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Dynamic Kinetic Asymmetric Synthesis of Five Contiguous Stereogenic Centers by Sequential Organocatalytic Stetter and Michael−Aldol Reaction: Enantioselective Synthesis of Fully Substituted Cyclopentanols Bearing a Quaternary Stereocenter

Bor-Cherng Hong,*,† Nitin S. Dange,† Che-Sheng Hsu,† Ju-Hsiou Liao,† and Gene-Hsiang Lee‡

Department of Chemistry and Biochemistry, National Chung Cheng University, Chia-Yi, 621, Taiwan, R.O.C. and Instrumentation Center, National Taiwan University, Taipei, 106, Taiwan, R.O.C.

chebch@ccu.edu.tw

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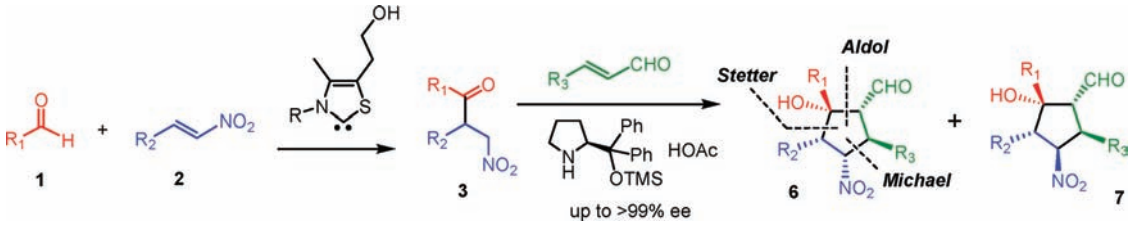
ABSTRACT



A synthesis of fully substituted cyclopentanes bearing a quaternary carbon center and five contiguous stereogenic centers has been achieved by sequential organocatalyzed Stetter and Michael−Aldol reactions of heteroaromatic aldehydes, nitroalkenes, and α,β-unsaturated aldehydes via the [1 + 2 + 2] annulation strategy with dynamic kinetic asymmetric transformation and excellent enantioselectivities (up to >99% ee).

The Stetter reaction is a long-standing, unique methodology in the synthesis of 1,4-dicarbonyl compounds and related derivatives.[1] With the recent advancements in the development of *N*-heterocyclic carbenes (NHCs),[2] the Stetter reaction has expanded its realm and provided a convenient route for the preparation of cyclic compounds.[3] The asymmetric intramolecular Stetter reaction was first introduced by Enders,[4] later studied by Rovis and the others.[5] Nevertheless, only a few examples of the organocatalytic enantioselective intermolecular Stetter reactions were reported.[6] Recently, we have disclosed a sequential organocatalytic Stetter and Michael−Aldol condensation

† National Chung Cheng University.
‡ National Taiwan University.

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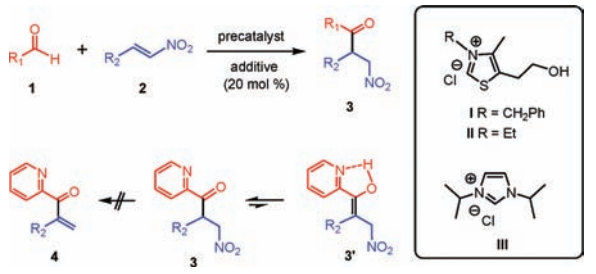
Table 1. Screening of Catalysts and Optimization Conditions for the Stetter Reaction of **1** and **2**[a]



entry	product	cat.	additive	time (h)	yield (%)[b]
1	**3a**: R_1 = pyridin-2-yl; R_2 = n-C_6H_{13}	**I**	Cs_2CO_3	0.5	78
2	**3a**: R_1 = pyridin-2-yl; R_2 = n-C_6H_{13}	**I**	K_2CO_3	2	16
3	**3a**: R_1 = pyridin-2-yl; R_2 = n-C_6H_{13}	**I**	Na_2CO_3	2	11
4	**3a**: R_1 = pyridin-2-yl; R_2 = n-C_6H_{13}	**I**	Et_3N	2	~0
5	**3a**: R_1 = pyridin-2-yl; R_2 = n-C_6H_{13}	**II**	Cs_2CO_3	3	39
6	**3a**: R_1 = pyridin-2-yl; R_2 = n-C_6H_{13}	**III**	Cs_2CO_3	3	~0
7	**3b**: R_1 = pyridin-2-yl; R_2 = $Ph(CH_2)_2$	**I**	Cs_2CO_3	0.5	72
8	**3c**: R_1 = pyridin-2-yl; R_2 = n-C_3H_7	**I**	Cs_2CO_3	0.4	62
9	**3d**: R_1 = pyridin-2-yl; R_2 = c-C_6H_{11}	**I**	Cs_2CO_3	0.7	60
10	**3e**: R_1 = furan-2-yl; R_2 = c-C_6H_{11}	**I**	Cs_2CO_3	0.7	61
11	**3f**: R_1 = quinolin-2-yl; R_2 = n-C_6H_{13}	**I**	Cs_2CO_3	0.5	80

[a] Unless otherwise noted, the reactions were performed in 0.46 M **1** with a 1/1.1 ratio of **1**/**2** in DMF at 25 °C. [b] Isolated yields of the adducts **3**.

for the asymmetric synthesis of fully substituted cyclopentenes, a methodology that demonstrated the first organocatalytic [1 + 2 + 2] annulation strategy.[7] Despite the success of our procedure, the cyclopentenes prepared from that method bore only three stereogenic centers, and an analogous annulation method toward the fully substituted cyclopentane derivatives with the maximum (five consecutive) stereogenic centers[8] is an attractive and compelling area of investigation.[9] Considering our earlier work in the context of asymmetric organocatalysis,[10] we envisioned an intramolecular H-bonding strategy involving the introduction of heteroaromatic components into the organocatalytic [1 + 2 + 2] annulation that could improve the reaction yields of the annulation as well as extend the study to the successful synthesis of the fully substituted cyclopentanes bearing a quaternary carbon center (tertiary alcohol). More interestingly, the intramolecular H-bonding strategy, with the subtle difference of the heteroaromatic substituent, not only furnished varied stereoselectivity of the products, but also provided a vehicle for organocatalytic dynamic kinetic asymmetric transformation (DYKAT).[11] Herein, we report the new stereoselective consecutive reaction starting with heteroaromatics (e.g., picolinaldehyde), nitroalkenes, and α,β-unsaturated aldehydes, affording highly functionalized cyclopentanecarbaldehyde with five new stereogenic centers in high yield and in high stereoselectivities (up to >99% ee).

In exploring the possibility of sequential organocatalytic DYKAT Stetter and Michael−Aldol reactions,[12] initially we examined the Stetter reaction of picolinaldehyde (**1**)[13] and (*E*)-1-nitrooct-1-ene with the precatalyst **I** and Cs_2CO_3 in DMF. The reaction was completed in 30 min and afforded the Stetter adduct in 78% yield (Table 1, entry 1). The same reaction in other solvents (e.g., EtOH, CH_3CN, CH_2Cl_2, THF) gave lower yields (14−48%). Similarly, the same reaction with other base additives, e.g., K_2CO_3, Et_3N, and Na_2CO_3, also gave lower yields of **3a** (Table 1, entries 2−4). Unlike its 1-(4-bromophenyl)-counterpart,[12] the 2-alkyl-3-nitro-1-(pyridin-2-yl)nitroalkanone was surprisingly stable under basic and acidic conditions, and no elimination or decomposition was observed in the above environment. Probably, the nature of the intramolecular H-bonding led to the enolization of the α-H of ketone **3a** and hampered the elimination of HNO_2 to give **4** (Table 1). Alternatively, the same reaction using the precatalyst **II** provided a lower yield, and attempts with precatalyst **III** afforded no product **3** (Table 1, entries 5 and 6). Accordingly, several β-nitroketones (**3b**−**f**) were prepared via the **I**−Cs_2CO_3 conditions (Table 1, entries 7−11).

With the β-nitroketone **3a** in hand, several catalysts and reaction conditions were screened to explore the feasibility and optimization of the domino Michael−Aldol reaction (Table 2). Initially, the reaction was conducted in 0.2 M **5a** with a 2.4/1 ratio of **3a**/**5a** in toluene. To our surprise, reaction of **3a** and **5a** with 30 mol % of Jørgensen−Hayashi catalyst (**IV**) and HOAc (30 mol %) in toluene gave the disappointing outcome of products in low yield after 5 days (Table 2, entry 1). Many attempts with various reaction conditions were applied in order to improve the reaction. Finally, the reaction proceeded smoothly with the same amount of catalyst **IV** (30 mol %), but with an

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(10) For our recent efforts in exploring new organocatalytic annulations, see: (a) Hong, B.-C.; Kotame, P.; Liao, J.-H. *Org. Biomol. Chem.* **2011**, 382. (b) Hong, B.-C.; Kotame, P.; Tsai, C.-W.; Liao, J.-H. *Org. Lett.* **2010**, *12*, 776. (c) Hong, B.-C.; Jan, R.-H.; Tsai, C.-W.; Nimje, R. Y.; Liao, J.-H.; Lee, G.-H. *Org. Lett.* **2009**, *11*, 5246. (d) Hong, B.-C.; Nimje, R. Y.; Liao, J.-H. *Org. Biomol. Chem.* **2009**, *7*, 3095. (e) Kotame, P.; Hong, B.-C.; Liao, J.-H. *Tetrahedron Lett.* 2009, *50*, 704 and references cited therein.

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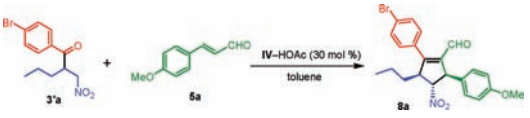
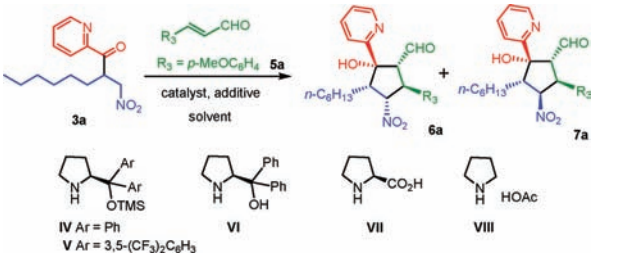
(12) For the previous results in the aldol condensation version of the reaction with 1-(4-bromophenyl)-2-(nitromethyl)pentan-1-one (**3′a**).



(13) (a) For a study of proton activating factors and keto−enol-zwitterion tautomerism of acetylpyridines, see: McCann, G. M.; O'Ferral, R. A. M.; Walsh, S. M. *J. Chem. Soc., Perkin Trans. 2* **1997**, 2761. (b) For study in the effect of OH---N hydrogen bonding on the oxidation potentials of enols, with the pyridin-2-yl ring on the α-ketone, see: Lal, M.; Langels, A.; Deiseroth, H.-J.; Schlirf, J.; Schmittel, M. *J. Phys. Org. Chem.* **2003**, *16*, 373.

Table 2. Catalysts Screening and Optimization for Domino Michael−Aldol Reaction[a]



entry	cat. (mol %)	additive (mol %)	solvent	time (h)	ratio **6a**/**7a**	yield[b] (%)
1	**IV** (30)	HOAc (30)	toluene	120	1/1	28
2	**IV** (30)	HOAc (300)	toluene	80	1.4/1	54[c]
3	**IV** (30)	HOAc (300)	DMF	2	3/1	72[d]
4	**IV** (30)	HOAc (300)	EtOH	3	2.2/1	73[e]
5	**V** (30)	HOAc (300)	DMF	65	3.5/1	48
6	**VI** (30)	HOAc (300)	DMF	65	3.3/1	60[f]
7	**VII** (30)	HOAc (300)	DMF	65	3.8/1	20[g]
8	**VIII** (30)	HOAc (300)	DMF	3	4/1	64
9	**IV** (5)	HOAc (300)	EtOH	20	3/1	70
10	**IV** (1)	HOAc (300)	EtOH	70	2.3/1	38
11	**IV** (5)	DABCO (300)	DMF	67	1/6.2	20
12	**IV** (30)		EtOH	9	1/2.5	51

[a] Unless otherwise noted, the reactions were performed in 0.2 M **5a** with a 1.2/1 ratio of **3a**/**5a** at 28 °C. [b] Isolated yields of the adducts **6a** and **7a**. [c] 94% ee of **6a**. [d] 95% ee of **6a**. [e] 99% ee of **6a**. [f] 35% ee of **6a**. [g] 3% ee of **6a**.

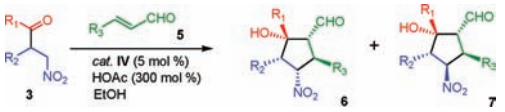
excess of acetic acid (300 mol %) to give **6a** and **7a** in a ratio of 1.4 to 1 and 54% overall yield (Table 2, entry 2). The same reaction in CH_3CN, CH_2Cl_2, MeOH, and dioxane also provided **6a** and **7a** in various ratios but with lower yields and/or at slower rates for completion, except for the reactions in DMF and EtOH that respectively provided 72% and 73% yields of the adducts in reaction times of 2 and 3 h (Table 2, entries 3 and 4). The reactions in DMF and EtOH were completed in much shorter times, as compared with the 1-(4-bromophenyl)-counterpart[12] (2 h vs hundreds of hours), and with higher yields. In addition, the reaction not only produced the aldol adducts, **6a** and **7a**, bearing a tertiary alcohol without undergoing the elimination to the more stable enal, but also afforded products of different stereoselectivities.[12] In addition, the reaction condition of **IV**−HOAc (excess) in EtOH provided **6a** with the highest enantioselectivity (99% ee) (Table 2, entry 4). On the other hand, the reactions with other catalysts, e.g., **V**−**VIII**, gave lesser yields of the products (Table 2, entries 5−8). Moreover, the reaction with less catalyst loading was feasible and even proceeded with only 1 mol % of **IV** and 300 mol % of HOAc, although longer time was required for completion (Table 2, 9 and 10). Conducting the reaction at higher concentrations (e.g., 0.2 and 0.4 M) did not enhance the reaction rate or increase the yields. Replacement of acetic acid with other additives (e.g., $PhCO_2H$, PNBA, TFA, DABCO, *i*-PrNEt, DBU, K_2CO_3) in DMF afforded lower yields or only trace amounts of the products (e.g., DABCO, Table 2, entry 11). Interestingly, the reaction was feasible with less HOAc or even in the absence of any additive in EtOH, a polar protic solvent (Table 2, entry 12). It is worth noting that the ratio of **6a**/**7a** was changed to 1/2.5 in the absence of HOAc, where **IV** acted as both a catalyst and a base, vide infra. Owing to a kinetic asymmetric transformation (KAT) and easy decomposition of 1-(4-bromophenyl)-2-(nitromethyl)alkanones observed in the previous study in the Michael−Aldol condensation with α,β-unsaturated aldehydes, vide supra,[12] a 2.4/1 ratio of **3a**/**5a** was initially applied in the reactions in Table 2. However, since **3a** was quite stable and possessed a possible intramolecular H-bonding for racemization, a dynamic kinetic asymmetric transformation (DYKAT) of **3a** may have taken place. In fact, the occurrence of DYKAT was further supported by the fact that a racemic mixture of **3a** was recovered after the reaction of (±)-**3a** with 0.7 equiv of cinnamaldehyde (**5a**), and the reaction of a 1.2/1 ratio of **3a**/**5a** gave the same yields and ee values of the reactions in Table 2.

Having established the optimal reaction conditions for **6a** and **7a**, we investigated the use of the β-nitroketone **3** and α,β-unsaturated aldehydes **5**, in a ratio of 1.2/1 of (±)-**3** to **5**, for synthesizing a variety of fully substituted cyclopentane derivatives. The two isomers (**6** and **7**) were, in all cases, the only two observable diastereoisomers with high enantioselectivities (up to > 99% ee, entries 1−12, Table 3).[14] This transformation contributes to the few examples of the organocatalytic aldol reaction of aromatic ketones with aldehydes, and has become a valuable addition to the limited repertoire of the asymmetric organocatalytic synthesis of stable β-hydroxy aldehydes bearing a tertiary alcohol.[15] Some variations in the diastereoselectivities of **6**/**7** were observed in the study. For most cases, **6** predominated as the major product with the ratio of **6**/**7** up to 85:15 (Table 3, entries, 1, 2, 3, 4, 6, 7, and 12). The **6**/**7** ratio was decreased when a highly electronegative group was attached at R_3 (e.g., NO_2 group, Table 3, entries 5 and 11). The same decreasing trend in the **6**/**7** ratio was observed in the examples with bulky substituents at R_2 (e.g., *c*-C_6H_{11} and $Ph(CH_2)_2$ group, Table 3, entries 8−11). The structure and the absolute configuration of the reaction adduct was revealed by single-crystal X-ray analysis of (+)-7**d**, (−)-**6a**, (−)-**6g**, and (−)-**6j** (Figure 1). The evidence of the intramolecular H-bonding of pyridine to alcohol in the X-ray diffraction may account for the stabilization of these β-hydroxy

(14) Reactions of the aliphatic α,β-unsaturated aldehydes gave complicate self-dimerization products. For examples, see: (a) Bertelsen, S.; Dinér, P.; Johansen, R. L.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 1536. (b) Hong, B.-C.; Tseng, H.-C.; Chen, S.-H. *Tetrahedron* **2007**, *63*, 2840.

(15) For examples, see: (a) Hara, N.; Nakamura, S.; Shibata, N.; Toru, T. *Adv. Synth. Catal.* **2010**, *352*, 1621–1624. (b) Rueping, M.; Kuenkel, A.; Tato, F.; Bats, J. W. *Angew. Chem., Int. Ed.* **2009**, *48*, 3699–3702. (c) Xue, F.; Zhang, S.; Duan, W.; Wang, W. *Chem. J. Asian* **2009**, *4*, 1664–1667.

Table 3. Scope of Domino Michael−Aldol Reaction[a]



entry	product	time (h)	dr (%)[b] **6**/**7**	yield (%)[c]	ee (%)[d] **6**/**7**
1	**6a**, **7a**: R_1 = pyridin-2-yl; R_2 = *n*-C_6H_{13}; R_3 = 4-$MeOC_6H_4$	20	73:27	73	99/99[e]
2	**6b**, **7b**: R_1 = pyridin-2-yl; R_2 = *n*-C_6H_{13}; R_3 = Ph	32	85:15	63	99/nd
3	**6c**, **7c**: R_1 = pyridin-2-yl; R_2 = *n*-C_6H_{13}; R_3 = 4-BrC_6H_4	16	66:34	71	97/99[e]
4	**6d**, **7d**: R_1 = pyridin-2-yl; R_2 = *n*-C_6H_{13}; R_3 = 4-ClC_6H_4	24	63:37	60	96/90[e]
5	**6e**, **7e**: R_1 = pyridin-2-yl; R_2 = *n*-C_6H_{13}; R_3 = 4-$NO_2C_6H_4$	17	44:56	62	99/98[e]
6	**6f**, **7f**: R_1 = pyridin-2-yl; R_2 = *n*-Pr; R_3 = 4-$MeOC_6H_4$	21	81:19	73	99/nd
7	**6g**, **7g**: R_1 = pyridin-2-yl; R_2 = *n*-Pr; R_3 = 4-BrC_6H_4	13	80:20	63	97/nd
8	**6h**, **7h**: R_1 = pyridin-2-yl; R_2 = $Ph(CH_2)_2$; R_3 = 4-BrC_6H_4	14	53:47	66	98/99[e]
9	**6i**, **7i**: R_1 = pyridin-2-yl; R_2 = *c*-C_6H_{11}; R_3 = 4-$MeOC_6H_4$	82	53:47	80	98/97[e]
10	**6j**, **7j**: R_1 = pyridin-2-yl; R_2 = *c*-C_6H_{11}; R_3 = 4-BrC_6H_4	87	43:57	66	96/99[e,f]
11	**6k**, **7k**: R_1 =pyridin-2-yl; R_2 = *c*-C_6H_{11}; R_3 = 4-$NO_2C_6H_4$	68	29:71	74	96/90
12	**6l**, **7l**: R_1 = quinolin-2-yl; R_2 = *n*-C_6H_{13}; R_3 = 4-$MeOC_6H_4$	36	70:30	82	99/nd
13	**6m**, **7m**: R_1 = furan-2-yl; R_2 = *c*-C_6H_{11}; R_3 = 4-$MeOC_6H_4$	91	16:5:12:3:1	72[g]	nd

[a] Unless otherwise noted, the reactions were performed in 0.2 M of **5** with a 1.2/1 ratio of **3**/**5** at 25 °C. [b] Determined by ^{1}H NMR of the crude products. [c] Isolated yields of the adducts **6** and **7**. [d] Unless otherwise noted, determined by HPLC with a chiral column (Chiralpak IC). [e] Determined as their corresponding esters by subjecting **6** to Wittig reagent ($Ph_3PCH_2CO_2Et$). [f] Determined by HPLC with a chiral column (Chiralpak IA). [g] Mixtures of the alcohol and enal products was obtained, and the stereochemistry of the adducts was not determined.

aldehydes. Furthermore, the hypothesis can be further supported by the fact that the example of an aromatic group (R_1) with less H-bonding ability, e.g., a furan-2-yl group, afforded complicated mixtures of stereoisomers of **6**, **7**, and **8** and the elimination of enals (Table 3, entry 13)

To explain the stereochemistry of this transformation, we proposed a plausible mechanism (Scheme 1).[16] The selective formation of adducts **6** and **7** in these reactions is noteworthy. Different stereoselectivity was obtained in the counterpart reaction where R_1 was the 4-bromophenyl group and adduct **8** was the predominant product, as opposed to the reactions affording **6** and **7** in which the R_1 was the pyridin-2-yl group.[12] The different stereoselectivity may arise from the fact that 4-bromophenyl ketone **3** favors the (*E*)-like conformer while the pyridin-2-yl ketone **3** favors the (*Z*)-like conformer during the nitro-Michael addition. Thus, the reaction underwent the subsequent intramolecular aldol transformation (Scheme 1).[16] In addition, under these reaction conditions, **6** could isomerize to **7**, which became an important factor when the bulky R_2 group (e.g., *c*-C_6H_{11}) and/or a strong electron-withdrawing group (e.g., NO_2) were present on R_3 in **6**.[17]

In conclusion, we have discovered an unprecedented sequential organocatalytic Stetter and Michael−Aldol reaction with the evidence of a dynamic kinetic asymmetric transformation. The introduction of an intramolecular H-bonding strategy in this system for increasing the yields, enabling DYKAT, and obtaining a stable β-hydroxyaldehyde is especially noteworthy.

(16) See Supporting Information for Scheme 1.

(17) The isomerization of **6** to **7** was further supported by the following experiments: (a) treatment of **6k** with DABCO in EtOH for 36 h gave a mixture of **6k** and **7k** with a ratio of 1:6. (b) Reaction with **IV**−DABCO afforded a 1:6.2 ratio of **6a**/**7a** (Table 2, entry 11). (c) Reaction with only catalyst **IV**, a base, without any additive provided a 1:2.5 ratio of **6a**/**7a** (Table 2, entry 12).

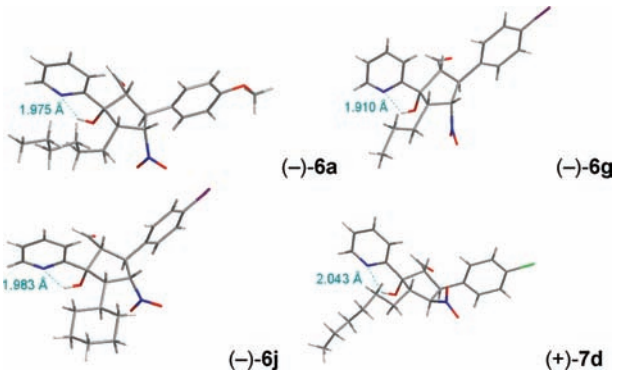


Figure 1. Stereo plots of the X-ray crystal structures of (−)-**6a**, (−)-**6g**, (−)-**6j**, and (+)-**7d**. Color code: C, gray; N, blue; O, red; Cl, green; Br, purple. The hydrogen bonding distance is noted in teal.

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Supporting Information Available. Experimental procedures and characterization data for the new compounds and X-ray crystallographic data for compounds (+)-**7d**, (−)-**6a**, (−)-**6g**, and (−)-**6j** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.