (Table 1, entry 1). The yield was further improved to 86% just by increasing the ratio of 2-aminobenzyl alcohol and benzonitrile (Table 1, entry 2). An investigation on the influence of base showed that tBuOK was more effective than KOH or Cs₂CO₃, whereas K₃PO₄ showed comparable activity (Table 1, entries 9–11). The reaction either in the absence of a catalyst or in the absence of base gave no detectable conversion (Table 1, entries 15 and 16). Thus, the presence of both is essential for

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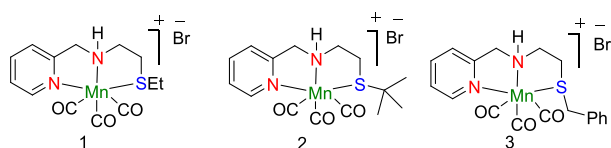


Figure 1. Tridentate ligand derived NNS–Mn(I) complexes.

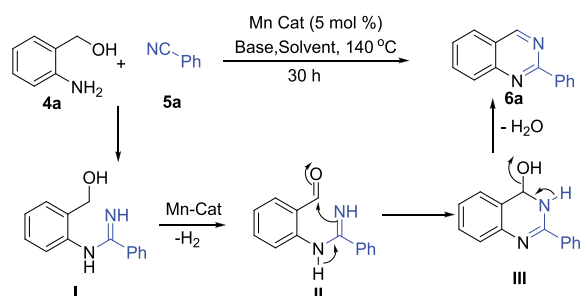
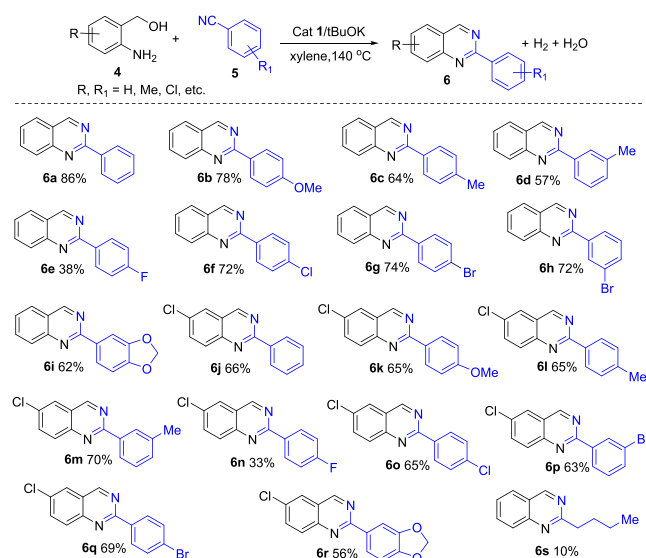


Figure 2. Proposed mechanism.

this protocol. $\text{MnBr}(\text{CO})_5$ gave only 14% yield of **6a** under similar reaction conditions.

After the reaction conditions were optimized, we tried to explore the generality and the limitations of this protocol (Scheme 1). At first, 2-aminobenzyl alcohol was reacted with the nitriles bearing electron-withdrawing and electron-donating functionalities in the aromatic nucleus. In most of the cases, good yields of the desired quinazoline **6a–i** were isolated. Chloro-substituted 2-aminobenzyl alcohol also reacted well with various nitriles to afford the desired quinazoline in good yield. It is worth mentioning that the halo-substituted quinazolines were obtained in good yield, which could be further used for functionalization. Surprisingly, 4-fluorobenzonitrile gave only 38% yield of the desired product **6e**. The reaction with aliphatic nitrile such as valeronitrile gave a

Scheme 1. Synthesis of Quinazoline from 2-Aminobenzyl Alcohol and Nitrile^{a,b}

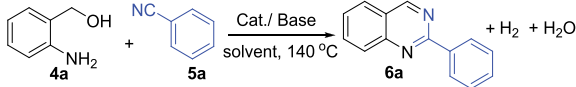


^aReaction conditions: 2-aminobenzyl alcohol (0.5 mmol), benzonitrile (0.75 mmol), tBuOK (0.5 mmol), cat. **1** (5 mol %), under argon in xylene (1 mL) at 140 °C (oil bath temp), for 30 h. ^bIsolated yield.

complicated mixture from which only 10% of the desired quinazoline was isolated. It is important to note that all the obtained quinazolines molecules offer the potential for C–H functionalization to synthesize complex building blocks.¹⁸ The evolved H_2 via dehydrogenation reaction has been utilized to convert styrene to ethylbenzene through Pd/C-catalyzed hydrogenation (see the SI).

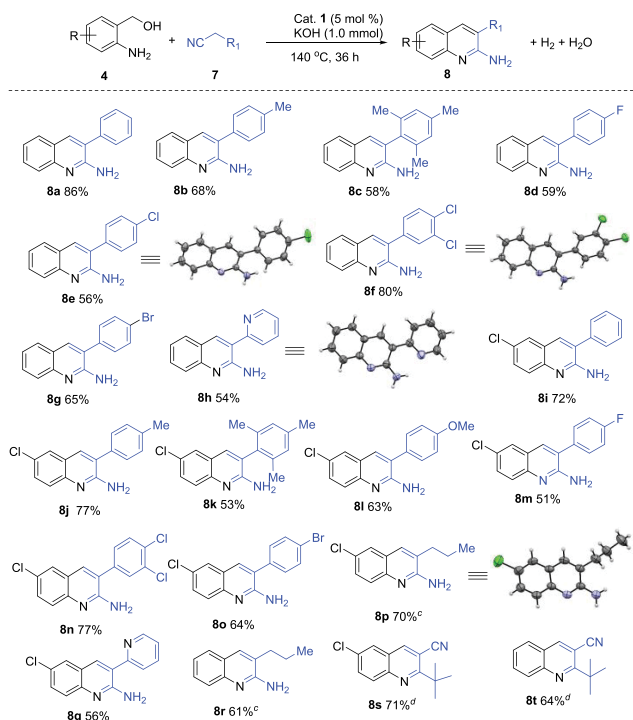
2-Aminoquinoline derivatives have received much attention due to their important pharmacological properties and wide application in medicinal chemistry.¹⁹ Therefore, development

Table 1. Optimization of the Reaction Conditions for the Synthesis of Quinazoline^a

						
entry	cat.	solvent	base (mmol)	4a/Sa	time (h)	yield ^b (%)
1	cat-1	xylene	tBuOK (0.5)	1:1	36	68
2	cat-1	xylene	tBuOK (0.5)	1:1.5	36	86
3	cat-1	xylene	tBuOK (0.5)	1:1.5	30	86
4	cat-1	xylene	tBuOK (0.5)	1:1.2	30	69
5	cat-1	xylene	tBuOK (0.5)	1:1.5	15	38
6	cat-1	toluene	tBuOK (0.5)	1:1.5	30	62
7	cat-1	xylene	tBuOK (0.2)	1:1.5	30	58
8	cat-1	Neat	tBuOK (0.5)	1:1.5	30	65
9	cat-1	xylene	KOH (0.5)	1:1.5	30	72
10	cat-1	xylene	Cs_2CO_3 (0.5)	1:1.5	30	52
11	cat-1	xylene	K_3PO_4 (0.5)	1:1.5	30	84
12	cat-1	xylene	tBuOK (0.5)	1:1.5	30	56 ^c
13	cat-2	xylene	tBuOK (0.5)	1:1.5	30	70
14	cat-3	xylene	tBuOK (0.5)	1:1.5	30	58
15		xylene	tBuOK (0.5)	1:1.5	30	trace
16	cat-1	xylene	tBuOK (0.5)	1:1.5	30	trace
17	$\text{MnBr}(\text{CO})_5$	xylene	tBuOK (0.5)	1:1.5	30	14

^aReaction conditions: 2-aminobenzyl alcohol (0.5 mmol), benzonitrile (0.5–0.75 mmol), base (0.2–0.5 mmol), cat. (5 mol %), under argon.

^bIsolated yield. ^c2 mol % of cat. **1**

Scheme 2. Synthesis of 2-Aminoquinoline through Acceptorless Dehydrogenative Annulation^{a,b}

^aReaction conditions: 2-aminobenzyl alcohol (1.0 mmol), nitrile (1.5 mmol), KOH (1.0 mmol), toluene (2 mL), cat. 1 (5 mol %), 140 °C (oil bath temp), pressure tube, 36 h, ^bIsolated yield, ^c48 h, nitrile (2.0 mmol). ^dPivaloylacetone nitrile used (product via Friedländer type pathway).

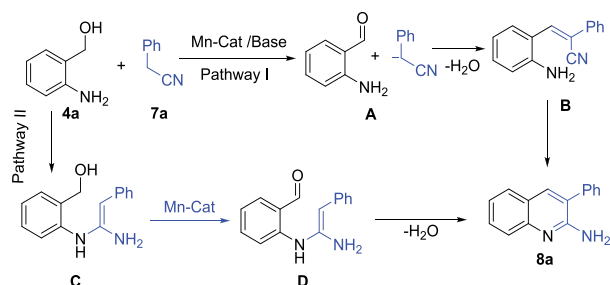
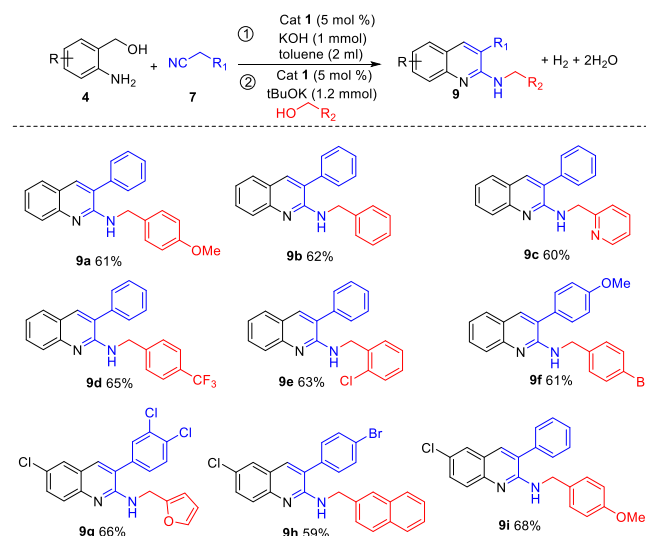


Figure 3. Proposed mechanistic pathways for the formation of 2-aminoquinoline.

of new synthetic strategies to prepare 2-aminoquinoline derivatives continues to be an important target in organic chemistry.²⁰ Thus, we are interested in applying our Mn catalysts to synthesize these compounds through acceptorless dehydrogenation and consecutive C–C and C–N bond-forming reactions. Hence, to examine the potential of our catalyst, dehydrogenative annulation of 2-aminobenzyl alcohol and benzyl cyanide was studied. Thus, when a toluene solution containing 2-aminobenzyl alcohol (1 mmol) and benzyl cyanide (1.5 mmol) was refluxed in the presence of 5 mol % of cat. 1 and KOH (1 mmol), 86% 3-phenylquinolin-2-amine was obtained after 36 h (Scheme 2, entry 8a). Benzyl cyanide having both electron-donating and electron-withdrawing groups in the aromatic ring reacted well to give good yield of the desired 2-aminoquinolines. Not only mono- or disubstituted benzyl cyanide but also 1,3,5-trisubstituted

Scheme 3. One-Pot Synthesis of 2-Alkylaminoquinolines^{a,b}

^aReaction conditions: 2-aminobenzyl alcohol (1.0 mmol), nitrile (1.5 mmol), cat. 1 (5 mol %), and KOH (1.0 mmol) in toluene (2 mL) at 140 °C (oil bath temp), pressure tube, for 36 h followed by addition of cat. 1 (5 mol %), tBuOK (1.2 mmol), and primary alcohol (1.5 mmol) heated for 24 h. ^bIsolated yield.

benzyl cyanide reacted smoothly to give the corresponding product 8k in moderate yield. Heterocyclic cyanide worked successfully under the optimized conditions. Interestingly, the reaction with a more challenging aliphatic nitrile was found to be sluggish, and only 35% yield of 8p was obtained after 36 h, which could be further improved to 70% using longer reaction time (48 h). Next, we were interested in studying the dehydrogenative coupling of (2-amino-5-chlorophenyl)-methanol with pivaloylacetone nitrile. There is a possibility of the formation of two different quinoline derivatives: 2-*tert*-butyl-6-chloroquinoline-3-carbonitrile (via Friedländer-type pathway: nucleophilic addition of NH₂ to C=O) and 3-*tert*-butyl-6-chloroquinolin-2-amine (via nucleophilic addition of NH₂ to CN). In this protocol, 2-*tert*-butyl-6-chloroquinoline-3-carbonitrile 8s was obtained in 71% yield. Interestingly, no 3-*tert*-butyl-6-chloroquinolin-2-amine was observed; hence, it can be concluded that the amine preferred to attack ketone over the nitrile under the reaction conditions.

Two different pathways for the formation of 2-aminoquinoline are proposed (Figure 3). In pathway I, the reaction commences with the dehydrogenation of alcohol and subsequent formation of B via condensation at the α -carbon of phenyl acetonitrile. Then the nucleophilic addition of an amino group to the cyano functionality followed by tautomerization led to the formation of 2-aminoquinoline. In pathway II, the reaction began with the formation of C via nucleophilic addition of NH₂ to CN followed by tautomerization, which upon dehydrogenation followed by condensation reaction led to the formation of 8a. The reaction of benzyl alcohol with phenyl acetonitrile under the optimized reaction conditions led to the formation of 2,3-diphenylacrylonitrile via dehydrogenative condensation at α -phenyl acetonitrile, suggesting that the formation 2-aminoquinoline B through path I is more likely.

Next, we wanted to investigate the catalytic applicability of our Mn complexes toward the synthesis of 2-(alkylamino)-quinolines through sequential dehydrogenative annulation and

N-alkylation reaction. Thus, the dehydrogenative annulation between 2-aminobenzyl alcohol and phenylacetonitrile followed by the N-alkylation reaction with benzyl alcohol were examined in the presence of cat. **1**. Gratifyingly, a 61% yield of the desired N-(4-methoxybenzyl)-3-phenylquinolin-2-amine was isolated after column chromatography. Next, a wide range of 2-(alkylamino)quinolines **9a–9i** were synthesized as summarized in Scheme 3. To the best of our knowledge, the first Mn-catalyzed one-pot sequential dehydrogenative annulation and N-alkylation reaction to synthesize 2-alkylaminoquinolines have been achieved.

In conclusion, we report the first sustainable synthesis of quinazoline and 2-aminoquinoline through dehydrogenative annulation of 2-aminobenzyl alcohol with nitriles using a well-defined Mn(I) pincer complex. The reaction proceeds via dehydrogenation and concomitant formation of C–C and C–N bond with high atom economy. Furthermore, the synthesis of 2-(alkylamino)quinolines was achieved through sequential dehydrogenative annulation and N-alkylation reaction with alcohols. The structural importance of the obtained compounds and the use of nontoxic, earth-abundant Mn metals make this approach attractive and sustainable.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00939.

¹H NMR and ¹³C NMR spectra of all compounds; X-ray crystallographic data for **8e**, **8f**, **8h**, and **8p** (PDF)

■ Accession Codes

CCDC 1895879–1895882 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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