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Montmorillonite K10 Clay: An Efficient Catalyst for the One-Pot Stereoselective Synthesis of β-Acetamido Ketones

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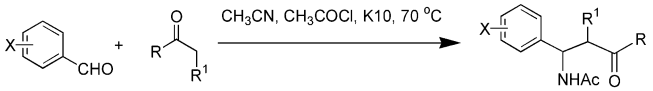
Abstract: An efficient one-pot three-component coupling process for the synthesis of β-acetamido ketones catalyzed by montmorillonite K10 clay is described. The reaction is highly stereoselective and the catalyst can be recycled.

Clays are known for their Lewis acid activity and have acquired an important place in synthetic organic chemistry.[1] Clays have been widely used in organic chemistry over two decades. Their importance is likely to increase with demanding environmental legislation, public and corporate pressure, and the drive toward clean technology. The use of efficient solid catalysts can go a long way toward achieving these goals.[2] While many reagents are used in stoichiometric amounts the development of catalytic use is genuinely a valuable addition to organic reactions especially in the liquid phase. It is important to assess the potential of these solid acids. These supported reagents, especially Montmorillonite K10 (Mont. K10), are most widely studied and found useful in many reactions, viz., the synthesis of γ-lactones,[3a] the synthesis of fused heterocycles,[3b] the Friedel−Crafts reaction,[3c] acetal and ketal deprotection reactions,[3d] selective bromination of alkyl benzenes,[3e] oxidation of organic sulfides to sulfoxides,[3f] the synthesis of biomarkers,[3g] oxidative demethylation of methylphenols to benzoquinones,[3h] (2,5) intramolecular ene cyclization,[3i] Michael addition,[3j] Boc group removal from aromatic amines,[3k] the Diels−Alder reaction,[3l] and so on. Mont. K10 has also been used in many microwave reactions under liquid phase as well as in solvent-free conditions.[4]

SCHEME 1



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The multicomponent coupling reactions[5] are emerging as useful tools for synthesizing small drug-like molecules with several degrees of structural diversity. Pioneering work by several research groups in this area has already established the versatility and uniqueness of one-pot multicomponent coupling protocols as a powerful methodology for the synthesis of diverse structural scaffolds required in the search of novel therapeutic molecules. In earlier studies[6] we have demonstrated that cobalt(II) chloride catalyzes the coupling between a ketone or ketoester, an aldehyde, and acetonitrile in the presence of acetyl chloride to provide a general route to β-acetamido carbonyl compounds. Encouraged by these results, we have now explored the possibilities of Mont. K10-catalyzed three-component one-pot stereoselective synthesis of β-acetamido ketone **1** following the protocol described by us earlier (Scheme 1).

As described in our earlier work,[6f] an aldehyde and a ketone in equimolar ratios were stirred for 7 h at 70 °C in acetonitrile (25 mL) with acetyl chloride (4 equiv) in the presence of 2 g of K10 clay to afford the acetamido ketones **1** in good to excellent yields. As shown in Table 1, we studied the reaction of acetophenone with various substituted benzaldehydes (Table 1, entries 2−8). The reactions of ortho-substituted benzaldehydes (entries 2−4) afforded higher yields of the desired β-acetamido ketones **1b**−**d** and maximum yield (88%) was obtained with *o*-nitrobenzaldehyde (Table 1, entry 4). Interestingly the reaction between salicylaldehyde and acetophonone

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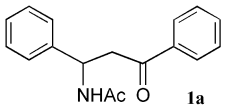
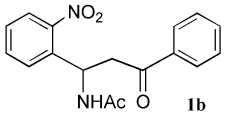
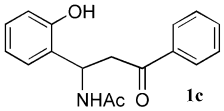
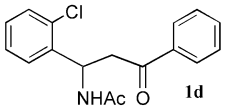
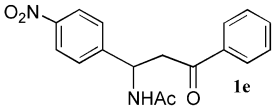
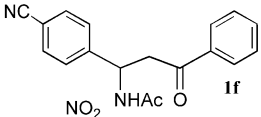
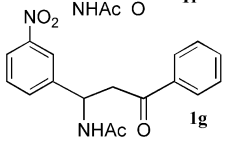
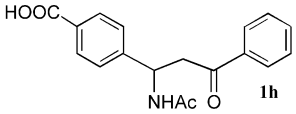
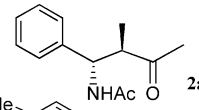
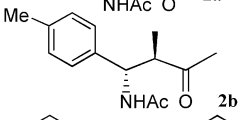
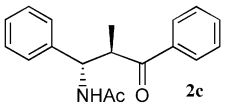
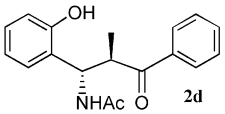
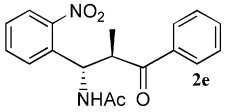
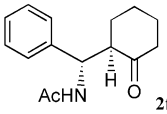
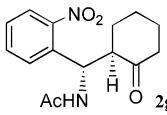
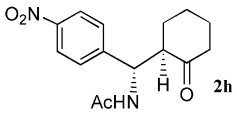
TABLE 1. Montmorillonite K10-Catalyzed Formation of *β*-Acetamido Ketones

Entry	β-Acetamidoketone	%Yield[a]
1.	 **1a**	80
2.	 **1b**	88
3.	 **1c**	81
4.	 **1d**	85
5.	 **1e**	74
6.	 **1f**	78
7.	 **1g**	76
8.	 **1h**	64

[a] The yield is based on the weight of the pure products obtained from aqueous workup.

TABLE 2. Montmorillonite K10-Catalyzed Formation of *β*-Acetamido Ketones from α-Subsituted Ketones

Entry	β-Acetamidoketone	Syn : anti[c]	%Yield*
1.	 **2a**	9:91	70[a]
2.	 **2b**	10:90	78[a]
3.	 **2c**	15:85	61[a]
4.	 **2d**	5:95	69[a]
5.	 **2e**	8:92	79[a]
6.	 **2f**	10:90	61[b]
7.	 **2g**	12:88	67[b]
8.	 **2h**	10:90	60[b]

* Yield of the isolated anti-diastereomers (stereochemistry assigned based on the coupling constant of methine protones). [a] Reactions at 70 °C. [b] Reaction at rt. [c] Syn/anti ratio determined from ^{1}H NMR of the crude mixture.

yielded the corresponding *β*-acetamido ketone **1c** (Table 1, entry 3) and not the OH-acetylated product, which is in contrast to the observation made in the corresponding cobalt-catalyzed reactions.[6f] We do not have any definite explanation for this anomaly but it appears that cobalt is also an efficient catalyst for the acylation of phenolic groups. The reactions of 4-nitro, 4-cyano, 3-nitro, and 4-carboxy benzaldehydes with acetophenone yielded the corresponding *β*-acetamido ketones in 64−75% yields (Table 1, entries 5−8). The isolation of these products was pretty much straightforward as the catalyst was removed by filtration and the filtrate was poured into ice-cold water, which resulted in precipitation of the desired *β*-acetamido ketones. The precipitated solid materials were filtered, dried, and washed with diethyl ether to afford highly pure *β*-acetamido ketones (by ^{1}H NMR).

In our previous publication,[6d] we have shown that aromatic aldehydes reacted with α-substituted ketones to afford the *β*-acetamido ketones **2** in a diastereoselective manner. To demonstrate the versatility of this catalyst (K10 clay) we have examined the reactions of benzaldehyde derivatives with ethyl methyl ketone, propiophenone, and cyclohexanone. With ethyl methyl ketone, we have studied the reactions of benzaldehyde and *p*-methylbenzaldehyde and in both cases the anti-diastereomers **2a** and **2b**, respectively, were obtained as major products (Table 2, entries 1 and 2). The separation of the products was done by chromatography on silica gel column. In a similar manner propiophenone also yielded the corresponding anti-diastereomers **2c**−**e** (Table 2, entries 3−5) and again salicylaldehyde afforded a product without acetylating the OH group (Table 2, entry 4). Interestingly, the reactions with cyclohexanone were found to proceed smoothly at room temperature to afford **2f**−**h** (Table 2, entries 6−8). When these reactions were conducted at 70 °C, polymeric materials were isolated as end products.

We have also examined the reusability of the catalyst as the latter obtained after the removal of the product was repeatedly washed with acetonitrile and finally with acetone. The acetone-washed catalyst was dried in an air oven at 110 °C for 3 h and used for the reactions. We have not carried out reactions with the several batches of recovered catalyst; however, repetition with one batch indicated that its efficiency is similar to that of the fresh catalyst. The performance of the recovered catalyst during the synthesis of *β*-acetamido ketones was found to be satisfactory and no considerable variation in yield,

stereoselectivity, and efficiency was noticed from the initial observations.

In conclusion, we have demonstrated an alternative simple procedure for the stereoselective synthesis of β-acetamido ketones using an eco-friendly, reusable, and inexpensive catalyst.

Experimental Section

A Typical Procedure for the Synthesis of β-Acetamido Ketone 1a. To a stirred suspension of Mont. K10 (2 g) in acetonitrile (25 mL) were added benzaldehyde (1.06 g, 10 mmol), acetophenone (1.20 g, 10 mmol), and acetyl chloride (4.0 mL) and the mixture was allowed to stand at the same temperature for 15 min. The temperature was increased to 70 °C and the stirring was continued for 7 h. The reaction mixture was filtered to remove the catalyst and the filtrate was poured into ice-cold water and stirred for 1 h. The precipitated solid was filtered and dried. The dried sample was washed with diethyl ether (3 × 15 mL) and again dried. The β-acetamido ketone **1a** (80%, mp 102−104 °C) thus obtained was sufficiently pure as indicated by ^{1}H NMR. The same procedure was repeated for all acetophenone and propiophenone reactions.

The products obtained from the reactions of ethyl methyl ketone and cyclohexanone were separated by silica gel chromatography. In these cases the workup procedure is little different from the earlier case. After removal of the catalyst the reaction mixture was concentrated to remove the acetonitrile and the residue was dissolved in chloroform (20 mL). The chloroform solution was washed with 2% NaOH solution (2 × 20 mL) and the organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified on a column of silica gel with petroleum ether−chloroform (1:1) for ethyl methyl ketone reactions and ethyl acetate−petroleum ether (1:1) for cyclohexanone reactions to afford the corresponding β-acetamido ketones as solids. The solids were crystallized from diethyl ether−petroleum ether.

***β*-Acetamido-*β*-phenylpropiophenone (1a).** Mp 102−104 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, J = 7.3 Hz, 2H), 7.58−7.20 (m, 8H), 6.77 (d, J = 8.9 Hz, 1H), 5.56 (dd, J = 5.7 and 13.4 Hz, 1H), 3.77 (dd, J = 5.2 and 16.9 Hz, 1H), 3.43 (dd, J = 6.1 and 16.9 Hz, 1H), 2.0 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.5, 169.45, 140.8, 133.46, 128.6, 128.07, 127.3, 126.4, 49.8, 43.14, 23.37; FT-IR (KBr) ν_{max} 3423, 1772, 1659, 1500, 1374, 1295, 1188, 1023, 704, 585 cm^{-1}; MS m/z 266 (M − 1), 208, 179, 162, 120, 107, 106, 77, 50.

***β*-Acetamido-*β*-(2-nitrophenyl)propiophenone (1b).** Mp 186−188 °C; ^{1}H NMR (300 MHz, $CDCl_3$ + DMSO) δ 8.29 (d, J = 6.6 Hz, 1H), 7.97 (d, J = 7.3 Hz, 2H), 7.88 (d, J = 8.1 Hz, 1H), 7.72 (d, J = 7.2 Hz, 1H), 7.65−7.51 (m, 2H), 7.51−7.40 (m, 3H), 5.90 (dd, J = 3.9 and 15.8 Hz, 1H), 3.65 (dd, J = 9.2 and 17.3 Hz, 1H), 3.48 (dd, J = 3.8 and 17.3 Hz, 1H), 1.25 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$ + DMSO) δ 195.38, 168.93, 147.34, 137.3, 135.4, 132.5, 132.49, 127.8, 127.7, 127.1, 127.05, 123.35, 44.83, 42.89, 21.76; FT-IR (KBr) ν_{max} 3310, 3071, 1686, 1646, 1580, 1513, 1354, 1301, 1222, 990, 751, 685 cm^{-1}; MS m/z 312 (M$^+$), 311 (M − 1), 267, 235, 211, 202, 194, 165, 153, 146, 134, 123, 120, 105, 85, 71, 40.

***β*-Acetamido-*β*-(2-hydroxyphenyl)propiophenone (1c).** Mp 129−130 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.17 (d, J = 5.6 Hz, 2H), 7.89 (d, J = 6.0 Hz, 2H), 7.60−7.47 (m, 5H), 6.99 (s, 1H), 5.67 (s, 1H), 3.79 (d, J = 7.4 Hz, 1H), 3.53 (d, J = 7.2 Hz, 1H), 2.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.16, 178.46, 136.09, 134.02, 130.94, 128.85, 128.06, 127.80, 123.80, 121.65, 49.14, 42.53, 37.08; FT-IR (KBr) ν_{max} 3290, 1686, 1646, 1600, 1507, 1454, 1348, 1295, 857, 751, 685, 592 cm^{-1}; MS m/z 281 (M − 2), 237, 208, 207, 194, 175, 165, 152, 121, 102, 89, 76.

***β*-Acetamido-*β*-(2-chlorophenyl)propiophenone (1d).** Mp 135−136 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, J = 7.4 Hz, 2H), 7.57−7.13 (m, 6H), 7.0 (s, 1H), 5.83 (s, 1H), 3.74 (dd, J = 5.5 and 16.4 Hz, 1H), 3.46 (dd, J = 5.1 and 16.6 Hz, 1H), 2.0 (s, 3H); FT-IR (KBr) ν_{max} 3290, 3065, 2362, 1688, 1646, 1546.9, 1367, 1202, 758, 685 cm^{-1}; MS m/z 304 (M + 2), 207, 182, 148, 120, 105, 69, 55.

***β*-Acetamido-*β*-(4-nitrophenyl)propiophenone (1e).** Mp 148−149 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (d, J = 8.4 Hz, 2H), 7.89 (d, J = 9.6 Hz, 2H), 7.62−7.46 (m, 5H), 7.02 (d, J = 9.0 Hz, 1H), 5.66 (s, 1H), 3.80 (dd, J = 4.8 and 17.6 Hz, 1H), 3.50 (dd, J = 5.2 and 17.6 Hz, 1H), 2.0 (s, 3H); FT-IR (KBr) ν_{max} 3310, 1686, 1645, 1580, 1513, 1352, 1300, 751 cm^{-1}; MS m/z 311 (M − 1), 295, 270, 194, 175, 165, 151, 129, 120, 105, 102, 90, 68, 54.

***β*-Acetamido-*β*-(4-cyanophenyl)propiophenone (1f).** Mp 88−90 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.91 (d, J = 8.1 Hz, 2H), 7.80 (s, 1H), 7.61−7.59 (m, 3H), 7.49−7.41 (m, 4H), 5.57 (d, J = 6.7 Hz, 1H), 3.70 (dd, J = 6.4 and 17.3 Hz, 1H), 3.43 (dd, J = 5.9 and 16.6 Hz, 1H), 1.99 (s, 3H); FT-IR (KBr) ν_{max} 3297, 2236, 1699, 1646, 1533, 1447, 1228, 983, 758, 685, 552 cm^{-1}; MS m/z 292 (M + 1), 231, 145, 129, 120, 91, 79.

***β*-Acetamido-*β*-(3-nitrophenyl)propiophenone (1g).** Mp 112−115 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.39−8.31 (m, 1H), 8.06 (d, J = 6.4 Hz, 2H), 7.94 (d, J = 6.0 Hz, 2H), 7.48 (d, J = 5.9 Hz, 2H), 5.62 (s, 1H), 3.72 (d, J = 12.3 Hz, 1H), 3.44 (d, J = 16.6 Hz, 1H), 1.95 (s, 3H); FT-IR (KBr) ν_{max} 3277, 1686, 1639, 1527, 1341, 1288, 1228, 751, 685, 632 cm^{-1}; MS m/z 267 (M + 1 − NO_2), 212, 196, 147, 120, 89, 71, 40.

***β*-Acetamido-*β*-(4-carboxyphenyl)propiophenone (1h).** Mp 228−230 °C; ^{1}H NMR (300 MHz, DMSO) δ 10.09 (s, 1H), 8.42 (s, 1H), 8.11−7.86 (m, 5H), 7.61−7.49 (m, 4H), 5.39 (s, 1H), 1.88 (s, 3H); FT-IR (KBr) ν_{max} 3051−2826, 1719, 1686, 1580, 1500, 1420, 1295, 1248, 1195, 1102, 758, 685 cm^{-1}; MS m/z 311 (M$^+$), 266, 219, 211, 146, 120, 81, 60, 52.

***N*-1-[(1*S*,2*R*)-2-Methyl-3-oxo-1-phenylbutyl]acetamide (2a).** Mp 126−127 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33−7.21 (m, 5H), 7.12 (d, J = 7.8 Hz, 1H), 5.16 (dd, J = 5.9 and 9.0 Hz, 1H), 3.10 (dd, J = 6.9 and 14.2 Hz, 1H), 2.04 (d, J = 10.2 Hz, 6H), 1.17 (d, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.4, 169.7, 140.5, 128.5, 127.3, 126.25, 55.2, 51.1, 29.65, 23.23, 15.13; FT-IR (KBr) ν_{max} 3290, 1719, 1653, 1553, 1374, 1308, 1129, 758, 704 cm^{-1}; MS m/z 219 (M$^+$), 176, 148, 134, 118, 106, 104, 91, 77, 58, 43.

***N*-1-[(1*S*,2*R*)-2-Methyl-1-(4-methylphenyl)-3-oxobutyl]-acetamide (2b).** Mp 133−134 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.1 (s, 4H), 6.93 (d, J = 8.4 Hz, 1H), 5.12 (dd, J = 5.8 and 9.0 Hz, 1H), 3.07 (dd, J = 6.6 and 13.2 Hz, 1H), 2.3 (s, 3H), 2.17−1.97 (m, 6H), 1.19−1.08 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.85, 169.53, 137.74, 137.01, 129.28, 126.87, 126.24, 55.16, 51.28, 29.62, 23.28, 20.92, 15.11; FT-IR (KBr) ν_{max} 3297, 2985, 1706, 1653, 1553, 1451, 1427, 1374, 1308, 1135, 724, 545 cm^{-1}; MS m/z 233 (M$^+$), 190, 174, 163, 148, 131, 121, 106, 90, 88, 76, 62, 51.

***N*-1-[(1*S*,2*R*)-2-Methyl-3-oxo-1,3-diphenylpropyl]acetamide (2c).** Mp 140 °C; ^{1}H NMR (300 MHz, DMSO) δ 8.44 (d, J = 7 Hz, 1H), 8.16 (s, 1H), 7.77−7.53 (m, 4H), 7.43−7.30 (m, 5H), 5.09 (s, 1H), 1.83 (s, 1H), 1.65 (s, 3H), 0.80 (s, 3H); FT-IR (KBr) ν_{max} 3290, 2972, 1679, 1653, 1546, 1454, 1367.9, 970, 704, 605 cm^{-1}; MS m/z 281 (M$^+$), 238, 221, 207, 176, 165, 148, 132, 118, 105.

***N*-1-[(1*S*,2*R*)-1-(2-Hydroxyphenyl)-2-methyl-3-oxo-3-phenylpropyl]acetamide (2d).** Mp 142 °C; ^{1}H NMR (300 MHz, DMSO) δ 8.09−8.03 (m, 2H), 7.97−7.83 (m, 3H), 7.62−7.03 (m, 4H), 6.81 (d, J = 8.8 Hz, 1H), 5.57 (d, J = 9.6 Hz, 1H), 4.07 (m, 1H), 1.9 (s, 3H), 1.68 (s, 3H); FT-IR (KBr) ν_{max} 3390, 1759, 1679, 1646, 1520, 1487, 1447, 1367, 1195, 758, 585 cm^{-1}; MS m/z 297 (M$^+$), 251, 237, 221, 199, 189, 174, 156, 148, 121, 105.

***N*-1-[(1*S*,2*R*)-2-Methyl-1-(2-nitrophenyl)-3-oxo-3-phenylpropyl]acetamide (2e).** Mp 122−124 °C; ^{1}H NMR (300 MHz, DMSO) δ 8.52−8.44 (m, 1H), 8.14−7.97 (m, 1H), 7.80−7.30 (m, 8H), 5.67 (dd, J = 7.7 and 13.7 Hz, 1H), 4.13−3.98 (m, 1H), 1.56 (s, 3H), 0.87 (d, J = 7.0 Hz, 3H); FT-IR (KBr) ν_{max} 3264, 3058, 1979, 1646, 1527, 1454, 1354, 1295, 970, 711 cm^{-1}; MS m/z 327 (M + 1), 280, 266, 237, 211, 193, 177, 133, 120, 105.

***N*-1-{(1*S*)-1-[(2*R*)-2-Oxocyclohexyl]-1-phenylmethyl}-acetamide (2f).** Mp 221−222 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.52 (d, J = 8.4 Hz, 1H), 7.30−7.10 (m, 5H), 6.26 (s, 1H), 5.77 (d, J = 8.3 Hz, 1H), 2.7 (br s, 1H), 2.58 (d, J = 5.6 Hz, 2H), 2.44

(d, J = 5.4 Hz, 2H), 2.27 (m, 4H), 2.0 (s, 3H); FT-IR (KBr) ν_{max} 3270, 1699, 1646, 1546.9, 1367.9, 1222, 698 cm^{-1}; MS m/z 245 (M^+), 226, 201, 149, 104, 91, 76, 63, 43.

***N*-1-{(1*S*)-1-(2-Nitrophenyl)-1-[(2*R*)-2-oxocyclohexyl]-methyl}acetamide (2g).** Mp 139−140 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (d, J = 7.3 Hz, 1H), 7.82 (s, 2H), 7.69−7.54 (m, 2H), 5.57 (m, 1H), 2.64−2.51 (m, 8H), 1.65 (s, 3H); FT-IR (KBr) ν_{max} 3423, 2932, 1666, 1599, 1520, 1341, 1267, 1175, 1142, 970, 718, 519 cm^{-1}; MS m/z 291 (M + 1), 275, 254, 222, 218, 198, 193, 186, 169, 154, 136, 125, 111, 107.

***N*-1-{(1*S*)-1-(4-Nitrophenyl)-1-[(2*R*)-2-oxocyclohexyl]-methyl}acetamide (2h).** Mp 192−194 °C; ^{1}H NMR (300 MHz, DMSO) δ 8.34−8.24 (m, 2H), 7.75−7.62 (m, 2H), 5.48 (s, 1H), 2.23−2.20 (m, 8H), 1.81 (s, 3H); FT-IR (KBr) ν_{max} 3383, 2933, 1646, 1600, 1520, 1341, 1228, 850, 698 cm^{-1}; MS m/z 268 (M + 2 − NO_2), 241, 232, 214, 190, 176, 150, 140, 116, 103.

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Supporting Information Available: ^{1}H NMR and MS spectra of **1a**,**c**,**d**,**e** and **2a**,**b**,**e**, **f**, ^{13}C NMR spectra of **1a**,**c**,**b** and **2b**, MS of **1a**,**c**,**d**,**e** and **2a**,**b**,**e**,**f**, and FT-IR spectra of **1a**,**c**,**d** and **2a**,**b**,**e**,**f**. This material is available free of charge via the Internet at http://pubs.acs.org.

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