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Hydrazo coupling: the efficient transition-metal-free C–H functionalization of 8-hydroxyquinoline and phenol through base catalysis†

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Azodicarboxylate esters are common reagents in organic synthesis laboratories due to their utility in the Mitsunobu reaction. They can also be regarded as possible starting compounds for C–H functionalization, which up until now has been mainly achieved by transition-metal-catalyzed reactions. We have developed a novel reaction involving the quantitative coupling of 8-hydroxyquinoline or phenol with azodicarboxylate esters. The functionalization proceeds under mild base-catalyzed conditions selectively, and either the *ortho*-position of 8-hydroxyquinoline or *para*-position of the phenol/naphthol is involved in the reaction. This type of transformation can be considered as "hydrazo coupling" (by analogy with azo coupling). Herein, we discuss a plausible mechanism for this catalyzed substitution, backing up our findings with deuterium NMR experiments and by varying the starting compounds and bases. Using Boc-N=N-Boc as a substrate, we have developed the convenient and efficient synthesis of (8-hydroxyquinolin-7-yl)hydrazines, as well as demonstrating a new stereoselective route for the synthesis of medicinally important 4-hydroxyphenylhydrazine for laboratory use, which almost doubles the yield of the common industrial process and reduces the number of synthetic steps. A new "one-pot" procedure for the synthesis of aromatic 8-hydroxyquinolin-7-yl hydrazones was applied.

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Introduction

Selective functionalization of C(sp^2)–H bonds has been a hot topic in organic synthesis for the last decade. Aromatic structures prevail in complex natural products and simple organic molecules, so it is no surprise that many strategies have been developed to functionalize heterocycles and drug precursors.[1] Every method presents challenges in terms of yield, site selectivity, and others. As a result, experimental techniques are becoming more complex, catalysts are becoming more exotic and expensive, and harsh conditions are often required.

Azodicarboxylate (AD) esters can be regarded as possible starting compounds for feasible C–H functionalization. Their use in the Mitsunobu reaction makes them common reagents in organic synthesis laboratories, although their utility is not limited to activators alone.

Without the assistance of transition metal catalysis, azodicarboxylate coupling has demonstrated narrow perspectives in organic synthesis for several decades. In early research, such coupling was postulated to be a radical process.[2] Intensive research over the last two decades has resulted in a collection of studies concerning the use of ADs for the amination of aromatic substrates, such as benzene derivatives and phenols. In general, these approaches include either acidic conditions, Lewis acids, or radical initiators, and they are mainly based on transition-metal-catalyzed hydrazination *via* electrophilic substitution at 40–70 °C (Table 1).

However, acidic conditions are harmful to many functionalized derivatives, and moreover, expensive and complex transition metal catalysts need to be completely removed from the products, especially when dealing with the pharmaceutical industry.

There was a spike in the number of novel publications on ADs in the 1990s, due to studies on the reductive addition of DEAD to allyl fragments,[13] Buchwald–Hartwig amination[6] and B. Sharpless's group's discovery of azodicarboxylates as convenient substrates for unique "on-water" reactions and 2σ + 2σ + 2π cycloadditions to double bonds.[14]

Research into reactions of phenol-type compounds with azodicarboxylates is scarce. A direct reaction of phenol with azodicarboxylate esters gives an approximately equimolar mixture of oxidation and substitution products; an excess of DEAD leads to further oxidation of 3,3′,5,5′-tetraalkyl-4,4′-

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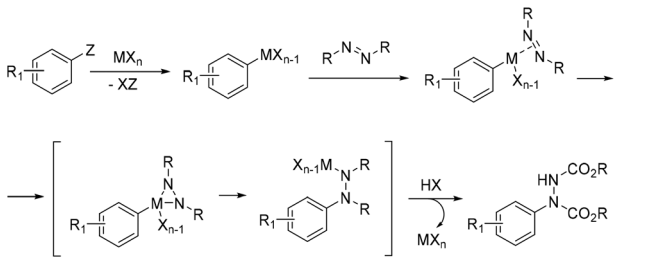
†Electronic supplementary information (ESI) available: Materials and methods, procedures for synthesis, and ^{1}H, ^{13}C and 2D NMR and HRMS spectra of the products. See DOI: 10.1039/c9gc02824b

Table 1 Transition-metal-catalyzed approaches for the hydrazination of arenes



Z	Lewis acid or catalyst
H	$Sc(OTf)_3$ [3] or 3 mol% $RuCl_3$,[4] or 1 mol% $AuCl_3$ [5]
Br	2–4 mol% $Pd(dba)_2$ + 1.5 eq. Cs_2CO_3 + 3–6 mol% TrixiePhos-type ligand (100 °C)[6]
Br, I	10 mol% CuI(I) + PPh_3 + 20 mol% phen[7]
H, Cl	$ZrCl_4$ [8]
$B(OH)_2$	η^1-Hydrazinato(phen)Pd[9] or 5 mol% $Cu(OAc)_2$ [10]
OTf	10 mol% Cu_2O + NaH + LiI (70 °C)[11]
$-N^+\equiv N$	$FeCl_2$ [12]

biphenyldiol into diphenylquinone (Scheme 1A).[15] Previously, these products were obtained only *via* radical oxidation with $K_3Fe(CN)_6$ and peroxides,[16] which is why S. H. Schroeter suggested that azodicarboxylate esters might act through the same mechanism with phenol compounds. That assumption lasted for more than 25 years, until the topic was reborn with catalysts introduced into the reaction. The use of activated bis(2,2,2-trichloroethyl) azodicarboxylate (BTCEAD) in triflic acid and/or $LiClO_4$ medium conditions was described by Y. Leblanc and colleagues, suggesting a synchronous mechanism between the HOMO of phenol and the LUMO of BTCEAD.[17]

Later, W. J. Kinart and C. M. Kinart proposed two mechanisms of phenol/β-naphthol hydrazination: *via* N: → Sn-coordinated metallo-ene mechanism or *via* electrophilic substitution through a stabilized Wheland intermediate[18] (Scheme 1C).

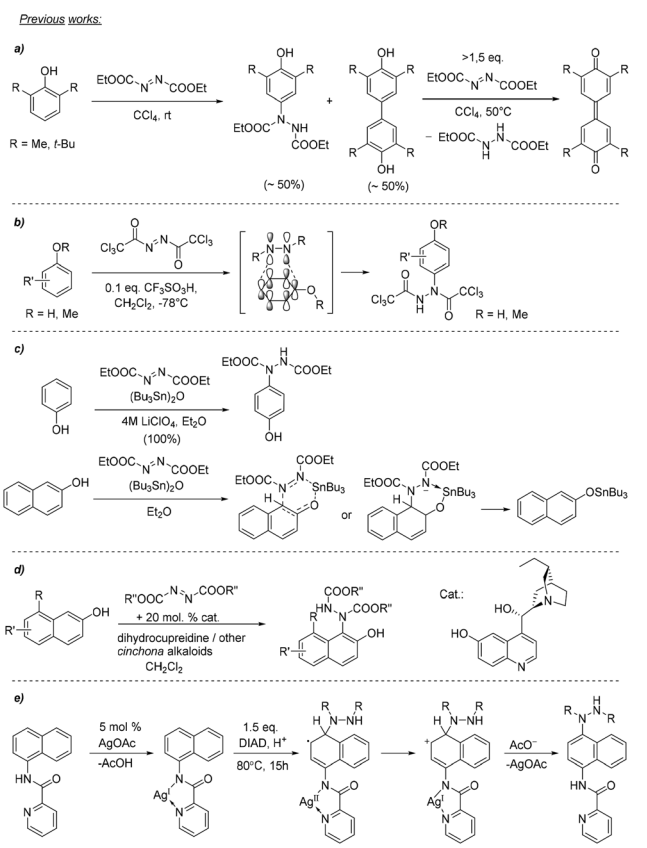
There is an example of atropisomer synthesis described *via* cinchona-alkaloid-catalyzed amination of β-naphthol with Di-*t*Bu-AD (Scheme 1D). The authors mentioned that a quinolin-6-ol system of dihydrocupreidine was also affected and could be aminated at the 5th position under more severe reaction conditions.[19]

Quite recently, a SET mechanism of DIAD substitution with AgOAc catalyst was proposed (Scheme 1e).[20] However, this reaction demonstrates the necessity of the pyridine-containing directing group and the α-aminonaphthalene moiety, as no reaction occurs in the corresponding aniline derivative.

Thus, there are five different mechanisms and catalytic approaches described for a one-type reaction, and every method requires additional steps of purification from the single-use catalyst.

8-Hydroxyquinoline (8-HQ) has gained a great deal of attention in medicinal chemistry, photochemistry and agrochemistry because of its strong coordinative nature. It is the most widely produced quinoline derivative due to its cheap energy-effective and simple synthesis. It is worth noting that levofloxacin, a fluoroquinolone derivative containing an 8-HQ scaffold with 7-amino fragments in its structure, comprised almost 30% of all the fluoroquinolone antibiotics on the market in 1991–2013.[21] 8-HQ is a framework for new generations of anti-HIV agents, as integrase or Rev protein inhibitors.[22] Activities against key targets in Alzheimer's disease have also been found.[23] However, the lack of known functionalization methods described for 8-HQ restricts the variety of product structures that can be obtained. Mainly, the Betti reaction (a type of Mannich base synthesis),[24] esterification and etherification of hydroxyl groups,[25] electrophilic substitution giving the 5-substituted 8-HQ derivatives[24,26] and some transition-metal-catalyzed approaches are used. Most of the processes used to access quinoline functionalization are performed by substitution using several major methods (some of them under harsh reaction conditions).[24,27]

Finally, the Mitsunobu reaction has hardly ever been a method of choice for phenolic substrates. Although the Mitsunobu reaction can be set with phenols and various hydroxyquinolines, the products are formed with poor selectivity and in moderate yields.[28] It has been stated that salicylaldehyde tends to form hydrazine derivatives under Mitsunobu reaction conditions.[29]



Scheme 1 The hydrazination of phenolic substrates and other arenes with directing groups.

In fact, dialkyl azodicarboxylate by itself is a good substrate for the reaction with 8-hydroxyquinoline, and this is the subject of the discussion below.

The aim of this work was to develop a new and facile synthetic method for obtaining 7-hydrazino-8-hydroxyquinoline derivatives and to explore the scope of base-catalyzed reactions of azodicarboxylate ester coupling to other substrates (with phenolic OH as a directing group).

Up until now, there were no 8-HQ hydrazine derivatives described. Here, we report the first synthesis of 7-hydrazino-8-hydroxyquinoline derivatives and a "one-pot" method for their transformation to aromatic hydrazones, using cost-effective and transition-metal-free mild conditions. The proposed method was also applied to the synthesis of 4-hydroxyphenylhydrazine in our laboratory, resulting in double the yield compared to the commonly used industrial process. Access to this type of compound could reveal a new chemistry of azo reactions and products with potential biological activity. A mechanism discussed below resembles azo coupling, and that is why we suggest the use of the term "hydrazo coupling" for this kind of reaction.

Results and discussion

Our initial investigation into the reaction of 8-hydroxyquinoline with diisopropyl azodicarboxylate (DIAD) as a model reaction resulted in moderate conversion of the starting 8-HQ. The amination proceeded smoothly at room temperature and the sole product obtained was purified and identified using ^{1}H, ^{13}C, ^{15}N and 2D NMR and HRMS spectra, which confirmed its structure to be diisopropyl 1-(8-hydroxyquinolin-7-yl)hydrazinyl-1,2-dicarboxylate **1a**. The formation of **1a** proceeded both in THF and dioxane with similar efficacy and the solvents did not need to be freshly dried, though the reaction stopped each time when the conversion reached 55–65%. No by-products were found. Increasing the temperature up to 40 °C did not lead to changes, but the yield significantly decreased above that temperature level. We also studied phenol utilization as an active part of the 8-HQ molecule in the reaction; in this case, the *para*-adduct was formed. Furthermore, we proceeded to investigate this reaction in order to facilitate the coupling of 8-HQ/phenol and azodicarboxylate esters and reveal the reaction mechanism.

Finding the appropriate catalyst

We varied the conditions and determined the optimal ones for the reaction of 8-HQ with DIAD (Table 2). One of the principle restrictions in this search was not to use transition metal catalysts, which would otherwise lead to a different mechanism of the process. Furthermore, transition metal catalysts would form products in a less environmentally friendly manner, requiring additional chromatography to remove these catalysts.

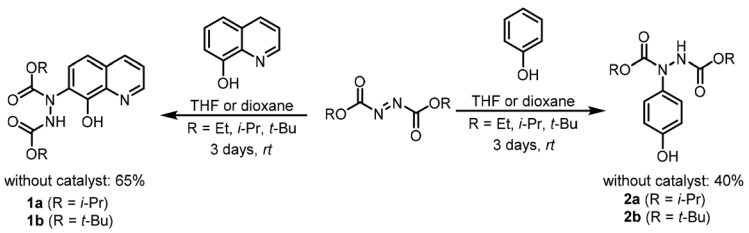
Based on previously known studies of azodicarboxylate ester substitution to form benzene hydrazines, we tried using TFA and a combination of TFA and TfOH as catalysts.[30] However, in the case of 8-HQ, the acidic medium converted the starting compound into a salt that was insoluble in THF/dioxane, and no reaction was observed. However, there have been reports on direct reactions of phenol with azodicarboxylate ester, which have given moderate yields of 50–60%,[15] and some later works that employed harsher conditions with $LiClO_4$ or triflic acid catalysis.[17] In contrast to these already studied conditions, we conducted our syntheses with base catalysts. The same base catalysis was applied for phenol functionalization.

We found that the desired coupling reaction can be provided by many bases in excellent yields, with sodium hydride proving to be the best. In fact, it facilitates the full conversion of 8-HQ in several gram scale, and the product can be easily isolated by partitioning in CH_2Cl_2/water and can be used without further purification. We assume that NaH acts as a base initiator of the activation, since the reaction continues with adding new portions of the starting reagents until it is quenched with a saturated $NaHCO_3$ solution. Using more than 5 mol% NaH is not necessary: the excess of the hydride remains uninvolved at the bottom of the flask. In the model reaction with DIAD, we reached the 5,7-bis-adduct after full conversion of the first DIAD equivalent into **1a** (Scheme 2).

Other alkali metal hydrides and mild bases were tested and found to effectively catalyze the functionalization. Nevertheless, only with NaH was it possible to exclude the mixture of mono- and bis-products and to obtain pure **1a** and **1b**. Interestingly, phenol gained a higher yield of **2a** with the less reactive Li-containing bases, LiH and $LiNH_2$. The latter gives almost the same excellent yield as LiH, and has practically the same commercial price as NaH for a slightly slower reaction rate, but $LiNH_2$ significantly lowers the contamination of the product with oxidation by-products.[31] In contrast, phenol and 8-hydroxyquinoline remained unreactive when relatively weaker bases such as CaH_2 and alkylamines were used. Amines were found to be the least effective bases in the reaction because they can form ion pairs with ADs and convert the latter into nucleophiles, leading to AD self-condensation by-products and preventing AD from coupling with 8-HQ or phenol.[32] However, this is not observed when using DBU as the base.

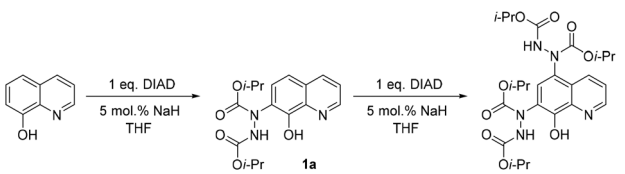
Solvent selection is limited to base-capable solvents, so DMSO and DMF were excluded. Instead, replacing THF or dioxane with greener industrial sulfolane led to a similar efficacy but a three-fold decrease in the reaction rate, while 2-methyltetrahydrofuran did not lead any decrease in the reaction rate. Elevated temperature did not facilitate the reaction: the yield of the non-catalyzed reaction significantly dropped while it was heated above 45 °C, and the starting material and by-products prevailed in the reaction mixture. One would expect to see the opposite effect, bearing in mind the Arrhenius equation, but it can be speculated that 8-HQ molecules are capable of stable self-dimerization, and intra- and intermolecular proton-transfer reactions become the major processes in further molecule excitation.[33] In this case, C–H activation is suppressed, since the phenol part of the molecule

Table 2 Screening for reaction conditions



Conditions[a]	Catalyst eq.	Time	Yield of the major quinolin-8-ol product (**1a**)	Yield of the major phenol product (**2a**)
Without a catalyst	—	3 days	65%	40%
Without a catalyst, >45 °C	—	3 days	Traces	24%
TFA	5	1.5 h	5%	—
NaH	1	1.5 h	99%	70%
NaH	**0.05**	**1.5 h**	**99%**	90%
NaH	<0.04	1.5 h	<90%	<70%
NaOH	1	12 h	0%	90%
KHMDS	1.1	12 h	70%	63%
DBU	**1.1**	**12 h**	**92%**[c]	**90%**
Cs_2CO_3	0.5	12 h	90%	77%
NEti-Pr_2	1.1	12 h	32%	0%
LiH	**1**	**12 h**	45%	**95%**
KH	1	1.5 h	90%[b]	90%[d]
KH	0.05	1.5 h	87%[b]	90%[d]
CaH_2	1	1.5 h	60%[b]	10%
CaH_2	0.05	1.5 h	60%[b]	5%
*t*BuOK	1	1.5 h	20%[b]	90%
*t*BuOK	0.05	1.5 h	90%[b]	83%
$LiNH_2$	**1**	**1.5 h**	87%[c]	**95%**
$LiNH_2$	0.05	1.5 h	80%[b]	70%
$NBu_4^+OH^-$	1	1.5 h	60%	15%

[a] Standard reaction conditions: 0.50 mmol of the reagent, 0.50 mmol of azodicarboxylate ester, in 2 ml of THF under an air atmosphere while stirring at rt (if not stated otherwise). [b] +Bis-hydrazinated product and starting compound. [c] +Bis-hydrazinated product. [d] +Biphenyldiol.



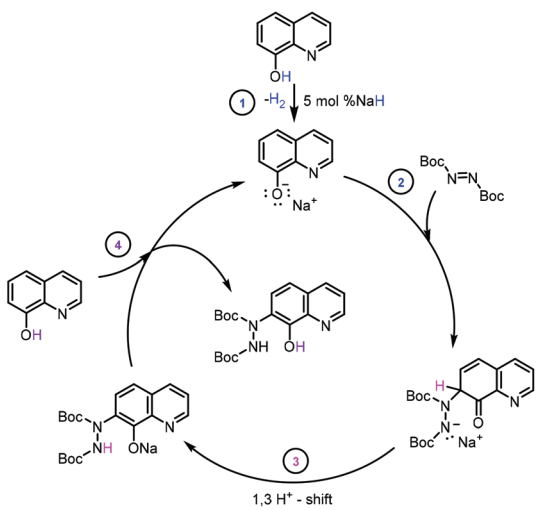
Scheme 2 Synthesis of the bis-adduct of DIAD coupling to 8-HQ.

loses the proton in favor of the nitrogen of the neighboring cycle.

To summarize, sodium hydride and lithium amide are two environmentally friendly, cheap and affordable initiators for this functionalization reaction. Although not officially claimed as "green" reagents, they are involved in sufficiently clean reactions and are used in small amounts. NaH and $LiNH_2$ can be easily quenched and isolated during the extraction of the product, thus, reducing purification steps to a minimum. This simplification cannot be achieved by the known methods employing transition metal catalysts.

Mechanism discussion

On the basis of these results and the related literature,[18] herein, we propose the following mechanism (Scheme 3). First, a catalytic amount of NaH induces phenolate formation. The charged quinoxide shows a higher +M effect for electron delocalization to the *o*-position than the neutral OH group. Then (step 2), the electrophilic carbon attacks the diazene molecule.



Scheme 3 The mechanism for azodicarboxylate esters to couple with 8-HQ under NaH-catalyzed conditions.

At this step the electron density migrates to the nitrogen atom from the –N=N– double bond. Further (step 3), a hydrogen shift occurs and the aromaticity of the phenol ring is restored.

It is common knowledge that in electrophilic substitutions, the highest rate of substitution is achieved by the interaction of the most acidic equilibrium form of the electrophilic reagent (azodicarboxylate ester) and the most basic form of the nucleophilic substrate (phenolic substrate). Historically, the first evidence for this was found in azo coupling reactions,[34] which are closely related to this topic.

One might suggest a different explanation for the surprising selectivity of the NaH catalytic reaction, which is slightly superior to Cs_2CO_3 and DBU catalysis in the product outcome (see Table 1). Diazene compounds are known to be good substrates for cyclometallation reactions,[35] and at the same time, there is a class of nucleophilic substitution/addition reactions of anionic *N*-sodio hydrazine derivatives.[36] Hence, a different mechanism of coupling might have been assumed, involving the initial addition of NaH to the –N=N– bond and further nucleophilic attack by the formed *in situ* hydrazinide derivative. However, it seems unlikely for the unstable hydrazinide intermediate to be formed at room temperature.

Therefore, we suggest the electrophilic amination mechanism instead. To clarify the issue, we conducted NMR experiments: ^{1}H and ^{2}H NMR spectroscopy was conducted with partially deuterated substrates to assess the mechanism *in situ* (Fig. 1). 8-Deuteroxyquinoline reacts with NaH (0.5 eq.) forming the phenolate and deuterohydrogen. The reaction between LiD and 8-HQ is hardly observed in this short time period. That makes us consider the metallic nature of the Li–D bond and the lower basicity (which is also required for activation) to be diminishing factors for the reaction. As expected, no reaction of NaH/LiD with the azodicarboxylate ester is observed at 20 °C in the ^{1}H and ^{2}H NMR spectra, as well as the HRMS spectra.

We also conducted reactions to check whether a radical mechanism takes place (or $1H^+/1e^-$ transfer) instead of the proposed ionic species. For this purpose, several test reactions with and without base catalysts were carried out with additives to facilitate/quench hypothetical radical species. Irradiation should facilitate radical generation. Therefore, we tried UV lamp conditions (254 nm and 360 nm, 6 W, quartz test-tubes, stirring for 6 hours) and incandescent lamp irradiation (150 W and 300 W at 30 cm distance, in the closed and specially cooled reflecting tank, in quartz test-tubes, for 1 h), but the yield of the catalyzed process did not increase compared to the non-catalyzed reaction. Darkroom conditions also did not decrease the yield. Second, if the reaction follows a radical mechanism, such as SET or PCET, then the addition of radical scavengers or initiators would affect the yield and rate of the reaction. We used TEMPO as an active catalyst for hydrogen transfer and as a radical scavenger, and found no sign of its influence on the yield or product ratio. 1,4-Dinitrobenzene was also tested as a SET inhibitor, but again, it did not affect the reaction. Thus, the possible SET (single electron transfer) and PCET (proton-coupled electron transfer) mechanisms were excluded. The plausible reactive species are ions, and this can be supported by the closely related reactions with phenol.

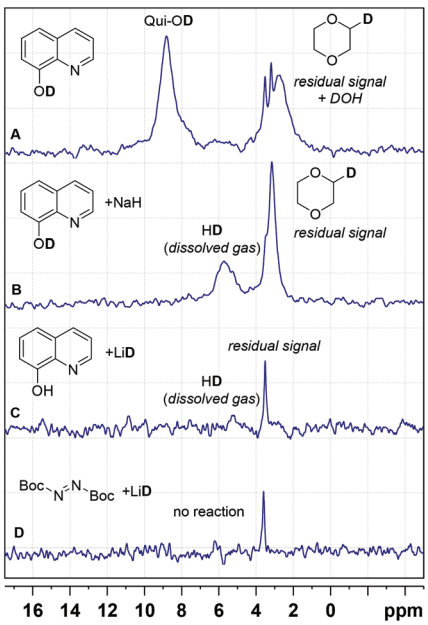
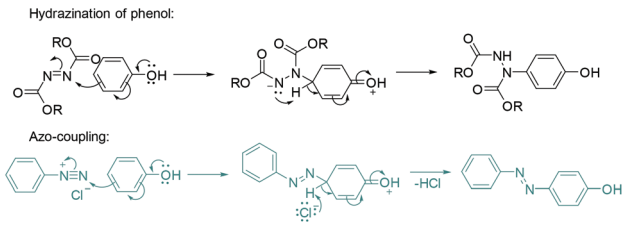


Fig. 1 Deuterium NMR spectra (solvent: dioxane) from different steps of the possible activation mechanism.

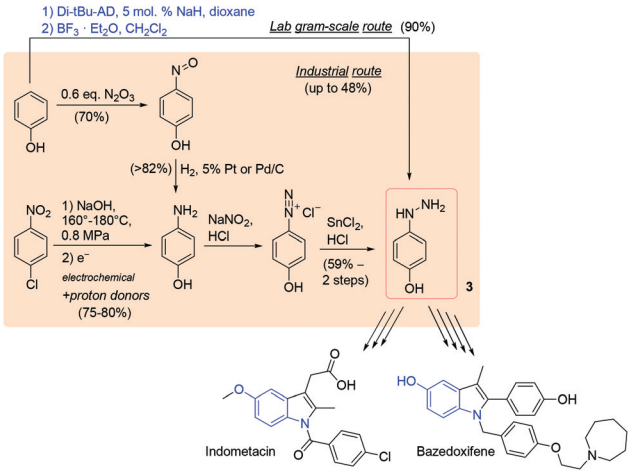
Replacing 8-hydroxyquinoline with phenol

It was interesting to explore this transition-metal-free approach to obtain closely related structures. As shown in Table 2, phenol amination shows less selectivity towards base catalysts. Both NaOH and NaH act equally well. The phenol OH group acts as a directing group in this coupling.

The reaction of azodicarboxylate esters with phenol results in *para*-substitution. This mechanism resembles the well-known azo-coupling reaction, offering the same product regioselectivity, except that the azodicarboxylate ester and the product possess one less π-bond (Scheme 4). Thus, the whole conception of the reaction can be changed for the simple general base catalysis, and the process itself can be regarded as a coupling reaction. Using di(*tert*-butyl)azodicarboxylate (or di-Boc-diazene) and degrading Boc-groups of the product, it is possible to obtain 4-hydroxyphenylhydrazine in excellent yield (Scheme 5).



Scheme 4 The mechanisms for azodicarboxylate esters to couple with phenol and for azo-coupling.



Scheme 5 4-Hydroxyphenylhydrazine synthesis.

Although 4-hydroxyphenylhydrazine has a history of more than 120 years,[37] not many methods have been described for its synthesis. As a result, modern chemists seldom use this compound as a starting reagent or during screening in medicinal chemistry (in contrast to phenyl- and 2,4-dinitrophenylhydrazine). Another issue is that currently, there are only a few commercial suppliers for laboratory synthesis, selling at a price of more than $800 per 1 gram.[38] To compare, the same amount of money spent on all the reagents (phenol, Di-*t*Bu-AD, $LiNH_2$, $BF_3{\cdot}Et_2O$ and solvents) required for the synthesis of 4-hydroxyphenylhydrazine described in the current work would result in about 65 grams of product in a 1–2-day routine procedure.[38] To check whether the new method is reliable, we scaled up the synthesis to a 5-gram PhOH loading and achieved (for 2 steps) 90% yield with 0.05 eq. NaH or 95% with an equimolar amount of $LiNH_2$. Previously, the most reliable laboratory methods involved diazobenzene formation *via* diazotization, followed by hydrogenation (a well-established protocol in the Fischer indole synthesis), or substitution of halo-derivatives with hydrazine.[39]

Several important medicines are synthesized from 4-hydroxyphenylhydrazine as an intermediate product, *e.g.* the well-known non-steroidal anti-inflammatory drug (NSAID) indometacin,[40] which has now been used for 50 years in practice and has inspired drug design towards a new triptan class of NSAIDs. 4-Hydroxyphenylhydrazine is a key intermediate in the synthesis of a new and still expensive drug, bazedoxifene, the latest generation selective estrogen receptor modulator (by Pfizer). It is prepared in 59% yield, thus being the lowest-yield product in the total synthesis of bazedoxifene.[41] In industry, 4-hydroxyphenylhydrazine is synthesized from 4-aminophenol, a precursor of antipyretic agents such as paracetamol (acetaminophen), acetanilide and phenacetin. Nowadays, bulk 4-aminophenol for industrial paracetamol synthesis is produced through different manufacturing routes requiring mineral acids: (1) from 4-nitrochlorobenzene; (2) from phenol; (3) through the electrolytic reduction of nitrobenzene (also, catalytic hydrogenation is possible); (4) from 4-hydroxyacetophenone.[42] The drawbacks of the industrial route are that nitration of chlorobenzene gives a mixture containing one-third *ortho*-substituted products and two-thirds *para*-substituted products and the opposite ratio for the nitrosation of phenol.

They are separated by careful fractionation through an efficient column. The ecological impact of these industrial and previously known laboratory methods is that they generate oxidizers or free radicals as gas or liquid by-products, whereas our new method generates non-hazardous by-product gases during Boc-deprotection.

The proposed hydrazo coupling approach proves to be an efficient gram-scale protocol that eliminates two steps of synthesis with harsh reagents and doubles the overall yield. This makes it perfect for laboratory synthesis and for screening in medicinal chemistry. Boc-diazene is a commercially available, shelf-stable and easy-to-handle solid. It would be a promising addition to the well-established methods.

Scope of the reaction

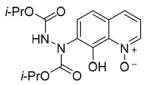
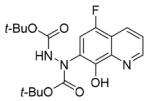
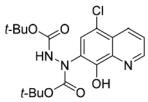
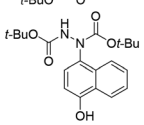
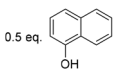
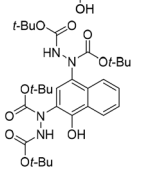
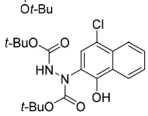
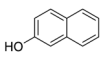
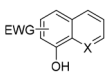
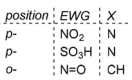
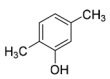
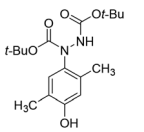
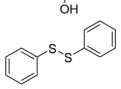
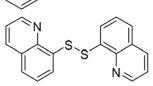
To explore the scope of the reaction, we investigated the possibility of selective functionalization of substituted quinolines, 8-HQ *N*-oxide, α- and β-naphthol (Table 3). 8-HQ *N*-oxide can be regarded as a masked form of 8-HQ, which can be easily reduced back to the 8-HQ moiety at any stage *via* enzymatic reduction by oxidoreductases (*e.g.*, from baker's yeast[43]). *N*-Oxide is capable of the same coupling reaction as 8-HQ. However, we obtained the same product **1c** through another pathway, oxidizing **1a** with *m*-CPBA, in 57% yield. The oxidation is feasible at the N^1 atom regardless of the 7-hydrazinyl substituent and this *N*-oxide can be used for further functionalization at the 2nd position.[44] 5-Substituted 8-hydroxyquinolines with EDG react smoothly in the same way as 8-HQ, although some by-products are formed as well.

It is worth noting that 5-fluoro-8-HQ barely reacts with AD esters without NaH catalysis. We investigated the ^1H NMR and ^{19}F NMR spectra during this reaction in the NMR tube in dioxane-d_8, with and without 1 eq. NaH, without stirring of the heterogeneous reaction mixture. We observed an increase of several orders of magnitude in the rate of the catalytic process. In the base-initiated reaction, the product yield reached ~50% in 6 h and conversion continued to increase linearly, while non-catalyzed conditions gave barely 2% of the product in 12 h.

α-Naphthol is substituted at the *para*-position during the reaction, if the *para*-position is not occupied by another substituent. In the case of β-naphthol, the coupling takes place presumably both at the α- and γ-positions, and the conversion is drastically lower. Quinolines without an 8-OH group do not interact with DIAD, because there is no directing group in their structure.

Even with several equivalents of NaH added as an initiator or other bases, 8-hydroxyquinoline-5-sulfonic acid barely reacts with ADs, with insufficient traces of the product (detected by NMR), and 5-nitro-8-HQ does not react at all. These two EWG-substituted hydroxyquinolines possess strong deactivating groups (–I, –M), which decrease the nucleophilicity of the aro-

Table 3 The substrate scope for substituted substrates. The reaction of arenes with DIAD or Di-*t*Bu-AD in the presence of 5 mol% NaH in THF

Reagent	Conversion (obtained yield)	Product
 R = H, CH_3	0%	—
	99% (83%)	 **1c**
	95% (70%)	 **1d**
	97% (97%)	 **1e**
	90% (80%)	 **1f**
0.5 eq. 	86% (84%)	 **1g**
	99% (95%)	 **1h**
	60% ([a])	A mixture of α- and γ-hydrazinyldicarboxylates of β-naphthol
 	0%	—
	97% (93%)	 **2c**
	92% (90%)	 **6a**
	95% (88%)	 **6b**

[a] β-Naphthol products were not isolated and were identified only by HPLC-HRMS.

matic ring. 2-Nitroso-1-naphthol is also unreactive with its prevalent –M effect of the nitroso group. All this clearly supports the proposed mechanism.

Thiophenol and 8-mercaptoquinoline oxidation to disulfides

Thio-analogues of phenol and 8-hydroxyquinoline do not form hydrazo coupling products; instead, they tend to be almost quantitatively oxidized by ADs to disulfides. This phenomenon is a known process for related classes, such as diazenecarboxamides[45] and phenylazocarboxylate esters,[46] but has not been associated with symmetrical AD esters yet.

Hydrazone synthesis

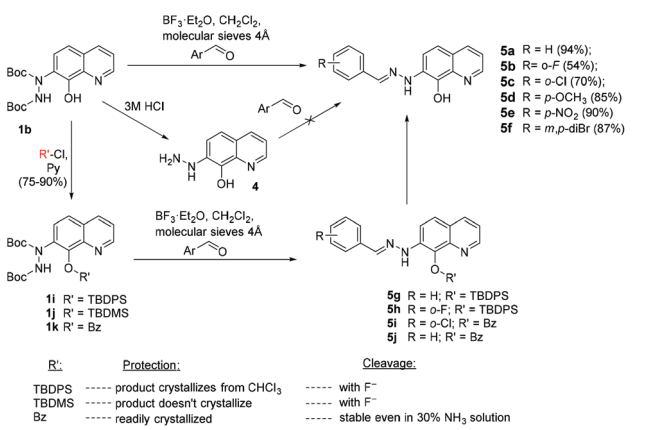
One of the most efficient and fastest ways of obtaining 7-hydrazino-8-hydroxyquinoline derivatives is the synthesis of hydrazones. Diethyl or diisopropyl hydrazinocarboxylate esters are stable under highly acidic or basic conditions, even when heated to 80 °C, and the only previously reported achievable transformation involves the reduction to amines; however, we could not achieve the product following the described method[47] with **1a**. At the same time, the di-*tert*-butyl ester of azodicarboxylate (*i.e.*, Boc-diazene) is suitable for carboxylate elimination. The 7-(*N*,*N*′-di-Boc-hydrazino)8-HQ derivative **1b** has been readily hydrolyzed in 3 M HCl solution, giving a maroon-colored precipitate of 7-hydrazino-8-hydroxyquinoline **4** (Scheme 6). Surprisingly, even after acid neutralization, filtration and complete drying, this compound remains unreactive with aldehydes, possibly owing to the formation of hydrochloride salt obtained during the reaction.

We tested some additives described earlier for facilitating hydrazone synthesis, such as anthranilic acid derivatives.[48] We could not bypass this problem of unreactive **4** except for to use another method of Boc cleavage for **1b**. Oxidative methods, such as treatment with CAN, were unsuitable and resulted in quinoline residue destruction and self-condensation.[49] We also tried KI-catalyzed basic conditions[50] that appeared to be incapable of the cleavage. Finally, the most convenient and steady Boc degradation was achieved with $BF_3{\cdot}Et_2O$.[51] This procedure allows us not only to obtain the desired reactive **4** but also to use it *in situ* with initially added aldehydes and to make this reaction a "one-pot" process. The co-products formed by Boc and boron trifluoride etherate are totally evaporated *in vacuo*, so there is no need for laborious isolation procedure.

The synthesized hydrazones possess great potential for chelation of metals with different selectivities depending on the substituent.

Isolation issues with 8-HQ derivatives

One of the major difficulties while working with 8-HQ derivatives is their isolation or purification with chromatography.



Scheme 6 Synthesis of hydrazones.

The compounds show vast "tailing" on columns and TLC plates in the common eluting systems consisting of DCM, ethanol, EtOAc or hexane due to the zwitterionic nature of the N^1 – 8-OH motif. Not only are the products discussed in this manuscript affected, but the whole class of 8-HQ derivatives possesses this problem, lowering the yield of the final products and exacerbating the separation procedure. We thoroughly adjusted the eluting system and found that the crucial additive was 1% AcOH; as a result, CCl_4–dioxane (4 : 1) + 1% AcOH appeared to be the optimal system for our derivatives. In the case of the hydrazine derivatives **5a–f**, we found that the products are insoluble in DCM. To make product isolation easier, the excess aldehyde in the reaction mass can be first washed out through the filter in chloroalkanes, and then, the sole clear product can be washed with ethanol.

There is another approach to solve the problem: masking the OH group in **1b** prevents peak tailing in chromatography. For this purpose, we tried three protective groups. Benzoyl and silyl ester protection proceeded smoothly, but the following deprotection of derivatives **5g–i** revealed some peculiarities of stability. [Si]-cleavage with TBAF was less effective even with excess reagent, and at the same time the [Si]–F by-products were difficult to separate from the target products. Inorganic fluorides were among the best in this cleavage reaction:[52] we tried KHF_2 and found that the products were partially affected, but ammonium fluoride appeared to be better (and it was almost insoluble in acetone, making it easy to isolate the excess reagent). Basic conditions (Cs_2CO_3 with imidazole, or NaH) did not lead to the cleavage of the [Si] groups from the 8-HQ moiety,[53] whereas benzoyl protection led to extremely stable derivatives **1k** and **5i**, which were not affected in 3 M NaOH solution or even 33% ammonia. This surprising effect may be due to the intermolecular hydrogen bonding of the 7-hydrazinyl fragment.

Conclusions

A new reaction involving the catalyzed C–H functionalization of 8-hydroxyquinoline, phenol and α-naphthol derivatives has been developed. It can be carried out under mild conditions and room temperature using commercially available inexpensive materials: NaH as an initiator, and THF or dioxane as a solvent. We have also proposed and confirmed the mechanism of this reaction, backing up our suggestions with NMR data. The participation of the phenolate as a directing group results in excellent yields of the coupling reaction, and the transformation can be regarded as "hydrazo coupling" (by analogy with azo coupling). Moreover, Boc-protected 7-hydrazino-8-hydroxyquinoline was then employed in the synthesis of aromatic hydrazones using a novel efficient "one-pot" protocol. Several approaches were investigated to overcome technical problems in the chromatography procedures of 8-hydroxyquinoline compounds as zwitterionic structures. To summarize, we have synthesized previously undescribed products bearing potential as new building blocks and biologically active compounds. In addition to the practical application of this method for laboratory use, 4-hydroxyphenylhydrazine, an industrial intermediate product for total synthesis in medicinal chemistry, has been obtained through a straightforward and fast gram-scale protocol that allows the elimination of two steps used in industrial synthesis with harsh reagents, while also doubling the overall yield.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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