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A highly efficient resolution protocol for 2′-halo-α-methylbenzylamines

Liane M. Klingensmith, Kelly A. Nadeau and George A. Moniz*

Chemical Process R&D, Amgen, Inc., One Kendall Square, Bldg. 1000, Cambridge, MA 02139, United States

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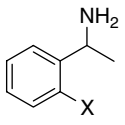
Abstract—A highly efficient resolution protocol for 2′-halo-α-methylbenzylamines is reported. Commercially available and inexpensive mandelic acid can be used for the resolution of the Br, Cl, and F derivatives to >99% de in a single crystallization. In addition, the reduction of acetophenone oximes using borane-dimethylsulfide is presented as a method for the preparation of racemic amine precursors.

1. Introduction

The process of resolving enantiomers through diastereomeric salt formation is a widely used method for obtaining optically enriched acids or bases.[1] As part of an ongoing development program, we required large quantities of 2′-halo-substituted α-methylbenzylamines (Fig. 1, **1a**–**c**) in high optical purity.

There are numerous asymmetric synthetic strategies that afford enantiomerically enriched α-methylbenzylamines.[2] However, from our standpoint, a resolution-based process was more practical for two reasons: (1) the degree of enantiomeric enrichment required for our purposes (>99% ee) might exceed the capacity of available asymmetric methods. In this case, a secondary salt-based chiral upgrade would still be required, and (2) if a relatively inexpensive resolving agent could be found, the ease and cost of resolving the racemic amine might outweigh the benefits of an asymmetric synthesis.[1b]

The literature contains many reports of the resolution of various α-methylbenzylamines, including the use of chiral acids such as 6-(1,2:3,4-di-*O*-isopropylidene-α-D-galactopyranosyl)hydrogen phthalate,[3] isopropylidene glycerol hydrogen phthalate,[4] 3,4-dihydro-2*H*-1-benzopyran-2-carboxylic acid,[5] mandelic acid,[6] substituted mandelic acids,[6a,7] tartaric acid,[8,9] *N*-Ac-L-leucine derivatives,[10] and malic acid.[9b] Surprisingly, there are few examples of the resolution of 2′-halo-α-methylbenzylamines,[3–5,6e,10] and those examples produced only modest enantioselectivity, or required multiple crystallizations to achieve high levels of enantioenrichment. Our goal was to develop a general and efficient resolution protocol, employing a single resolving agent that could be applied to the series depicted in Figure 1.



X = Br, Cl, F

1a-c

Figure 1. 2′-Halo-α-methylbenzylamines (**1a**–**c**).

2. Results and discussion

At the outset, a general and mild approach was needed to obtain large quantities of racemic 2′-halo-substituted α-methylbenzylamines, as racemate was not commercially available. There is a large body of literature regarding the preparation of racemic versions of these compounds. Starting from the ketone, reductive amination, including the Leuckart reaction,[11] can be used. Oximes and oxime ethers can be converted to the corresponding amine utilizing both catalytic and non-catalytic transfer hydrogenation agents,[12] lithium

Keywords: Reduction; Halogenated; Resolution; Enantioselective.
* Corresponding author. E-mail: gmoniz@amgen.com

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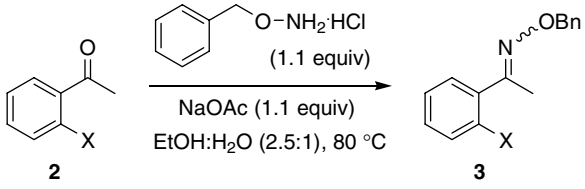
aluminum hydride,[13] and various methods which use combinations of metals and hydride reducing agents.[14] Borane-based reduction methods have been reported less frequently in the literature,[15] despite the fact that they are mild in comparison to other reduction protocols. We chose this as the starting point for our studies since we expected minimal reduction of the carbon–halogen bond with these relatively mild reagents.

Table 1 shows the results of oxime formation using an optimized procedure for the condensation of the corresponding ketone (**2a**–**c**) with *O*-benzylhydroxylamine, which was found to be the optimal oxime substrate for reduction to the amine. Both cis and trans regioisomers were obtained as products, and notably were used without further purification following an aqueous workup.

With the oximes in hand, investigations into the reduction focused on utilizing mild boron reagents to produce the racemic amine. It was found that 2 equiv of borane-dimethylsulfide effected the reduction efficiently and preserved the aryl–halogen bond, producing the desired amine in good yields (Table 2). An acid/base extractive workup yielded the desired amine without need for further purification. This reduction process was demonstrated on scale with 287 g of 2-fluoroacetophenone oxime (**3c**) (Table 2, entry 3), and found to produce amine with equivalent yield and quality to smaller scale experiments.

With an efficient process for racemic amine in hand, a preliminary screen of several commercially available chiral resolving agents was performed with 2′-fluoro-α-methylbenzylamine (Table 3). Ethyl acetate was chosen as the initial screening solvent to evaluate any solubility difference between the diastereomeric salts while maximizing crystallization. In some cases, methanol was employed as a co-solvent to facilitate dissolution of the acid

Table 1. Synthesis of 2-halo-*O*-benzylacetophenone oximes **3a**–**c**

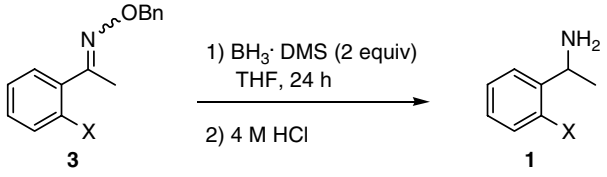


2 **3**

Entry	Ketone	X	Oxime	Yield[a] (%)
1	**2a**	Br	**3a**	96
1	**2b**	Cl	**3b**	96
3[b]	**2c**	F	**3c**	96

[a] Isolated yields.
[b] 170 g reaction.

Table 2. Synthesis of α-methylbenzylamines **1a**–**c**

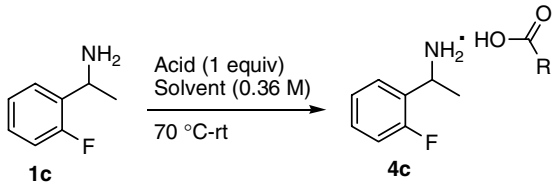


3 **1**

Entry	Oxime	X	Temperature (°C)	Amine	Yield[a] (%)
1	**3a**	Br	rt	**1a**	72
2	**3b**	Cl	rt	**1b**	68
3[b]	**3c**	F	40	**1c**	66

[a] Isolated yields, average of two reactions.
[b] 287 g reaction.

Table 3. Results of initial resolving agent screen



1c **4c**

Entry	Acid	Solvent	Yield (%)	de[a] (%)
1	(*S*)-(+)-Mandelic acid	EtOAc	NA	5.7
2	L-Malic acid	EtOAc	NA	0.4
3	(*S*)-(+)-2-Phenylglycine	EtOAc/MeOH (5:3), 0.22 M	NA	NA[b]
4	(*S*)-(−)-2-Pyrrolidine-5-carboxylic acid	EtOAc	NA	6.7
5	*N*-Acetyl-L-phenylalanine	EtOAc/MeOH (10:3), 0.27 M	NA	0.7
6	*N*-Acetyl-L-leucine	EtOAc/MeOH (10:3), 0.27 M	NA	0.7
7	(*S*)-(−)-2-Pyrrolidine-5-carboxylic acid	EtOH	NA	NA[b]
8	(*S*)-(−)-2-Pyrrolidine-5-carboxylic acid	MeOH	NA	NA[b]
9	(*S*)-(+)-Mandelic acid	MeOH	NA	NA[b]
10	(*S*)-(+)-Mandelic acid	EtOH	22	93
11	(*S*)-(+)-Mandelic acid	IPA	41	89
12	(*S*)-(+)-Mandelic acid	EtOH/IPA (3:2), 0.72 M	39	98
13	(*S*)-(+)-Mandelic acid	EtOH/IPA (1:1), 0.72 M	34	99

[a] Determined by chiral GC.
[b] No crystallization observed.

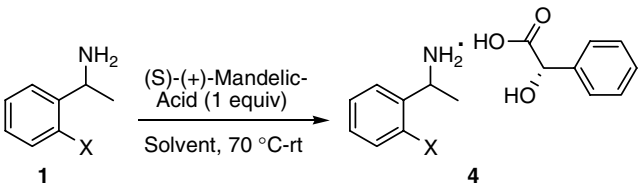
prior to the addition of the amine. As seen in Table 3 (entries 1–6), initial upgrades were poor. However, both mandelic acid and 2-pyrrolidine-5-carboxylic acid afforded modest levels of enrichment, revealing a difference in solubility between the two diastereomeric salts generated with these two resolving agents.[16]

The initial hits using mandelic acid and 2-pyrrolidine-5-carboxylic acid were subjected to a more extensive solvent screen (Table 3, entries 7–10), which revealed mandelic acid to be a very effective resolving agent in ethanol. The conditions for resolution utilizing mandelic acid were optimized to afford a diastereoenrichment of 99% in a single crystallization from ethanol and isopropyl alcohol (entry 13). The solubility and nucleation curves were generated for this salt and revealed a high nucleation temperature and narrow metastable zone (Fig. 2).

Application of these conditions to the other 2′-halo-α-methylbenzylamines of interest revealed that the optimal conditions for 2′-fluoro-α-methylbenzylamine did not directly translate to the other amine substrates. However, upon further optimization for each derivative, mandelic acid continued to be an outstanding resolving agent (Table 4).

Qualitatively, nucleation and crystallization for the 2′-chloro derivative were observed to be slower than that of the 2′-fluoro series, and to take place at a lower temperature. This was quantified by the solubility and nucleation curves for this salt (Fig. 3), which confirmed that nucleation of the (*R*)-2′-chloro-α-methylbenzylamine·(*S*)-mandelate salt only commences at 30 °C at concentrations relevant to the resolution protocol. It was expected that holding the mixture at 30 °C would promote nucleation of the desired diastereomer and subsequent crystallization within the metastable zone, while still maintaining temperature above the solubility limit of the undesired diastereomer. The impact of this hold time is demonstrated by entries 3 and 4 in Table 4, which show that holding the mixture at 30 °C for crystallization results in a substantial increase in % de with minimal impact in % yield.

Table 4. Expanded screen of scope using mandelic acid



1 4

Entry	X	Solvent	Yield (%)	de[a] (%)
1	Cl	IPA/EtOH (1:1), 0.32 M	25	87
2	Cl	IPA, 0.4 M	37	45
3	Cl	IPA/EtOH (1:6:1), 0.4 M	34	77
4	Cl	IPA/EtOH (1:6:1), 0.4 M[b]	29	98
5	Cl	IPA/EtOH (1:7:1), 0.32 M[b]	25	99
6	Br	IPA/EtOH (1:1), 0.25 M	NA	NA[c]
7	Br	IPA, 0.5 M	NA	NA[c]
8	Br	IPAC, 0.5 M	67	9.6
9	Br	IPAC/EtOH (3:1), 0.5 M	34	92
10	Br	IPAC/EtOH (3:1), 0.33 M[b]	37	94
11	Br	IPAC/EtOH (3:1), 0.25 M[b]	35	99

[a] Determined by chiral GC.
[b] The reaction was first cooled to 30 °C and slurried for 24 h before cooling to 23 °C.
[c] No crystallization observed.

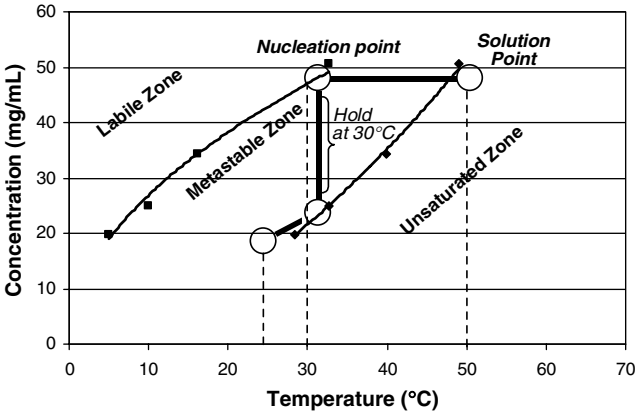


Figure 3. Solubility and nucleation curves for (*R*)-2′-chloro-α-methylbenzylamine·(*S*)-mandelate salt (**4b**) in 1.7:1 IPA/EtOH.

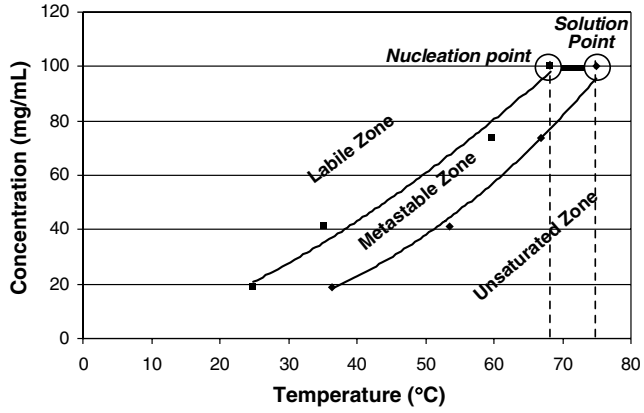


Figure 2. Solubility and nucleation curves for (*S*)-2′-fluoro-α-methylbenzylamine·(*S*)-mandelate salt (**4c**) in 1:1 IPA/EtOH.

For the 2′-bromo derivative, use of isopropyl acetate (IPAC) as an antisolvent in combination with ethanol was required to achieve the optimal balance of enrichment and recovery. The solubility and nucleation curves for this salt are shown in Figure 4. Although the nucleation temperature is relatively high for this salt, in practice, nucleation was slow. Again, holding the crystallization at 30 °C allowed sufficient nucleation time at a slightly elevated temperature, affording very good % de's in a single crystallization.

Final optimized conditions as well as absolute configurations for the entire amine series are shown in Table 5. Under the optimized conditions,[17] these resolutions achieve high diastereoenrichments and good yields in a single crystallization, employing a readily available

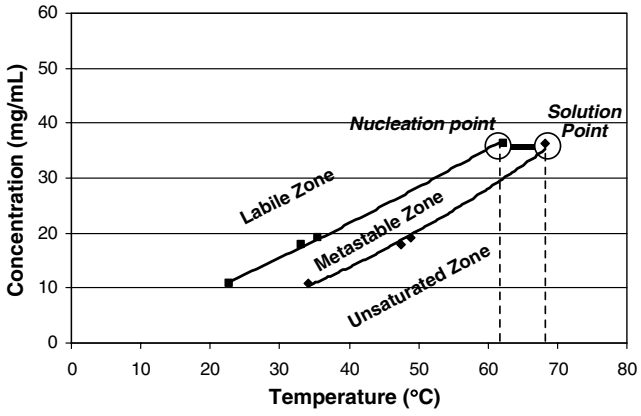


Figure 4. Solubility and nucleation curves for (*R*)-2′-bromo-α-methylbenzylamine·(*S*)-mandelate salt (**4a**) in 3:1 IPAC/EtOH.

and inexpensive ($25/kg)[18] resolving agent. Demonstration of this process on larger scale produced 76.4 g of 2′-fluoro-α-methylbenzylamine-mandelic acid salt (**4c**), with the expected yield and diastereoselectivity (Table 5, entry 3).[19]

In conclusion, the borane reduction of 2′-haloacetophenone oximes has been demonstrated to be a viable route for large scale generation of racemic α-methylbenzylamines. These materials can be resolved to >99% de in a single crystallization using commercially available and inexpensive mandelic acid.

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Supplementary data

Experimental procedures and full spectroscopic data for all new compounds are available as supplementary data. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.04.120.

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2. For reviews see: (a) Kobayashi, S.; Ishitani, H. *Chem. Rev.* **1999**, *99*, 1069; (b) Enders, D.; Reinhold, U. *Tetrahedron: Asymmetry* **1997**, *8*, 1895.
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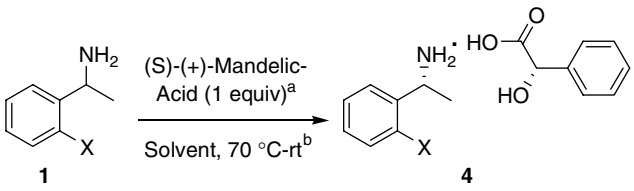
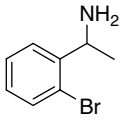
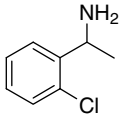
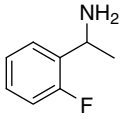
Table 5. Optimized resolutions of 2′-halo-α-methylbenzylamines (**1a**–**c**)



Entry	Amine	Solvent	Product	Yield[c] (%)	de[d] (%)	Amine configuration
1	 **1a**	IPAC/EtOH (3:1), 0.25 M	**4a**	35	99.3	*R*
2	 **1b**	IPA/EtOH (1:7:1), 0.32 M	**4b**	25	99.6	*R*
3[e]	 **1c**	IPA/EtOH (1:1), 0.72 M	**4c**	34	−99.1	*S*

[a] See Ref. 17.
[b] Entry 1: 60 °C–rt, held at 30 °C for 24 h before cooling to 23 °C.
[c] Isolated yields, average of two reactions, with a maximum yield of 50%.
[d] Determine by chiral GC, average of two resolutions. See Supplementary data for absolute configuration analysis.
[e] Performed with 108 g of racemate.

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16. Solubility differences for diastereomeric salts are generally manifested in a range of organic solvents. See: Wilen, S. H.; Collet, A.; Jacques, J. *Tetrahedron* **1977**, *33*, 2725.
17. Use of less than 1 equiv of mandelic acid results in reduced yield (24% for 2′-fluoro).
18. Price quotation at 100 kg scale. Cost at 25 kg scale is $30/kg.
19. See Supplementary data for a representative salt break procedure.