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O-Cyclopropyl Hydroxylamines as Precursors for *[3,3]*-Sigmatropic Rearrangements

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ARTICLE

O-Cyclopropyl Hydroxylamines: Gram-Scale Synthesis and Utility as Precursors for *N*-Heterocycles

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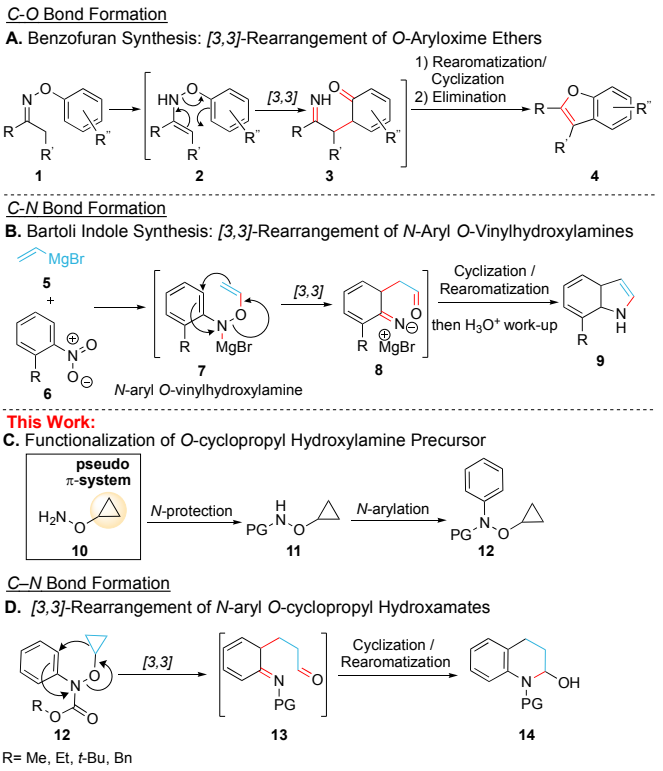
O-Cyclopropyl hydroxylamines, now accessible via a novel and scalable synthetic route, have been demonstrated to be bench-stable and practical precursors for the synthesis of *N*-heterocycles via a di-heteroatom *[3,3]*-sigmatropic rearrangement. In order to study the reactivity of these compounds in depth, a robust synthesis of both ring-substituted and ring-unsubstituted *O*-cyclopropyl hydroxylamines has been developed. Metal-free conditions for the facile *N*-arylation of these precursors were also identified. It was found that the *N*-Arylated *O*-cyclopropyl hydroxamates can efficiently undergo a one-pot *[3,3]*-sigmatropic rearrangement/cyclization/rearomatization cascade under base-mediated conditions to furnish a structurally diverse set of substituted tetrahydroquinolines.

Introduction

[3,3]-Sigmatropic rearrangements are highly valuable transformations *en route* to both carbo- and heterocycles due to their overall synthetic efficiency and atom economy. For the preparation of oxygen- and nitrogen-containing heterocycles, *[3,3]*-rearrangements that involve cleavage of weak *N-O* bonds are of particular interest. The acid-catalyzed *[3,3]*-rearrangement of aryloxime ethers to form benzofurans is an excellent example of *O*-heterocycle formation (Scheme **1A**).[1] This reaction mechanism is comparable to that of the Fischer-indole synthesis, in which the key *[3,3]*-rearrangement involves cleavage of the weak *N-N* bond in *N*-arylhydrazone substrates. Another noteworthy *N*-heterocycle-forming reaction is the Bartoli indole synthesis, which involves the *[3,3]*-rearrangement of an *in situ*-generated *N*-aryl-*O*-vinylhydroxylamine intermediate via *N-O* bond cleavage (Scheme **1B**).[2] These types of cascade reactions have been shown to be robust methods to produce substituted heterocycles.

Inspired by the *N*-aryl-*O*-vinylhydroxylamine intermediate (**7**, Scheme **1B**) that is involved in the Bartoli indole synthesis, we proposed that *O*-cyclopropyl hydroxylamine, an analogous and potentially bench-stable compound, could serve as a *[3,3]*-sigmatropic rearrangement precursor to furnish a variety of substituted heterocycles. It is likely that *O*-cyclopropyl hydroxylamines can be further derivatized, which would make them homologues of the highly reactive and transient precursors for *[3,3]*-rearrangements that involve *N-O* bond cleavage. *O*-Cyclopropyl hydroxylamine is hypothesized to possess similar reactivity to the *O*-vinyl hydroxylamine intermediates shown in the heterocycle-forming reactions above in Schemes **1A** & **1B**, because it features both a readily cleavable *N-O* bond[3] and a strained cyclopropane *C-C* bond (i.e., banana bond) that ultimately could serve as a three-carbon homoenolate equivalent (Scheme **1C**).[4] Therefore, these two



Scheme 1 *[3,3]*-Sigmatropic Rearrangements that Involve *N-O* bonds and Lead to the Formation of *C-O* and *C-N* Bonds.

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reactive sites have the potential to participate in a homologous *[3,3]*-sigmatropic rearrangement when a π-system (i.e., vinyl or aryl group) is directly attached to the nitrogen atom.[5]

As an initial proof of concept, we proposed that *N*-protected/*N*-arylated derivatives of *O*-cyclopropyl hydroxylamine (**12**, Scheme **1D**) should undergo a *[3,3]*-rearrangement to furnish 2-hydroxy-tetrahydroquinolines (**14**). If these types of compounds efficiently undergo *[3,3]*-rearrangement, it can be envisioned that other *O*-cyclopropyl hydroxylamine derivatives such as *N*-vinyl or *N*-acyl derivatives could be synthesized and would in turn undergo *[3,3]*-rearrangement to afford a variety of other heterocycles.

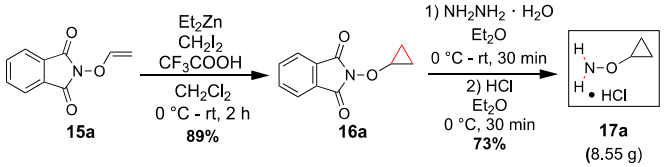
Herein we report a gram-scale synthesis for *O*-cyclopropyl hydroxylamines as well as a protocol for the facile *N*-arylation of these compounds. Additionally, we disclose the synthesis of twenty α-functionalized tetrahydroquinolines from *O*-cyclopropyl *N*-aryl hydroxamate substrates, demonstrating that these compounds can in fact function as suitable *[3,3]*-rearrangement precursors.

Results and Discussion

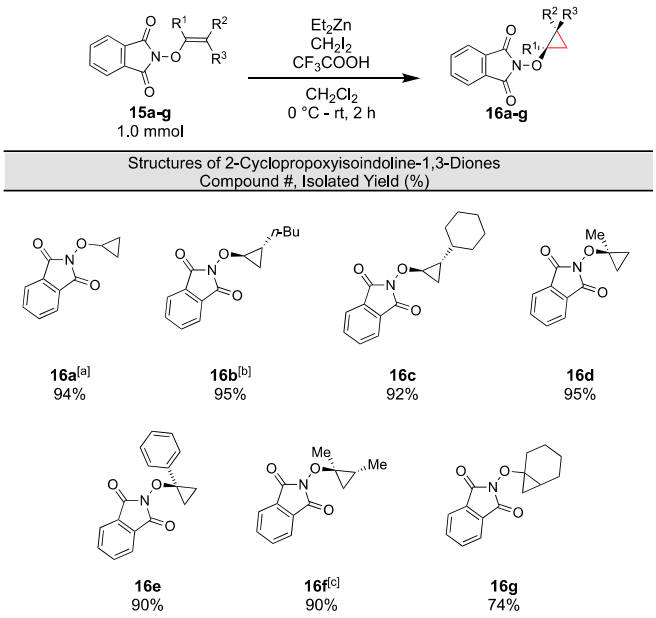
Initially, we set out to synthesize the target *O*-cyclopropyl hydroxylamine compound (**10**) via direct *O*-cyclopropanation of *N*-Boc hydroxylamine. Unfortunately, neither *O*-alkylation with bromocyclopropane/strong base nor transition metal-catalyzed cross-coupling with cyclopropyl boronic acid were successful in our hands.[6] Subsequently, a novel approach where the cyclopropane ring could be installed via olefin cyclopropanation was identified as an alternate synthetic route.[7]

We proposed that 2-(vinyloxy)isoindoline-1,3-dione (**15a**)[5d, 8] could function as an ideal cyclopropanation substrate because it contains the desired *N*-*O*-vinyl connectivity. After several optimizations, it was found that efficient cyclopropanation of **15a** was possible under Simmons-Smith-type conditions with trifluoracetic acid used as an additive (Scheme 2).[9] The product, 2-cyclopropoxyisoindoline-1,3-dione (**16a**), was then subjected to standard hydrazine hydrate-mediated phthalimide-cleavage conditions,[10] followed by hydrochloride salt-formation. Utilizing this three-step approach, over eight grams of the desired *O*-cyclopropyl hydroxylamine was prepared and fully characterized as the hydrochloride salt **17a**. It is noteworthy that the free-base form of *O*-cyclopropyl hydroxylamine **10** was volitile under vacuum.

In addition to the synthesis of ring-unsubstituted 2-cyclopropoxyisoindoline-1,3-dione (**16a**), six ring-substituted derivatives **16b**-**g** were also synthesized in high yields



Scheme 2 Gram-scale synthesis of *O*-cyclopropyl hydroxylamine hydrochloride salt.

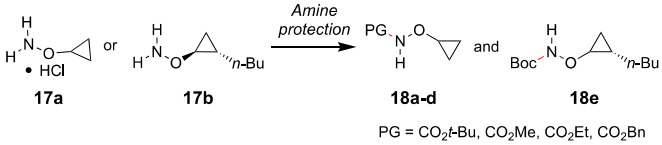


Scheme 3 Ring-unsubstituted and ring-substituted *O*-cyclopropyl *N*-hydroxyphthalimide products.
[a] 11.33 mmol scale. [b] 5.0 mmol scale. [c] 6 hours reaction time.

(Scheme 3). Substituted 2-(vinyloxy)isoindoline-1,3-diones with an aliphatic or aromatic substituent in either the α– or β–position (**15b**-**e**) were successfully converted to their corresponding cyclopropoxy products **16a**-**e** under these conditions. Di-substituted olefins also efficiently underwent cyclopropanation to form **16f** and **16g**. From these examples, **16b** was subjected to the phthalimide-cleavage conditions to produce ring-substituted *O*-cyclopropyl hydroxylamine **17b** (Scheme 4) in 78% isolated yield. Unlike *O*-cyclopropyl hydroxylamine **10,** the free-base form of the ring-substituted *O*-cyclopropyl hydroxylamine **17b** was non-volatile under reduced pressure. Both HCl salt **17a** and free-base **17b** were bench-stable compounds and could be stored in a –20 °C freezer for several months. Even after long-term storage, no significant amounts of decomposition were observed, and these compounds were successfully carried through further functionalization steps.

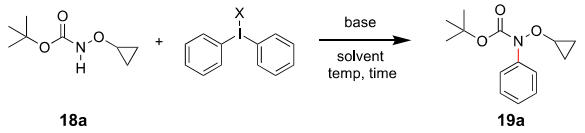
Ring-unsubstituted and ring-substituted *O*-cyclopropyl hydroxylamines (**17a** and **17b**) were then converted to the corresponding *tert*-butyl, methyl, ethyl and benzyl cyclopropoxy-carbamates (**18a**-**e**, Scheme 4).

With the synthesis of *O*-cyclopropyl hydroxamates now optimized, the next step was to identify suitable *N*-arylation conditions for these substrates. In our hands, established *N*-arylation methods such as Buchwald-Hartwig or Chan-Lam cross-couplings[11] failed, which prompted us to explore metal-



Scheme 4 *N*-Protection of *O*-cyclopropyl hydroxylamines.

Table 1 Reaction optimization for *N*-arylation of *O*-cyclopropyl hydroxamates.



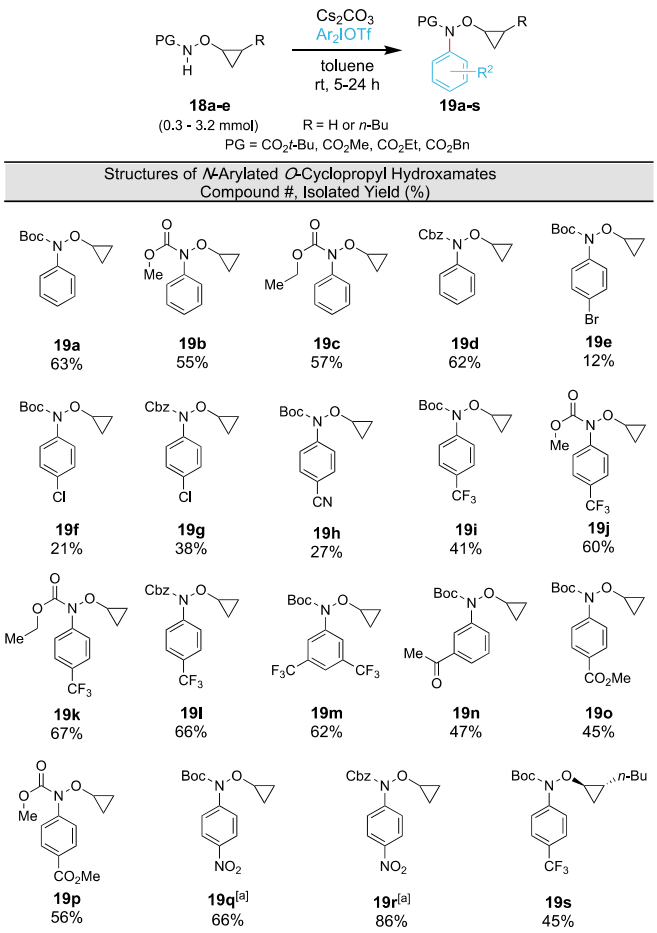
18a **19a**

Entry[a]	Ph_2IX (equiv.)	Base (2.0 equiv.)	Solvent (0.1 M)	Temp (°C)	Time (h)	**19a**[b] (%)
1	BF_4 (1.5)	Cs_2CO_3	toluene	25	12	20
2	OTs (1.5)	Cs_2CO_3	toluene	25	12	29
3	OMs (1.5)	Cs_2CO_3	toluene	25	12	< 5
4	OTf (1.5)	Cs_2CO_3	toluene	25	6	75
5	OTf (1.2)	Cs_2CO_3	toluene	25	6	22
6	OTf (1.5)	Cs_2CO_3	toluene	50	6	52
7	**OTf (1.5)**	**Cs_2CO_3**	**toluene**	**25**	**9**	**82**
8	OTf (2.0)	Cs_2CO_3	toluene	25	6	56
9	OTf (2.0)	K_2CO_3	toluene	25	12	14
10[c]	OTf (2.0)	Na_2CO_3	toluene	25	12	0
11	OTf (2.0)	KO*t*-Bu	toluene	25	12	53
12	OTf (2.0)	NaH	toluene	25	12	19
13[d]	OTf (2.0)	Cs_2CO_3	DMF	25	12	< 5
14[d]	OTf (2.0)	Cs_2CO_3	CH_3CN	25	12	33

[a] The reactions were performed on 0.2 mmol scale with a 0.1 M concentration of the *N*-protected *O*-cyclopropyl hydroxamate and stirred for the indicated amount of time. [b] NMR yields by analysis of 1H NMR of crude reaction mixtures with CH2Br2 as an internal standard. [c] 89% of *O*-cyclopropyl hydroxamate starting material observed. [d] tert-butyl 2-hydroxy-3,4-dihydroquinoline-1(2H)-carboxylate (rearranged product) observed in crude 1H NMR (< 10%).

free (i.e., diaryliodonium salt-mediated) *N*-arylation conditions.[12] Through optimization studies (Table 1), it was found that the triflate diphenyliodonum salt yielded the largest amount arylated product compared to other salts (Entries 1-4, Table 1). When the amount of Ph_2IOTf was decreased from 1.5 to 1.2 equivalents the yield was nearly quartered (75%→22%, [Entry 4 vs Entry 5, Table 1]). Increasing the equivalents of diphenyliodonium salt to 2.0, and conducting a reaction (1.5 equiv. of Ph_2IOTf) at elevated temperatures also resulted in lower yields of the arylated product (Entry 8 and Entry 6, Table 1). However, it was observed that when a reaction with 1.5 equivalents of diphenyliodonium salt was stirred for an additional 3 hours, the yield could be further improved (6 h→9 h, 75%→82%, [Entry 4 vs Entry 7, Table 1]). The testing of different inorganic bases (Entries 9-12, Table 1) revealed that, Cs_2CO_3 was the ideal base for this transformation and could produce the highest yield of arylated product with the shortest reaction time. Solvents other than toluene were tested, but the use of dimethylformamide (DMF) and acetonitrile (CH_3CN) resulted in low yields of the desired *N*-arylated product and observable yields of the 2-hydroxy-tetrahydroquinoline *[3,3]*-rearrangement product (Table 1, Entries 13 & 14). The optimal *N*-arylation conditions were found to be 1.5 equivalents of diaryliodonium triflate salt and 2.0 equivalents of Cs_2CO_3 in toluene (0.1 M in *O*-cyclopropyl hydroxamate) at room temperature.

With the optimized *N*-arylation conditions in hand, the scope of substrates was explored using a variety of diaryliodonium salts. With Ph_2IOTf, the ring-unsubstituted *tert*-butyl, methyl, ethyl and benzyl *O*-cyclopropyl hydroxamates (**18a-d**) furnished comparable yields of their corresponding



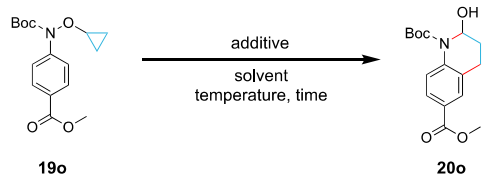
Scheme 5 *N*-arylation of *O*-cyclopropyl hydroxamates. [a] from Ph(p-nitro-Ph)IOTf.

arylated products (**19a**-**d**, Scheme 5). A diverse set of electron-withdrawing groups (i.e. nitriles, trifluoromethyl groups, ketones, esters and nitro groups) were tolerated on the aryl ring to furnish a total of nineteen (19) *N*-arylated products (**19a-s**, Scheme 5). The presence of an electron-donating group (i.e. methyl) on the aromatic ring allowed the hydroxamate substrate to undergo the *N*-arylation/*[3,3]*-sigmatropic rearrangement cascade in one-pot. Therefore, when *p*-tolyl-and *m*-tolyliodonium salts were used, the *N*-arylated intermediates were not isolated, but were subsequently subjected to rearrangement conditions to ensure their complete conversion to the corresponding heterocyclic products **20q-10t** (Scheme 6). In our hands, when electron-rich diaryliodonium salts (e.g. *p*-methoxybenzeneiodonium salt) were utilized, significant decomposition occurred and only trace amounts of the desired *N*-arylated product could be observed. This result is consistent with other reported metal-free arylation conditions which demonstrate that the use of electron-rich diaryliodonium salts affords lower yields of the corresponding arylated products.[13] All of the *N*-arylated products were synthesized from symmetrical diaryliodonium salts, except for **19q** and **19r**. These examples were prepared by using the unsymmetrical diaryliodonium salt Ph(p-nitro-Ph)IOTf. The analysis of these examples allowed us to identify a clear reactivity trend: with the use of an unsymmetrical diaryliodonium salt the major product was formed as a result of the more electron-deficient aryl group being transferred, which is in alignment with previously reported findings.[14]

To demonstrate the utility of *O*-cyclopropyl hydroxylamines as sigmatropic rearrangement precursors, optimal conditions for the *[3,3]*-rearrangement of *N*-arylated *O*-cyclopropyl hydroxamates to the corresponding 2-hydroxy-tetrahydroquinolines were identified (Table 2). Stirring the *N*-arylated starting material (**19o**) at ambient temperature without additives did not trigger the rearrangement (Entries 1 & 2, Table 2). Additionally, when Lewis acidic additives such as TfOH and $ZnCl_2$ were used, formation of the desired product was not observed. It was found that with the addition of a base [i.e. triethylamine (Et_3N)], the desired 2-hydroxy-tetrahydroquinoline (**20o**) was formed in THF, but not in toluene (Entries 3 & 4, Table 2). Screening of multiple solvents (Entries 5-8, Table 2) revealed trifluoroethanol (TFE) to be the ideal solvent for this transformation. Despite the fact that other basic additives were capable of producing the 2-hydroxy-tetrahydroquinoline product, none were as efficient as Et_3N (Entries 10 &11, Table 2).

With the optimal conditions identified, the next step was to demonstrate the robustness of this *[3,3]*-sigmatropic rearrangement by exploring its scope of substrates. In this study, twenty (20) 2-hydroxy-tetrahydroquinoline products (**20a**-**20p**, Scheme 6) were successfully synthesized in moderate to good yields. The set of *N*-phenyl *O*-cyclopropyl hydroxamates **19a**-**d**, which each possessed a different *N*-protecting group, efficiently underwent rearrangement producing their respective tetrahydroquinoline product in comparable yields (**20a**-**d**). A variety of functional groups on the aryl ring were tolerated and twelve (12) of the substituted *N*-aryl *O*-cyclopropyl hydroxamates synthesized in the previous transformation (**19e**-**p**) were successfully rearranged to the corresponding *N*-heterocycles (**20e-20t**). It was observed that substrates with more electron-deficient aromatic rings took longer to undergo the rearrangement/cyclization cascade compared to the less electron-deficient substrates. As previously stated, the *N*-arylated *O*-cyclopropyl hydroxamate examples with a methyl substituent on the aryl ring were not isolated but were successfully carried through the rearrangement conditions to produce tetrahydroquinoline products **20q**-**t** in moderate yields. Interestingly, the *m*-tolyl Boc-protected substrate rearranged into a mixture of isolable regioisomers **20q** and **20r**. However, rearrangement of the *m*-tolyl Cbz-protected substrate produced only one regioisomer (**20t**). We hypothesize that this regioselectivity could be due to π-stacking interactions between the Cbz group and the *N*-aryl group prior to the *[3,3]*-rearrangement.

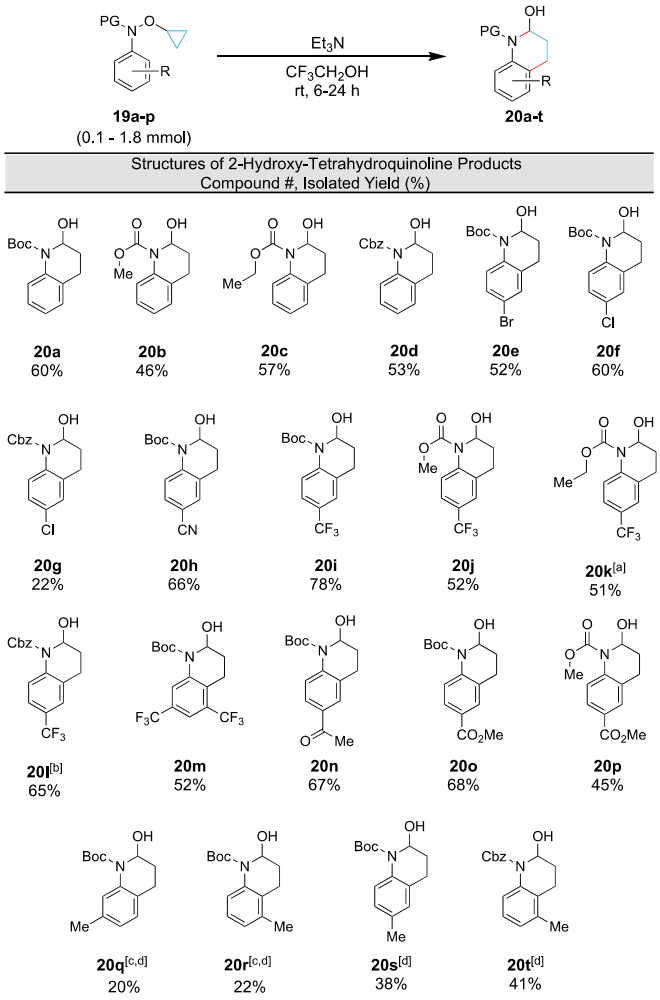
Table 2 Reaction optimization for *[3,3]*-sigmatropic rearrangement of *N*-arylated *O*-cyclopropyl hydroxamates.



19o **20o**

Entry[a]	Additive (2.0 equiv.)	Solvent (0.1 M)	Time (h)	**20o**[b] (%)
1	None	toluene	48	0
2	None	THF	48	0
3	Et_3N	toluene	48	0
4	Et_3N	THF	48	22
5	Et_3N	DCM	48	33
6	Et_3N	MeCN	48	26
7	Et_3N	EtOH	48	51
8	**Et_3N**	**TFE**	**26**	**66**
9[c]	Et_3N	TFE	3	54
10	DIPEA	TFE	34	62
11	Cs_2CO_3	TFE	30	59

[a] Reactions performed on 0.1 mmol scale with a 0.1 M concentration of the *N*-arylated *O*-cyclopropyl hydroxamate. Stirred for the indicated amount of time at room temperature unless otherwise stated. [b] Isolated yields after column chromatography. [c] Reaction performed at 60 °C.

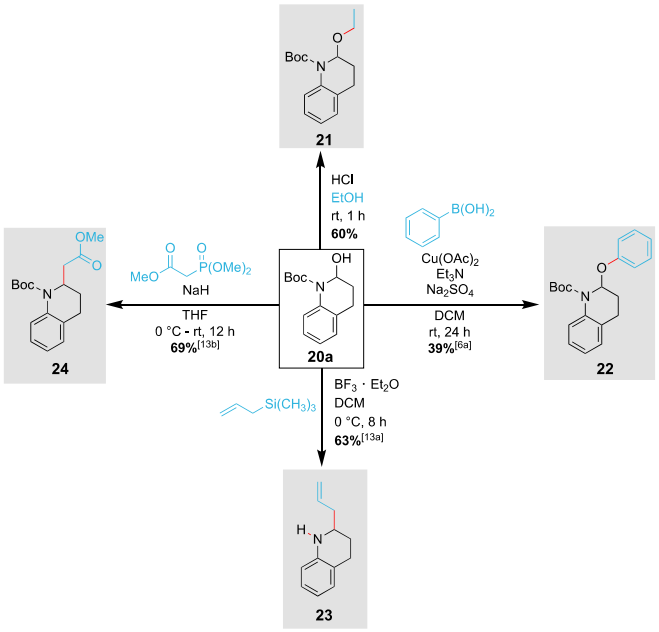


Scheme 6 2-hydroxy-tetrahydroquinoline products obtained via *[3,3]*-sigmatropic rearrangement.

[a] 60 °C, over 7 hours. [b] 80 °C, over 7 hours. [c] Isolated from one reaction of *meta*-substituted substrate. [d] From crude arylation reaction mixture that was directly subjected to rearrangement conditions.

Additionally, it was demonstrated that the hydroxy-tetrahydroquinoline products could be further functionalized at their 2-position via straightforward *C-C* and *C-O* bond-forming transformations (Scheme 7).[6a, 15] Tetrahydroquinoline **20a** was converted to an aliphatic or aromatic ether (**21** or **22**) under acidic condensation conditions or via a *Chan-Lam*-type coupling. Under *Hosomi-Sakurai*-type allylation conditions **20a** was transformed into 2-allyl free amine **23**. Finally, an *in situ*-generated phosphonium ylide from methyl 2-(diethoxyphosphoryl)acetate, was reacted with tetrahydroquinoline **20a** to form 2-methoxy-2-oxoethyl addition product **24**.

The *[3,3]*-rearrangement of ring-substituted *N*-aryl *O*-cyclopropyl hydroxamate substrate **19s** has so far been suboptimal under the reaction conditions detailed above. Therefore, further refinement of the reaction conditions is required to achieve the facile and efficient *[3,3]*-rearrangement of the cyclopropyl ring-substituted substrates.



Scheme 7 Further functionalization of 2-hydroxy-tetrahydroquinoline product **20a**.

Conclusions

A scalable method for the direct synthesis of previously reported but uncharacterized ring-unsubstituted *O*-cyclopropyl hydroxylamine and previously unreported ring-substituted *O*-cyclopropyl hydroxylamines has been developed. These precursors were successfully *N*-protected/*N*-arylated and the resulting *N*-aryl *O*-cyclopropyl hydroxamate products were obtained in good to moderate yields. It was demonstrated that these hydroxamates could undergo a facile *[3,3]*-sigmatropic rearrangement followed by cyclization/rearomatization to efficiently produce the corresponding 2-hydroxy tetrahydro-quinolines in a one-pot, three-step cascade reaction. Our studies clearly established the synthetic utility of bench-stable *O*-cyclopropyl hydroxylamines as precursors for the preparation of substituted *N*-heterocycles. Further exploitation of these valuable *O*-cyclopropyl hydroxylamine building blocks is currently underway in our laboratory.

Experimental Section

General Information

All starting material syntheses were performed in oven-dried 50 mL or 100 mL round-bottomed flasks. Commercially available solvents and reagents were used without further purification. All arylation reactions were carried out in oven-dried 8 mL scintillation vials, while rearrangement reactions were carried out in oven-dried 20 mL scintillation vials. All reactions were monitored by thin-layer chromatography (TLC) with E. Merck silica gel 60 F254 pre-coated plates (0.25 mm). Flash chromatography was carried out using a Biotage Isolera One system with 10g KP-Sil cartridges utilizing ethyl acetate (EA) and hexane (hex) as eluents. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were obtained using a Bruker DRX-600 NMR

spectrometer. Chemical shifts are documented in parts per million (δ, ppm). ^{1}H NMR spectra are referenced to 7.26 ($CDCl_3$) and ^{13}C NMR spectra are referenced to 77.16 ($CDCl_3$). High Resolution Mass Spectrometry was performed on an Agilent 1290/6230 LCMS-TOF under electrospray ionization (ESI) conditions in both positive and negative mode. Melting points were recorded on a Mettler Toledo MP50 melting point system.

The preparation of the *N*-enoxyphthalimides was carried out following literature reported protocols. *N*-enoxyphthalimide **15a** was synthesized following protocol A[8] and the *N*-enoxyphthalimides (**15b**-**g**) were synthesized following copper promoted protocol B.[5d] The ^{1}H and ^{13}C NMR spectra of the obtained *N*-enoxyphthalimides were consistent with those reported in the literature.[8, 5d, 16]

General Procedure for the Preparation of 2-cyclopropoxyisoindoline-1,3-diones

Neat diethylzinc (20.5 mL, 200 mmol, 2.0 equiv.) was added to 250 mL of dry DCM under inert atmosphere in a glove box. The diethylzinc solution was removed from the glove box and kept under inert gas. A solution of trifluoroacetic acid (15.3 mL, 200 mmol, 2.0 equiv.) in DCM (125 mL) was slowly added to the diethylzinc solution at 0 °C and stirred until gas evolution ceased. After stirring at 0 °C for about 20 minutes, a solution of diiodomethane (16.13 mL, 200 mmol, 2.0 equiv.) in DCM (125 mL) was added. The mixture was stirred for an additional 20 minutes. Upon further stirring, a solution of *N*-enoxyphthalimide **15a** (22.7 g, 120 mmol, 1.0 equiv.) in DCM (100 mL) was added. Then the reaction was removed from the ice bath, allowed to warm to rt and stirred for 2 h or until the reaction was complete by TLC analysis. Once the starting material was consumed, the reaction mixture was decanted into a separatory funnel and carefully quenched with 0.1 N HCl (500 mL). The organic layer was separated and washed with saturated $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4, filtered and concentrated. The crude mixture was purified via flash chromatography (30% EA in hexanes) to give 2-cyclopropoxyisoindoline-1,3-dione **16a** as a white solid. The same procedure was used to synthesize **16b**-**g** from the corresponding *N*-enoxyphthalimides.

General Procedure for the Preparation of *O*-cyclopropyl Hydroxylamines

Hydrazine hydrate (50-60 %, 7.5 ml, 118 mmol, 2.8 equiv.) was added dropwise (over 3 minutes) to a solution of 2-cyclopropoxyisoindoline-1,3-dione 16a (8.5 g, 42 mmol, 1.0 equiv.) in diethyl ether (167 ml, 0.25 M) at 0 °C. The reaction mixture was allowed to warm to rt and stirred for 30 minutes. The turbid mixture turned clear with a white precipitate. The precipitated diazine by-product was filtered and washed with diethyl ether (60 ml). The combined ether filtrate was re-cooled to 0 °C and 2M HCl in ether (31.5 ml, 63 mmol, 1.5 equiv.) was added over 3 minutes. The flask was stirred at 0 °C for an additional 30 minutes. The mixture was filtered, and the white solid was collected and dried to give the desired *O*-cyclopropyl hydroxylamine hydrochloride salt **17a** as a white solid.

For the synthesis of **17b** the same procedure was followed. Once the precipitated diazine by-product was removed, the filtrate was concentrated and yielded the desired *O*-((1R,2R)-2-butylcyclopropyl)hydroxylamine product **17b** as a colorless oil.
To furnish *O*-cyclopropyl hydroxamates **18a**-**e,** *N*-protection of **17a** and **17b** was accomplished utilizing standard literature reported conditions. Further experimental details for the *N*-protection procedures can be found in the supplementary information.

General Procedure for the Preparation of *N*-arylated-*O*-cyclopropyl Hydroxamates

In an oven-dried 8 mL vial, *O*-cyclopropyl hydroxamate (**18a**-**e**) (0.3 mmol, 1.0 equiv.) and cesium carbonate (196mg, 0.6 mmol, 2.0 equiv.) were suspended in dry toluene (1.5 mL, 0.1 M). The desired diaryliodonium salt (0.45 mmol, 1.5 equiv.) was added at room temperature in one portion. The mixture was stirred for 5-24 hours at room temperature, until TLC indicated complete consumption of the *O*-cyclopropyl hydroxamate starting material. Upon reaction completion, the mixture was filtered through celite. The celite was washed four times with ethyl acetate (5 ml each), the filtrate was collected, and the solvent was removed in vacuo. The crude product was purified using flash chromatography (10% EA in hexanes) on a Biotage Isolera system to give the desired *N*-arylated-*O*-cylcopropyl hydroxamate products (**19a**-**s**).

General Procedure for the Preparation of 2-Hydroxy-tetrahydroquinolines via *[3,3]*-Rearrangement

N-arylated-*O*-cyclopropyl hydroxamate (**19a**-**s**, 50 mg, 0.2 mmol, 1.0 equiv.) was added to an 8 mL oven-dried vial equipped with a stir bar. The vial was capped, placed under an argon atmosphere and trifluoroethanol (2.0 mL, 0.1M) was added. Triethylamine (55.8 µL, 0.4 mmol, 2.0 equiv.) was then added to the solution via syringe. The reaction mixture was stirred at rt for 6-24 hours. After complete consumption of the starting material was confirmed via TLC, the reaction mixture was concentrated under reduced pressure. The crude mixture was then purified using flash chromatography (12 % EA in hexanes) on a Biotage Isolera system to give the desired tetrahydroquinoline products (**20a**-**s**).
Tetrahydroquinoline **20a** was further functionalized at the 2-position to furnish products **21**-**24** via modified literature procedures. Further experimental details for these procedures can be found in the supplementary information.

Conflicts of interest

There are no conflicts to declare.

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