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Enantio- and Diastereoselective Synthesis of *cis*-2-Aryl-3-methoxycarbonyl-2,3-dihydrobenzofurans via the Rh(II)-Catalyzed C–H Insertion Process

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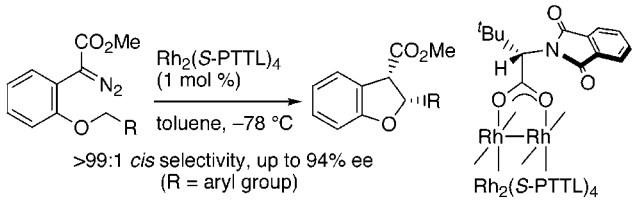
ABSTRACT



The enantioselective intramolecular C–H insertion reaction of aryldiazoacetates has been explored with use of dirhodium(II) carboxylate catalysts, which incorporate *N*-phthaloyl- or *N*-benzene-fused-phthaloyl-(*S*)-amino acids as chiral bridging ligands. Dirhodium tetrakis[*N*-phthaloyl-(*S*)-*tert*-leucinate], Rh_2(*S*-PTTL)$_4$, has proven to be the catalyst of choice for this process, providing exclusively *cis*-2-aryl-3-methoxycarbonyl-2,3-dihydobenzofurans in up to 94% ee.

Chiral dirhodium(II) carboxamidate and carboxylate catalysts offer a potentially powerful strategy for synthesizing optically active carbocyclic and heterocyclic rings. The dirhodium catalyst forms C−C bonds with a newly created stereogenic center at an unactivated carbon atom by the enantioselective intramolecular C−H insertion reactions of α-diazocarbonyl compounds.[1] Davies and co-workers recently developed a major breakthrough in this field when they achieved intermolecular C−H insertion reactions with high enantioselectivity.[2] It is well-documented that the enantioselectivity of C−H insertion reactions depends on many factors including the type of α-diazocarbonyl compound, the substitution pattern at the C−H insertion site, the polarity of the solvent, and the nature of chiral dirhodium(II) catalysts.[1]

(1) For recent books and reviews, see: (a) Ye, T.; McKervey, M. A. *Chem. Rev.* **1994**, *94*, 1091. (b) Doyle, M. P. *Aldrichimica Acta* **1996**, *29*, 3. (c) Hashimoto, S.; Watanabe, N.; Anada, M.; Ikegami, S. *J. Synth. Org. Chem. Jpn. (Engl.)* **1996**, *54*, 988. (d) Davies, H. M. L. *Aldrichimica Acta* **1997**, *30*, 107. (e) Davies, H. M. L. *Curr. Org. Chem.* **1998**, *2*, 463. (f) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; Wiley-Interscience: New York, 1998. (g) Doyle, M. P.; Forbes, D. C. *Chem. Rev.* **1998**, *98*, 911. (h) Sulikowski, G. A.; Cha, K. L.; Sulikowski, M. M. *Tetrahedron: Asymmetry* **1998**, *9*, 3145. (i) Lydon, K. M.; McKervey, M. A. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, Germany, 1999; Vol. 2, Chapter 16.2. (j) Doyle, M. P. In *Catalytic Asymmetric Synthesis*; Ojima, I., Ed.; Wiley-VCH: New York, 2000; Chapter 5. (k) Timmons, D. J.; Doyle, M. P. *J. Organomet. Chem.* **2001**, *617*, 98. (l) Forbes, D. C.; McMills, M. C. *Curr. Org. Chem.* **2001**, *5*, 1091.

(2) (a) Davies, H. M. L.; Hansen, T. *J. Am. Chem. Soc.* **1997**, *119*, 9075. (b) Davies, H. M. L. *Eur. J. Org. Chem.* **1999**, 2459. (c) Davies, H. M. L.; Hansen, T.; Churchill, M. R. *J. Am. Chem. Soc.* **2000**, *122*, 3063. (d) Davies, H. M. L.; Antoulinakis, E. G. *Org. Lett.* **2000**, *2*, 4153. (e) Davies, H. M. L.; Ren, P.; Jin, Q. *Org. Lett.* **2001**, *3*, 3587. (f) Davies, H. M. L.; Antoulinakis, E. G. *J. Organomet. Chem.* **2001**, *617*, 47. (g) Davies, H. M. L.; Venkataramani, C. *Angew. Chem., Int. Ed.* **2002**, *41*, 2197. (h) Davies, H. M. L.; Jin, Q.; Ren, P.; Kovalevsky, A. Y. *J. Org. Chem.* **2002**, *67*, 4165. (i) Davies, H. M. L.; Gregg, T. M. *Tetrahedron Lett.* **2002**, *43*, 4951. (j) Davies, H. M. L.; Walji, A. M.; Townsend, R. J. *Tetrahedron Lett.* **2002**, *43*, 4981.

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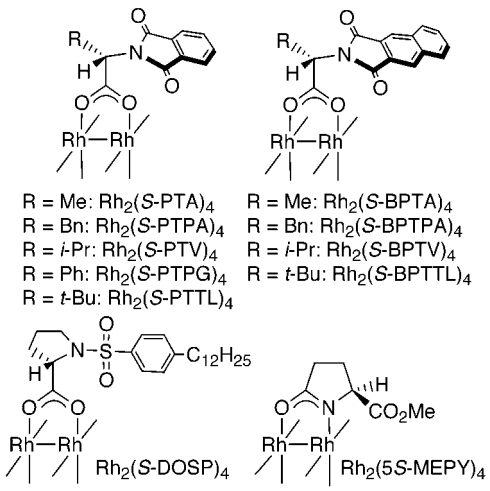
For example, the salient ability of Doyle's chiral dirhodium(II) carboxamidate catalysts such as Rh_2(5*S*-MEPY)$_4$, Rh_2(4*S*-MEOX)$_4$, and Rh_2(4*S*-MPPIM)$_4$ is characteristic of intramolecular reactions with diazoacetates and diazoacetamides, but not with diazo ketones or diazo ketoesters.[1,3] Davies and co-workers have demonstrated that combining Rh_2(*S*-DOSP)$_4$ as a catalyst and aryl- or arylvinyldiazoacetates as a carbene precursor in a hydrocarbon solvent is crucial for highly enantioselective intermolecular C−H insertion reactions.[2] In recent years we have developed dirhodium(II) carboxylate catalysts, which incorporate *N*-phthaloyl- or *N*-benzene-fused-phthaloyl-(*S*)-amino acids as bridging ligands.[1c,4] These catalysts mediate intramolecular C−H insertion reactions of diazo ketoesters, diazo ketones, or α-methoxycarbonyldiazoacetamides site-selectively to give optically active cyclopentanone,[5] 2-indanone,[6] 2-azetidinone,[7] and 2-pyrrolidinone[8] derivatives with a maximum of 80%, 98%, 96%, and 90% ee, respectively.



Recently, we found that insertion reactions of methyl phenyldiazoacetate into the Si−H bond of silanes under the influence of Rh_2(*S*-PTPA)$_4$ proceeded smoothly even at −90 °C to give enantioselectivities up to 74% ee.[9] On the basis of this result and the general finding that the insertion reaction into a C−H bond is activated by an adjacent ether oxygen,[10] we envisaged that an intramolecular C−H insertion of aryldiazoacetates with an arylmethoxy group at the ortho position should produce a dihydrobenzofuran neolignan system with high levels of enantioselection. Using this process, we now report that dirhodium tetrakis[*N*-phthaloyl-(*S*)-*tert*-leucinate], Rh_2(*S*-PTTL)$_4$, provides *cis*-2-aryl-3-methoxycarbonyl-2,3-dihydrobenzofurans as the sole product in up to 94% ee.[11]

In our initial studies, we explored the intramolecular C−H insertion of methyl 2-(2-benzyloxyphenyl)-2-diazoacetate (**1a**) in toluene using 1 mol % of Rh_2(*S*-PTPA)$_4$ (Table 1, entry 1). As expected, the reaction proceeded smoothly at −60 °C to completion within 0.5 h, giving 2-phenyl-3-methoxycarbonyl-2,3-dihydobenzofurans **2a** and **3a** in a 70:30 ratio of *cis* to *trans* isomers and 86% combined yield. The enantioselectivities in this reaction were 70% ee and 80% ee, respectively, as determined from HPLC (Daicel Chiralcel OD-H for the *cis* isomer and Daicel Chiralcel OJ-H for the *trans* isomer). The preferred absolute stereochemistry of the *trans* isomer **3a** [$[\alpha]^{21}_D$ −58.2 (*c* 1.12, $CHCl_3$) for 80% ee] was (2*R*,3*R*), which was established by comparing the sign of the optical rotation with the literature value [lit.[12] $[\alpha]_D^{21}$ +32.0 (*c* 0.3, $CHCl_3$) for 50% ee of (2*S*, 3*S*)-**3a**]. The major *cis* isomer **2a** [$[\alpha]^{21}_D$ +57.9 (*c* 1.00, $CHCl_3$) for 70% ee] was quantitatively epimerized with a catalytic amount of sodium methoxides in THF to the thermodynamically more stable *trans* isomer **3a** [$[\alpha]^{22}_D$ −54.4 (*c* 0.83, $CHCl_3$) for 70% ee], which determined that (2*R*,3*S*) was the preferred absolute configuration of **2a**. While the stereochemical course of the reaction cannot be rationalized at present,[13] it is worth noting that similar levels of asymmetric induction with the same sense at the insertion site (C2) and the opposite sense at C3 were observed with *cis* and *trans* isomers.[14] To further enhance the enantio- and diastereoselectivity, we evaluated the abilities of two classes of dirhodium(II) carboxylate catalysts, which incorporate *N*-phthaloyl- or *N*-benzene-fused-phthaloyl-(*S*)-amino acids as bridging ligands. While a uniform sense of asymmetric induction was observed in all cases, the enantio- and diastereoselectivities were highly dependent on the catalyst. Clearly, the best catalysts were Rh_2(*S*-PTTL)$_4$ and Rh_2(*S*-BPTTL)$_4$, which are characterized by a bulky *tert*-butyl group, as they provided the thermo-

(3) (a) Doyle, M. P.; Tedrow, J. S.; Dyatkin, A. B.; Spaans, C. J.; Ene, D. G. *J. Org. Chem.* **1999**, *64*, 8907. (b) Doyle, M. P.; Hu, W. *J. Org. Chem* **2000**, *65*, 8839. (c) Doyle, M. P.; Yan, M.; Phillips, I. M.; Timmons, D. J. *Adv. Synth. Catal.* **2002**, *344*, 91. (d) Doyle, M. P.; Hu, W. *Chirality* **2002**, *14*, 169. (e) Doyle, M. P.; Hu, W.; Valenzuela, M. V. *J. Org. Chem.* **2002**, *67*, 2954.

(4) Kitagaki, S.; Anada, M.; Kataoka, O.; Matsuno, K.; Umeda, C.; Watanabe, N.; Hashimoto, S. *J. Am. Chem. Soc.* **1999**, *121*, 1417.

(5) (a) Hashimoto, S.; Watanabe, N.; Sato, T.; Shiro, M.; Ikegami, S. *Tetrahedron Lett.* **1993**, *34*, 5109. (b) Hashimoto, S.; Watanabe, N.; Ikegami, S. *Synlett* **1994**, 353.

(6) (a) Watanabe, N.; Ohtake, Y.; Hashimoto, S.; Shiro, M.; Ikegami, S. *Tetrahedron Lett*. **1995**, *36*, 1491. (b) Watanabe, N.; Ogawa, T.; Ohtake, Y.; Ikegami, S.; Hashimoto, S. *Synlett* **1996**, 85. (c) Takahashi, T.; Tsutsui, H.; Tamura, M.; Kitagaki, S.; Nakajima, M.; Hashimoto, S. *Chem. Commun.* **2001**, 1604.

(7) (a) Watanabe, N.; Anada, M.; Hashimoto, S.; Ikegami, S. *Synlett* **1994**, 1031. (b) Anada, M.; Watanabe, N.; Hashimoto, S. *Chem. Commun.* **1998**, 1517.

(8) (a) Anada, M.; Hashimoto, S. *Tetrahedron Lett.* **1998**, *39*, 79. (b) Anada, M.; Mita, O.; Watanabe, H.; Kitagaki, S.; Hashimoto, S. *Synlett* **1999**, 1775.

(9) Kitagaki, S.; Kinoshita, M.; Takeba, M.; Anada, M.; Hashimoto, S. *Tetrahedron: Asymmetry* **2000**, *11*, 3855.

(10) (a) Adams, J.; Poupart, M.-A.; Grenier, L.; Schaller, C.; Ouimet, N.; Frenette, R. *Tetrahedron Lett.* **1989**, *30*, 1749. (b) Wang, P.; Adams, J. *J. Am. Chem. Soc.* **1994**, *116*, 3296.

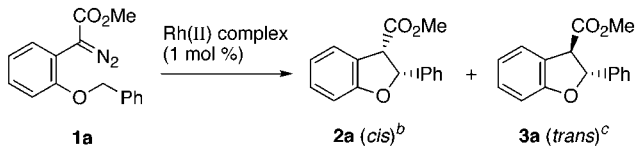
(11) During the course of our studies, Davies and co-workers reported Rh_2(*S*-DOSP)$_4$-catalyzed C−H insertion in a related system, where reactions in hexanes at −50 °C took 72 h for completion. In their work, the enantioselectivity up to 94% ee was obtained for insertion into methine C−H bonds, whereas C−H insertion into a methylene group produced a mixture of *cis*- and *trans*-dihydrobenzofurans with up to 63% ee of the *cis* isomer. See: Davies, H. M. L.; Grazini, M. V. A.; Aouad, E. *Org. Lett.* **2001**, *3*, 1475.

(12) Luhász, L.; Szilágyi, L.; Antus, S.; Visy, J.; Zsila, F.; Simonyi, M. *Tetrahedron* **2002**, *58*, 4261.

(13) Very recently, Nakamura and co-workers have reported a mechanism of dirhodium(II) tetracarboxylate-catalyzed C−H insertion reactions based on a detailed computational analysis. See: Nakamura, E.; Yoshikai, N.; Yamanaka, M. *J. Am. Chem. Soc.* **2002**, *124*, 7181.

(14) We confirmed that *cis* isomer **2a** did not isomerize to *trans* isomer **3a** under the C−H insertion reaction conditions [1 mol % of Rh_2(*S*-PTPA)$_4$, toluene, −78 °C or room temperature].

Table 1. Enantioselective C−H Insertion Reaction of α-Phenyldiazoacetate **1a** Catalyzed by Chiral Rh(II) Complexes[a]



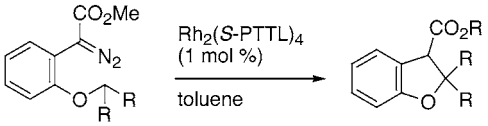
1a **2a** (*cis*)[b] **3a** (*trans*)[c]

entry	Rh(II) catalyst	solvent	temp, °C	time, h	yield, %[d]	**2a**:**3a**[e]	% ee **2a**[f]	% ee **3a**[g]
1	Rh_2(*S*-PTPA)$_4$	toluene	−60	0.5	86	70:30	70	80
2	Rh_2(*S*-PTA)$_4$	toluene	−60	0.5	84	81:19	61	79
3	Rh_2(*S*-PTV)$_4$	toluene	−60	0.5	86	89:11	61	69
4	Rh_2(*S*-PTPG)$_4$	toluene	−60	0.5	83	99:1	71	
5	Rh_2(*S*-PTTL)$_4$	toluene	−60	0.5	87	>99:1	90	
6	Rh_2(*S*-BPTPA)$_4$	toluene	−60	1	57	68:32	65	77
7	Rh_2(*S*-BPTA)$_4$	toluene	−60	1	69	82:18	63	80
8	Rh_2(*S*-BPTV)$_4$	toluene	−60	0.5	73	89:11	61	57
9	Rh_2(*S*-BPTTL)$_4$	toluene	−60	0.5	84	>99:1	86	
10	Rh_2(*S*-PTTL)$_4$	CH_2Cl_2	−45[h]	0.5	63	>99:1	90	
11	Rh_2(*S*-PTTL)$_4$	Et_2O	−10[h]	0.5	78	>99:1	88	
12	Rh_2(*S*-PTTL)$_4$	hexane	23[h]	0.2	78	>99:1	70	
13	Rh_2(*S*-PTTL)$_4$	toluene	−78	1	86	>99:1	94	
14	Rh_2(*S*-BPTTL)$_4$	toluene	−78	12	70	>99:1	91	

[a] Typical procedure for the C−H insertion reaction (entry 1): Rh_2(*S*-PTPA)$_4$ (7.0×10^{-3} M in toluene, 0.5 mL, 0.0035 mmol) was added to a solution of **1a** (100 mg, 0.35 mmol) in toluene (3.0 mL) at −60 °C. After 0.5 h, the mixture was concentrated and the residue was purified by column chromatography (silica gel, hexane/EtOAc = 20:1). [b] Absolute stereochemistry of **2a** was determined to be (2*R*,3*S*) by chemical correlation with **3a**. See the text. [c] Absolute stereochemistry of **3a** was determined to be (2*R*,3*R*) by specific rotation. See the text. [d] Combined yield of **2a** and **3a**. [e] Determined by ^{1}H NMR analysis. [f] Determined by HPLC (Daicel Chiralcel OD-H). [g] Determined by HPLC (Daicel Chiralcel OJ-H). [h] The temperature limit allowing for smooth cyclization. Below this temperature the reaction in this solvent markedly reduced a product yield as azine formation increased.

dynamically less stable *cis* isomer **2a** as the sole product in high yields with 90% ee and 86% ee, respectively (entries 5 and 9). The other catalysts afforded a mixture of *cis* and *trans* isomers **2a** and **3a** with reasonable degrees of enantioselectivity. It is worth noting that the substituents of the amino acids more markedly influenced the enantio- and diastereoselectivities than the choice of *N*-phthaloyl- or *N*-benzene-fused-phthaloyl groups in the bridging ligands. The solvent survey with Rh_2(*S*-PTTL)$_4$ revealed that toluene was the optimal solvent for this transformation in terms of both product yield and enantiocontrol, though little effect of solvents on diastereoselectivity was observed (entries 5 vs 10−12). Although dichloromethane and ether exhibited nearly the same enantioselectivities as toluene, −45 or −10 °C was found to be the temperature limit for allowing smooth cyclization. Below these temperatures product yields substantially reduced as azine formation increased. The use of hexane, which is highly beneficial for Rh_2(*S*-DOSP)$_4$, was also found to be less effective. Thus we were gratified to find that the enantioselectivity was further enhanced up to 94% ee using toluene and Rh_2(*S*-PTTL)$_4$ by lowering the temperature to −78 °C without affecting the reaction rate much (entry 13). However, catalysis with Rh_2(*S*-BPTTL)$_4$ under the same condition required significantly longer time to reach completion and produced 91% ee (entry 14).

Having identified the effectiveness of the combinational use of Rh_2(*S*-PTTL)$_4$ as the catalyst and toluene as the solvent, we then investigated the scope of this process with respect to the substituents at the insertion site. Aside from virtually exclusive *cis* selectivity, a high enantioselectivity (up to 94% ee) was maintained with either electron-donating or electron-withdrawing groups at the *para* position on the benzene ring (Table 2, entries 1−4). The result obtained with the 3,4-(TBSO)$_2$C$_6$H$_3$ group is particularly noteworthy (entry 5), because product **2e** contains a structural motif found in a dihydrobenzofuran-type neolignan blechnic acid.[15] The present protocol also allowed for substituents other than aryl groups at the insertion site, though a slight decrease or a dramatic reversal in the diastereoselectivity was observed (entries 6−8). To our disappointment, Rh_2(*S*-PTTL)$_4$-catalyzed insertion into a methine C−H bond or a methyl group resulted in 22% ee and 44% ee, respectively (eq 1).[11]



(1)

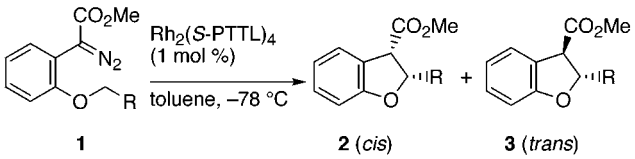
1i (R = Me) −78 °C, 1.5 h (R = Me) **4** (R = Me) 88%, 22% ee
1j (R = H) −23 °C, 1.0 h (R = H) **5** (R = H) 69%, 44% ee

Finally, the Rh_2(*S*-PTTL)$_4$-catalyzed cyclizations of a methylene analogue **6** and an aliphatic substrate **8** were

(15) (a) Wada, H.; Kido, T.; Tanaka, N.; Murakami, T.; Saiki, Y.; Chen, C.-M. *Chem. Pharm. Bull.* **1992**, *40*, 2099. (b) Wang, C.-Z.; Davin, L. B.; Lewis, N. G. *Chem. Commun.* **2001**, 113.

(16) Baker, R.; Cooke, N. G.; Humphrey, G. R.; Wright, S. H. B.; Hirshfield, J. *J. Chem. Soc., Chem. Commun.* **1987**, 1102.

Table 2. Enantioselective Synthesis of Dihydrobenzofurans via C−H Insertion Reaction Catalyzed by Rh_2(*S*-PTTL)$_4$

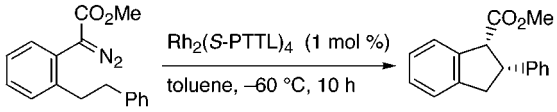


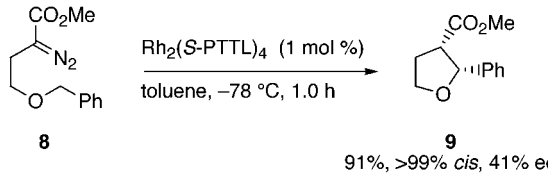
entry	substrate no.	R	time, h	yield, %[a]	2:3[b]	% ee 2	% ee 3
1	**1a**	C_6H_5	1	86	>99:1	94[c]	
2	**1b**	4-ClC_6H_4	1.5	79	>99:1	94[d,e]	
3	**1c**	4-MeC_6H_4	1.5	84	>99:1	91[c,e]	
4	**1d**	4-$MeOC_6H_4$	1	89	>99:1	94[c,f]	
5	**1e**	3,4-$(TBSO)_2C_6H_3$	2	85	99:1	91[d,e]	
6[g]	**1f**	CH_2=CH	2	62	77:23	86[e,h]	92[c,e]
7	**1g**	$^cC_6H_{11}$	7	63	96:4	96[e,h]	
8	**1h**	Me	0.5	91	14:86	78[e,h]	97[c,e]

[a] Combined yield of **2** and **3**. [b] Determined by ^{1}H NMR analysis. [c] Determined by HPLC (Daicel Chiralcel OD-H). [d] Determined by HPLC (Daicel Chiralcel AD-H). [e] Absolute stereochemistry of the product was not determined. [f] Absolute stereochemistry of **2d** was determined to be (2*R*,3*S*) by chemical correlation with the known compound.[16] See the Supporting Information. [g] This reaction was carried out at −23 °C. [h] Determined by HPLC (Daicel Chiralcel OJ-H).

examined (eqs 2 and 3). While virtually exclusive *cis* selectivities were observed in both cases, only modest enantioselectivities were obtained. These results suggest that the presence of both a phenyl ring and an oxygen atom adjacent to the target C−H bond is responsible for the high enantioselectivity.

In summary, we have developed a highly efficient method for the catalytic enantio- and diastereoselective synthesis of *cis*-2-aryl-3-methoxycarbonyl-2,3-dihydrobenzofurans, which are otherwise difficult to prepare. The combination of Rh_2(*S*-PTTL)$_4$ as the catalyst and toluene as the solvent is crucial for the present methylene C−H insertion process to be successful. It is also noteworthy that Rh_2(*S*-PTTL)$_4$ and Rh_2(*S*-DOSP)$_4$ can complement each other in the enantioselective intramolecular C−H insertion reactions of this type of aryldiazoacetates.[11] Mechanistic and stereochemical studies are currently underway, as well as applications of this method to the catalytic asymmetric synthesis of pharmacologically active neolignans containing a dihydrobenzofuran skeleton.





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

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