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Electrophilic Zinc Homoenolates: Synthesis of Cyclopropylamines from Cyclopropanols and Amines

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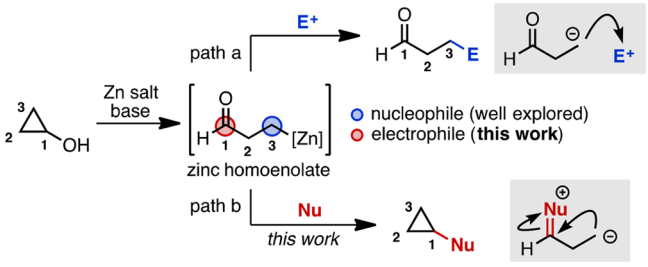
Supporting Information

ABSTRACT: Metal homoenolates, produced via C−C bond cleavage of cyclopropanols, have been extensively investigated as nucleophiles for the synthesis of β-substituted carbonyl derivatives. Herein, we demonstrate that zinc homoenolates can react as carbonyl-electrophiles in the presence of nucleophilic amines to yield highly valuable *trans*-cyclopropylamines in good yields and high diastereoselectivities. GSK2879552, a lysine demethylase 1 inhibitor currently in clinical trials for the treatment of small cell lung carcinoma, was synthesized using this strategy.

The chemistry of metal homoenolates has a rich history.[1] These reagents are traditionally used as nucleophiles that can be trapped by various electrophiles or transition metal catalysts to generate β-functionalized aldehydes and ketones (Scheme 1, path a). Zinc homoenolates participate in a range of

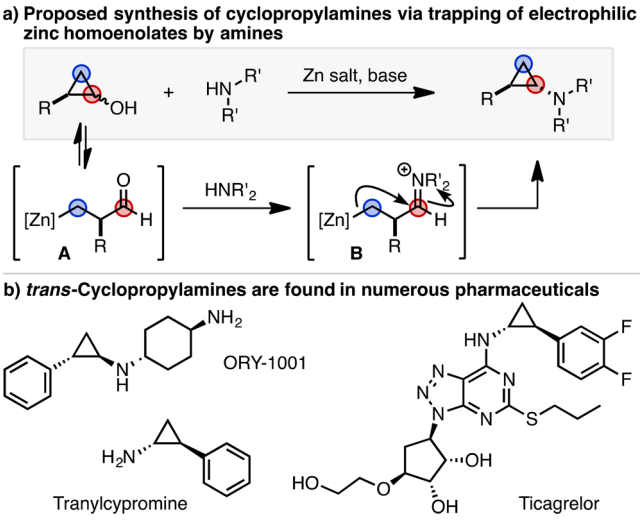
Scheme 1. Typical Homoenolate Reactivity of Cyclopropanols Towards Electrophiles (E^+, Path a) and Proposed Inverse Electrophilic Reactivity in the Presence of Nucleophiles (Nu, Path b)



reactions including additions to carbonyls, copper-catalyzed conjugate additions, and allylation reactions.[2] Metal homoenolates have also been used as nucleophiles in transition-metal-catalyzed C−C and C−X bond-forming reactions.[3]

While the nucleophilic reactivity of zinc homoenolates at C3 has been extensively explored, we hypothesized that these reagents could also behave as electrophiles at C1, leading to new opportunities for method development with this class of compounds (Scheme 1, path b).[4] To test this hypothesis, we chose to explore the reactivity of zinc homoenolates derived from cyclopropanols with nucleophilic amines (Scheme 2a).[5] In the presence of base and a zinc salt, the cyclopropanol can ring-

Scheme 2. (a) Reaction Design for the Synthesis of Cyclopropylamines from Zinc Homoenolates; (b) Prevalence of the *trans*-Cyclopropylamine Motif in the Pharmaceutical Industry



open to generate zinc homoenolate **A**.[5,6] Formation of intermediate **B**, via reaction of the amine at the electrophilic carbonyl position and subsequent nucleophilic ring closure, would yield *trans*-cyclopropylamine products.[7,8] Following this synthetic strategy allows us to fully realize the amphoteric nature of the zinc-homoenolate, with both the electro- and nucleophilic carbons being important for cyclopropylamine formation.[9,10] The products of these transformations are also of high synthetic interest due to their prevalence in pharmaceuticals (Scheme 2b).[11] While several methods for the synthesis of *trans*-cyclopropylamines have been reported, achieving high levels of diastereo- and enantioselectivity often remains a challenge.[11b,12,13]

We initiated our investigation into the electrophilic reactivity of homoenolates for the synthesis of cyclopropylamines by exploring the reaction of cyclopropanol **1a** with morpholine in the presence of zinc salts (Table 1). We chose zinc salts for the generation of the homoenolate based on previous reports, which suggested that zinc cyclopropoxides undergo rapid and reversible ring opening/ring closing via the formation of a short-lived zinc homoenolate intermediate (cyclopropanol ⇌

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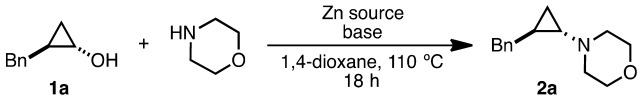
Table 1. Effect of Zinc Salts on the Reaction of Cyclopropanols with Amines[a]



entry	Zn source	base	equiv of **1a**	yield[b]	d.r.[b]
1	Et_2Zn	–	1.0	64%	>20:1
2	Et_2Zn	–	1.5	83%	>20:1
3	$ZnCl_2$	–	1.5	69%	6.2:1
4	$ZnCl_2$	Na_2CO_3	1.5	89%	4.9:1
5	$Zn(OAc)_2$	Na_2CO_3	1.5	95%	7.1:1
6	$Zn(CN)_2$	Na_2CO_3	1.5	99%	20:1
7	$Zn(CN)_2$	Na_2CO_3	1.2	91%	>20:1
8	–	–	1.5	0%	–
9	–[c]	NaH	1.0	0%	–

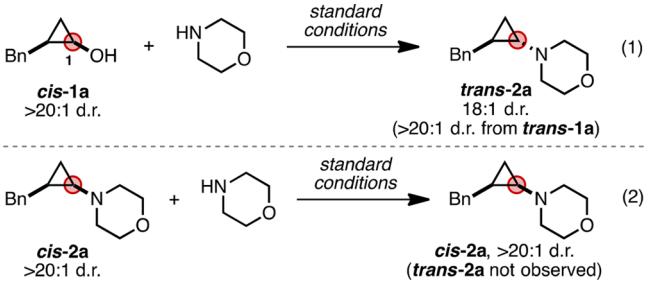
[a]Reactions were performed using morpholine (0.1 mmol, 1.0 equiv), cyclopropanol **1a** (1.0–1.5 equiv), Zn source (2.0 equiv), and base (2.0 equiv, if added) in 1,4-dioxane (0.1 M) at 110 °C for 18 h. [b]Determined by GC-MS using dodecane as an internal standard. Yield of both diastereomers. [c]$MgCl_2$ (2.0 equiv) instead of a source of zinc.

A, Scheme 2a).[6] Treating **1a** and morpholine with Et_2Zn in 1,4-dioxane at 110 °C for 18 h yielded cyclopropylamine **2a** in 64% yield and >20:1 d.r. (Table 1, entry 1). The use of **1a** in slight excess (1.5 equiv) led to an increase in yield to 83% (entry 2).

To avoid functional group limitations associated with the use of Et_2Zn, we next explored whether other zinc salts could promote this transformation. Replacing Et_2Zn with $ZnCl_2$ was surprisingly effective, affording **2a** in 69% yield, with a decrease in diastereoselectivity to 6.2:1 (entry 3). Adding Na_2CO_3 to the reaction further increased the yield to 89% (entry 4). A screen of various zinc salts revealed that $Zn(CN)_2$ was optimal, affording **2a** in quantitative yield with an excellent diastereoselectivity of 20:1 (entries 4–6). Using $Zn(CN)_2$, the amount of **1a** could be lowered to 1.2 equiv without a significant drop in yield or diastereoselectivity (entry 7).

Two control experiments illustrated the crucial role of zinc in the reaction. The desired product was not detected in the absence of zinc (entry 8) or when using a combination of a strong base (NaH) and $MgCl_2$ (entry 9). While other metals can generate homoenolates from cyclopropanol derivatives, zinc is necessary for reversible ring opening and ring closing of the homoenolate intermediate.[3,5,6]

To support our hypothesis that **2a** can be generated via an amphoteric zinc homoenolate intermediate, side-by-side reactions with ***trans*-1a** and ***cis*-1a** were performed.[14] In both reactions, ***trans*-2a** was obtained as the major product in >20:1 and 18:1 d.r., respectively (eq 1). This result supports the formation of a common intermediate in both transformations (**A**/**B** in Scheme 2a), which destroys the stereochemical



information at C1 of the cyclopropane. Ring closure to form the cyclopropylamine appears to be an irreversible process (under kinetic control) since product ***cis*-2a** does not equilibrate to the more stable ***trans*-2a** under the standard reaction conditions (eq 2). The formation of ***trans*-2a** as the major product is controlled by the minimization of the 1,3-allylic strain in iminium intermediate **B**.

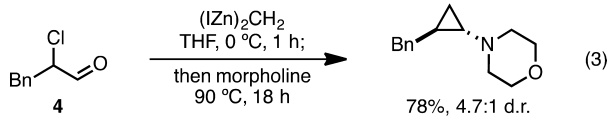
Table 2a highlights the scope of cyclopropylamines that can be prepared using cyclopropanol **1a** as starting material. Heterocyclic amines of various ring sizes could be efficiently converted to the corresponding cyclopropylamines **2a–c**. Indoline could be transformed to **2d** in 87% yield and >20:1 d.r. using Et_2Zn. Various functional groups such as ketals, carbamates, nitroaromatics, and unsaturated heterocycles were tolerated under these reaction conditions and gave products **2e–h** in moderate to good yields (61–89%) and high levels of diastereoselectivity. Acyclic secondary amines required more reactive Et_2Zn for product formation (**2i–2k**). The benzyl group in cyclopropylamine **2j** can be removed in quantitative yield upon treatment with Pd/C under a H_2 atmosphere.[15] *bis*-Cyclopropylamine **2l** was formed in 44% yield using 2.2 equiv of **1a**. Finally, reactions with primary amines required that the temperature be lowered to 60 °C for 1 h at the end of the reaction for optimal product yields (**2m**). Without this temperature adjustment, the ring-opened imine byproduct, resulting from the condensation of benzylamine with the homoenolate, was observed as the major product.

The scope of cyclopropanol starting materials is highlighted in Table 2b. Arylcyclopropylamines **2n–2p** were isolated in moderate to good yields. Product **2p** is reminiscent of the cyclopropylamine motif found in Ticagrelor (Scheme 2b).[11] The sterically demanding 2-cyclohexyl product **2r** required longer reaction times (42 h) to reach completion. Cyclopropylamine **2s** was obtained in 70% yield and >20:1 d.r. using substoichiometric quantities of $Zn(CN)_2$ (40 mol %). Lastly, cyclopropylamine **2u** was prepared in 52% yield using dimethylformamide (DMF) as the source of dimethylamine.

To validate our method as a means to access complex targets relevant to the pharmaceutical industry, we explored the synthesis of GSK2879552. This compound, an inhibitor of lysine demethylase 1 (LSD1), is currently in clinical trials for the treatment of small cell lung cancer.[16] In our laboratory, GSK2879552 was prepared from amine **3** and *trans*-2-phenylcyclopropanol **1b** in 50% yield over two steps (Scheme 3).[15] The late-stage incorporation of the cyclopropane motif should provide an interesting opportunity for further SAR studies on the cyclopropylamine ring.[17]

Initial experiments indicate that this reaction occurs with high levels of enantiospecificity (es) despite the high reaction temperature of 110 °C. Starting from enantioenriched **1a** (99% ee), **2a**, **2e**, **2f**, **2g**, **2h**, and **2j** can be obtained in 89–93% es (Table 3).[18]

We have also found that cyclopropylamines can be prepared in a one-pot fashion from readily available α-chloroaldehydes (eq 3). Addition of $(IZn)_2CH_2$ to α-chloroaldehyde **4** yields a



zinc-cyclopropoxide species.[6a] Instead of quenching the reaction to isolate cyclopropanol **1a**, the desired amine can

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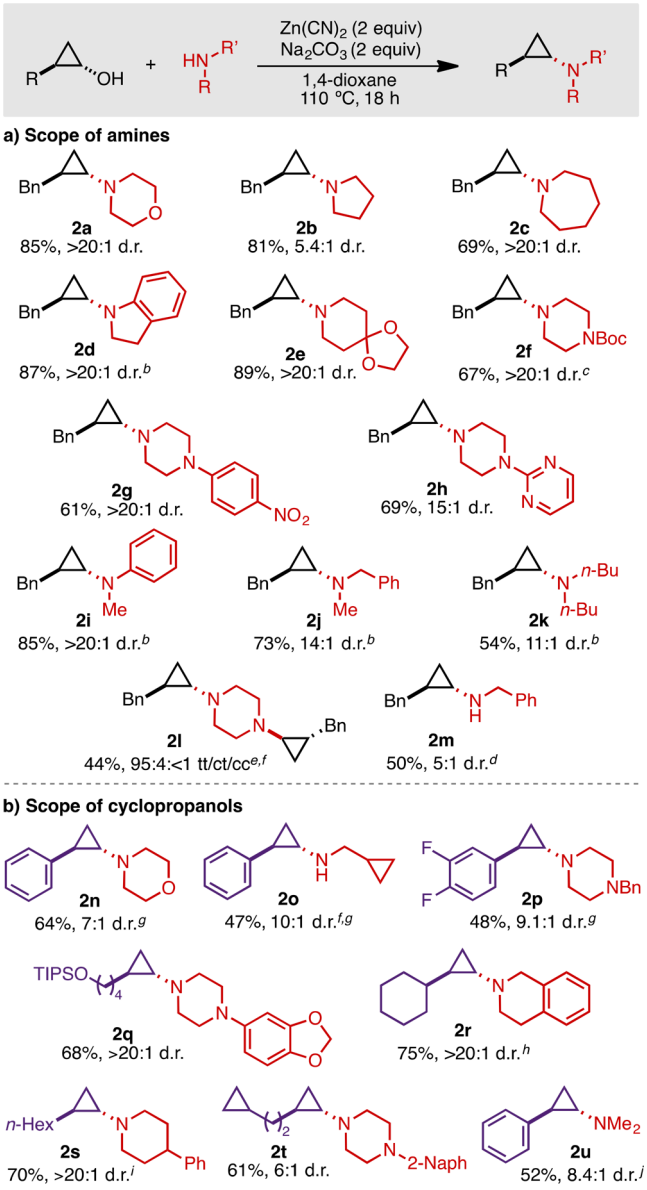
Table 2. Reaction Scope for the Synthesis of Cyclopropylamines from Zinc Homoenolates[a]



[a]Reactions were performed using 1.2 equiv of cyclopropanol, 1.0 equiv of amine, 2.0 equiv of $Zn(CN)_2$, and 2.0 equiv of Na_2CO_3 in 1,4-dioxane (0.1 M) at 110 °C for 18 h. Yields are isolated yields of major diastereomer (average of 2 runs); d.r.'s were determined by ^{1}H NMR analysis of crude reaction mixtures. [b]Et_2Zn was used instead of $Zn(CN)_2$ and Na_2CO_3. [c]80 mol % of $Zn(CN)_2$. [d]2.2 equiv of **1a** and 4 equiv of $Zn(CN)_2$; 42 h reaction time. [e]tt = *trans,trans* isomer, ct = *cis,trans* isomer, cc = *cis,cis* isomer. [f]18 h at 110 °C, then 1 h at 60 °C. [g]1 equiv of $Zn(CN)_2$. [h]4 equiv of $Zn(CN)_2$; 42 h. [i]40 mol % of $Zn(CN)_2$. [j]Using DMF as solvent and source of amine (0.1 M) and Et_2Zn (2.0 equiv). ^{1}H NMR yield due to product volatility.

be added to the mixture and **2a** is obtained in good yield and moderate d.r. after heating at 90 °C for 18 h. Based on these results, we anticipate that enantioenriched cyclopropylamines should be readily available from enantioenriched α-chloroaldehydes, and work toward this goal is ongoing in our laboratory.

In summary, zinc homoenolates, generated *in situ* via cyclopropanol ring opening, can react as electrophiles in the presence of amines to yield *trans*-cyclopropylamines. This transformation reveals the amphoteric nature of zinc homoenolate derivatives, which we anticipate will provide exciting opportunities for the development of new synthetic methods using these reagents. The application of this method to the synthesis of enantioenriched cyclopropylamines and the use of other nucleophiles in similar ring-closing processes are currently being explored in our laboratory.

Scheme 3. Synthesis of (±)-GSK2879552

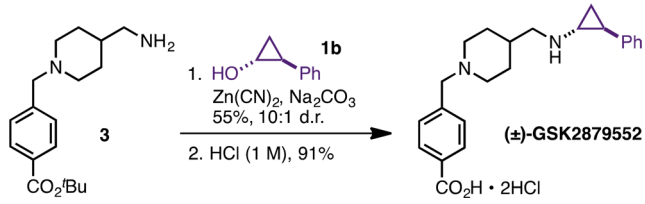
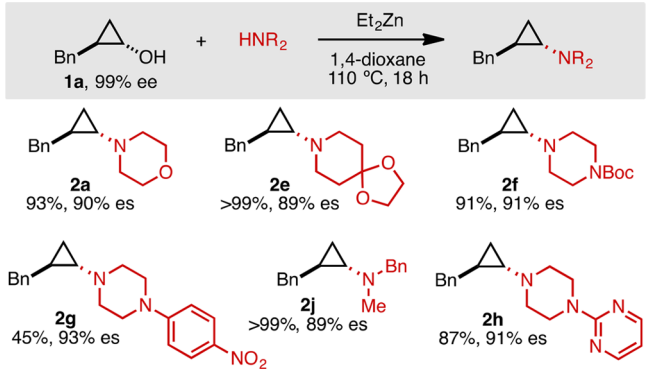


Table 3. Enantiospecific Synthesis of Cyclopropylamines



■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.7b07104.

Experimental procedures, characterization data, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(14) Nucleophilic substitution reactions at cyclopropanol derivatives typically lead to ring-opened products. See ref 3 and (a) Banert, K. *Chem. Ber.* **1985**, *118*, 1564−1574. (b) Aksenov, V. S.; Terent'eva, G. A.; Savinykh, Y. V. *Russ. Chem. Rev.* **1980**, *49*, 549−557 and references therein. Thus, the formation of cyclopropylamine **2a** under these reaction conditions is unlikely to occur via direct substitution of the alcohol (S_N2 or S_N1 mechanism). This is further evidenced by mesylate-protected cyclopropanol, which is unreactive under these reaction conditions. See Supporting Information for additional details.

(15) See Supporting Information for additional information.

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(17) GSK2879552 was originally prepared via reductive amination of commercially available *trans*-2-phenylcyclopropylamine (tranylcypromine) and the corresponding aldehyde. See ref 16.

(18) Enantiospecificity is calculated as follows:

$$\text{es} = (\text{ee of product}) \div (\text{ee of starting material}) \times 100\%$$

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