New Stereoselective Intramolecular [2 + 2] Cycloadditions between Ketenimines and Imines on an *ortho*-Benzylic Scaffold: 1,4-Asymmetric Induction

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Efficient 1,4-asymmetric induction has been achieved in the highly stereocontrolled intramolecular [2 + 2] cycloadditions between ketenimines and imines, leading to 1,2-dihydroazeto[2,1-*b*]-quinazolines. The chiral methine carbon adjacent to the iminic nitrogen controls the exclusive formation of the cycloadducts with relative *trans* configuration at C2 and C8. The stepwise mechanistic model, based on theoretical calculations, fully supports the stereochemical outcome of these cycloadditions.

Introduction

Although numerous strategies exist for 1,2- and 1,3-asymmetric induction,[1] one of the more challenging aspects of organic synthesis is the controlled construction of molecules with remote (i.e., greater than 1,3-related) stereogenic centers with high levels of diastereo- and enantioselectivity.[2] Cycloaddition reactions are of widespread application and value to achieve this goal and constitute a testing ground for theoretical arguments of chemical reactivity.[3]

We have recently studied[4−6] the intramolecular [2 + 2] cycloaddition reaction between ketenimine and imine functions supported on an *ortho*-benzylic scaffold, which was useful for achieving 1,2- and 1,3-asymmetric induction in a highly stereocontrolled manner.[6]In parallel to these experimental findings we performed density functional studies (DFT) at the B3LYP level in order to understand the mechanism of these transformations. We found that the reaction between ketenimines and imines

Chart 1

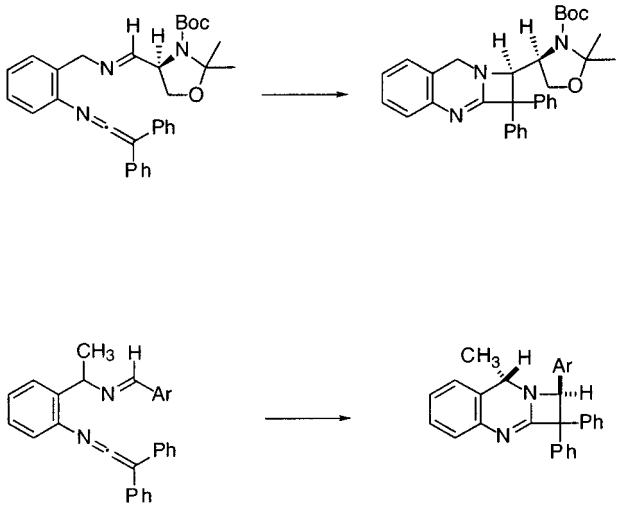
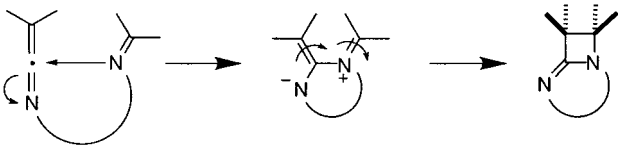


Chart 2



does not take place via a concerted mechanism but consists of a stepwise process.[5] In the first step, the nitrogen lone pair of the imine adds to the sp-hybridized carbon atom of the ketenimine. In the second step, the resulting zwitterionic intermediate is then transformed into the cycloadduct by a conrotatory ring closure.This mechanism is qualitatively similar to the well-known Staudinger reaction between ketenes and imines.[7]

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(1) (a) Bartlett, P. A. *Tetrahedron* **1980**, *36*, 2. (b) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307. (c) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841. (d) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1. (e) Reetz, M. T. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 556.

(2) For a review on 1,4- and 1,5-asymmetric induction, see: Mikami, K.; Shimizu, M. *Yuki Gosei Kagaku Kyokaishi* **1993**, *51*, 3.

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(5) Alajarín, M.; Vidal, A.; Tovar, F.; Arrieta, A.; Lecea, B.; Cossío, F. P. *Chem. Eur. J.* **1999**, *5*, 1106.

(6) Cossío, F. P.; Arrieta, A.; Lecea, B.; Alajarín, M.; Vidal, A.; Tovar, F. *J. Org. Chem.* **2000**, *65*, 3633.

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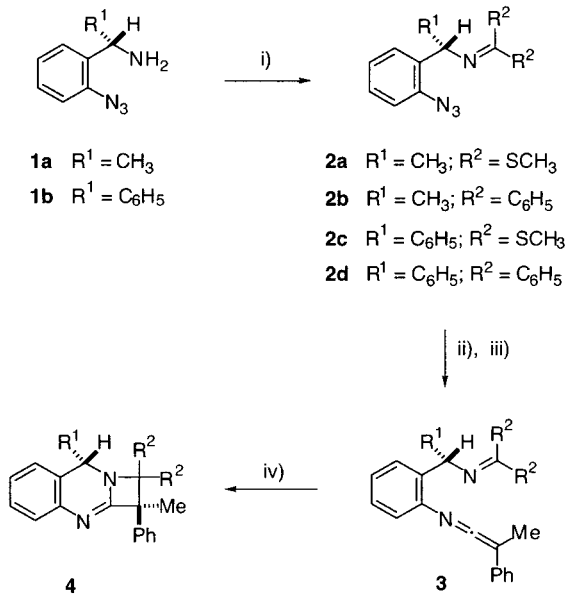
Scheme 1[a]



[a] Key: i) Method A: $Ph_2C{=}NH$, 50°C, 6 h; Method B: CS_2,CH_3I, NaOH 20%, DMF, 0°C, 15 min; ii) PMe_3, toluene, 25°C, 30 min; iii) PhMeC=C=O, toluene, 25°C, 5 min; iv) 25°C, 1 h.

Whereas the rate-limiting step of this last reaction is the second one, in which the two new chiral centers are formed, the energetic balance of the reaction between ketenimines and imines transfers the stereocontrol to the first step, thus allowing remarkable levels of stereoselectivity even when torquoelectronic effects operating in the second step are canceled.[5]

Herein we report that the intramolecular [2 + 2] cycloaddition between imine fragments derived from α-chiral amines and ketenimine functions with enantiotopic faces occurs with high stereocontrol, thus yielding a new example of efficient 1,4-asymmetric induction.

Results and Discussion

The reaction of 1-(*o*-azidophenyl)ethylamine **1a**[8] and 2-azido-α-phenylbenzylamine **1b**[6] with benzophenoneimine[9] (Method A in Scheme 1) or with carbon disulfide, methyl iodide, and base[10] (Method B) gave titled compounds **2**, where both substituents on the iminic carbon atom are identical, thus making that atom a nonstereogenic center. Sequential treatment of compounds **2** with trimethylphosphane and the prochiral ketene $Ph(CH_3)$-C=C=O provided transient imino-ketenimines **3**, which contain a ketenimine fragment with enantiotopic faces. The nonisolated species **3** underwent the expected intramolecular formal [2 + 2] cycloaddition giving rise to the 1,2-dihydroazeto[2,1-*b*]quinazolines **4** having a new stereogenic center C2, apparently[11] *as single diastereoisomers* (Scheme 1).

Table 1. 1,1,2,2,8-Pentasubstituted 1,2-Dydhydroazeto[2,1-*b*]quinazolines 4

compound	R^1	R^2	yield (%)[a]
4a	CH_3	CH_3S	85
4b	CH_3	C_6H_5	42
4c	C_6H_5	CH_3S	86
4d	C_6H_5	C_6H_5	51

[a] Yield of pure isolated product.

1,2-Dihydroazeto[2,1-*b*]quinazolines **4** were obtained in medium to good yields (see Table 1), isolated as crystalline solids after purification by column chromatography and characterized by their analytical and spectral data, which were essentially similar to those of the structural analogues previously reported.[4−6] As anticipated, neither these spectral data nor NOE experiments showed relevant features for assigning the *cis* or *trans* configuration to the compounds **4** here prepared. The X-ray structure determination of **4a** unequivocally revealed that the phenyl (at C2) and methyl (at C8) groups present a relative *trans* disposition (see Supporting Information).

On the basis of mechanistic considerations (see below) we reasoned that the sense of the stereocontrol observed in the transformation **3a** → **4a** is the same in the rest of the cycloadditions here reported, yielding compounds **4** as single *trans* diastereoisomers. This excellent level of diastereoselectivity has been achieved by means of the efficient induction exerted by a chiral carbon atom C8 at a distance of three bonds from the new stereogenic center C2. Although in this work we have not carried out reactions on optically active substrates but only on racemic ones, the easy availability of enantioenriched (*S*)-(−)-**1a**[8] enables the application of the cycloadditions above to the preparation of 1,2-dihydroazeto[2,1-*b*]-quinazolines **4** in nonracemic forms.

The degree and sense of the stereocontrol operating in these cycloadditions can be predicted and explained by our mechanistic model based on theoretical calculations.[5,6] In the intramolecular [2 + 2] cycloadditions between homotopic ketenimine functions and diastereotopic imine fragments derived from α-chiral amines, that model predicted that the source of stereocontrol lies in the proximity between the CH_3 or Ph substituent at the chiral methine carbon and the groups attached to the iminic carbon.[6] The expected major stereoisomer would be the one that minimizes the proximity between those groups by occupying an axial position in the half-chair conformation of the developing six-membered ring in the first transition state.

In that previous work, the imine fragments analyzed were (*E*)-aldimines, and so the substituent on the iminic carbon involved in the steric interaction with the substituent at the future C8 was a hydrogen atom. Reasonably, we anticipated that *an iminic part formed from a ketone should induce even larger diastereoselection*,[6] as in such event the interacting substituent at the iminic carbon, being more bulky than the H atom, would differentiate in greater extension the energies of the two possible transition states. This is the present case.

(7) (a) Lecea, B.; Arrastia, Y.; Arrieta, A.; Roa, G.; López, X.; Arriortua, M. Y.; Ugalde, J. M.; Cossío, F. P. *J. Org. Chem.* **1996**, *61*, 3070. (b) Cossío, F. P.; Arrieta, A.; Lecea, B.; Ugalde, J. M. *J. Am. Chem. Soc.* **1994**, *116*, 2085. (c) López, X.; Sordo, T. L.; Sordo, J. A.; Gonzalez, J. *J. Org. Chem.* **1993**, *58*, 7036. (d) Cossío, F. P.; Ugalde, J. M.; López, X.; Lecea, B.; Palomo, C. *J. Am. Chem. Soc.* **1993**, *115*, 995. (e) Sordo, J. A.; González, J.; Sordo, T. L. *J. Am. Chem. Soc.* **1992**, *114*, 6249. (f) Cooper, R. D. G.; Daugherty, B. W.; Boyd, D. B. *Pure Appl. Chem.* **1987**, *59*, 485.

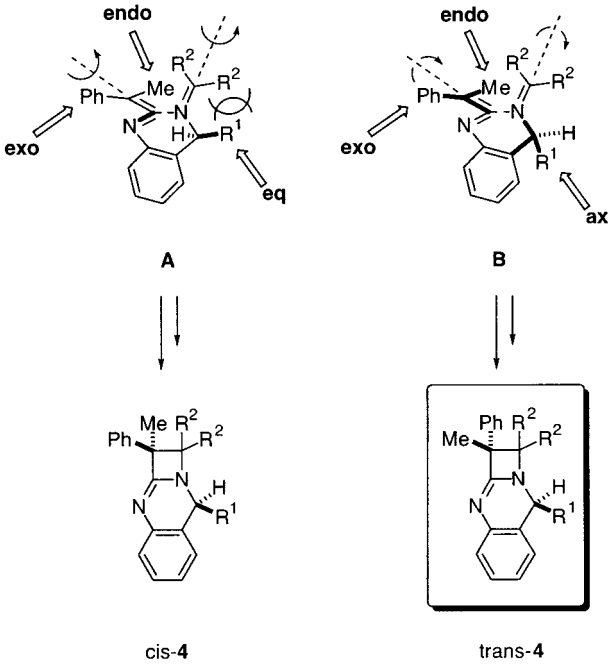
(8) Molina, P.; Alajarín, M.; Vidal, A. *J. Org. Chem.* **1993**, *58*, 1687.

(9) Ding, C. Z. *Tetrahedron Lett.* **1996**, *37*, 945.

(10) Merchan, F.; Garín, J.; Meléndez, E. *Synthesis* **1982**, 590.

(11) In all the cyloadditions here reported, only one diastereoisomer of **4** could be detected by ^1H NMR (300 MHz, $CDCl_3$) in each one of the final reaction mixtures before the purification step.

Scheme 2



The key features of the two possible diastereoisomeric first transition structures, A and B, and the final compounds **4** are depicted in Scheme 2.

In accordance with our previous study,[5] the most stable transition structures are those in which the methyl and phenyl groups on the ketenimine moiety occupy the *endo* and *exo* positions, respectively. In structure A there is an important destabilizing steric interaction between R^1 and R^2, whereas in structure B the distance between R^1 and R^2 is larger as a result of the axial disposition of R^1. Therefore, clockwise[12] conrotation of the zwitterionic intermediate resulting from transition structure B should lead to the preferential or exclusive formation of *trans*-**4**, as has been found experimentally. The nonstereogenic character of the iminic carbon bearing both R^2 groups is not relevant, since we have previously shown that the final electrocyclization step has no significant impact on the stereochemical outcome.

In conclusion, the intramolecular [2 + 2] cycloadditions between ketenimine and imine fragments supported on a *ortho*-benzylic scaffold have been proven to occur in a highly stereocontrolled manner. Their general mechanistic pathway and the stereochemical outcomes attained in some diastereoselective versions have been previously rationalized on the basis of high-level theoretical calculations. In this paper we have presented evidence of the effective stereocontrol operating in these reactions that allows asymmetric induction even at three bonds distance between the stereocenters in the cycloadducts. The mechanistic model exactly predicts the sense and extent of the experimentally observed diastereoselectivity.

Experimental Section

For general experimental information see references 5 and 6.

Materials. 1-(*o*-Azidophenyl)ethylamine **1a**,[8] 2-azido-α-phenylbenzylamine **1b**,[6] and methyl phenyl ketene[13] were prepared following previously reported procedures. Azidoimines **2b** and **2d** were prepared following a standard procedure,[9] were neither isolated nor purified as a result of their high hydrolytic sensitivity, and were used as crude materials.

General Procedure for the Preparation of Dimethyl Dithiocarbonimidates 2a and 2c. An aqueous solution of NaOH (20 M, 0.27 mL), carbon disulfide (0.54 mL), more aqueous NaOH (20 M, 0.27 mL), and methyl iodide (2.84 g, 11 mmol) were sequentially added to a well-stirred solution of the corresponding amine **1** (5 mmol) in DMF (5 mL) with external cooling (ice/water bath). Portionwise addition of the base and time between additions (15 min) was necessary in order to improve the yields. Stirring was continued for 30 min, and the mixture was poured into water (25 mL) and extracted with CH_2Cl_2 (3 × 25 mL). The combined organic layers were washed with water (50 mL) and dried over anhydrous $MgSO_4$. After filtration, the solvent was removed under reduced pressure, and the resulting oil was chromatographed on a silica gel column with hexanes/ethyl acetate (4:1 v/v) as eluent.

Dimethyl *N*-[1-(2-Azidophenyl)ethyl]dithiocarbonimidate (2a): yield 65%; yellow oil; IR (Nujol) 2126 (N_3), 1571 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.37 (d, 3 H, J = 6.5 Hz), 2.45 (s, 3 H), 2.53 (s, 3 H), 5.13 (q, 1 H, J = 6.5 Hz), 7.09−7.14 (m, 2 H), 7.17−7.28 (m, 1 H), 7.62−7.65 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.88, 23.74, 55.93, 117.84, 125.02, 127.65, 127.89, 136.40 (s), 137.37 (s), 157.23 (s); MS *m*/*z* (relative intensity) 266 (M^+, 5), 91 (100). Anal. Calcd for $C_{11}H_{14}N_4S_2$: C, 49.60; H, 5.30; N, 21.03. Found: C, 49.43; H, 5.37; N, 20.88.

Dimethyl *N*-(2-Azido-α-phenylbenzyl)dithiocarbonimidate (2c): yield 76%; yellow oil; IR (Nujol) 2122 (N_3), 1573 (C=N) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.51 (s, 6 H), 6.21 (s, 1 H), 7.08−7.29 (m, 6 H), 7.41−7.46 (m, 2 H), 7.68−7.71 (m, 1 H); ^{13}C NMR ($CDCl_3$) δ 15.09, 63.24, 118.03, 125.13, 126.78, 127.53, 128.03, 128.27, 128.88, 135.69 (s), 136.91 (s), 143.58 (s), 159.60 (s); MS *m*/*z* (relative intensity) 328 (M^+, 7), 180 (100). Anal. Calcd for $C_{16}H_{16}N_4S_2$: C, 58.51; H, 4.91; N, 17.06. Found: C, 58.35; H, 5.07; N, 17.19.

General Procedure for the Preparation of Azeto[2,1-*b*]quinazolines 4. Trimethylphosphane (3 mmol, 1 M toluene solution) was added to a solution of the corresponding azide **2** (3 mmol) in dry toluene (15 mL), and the reaction mixture was stirred at room temperature until the evolution of nitrogen ceased (15−30 min). Then, methyl phenyl ketene (0.40 g, 3 mmol) was added, and the reaction mixture was stirred at room temperature until the ketenimine band around 2000 cm^{-1} was not observed by IR spectroscopy (3−4 h). The solvent was removed under reduced pressure, and the resulting material was chromatographed on a silica gel column, with hexanes/ethyl acetate (4:1 v/v) as eluent.

***trans*-2,8-Dimethyl-1,1-bis(methylthio)-2-phenyl-1,2-dihydroazeto[2,1-*b*]quinazoline (4a)**: yield 85%; mp 141−142 °C; colorless prisms (diethyl ether); IR (Nujol) 1677 cm^{-1} (C=N); ^1H NMR ($CDCl_3$) δ 1.65 (d, 3 H, J = 6.2 Hz), 1.93 (s, 3 H), 2.00 (s, 3 H), 2.31 (s, 3 H), 5.06 (q, 1 H, J = 6.2 Hz), 7.00−7.10 (m, 2 H), 7.17−7.37 (m, 5 H), 7.59 (s, 2 H); ^{13}C NMR ($CDCl_3$) δ 15.11, 15.56, 23.28, 24.12, 48.69, 66.98 (s), 91.41 (s), 124.92, 125.47, 126.04, 127.04 (s), 127.61, 127.64, 128.01, 128.43, 136.10 (s), 141.55 (s), 161.96 (s); MS *m*/*z* (relative intensity) 354 (M^+, 20), 339 (100). Anal. Calcd for $C_{20}H_{22}N_2S_2$: C, 67.77; H, 6.24; N, 7.90. Found: C, 67.47; H, 6.35; N, 7.81. X-ray crystal structure determination: colorless block of 0.74 × 0.44 × 0.42 mm^3 size, monoclinic, $P2_1/n$, a = 9.4890(12), b = 11.2157(12), c = 17.3460(14) Å, β = 95.764(8)°, V = 1836.7(4) $Å^3$, Z = 4, 2θmax = 55°, diffractometer Siemens P4, Mo Kα (λ = 0.71073 Å), ω-scan, T = 193(2) K, 6975 reflections collected of which 4215 (R_{int} = 0.0137) were independent, heavy atom method solution and refinement on F^2 using the SHELX97 program (G. M. Sheldrick, University of Göttingen, 1997), 221 refined parameters, rigid methyl groups hydrogen atoms, others riding, $R_1[I > 2\sigma(I)]$ = 0.0302, wR_2 (all data) = 0.0810, residual electron density 0.34 e $Å^{-3}$.

***trans*-2,8-Dimethyl-1,1,2-triphenyl-1,2-dihydroazeto-[2,1-*b*]quinazoline (4b)**: yield 42%; mp 220−221 °C; colorless prisms (diethyl ether); IR (Nujol) 1664 cm^{-1} (C=N); ^1H NMR

(12) The conrotatory motion of lowest energy, following the mechanistic model in ref 6.

(13) Pracejus, H.; Wallura, G. *J. Prakt. Chem.* **1963**, *19*, 33.

($CDCl_3$) δ 1.27 (s, 3 H), 1.32 (d, 3 H, J = 6.3 Hz), 4.22 (q, 1 H, J = 6.3 Hz), 6.98−7.28 (m, 11 H), 7.40−7.51 (m, 4 H), 7.65−7.75 (m, 2 H), 7.57 (d, 2 H, J = 7.3 Hz); ^{13}C NMR ($CDCl_3$) δ 19.78, 29.09, 47.57, 64.06 (s), 80.81 (s), 124.74, 124.87, 126.48, 127.13, 127.40, 127.53, 127.60, 127.98, 128.30 (s), 128.41, 128.81, 131.48, 134.98 (s), 138.91 (s), 142.05 (s), 142.50 (s), 168.55 (s), two methine carbons were not observed; MS *m*/*z* (relative intensity) 414 (M^+, 50), 77 (100). Anal. Calcd for $C_{30}H_{26}N_2$: C, 86.92; H, 6.32; N, 6.75. Found: C, 87.07; H, 6.15; N, 6.78.

***trans*-2,8-Diphenyl-2-methyl-1,1-bis(methylthio)-1,2-dihydroazeto[2,1-*b*]quinazoline (4c)**: yield 86%; mp 144−145 °C; colorless prisms (diethyl ether); IR (Nujol) 1679 cm^{-1} (C═N); ^{1}H NMR ($CDCl_3$) δ 1.74 (s, 3 H), 1.81 (s, 3 H), 2.06 (s, 3 H), 5.81 (s, 1 H), 6.63 (d, 1 H, J = 7.6 Hz), 6.90 (td, 1 H, J = 7.6, 1.5 Hz), 7.12−7.49 (m, 10 H), 7.63−7.66 (m, 2 H); ^{13}C NMR ($CDCl_3$) δ 14.71, 24.35, 57.60, 66.94 (s), 91.77 (s), 124.86, 125.60, 125.99 (s), 127.54, 127.81, 127.95, 128.26, 128.32, 128.40, 128.56, 128.73, 138.30 (s), 141.13 (s), 142.88 (s), 162.01 (s); MS *m*/*z* (relative intensity) 416 (M^+, 20), 401 (100). Anal. Calcd for $C_{25}H_{24}N_2S_2$: C, 72.08; H, 5.81; N, 6.72. Found: C, 72.25; H, 5.70; N, 6.97.

***trans*-2-Methyl-1,1,2,8-tetraphenyl-1,2-dihydroazeto-[2,1-*b*]quinazoline (4d)**: yield 51%; mp 206−208 °C; white prisms (diethyl ether); IR (Nujol) 1663 cm^{-1} (C═N); ^{1}H NMR ($CDCl_3$) δ 1.34 (s, 3 H), 5.25 (s, 1 H), 6.53 (d, 1 H, J = 7.8 Hz), 6.98 (td, 2 H, J = 7.5, 1.8 Hz), 6.98−7.26 (m, 17 H), 7.34 (dd, 2 H, J = 6.3, 1.2 Hz), 7.73 (d, 2 H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$) δ 29.37, 58.27, 64.04 (s), 82.97 (s), 124.45, 125.06, 126.22 (s), 126.32, 126.87, 127.28, 127.34, 127.54, 127.61, 128.11, 128.19, 128.50, 130.21, 131.30, 136.52 (s), 137.83 (s), 141.81 (s), 142.47 (s), 142.63 (s), 166.98 (s), three methine carbons were not observed; MS *m*/*z* (relative intensity) 476 (M^+, 100). Anal. Calcd for $C_{35}H_{28}N_2$: C, 88.12; H, 5.87; N, 5.88. Found: C, 87.95; H, 5.63; N, 5.99.

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Supporting Information Available: Crystallographic data and ORTEP diagram of **4a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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