JOC Article

Easy-to-Execute Carbonylations: Microwave Synthesis of Acyl Sulfonamides Using $Mo(CO)_6$ as a Solid Carbon Monoxide Source

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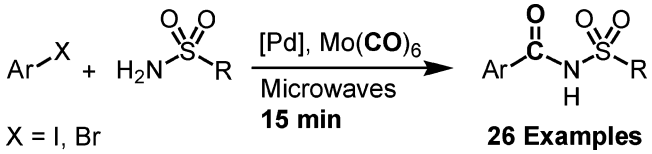

The development of a robust palladium-catalyzed amidocarbonylation protocol for the preparation of aromatic acyl sulfonamides utilizing high-density microwave heating is described. This synthetic approach employs $Mo(CO)_6$ as a convenient CO-releasing reagent and allows for the direct preparation of acyl sulfonamides from both aryl iodides and aryl bromides. The reactions can be performed under air, employing only 15 min of microwave irradiation, to produce acyl sulfonamide derivatives in good to excellent yields. To illustrate the usefulness of this method, we reported the synthesis of a novel hepatitis C virus NS3 protease inhibitor.

Introduction

In the discipline of preparative high-throughput chemistry, the value of robust and user-friendly reaction protocols is clear.[1,2] Specific approaches, such as the use of solid-supported reagents and scavengers, enabling ease of monitoring and rapid purification, have been proven to be valuable for speeding up the compound production in modern laboratories.[3,4] Conceptually, the use of high-density microwave irradiation offers a complementary technology to solid-phase reagents by improving the efficiency of energy transfer to the reaction mixture.[5−7] Thus, in the last two decades fast microwave heating has accelerated numerous organic transformations.[8−10]

Transition-metal-catalyzed carbonylations are of utmost importance in organic syntheses, allowing unique and chemoselective preparations of carbonyl-containing derivatives.[11] Despite the power of carbonylative reactions, there is often a considerable degree of effort required to use gaseous carbon monoxide in high-speed chemistry when sealed vessels and heating are used.[12] To address this issue, we introduced molybdenum hexacarbonyl as an appropriate solid source of carbon monoxide.[13] The combination of microwave heating and in situ release of CO from $Mo(CO)_6$ has been proven to enable the fast development of new easy-to-execute carbonylation protocols.[14−16]

Palladium-catalyzed carbonylation of aryl halides provides different benzoic acid derivatives in a smooth manner. Depending on the nucleophile used, aromatic acids, esters, amides, aldehydes, and ketones are readily prepared. Surprisingly, this methodology has not been

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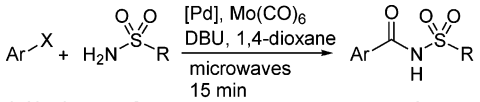
studied much using sulfonamides (**3**) as nucleophiles,[17] affording acyl sulfonamide structures that have important applications in medicinal chemistry as carboxylic acid bioisosteres. We now report that sulfonimides (**4**) can be rapidly prepared from both aryl iodides (**1**) and aryl bromides (**2**) by direct carbonylation using controlled microwave heating and $Mo(CO)_6$ as the CO source. Furthermore, the synthesis of a potent hepatitis C virus (HCV) NS3 protease inhibitor (**8**) comprising acyl sulfonamide elements is presented.

Results and Discussion

We began our study of carbonylative acyl sulfonamide synthesis by examining the conditions reported recently for the related in situ hydrazidocarbonylation[18] with aryl iodides using 10% $Pd(OAc)_2$ as the precatalyst but exchanging the nitrogen nucleophile for *p*-tolylsulfonamide (**3a**). The amidocarbonylations were executed under air using sealed vessels and microwave heating. The reaction time was locked to 15 min, and the temperature was set to 110 °C (eq 1) to identify a standard protocol for both electronically and sterically diverse aryl iodides. Gratifyingly, the investigated examples provided full conversion of **1a**−**i** and good isolated yields of target **4a**−**i** (65−88%) by simply switching from THF, which was used in the literature, to the related solvent, 1,4-dioxane. Therefore, the optimization efforts were halted, and the identified conditions were directly used. The preparative results are summarized in Table 1.



(1)

A variety of functional groups were tolerated, and the reaction proceeded efficiently with both ortho-substituted phenyl iodides and heterocyclic 2- and 3-iodothiophene. Aryl iodide **1b** was also carbonylated with different sulfonamides **3b**−**e** (entries 10−13), expanding the scope of the method and providing products **4j**−**m** in high yields (71−88%). Please note the chemoselective reaction in entry 11 in which only the iodide is activated despite the high reaction temperature. Although the process occurred in a very general and high-yielding fashion with all of the investigated aryl iodides and primary sulfonamides, the reaction did not proceed equally satisfactorily with secondary sulfonamides although *N*-methylated **4n** was isolated in useful yield (47%, entry 14).

Aryl bromides (**2**) are generally less reactive in palladium(0)-catalyzed couplings and often require higher temperatures for reaction compared to those of aryl iodides.[19] However, employing 15 min of microwave heating at an elevated temperature of 140 °C and in the presence of the thermostable catalytic combination of Herrmann's palladacycle[20] and the Fu salt, $[(t\text{-}Bu)_3PH]BF_4$,[21] the investigated amidocarbonylation route was also found to be amenable to aryl bromides (Table 2). Despite the higher reaction temperature and noninert conditions, the isolated yields of sulfonimide products **4** were found to be superior to the outcome with aryl iodides. In fact, the yields were excellent (79−96%) in all of the attempted entries, regardless of the substitution pattern of the aryl bromide.

Aryl bromide moiety **5** represents a building block of a class of HCV NS3 protease inhibitors under development. We envisaged that carbonylative displacement of the bromide with a primary sulfonamide would be highly possible, exemplifying the use of the amidocarbonylation method for potential analogue generation. Arylpalladium precursor **5** was therefore reacted with **3d** using a slightly more diluted version of the protocol presented in Table 2, producing target sulfonimide **6** as the main product together with traces of debrominated byproduct (Scheme 1). After careful preparative HPLC-MS purification, product **6** was isolated in 52% yield. The building block was subsequently deprotected and coupled to **7**[22] using standard peptide bond formation procedures to yield final compound **8** in 76% yield. Notably, no racemization occurred during the synthesis of **6**, as is evident by the formation of only one diastereomer of **8**. When evaluated in an in vitro assay comprising the full-length NS3 protein,[23,24] **8** proved to be a highly potent inhibitor with a K_i value of 85 ± 7 nM. Introduction of acidic functionalities in similar positions in inhibitors of the NS3 protease has been employed previously with success.[25,26]

Conclusions

We have identified a palladium-catalyzed protocol for the microwave-assisted generation of acyl sulfonamides from aryl iodides and bromides. Compared to carbonylative methods utilizing external delivery of CO gas, the use of CO-liberating $Mo(CO)_6$ was found to be highly convenient. Thus, aromatic acyl sulfonamide products could be generated in high yields after only 15 min of irradiation of septum-sealed reaction mixtures employing noninert conditions. The usefulness of this in situ carbonylation method was further demonstrated in the construction of a new hepatitis C virus NS3 protease inhibitor. In view of the versatility and robustness of the presented amidocarbonylation, as well as the large commercial availability of both sulfonamides and aryl halides, we anticipate that our work will be of importance in various medicinal-chemistry-related applications.

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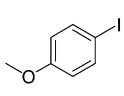
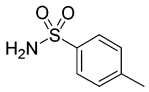
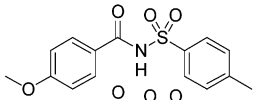
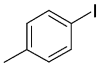
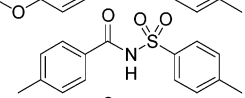
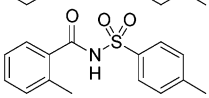
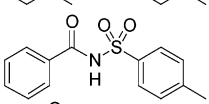
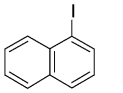
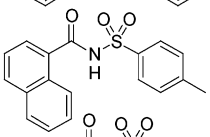
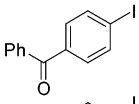
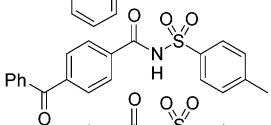
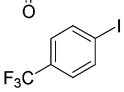
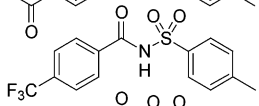
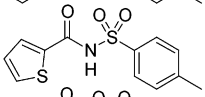
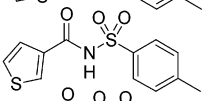
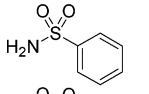
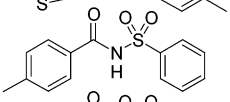
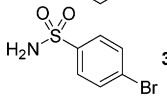
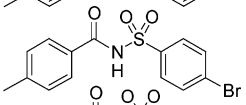
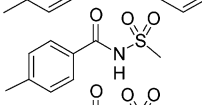
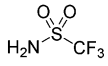
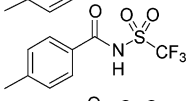
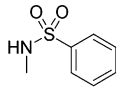
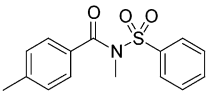
TABLE 1. Microwave-Heated Carbonylation of Aryl Iodides with Primary and Secondary Sulfonamides Using $Mo(CO)_6$ as the CO Source[a]

Entry	Iodide	Sulfonamide	Product	Isolated yield (%)
1	 **1a**	 **3a**		**4a** 88
2	 **1b**	**3a**		**4b** 87
3	 **1c**	**3a**		**4c** 88
4	 **1d**	**3a**		**4d** 80
5	 **1e**	**3a**		**4e** 74
6	 **1f**	**3a**		**4f** 70
7	 **1g**	**3a**		**4g** 76
8	 **1h**	**3a**		**4h** 65
9	 **1i**	**3a**		**4i** 79
10	**1b**	 **3b**		**4j** 88
11	**1b**	 **3c**		**4k** 84
12	**1b**	 **3d**		**4l** 72
13	**1b**	 **3e**		**4m** 71
14	**1b**	 **3f**		**4n** 47

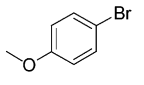
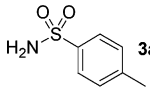
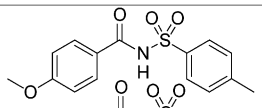
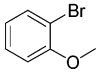
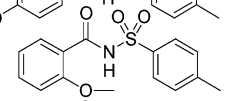
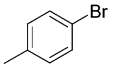
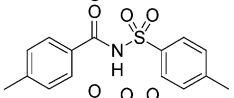
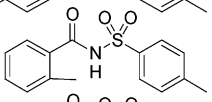
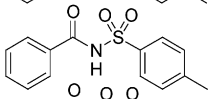
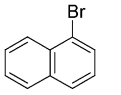
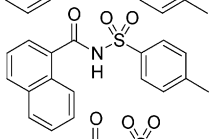
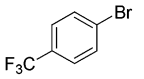
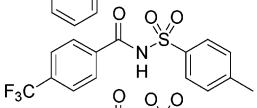
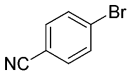
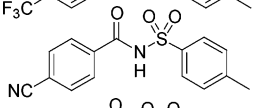
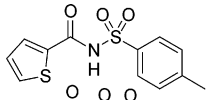
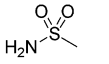
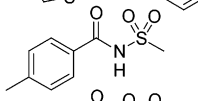
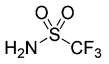
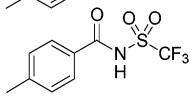
[a] Reaction conditions: 0.40 mmol aryl iodide, 0.10 equiv $Pd(OAc)_2$, 1.0 equiv $Mo(CO)_6$, 3.0 equiv DBU, 3.0 equiv sulfonamide, 1.0 mL 1,4-dioxane, single-mode microwave heating at 110 °C for 15 min using sealed vessels.

Experimental Section

General Procedure for the Amidocarbonylation of Aryl Iodides (Table 1) and the Purification of 4i. A 5-mL process vial was charged with **1** (0.40 mmol), $Mo(CO)_6$ (105 mg, 0.40 mmol), $Pd(OAc)_2$ (9.0 mg, 0.04 mmol), DBU (183 mg, 1.2 mmol), sulfonamide **3** (3.0 equiv), and 1,4-dioxane (1.0 mL). The vessel was sealed under air and exposed to microwave heating for 15 min at 110 °C. The reaction tube was thereafter cooled to room temperature, and the mixture was concentrated and dissolved in a small volume of dichloromethane. The crude product was thereafter first purified on silica gel (3:97 to 6:94 CH_3OH/CH_2Cl_2) and then on a short aluminum oxide column (3:97 to 6:94 CH_3OH/CH_2Cl_2, then 1:5:95 $HCOOH/CH_3OH/CH_2Cl_2$) to afford products **4a**−**m**. Compound **4n** was purified only on silica gel (15:85 EtOAc/*i*-hexane). Compound **4i** was prepared in 79% yield, 90 mg. ^1H NMR (400 MHz, $CD_3OD/CDCl_3$): δ 2.36 (s, 3H), 7.22−7.29 (m, 3H), 7.42 (d, $J = 5.2$ Hz, 1H), 7.92 (apparent d, $J = 8.0$ Hz, 2H), 8.08−8.12 (m, 1H); ^{13}C NMR (100 MHz, $CD_3OD/CDCl_3$): δ 21.6, 126.7, 127.3, 128.4, 129.6, 132.0, 135.0, 136.4, 144.9, 161.2; ESI$^+$-MS (*m*/*z*, relative intensity) 282 ($[M + H]^+$, 85), 563 ($[2M + H]^+$, 100); Anal. Calcd for $C_{12}H_{11}NO_3S_2$: C, 51.23; H, 3.94; N, 4.98. Found: C, 51.07; H, 3.83; N, 4.83.

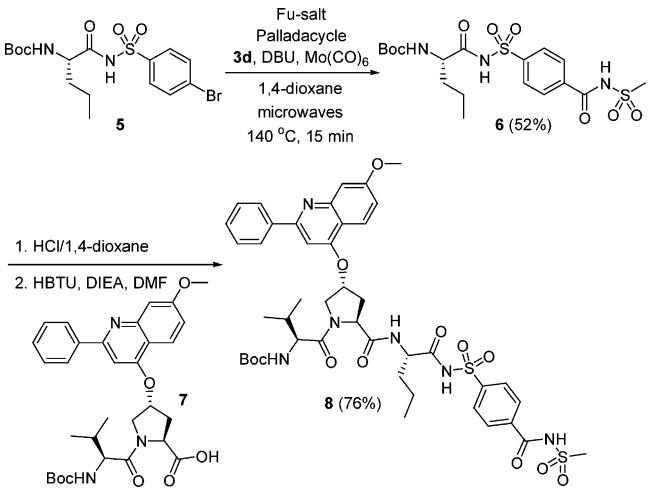
General Procedure for the Amidocarbonylation of Aryl Bromides (Table 2) and the Purification of 4l. A 5-mL process vial was charged with **2** (0.40 mmol), $Mo(CO)_6$ (105 mg, 0.40 mmol), Herrmann's palladacycle (18.8 mg, 0.02 mmol), $[(t\text{-}Bu)_3PH]BF_4$ (11.6 mg, 0.04 mmol), DBU (183 mg, 1.2 mmol), sulfonamide **3** (3.0 equiv), and 1,4-dioxane (1.0 mL). The vessel was sealed under air and exposed to microwave heating for 15 min at 140 °C. The reaction tube was thereafter cooled to room temperature, and the mixture was concentrated

TABLE 2. Microwave-Heated Carbonylation of Aryl Bromides with Primary Sulfonamides Using $Mo(CO)_6$ as the CO Source[a]

Entry	Bromide	Sulfonamide	Product	Isolated yield (%)
1	 **2a**	 **3a**		**4a** 93
2	 **2b**	**3a**		**4o** 94
3	 **2c**	**3a**		**4b** 91
4	 **2d**	**3a**		**4c** 93
5	 **2e**	**3a**		**4d** 95
6	 **2f**	**3a**		**4e** 96
7	 **2g**	**3a**		**4g** 95
8	 **2h**	**3a**		**4p** 83
9	 **2i**	**3a**		**4h** 79
10	**2c**	 **3d**		**4l** 88
11	**2c**	 **3e**		**4m** 80

[a] Reaction conditions: 0.40 mmol aryl bromide, 1.0 equiv $Mo(CO)_6$, 0.05 equiv palladacycle, 0.10 equiv Fu salt, 3.0 equiv DBU, 3.0 equiv sulfonamide, 1.0 mL 1,4-dioxane, single-mode microwave heating at 140 °C for 15 min using sealed vessels.

SCHEME 1. Synthesis of the Hepatitis C Virus NS3 Protease Inhibitor 8



and dissolved in a small volume of dichloromethane. The crude product was thereafter first purified on silica gel (3:97−6:94 CH_3OH/CH_2Cl_2) and then on a short aluminum oxide column (3:97−6:94 CH_3OH/CH_2Cl_2, then 1:5:95 $HCOOH/CH_3OH/CH_2Cl_2$) to afford products **4a**−**e**, **g**, **h**, **l**, **m**, **o**, and **p**. Compound **4l** was prepared in 88% yield, 75 mg. ^1H NMR (400 MHz, $CD_3OD/CDCl_3$): δ 2.33 (s, 3H), 3.29 (s, 3H), 7.19 (apparent d, J = 7.2 Hz, 2H), 7.73 (apparent d, J = 7.2 Hz, 2H); ^{13}C NMR (100 MHz, $CD_3OD/CDCl_3$): δ 21.3, 41.2, 128.1, 128.5, 129.3, 144.2, 166.6; EI$^+$-MS (*m/z*, relative intensity) 213 (M^+, 20); Anal. Calcd for $C_9H_{11}NO_3S$: C, 50.69; H, 5.20; N, 6.57; Found: C, 50.43; H, 5.33; N, 6.64.

[(*S*)-1-(4-Bromo-benzenesulfonylaminocarbonyl)-butyl]-carbamic Acid *tert*-Butyl Ester (5).[22] Prepared according to a method reported previously. ^1H NMR (400 MHz, $CDCl_3$): δ 0.89 (t, J = 7.2 Hz, 3H), 1.24−1.40 (m, 2H), 1.43 (s, 9H), 1.47−1.58 (m, 1H), 1.70−1.79 (m, 1H), 3.97−4.03 (m, 1H), 4.85−4.89 (m, 1H), 7.65−7.68 (m, 2H), 7.91−7.93 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.7, 18.8, 28.3, 32.7, 54.8, 81.7, 129.4, 130.1, 132.4, 137.7, 156.6, 170.4; ESI$^+$-MS (*m/z*, relative intensity) 435, 437 ([M + H]$^+$, 100), 869, 873 ([2M + H]$^+$, 60); Anal. Calcd for $C_{16}H_{23}BrN_2O_5S$: C, 44.14; H, 5.33; N, 6.43; Found: C, 43.99; H, 5.28; N, 6.39.

[(*S*)-1-(4-Methanesulfonylaminocarbonyl-benzenesulfonylaminocarbonyl)-butyl]-carbamic Acid *tert*-Butyl Ester (6). A 5-mL process vial was charged with **5** (81 mg, 0.19 mmol), $Mo(CO)_6$ (49 mg, 0.19 mmol), Herrmann's palladacycle (8.7 mg, 0.0093 mmol), [(t-Bu)$_3$PH]BF_4 (5.3 mg, 0.018 mmol), DBU (83 mg, 0.55 mmol), sulfonamide **3d** (87 mg, 0.91 mmol), and 1,4-dioxane (1.0 mL). The vessel was sealed under air and exposed to microwave heating for 15 min at 140 °C. The crude, cool mixture was diluted with CH_2Cl_2 and CH_3OH, and one

drop of HCOOH was added. The mixture was then evaporated and purified on silica gel (1:99−5:95 CH_3OH/CH_2Cl_2, then 0.1:5:95 $HCOOH/CH_3OH/CH_2Cl_2$) followed by preparative HPLC to give **6** as a white solid (46 mg, 52%). ^{1}H NMR (400 MHz, $CD_3OD/CDCl_3$): δ 0.86 (t, J = 7.2 Hz, 3H), 1.22−1.32 (m, 2H), 1.35 (s, 9H), 1.42−1.52 (m, 1H), 1.53−1.65 (m, 1H), 3.35 (s, 3H), 3.93−3.96 (m, 1H), 8.02−8.04 (m, 2H), 8.08−8.10 (m, 2H); ^{13}C NMR (100 MHz, $CD_3OD/CDCl_3$): δ 13.7, 19.0, 28.4, 34.3, 41.5, 55.2, 80.7, 128.8, 129.3, 137.1, 143.5, 156.6, 166.7, 172.8; ESI$^+$-MS (*m/z*, relative intensity) 478 ($[M + H]^+$, 40), 955 ($[2M + H]^+$, 30); Anal. Calcd for $C_{18}H_{27}N_3O_8S$: C, 45.27; H, 5.70; N, 8.80; Found: C, 45.04; H, 5.55; N, 8.92.

{(*S*)-1-[(2*S*,4*R*)-2-[(*S*)-1-(4-Methanesulfonylaminocarbonyl-benzenesulfonylaminocarbonyl)-butylcarbamoyl]-4-(7-methoxy-2-phenyl-quinoline-4-yloxy)-pyrrolidine-1-carbonyl]-2-methyl-propyl}-carbamic Acid *tert*-Butyl Ester (8). A solution of **6** (15 mg, 0.031 mmol) in 1,4-dioxane (0.2 mL) and HCl in 1,4-dioxane (0.16 mL, 4.0 M) was stirred at room temperature for 2 days before evaporation. The remaining white solid was thereafter dissolved in DMF (0.5 mL) and **7**[22] (12 mg, 0.021 mmol), and then *O*-(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HBTU) (9.5 mg, 0.025 mmol) and *N*,*N*′-diisopropylethylamine (DIEA) (24 μL, 0.14 mmol) were added. The mixture was stirred for 3 h at room temperature, diluted with EtOAc, and washed with aqueous citric acid and brine. The organic layer was dried ($MgSO_4$), filtered, and evaporated. Purification by preparative HPLC gave **8** (15 mg, 76%) as a white solid. ^{1}H NMR (400 MHz, CD_3OD): δ 0.91 (dd, J = 7.3, 7.4 Hz, 3H), 0.96 (d, J = 6.7 Hz, 3H), 1.01 (d, J = 6.7 Hz, 3H), 1.17 (s, 9H), 1.28−1.44 (m, 2H), 1.52−1.71 (m, 2H), 1.93 (dm, J = 8.8 Hz, 1H), 2.03 (ddd, J = 4.3, 9.4, 14.1 Hz, 1H), 2.59 (ddm, J = 7.5, 14.1 Hz, 1H), 3.20 (s, 3H), 3.96 (d, J = 8.8 Hz, 1H), 3.99 (s, 3H), 3.99−4.02 (m, 1H), 4.19 (dd, J = 5.7, 8.6 Hz, 1H), 4.62−4.65 (m, 1H), 4.64 (dd, J = 7.5, 9.4 Hz, 1H), 5.57−5.59 (m, 1H), 7.25 (dd, J = 2.6, 9.2 Hz, 1H), 7.44 (d, J = 2.6 Hz, 1H), 7.45 (s, 1H), 7.64−7.67 (m, 3H), 7.95−8.09 (m, 6H), 8.21 (d, J = 9.2 Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD): δ 14.0, 19.2, 19.6, 19.9, 28.5, 31.7, 34.5, 36.1, 41.1, 54.3, 55.5, 56.6, 59.5, 59.8, 80.0, 80.1, 101.7, 103.0, 116.2, 120.8, 125.7, 129.2, 129.73, 129.74, 130.4, 132.6, 136.3, 141.0, 143.9, 146.7, 157.9, 159.3, 165.2, 165.7, 170.7, 173.2, 174.1, 174.6; ESI$^+$-MS (*m/z*, relative intensity) 923 ($[M + H]^+$, 100); Anal. Calcd for $C_{44}H_{54}N_6O_{12}S_2 \cdot 1/2H_2O$: C, 56.70; H, 5.95; N, 9.02; Found: C, 56.80; H, 5.73; N, 8.94.

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Supporting Information Available: Experimental procedures and spectral data for all of the new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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