JOC*Note*

Enantioselective Mannich Reactions with the Practical Proline Mimetic *N*-(*p*-Dodecylphenylsulfonyl)-2-pyrrolidinecarboxamide

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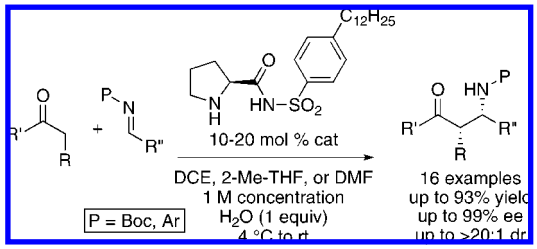
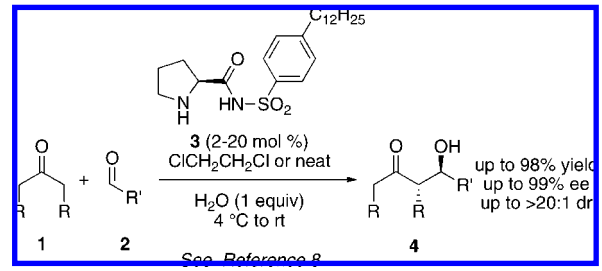


A highly enantioselective and diastereoselective protocol for performing Mannich reactions has been developed by using a *p*-dodecylphenylsulfonamide-based proline catalyst. This catalyst facilitates the use of common, nonpolar solvents and increased concentrations as compared to alternative methods. A series of *syn*-selective Mannich reactions is reported, including the rapid access of α- and *β*-amino acids surrogates. The use of the industrially attractive nonpolar solvents, such as 2-methyl-tetrahydrofuran, is also demonstrated.

Mannich reactions occupy an important position in the lore of organic synthesis—owing to their critical importance for the construction of alkaloids and amino acids structures.[1] Consequently, considerable energy has been focused on optimizing this reaction for enantioselective and diastereoselective processes.[2] Organocatalysis has proven particularly effective at constructing these enantioselective *β*-amino carbonyl motifs.[3]

SCHEME 1. Highly Enantioselective Aldol Reactions Utilizing a *p*-Dodecylphenylsulfonamide Proline Mimetic



The vast majority of examples have employed proline as the viable organocatalyst for these transformations.[4,5] These reactions are typically performed in polar organic solvents,[6] such as DMSO and MeCN—in large part to improve the solubility of the organocatalyst in the solution. Consequently, a series of pyrrolidine-based alternatives have been developed which offer improved solubility profiles.[7] Unfortunately, many of these catalysts are derived from expensive starting materials and/or are nontrivial to prepare in large quantities. Our laboratory has recently reported the development of a *p*-dodecylphenylsulfonamide proline derivative **3** that has shown a remarkable solubility and reactivity profile in nonpolar organic solvents (Scheme 1).[8] This catalyst **3** is readily available from inexpensive starting materials (proline and *p*-dodecylphenylsulfonic chloride) and we routinely prepare this catalyst on >40 mmol scale. As both D- and L-proline are commercially available and inexpensive, this catalyst system allows ready access to both enantiomeric series of products—an attribute that the catalysts derived from 4-hydroxyproline do not share. In this Note, we disclose the application of this catalyst system to enantioselective and diastereoselective Mannich reactions.

We first screened the reactivity of imine **6** with a series of carbonyl-containing nucleophiles (Scheme 2). Using our previously optimized conditions for the aldol reaction, we were pleased to find that the *syn*-selective Mannich product **7** could be produced from cyclohexanone (**5**) and imine **6** in excellent enantio- and diastereoselectivity using catalyst **3** (93% yield, >20:1 dr, 96% ee). As we[8] and others[9] have observed, the addition of water had a beneficial effect particularly on the rate of the reaction. For example, the Mannich reaction of **5** and **6** performed in the absence of water proceeded at approximately

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(2) *Enantioselective Synthesis of Beta-Amino Acids*; Juaristi, E., Soloshonok, V. A., Eds.; Wiley-VCH: Hoboken, NJ, 2005.
(3) For recent reviews, see: (a) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartolim, G. *Angew. Chem., Int. Ed.* **2008**, *47*, 6138–6171. (b) Dondoni, A.; Massi, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 4338–4360. (c) Longbottom, D. A.; Franckevicius, V.; Kumarn, S.; Oelke, A. J.; Wascholowski, V.; Ley, S. V. *Aldrichim. Acta* **2008**, *41*, 3–11. (d) Verkade, J. M. M.; van Hemert, L. J. C.; Quaedflieg, P. J. L. M.; Rutjes, F. P. J. T. *Chem. Soc. Rev.* **2008**, *37*, 29–41. (e) Mukherjee, S.; Yang, J. W.; Hoffmann, S.; List, B. *Chem. Rev.* **2007**, *107*, 5471–5569. (f) Ting, A.; Schaus, S. E. *Eur. J. Org. Chem.* **2007**, *2007*, 5797–5815.
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(5) For a computational investigation in proline-catalyzed Mannich reactions, see: (a) Parasuk, W.; Parasuk, V. *J. Org. Chem.* **2008**, *73*, 9388–9392. (b) Allemann, C.; Gordillo, R.; Clemente, F. R.; Cheong, P. H.-Y.; Houk, K. N. *Acc. Chem. Res.* **2004**, *37*, 558–569.
(6) One impressive exception is a series of glycolate imine-derived Mannich reactions performed in dioxane: Córdova, A.; Watanabe, S.; Tanaka, F.; Notz, W.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2002**, *124*, 1866–1867.
(7) (a) Cobb, A. J. A.; Shaw, D. M.; Longbottom, D. A.; Gold, J. B.; Ley, S. V. *Org. Biomol. Chem.* **2005**, *3*, 84–96. (b) Franzén, J.; Marigo, M.; Fielenbach, D.; Wabnitz, T. C.; Kjaersgaard, A.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2005**, *127*, 18296–18304. (c) Enders, D.; Grondal, C.; Vrettou, M. *Synthesis* **2006**, 3597–3604. (d) Ibrahem, I.; Córdova, A. *Chem. Commun.* **2006**, 1760–1762. (e) Hayashi, Y.; Urshima, T.; Aratake, S.; Okano, T.; Obi, K. *Org. Lett.* **2008**, *10*, 21–24. (f) Kano, T.; Hato, Y.; Yamamoto, A.; Maruoka, K. *Tetrahedron* **2008**, *64*, 1197–1203. (g) Pouliquen, M.; Blanchet, J.; Lasne, M. C.; Rouden, J. *Org. Lett.* **2008**, *10*, 1029–1032. (h) Hayashi, Y.; Okano, T.; Itoh, T.; Urushima, T.; Ishikawa, H.; Uchimaru, T. *Angew. Chem., Int. Ed.* **2008**, *47*, 9053–9058.
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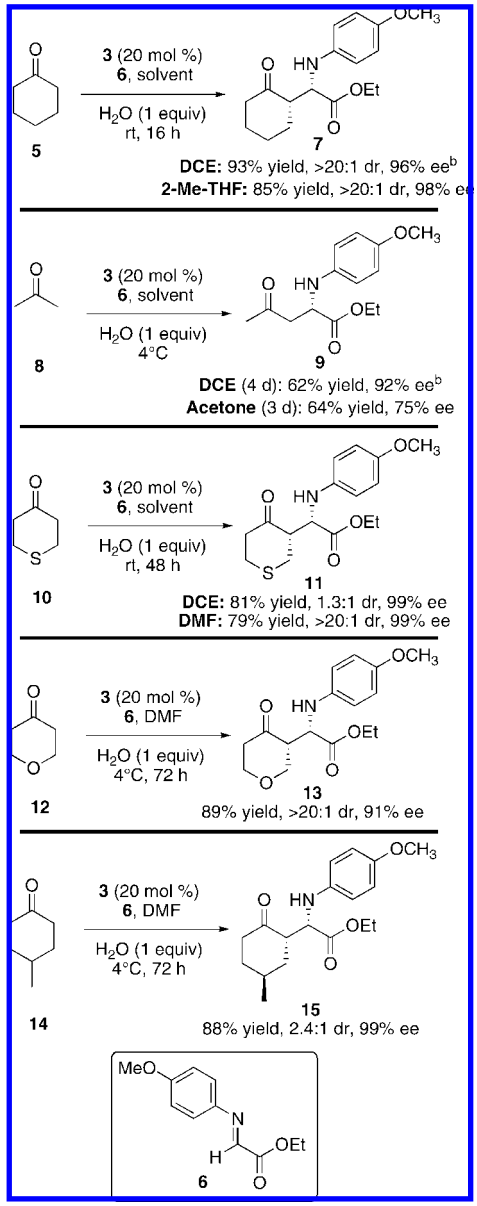
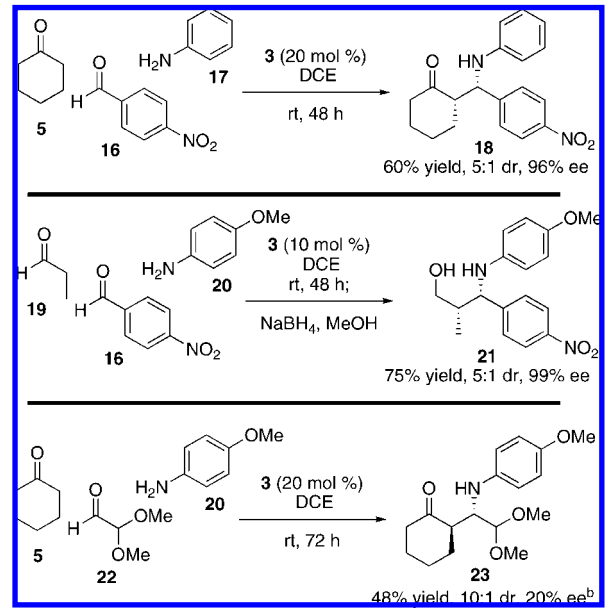
SCHEME 2. Enantioselective Mannich Reactions with Imine 6[a]



[a] All reactions were performed at 1 M. Five equivalents of ketone was used. Dr was determined by ^{1}H NMR of crude reaction mixture. Ee was determined by chiral HPLC. [b] Absolute configuration established by comparison of optical rotation to literature value.

half the rate (36 h without H_2O vs 16 h with H_2O). Additionally, alternate nonpolar solvents such as industrially attractive 2-methyltetrahydrofuran (2-Me-THF) could be substituted with only slightly reduced yield (93% in DCE vs 85% in 2-Me-THF). Acetone (**8**) proved to be a viable substrate in these transformations. Use of a nonpolar solvent was important to this transformation as performing the reaction in straight acetone

SCHEME 3. Three-Component Enantioselective Mannich Reactions[a]



[a] All reactions were performed at 1 M. Five equivalents of **5** or **19** was used. Dr was determined by ^{1}H NMR of crude reaction mixture. Ee was determined by chiral HPLC. [b] Absolute configuration for this product was not determined.

led to a noticeable decrease in enantioselectivity (92% ee in DCE vs 75% ee in acetone). Interestingly, with thiopyran-4-one (**10**), pyran-4-one (**12**), and 4-methylcyclohexanone (**14**), we found that the use of DMF led to an improvement in diastereoselectivity for these reactions (e.g., compound **11**). We noticed no impact on enantioselectivity by changing the solvent choice between DMF and DCE.

Three-component couplings could also be accomplished by using this protocol (Scheme 3). By using aldehyde **16** and anilines **17** and **20**, the cyclohexanone-derived product **18** and the β-amino alcohol **21** could be prepared in excellent enantioselectivity and good *syn* diastereoselectivity. No water was added to these experiments as 1 equiv is released during imine formation. Interestingly, this coupling was highly dependent on the structure of the imine-forming component. Using α,α-dimethoxyaldehyde **22**[7e] and amine **20** led to a complete reversal in diastereoselectivity—now favoring the *anti* diastereomer in modest enantioselectivity. Access to *anti*-selective Mannich reactions has recently been of considerable interest to the synthetic community.[7b,d,f,g,10]

We were also interested in exploring the synthesis of *N*-Boc-protected β-amino aldehydes using an asymmetric Mannich

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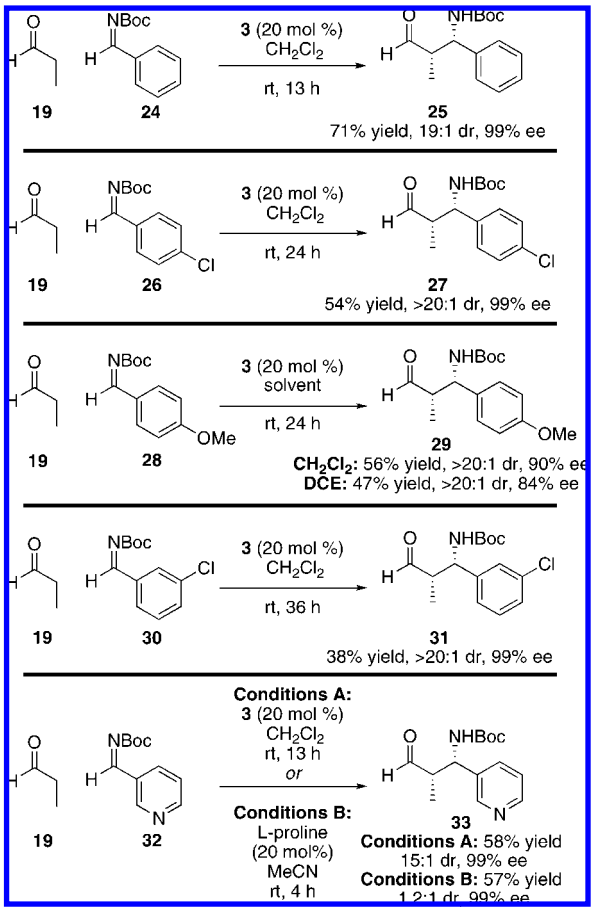
(10) Secondary amine catalysts: (a) Córdova, A.; Barbas, C. F. *Tetrahedron Lett.* **2002**, *43*, 7749–7752. (b) Kano, T.; Yamaguchi, Y.; Tokuda, O.; Maruoka, K. *J. Am. Chem. Soc.* **2005**, *127*, 16408–16409. (c) Mitsumori, S.; Zhang, H.; Cheong, P. H.-Y.; Houk, K. N.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 1040–1041. (d) Zhang, H.; Mifsud, M.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2006**, *128*, 9630–9631. (e) Kano, T.; Hato, Y.; Maruoka, K. *Tetrahedron Lett.* **2006**, *47*, 8467–8469. (f) Ramasastry, S. S. V.; Zhang, H.; Tanaka, F.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2007**, *129*, 288–289. (g) Dziedzic, P.; Córdova, A. *Tetrahedron: Asymmetry* **2007**, *18*, 1033–1037. (h) Zhang, H.; Mitsumori, S.; Utsumi, N.; Imai, M.; Garcia-Delgado, N.; Mifsud, M.; Albertshofer, K.; Cheong, P. H.-Y.; Houk, K. N.; Tanaka, F.; Barbas, C. F., III *J. Am. Chem. Soc.* **2008**, *130*, 875–886. (i) Zhang, H.; Ramasastry, S. S. V.; Tanaka, F.; Barbas, C. F., III. *Adv. Synth. Catal.* **2008**, *350*, 791–796. (j) Gianelli, C.; Sambri, L.; Carlone, A.; Bartoli, G.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 8700–8702. For a review of primary amine organocatalysts, see: (k) Xu, L.-W.; Lu, Y. *Org. Biomol. Chem.* **2008**, *6*, 2047–2053.

SCHEME 4. Synthesis of *N*-Boc-Protected *β*-Amino Aldehydes[a]

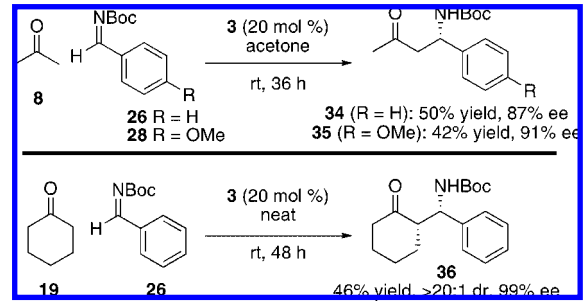


[a] All reactions were performed at 1 M. Two equivalents of **19** was used. Dr was determined by ^{1}H NMR of crude reaction mixture. Ee was determined by chiral HPLC

reaction (Scheme 4). Recent reports of proline-catalyzed methods for accomplishing these types of transformations have been published with use of primarily polar aprotic solvents MeCN and DMF.[7c,11] We were pleased to find that we can perform Mannich reactions in nonpolar solvents on *N*-Boc imines using catalyst **3** in excellent enantioselectivity and diastereoselectivity. Interestingly, CH_2Cl_2 proved to be a slightly better solvent for these transformations than DCE in more challenging examples (e.g., **28**). The exact rationale for this difference is not apparent at this juncture. Additionally, the inclusion of water in these reactions proved detrimental. We attribute this behavior to the increased susceptibility of *N*-Boc-protected imines to hydrolysis. This transformation appears to work on a range of substrates. The pyridyl example **32** is particularly noteworthy as proline gave inferior diastereoselectivity (15:1 dr using catalyst **3** vs 1.2:1 dr using proline) in a side-by-side comparison. It should be noted that these *N*-Boc imines are in general challenging substrates as decomposition is slowly observed in CH_2Cl_2 at rt.

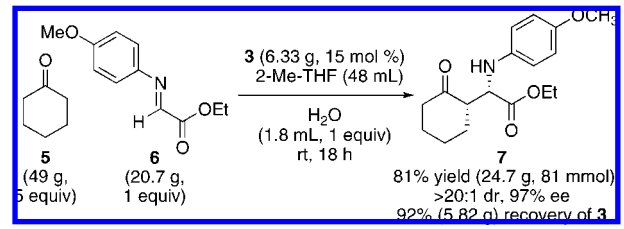
This technology could be extended to the synthesis of *N*-Boc-protected *β*-amino ketones as well (Scheme 5). These reactions were typically run in a neat solution of the ketone component

SCHEME 5. Synthesis of *N*-Boc-Protected *β*-Amino Ketones[a]



[a] All reactions were performed at 1 M with the ketone as solvent. Dr was determined by ^{1}H NMR of crude reaction mixture. Ee was determined by chiral HPLC

SCHEME 6. Large-Scale Example of the Enantioselective Mannich Reaction



to improve reaction turnover. Both the acetone and cyclohexanone-derived products **34**−**36** could be obtained with this method.

We have also demonstrated the scalability of this protocol by performing the Mannich reaction of cyclohexanone (**5**) and imine **6** on 100 mmol scale (Scheme 6) in a single 250 mL round-bottomed flask. In this example, the catalyst loading was reduced to 15 mol % and the experiment was conducted in 2-Me-THF. We were pleased to observe excellent conversion to the desired product (81% yield, 97% ee, >20:1 dr). The catalyst **3** could be easily recovered in 92% yield.

In conclusion, we have developed an enantio- and diastereoselective Mannich protocol using the practical and readily available proline derivative **3**. The use of industrially attractive solvents such as 2-Me-THF has also been shown to be viable. Further applications of this catalyst **3** will be reported in due course.

Experimental Section

General Procedure for Mannich Reaction with Iminoester 6 in Solvent (20 mol % Catalyst). To a solution of iminoester **6**[7a] (0.125 mmol) and the corresponding ketone (0.625 mmol, 5 equiv) in the appropriate solvent (DCE, 2-Me-THF or DMF) was added sulfonamide **3** (10.6 mg, 0.025 mmol) and water (0.125 mmol, 2.3 mg, 1 equiv) at 4 °C or room temperature. After being stirred at same temperature for the denoted time, the reaction was loaded directly onto silica gel and was purified by chromatography, eluting with 10−30% EtOAc/hexanes, to give the corresponding Mannich product (62−93%).

(2*S*,1′*S*)-Ethyl 2-(*p*-Methoxyphenylamino)-2-(2′-oxocyclohex-1′-yl)acetate, 7:[7a] purified by chromatography over silica gel, eluting with 10−30% EtOAc/hexanes, to give the known amine **7** (in DCE: 35.4 mg, 0.116 mmol, 93%, >20:1 dr; in 2-Me-THF: 32.5 mg, 0.106 mmol, 85%, >20:1 dr). Enantiomeric excess was determined by chiral HPLC [4.6 × 250 mm Daicel OD column, 92:8 hexanes/*i*-PrOH, 1.0 mL min^{-1}, retention times 23.5 (minor) and 25.2 (major)] to be 96% ee: $[\alpha]^{23}_D$ −41.3 (*c* 1.4, $CHCl_3$); ^{1}H NMR (400

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MHz, $CDCl_3$) δ 6.80 (d, J = 9.2 Hz, 2H), 6.75 (d, J = 9.2 Hz, 2H), 4.25 (br s, 1H), 4.21−4.14 (m, 2H), 3.92 (br s, 1H), 3.77(s, 3H), 2.83 (dt, J = 12.4, 5.2 Hz, 1H), 1.58−2.51 (m, 8H), 1.25 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.1, 173.5, 153.1, 141.1, 116.1, 114.8, 61.1, 58.1, 55.7, 53.4, 41.9, 29.6, 26.9, 24.8, 14.2.

Large-Scale Preparation of Mannich Product 7. To a solution of iminoester **6** (20.7 g, 100 mmol) and cyclohexanone **5** (49.0 g, 51.7 mL, 500 mmol, 5 equiv) was added sulfonamide **3** (6.33 g, 15 mmol) and water (1.8 g, 1.8 mL, 100 mmol) at rt. After being stirred at same temperature for 18 h, the reaction mixture was filtered, and the solid filtrate **3** (3.24 g, 7.68 mmol) was kept. The mother liquor was diluted with hexanes (50 mL) and filtered through a silica gel pad (MTBE−20% MeOH/CH_2Cl_2) to give Mannich product **7** (24.7 g, 81 mmol, 81% yield, 97% ee, >20:1 dr) and recovered catalyst **3** (2.58 g, 6.11 mmol, 92% overall recovery).

General Procedure for Mannich Reaction with *N*-Boc-Protected Imine in CH_2Cl_2 (20 mol % Catalyst). To a solution of *N*-Boc-protected imine[12] (0.125 mmol) and propionaldehyde **19** (14.5 mg, 0.018 mL, 0.25 mmol, 2 equiv) in CH_2Cl_2 (0.107 mL) was added sulfonamide **3** (10.6 mg, 0.025 mmol) at room temperature. After being stirred at the same temperature, the reaction was loaded directly onto silica gel and purified by chromatography, eluting with 10−30% EtOAc/hexanes, to give the corresponding Mannich product (38−71%).

***syn-tert*-Butyl-(2*S*)-formyl-(1*S*)-phenylpropylcarbamate, 25:**[11a] purified by chromatography over silica gel, eluting with 10−30% EtOAc/hexanes, to give the known amine **25** (23.4 mg, 0.089 mmol, 71%, 19:1 dr). Enantiomeric excess was determined by chiral HPLC [4.6 × 250 mm Daicel OD column, 90:10 hexanes/*i*-PrOH, 1.0 mL min^{-1}, retention times 11.4 (minor) and 14.9 (major)] to be 99% ee: $[\alpha]^{23}_D$ −5.5 (*c* 0.8, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.74 (s, 1H), 7.26−7.41 (m, 5H), 5.16−5.21 (m, 2H), 2.89 (br s, 1H), 1.44−1.47 (m, 9H), 1.09 (d, J = 3.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 203.0, 155.1, 128.8, 127.7, 126.7, 125.8, 80.1, 54.7, 51.6, 28.3, 9.3.

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Supporting Information Available: Complete experimental procedures are provided, including ^{1}H and ^{13}C spectra, of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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