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A Simple, Scalable Synthetic Route to (+)- and (−)-Pseudoephenamine

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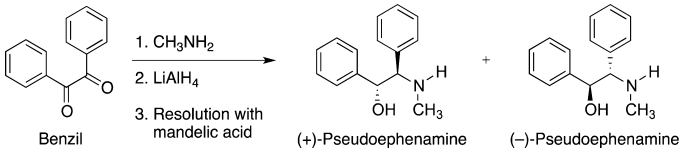
ABSTRACT

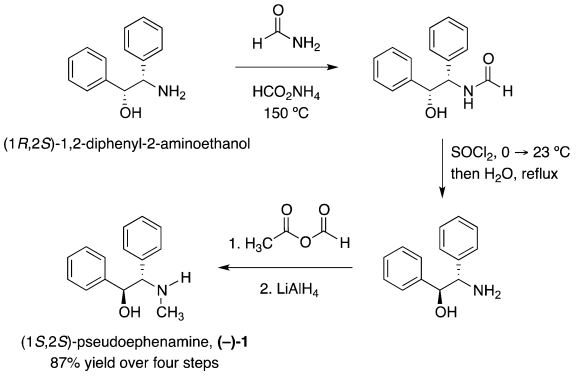


A three-step synthesis of pseudoephenamine suitable for preparing multigram amounts of both enantiomers of the auxiliary from the inexpensive starting material benzil is described. The sequence involves synthesis of the crystalline monomethylimine derivative of benzil, reduction of that substance with lithium aluminum hydride, and resolution of pseudoephenamine with mandelic acid.

Pseudoephenamine (**1**) is a useful chiral auxiliary for the synthesis of enantioenriched carboxylic acids, ketones, primary alcohols, and α-methyl α-amino acids, and in many instances it proves to be superior to the regulated substance pseudoephedrine in parallel transformations.[1] The primary disadvantage of pseudoephenamine relative to pseudoephedrine is that it is not yet commercially available. Previously, we reported a four-step synthesis of pseudoephenamine from the commercially available chiral amino alcohol 1,2-diphenyl-2-aminoethanol (the synthesis of (1*S*,2*S*)-pseudoephenamine, **(−)-1**, is depicted in Scheme 1).[2,3] Here we report a shorter, more facile, and readily scalable procedure for the preparation of optically pure pseudoephenamine from the inexpensive starting material benzil (**2**).[4]

Wheatley and co-workers first described the preparation of methylimino benzil (**3**) by the condensation of methylamine and benzil in methanol−water at 50 °C, reporting a yield of 84%.[5] In adapting this synthesis, we found that it is critical to use a fresh (commercial) 40 wt % solution of methylamine in water (such that the titer of the volatile methylamine reactant is accurate) and crystalline benzil as a coreactant. After the reactants are combined, we heat the heterogeneous mixture in an oil bath while stirring until an internal temperature of 50 °C is achieved and all solids are dissolved. Heating is immediately discontinued at this point; upon cooling, we observed that the monoimine crystallizes from the reaction mixture. The product is

Scheme 1. First-Generation Synthesis of Pseudoephenamine



(1) (a) Morales, M. R.; Mellem, K. T.; Myers, A. G. *Angew. Chem., Int. Ed.* **2012**, *51*, 4568–4571. (b) Medley, J. W.; Movassaghi, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 4572–4576. (c) Hugelshofer, C. L.; Mellem, K. T.; Myers, A. G. *Org. Lett.* **2013**, *15*, 3134–3137.

(2) For alternative syntheses of pseudoephenamine, see: (a) Yamashita, J.; Kawahara, H.; Ohashi, S.; Honda, Y.; Kenmotsu, T.; Hashimoto, H. *Tech. Rep. Tohuku University* **1983**, *48*, 211–219. (b) Meyers, A. I.; Marra, J. M. *Tetrahedron Lett.* **1985**, *26*, 5863–5866. (c) Lour, R.; Mi, A.; Jiang, Y.; Qin, Y.; Li, Z.; Fu, G.; Chan, A. S. C. *Tetrahedron* **2000**, *56*, 5857–5863.

(3) Currently, both enantiomers of 1,2-diphenyl-2-aminoethanol are available from Ace Synthesis, LLC at a cost of $550 for 100 g.

(4) Currently, benzil is available from Alfa Aesar at a cost of $225 for 2.5 kg.

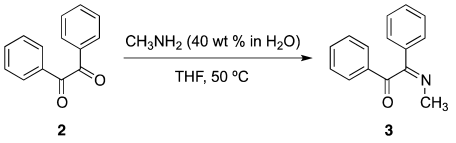
(5) Wheatley, W. B.; Fitzgibbon, W. E.; Cheney, L. C. *J. Org. Chem.* **1953**, *18*, 1564–1571.

(6) Hahn, W. E.; Bartnik, R.; Mloston, G. *Acta Pol. Pharm.* **1979**, *36*, 619–620.

10.1021/ol402815d

isolated in pure form by simple filtration (≥88% yield, 100−600-g scale, Table 1). Without careful control of the reaction time and temperature, further reaction to produce bis-methylimino benzil can occur. We have established that the crystalline methylimino benzil we obtain has (*Z*)-geometry by NOE and HMBC NMR correlations as well as X-ray crystallography (see Supporting Information).

Table 1. Synthesis of Methylimino Benzil



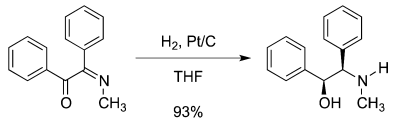
2 **3**

scale (g)	isolated yield (%)
100	88
300	92
600	91

Two prior studies of the reduction of methylimino benzil explored the use of Raney nickel[5] and sodium borohydride[6] as reductants, and in each case ephenamine was reported to be the major or exclusive product. We are unaware of any reports of the reduction of methylimino benzil to form pseudoephenamine as the primary product. Initially, we attempted to achieve both an enantio- as well as diastereoselective reduction of monoimine **3** by exploring various chiral reductants;[7] however, in each instance we obtained only racemic ephenamine. Parenthetically, we found that mixtures of the four possible stereoisomeric amino alcohols are conveniently assayed by admixing an equimolar quantity of (*S*)-mandelic acid in $CDCl_3$ followed by ^1H NMR analysis (500 MHz). Multiple resonances are found to be well-resolved for each diastereomer (see Supporting Information). Although reduction of **3** to form racemic ephenamine was not our objective, in Scheme 2 we depict a convenient method by which we achieved this transformation with ≥19:1 dr.[8,9]

Based upon the promising report of the reduction in the desired sense of achiral *N*-aryl and *N*-benzyl benzil monoimines using lithium aluminum hydride (LAH),[10] we investigated the use of this reagent for the reduction of methylimino benzil.[11] In an initial experiment, reduction of methylimino benzil with LAH in THF at −78 °C afforded a 4:1 mixture of diastereomeric amino alcohols favoring pseudoephenamine. Further investigations revealed that the diastereoselectivity of the reduction varied as a function of the rate of addition of LAH to the reaction mixture, and it was noted that addition of powdered LAH too quickly led to delayed exotherms. Controlled addition of LAH with a powder addition funnel prevented this and allowed an internal temperature of −70 °C to be maintained. It is useful to note that exotherms more commonly occur early in the course of the reaction; thus, the rate of LAH addition may be increased as the reaction progresses. Efficient mechanical stirring of the reaction is very important, especially on a large scale, so as to prevent the aggregation of powdered LAH on the surface of the reaction mixture. In this manner, we routinely obtained racemic pseudoephenamine of 4.7−5.4:1 dr on 75−570 g scales in reproducibly high yield (>85%; see Table 2). As noted by Alcaide et al. in their study of the reduction of *N*-aryl and *N*-benzyl benzil monoimines, the observed diastereoselectivity of the reduction is consistent with the polar Felkin−Ahn model.[10]

Scheme 2. Hydrogenation of Methylimino Benzil To Form (±)-Ephenamine



3 **(±)-4**
≥19:1 dr[a]

[a] dr refers to the ratio of **(±)-4** to **(±)-1**.

Direct resolution of pseudoephenamine from the mixture of diastereomers obtained in the LAH reduction was achieved with mandelic acid. We found that (*R,R*)-pseudoephenamine preferentially formed a highly crystalline salt with (*R*)-mandelic acid but not with (*S*)-mandelic acid.[12,13] Beneficially, neither diastereomeric ephenamine mandelate salt crystallized in our experiments. Two procedures for the direct resolution of the LAH reduction products were developed, one with and one without stirring. Both methods yield highly diastereoenriched mandelate crystals (≥19:1 dr by ^1H NMR, with no trace of either ephenamine mandelate salt) with good recovery (defined as the percent of the theoretical amount of the targeted enantiomer of

(7) See, for example: (a) Prasad, K. R. K.; Joshi, N. N. *J. Org. Chem.* **1996**, *61*, 3888–3889. (b) Murata, K.; Okano, K.; Miyagi, M.; Iwane, H.; Noyori, R.; Ikariya, T. *Org. Lett.* **1999**, *1*, 1119–1121. (c) Touge, T.; Hakamata, T.; Nara, H.; Kobayashi, T.; Sayo, N.; Saito, T.; Kayaki, Y.; Ikariya, T. *J. Am. Chem. Soc.* **2011**, *133*, 14960–14963.

(8) Reductive amination of benzil in the presence of methylamine and a platinum catalyst has been reported to form ephenamine: Skita, A.; Keil, F. Manufacture of Aminoalcohols. U.K. Patent 313,217, July 24, 1930.

(9) While we recognize the importance of ephenamine in asymmetric synthesis, we have made no attempt to resolve the racemic substance. For a resolution of racemic ephenamine with penicillin, see ref 5.

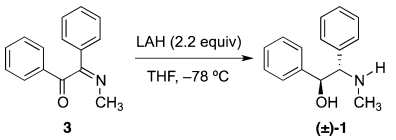
(10) Alcaide, B.; López-Mardomingo, C.; Pérez-Ossorio, R.; Plumet, J. *J. Chem. Soc., Perkin Trans. 2* **1983**, 1649–1653.

(11) For the use of LAH in the reduction of chiral benzil monoimines, see: (a) Haro-Ramos, R.; Jimenez-Tebar, A.; Pérez-Ossario, R.; Plumet, J. *Tetrahedron Lett.* **1979**, *20*, 1355–1356. (b) Alcaide, B.; Fernández de la Pradilla, R.; López-Mardomingo, C.; Pérez-Ossorio, R.; Plumet, J. *J. Org. Chem.* **1981**, *46*, 3234–3238. (c) Alcaide, B.; Dominguez, G.; López-Mardomingo, C.; Pérez-Ossorio, R.; Plumet, J. *J. Chem. Soc., Perkin Trans. 2* **1986**, 99–103.

(12) For a comprehensive guide to the optical resolution of racemic compounds via formation of diastereomeric salts, see: *CRC Handbook of Optical Resolutions via Diastereomeric Salt Formation*; Kozma, D., Ed.; CRC Press: Boca Raton, FL, 2002.

(13) For selected resolutions of structurally similar amino alcohols, see: (a) Erlenmeyer, E.; Arnold, A. *Justus Liebigs Ann. Chem.* **1904**, *337*, 307–328. (b) Manske, R. H. F.; Johnson, T. B. *J. Am. Chem. Soc.* **1929**, *51*, 1906–1909. (c) Weijlard, J.; Pfister, K., III; Swanezy, E. F.; Robinson, C. A.; Tishler, M. *J. Am. Chem. Soc.* **1951**, *73*, 1216–1218. (d) Saigo, K.; Sugiura, I.; Shida, I.; Tachibana, K.; Hasegawa, M. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 2915–2916.

Table 2. Synthesis of (±)-Pseudoephenamine



scale (g)	dr[a]	isolated yield (%)
75	5.4:1	86
290	5.0:1	92
570	4.7:1	96

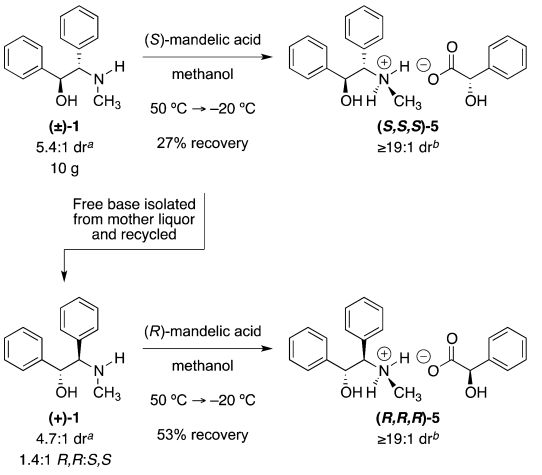
[a] dr refers to the ratio of **(±)-1** to **(±)-4**.

pseudoephenamine). Seed crystals are typically unnecessary for these resolutions, though they will effectively initiate resolution if crystal formation is sluggish.

In the first method, a solution of pseudoephenamine mandelate in methanol was allowed to stand at −20 °C for several days without stirring, producing orthorhombic crystals. One representative set of experiments demonstrating this protocol is illustrated in Scheme 3. In the optimized procedure, pseudoephenamine (10 g, 5.4:1 dr, racemic) is mixed with (*S*)-mandelic acid (1 equiv) in methanol (2.2 M in pseudoephenamine and ephenamine combined), and the mixture is warmed to 50 °C in a 100-mL round-bottom flask to effect dissolution of the solid materials.[14] After cooling to room temperature and removing the stir bar, the base of the flask is carefully scratched with a spatula, and the vessel is transferred to a −20 °C freezer to promote crystallization. After standing for several days (incubation times ranging from 2 to 10 days are typical), crystalline (*S*,*S*,*S*)-**5** of ≥19:1 dr is obtained by filtration using a Büchner funnel. The mother liquor is concentrated, and after formation of the free base, resolution with the opposite enantiomer of mandelic acid is conducted. The pseudoephenamine mandelate salts obtained by this process serve as suitable seed crystals for later resolutions. Pseudoephenamine is isolated as the free base, and after recrystallization from hot absolute ethanol, an optically pure auxiliary is obtained (81% recovery, ≥99% ee; see Scheme 4).[15] The mandelic acid is also easily recovered and recycled (see Supporting Information).

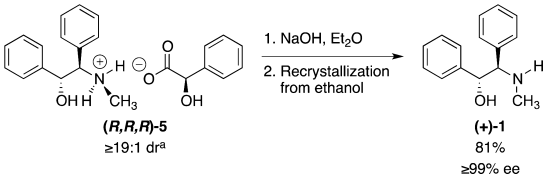
Conducting resolutions of pseudoephenamine on a larger scale (> 300 g) required the development of a second protocol involving gentle stirring of the cooled solution of pseudoephenamine mandelate in methanol.[16] Resolutions employing this method produce fine, powdery crystals and progress much more rapidly than those performed using the earlier protocol, with typical resolution times in the

Scheme 3. Resolution of (±)-Pseudoephenamine with Mandelic Acid at −20 °C without Stirring



[a] dr refers to the ratio of **(+)-** and **(−)-1** to **(±)-4**. [b] dr refers to the ratio of **(*S*,*S*,*S*)-** or **(*R*,*R*,*R*)-5** to **(*R*,*R*,*S*)-** or **(*S*,*S*,*R*)-5**, respectively.

Scheme 4. Isolation of (+)-Pseudoephenamine



[a] dr refers to the ratio of (***R***,***R***,***R***)**-5** to (***S***,***S***,***R***)**-5**.

range of 2−12 h. Several rounds of resolution were routinely conducted in the time it would take to conduct a single resolution using the first method. A series of iterative resolutions conducted on a single batch of 570 g of pseudoephenamine (4.7:1 dr, racemic) demonstrate the utility of the stirring protocol to produce highly enriched mandelate crystals (≥19:1 dr by ^{1}H NMR; see Scheme 5), providing approximately 100 g of each enantiomer of pseudoephenamine (≥92% ee). Recrystallization of the auxiliary from absolute ethanol provided more than 80 g of each enantiomer of ≥99% ee. This protocol is our preferred method of resolving pseudoephenamine, and we have routinely performed it on large amounts of material (> 300 g), although it also works well on much smaller scales (< 50 g).

When pseudoephenamine is appreciably contaminated with ephenamine (< 2.5:1 dr), recoveries upon resolution with mandelic acid are low. To circumvent this problem, mixtures of low dr can be diastereomerically enriched by recrystallization from methanol in the presence of a seed crystal of optically pure pseudoephenamine (Scheme 6).

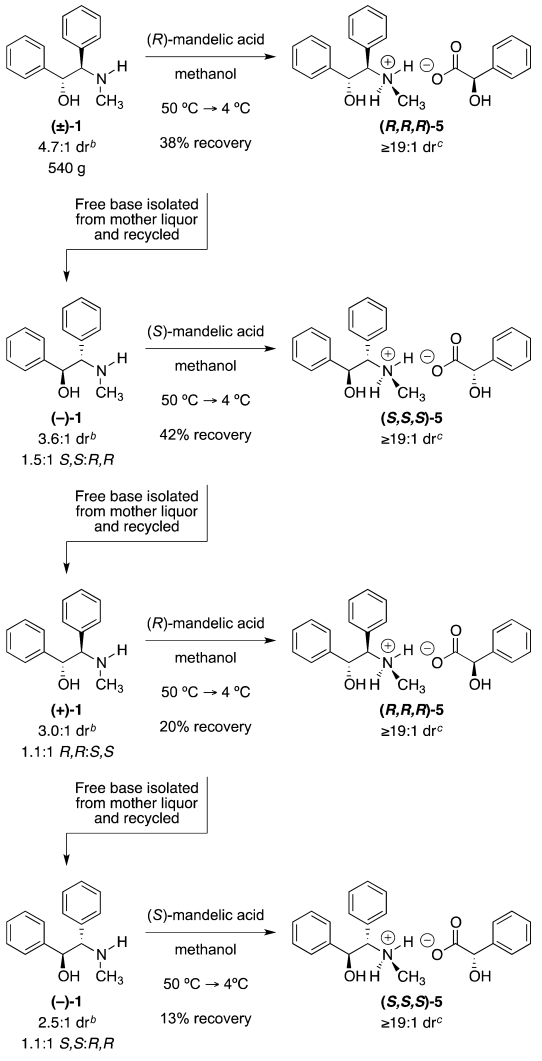
(14) We recommend the solution be filtered through a fritted funnel while warm if insoluble impurities are observed in the flask.

(15) Crystallization of pseudoephenamine is an exothermic process, and concentrated solutions of the auxiliary in volatile solvents such as ethyl ether (employed in the workup of these reactions) can produce pressure buildup in a sealed vessel if spontaneous crystallization occurs.

(16) See chapter 3 of ref 12 for a discussion of the effect of stirring on the resolution of diastereomeric salts.

(17) A similar process has been reported to transform ephedrine to pseudoephedrine: Chou, T. Q. *J. Biol. Chem.* **1926**, *70*, 109–114.

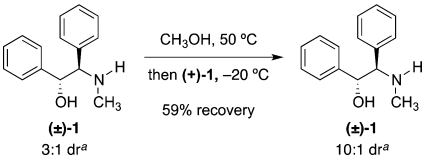
Scheme 5. Resolution of (±)-Pseudoephenamine with Mandelic Acid at 4 °C with Stirring[a]



[a] Total pseudoephenamine recovery after isolation of the free auxiliary and recrystallization from ethanol: 91.12 g (+)-**1** (≥99% ee) and 89.54 g (−)-**1** (≥99% ee). [b] dr refers to the ratio of (+)- and (−)-**1** to (±)-**4**. [c] dr refers to the ratio of (***R***,***R***,***R***)- or (***S***,***S***,***S***)-**5** to (***S***,***S***,***R***)- or (***R***,***R***,***S***)-**5**, respectively.

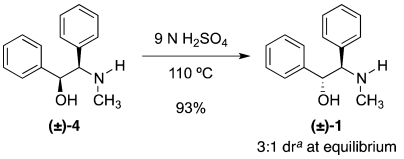
The diastereomerically enriched pseudoephenamine can then be subjected to mandelic acid resolution as in Scheme 5. In addition, we have discovered that ephenamine is slowly converted to pseudoephenamine upon heating (110 °C) in 9 N H_2SO_4 (Scheme 7).[17] At equilibrium, the diastereomeric ratio of the amino alcohols is ~3:1 favoring pseudoephenamine. Recrystallization from methanol as in Scheme 6 provides diastereomerically enriched pseudoephenamine suitable for mandelic acid resolution. In this way, it is possible to convert the majority of the amino alcohols obtained in the reduction of methylimino benzil to optically pure pseudoephenamine.

Scheme 6. Diastereoenrichment of Pseudoephenamine



[a] dr refers to the ratio of (±)-**1** to (±)-**4**.

Scheme 7. Isomerization of Ephenamine to Pseudoephenamine



[a] dr refers to the ratio of (±)-**1** to (±)-**4**.

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Supporting Information Available. Full experimental procedures, characterization data, and ^1H and ^{13}C NMR spectra for all synthetic intermediates. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.