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Graphical Abstract

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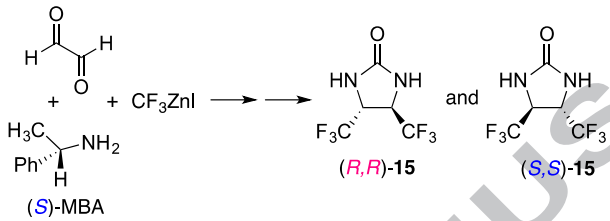

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Stereodivergent Synthesis of Novel Chiral C_2-Symmetric Bis-Trifluoromethyl-2-oxazolidinones

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ABSTRACT

A simplified effective synthetic process is described for the diastereoselective synthesis of the chiral C_2-symmetric CF_3-ureas (*R*,*R*)-**15** and (*S*,*S*)-**15** from (*S*)-α-phenylethylamine, glyoxal and CF_3I.

- Stereoselective double trifluoromethylation reaction of chiral bis-imines
- Stereodivergent synthesis of C_2-symmetric chiral 2-oxazolidinones
- Enantioselective [2+1]-cycloaddition with mixed-ligand dirhodium complexes

Several years ago, we described a detailed study of enantioselective [2+1]-cycloaddition of ethyl diazoacetate (EDA) to 1-heptyne (or other terminal acetylenes), using a variety of chiral amidate-bridged dirhodium (II) complexes of the type $Rh_2(RCO_2)_n(L^*_{4-n})$.[1] In the case of 1-heptyne, ethyl (1*S*)-2-*n*-amyl-2-cyclopropenylcarboxylate **1** was formed in >90% ee with the chiral catalysts **2**–**5** which contained the chiral ligands (*R*,*R*)-di-*tert*-butyl-*N*-triflylimidazolidinone (DTBTI) **6**, or (*R*,*R*)-diphenyl-*N*-triflylimidazolidinone (DPTI) **7** (Figure 1). Catalysts **2** and **4**, which have the *M*-*cis*-*anti* configuration,[2] gave 91% ee of the cyclopropene product, and the *cis*-2/1 catalyst **5** gave even higher ee (up to 95% ee).

From these and other results, we surmised that both steric bulk of the substituent alpha to N and lower electron density of the

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nitrogen ligand are favorable to enantioselectivity. The calculated p*K*a value of the DPTI ligand **7** is 9.5, whereas that of the DTBTI ligand **6** is 10.8.[3] In an effort to design a 2-imidazolidinone ligand with a lower p*K*a than DPTI, while maintaining much of the bulk of the *tert*-butyl group in DTBTI, we focused on the trifluoromethyl (CF_3) analog. The calculated p*K*a of the analogous di-trifluoromethyl-*N*-triflylimidazolidinone (DTFTI) derivative is 6.6, and sterically the CF_3 group is reported to be similar in size to an isopropyl group, having a Van der Waals' volume (hemisphere) of 42.6 Å^3 (relative to 16.8 Å^3 for CH_3).[4]

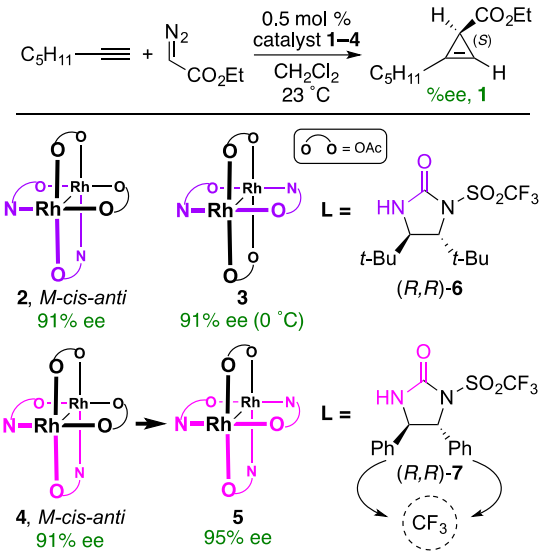
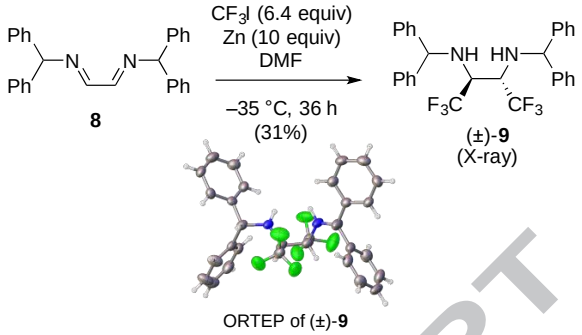


Figure 1. Enantioselective cyclopropenation reactions with mixed-ligand Rh_2(II) catalysts **2**–**5**.

Surprisingly, at the onset of this work, there were no reports of the synthesis of the required chiral C_2-symmetric bis-trifluoromethylethylenediamine, the required precursor to the 2-oxazolidinone of DTFTI, probably due to the challenge of introducing *trans* vicinal CF_3 groups stereoselectively.[5] Herein, we report studies directed at the synthesis of the required hexafluorodiamines and the corresponding cyclic ureas.[6] Generation of highly reactive nucleophilic sources of trifluoromethyl such as CF_3Li and CF_3Mg are not practical to use due to their instability,[7] however, the CF_3ZnI complex has been reported and used for the trifluoromethylation of carbonyl compounds.[8] This complex is formed *in-situ* by reaction of Zn with trifluoromethyl iodide (CF_3I, bp –23 °C) in the presence of the aprotic donor solvent DMF. Our first successful trifluoromethylation reaction was with this reagent and the simple achiral benzhydryl-substituted bis-imine **8**.[9] The reaction of CF_3I with a cooled mixture of Zn, **8**, and DMF, produces an orange to deep red mixture and after a period of 36 h, the starting material was mostly consumed as indicated by TLC analysis. The desired 1,2-*trans* CF_3 diamine (±)-**9** was isolated in 31% yield after chromatography (Scheme 2), the stereochemistry being confirmed by X-ray crystallographic analysis. Further optimization studies with bis-imine **8** did not lead to improved reaction yields.[10] Because it was problematic to install both CF_3 groups efficiently, and because resolution would be required, we focused on using the chiral bis-imine **11** derived from (*S*)-α-phenylethylamine (Scheme 4).[11]



Scheme 3. Double trifluoromethylation of bis-imine **8**.

Under similar reaction conditions described above, the reaction with bis-imine **11** again resulted in a mixture of mono- and bis-CF_3-addition products after 24 h reaction time. Purification by silica gel chromatography resulted in a 1:1.5 mixture of C_2-symmetric diastereomers in 32% yield.[12] The two products, later assigned as (*S*,*S*,*S*,*S*)-**12** and (*S*,*R*,*R*,*S*)-**13** respectively, had one diagnostic ^{19}F NMR signal each, thus also supporting the C_2-symmetry.

Optimization studies were performed with bis-imine **11** and several key variables were identified. Highest yields were obtained using DMF solvent, presumably due to the stabilized CF_3ZnI-DMF complex that is formed. The use of freshly activated Zn[13] was helpful since the reaction of Zn and CF_3I is highly exothermic, and rapid initiation is critical. An initial temperature of *ca.* –50 °C for addition of CF_3I and then maintaining the reaction temperature between –45 and –25 °C was optimal. Initiating the reaction at 0 °C or above have led to complex reaction mixtures and no product formation. Substrate concentration between 0.1–0.8M gave similar results with the dr of **12**/**13** between 1:1.1–1.5. More concentrated mixtures often resulted in complex, intractable mixtures of products, whereas lower concentrations led to slow reaction and stalling. Additives did not lead to improved dr or reaction yields, including the following: I_2 (>1 equiv), $ZnCl_2$ (1 equiv), NaI (5 equiv), LiI (1 equiv), and $TiCl_4$ (1 equiv).

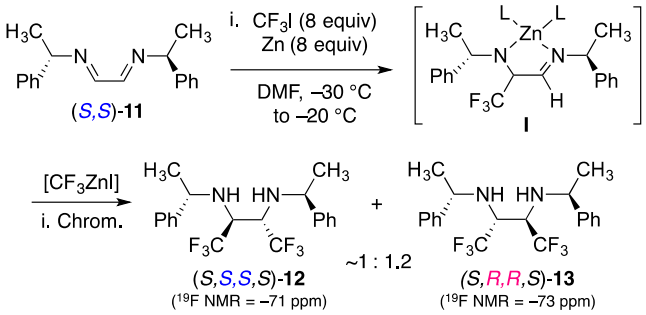
The optimal reaction conditions found to date involve using up to 8 equiv of activated Zn and 8 equiv CF_3I relative to bis-imine **11** in DMF cooled to –30 °C. The reaction mixture is maintained between –25 and –20 °C for a period of 24 h under an inert atmosphere. After workup and purification by chromatography, a ~1:1.2 mixture of (*S*,*S*,*S*,*S*)-**12** and (*S*,*R*,*R*,*S*)-**13** can be obtained in yields up to 65%.[14]

The lack of diastereoselectivity in the addition to **11** suggests the possibility that the first addition is non-enantioselective and that the second reaction proceeds via a Zn(II) chelate (**I** in Scheme 4). Also of mechanistic interest is the fact that only the (*S*,*R*,*R*,*S*) and (*S*,*S*,*S*,*S*) diastereomers are formed and that none of the meso isomer is detected. This result is contrary to high diastereoselectivity observed in similar systems and in the absence of the strong donor solvent DMF that are governed by chelate control.[15] Thus, the first CF_3 addition to **11** is not 1,3-stereoselective with respect to the chiral auxiliary, whereas the addition of second CF_3 group occurs with high 1,2-stereoselectivity. By following the reaction using ^{19}F NMR spectroscopy and an internal standard $PhCF_3$ (–63.5 ppm), we have observed that the reaction of Zn and CF_3I (–12 ppm) gives a *ca.* 1:1 mixture of CF_3ZnI (–44.6 ppm) and $(CF_3)_2Zn$ (–43.1 ppm, s), confirming previous reports.[16] The CF_3ZnI-DMF complex (–77 ppm, d, J = 4.5 Hz) can also sometimes be detected at the reactions temperatures, but can lead to formation of fluoral

(CF_3CHO) (–84 ppm) at warmer temperatures. Protic sources can also lead to the formation of fluoroform (–80 ppm, d, J = 79 Hz).

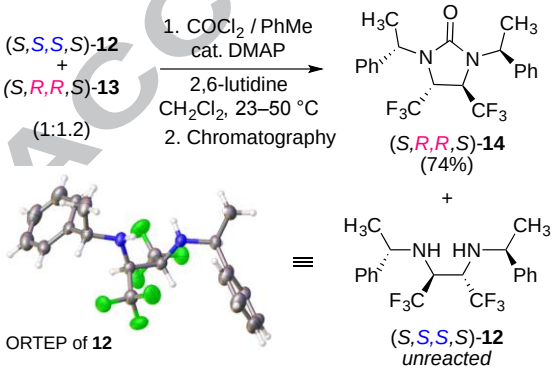
The formation of the less reactive $(CF_3)_2Zn$ is unavoidable using this procedure, and necessitates the use of 6-8 equiv of CF_3I in the reaction. A control experiment in which the $(CH_3)_2Zn$ reagent was added to a DMF solution of **11** cooled to –40 °C resulted in diimine decomposition and no dimethyl addition product. In another control experiment to test if radicals are involved, the radical scavenger 2-methyl-2-butene (8 equiv) was added to the reaction mixture with 8 equiv of both CF_3I and Zn relative to bis-imine **11**. There was no impact to the trifluoromethylation reaction, and a 1:1.2 mixture of **12**/**13** was still produced in ~60% yield.

Scheme 4. Trifluoromethylation of chiral bis-imine **11**.



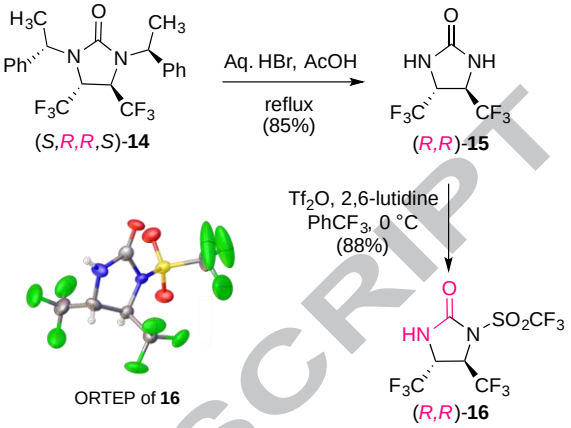
Although the diastereomers **12** and **13** were not separable by chromatography or crystallization, treatment with excess phosgene (1.2–1.5 equiv) resulted in reaction only with the (*S*,*R*,*R*,*S*)-**13** isomer to give the urea (*S*,*R*,*R*,*S*)-**14** (oil) and recovered unreacted diamine **12** (Scheme 5). The two products were easily separated by silica gel chromatography and upon isolation of (*S*,*S*,*S*,*S*)-**12** (low-melting solid, mp 81 °C) crystallization occurred upon standing. The structure and the absolute stereochemistry of **12** was determined by single-crystal X-ray diffraction analysis and illustrated as an ORTEP in Scheme 5.

Scheme 5. Stereodivergent synthesis of urea **14**.



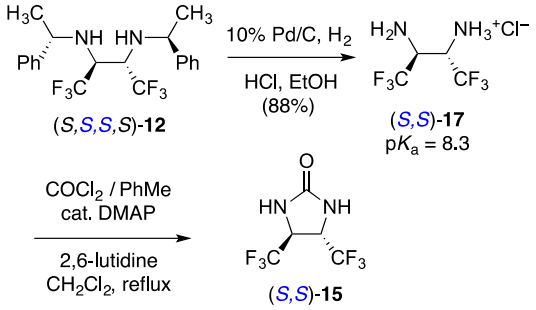
Reaction of pure **14** with HBr in refluxing acetic acid gave 2-oxazolidinone (*R*,*R*)-**15** (mp 223 °C, onset by DSC) in 85% yield after 18 h (Scheme 6).[17] The corresponding cleavage using 12 N HCl at reflux was too slow to be useful. The conversion of **15** to the mono-triflimide **16** required careful selection of conditions because of solubility issues, the need to avoid bis-triflimide formation and the unsuitability of many bases, but an excellent process was developed as indicated in Scheme 6 which provided crystalline **16**, **(**mp 129 °C, onset by DSC). The structure of **16** (DTFTI) was confirmed by X-ray crystallographic analysis.

Scheme 6. Synthesis of DTFTI ligand (*R*,*R*)-**16**.



For the converson of the unreacted diastereomer (*S*,*S*,*S*,*S*)-**12** to urea (*S*,*S*)-**16**, a two-step process was requried (Scheme 7). First, cleavage of the *N*-α-phenethyl groups with Pd/C and hydrogen in EtOH (or MeOH) provided good conversion to the TREC-diamine **17**.[18] Then, reaction of **17** with phosgene, under less forcing conditions than used previously, afforded the urea **15** in 79% yield.

Scheme 7. Synthesis of 2-oxazolidinone (*S*,*S*)-**15**.



To compare the chiral ligand DTFTI with the DPTI and DTBTI from Figure 1, we prepared several mixed-ligand dirhodium complexes using the methods previously reported.[1a] Of the 14 possible $Rh_2(RCO_2)_n(DTFTI^*_{4-n})$ complexes that can be prepared, we isolated nine distinct catalysts to test in the asymmetric [2+1]-cycloaddition reaction. Out of these, the three that provided the highest enantioselection are illustrated in Figure 2. It's important to note that the stereochemical arrangement in the (*R*,*R*)-**16** DTFTI ligand is opposite to that from ligands (*R*,*R*)-**3** and (*R*,*R*)-**4** due to the higher CIP priority of the CF_3 group vs phenyl. Thus, all the catalysts with ligands of the (*R*,*R*)-configuration gave the same (*S*) enantiomer of the cyclopropene product. However, opposite trends were observed with the DTFTI complexes. For example, complexes **2** and **4**, which are in the *M-cis-anti* configuration (Figure 1), gave the highest %ee in the $Rh_2(RCO_2)_2(L)_2$ series of catalysts, whereas with the DTFTI ligand, complex **18** having the *P-cis-anti* configuration performed the best.

Cyclopropene formation using the mixed-ligand complexes **18**–**20** led to product of lower %ee at room temperature than reactions at 0 °C. The *P-cis-anti* complex **18** containing one trifluoroacete and one acetate bridging ligand, was superior to all other complexes examined, resulting in 98% ee of the cyclopropene product **1**. In comparison, the mixed-ligand

complexes **2** and **4**, with the *M*-*cis*-*anti*, both gave product of 91% ee at room temperature.

For the mixed-ligand complexes in the $Rh_2(RCO_2)_1(L)_3$ series, complex **19** (Figure 2), which was derived from **18** (*P*-*cis*-*anti*) by displacement of an acetate with DTFTI, gave 91% ee in the [2+1]-cycloaddition reaction. In contrast, a similar trend was observed with complex **5**, which was derived from the complex having the *M*-*cis*-*anti* configuration, and provided the highest enantioselection the (1,3)-$Rh_2(RCO_2)_1(L)_3$ series.

The mixed-ligand complex **20**, having the configuration corresponding to complex **5**, (confirmed by X-ray structural analysis, and both derived from their respective *M*-*cis*-*anti* complexes), gave only 75% ee for the cyclopropene product. This result in accordance with the trend reversal observed in the DTFTI ligand series.

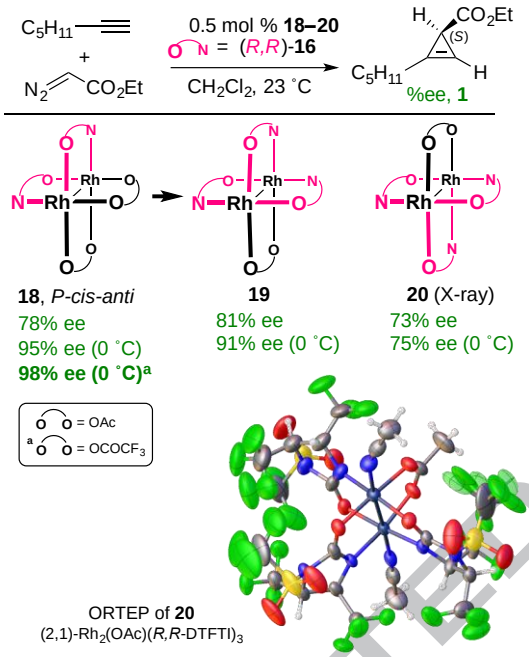


Figure 2. Enantioselective cyclopropenation with mixed-ligand Rh_2(II) catalysts **18**–**20** containing chiral ligand (*R*,*R*)-**16**.

Conclusion

In summary, we successfully developed a useful bis-trifluoromethylation process to prepare the chiral C_2-symmetric *R*,*R*-oxazolidinone **15** and its enantiomer from a common intermediate. These compounds were then converted to the corresponding *N*-triflimides and used for the synthesis of various mixed-ligand dirhodium(II) complexes. Three such chiral mixed-ligand Rh(II) complexes catalyzed the asymmetric [2+1]-cycloaddition reaction of ethyl diazoacetate with terminal acetylenes to form chiral cyclopropenes in high ee.

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Supplementary Material

Synthetic procedures and characterization data for the new compounds and Rh_2(II) complexes reported herein (PDF); X-ray crystallographic data for compounds (±)-**9**, (*S*,*S*,*S*,*S*)-**12**, (*R*,*R*)-**16**, and $Rh_2(OAc)(DTFTI)_3$ **20** (CIF). This material is available free of charge via the Internet.

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[2] The descriptors for axial-chirality are *M* (counter clockwise) and *P* (clockwise), whereas "*cis*" refers to two ligands adjacent to one another and "*anti*" indicates the ligands are orientated on the opposite rhodium.

[3] The experimental pK_a value of each ligand was determined by measuring the pH at one-half the equivalence point in a 1:1 EtOH-H_2O mixture: DTBTI (p*K*a = 13.2) and DPTI (p*K*a = 11.9).

[4] (a) McClinton, M.A.; McClinton, D. A. *Tetrahedron* **1992**, *48*, 6555–6666; (b) Seebach, D. *Angew. Chem. Int. Ed. Engl.* **1990**, *29*, 1320–1367.

[5] Zard and coworkers unexpectedly prepared a *meso* 1,2-CF_3-diamine derivative via a radical dimerization: (a) Gagosz, F.; Zard, S. *Org Lett*., **2004**, *5*, 2655–2657; (b) Zard, S.; Gagosz, F. Fr. Demande (2004) FR 2844264.

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[7] H. J. Emeleus and R. N. Haszeldine, *J. Chem. Soc.*, **1949**, 2948–2952.

[8] (a) Trifluoromethylation of carbonyl compounds with the [CF_3ZnI] reagent was reported by: Kitazume, T.; Ishikawa, N. *Chemistry Letters*, **1981**, 1679–1680, and also employed within our group (Letavic, M., 1993) to prepare 1-(2-bromophenyl)-2,2,2-trifluoroethan-1-ol; (b) For a good review of nucleophilic trifluoromethylation, see: Rubiales, G.; Alonso, C.; Martinez de Margorta, E.; Palacios, F. ARKIVOC **2014** (ii) 362–405.

[9] Bis-imine **8** is a crystalline white solid: (a) Neumann, W. L.; Rogic, M.; Dunn, T. J. *Tetrahedron Lett.* **1991**, *32*, 5865–5868; (b) Liu, L.; Ishida, N.; Ashida, S.; Murakami, M. *Org. Lett.* **2011**, *13*, 1666–1669.

[10] Alternative solvents such as THF and Et_2O resulted in complex reaction mixtures, as did warming the reaction mixtures in DMF. Using a 5:1 CH_3CN/DMF mixture resulted in only the mono-addition product being formed.

[11] For preparation of *bis*-imine (*S*,*S*)-**11**, see: (a) Alvaro, G.; Grepioni, F.; Savoia, D. *J. Org. Chem.* **1997**, 62, 4180; (b) Roland, S.; Mangeney, P.; Alexakis, A. *Synthesis* **1999**, 228–230; (c) Roland, S.; Mangeney, P. *Eur. J. Org. Chem.* **2000**, 611–616; (d) Alvaro, G.; Grepioni, F.; Grilli, S.; Maini, L.; Martelli, G.; Savoia, D. *Synthesis* **2000**, 581–587; (e) Sun, X.; Wang, S.; Sun, S.; Zhu, J.; Deng, J. *Synlett* **2005**, 2776−2780.

[12] The mixture of diastereomers is isolated as yellow oil that solidifies on standing to a wax-like product. Crystallization to separate the diastereomers was unsuccessful.

[13] For zinc activation, see: Organic Syntheses, Coll. Vol. 6, p.289 (1988); Vol. 53, p.86 (1973).

[14] (a) Other approaches examined to access **12**/**13** include: Pd(0)-catalyzed homocoupling of CF_3-imidoyl iodide (Amii, H.; Kohda, M.; Seo, M.; Uneyama, K. *Chem. Commun*., **2003**, 1752–1753), and (b) the widely used $TMSCF_3$ reagent (Prakash, G. K. S.; Mandal, M. *J. Am. Chem. Soc.* **2002**, *124*, 6538–6539) in the presence of TBAT. Both approaches failed to give any product; (c) Preparation of the [CF_3Cd] reagent (Burton, D. J. Wiemers, D. M. *J. Am. Chem. Soc.* **1985**, *107*, 5014–5015), prepared from difluorodibromomethane (CBr_2F_2, bp 24 °C) and Cd, resulted in trace mono CF_3-addition product from **11**.

[15] (a) Our group recently reported the preparation of 1,2-pentafluoro-ethyl-1,2-diaminoethane where high (98:2) diastereoselectivity starting with chiral bis-imine **11** was achieved. Vemula, R.; Wilde, N. C.; Goreti, R.; Corey, E. J. *Org. Lett.*, **2017**, *19*, 3883–3886; (b) For discussion of the Cram chelate model, see: Bambridge, K.; Begley, M. J.; Simpkins, N. S. *Tetrahedron Lett.* **1994**, *35*, 3391–3394.

[16] (a) A similar NMR study was done with CF_3Br and Zn, see: Francese, C.; Tordeux, M.; Wakselman, C. *Tet. Lett*, **1988**, *29*, 1029–1030. The CF_3Br is much less reactive with Zn than CF_3I; (b) Prakash, G. K. S.; Wang, F.; Zhang, Z.; Haiges, R.; Rahm, M.; Christe, K. O.; Mathew, T.; Olah, G. A. *Angew. Chem. Int. Ed.*, **2014**, *53*, 11575–11578.

[17] Hydrogenolysis of the *N*-α-phenethyl group with Pd/C and H_2 (up to 400 psi) and with acid additives (HCl or AcOH) was unsuccessful.

[18] The freebase of **17** (generated by Et_2O/saturated aqueous $NaHCO_3$) is volatile and not easily isolated in good yield (see SI).