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A New, Short, and Stereocontrolled Synthesis of C_2-Symmetric 1,2-Diamines

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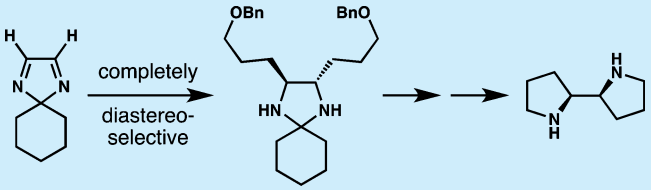
Supporting Information

ABSTRACT: The previously unknown 5-spirocyclohexylisoimidazole has been made efficiently and simply by reaction of ammonia, glyoxal hydrate, and cyclohexanone. It is a very useful precursor for the diastereocontrolled synthesis of many C_2-symmetric 1,2-diamines, a class which is important for the generation of a variety of C_2-symmetric reagents and catalysts for enantioselective synthesis.



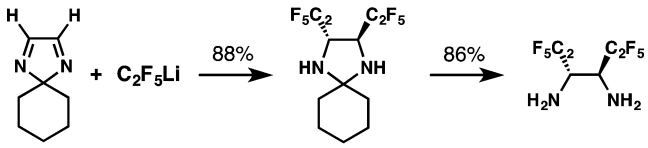
We describe herein a new, stereocontrolled, short, and widely applicable synthesis of C_2-symmetric 1,2-diamines. This diamine class represents one of the most important structural subunits for numerous reagents and catalysts that have advanced synthetic carbomolecular chemistry over the past three decades.[1,2] Since racemic C_2-symmetric amines are usually easily resolved as the salts with (+)- or (−)-tartaric acid, our objective was to develop a method for the synthesis of the racemic 1,2-diamines, free of contamination by the meso diastereomers. This approach is time saving since both enantiomers of the 1,2-diamine result from this process and are available for applications after resolution.

The most widely used chiral C_2-symmetric 1,2-diamines are 1,2-diphenyl-1,2-diaminoethane (DPEN)[3] and *trans* 1,2-diaminocyclohexane (DAC),[4] which have proven to be immensely useful for enantioselective synthesis. The versatility of DPEN is clear from its application to many enantioselective reactions, including Diels−Alder,[3a] 1,2-dihydroxylation of olefins,[3b] *syn*- or *anti*-aldol,[3c] carbonyl allylation,[3d] Ireland−Claisen rearrangement,[3e−g] Darzens reaction,[3h] *β*-lactam and *β*-amino acid synthesis,[3i] prostanoid synthesis,[3j,k] Jacobsen olefin epoxidation,[3l] Noyori carbonyl reduction.[3m] and Fu C−C coupling.[3n,o] *trans*-1,2-Diaminocyclohexane has been especially useful for enantioselective Horner−Wadsworth−Emmons reactions,[4a,b] Jacobsen olefin epoxidation,[4d] and Pd-catalyzed allyl coupling reactions via the Trost bisphosphine ligand.[4f]

One motivation for this research came from an initial interest in synthesizing C_2-symmetric 1,2-diamine derivatives in which the electron density at nitrogen is greatly diminished. Such compounds offer new possibilities as ligands for enantioselective catalysis because of greatly attenuated electron density at nitrogen. One of our objectives was a simple synthesis of (±)-1,2-pentafluoroethyl-1,2-diaminoethane (PFEEN) (**1**). As described below, that goal was readily achieved by the addition of perfluoroethyllithium to the previously unknown cyclic bis-imine **2**, as shown in Scheme 1.

A practical synthesis of the previously unknown precursor **2** for this synthetic approach to *vic*-diamines could be developed from inexpensive starting materials. The bis-imine **2** was

Scheme 1. Projected Route to the Decafluoro Diamine 1



formed in 90% yield simply by reaction of glyoxal trimer·$2H_2O$, cyclohexanone (3 equiv), and ammonium acetate (4 equiv) in THF−anhydrous ammonia at 23 °C for 8 h, followed by removal of solvents, extractive workup, and distillation (52 °C, 0.8 barr) as reported in detail in the Supporting Information. Pure **2** is stable indefinitely when stored in a sealed container in a−20 °C freezer. The conversion of the bis-imine **2** to the fluorinated 1,2-diamine **3** was accomplished in 88% yield by the following sequence of operations: (1) deprotonation of pentafluoroethane in ether below −78 °C by slow addition of precooled *n*-butyllithium to form the perfluoroethyllithium;[5,6] (2) gradual addition of the cold solution of C_2F_5Li via cannula to a stirred solution of **2** and BF_3·Et_2O (2 equiv) in ether at −78 °C; (3) gradual increase in the temperature of the reaction mixture to −50 °C for 12 h; (4) addition of aqueous $NaHCO_3$ solution, extractive isolation with ether, and flash chromatography. The C_2-symmetric (±)-1,2-diamine **3** was formed with *complete exclusion* of the meso isomer as shown by ^1H and ^{13}C NMR analysis. As expected, the hydrolysis of the cyclohexylidine diamine **3** required vigorous conditions: heating to boiling with 6 N HCl and removal of a cyclohexanone−aq HCl mixture by distillation. (±)-1,2-Perfluoroethyl-1,2-diaminoethane (PFEEN) was isolated by basification of the aqueous acid, extraction with ether, and flash chromatography on neutral alumina (86% yield). The stereochemistry of **1** was demonstrated by conversion to the cyclic C_2-symmetric aminal with benzaldehyde (either with or without HOAc as catalyst)

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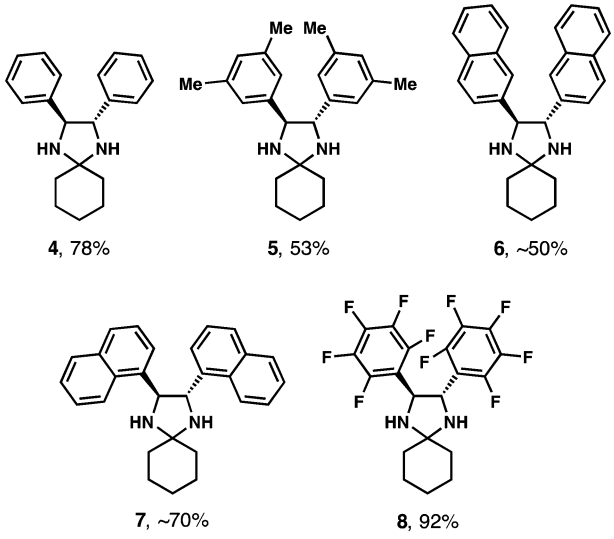
Org. Lett. XXXX, XXX, XXX−XXX

and separation of the resulting enantiomers by HPLC using a chiral OD-H column and 95% hexanes in 2-propanol as the eluent.[7,8] Further studies with this novel, very weakly basic diamine are in progress.

We were able to demonstrate the general utility of the cyclic bis-imine **2** as a key starting material for the completely diastereoselective synthesis of many racemic 1,2-diamines using the approach described above for the synthesis of the fluorinated diamine **1**. A series of cyclohexylidine derivatives of 1,2-diaryl-1,2-diaminoethanes was readily obtained by slow addition of the corresponding aryllithium reagents to a solution of $BF_3{\cdot}Et_2O$ and the bis-imine **2** in a ratio of 2:1. Aryl Grignard reagents could also be used. In each case, only the *trans*-cyclic amine was formed. These racemic cyclic diaryldiamines are shown in Scheme 2 together with the yields of isolated product.

Scheme 2. Arylation Products Derived from 2



4, 78% **5**, 53% **6**, ~50%

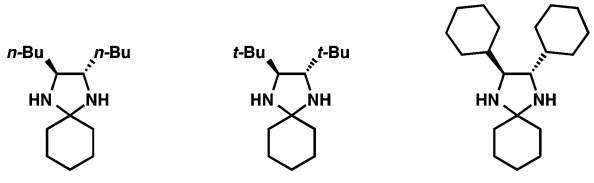
7, ~70% **8**, 92%

The conversion of the cyclic diamines **4**–**8** to the corresponding *rac*-1,2-diaryl-1,2-diaminoethanes was accomplished in high yields by heating with 6 equiv of 2 N aqueous HCl at 60 °C for 6 h followed by extractive isolation. Both cyclic diamine **4** and the corresponding hydrolysis product (DPEN) matched authentic samples, further confirming the *trans*-selectivity of these reactions with bis-imine **2**.

The attachment of two sp^3 carbon centered groups to the key cyclic intermediate **2** was also demonstrated as an effective stereocontrolled route to *trans*-4,5-disubstituted imidazolidines using *n*-butyllithium, *tert*-butyllithium, and cyclohexylmagnesium bromide, with ether as solvent in each case, to form the racemic C_2-symmetric products **9**–**11** shown in Scheme 3.

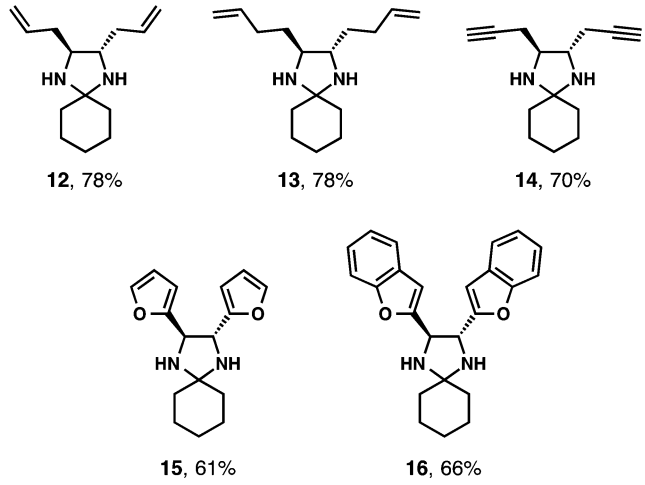
Furthermore, the addition of allyl, 3-butenyl, and propargyl Grignard reagents in ether to **2** produced smoothly the corresponding *trans*-4,5-disubstituted imidazolidines **12**, **13**, and **14**, as summarized in Scheme 4. The addition of 2-lithiated furan and 4,5-benzofuran to **2** was also successful and provided the *trans*-4,5-imidazolidines **15** and **16** (Scheme 4).

Scheme 3. Stereocontrolled Dialkylation of Bis-imine 2



9, 72% **10**, 80% **11**, 82%

Scheme 4. Unsaturated and Heteroaromatic 1,2-Diamines

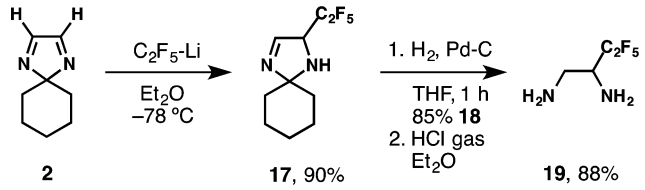


12, 78% **13**, 78% **14**, 70%

15, 61% **16**, 66%

The cyclic bis-imine **2** is a valuable intermediate for further elaboration into a variety of interesting nitrogen-containing compounds, most obvious of which in the context of the synthesis of **3**–**16** is the synthesis of monosubstituted 1,2-diamines. Thus, the reaction of **2** with $BF_3{\cdot}Et_2O$ and 1 equiv of C_2F_5Li in ether at −78 °C provided the cyclic monoamine **17** (90%), which was converted via the 4-substituted imidazolidine **18** to pentafluoroethylethylene diamine **19** (88% as the hydrochloride) as indicated in Scheme 5.

Scheme 5. Synthesis of Monosubstituted 1,2-Ethylenediamines



2 **17**, 90% **19**, 88%

Another aspect of the versatility of the new approach to the diastereoselective synthesis of 1,2-diamines that is disclosed herein involves the use of functionalized substituents. For example, catalytic olefin metathesis on the bis-olefinic diamines **12** and **13** (or *N*-protected derivatives) obviously could lead to 6- or 8-membered cyclic *trans*-1,2-diamines (or *N*-protected derivatives).[8] In addition, the facile synthesis of the useful C_2-symmetric bicyclic diamine[9] **23** by the route that is depicted in Scheme 6 provides a quite different example of the synthetic opportunities that our methodology enables. The key intermediate **20** was readily obtained from the addition of 3-(benzyloxy)propyllithium to **2**, as detailed in Scheme 6, and then converted to the bis-trifluoroacetyl bicyclic amide **22**. The free bicyclic diamine **23** was then obtained simply by hydrolysis with base. The usefulness of **23** in catalysis has previously been demonstrated.[10]

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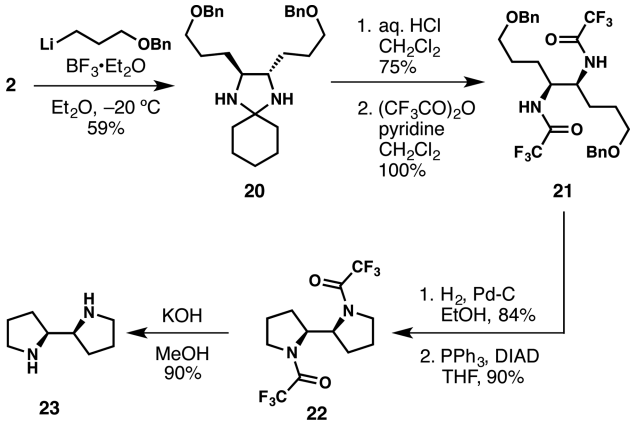
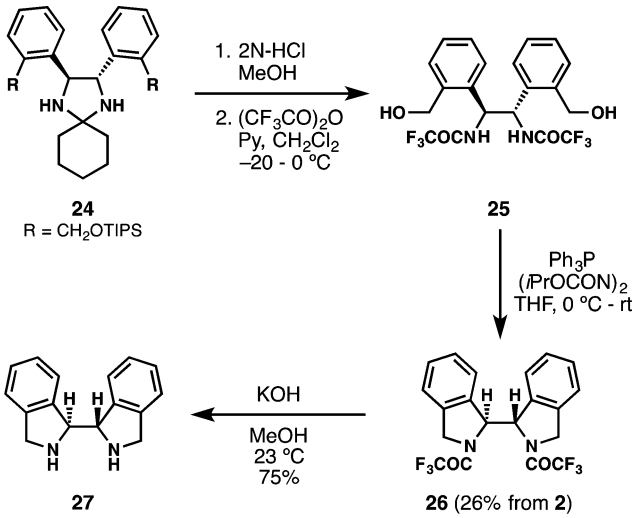
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 6. Synthesis of C_2-Symmetric Diamine 23



We have also been able to access the C_2-symmetric 2,2′-bisisoindoline **27** by an approach analogous to that used for the synthesis of **23**, as outlined in Scheme 7.

Scheme 7. Synthesis of C_2-Symmetric Diamine 27

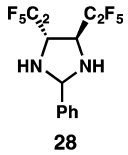


The key intermediate **24** was obtained by reaction of the bis-imine **2** with 2-[[(triisopropylsilyl)oxy]methyl]phenyllithium (from 2-[[(triisopropylsilyl)oxy]methyl]iodobenzene and *n*-BuLi in ether at −78 °C for 1 h) in the presence of 1 equiv of $BF_3{\cdot}Et_2O$ in ether at −78 to −50 °C for 24 h. Acidic cleavage of the TIPS ether and cyclohexylidine group in **24** was accomplished using 2 N methanolic HCl at 23 °C for 16 h. Trifluoroacetylation of the resulting dihydroxy diamine with trifluoroacetic anhydride−pyridine provided the dihydroxy bis-amide **25**. Mitsunobu cyclization of **25** furnished bis-amide **26** (26% overall yield from **2**), which by base treatment, afforded the desired C_2-symmetric diamine **27**.

A few of the diamines discussed above have been resolved by the traditional method using chiral 1:1 tartaric acid−diamine salts and simple recrystallization from ethanol, as described in detail in the Supporting Information for the diamines derived from **7** and **10**.

As expected, the basicity of 1,2-pentafluoroethyl-1,2-diaminoethane (**1**, PFEEN) is greatly attenuated, with a measured pK_a of 2.45 in 10% ethanol and 90% water at 23 °C. Thus, PFEEN is the least basic 1,2-disubstituted ethylenediamine now known. The *N,N*′-bistrifluoromethane sulfonamide derivative, mp 86−88 °C,[7] is actually a stronger acid than acetic acid with a measured pK_a of 3.57 in 1:9 ethanol−water at 23 °C. The applications of these unusual compounds as chiral subunits for enantioselective reactions (cf. ref 3) are now being studied.

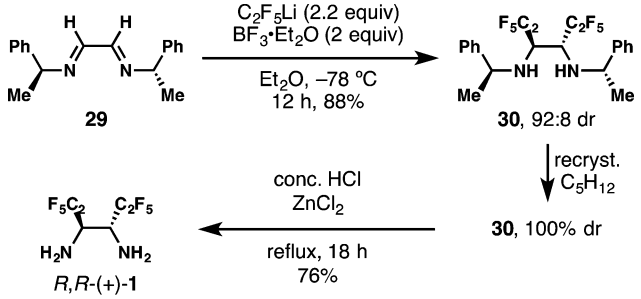
Reaction of **1** with benzaldehyde in CH_2Cl_2 at ambient temperature provided the corresponding aminal **28**, which was easily separated into the pure enantiomers by HPLC using Chiral Technologies Chiralcel OD-H column with 95:5 hexanes−isopropyl alcohol for elution (peak 1, t_R = 4.09 min, and peak 2, t_R = 6.00 min, on analytical scale, and t_R = 3.87 and 5.43 min on a multigram preparative scale).[7,8] Peaks 1 and 2 were shown to be *S,S*-**28** ($[\alpha]_D^{23}$ −17.2, *c* 1, $CHCl_3$) and *R,R*-**28** ($[\alpha]_D^{23}$ +17.5 *c* 1, $CHCl_3$), respectively, by the results described below. Hydrogenation of *R,R*-**28** using H_2, Pd−C afforded the *R,R*-enantiomer of **1**, $[\alpha]_D^{23}$ −8.0 (*c* 1, $CHCl_3$).



Three recrystallizations of the of (±)-**1** with *S,S*-di-*p*-toluoyltartaric acid and 9:1 1,2-dichloroethane−ethyl acetate afforded an 85:15 mixture of the *R,R*- and *S,S*-diamine **1** salts, indicating that resolution of (±)-**1** by this particular salt is less practical than the chromatographic separation described above. Studies of other methods for direct resolution of **1** are underway.

We have also synthesized *R,R*-**1** using as a starting point the bis-imine from glyoxal and *S*-α-methylbenzylamine (**29**) as shown in Scheme 8. This method was first used in our

Scheme 8. Synthetic Route to *R,R*-(+)-1



laboratories in 1988 for the synthesis of the *R,R*- and *S,S*-enantiomers of 1,2-di-*tert*-butylethylenediamine[11] and developed independently by Neumann et al.[12] Reaction of **29** with perfluoroethyllithium and $BF_3{\cdot}Et_2O$ at −78 °C afforded the bis-adduct **30** with 92:8 diastereoselectivity. The product could be purified by recrystallization from pentane or by conversion to the crystalline triflate.

The structure of **30**, mp 57 °C and $[\alpha]_D^{23}$ −87.6 (*c* 2, $CHCl_3$), was confirmed by X-ray crystallographic analysis (see Figure 1).[7] Cleavage of the *N*-α-phenethyl groups under strongly acidic conditions provided pure *R,R*-(+)-bis-pentafluoroethyl-1,2-diaminoethane in good yield.

In summary, the readily available cyclic bis-imine **2** serves as a useful starting point for the completely diastereoselective and very direct access to a wide variety of C_2-symmetric 1,2-

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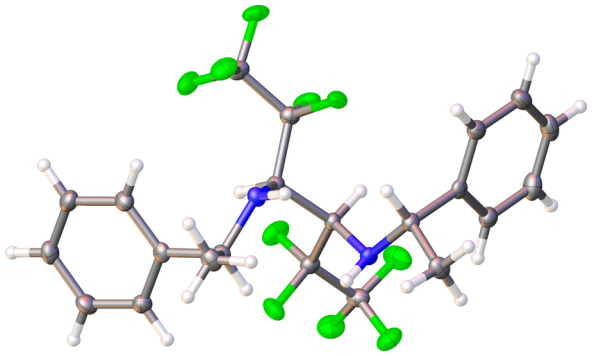

Figure 1. X-ray crystallographic structure of **30**.

diamines, compounds of broad utility as ligands for catalytic and enantioselective synthesis.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b01768.

Experimental methods and HPLC data for compound **28** (PDF)

^{1}H and ^{13}C NMR spectra for new compounds (PDF)

Crystallographic data for compound **30** (PDF)

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) For reviews, see: (a) Lucet, D.; Le Gall, T.; Mioskowski, C. *Angew. Chem., Int. Ed.* **1998**, *37*, 2580−2627. (b) Corey, E. J.; Kurti, L. *Enantioselective Chemical Synthesis*; Direct Books Publishing and Elsevier, 2010; pp 18−23, 41-2. (c) Corey, E. J. *Pure Appl. Chem.* **1990**, *62*, 1209−1216.

(2) For relevant recent papers on other approaches to the synthesis of 1,2-diamines, see: (a) Kim, H.; Nguyen, Y.; Yen, C. P. H.; Chagal, L.; Lough, A. J.; Kim, B. M.; Chin, J. *J. Am. Chem. Soc.* **2008**, *130*, 12184−12191. (b) Kim, H.; Staikova, M.; Lough, A. J.; Kim, B. M.; Chin, J. *Org. Lett.* **2009**, *11*, 157−160. (c) Denmark, S. E.; Fu, J.; Lawler, M. J. *Org. Synth.* **2006**, *83*, 121−130.

(3) (a) Corey, E. J.; Imwinkelried, R.; Pikul, S.; Xiang, Y. B. *J. Am. Chem. Soc.* **1989**, *111*, 5493−5495. (b) Corey, E. J.; Jardine, P. D.; Virgil, S.; Yuen, P.-W.; Connell, R. D. *J. Am. Chem. Soc.* **1989**, *111*, 9243−9244. (c) Corey, E. J.; Kim, S. S. *J. Am. Chem. Soc.* **1990**, *112*, 4976−4977. (d) Corey, E. J.; Kim, S. S. *Tetrahedron Lett.* **1990**, *31*, 3715−3718. (e) Corey, E. J.; Lee, D.-H. *J. Am. Chem. Soc.* **1991**, *113*, 4026−4028. (f) Corey, E. J.; Roberts, B. E.; Dixon, B. R. *J. Am. Chem. Soc.* **1995**, *117*, 193−196. (g) Corey, E. J.; Kania, R. *J. Am. Chem. Soc.* **1996**, *118*, 1229−1230. (h) Corey, E. J.; Choi, S. *Tetrahedron Lett.* **1991**, *32*, 2857−2860. (i) Corey, E. J.; Decicco, C. P.; Newbold, R. C. *Tetrahedron Lett.* **1991**, *32*, 5287−5290. (j) Corey, E. J.; Imai, N.; Pikul, S. *Tetrahedron Lett.* **1991**, *32*, 7517−7520. (k) Corey, E. J.; Sarshar, S. *J. Am. Chem. Soc.* **1992**, *114*, 7938−7939. (l) Zhang, W.; Loebach, J. L.; Wilson, S. R.; Jacobsen, E. N. *J. Am. Chem. Soc.* **1990**, *112*, 2801−2803. (m) Yamakawa, M.; Ito, H.; Noyori, R. *J. Am. Chem. Soc.* **2000**, *122*, 1466−1478. (n) Cordier, C.; Lundgren, R. J.; Fu, G. C. *J. Am. Chem. Soc.* **2013**, *135*, 10946−10949. (o) Schmidt, J.; Choi, J.; Liu, A. T.; Slusarczyk, M.; Fu, G. C. *Science* **2016**, *354*, 1265−1269.

(4) (a) Hanessian, S.; Delorme, D.; Beaudoin, S.; Leblanc, Y. *J. Am. Chem. Soc.* **1984**, *106*, 5754−5756. (b) Bennani, Y. L.; Hanessian, S. *Tetrahedron* **1996**, *52*, 13837−13860. (c) Hanessian, S.; Bennani, Y. L. *Tetrahedron Lett.* **1990**, *31*, 6465−6468. (d) Larrow, J.; Jacobsen, E. N. *Organic Syntheses*; Wiley: New York, 2004; Collect. Vol. *10*, pp 96−102. (e) Bennani, Y. L.; Hanessian, S. *Chem. Rev.* **1997**, *97*, 3161−3196. (f) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921−2943.

(5) For previous literature on perfluroethyllithium, see: (a) Shevchenko, N. E.; Nenajdenko, V. G.; Röschenthaler, G.-V. *J. Fluorine Chem.* **2008**, *129*, 390−396. (b) Kazabova, O.; Röschenthaler, G.-V. In *Efficient Preparation of Fluorine Compounds*; Roesky, H. W., Ed.; J. Wiley, 2013; pp 205−209.

(6) The formation of C_2F_5Li from C_2F_5H (commercial refrigerant HFC-125) and *n*-BuLi is strongly exothermic, which necessitates that *n*-BuLi be precooled and added slowly with good stirring and a bath temperature of −80 to −90 °C (liquid N_2−hexanes). Once formed, C_2F_5Li is stable for at least 2 h at −78 °C; see the experimental procedure in the Supporting Information for further details.

(7) See the Supporting Information for detailed HPLC information for compound **28**.

(8) For precedent, see: (a) Alvaro, G.; Grilli, S.; Martelli, G.; Savoia, D. *Eur. J. Org. Chem.* **1999**, *7*, 1523−1526. (b) Grilli, S.; Martelli, G.; Savoia, D.; Zazzetta, C. *Adv. Synth. Catal.* **2002**, *344*, 1068−1072.

(9) (a) Ferguson, R. R.; Boojamra, C. G.; Brown, S. H.; Crabtree, R. H. *Heterocycles* **1989**, *28*, 121−124. (b) Alexakis, A.; Tomassini, A.; Chouillet, C.; Roland, S.; Mangeney, P.; Bernardinelli, G. *Angew. Chem., Int. Ed.* **2000**, *39*, 4093−4095. (c) Denmark, S. L.; Fu, J.; Lawler, M. J. *Org. Synth.* **2006**, *83*, 121−130.

(10) Chen, M. S.; White, M. C. *Science* **2007**, *318*, 783−787.

(11) Yuen, P.-W. *Corey Group Research Report*; Harvard University, June 1988. See also: Lou, Y.; Remarchuk, T. P.; Corey, E. J. *J. Am. Chem. Soc.* **2005**, *127*, 14223−14230.

(12) (a) Neumann, W. L.; Rogic, M. M.; Dunn, J. *Tetrahedron Lett.* **1991**, *32*, 5865−5868. (b) See also: Roland, S.; Mangeney, P.; Alexakis, A. *Synthesis* **1999**, *1999*, 228−230.

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