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Application of the *N*-hydroxymethyl group to the stereoselective synthesis of (3*S*,4*S*)-3-aminodeoxystatine derivatives

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Abstract—Stereoselective synthesis of two 3-aminodeoxystatine derivatives was achieved. Chiral γ-amino-α,β-unsaturated esters containing an *N*-aminomethyl group undergo the stereoselective conjugate addition with an internal carbamate or amide nitrogen nucleophile. The diastereoselectivity was about 10:1 by ^{1}H NMR. Thus, the 3-aminodeoxystatine derivatives were prepared from commercially available *N*-Boc-L-leucine in nine steps in overall yields of 26% and 20% for the benzyl carbamate and the acetamide derivatives, respectively.

1. Introduction

Recently, we have reported an efficient stereoselective synthesis of statine **1** (Fig. 1).[1] The *N*-hydroxymethyl group tethered to the amino group of γ-amino-α,β-unsaturated ester **3** was highly effective for the stereoselective intramolecular conjugate addition to construct the γ-amino-β-hydroxycarboxylic acid moiety in statine.[2] As part of an ongoing study on the application of the *N*-hydroxymethyl group in natural product synthesis,[3] we wanted to synthesize 3-aminodeoxystatine **2** ((3*S*,4*S*)-3,4-diamino-6-methylheptanoic acid) derivatives by simply replacing the hydroxyl group of **3** with an amino group.[3d]

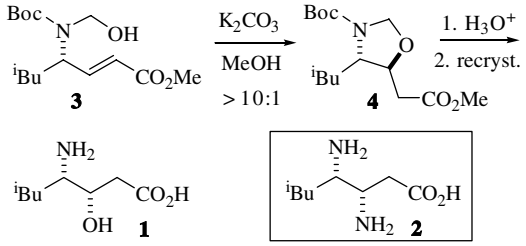

Figure 1. The stereoselective synthesis of (−)-statine **1**.

3-Aminodeoxystatine **2** is an isosterically modified statine analogue (Fig. 1).[4] The peptides containing **2** were needed to study the importance of hydrogen bonding and electrostatic interaction when the (3*S*)-hydroxyl group of **1** was replaced by a basic amino group. The β-amino group of **2** would be expected to be protonated at physiological pH. Indeed, some peptides derived from **2** were shown to be more biologically active than the corresponding congeners with **1**.[5] As far as the rat renin inhibition was concerned, the substitution of **1** with **2** resulted in better inhibitory activity for all the peptides studied. The reason would be the stronger hydrogen bonding interaction of the aspartyl residues with the protonated (3*S*)-amino group of **2** than that with the (3*S*)-hydroxyl group of **1**. Although it has some interesting biological activities, there are not many reports about the synthesis of **2** or the biological activities of the peptides containing it.[5,6] We herein report a stereoselective synthesis of (3*S*,4*S*)-3-aminodeoxystatine derivatives by an efficient intramolecular conjugate addition of nitrogen nucleophiles to the γ-amino-α,β-unsaturated ester.

2. Results and discussion

The required (*E*)-γ-amino-α,β-unsaturated ester **5** with the *N*-acetoxymethyl group was prepared from *N*-Boc-L-leucine as described previously (Scheme 1).[3c] The protected aminomethyl group could be established under the acid-catalyzed reaction of the *N*-acetoxymethyl group with an amide or carbamate nucleophile.[7] Initially, we selected an amide group as a protected nitrogen source. Thus, conjugated ester **6a** containing the amidomethyl

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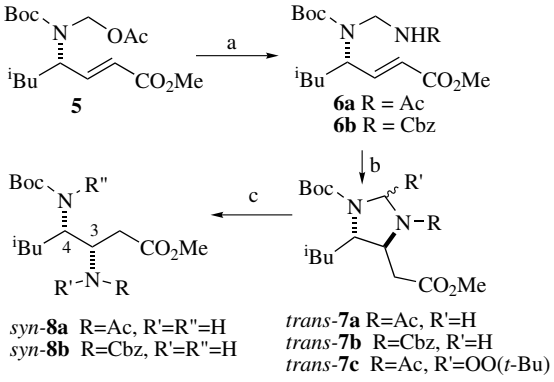
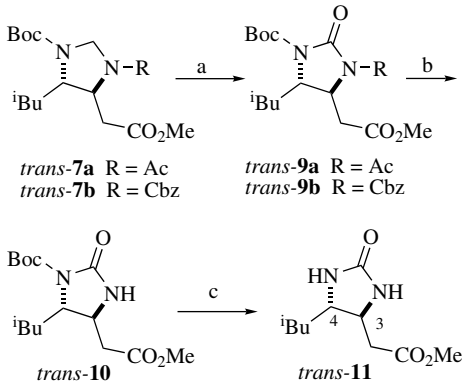


Scheme 1. Reagents and conditions: (a) PPTS, $AcNH_2$, 83% (**6a**) or PPTS, $CbzNH_2$, 82% (**6b**); (b) NaH, 78%; (c) cat. $RuCl_3$, TBHP then Pd/C, H_2 followed by Cs_2CO_3 in MeOH, 47% (**8a**) or cat. $RuCl_3$, TBHP then 3 N HCl followed by Cs_2CO_3 in MeOH, 60% (**8b**).



Scheme 2. Reagents and conditions: (a) cat. $RuCl_3$, $NaIO_4$, CH_3CN–CCl_4–H_2O = 2:2:3, 98%; (b) Cs_2CO_3, MeOH; (c) TFA, CH_2Cl_2, 72% (two steps, from **9a**) or 73% (two steps, from **9b**).

group was obtained in a good yield from the reaction of **5** with acetamide in the presence of a catalytic amount of PPTS. The use of PPTS instead of *p*-TsOH was crucial to give the desired aminal functionality.[8] We thought that the *N*-amidomethyl group of **6a** would be a good enough nucleophile to undergo a facile intramolecular conjugate addition. However, the weak bases such as K_2CO_3 or KOH that were effective in the synthesis of statine did not give a desired addition product. Stronger bases such as NaH or KHMDS were necessary to effect the intramolecular addition to give a diastereomeric mixture of imidazolidine **7a**. The addition reaction was fast at room temperature probably because of the intramolecular nature of the reaction. The intermolecular conjugate addition of methanolic ammonia to the similar unsaturated ester was slow even at higher temperature (80–90 °C, 16 h, 51%, see below).[6c] The diastereoselectivity in the conjugate addition was determined at the next stage because the diastereomers of **7a** were not distinguishable in the ^{1}H NMR spectrum. The ruthenium-catalyzed oxidation of **7a** resulted in a mixture of three compounds, **7c**, **8c** (R = Ac, R′ = CHO, R″ = H), and **8d** (R = Ac, R′ = H, R″ = CHO), that was treated without separation under the hydrogenolysis conditions to afford **8c** and **8d**.[9] Subsequent hydrolysis of the *N*-formyl groups of **8c** and **8d** yielded **8a**. The diastereomeric ratio of **8a** was shown to be about 10:1 by ^{1}H NMR. Similar selectivity was consistently observed with imidazolidinones **9**, **10**, and **11** (Scheme 2, see below).

With the synthesis of the (3*N*)-Ac and (4*N*)-Boc derivative **8a** of 3-aminodeoxystatine being successful, we needed to prepare another derivative with orthogonal protecting groups for the two amino groups. The two independent protecting groups would be important for the selective formation of a peptide bond at a desired amino group in the target peptides. In this regard, a benzyl carbamate should be good enough to be a protected nitrogen source. Moreover, separation of the *syn*-diastereomer of the methyl ester derivative **8b** from its *anti*-diastereomer by column chromatography has been reported.[6a] The desired **8b** with the (3*N*)-Cbz and (4*N*)-Boc protecting groups was then readily obtained following the same protocol (Scheme 1). The diastereomeric ratio was determined to be also about 10:1 based on the ^{1}H NMR spectrum.

To determine the relative configuration at the newly generated stereogenic center of the diastereomers, the mixture **7** was converted to imidazolidinone **11** as shown in Scheme 2. A smaller coupling constant of $J_{3,4}$ (5.4 Hz) has been reported for the *trans*-isomer of a similar imidazolidinone, whereas the larger value of $J_{3,4}$ (7.8 Hz) was observed for its *cis*-isomer.[6c] The same trend has been well established in oxazolidinone ring systems.[1,10] First, the ruthenium-catalyzed oxidation reaction of the aminal group of **7** gave the N-protected imidazolidinone **9**.[11] Then, both the acetyl (or Cbz) and the Boc protecting groups were removed by the sequential treatment with Cs_2CO_3 and TFA, respectively, to afford **11**. The ^{1}H NMR analysis of the major isomer of **11** showed the vicinal coupling constant of $J_{3,4}$ to be 5.1 Hz, which is consistent with the values reported for the *trans*-isomers of the imidazolidinone and the oxazolidinone analogs as mentioned above. The $J_{3,4}$ value of the minor *cis*-isomer was determined to be 7.7 Hz from the about 1:1 diastereomeric mixture of **11**.[12] The diastereomeric ratios of the imidazolidinones **9**, **10**, and **11** obtained here were all about 10:1 by their ^{1}H NMR spectra, which confirmed the initial assessment of the stereoselectivity of the intramolecular conjugate addition in Scheme 1.

The diastereoselection observed in the present study can be rationalized with the more favorable H-eclipsed allylic conformation (Fig. 2). The attack by the protected amino group on the same side as the allylic amino group to the double bond would result in the *trans* product.[13]

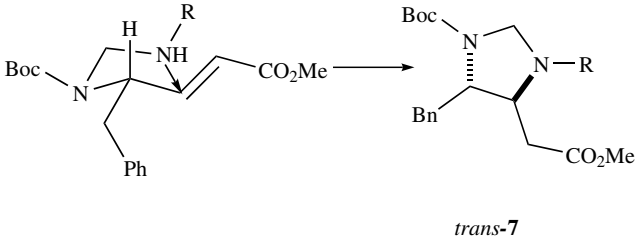


Figure 2. Favored conformation for the major product *trans*-**7**.

3. Conclusion

In summary, we have presented a stereoselective synthesis of two 3-aminodeoxystatine derivatives using an intramolecular conjugate addition of the *N*-aminomethyl group. The *N*-aminomethyl group was introduced from the amidation reaction of the *N*-acetoxymethyl group under mild acidic conditions. The diastereoselectivity of the intramolecular addition reaction was about 10 to 1 by ^{1}H NMR. Thus, the 3-aminodeoxystatine derivatives were prepared from commercially available *N*-Boc-L-leucine in nine steps with overall yields of 26% and 20% for the benzyl carbamate and acetamide derivatives, respectively. The orthogonally protected *N*-Cbz and *N*-Boc derivative **8b** should be useful for the selective formation of a peptide bond at the desired amino group in the target peptides. The method reported in the present study should be useful also for the efficient synthesis of other related β,γ-diaminocarboxylic acids with different side chains.

4. Experimental

Materials were obtained from commercial suppliers and were used without further purification. Methylene chloride was distilled from calcium hydride immediately prior to use. Likewise benzene and THF were distilled from sodium benzophenone ketyl. Air or moisture sensitive reactions were conducted under nitrogen atmosphere using oven-dried glassware and standard syringe/septa techniques. The reactions were monitored with a SiO_2 TLC plate under UV light (254 nm) followed by visualization with a molybdenum or ninhydrin staining solution. Column chromatography was performed on silica gel 60 (70–230 mesh). Optical rotations were determined at ambient temperature with a digital polarimeter and are the average of five measurements. ^{1}H and ^{13}C NMR spectra were measured at 300 and 75 MHz, respectively, in $CDCl_3$ unless stated otherwise and data were reported as follows in ppm (δ) from the internal standard (TMS, 0.0 ppm): chemical shift (multiplicity, integration, coupling constant in hertz).

4.1. Methyl (*E*)-(4*S*)-4-(*N*-benzyloxycarbonylaminomethyl-*N*-*tert*-butoxycarbonyl)amino-6-methylhept-2-enoate 6b

To a solution of **5** (600 mg, 1.71 mmol) in CH_2Cl_2 (40 mL) was added NH_2Cbz (3.34 g, 17.1 mmol) and PPTS (43 mg, 0.171 mmol). The mixture was heated under reflux for 18 h. The resulting mixture was partitioned twice between H_2O (20 mL) and Et_2O (20 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified with SiO_2 column chromatography (8:1 hexane/EtOAc) to give **6b** (617 mg, 83%) as a colorless oil. $R_f = 0.50$ (2:1 hexane/EtOAc); $[\alpha]_D^{26} = -34$ (*c* 0.94, $CHCl_3$); ^{1}H NMR (DMSO-d_6, 100 °C): δ 0.87 (d, 3H, $J = 5.7$), 0.89 (d, 3H, $J = 5.7$), 1.36–1.55 (m, 2H), 1.42 (s, 9H), 1.73–1.79 (m, 1H), 3.66 (s, 3H), 4.26–4.42 (m, 1H), 4.54 (dd, 1H, $J = 13.9$ and 6.4), 4.62 (dd, 1H, $J = 13.9$ and 6.2), 4.97–5.09 (m, 2H), 5.82 (d, 1H, $J = 15.9$), 6.89 (dd, 1H, $J = 15.9$ and 6.0), 7.33 (br s, 5H); ^{13}C NMR δ 21.7, 22.8, 24.5, 28.2, 40.5, 51.4, 54.1, 55.3, 66.7, 81.0, 121.0, 128.0, 128.4, 136.1, 147.7, 155.5, 155.8, 166.5; MS (CI) 435 ($[M+1]^+$, 45), 379 (35), 274 (14), 184 (100), 91 (46); HRMS (CI) calcd for $C_{23}H_{35}N_2O_6$ 435.2495 ($[M+1]^+$), found 435.2494.

4.2. (4*S*,5*S*)-3-Benzyloxycarbonyl-1-(*tert*-butoxycarbonyl)-5-isobutyl-4-methoxycarbonylmethylimidazolidine 7b

To a solution of **6b** (166 mg, 0.38 mmol) in THF (5 mL) was added NaH (3.48 mg, 0.38 mmol). The mixture was stirred for 1 h at room temperature. Then cold 1 N aq HCl solution was added to the resulting solution and the mixture was extracted with Et_2O (2 × 20 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified with SiO_2 column chromatography (4:1 hexane/EtOAc) to give **7b** (144 mg, 87%) as a colorless oil. Compound *trans*-**7b**: $R_f = 0.4$ (2:1 hexane/EtOAc); ^{1}H NMR (DMSO-d_6, 100 °C): δ 0.90 (d, 3H, $J = 6.4$), 0.91 (d, 3H, $J = 6.6$), 1.38–1.39 (m, 2H), 1.42 (s, 9H), 1.73–1.79 (m, 1H), 2.46–2.56 (m, 1H), 2.59 (dd, 1H, $J = 15.0$ and 4.8), 3.60 (s, 3H), 3.87–3.97 (m, 1H), 4.02–4.10 (m, 1H), 4.59 (d, 1H, $J = 7.1$), 4.72 (d, 1H, $J = 7.1$), 5.13 (br s, 2H), 7.25–7.42 (m, 5H); ^{13}C NMR (DMSO-d_6): δ 21.5, 22.3, 24.0, 27.5, 36.7, 41.3, 50.8, 57.3, 58.3, 58.5, 66.0, 79.4, 126.9, 127.3, 127.8, 136.1, 151.8, 152.2, 169.8; MS (CI) 435 ($[M+1]^+$, 61), 379 (56), 335 (100), 91 (14), 57 (7); HRMS (CI) calcd for $C_{23}H_{35}N_2O_6$ 435.2495 ($[M+1]^+$), found 435.2490.

4.3. Methyl (3*S*,4*S*)-3-(benzyloxycarbonyl)amino-4-(*tert*-butoxycarbonyl)amino-6-methylheptanoate 8b

To a mixture of **7b** (64 mg, 0.15 mmol) in benzene was added a mixture of $RuCl_3$ hydrate (3.1 mg, 0.02 mmol) and TBHP (91 mL, 0.44 mmol) and the reaction mixture was stirred for 10 h at room temperature. Then, 1 N aq HCl solution was added to the resulting solution and the mixture was extracted with Et_2O (2 × 20 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was dissolved in methanol and then Cs_2CO_3 (49 mg, 0.15 mmol) was added to the solution. The mixture was stirred for 30 min. The resulting mixture was partitioned between H_2O (2 × 10 mL) and Et_2O (2 × 10 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified with SiO_2 column chromatography (4:1 hexane/EtOAc) to give **8b** (38 mg, 60%) as an about 10:1 diastereomeric mixture and colorless oil. Compound *trans*-**8b**: $R_f = 0.31$ (2:1 hexane/EtOAc); $[\alpha]_D^{25} = -40$ (*c* 0.6, MeOH); ^{1}H NMR (toluene-d_8, 100 °C): δ 0.80 (d, 3H, $J = 6.6$), 0.82 (d, 3H, $J = 5.9$), 0.98–1.23 (m, 2H), 1.38 (s, 9H), 1.48–1.67 (m, 1H), 2.31 (dd, 1H, $J = 15.6$ and 6.6), 2.42 (dd, 1H, $J = 15.6$ and 5.9), 3.35 (s, 3H), 3.72–3.81 (m, 1H), 3.90–4.03 (m, 1H), 4.32 (br d, 1H, $J = 7.9$), 5.02 (br s, 2H), 5.13 (br d, 1H, $J = 8.2$), 6.98–7.25 (m, 5H); ^{13}C NMR δ 21.9, 23.2,

24.8, 28.3, 37.5, 41.6, 51.8, 52.4, 52.5, 66.8, 79.5, 128.0, 128.5, 136.5, 156.2, 156.4, 171.6; MS (CI) 423 ($[M+1]^+$, 12), 367 (34), 323 (100), 215 (12), 186 (7), 130 (7), 91 (12), 57 (10); HRMS (CI) calcd for $C_{22}H_{35}N_2O_6$ 423.2495 ($[M+1]^+$), found 423.2493.

4.4. (4*S*,5*S*)-3-Benzyloxycarbonyl-1-(*tert*-butoxycarbonyl)-5-isobutyl-4-methoxycarbonylmethylimidazolidin-2-one 9b

To a mixture of **7b** (114 mg, 0.26 mmol) in a mixture of solvents (CH_3CN 2 mL, CCl_4 2 mL and H_2O 3 mL) was added a mixture of $RuCl_3$ hydrate (5.39 mg, 0.03 mmol) and $NaIO_4$ (168 mg, 0.79 mmol) and the reaction mixture was stirred for 10 h at room temperature. The resulting mixture was partitioned between H_2O (2×20 mL) and Et_2O (2×20 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified with SiO_2 column chromatography (8:1 hexane/EtOAc) to give **9b** (107 mg, 0.24 mmol) as an about 10:1 diastereomeric mixture and colorless oil. Compound *trans*-**9b**: $R_f = 0.33$ (2:1 hexane/EtOAc); ^1H NMR δ 0.96 (d, 6H, $J = 6.6$), 1.44–1.51 (m, 2H), 1.54 (s, 9H), 1.71–1.85 (m, 1H), 2.62 (dd, 1H, $J = 15.9$ and 9.7), 2.83 (dd, 1H, $J = 15.9$ and 3.2), 3.69 (s, 3H), 3.87–3.96 (m, 1H), 4.14–4.22 (m, 1H), 5.29 (d, 1H, $J = 12.6$), 5.35 (d, 1H, $J = 12.6$), 7.27–7.46 (m, 5H); ^{13}C NMR δ 21.3, 23.7, 24.0, 28.0, 36.9, 42.2, 52.0, 53.7, 56.0, 68.4, 83.6, 127.8, 128.3, 128.5, 135.0, 147.6, 149.7, 151.7, 170.1; MS (CI) 449 ($[M+1]^+$, 2), 439 (8), 393 (29), 349 (100), 305 (17), 215 (9), 91 (34), 57 (17); HRMS (CI) calcd for $C_{23}H_{33}N_2O_7$ 449.2288 ($[M+1]^+$), found 449.2291.

4.5. (4*S*,5*S*)-5-Isobutyl-4-methoxycarbonylmethylimidazolidin-2-one 11

To a mixture of **9b** (97 mg, 0.22 mmol) in dry MeOH (5 mL) was added Cs_2CO_3 (70 mg, 0.21 mmol) at room temperature and the mixture was stirred for 30 min. Then, a cold 1 N aq HCl solution was added to the resulting solution and the mixture was extracted with Et_2O (2×20 mL). The combined organic layers were dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified with SiO_2 column chromatography (2:1 hexane/EtOAc) to give **10** (58 mg, 85%) as an about 10:1 diastereomeric mixture and colorless oil. Compound *trans*-**10**: $R_f = 0.07$ (2:1 hexane/EtOAc); ^1H NMR δ 0.95 (d, 3H, $J = 4.2$), 0.97 (d, 3H, $J = 4.4$), 1.44–1.48 (m, 1H), 1.53 (s, 9H), 1.56–1.73 (m, 2H), 2.53 (dd, 1H, $J = 16.5$ and 5.7) 2.63 (dd, 1H, $J = 16.5$ and 8.1), 3.58–3.64 (m, 1H), 3.69 (s, 3H), 3.82–3.87 (m, 1H), 6.07 (br s, 1H).

To a mixture of **10** (58 mg, 0.18 mmol) in CH_2Cl_2 (4 mL) was added TFA (1 mL) at room temperature and the reaction mixture was stirred for 30 min. The resulting mixture was evaporated. To completely remove TFA, another 4 mL of CH_2Cl_2 was added to the residue and then the solution was concentrated. This sequence was repeated 3 times. The residue was purified with SiO_2 column chromatography (2:1 hexane/EtOAc) to give **11** (33 mg, 86%) as an about 10:1 diastereomeric mixture and colorless oil. Compound *trans*-**11**: $R_f = 0.11$ (1:2 hexane/EtOAc); ^1H NMR δ 0.91 (d, 3H, $J = 6.6$), 0.97 (d, 3H, $J = 6.8$), 1.27–1.39 (m, 1H), 1.44–1.56 (m, 1H), 1.59–1.73 (m, 1H), 2.51–2.66 (m, 2H), 3.39–3.47 (m, 1H), 3.66–3.72 (m, 1H), 3.71 (s, 3H), 5.35–5.60 (m, 2H); ^{13}C NMR δ 21.9, 23.1, 25.1, 39.7, 44.5, 52.0, 55.3, 56.4, 163.1, 171.6; MS (CI) 215 ($[M+1]^+$, 100), 157 (2), 140 (3), 103 (1); HRMS (CI) calcd for $C_{10}H_{19}N_2O_3$ 215.1395 ($[M+1]^+$), found 215.1394.

Acknowledgement

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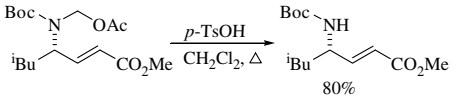
8. The use of *p*-TsOH as an acid catalyst[7] resulted in mostly the deacetoxymethylation as shown below.



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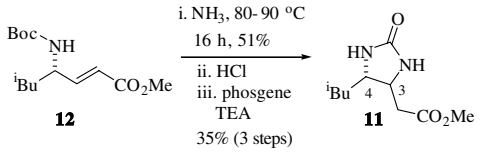
12. The approximately 1:1 diastereomeric mixture of **11** was prepared as follows. Conjugate addition of methanolic ammonia to **12** under pressure gave an about 1:1 mixture of adducts that was converted to imidazolidinone **11** after deprotection of the Boc group of the adducts with aq HCl. The diastereomeric ratio of **11** was also about 1:1 by its ^{1}H NMR spectrum. The smaller coupling constant of 5.1 Hz was attributed to the *trans*-isomer, whereas the larger coupling constant of 7.7 Hz to the *cis*-isomer.



13. (a) Johnson, F. *Chem. Rev.* **1968**, *68*, 375–413; (b) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841–1860.