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Concerted Conjugate Addition of Nucleophiles to Alkenoates. Part I: Mechanism of *N*-Alkylhydroxylamine Additions

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Concerted Conjugate Addition of Nucleophiles to Alkenoates. Part I: Mechanism of *N*-Alkylhydroxylamine Additions

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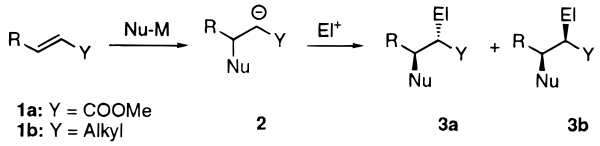
Abstract: Intermolecular conjugate additions of *N*-alkylhydroxylamines to α,β-unsaturated esters (alkenoates) produce β-hydroxyamino ester intermediates which cyclize to isoxazolidinones. The mechanism of the addition step was investigated by using deuterated starting materials. A five-atom-centered transition state was proposed to explain the stereoselective incorporation of deuterium atoms into the resulting isoxazolidinones. This "concerted" mechanism was further supported by the fact that hydroxylamines could add to trisubstituted alkenoates, resulting in the stereospecific synthesis of 3,4-dialkyl 5-isoxazolidinones. The use of sterically hindered alkenoates can produce conjugate addition products which are rarely obtained from the intermolecular conjugate additions of other nucleophiles. The stereochemistry of both α and β centers can be controlled to give a high level of selectivity even though simple substrates are used.

Olefins can be activated toward nucleophilic additions by the direct attachment of electron-withdrawing groups. This class of reactions are known as conjugate addition reactions or Michael reactions (when carbon nucleophiles are employed).[1] The common pathway for conjugate addition reactions involves the initial addition of a nucleophile to **1a** (*Y* = carbonyl group, sulfoxide, etc.) and subsequent coupling of the resulting intermediate **2** with an electrophile (Scheme 1). The stereochemistry of conjugate additions can be efficiently controlled by the use of Lewis acids or chiral auxiliaries in starting materials,[1,2] often producing anti addition products **3a**.[1,3] Unactivated olefins **1b** (*Y* = hydrogen and alkyl group) are electron-rich species and rarely accept nucleophiles. One known exception is the reverse-Cope elimination, which is viewed as the intramolecular addition of a hydroxylamine nucleophile to an olefin to produce a syn addition product.[4] It would be useful to achieve the intermolecular syn addition of nucleophiles and electrophiles for the synthesis of compounds such as **3b** which are otherwise difficult to obtain.

Scheme 1



Hydroxylamine derivatives are reported to efficiently add to unsaturated esters and lactones in good yields.[5,6] The reactivity of *N*-hydroxylamine derivatives toward sp^2 centers dramatically increases when compared with the corresponding amines. For example, reaction of benzylamine with **4a,b** in methanol gave desired products **6a,b** in moderate yields while no reaction was observed using dimethylformamide or methylene chloride as the solvent.[7] The addition of *N*-benzylhydroxylamine to **4c** gave **6c** in high yield under a variety of reaction conditions.[8] Therefore, it can be concluded that benzylhydroxylamine is more nucleophilic toward sp^2 centers than benzylamine. This finding is of interest since alkylamines react faster than the corresponding alkylhydroxylamines toward sp^3 centers such as in alkyl halides. These results cannot be sufficiently explained by the α-effect of N−O moieties, which generally account for the enhanced nucleophilicity toward sp^3 centers on the basis of pK_a.[9]

Fountain and co-workers reported that *N*-methylhydroxylamine reacted with ester **7** to give a hydroxamic ester intermediate which underwent intramolecular conjugate addition to give

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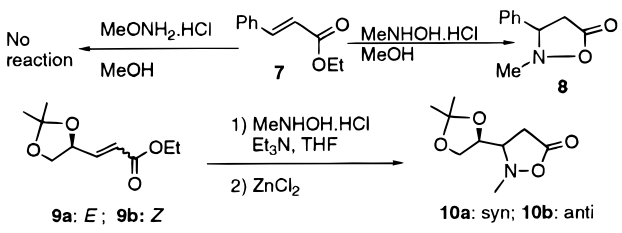
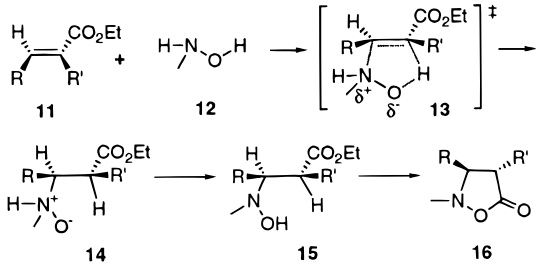
Scheme 2

Scheme 3



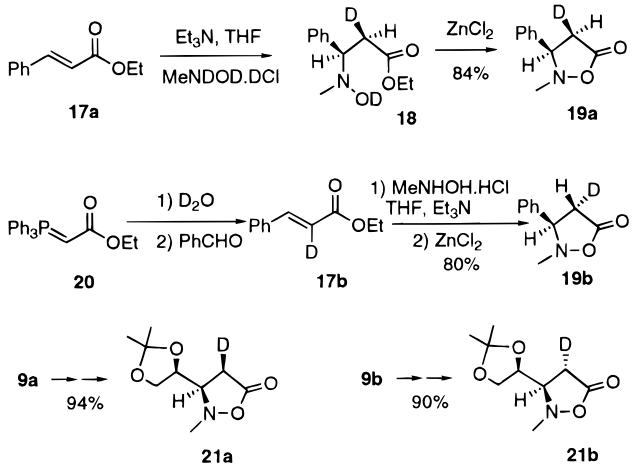
Scheme 4



isoxazolidinone **8** (Scheme 3).[5a] Remarkably, *O*-methylhydroxylamine, which should show a similar steric influence, did not produce any of the desired conjugate addition products.[10] Moreover, the α-effect of N−O moieties is not a convincing argument to explain the reactivity difference between *O*-alkyl- and *N*-alkylhydroxylamines due to the similar basicity of both hydroxylamines. A transition state with a hydrogen bond between the hydroxyl group of *N*-methylhydroxylamine and a carbonyl oxygen atom was proposed to account for the reactivity difference.[5c] We have also studied the hydroxylamine addition reaction by using both *Z*- and *E*-olefins **9** with the hope of producing two products **10a,b** in different ratios.[6a] To our surprise, both **9a** and **9b** gave a mixture of compounds in favor of the *cis*-isoxazolidinone **10** in similar ratios (10−14:1). Since the geometry of olefins **9** has a minimal influence on the outcome of the stereochemistry of **10**, the carbonyl oxygen atoms may not be important in the transition states of these conjugate additions.

A concerted mechanism can be suggested to explain the fact that *N*-alkylhydroxylamine derivatives add intermolecularly to alkenoates while the corresponding *O*-alkylhydroxylamines fail to react (Scheme 4).[10] Initially, the nitrogen nucleophile **12** approaches alkenoates **11** to give a concerted cyclic five-membered ring transition state **13**, which can be visualized to resemble [3 + 2] dipolar cycloaddition reactions[11] or retro-Cope-elimination reactions.[4] The reaction then proceeds further to

Scheme 5



intermediate **14** and is followed by a rapid proton shift to form compound **15**, which can be either isolated or cyclized to five-membered ring **16**, depending on the reaction conditions. This mechanism explains several of the unusual properties of alkylhydroxylamines, including reasons why the activities of *N*-alkylhydroxylamine (RNHOH), amine (RNH_2), and *O*-alkylhydroxylamine ($RONH_2$) in conjugate additions are dramatically different (Schemes 2 and 3). Conjugate additions with *N*-hydroxylamines are facilitated by a stabilized transition state which results from the concerted intramolecular proton-transfer process. *O*-Alkylhydroxylamine is not reactive toward alkenoates due to the lack of transition state stabilization. Second, the cyclic transition state limits the rotational freedom of both starting materials and magnifies the steric effects of the substituents. Thus, the conjugate addition of *N*-alkylhydroxylamines to optically active ester **9** occurs with a high level of diastereoselectivity (Scheme 3). Finally, minimal solvent effects which have been observed for the conjugate addition of *N*-alkylhydroxylamines are probably due to the formation of neutral transition state **13** (Scheme 4).

The possibility of using simple *E* unsaturated esters **17a,b** for achieving stereospecific conjugate additions was also investigated (Scheme 5). As expected, the reaction of deuterated *N*-methylhydroxylamine with ester **17a** gave intermediate **18**, which was cyclized to **19a** as a single isomer. The ^{1}H NMR spectrum of compound **19a** displayed a coupling constant of 5.5 Hz between the two protons at the 3,4-positions of the isoxazolidinone ring. The assignment of cis configuration of 3,4-protons is consistent with literature reports which are related to the [1,3]-cycloaddition products such as 3,4-dialkylisoxazolidinones.[12] The deuterated ester **17b** with *E* configuration, which was prepared by using Schneider's method,[13] reacted cleanly with *N*-methylhydroxylamine to give trans isomer **19b** (J_{3-4} = 12.8 Hz). Similarly, conjugate reactions of *E*- and *Z*-olefins **9a,b** were reexamined using the deuterated agent MeNDOD·DCl under the triethylamine-neutralization conditions. Compound **21a** was predominantly produced from *E*-alkenoate **9a**, and **21b** was the major product from *Z*-isomer **9b**.

Since concerted conjugate addition of nucleophiles to multisubstituted alkenoates should result in the control of both α- and β-centers, we became interested in investigating whether

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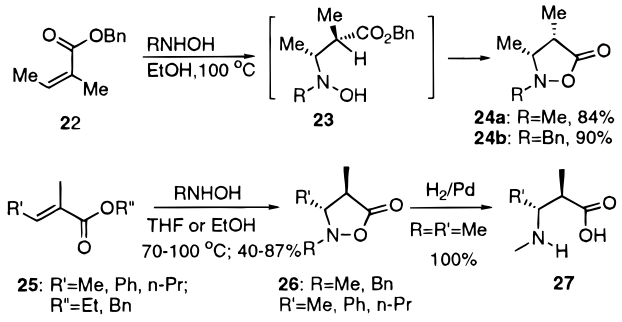
Scheme 6



hydroxylamine derivatives could add to multisubstituted alkenoates in a syn cycloaddition fashion. Trisubstituted alkenoate **22** was prepared according to a reported procedure[14] for studying the scope of this class of conjugate additions. Initially, no addition reactions were observed using the hydroxylamine hydrochloride salt; however, modified reaction conditions (Scheme 6)[15] promoted the conjugate addition reaction of (*Z*)-alkenoate **22** to give predominantly cis isoxazolidinones **24a,b** (cis:trans = 12−15:1). Intermediate **23**, which was not isolated, is shown to depict a syn transformation of stereocenters. Consistent with this, trans compounds **26** were produced as major products (cis:trans = 25−30:1) from *E*-alkenoates **25**. It appears that the reaction conditions and substrates have little influence on the course of the reaction. The same cycloaddition phenomenon was observed by using different solvents (such as THF and ethanol), ester moieties, and *N*-alkylhydroxylamine derivatives. The relative trans stereochemistry of **26a** (R = R′ = Me) was determined by the X-ray analysis of **27**,[16] a single isomer obtained from **26a** by palladium-catalyzed hydrogenation.

Conclusions

A cycloaddition mechanism was proposed to account for the stereospecific conjugate additions of hydroxylamine derivatives to simple α,*β*-unsaturated esters. The appropriate selection of deuterated starting materials allows introduction of the deuterium isotope in relative *R* or *S* stereochemistry. This method may be useful for the preparation of deuterium labeled analogues of biologically active compounds for the investigation of enzyme mechanisms.[17] Modification of the reaction conditions allows for the intermolecular addition of *N*-alkylhydroxylamine derivatives to trisubstituted alkenoates. This represents one of the rare cases of conjugate additions to sterically hindered substrates. The reported method offers a solution for the control of both α- and *β*-centers in the conjugate addition of nucleophiles to simple α,*β*-unsaturated esters. The resulting multisubstituted isoxazolidinones provide a useful synthon for the stereoselective synthesis of *β*-amino acids, *β*-lactams, or nucleoside analogues.[15] Further investigations of these conjugate reactions will be carried out using other addition agents such as hydrazine derivatives.

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(16) Crystal data for **27**: monoclinic, space group *P*2(1)/*c*, *a* = 7.729(2) Å, *b* = 9.392(1) Å, *c* = 10.081(1) Å, α = 90.00(1)°, *β* = 106.49(1)°, *γ* = 90.00(1)°, *V* = 701.7(2) Å^3, *Z* = 4. For more information, see the Supporting Information.
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Experimental Section

General details are as previously described.[18] GC−MS data were obtained by using an HP 5890 series II gas chromatograph with an HP 5971 series mass-selective detector. Carbon and hydrogen microanalyses were obtained from Atlantic Microlab, Inc. Elemental analysis detected all D atoms as if they were H.

***cis*-4-Deuterio-2-*N*-methyl-3-phenyl-1,2-isoxazolidin-5-one (19a).** To a suspension of MeNDOD·DCl (0.11 g, 1.2 mmol) in anhydrous THF (10 mL) was added ethyl (*E*)-cinnamate (**17a**, 0.18 g, 1.0 mmol), followed by anhydrous triethylamine (0.17 mL, 1.2 mmol). The mixture was allowed to stir at room temperature for 12 h, followed by addition of anhydrous $ZnCl_2$ (0.17 g, 1.2 mmol). Stirring was continued for another 6−8 h, at which time the reaction was quenched with water (20 mL). The mixture was extracted with methylene chloride (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by silica gel flash column chromatography (10% ethyl acetate in petroleum ether) to give compound **19a** (0.15 g, 84%): ^{1}H NMR (200 MHz, $CDCl_3$) *δ* 7.40 (5H, s), 4.10 (1H, d, *J* = 5.5 Hz), 2.98 (1H, m), 2.81 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) *δ* 172.9, 136.3, 129.5, 128.0, 73.77, 45.0, 40.7 (t); MS *m*/*e* (%), 178 (65, M^+), 134 (70), 131 (100). Anal. Calcd for $C_{10}H_{10}DNO_2$: C, 67.40; H and D, 6.23. Found: C, 67.65; H and D, 6.36.

***trans*-4-Deuterio-2-*N*-methyl-3-phenyl-1,2-isoxazolidin-5-one (19b).** To a suspension of MeNHOH·HCl (0.11 g, 1.2 mmol) in anhydrous THF (10 mL) was added ethyl (*E*)-2-deuteriumcinnamate[14] (**17b**, 0.18 g, 1.0 mmol), followed by addition of anhydrous triethylamine (0.17 mL, 1.2 mmol). The mixture was stirred at room temperature overnight, followed by the addition of anhydrous $ZnCl_2$ (0.17 g, 1.2 mmol). The workup and purification were the same as for **19a** (0.14 g, 80%). **19b**: ^{1}H NMR (200 MHz, $CDCl_3$) *δ* 7.40 (5H, s), 4.11 (1H, d, *J* = 12.4 Hz), 2.99 (1H, dt, *J* = 12.6, 2.43 Hz), 2.81 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) *δ* 172.9, 136.3, 129.5, 128.0, 73.8, 45.0, 40.8 (t); MS *m*/*e* (%), 178 (54, M^+), 134 (75), 132 (100).

(3*R*,4*R*,4′*S*)-4-Deuterio-2-*N*-methyl-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-1,2-isoxazolidin-5-one (21a) was prepared from **9a** (0.4 g, 2 mmol) as a colorless oil (0.37 g, 94%) by using a procedure similar to that of **19a**. **21a**: ^{1}H NMR (200 MHz, $CDCl_3$) *δ* 4.18 (1H, m), 4.05 (1H, dd, *J* = 6.52, 8.46 Hz), 3.70 (1H, dd, *J* = 8.50, 6.14 Hz), 3.25 (1H, t, *J* = 7.22 Hz), 2.98 (3H, s), 2.71 (1H, dt, *J* = 7.58, 2.51 Hz), 1.41 (3H, s), 1.33 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) *δ* 173.2, 110.8, 76.9, 70.3, 66.7, 47.6, 33.3 (t), 27.1, 25.8; MS *m*/*e* (%), 202 (0.1, M^+), 187 (20), 144 (60), 101 (100). Anal. Calcd for $C_9H_{14}DNO_4$: C, 53.45; H and D, 7.47. Found: C, 53.59; H and D, 7.45.

(3*R*,4*S*,4′*S*)-4-Deuterio-2-*N*-methyl-3-(2,2-dimethyl-1,3-dioxolan-4-yl)-1,2-isoxazolidin-5-one (21b) was prepared from **9b** (0.4 g, 2 mmol) as a colorless oil (0.36 g, 90%) by using a procedure similar to that of **19a**. **21b**: ^{1}H NMR (200 MHz, $CDCl_3$) *δ* 4.10 (1H, m), 3.97 (1H, dd, *J* = 6.72, 8.40 Hz), 3.62 (1H, dd, *J* = 8.44, 6.12 Hz), 3.17 (1H, dd, *J* = 10.26, 7.32 Hz), 2.90 (3H, s), 2.52 (1H, dt, *J* = 10.4, 2.23 Hz), 1.33 (3H, s), 1.25 (3H, s); ^{13}C NMR (50 MHz, $CDCl_3$) *δ* 173.1, 110.9, 76.9, 70.4, 66.7, 47.6, 33.4 (t), 27.1, 25.8; MS *m*/*e* (%), 187 (25, $M^+ - 15$), 144 (50), 101 (100). Anal. Calcd for $C_9H_{14}DNO_4$: C, 53.45; H and D, 7.47. Found: C, 53.57; H and D, 7.48.

***cis*-2-*N*,3,4-Trimethyl-1,2-isoxazolidin-5-one (24a).**[5b] To a solution of benzyl (*Z*)-2-methylcrotonate (**22**, 0.19 g, 1 mmol) in anhydrous ethanol was added MeNHOH·HCl (5 mmol) and NaOMe (0.27 g, 5 mmol). The mixture was allowed to reflux overnight. NaCl was then removed by filtration, and ethanol was removed under reduced pressure. The residue was subjected to GC−MS and ^{1}H NMR for the ratio of stereoisomers and then purified by silica gel flash column chromatography (10−15% ethyl acetate in petroleum ether) to afford pure **24a** (0.10 g, 84%): ^{1}H NMR (200 MHz, $CDCl_3$) *δ* 3.22 (1H, m), 2.70−2.85 (4H, m), 1.25 (3H, d, *J* = 7.54 Hz), 1.16 (3H, d, *J* = 6.3 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) *δ* 177.6, 67.0, 45.0, 41.5, 13.3, 10.3; MS *m*/*e* (%), 129 (55, M^+), 114 (20), 56 (100).

***cis*-2-*N*-Benzyl-3,4-dimethyl-1,2-isoxazolidin-5-one (24b)** was prepared from benzyl (*Z*)-2-methylcrotonate (**22**, 0.19 g, 1 mmol),

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BnNHOH·HCl (0.19 g, 1.2 mmol), and NaOMe (0.065 g, 1.2 mmol) in 90% yield (0.11 g). **24b**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.35 (5H, m), 4.13 (2H, dd, J = 14.0, 34.4 Hz), 3.53 (1H, m), 2.89 (1H, m), 1.26 (3H, d, J = 7.40 Hz), 1.19 (3H, d, J = 6.56 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 177.9, 135.9, 129.6, 129.0, 128.3, 69.5, 63.6, 40.9, 16.6, 10.4; MS *m*/*e* (%), 205 (16, M^+), 190 (4), 91 (100). Anal. Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37. Found: C, 70.37; H, 7.46.

3,4-*trans*-2,3,4-Trisubstituted-1,2-isoxazolidin-5-ones (26) were prepared from corresponding *E*-alkenoates **25** and *N*-alkylhydroxylamines by using the same procedure as described for compound **24a**. **26** (R = R′ = Me, 87%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.86 (3H, s), 2.45−2.75 (2H, m), 1.26 (3H, d, J = 5.82 Hz), 1.21 (3H, d, J = 6.76 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 176.2, 72.1, 44.9, 44.8, 16.1, 12.0; MS *m*/*e* (%), 129 (35, M^+), 114 (30), 42 (100). **26** (R = Me, R′ = Ph, 40%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40 (5H, s), 3.60 (1H, d, J = 12.5 Hz), 2.90−3.07 (1H, m), 2.80 (3H, s), 1.20 (3H, d, J = 7.08 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 175.5, 135.9, 129.6, 129.5, 128.1, 81.2, 46.7, 44.9, 11.8; MS *m*/*e* (%), 191 (65, M^+), 134 (100). Anal. Calcd for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85. Found: C, 69.08; H, 6.96. **26** (R = Bn, R′ = Me, 81%):[5b] ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.30−7.40 (5H, m), 4.07 (2H, dd, J = 14.44, 59.86 Hz), 2.95 (1H, m), 2.61 (1H, dq, J = 12.12, 7.04 Hz), 1.28 (3H, d, J = 5.98 Hz), 1.21 (3H, d, J = 7.04 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 176.1, 136.0, 129.5, 128.9, 128.3, 69.5, 61.8, 44.6, 16.6, 12.0; MS *m*/*e* (%), 205 (25, M^+), 190 (3), 91 (100). **26** (R = Me, R′ = *n*-Pr, 73%): ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.83 (3H, s), 2.63−2.71 (2H, m), 1.51−1.65 (2H, m), 1.30−1.49 (2H, m), 1.22 (3H, d, J = 6.8 Hz), 0.92 (3H, t, J = 7.06 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 174.4, 76.1, 45.8, 43.0, 33.4, 19.0, 14.9, 13.2; MS *m*/*e* (%), 157 (20, M^+), 114 (100). Anal. Calcd for $C_8H_{15}NO_2$: C, 61.12; H, 9.62. Found: C, 61.36; H, 9.79.

(2*R*,3*R*)- or (2*S*,3*S*)-3-(*N*-Methylamino)-2-methylbutanoic Acid (27).[16] Compound **26** (R = R′ = Me) was hydrogenated over palladium on activated carbon (5 wt %) in ethanol for 4 h. The reaction mixture was filtered through a short silica gel column. Ethanol was removed under reduced pressure. The residue was further dried under vacuum for approximately 30 min to give **27** as a white solid in quantitative yield. Recrystallization from ethyl acetate and methanol (3:1) afforded a single crystal of compound **27**: ^{1}H NMR (200 MHz, CD_3OD) δ 3.18 (1H, m), 2.68 (3H, s), 2.37 (1H, m), 1.32 (3H, d, J = 6.72 Hz), 1.25 (3H, d, J = 7.28 Hz); ^{13}C NMR (50 MHz, CD_3OD) δ 181.0, 59.7, 45.4, 30.8, 15.8, 15.0.

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Supporting Information Available: NMR spectra for all products described here and tables listing crystallographic data for **27** (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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