Synthesis of *trans*-2-Substituted-Cyclopropylamines from α-Chloroaldehydes

Michael S. West, L. Reginald Mills, Tyler R. McDonald, Jessica B. Lee,† Deeba Ensan,‡ Sophie A. L. Rousseaux*

Davenport Research Laboratories, Department of Chemistry, University of Toronto, 80 St. George Street, Toronto, Ontario, M5S 3H6, Canada

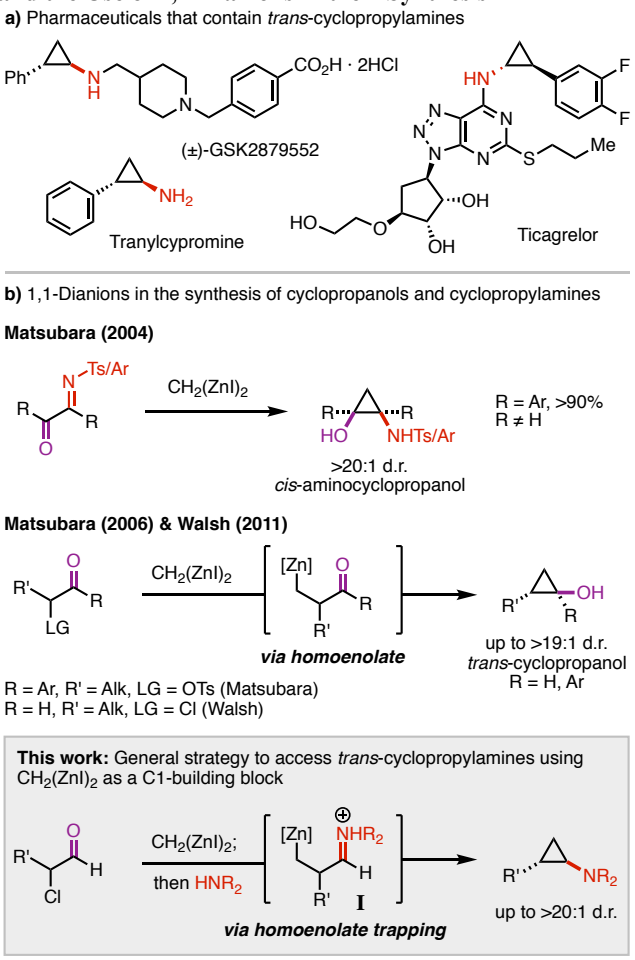
ABSTRACT: Cyclopropylamines are prevalent motifs in pharmaceuticals and agrochemicals. Herein, we report the synthesis of *trans*-2-substituted-cyclopropylamines in high diastereoselectivity from readily available α-chloroaldehydes. The reaction proceeds via trapping of an electrophilic zinc homoenolate with an amine followed by ring-closure to generate the cyclopropylamine product. We have also observed that *cis*/*trans*-isomerization of the cyclopropylamine can occur in the presence of zinc halide salts and that this process can be turned off by the addition of a polar aprotic co-solvent to the reaction.

The cyclopropylamine motif is present in a wide range of biologically active pharmaceutical compounds, natural products, and agrochemicals (Scheme 1a).[1-3] Cyclopropylamines have also been used as synthetic intermediates as they readily participate in ring-opening reactions.[4] Several methods[2] for the synthesis of *trans*-cyclopropylamines have been developed including the Kulinkovich–de Meijere and Kulinkovich–Szymoniak reactions,[5,6] the Curtius rearrangement of cyclopropyl acyl azides,[7] metal-catalyzed cyclopropanations using carbenoids,[8] and the metal-catalyzed desymmetrization of cyclopropenes.[9] However, achieving high levels of diastereoselectivity often remains a challenge for the synthesis of *trans*-2-substituted-cyclopropylamines.

Matsubara and coworkers have reported that bis(iodozincio)methane, a readily available one-carbon dianionic building block,[10] can efficiently generate substituted aminocyclopropanols from α-ketoimines (Scheme 1b, top arrow).[11,12] This protocol works with high yield and selectivity for 1,2-disubstituted derivatives (when R = Ar), but is not viable when R = H. In contrast, Walsh and coworkers have shown that α-chloroaldehydes are competent substrates for generating *trans*-cyclopropanols, where the C1 substituent is H (Scheme 1b, middle arrow).[13] This procedure works in high yield and high diastereoselectivity, and proceeds through a zinc homoenolate intermediate. However, a related transformation to access *trans*-2-substituted-cyclopropylamines using this dianionic building block strategy remains elusive.

Our group recently reported that cyclopropanols react with amines in the presence of Zn(II) to yield cyclopropylamines, via trapping of a zinc homoenolate intermediate.[14,15] Inspired by the contributions of Matsubara and Walsh, we wondered if *trans*-cyclopropylamines could be accessed from α-chloroaldehydes[16] and $CH_2(ZnI)_2$ by trapping the intermediate zinc homoenolate with an amine (Scheme 1b, grey box). Herein we report the

Scheme 1. Biologically Active *trans*-Cyclopropylamines and the Use of 1,1-Dianions in their Synthesis

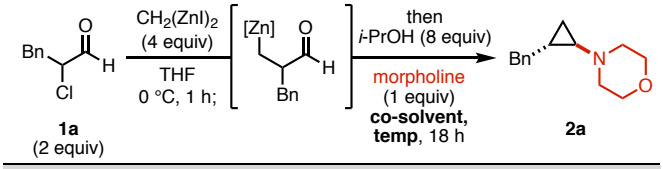


synthesis of *trans*-2-substituted-cyclopropylamines from readily accessible α-chloroaldehydes in up to >20:1 d.r. We have found that cyclopropylamines undergo reversible ring-

opening in the presence of certain zinc salts, leading to low diastereoselectivity, and that this process can be inhibited by the addition of DMF and other Lewis basic co-solvents to the reaction mixture.

We initiated our investigation by treating α-chloroaldehyde **1a** with $CH_2(ZnI)_2$ at 0 °C for 1 h, followed by addition of morpholine and subsequent heating of the reaction mixture at 90 °C for 18 h. Under these conditions, cyclopropylamine **2a** was obtained in 77% yield and 4.4:1 d.r. (Table 1, entry 1). Addition of *i*-PrOH to quench any remaining $CH_2(ZnI)_2$ prior to the addition of the amine led to quantitative yield of the desired product in 4.4:1 d.r. (entry 2). Screening a range of conditions, including the addition of polar aprotic co-solvents, revealed that the presence of DMF improved the d.r. to >20:1 while maintaining excellent product yield (entry 3). While a mixed solvent system of DMF/THF (3:2 ratio) proved optimal, DMA, DMSO and DMI also had a beneficial impact on the diastereoselectivity of the reaction (see Supporting Information). Raising the reaction temperature to 110 °C resulted in a decrease of the d.r. to 10:1 (entry 4). The order of addition of $CH_2(ZnI)_2$ followed by the amine is very important, as the inverse order (i.e. amine followed by $CH_2(ZnI)_2$) resulted in no detectable amount of **2a** (entry 5) with both secondary and primary amines.

Table 1. Effect of Co-Solvent and Temperature on Product Diastereomeric Ratio[a]

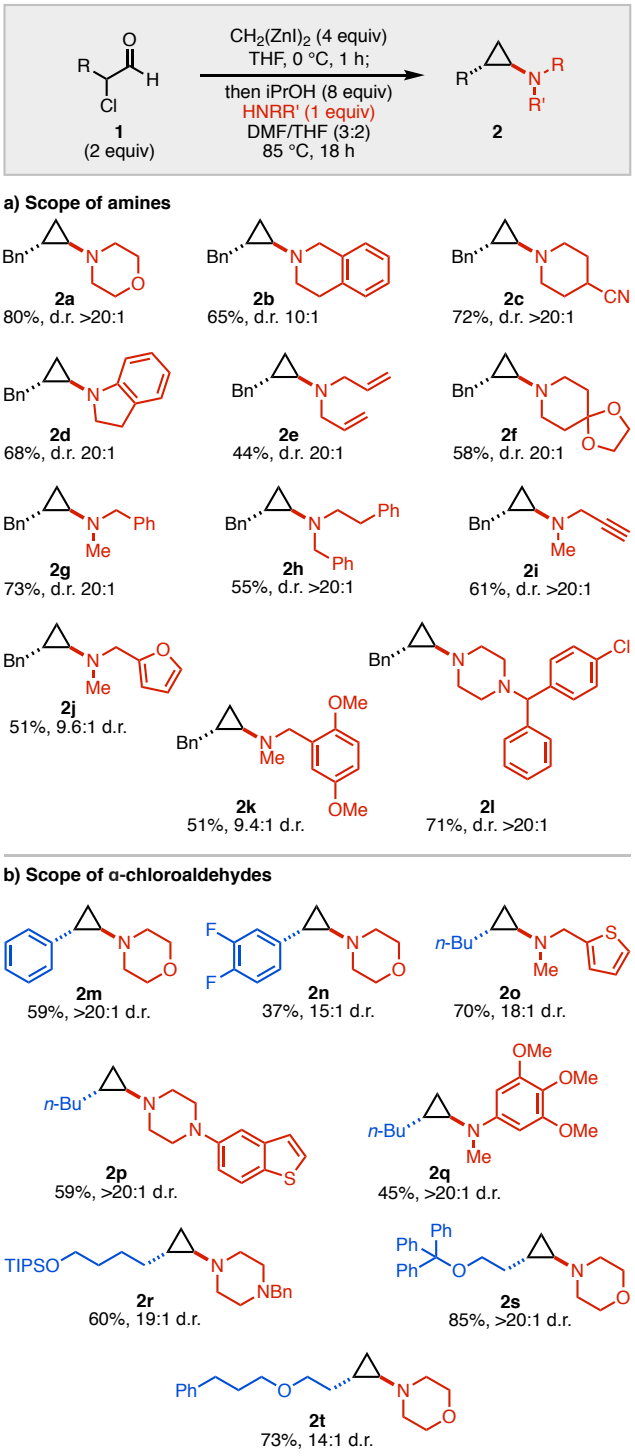


entry	co-solvent	temp (°C)	yield	d.r.
1[b]	–	90	(77%)	4.4:1
2	–	90	(99%)	4.4:1
3	DMF[c]	85	78%	>20:1
4	DMF[c]	110	85%	10:1
5[d]	–	85	n.r.	–

[a]Reactions were performed using α-chloroaldehyde **1a** (0.4 mmol, 2.0 equiv), a solution of $CH_2(ZnI)_2$ in THF (0.8 mmol, 4.0 equiv, typically 0.22–0.25 M), *i*-PrOH (1.6 mmol, 8.0 equiv), and morpholine (0.2 mmol, 1.0 equiv). Yield in parentheses determined by GC-MS with dodecane as internal standard, otherwise isolated yields; d.r. determined by GC-MS or ^{1}H NMR. [b]No *i*-PrOH. [c]The volume of DMF added was 1.5× the volume of THF. [d]Morpholine (0.2 mmol, 1.0 equiv) added to α-chloroaldehyde **1a** (0.4 mmol, 2.0 equiv) at 0 °C followed by addition of a solution of $CH_2(ZnI)_2$ in THF (0.8 mmol, 4.0 equiv) and heating at 85 °C for 18 h.

Table 2a displays the scope of cyclopropylamines that can be prepared in high d.r. using this method. Cyclic secondary amines afford cyclopropylamines in moderate to good yields and excellent d.r. as shown by products **2a-d, 2f**, and **2l**. Amines such as diallylamine and benzylamines, which can later be deprotected to reveal the free amine,[14] gave **2e**, **2g** and **2h** in moderate to good yields. Functional groups such as nitriles, protected ketals, terminal alkynes, and heterocycles are compatible as demonstrated by the synthesis of cyclopropylamines **2c**, **2f**, **2i**, and **2j**. Product **2k** contains a biologically-

Table 2. Reaction Scope for the Synthesis of *trans*-Cyclopropylamines from α-Chloroaldehydes[a]



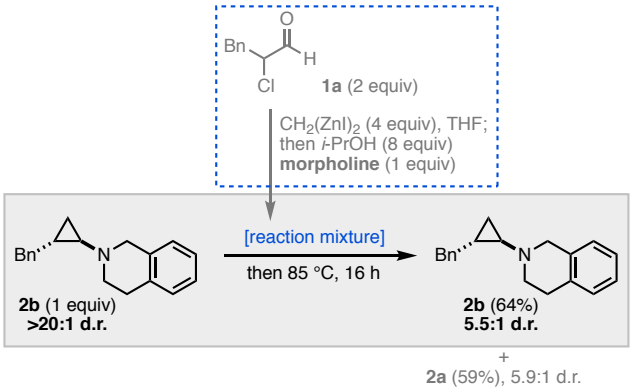
[a]Reactions were performed on 0.10–0.20 mmol scale. Yields are isolated and the average of two runs.

active piperazine derivative frequently used in active pharmaceutical ingredients such as antihistamines.[17] The scope of α-chloroaldehyde starting materials is demonstrated in Table 2b. *trans*-2-Arylcyclopropylamines **2m** and **2n** were isolated in moderate to good yield and excellent diastereoselectivity. Ali-

phatic aldehydes afforded cyclopropylamines **2o-2t** in good yields. Ethers and a silyl ether were also tolerated as shown by the efficient synthesis of **2r–2t.** Primary amines were not competent in the reaction due to the diminished stability of the resulting products.[18]

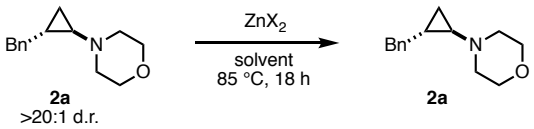
Intrigued by the significant improvement in the diastereoselectivity upon addition of DMF to the reaction mixture, we examined the stability of the product to the reaction conditions in the absence of DMF. To probe this, an equivalent of independently isolated cyclopropylamine **2b** (>20:1 d.r.) was added to a standard reaction for the synthesis of cyclopropylamine **2a** from α-chloroaldehyde **1a** (Scheme 2). At the end of the reaction, **2a** was obtained in 5.9:1 d.r. as expected, and **2b** was recovered in moderate 5.5:1 d.r. This suggests that under these conditions, the *trans*-cyclopropylamine product is able to epimerize to an approximately 5:1 mixture of *trans*- and *cis*-diastereomers, presumably via trapped homoenolate intermediate **I** (Scheme 1b). In the presence of DMF, the reaction appears to be under kinetic control; the >20:1 d.r. (Table 1, entry 3) is maintained and is consistent with the d.r. of our related transformation of cyclopropanols to cyclopropylamines, which we have shown is under kinetic control.[14]

Scheme 2. Probing Product Stability Under the Reaction Conditions in the Absence of DMF



To further understand the effect of DMF on the product d.r., as well as the parameters that control the reversibility/epimerization in this process, we investigated the impact of various zinc(II) salts and solvents on product formation. We found that the nature of the zinc salt was important, and that simply stirring *trans*-**2a** (>20:1 d.r.) with $ZnCl_2$ in THF at 85 °C led to efficient product epimerization to 6.3:1 d.r. (Table 3, entry 1). As previously observed, this epimerization does not occur when DMF is added to the reaction mixture, as demonstrated by the recovery of *trans*-**2a** in 77% yield and >20:1 d.r. (entry 2). We wondered if a change in overall solvent polarity upon the addition of DMF was key for preventing product epimerization. To test this hypothesis, we replaced DMF with acetonitrile, a solvent of similar dielectric constant. Upon heating this mixture, *trans*-**2a** was recovered in 7.1:1 d.r., suggesting that the observed effect is not due to solvent polarity (entry 3). Reactions using coordinatively saturated zinc(II) sources, such as $ZnCl_2$·TMEDA and $ZnCl_2$·2DMF, revealed that DMF may be playing an important role as a ligand for zinc to modulate its ability to ring-open cyclopropylamines. Using $ZnCl_2$·TMEDA and $ZnCl_2$·2DMF, *trans*-**2a** was isolated in >90% yield and >20:1 d.r. or 14:1 d.r., respectively, even when the reaction was performed in the absence of DMF as a co-solvent (entries 4–5).

Table 3. Effect of Zinc(II) Salt and Solvent on Epimerization of *trans*-Cyclopropylamine Product[a]



entry	ZnX_2	solvent	yield	d.r.
1	$ZnCl_2$	THF	87%	6.3:1
2	$ZnCl_2$	DMF/THF	77%	>20:1
3	$ZnCl_2$	MeCN/THF	54%	7.1:1
4	$ZnCl_2$·TMEDA	THF	94%	>20:1
5	$ZnCl_2$·2DMF	THF	90%	14:1

[a]Reactions were performed using *trans*-cyclopropylamine **2a** (0.1 mmol, 1.0 equiv) and $ZnCl_2$ (0.2 mmol, 2.0 equiv) in THF (0.1 M) at 85 °C for 18 h. Yield and d.r. determined by ^{1}H NMR with dibromomethane as internal standard. The volume of DMF and MeCN added was 1.5x the volume of THF used.

In summary, we have developed a highly diastereoselective synthesis of *trans*-2-substituted-cyclopropylamines from readily accessible α-chloroaldehydes. The reaction proceeds through a zinc homoenolate intermediate that is trapped by an amine and subsequently undergoes ring-closure to generate the cyclopropylamine. In the absence of a polar aprotic co-solvent, ring-closure is a reversible process and the cyclopropylamine product is isolated as the thermodynamic mixture of *trans*- and *cis*-diastereomers (≈5:1 d.r.). This protocol is compatible with a range of functional groups and a variety of pharmaceutically relevant cyclopropylamines have been prepared. Further work exploring the reactivity of these homoenolate intermediates is ongoing in our laboratory.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Synthetic procedures, characterization data and NMR spectra (PDF)

AUTHOR INFORMATION

Corresponding Author

* sophie.rousseaux@utoronto.ca

Present Addresses

† Paraza Pharma, Inc. 275 Boulevard Armand-Frappier, Laval, QC, H7V 4A7, Canada

‡ Ontario Institute for Cancer Research, 661 University Ave Suite 510, Toronto, ON, M5G 0A3, Canada.

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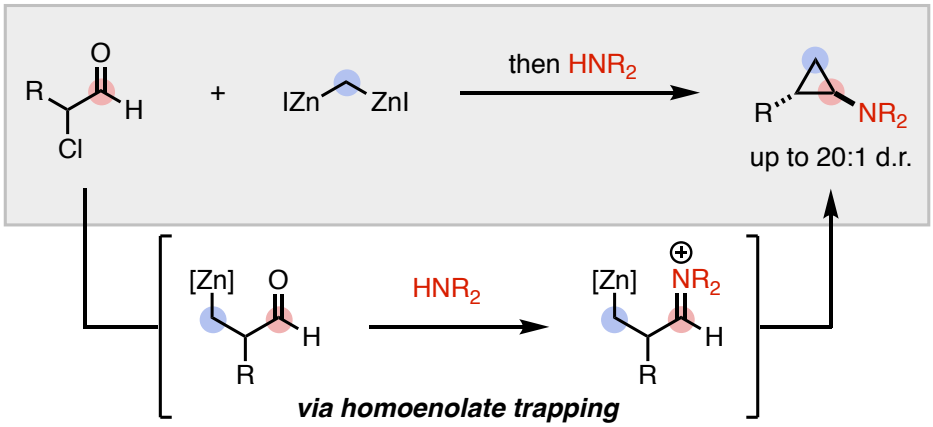
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