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Regio- and Stereoselective Addition of Allylmetal Reagents to Pyridinium–π and Quinolinium–π Complexes

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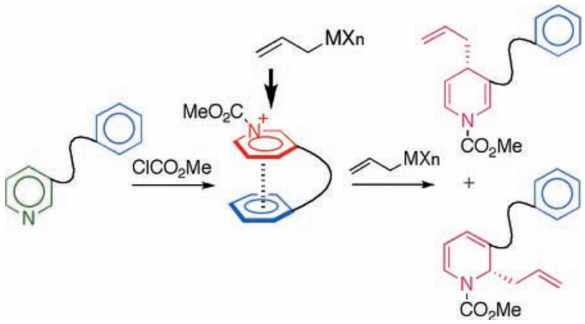
ABSTRACT



Regio- and stereoselective allylation of pyridinium and quinolinium salts was performed by the addition of allylindium and allyltributyltin reagents toward intermediary cation–π complexes. The reaction with allylindium and allyltributyltin reagents afforded a 1,2-adduct, whereas the addition of a prenylindium reagent gave a 1,4-adduct with good regio- and stereoselectivities. X-ray structural analysis, ^{1}H NMR studies, and DFT calculations elucidated the intermediary cation–π complex formation with face-to-face orientation.

The piperidine ring system constitutes a number of natural products and biologically active compounds. Approaches toward the efficient synthesis of the ring system are therefore a continuing challenge in organic synthesis.[1] One of the most promising ways is an approach through dihydropyridines[2] or dihydropyridones[3] because they are easily accessible to a variety of piperidine derivatives[4] and alkaloids.[3,5]

Various types of chiral dihydropyridines,[6] dihydroquinolines,[7] and dihydroisoquinolines[8] possessing an aryl, alkyl, and cyano group have been prepared by the nucleophilic addition toward pyridinium, quinolinium, and isoquinolinium salts, respectively. On the other hand, little is reported for stereoselective allylation of pyridinium and quindinium rings except for the reaction with chiral allylsilane[9] and allylcopper reagents.[10] We focused on the synthesis of allyl-substituted chiral dihydropyridines and dihydroquinolines because they are significantly important as the synthetic intermediates of natural products and related compounds.[11]

Since allylation generally occurs at the γ-position of the allylmetal reagent, it is often accompanied with lower face-

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(1) For reviews, see: (a) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701. (b) Felpin, F.-X.; Lebreton, J. *Eur. J. Org. Chem*. **2003**, 3693. (c) Laschat, S.; Dickner, T. *Synthesis* **2000**, 1781. (d) Bailey, P. D.; Millwood, P. A.; Smith, P. D. *Chem. Commun*. **1998**, 633.

(2) (a) Stout, D. M.; Meyers, A. I. *Chem. Rev*. **1982**, *82*, 223. (b) Eisner, U.; Kuthan, J. *Chem. Rev*. **1972**, *72*, 1. (c) Lavilla, R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1141.

(3) (a) Comins, D. L.; Joseph, S. P.; Goehring, R. R. *J. Am. Chem. Soc.* **1994**, *116*, 4719. (b) Huang, S.; Comins, D. L. *Chem. Commun*. **2000**, 569. (c) Kuethe, J. T.; Comins, D. L. *Org. Lett*. **2000**, *2*, 855. (d) Comins, D. L.; Huang, S.; McArdle, C. L.; Ingalls, C. L. *Org. Lett*. **2001**, *3*, 469.

(4) (a) Yamada, S.; Jahan, I. *Tetrahedron Lett*. **2005**, *46*, 8673. (b) Ichikawa, E.; Suzuki, M.; Yabu, K.; Albert, M.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc*. **2004**, *126*, 11808. (c) Lemire, A.; Grenon, M.; Pourashraf, M.; Charette, A. B. *Org. Lett*. **2004**, *6*, 3517. (d) Kumar, R.; Chandra, R. *Adv. Heterocycl. Chem*. **2001**, *78*, 269. (e) Charette, A. B.; Gernon, M.; Lemire, A.; Pourashraf, M.; Martel, J. *J. Am. Chem. Soc*. **2001**, *123*, 11829.

(5) (a) Bosh, J.; Bennasar, M.-L.; Amat, M. *Pure Appl. Chem*. **1996**, *68*, 557. (b) Bosh, J.; Bennasar, M.-L. *Synlett* **1995**, 587. (c) Itoh, T.; Nagata, M. Miyazaki, M.; Ohsawa, A. *Synlett* **1999**, 1154.

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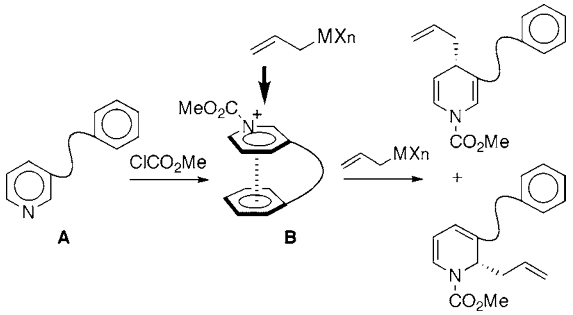
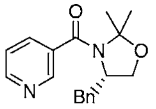
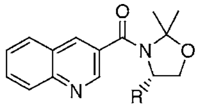
selectivity for pyridine systems.[8h] We anticipated that the stereoselective allylation of a pyridinium would be performed based on our previous strategy of the face-selective addition reaction as shown in Scheme 1:[12] Conversion of a pyridine derivative **A** into a pyridinium salt with methyl chloroformate will give a cation−π complex **B**. The selective face shielding of one side of the pyridinium face by the phenyl ring enables allyl metal reagents to attack the complex only from the open side, leading to 1,2- and 1,4-dihydropyridines stereoselectively. We report here that allylation of pyridinium and quinolinium salts with allylindium or allyltributyltin reagents provides 1,2- and 1,4-adducts regio- and stereoselectively.

Scheme 1. Strategy for the Stereoselctive Addition of Allyl Reagents

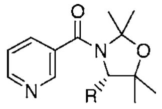




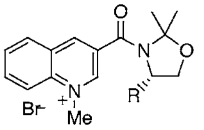
1: R = Bn



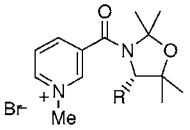
2: R = Bn
3: R = H



4: R = Bn
5: R = H



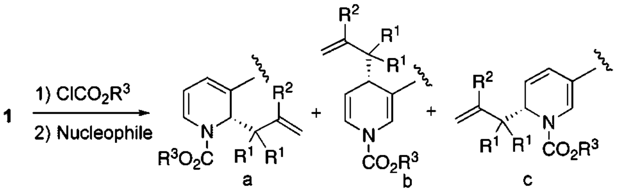
6: R = Bn
7: R = H



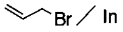
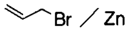
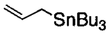
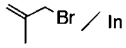
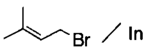
8: R = Bn
9: R = H

As substrates, we prepared nicotinic amides **1**,[12] **4**, and **5**, quinolinic amides **2** and **3**, and the corresponding *N*-methyl salts **6**−**9** as reference compounds for the geometrical studies. Among various allylmetal reagents, we focused on allylindium and allyltributyltin reagents as nucleophiles because of the establishment of their regioselectivity in the addition to pyridinium and quinolinium salts.[13,14] Attempted addition reaction of allylindium reagent to **1** in the presence of methyl chloroformate in DMF and CH_2Cl_2 gave no adduct (Table 1, entries 1 and 2). On the other hand, the reaction was successfully performed in THF to give 1,2-adduct **10a** as a major product in 84% de (entry 3). Using phenyl chloroformate instead of methyl chloroformate improved the stereo-

Table 1. Face-Selective Addition Reaction of Allylmetal Reagents to a Cation−π Complex



10a-c: R^1, R^2 = H, R^3 = Me
11a-c: R^1, R^2 = H, R^3 = Ph
12a-c: R^1 = H, R^2 = Me, R^3 = Me
13a-c: R^1 = Me, R^2 = H, R^3 = Me

entry	nucleophile	solvent	product	% yield	product ratio[a] a : b : c	% de[b]
1		DMF	10	0	-	-
2		CH_2Cl_2	10	0	-	-
3		THF	10	64	72 : 0 : 28	84
4		THF	11[c]	78	70 : 0 : 30	90
5		THF	10	53	60 : 0 : 40	86
6		CH_2Cl_2	10	90	92 : 0 : 8	84
7		THF	12	60	25 : 42 : 33	84[d]
8		THF	13	82	0 : 94 : 6	84

[a] Determined by ^{1}H NMR spectra. [b] The de values are reported for the major products unless otherwise noted. [c] Phenyl chloroformate was used instead of methyl chloroformate. [d] The de value is reported for **12b**.

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(8) (a) Taylor, M. S.; Tokunaga, N.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2005**, *44*, 6700. (b) Frisch, K.; Landa, A.; Saaby, S.; Jørgensen, A. K. *Angew. Chem., Int. Ed.* **2005**, *44*, 6058. (c) Pauvert, M.; Collet, S. C.; Bertrand, M.-J.; Guingant, A. Y.; Evain, M. *Tetrahedron Lett.* **2005**, *46*, 2983. (d) Youte, J.-J.; Barbier, D.; Al-Mourabit, A.; Gnecco, D.; Marazano, C. *J. Org. Chem.* **2004**, *69*, 2737. (e) Surygina, O.; Ehwald, M.; Liebscher, J. *Tetrahedron Lett.* **2000**, *41*, 5479. (f) Rezgui, F.; Mangeney, P.; Alexakis, A. *Tetrahedron Lett.* **1999**, *40*, 6241. (g) Yamaguchi, R.; Tanaka, M.; Matsuda, T.; Fujita, K.-I. *Chem. Commun.* **1999**, 2213. (h) Nakamura, M.; Hirai, A.; Nakamura, E. *J. Am. Chem. Soc.* **1996**, *118*, 8489.

(9) Yamaguchi, R.; Tanaka, M.; Matsuda, T.; Okano, T.; Nagura, T.; Fujita, K. *Tetrahedron Lett.* **2002**, *43*, 8871.

(10) Mangeney, P.; Gosmini, R.; Raussou, S.; Commerçon, M.; Alexakis, A. *J. Org. Chem.* **1994**, *59*, 1877.

(11) (a) Loh, T.-P.; Lye, P.-L.; Wang, R.-B.; Sim, K.-Y. *Tetrahedron. Lett.* **2000**, *41*, 7779. (b) Yamaguchi, R.; Moriyasu, M.; Yoshioka, M.; Kawanisi, M. *J. Org. Chem.* **1985**, *50*, 287.

(12) Yamada, S.; Morita, C. *J. Am. Chem. Soc.* **2002**, *124*, 8184.

(13) (a) Lee, J. H.; Kweon, J. S.; Yoon, C. M. *Tetrahedron Lett.* **2002**, *43*, 5771. (b) Lee, S. H.; Park, Y. S.; Nam, M. H.; Yoon, C. M. *Org. Biomol. Chem.* **2004**, *2*, 2170.

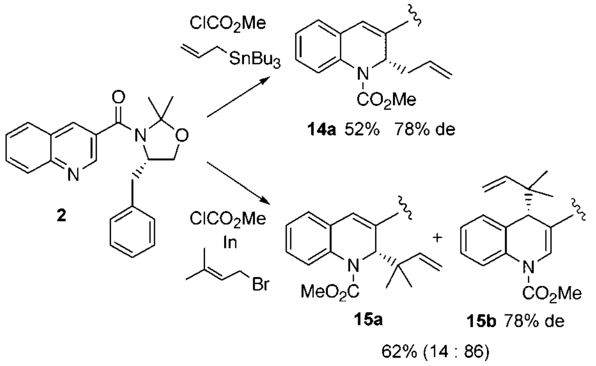
(14) Yamaguchi, R.; Moriyasu, M.; Yoshioka, M.; Kawanisi, M. *J. Org. Chem.* **1988**, *53*, 3507.

selectivity (entry 4). Addition of an allylzinc reagent resulted in much lower regioselectivity with similar stereoselectivity to the case of entry 3 (entry 5). Allyltributyltin also served as a good nucleophile to afford **10a** in good regio- and stereoselectivity (entry 6). The nucleophile dependence on the regioselectivity can be explained by the HSAB rule; harder allylation reagent preferentially attacks the harder 2-position than the 4- and 6-position.

Methallyl- and prenylindium reagents are also reported to serve as nucleophiles to a pyridinium salt.[13] Although regioselectivity was scarcely observed in the reaction with a methallylindium reagent (entry 7), the addition of a prenylindium reagent preferentially gave 1,4-adduct **13b** in good regio- and stereoselectivities (entry 8). This regioselectivity is in agreement with that of the reaction with prenyltributyltin reported by Yamaguchi.[14] To the best of our knowledge, this is the first example of the stereoselective allylation at the 4-position. It is worthwhile to note that the chiral auxiliary of the adducts can be removed by the reduction with $Cp_2Zr(H)Cl$[15] to give the corresponding aldehydes.

This allylation is applicable to the synthesis of dihydroquinoline derivatives. The addition of an allylmetal reagent to a quinolinium was carried out under similar reaction conditions described above (Scheme 2). Allylation of **2** with allyltributyltin exclusively yielded 2-allyldihydroquinoline **14a** in 78% de. On the other hand, the reaction with a prenylindium reagent gave 1,4-adduct **15b** as a major product, the stereoselectivity of which is 78% de. It is interesting to note that this regioselectivity contrasts with the indium-mediated prenylation of 2-ethoxy-1-(ethoxycarbonyl)-1,2-dihydroquinoline that yields 1,2-adduct as a major product.[13]

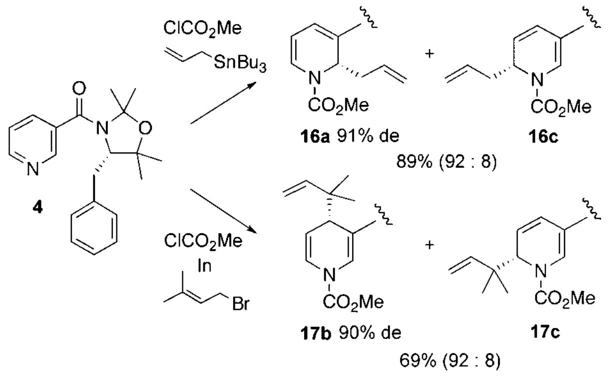
Scheme 2



The absolute configuration of the stereogenic center was determined by X-ray structural analysis. Crystals suitable for X-ray analyses were obtained for 1,2-dihydropyridine **11a**[16] and 1,2-dihydroquinoline **14a**.[17] The X-ray structures clarified that both stereogenic centers have *S* configuration.

To improve the stereoselectivity, we used a chiral auxiliary possessing *gem*-dimethyl groups at the 4-position of the oxazolidine moiety. Kanemasa and his co-workers have reported the effectiveness of this chiral auxiliary for asymmetric Diels–Alder reactions, where the *gem*-dimethyl groups help the benzyl group to block the diene moiety by the steric repulsion.[18] Addition of an allyltributyltin reagent to the pyridinium salt of **4** gave **16a** as a major product in 91% de (Scheme 3). On the other hand, the reaction with the prenylindium reagent gave a 1,4-adduct **17b** in 90% de. These results clearly show the effectiveness of this chiral auxiliary on the stereoselectivity. The stereogenic center of 1,4-adduct **17b** was also assigned to be *S* by X-ray analysis.[19]

Scheme 3



To elucidate the role of a cation-π interaction on the conformation of the intermediate pyridinium salt, ^1H NMR studies of **2**–**9** and X-ray structural analysis of **6** were carried out. Table 2 lists the $\Delta\delta$ values for the quinoline and quinolinium protons of **2** and **6**, and those for the pyridine and pyridinium protons of **4** and **8**, which are the differences

Table 2. $\Delta\delta$ Values (ppm) for **2**, **4**, **6**, and **8**[a,b]

	$\Delta\delta$**2**	$\Delta\delta$**6**	$\Delta\delta$**4**	$\Delta\delta$**8**
H2	−0.15	0.26	−0.42	−1.45
H4	−0.20	−0.59	−0.69	−0.50
H5			−0.30	−0.18
H6			−0.19	0.23

[a] Measured at 400 MHz in $CDCl_3$. [b] $\Delta\delta$**2** = δ**2** − δ**3**, $\Delta\delta$**4** = δ**4** − δ**5**, $\Delta\delta$**6** = δ**6** − δ**7**, $\Delta\delta$**8** = δ**8** − δ**9**.

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(15) White, J. M.; Tunoori, A. R.; Georg, G. I. *J. Am. Chem. Soc.* **2000**, *122*, 11995.

(16) Crystal data for **11a**: $C_{28}H_{30}N_2O_4$, $M = 458.56$, orthorhombic, space group $P2_12_12_1$, $a = 12.557(2)$ Å, $b = 21.638(3)$ Å, $c = 9.4914(15)$ Å, $V = 2578.8(7)$ Å^3, $Z = 4$, $D_{calcd} = 1.181$ g cm^{-3}, $m = 0.6369$ mm^{-1} (Cu Kα, $\lambda = 1.54178$ Å), $T = 293$ K. $R1 = 0.0431$ and $wR2 = 0.1335$ for 3034 unique reflections > $2\sigma(I)$.

(17) Crystal data for **14a**: $C_{27}H_{30}N_2O_4$, $M = 446.54$, monoclinic, space group $P2_1$, $a = 9.7426(10)$ Å, $b = 10.9058(12)$ Å, $c = 11.6685(12)$ Å, $\beta = 91.856(6)°$, $V = 1239.1(2)$ Å^3, $Z = 2$, $D_{calcd} = 1.197$ g cm^{-3}, $m = 0.6482$ mm^{-1} (Cu Kα, $\lambda = 1.54178$ Å), $T = 293$ K. $R1 = 0.0376$ and $wR2 = 0.1195$ for 4065 unique reflections > $2\sigma(I)$.

(18) Kanemasa, S.; Onimura, K. *Tetrahedron* **1992**, *48*, 8631.

(19) Crystal data for **17b**: $C_{27}H_{36}N_2O_4$, $M = 452.59$, monoclinic, space group $P2_1$, $a = 10.3437(11)$ Å, $b = 11.8652(14)$ Å, $c = 11.4054(12)$ Å, $\beta = 117.248(7)°$, $V = 2293.5(13)$ Å^3, $Z = 2$, $D_{calcd} = 1.208$ g cm^{-3}, $m = 0.646$ mm^{-1}(Cu Kα, $\lambda = 1.54178$ Å), $T = 293$ K. $R1 = 0.0718$ and $wR2 = 0.2041$ for 11934 unique reflections > $2\sigma(I)$.

in the chemical shifts between their δ values and those of reference compounds **3**, **5**, **7** and **9**, respectively.

As can be seen from Table 2, $\Delta\delta$**6** values for H2 and H6 are significantly different from those of the $\Delta\delta$**2** values. The H2 remarkably shifts to higher field and H4 shifts to lower field. Similarly, $\Delta\delta$ values of **8** are significantly different from those of **4**. These results suggest a significant conformational difference between the neutral and the cationic compounds; the quinoline and the pyridine rings of **2** and **4** may be apart from the benzyl ring, whereas the quinolinium and pyridinium rings of **6** and **8** would be close to the benzyl group.

The opposite tendency in the chemical shift change between $\Delta\delta6$ and $\Delta\delta8$ may be due to the difference in the shielding and deshielding area by the phenyl ring. The much larger absolute values of $\Delta\delta8$ would be responsible for the effective shielding of the benzyl group by introducing *gem*-dimethyl groups.

X-ray analysis of compound **6** clearly shows the effective blocking of the quinolinium plane by the benzyl group through an intramolecular cation−π interaction (Figure 1).[20]

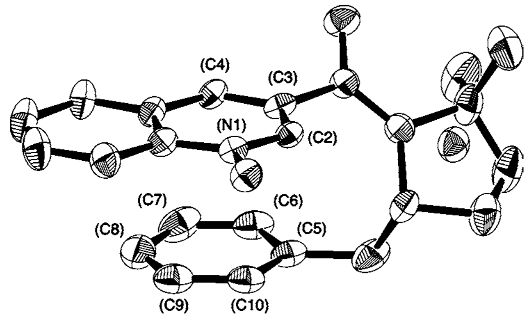

Figure 1. ORTEP drawing of compound **6**.

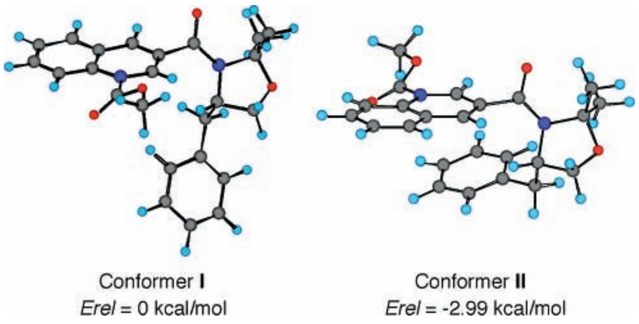

Figure 2. Structural optimization of quinolinium cation.

The quinolinium and the phenyl rings lie parallel to each other, and the two rings are arranged face-to-face, the distance between which is about 3.4 Å.

DFT calculations of the intermediate N-CO_2Me quinolinium cation at the B3LYP/6-31G* level[21] predict the preference of conformer **II** to **I**; conformer **II** is 2.99 kcal/mol more stable than conformer **I** (Figure 2). The geometrical difference between the crystal structure of **6** and conformer **II** may be due to the difference in the N-substituent or packing effect in the crystal.

These results lead to a working model outlined in Figure 3. The equilibrium between conformers **I** and **II** favors **II**. Allylmetal reagents would attack the conformer **II** from the less-hindered side to give a chiral dihydropyridine with good stereoselectivity. The predicted absolute configuration of the stereogenic center is in agreement with that determined by the X-ray analysis. The coordination of the carbonyl oxygen toward metal reagents during the addition reaction may also help this face selectivity.

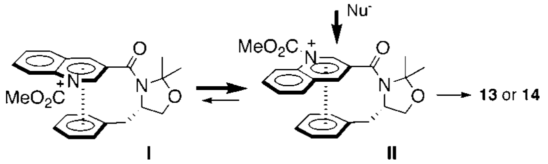

Figure 3. Working model for face-selective addition to a cation−π complex.

In summary, regio- and stereoselective allylation of pyridinium and quinolinium salts was performed based on the strategy through a cation−π complex. The reaction with allylindium and allyltributyltin reagents afforded 1,2-adducts, whereas the addition of a prenylindium reagent gave 1,4-adducts in good regio- and stereoselectivities. The key feature in this reaction is that the cation−π complex formation plays an essential role in the face-selective allylation reaction.

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Note Added after ASAP Publication. The structures of compounds **1**−**9** were omitted in the version published ASAP March 16, 2007; the corrected version was published ASAP March 21, 2007.

Supporting Information Available: Crystallographic data for **6**, **11a**, **14a**, and **17b**. Synthetic procedures and spectral data and ^{1}H NMR spectra for **2**−**17**. Optimized structures for three rotamers of the N-CO_2Me cation of **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) Crystal data for **6**: $C_{23}H_{25}N_2O_2Br$, $M = 441.37$, triclinic, space group $P1$, $a = 6.8268(8)$ Å, $b = 12.5858(14)$ Å, $c = 14.2335(16)$ Å, $\alpha = 79.547(7)°$, $\beta = 12.5858(14)°$, $\gamma = 14.2335(16)°$, $V = 1158.2(2)$ Å^3, $Z = 2$, $D_{calcd} = 1.266$ g cm^{-3}, $m = 2.564$ mm^{-1} (Cu Kα, $\lambda = 1.54178$ Å), $T = 293$ K. $R1 = 0.0537$ and $wR2 = 0.1518$ for 4068 unique reflections $> 2\sigma(I)$.

(21) DFT calculations were carried out by using PC SPARTAN '06. The optimized energies of **I** and **II** are -840742.707 kcal/mol and -840745.695 kcal mol^{-1}, respectively.