Stereoelectronic Control

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Regiospecific Reductive Elimination from Diaryliodonium Salts**

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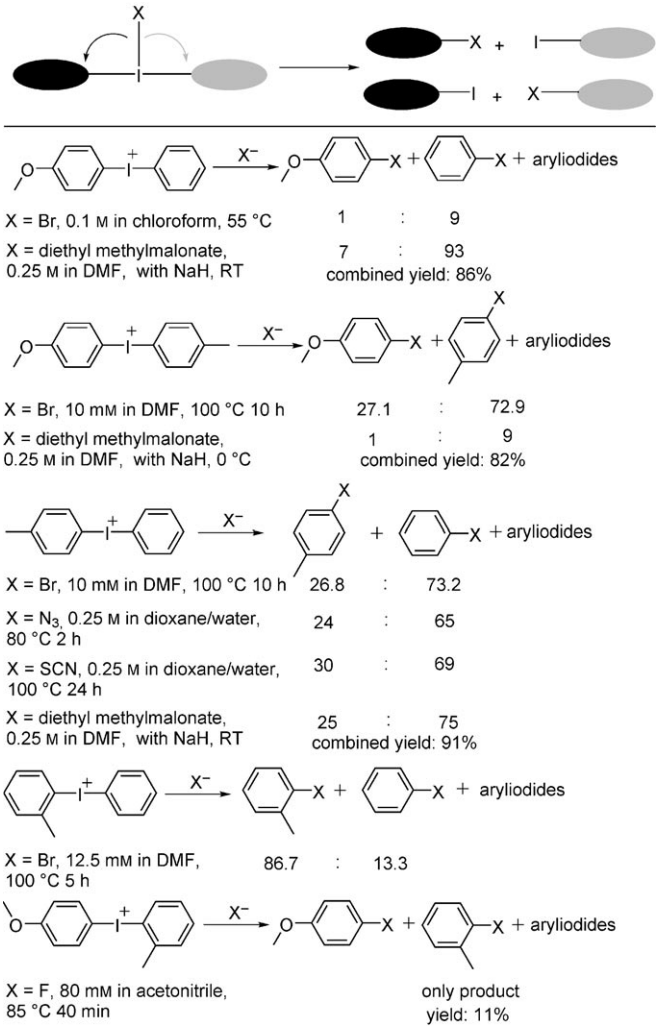
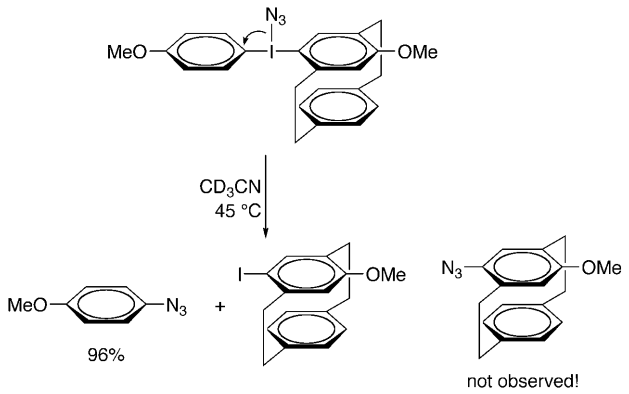
Diaryliodonium salts are useful precursors for arylation of diverse carbon and heteroatom nucleophiles.[1–4] In practice, poor regioselectivity for the reductive elimination narrows the synthetic scope of these salts (Scheme 1). Efficient conversion is best obtained when two identical aryl substituents are on I^{III}; however, the preparation of symmetrical diaryliodonium salts can be problematic and uneconomical.[11] For relatively complex aromatic molecules, the tandem synthesis and protection of the oxidized (I^{III}) and reduced (organometallic) coupling partners, necessary for the preparation of the symmetrical diaryliodonium salt, is often a significant challenge, and purification of the functionalized product from the reductively eliminated aryl iodide can prove difficult.



Scheme 1. Examples of regioselectivities obtained in thermal decomposition reactions of unsymmetrical diaryliodonium salts.[5–10]

In the thermal decomposition of unsymmetrical diaryliodonium salts, the identity of the reductively eliminated aryl iodide is typically dictated by electronic effects; the electron-rich aryl iodide and the functionalized electron-poor aromatic compound are formed predominantly (Scheme 1). Selectively functionalized electron-rich aromatic rings are often the desired target compounds, but extremely electron-rich diaryliodonium salts are prone to side-reactions involving redox and inner-sphere electron transfer; thus, there is a limit to using electronic control to achieve regioselectivity.

We sought a universal "locked" aryl substituent that would result in stereoelectronic control of unidirectional reductive elimination (SECURE) from diaryliodonium salts. As electronic effects cannot be used exclusively to achieve this end, steric and/or stereoelectronic effects must be exploited to gain regiocontrol of the reductive elimination. Herein, we show that the use of cyclophane-derived iodonium salts permits regiospecific reductive elimination (Scheme 2).



Scheme 2. Regiochemically controlled reductive elimination of an electron-rich, cyclophane-derived diaryliodonium salt.

The impact of steric effects upon reductive elimination in diaryliodonium salts has been investigated in some detail. Aryl methyl substituents *ortho* to the I^{III} center offer a modest acceleration in elimination rates, so that there is a slight preference for the more-highly substituted product to be functionalized (Scheme 1).[7,12] Two potential origins of this

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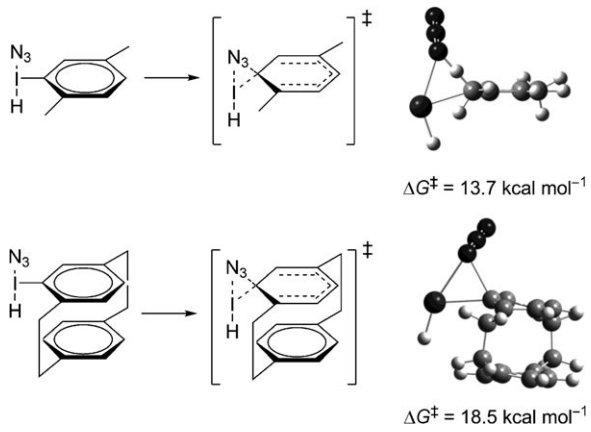
"*ortho* effect" are: 1) that the more-sterically demanding aromatic ring prefers an equatorial position *syn* to the nucleophile, or 2) that the *ortho*-substituted aromatic ring is more likely to prefer a conformation in which the π-system aligns with the incoming nucleophile.[13–15] In an exception to this rule, Ochiai and co-workers have shown that for binaphthyl aryl iodonium salts, *ortho* substitution coupled with sterically demanding enolate nucleophiles results in alkylation of the less-hindered ring, though only a small number of electronically similar aryl rings were investigated.[16] Selective functionalization of the more-electron-rich aromatic ring in an unsymmetrical diaryliodonium salt remains an unsolved problem.

Our approach was to design an aryl ligand on the iodine center that would generate a highly strained reductive-elimination transition state. If the mechanistic assumption of a concerted reductive elimination process is adopted, selective destabilization of this transition state requires significant steric congestion above and/or below the aromatic ring and little steric congestion in the plane of the ring. Thus, "strapped" or "capped" aromatic compounds were the initial leads for investigating this SECURE methodology. [2.2]Paracyclophane[17,18] is a particularly attractive potential iodine(III) ligand because of its commercial availability, its efficient and established functionalization chemistry,[19] its severe out-of-plane steric congestion, and the potential to exploit the planar chiral ligand in stereoselective reactions.[20] However, compounds in which an I^{III} center is bonded directly to [2.2]paracyclophane have not been reported to date.

The results of an initial computational study (B3LYP/DGDZVP, ZPE-corrected) are shown in Scheme 3. We selected azide transfer in diaryliodonium salts for our test reaction because diaryliodonium azides are known to undergo reductive elimination at or near room temperature,[9,21] and because the small azide nucleophile has a relatively modest steric demand. Ground and transition state energies were calculated for a highly simplified model of azide substitution, loss of HI from the HIN_3Ar complexes of *para*-xylene and [2.2]paracyclophane. Inspection of Scheme 3 shows that movement from the ground state geometry to the transition state geometry for azide substitution is accompanied by *ipso* carbon rehybridization and deflection of the HI group out of the plane. For the xylyl derivative, the C4–C1–I angle is 161.9°. However, in the [2.2]paracyclophan-4-yl transition state structure, the significant steric demand of the second ring in the planar chiral ligand inhibits out-of-plane movement of the iodine atom (C4–C1–I angle is 167.2°). This structural difference is associated with an energetic penalty; the calculated Gibbs energy of activation for reductive elimination of HI from the *para*-xylene salt is 13.7 kcal mol^{-1}, and the barrier for the cyclophane derivative is 4.8 kcal mol^{-1} higher. Armed with an "in silico" justification for the SECURE concept, we sought its empirical validation.



Scheme 3. Calculated transition state (TS) structures and activation barriers for 2,5-dimethylphenyl and [2.2]paracyclophan-4-yl iodonium salts.

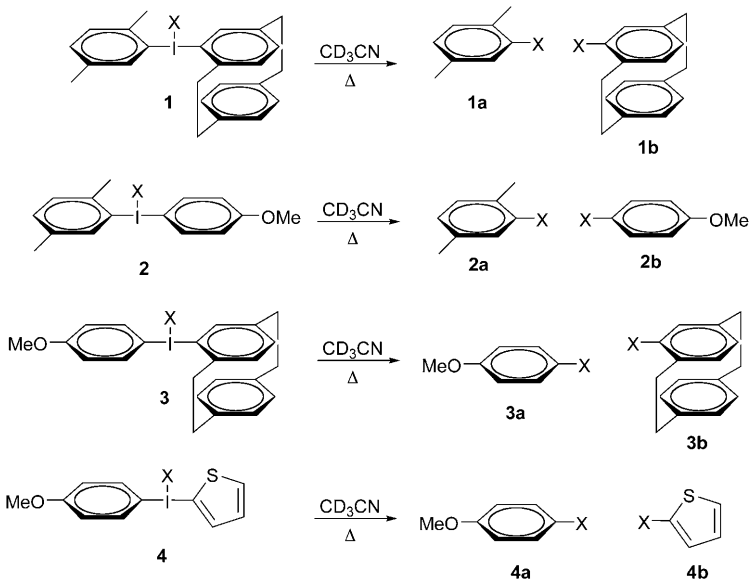
To compare the directing effects of the electronically similar *para*-xylyl and [2.2]parcyclophan-4-yl groups experimentally, we synthesized the appropriate unsymmetrical diaryliodonium salts **1**. 4-Bromo-[2.2]paracyclophane[19,22] was lithiated (*t*BuLi, Et_2O, −78 °C) and transmetalated with anhydrous zinc chloride. Following removal of the ether solvent, the organozinc chloride reagent was treated with 2,5-dimethyl(diacetoxyiodo)benzene in acetonitrile at −40 °C. After isolation and ion exchange to the hexafluorophosphate salt, compound **1** ($X = PF_6$) was formed in 18% yield. Although organolithium,[23,24] organoboron,[25] organosilicon,[26] and organotin[27] compounds have been used for the synthesis of diaryliodonium salts, to our knowledge this is the first example of the preparation of a diaryliodonium salt from an aryl zinc chloride. The unusual reaction conditions were required because 4-trialkylstannyl[2.2]paracyclophanes do not transfer the cyclophane moiety cleanly in transmetalation reactions.[28] A likely explanation for the poor reactivity of the stannane is that the transition state for cyclophane transfer is highly congested and resembles that shown in Scheme 3.

The hexafluorophosphate salt of **1** is particularly convenient because a wide range of nucleophiles may be introduced using their tetraalkylammonium or sodium salts. Accordingly, when compound **1**, $X = PF_6$, was treated with $TBAN_3$ (TBA: tetrabutylammonium) and heated at 45 °C in CD_3CN (0.04 M), conversion of the diaryliodonium azide was complete within a few hours (Scheme 4). In support of the initial hypothesis, the azidoxylene is formed exclusively in excellent yield, and no azidocyclophane is observed at the detection limit of ^1H NMR spectroscopy. This unidirectional elimination is also observed with thiocyanate, phenoxide, thiophenoxide, trifluoroethoxide, and acetate (Table 1). The observed selectivity (> 99:1)

Table 1: Yields[a] of reductive elimination products from the I^{III} salts shown in Scheme 4.

X	1		2		3		4	
	1a	1b	2a	2b	3a	3b	4a	4b
N_3	> 99	0	> 99	0	86	14	66	0[b]
OAc	85	0	> 99	0	68	31	18	0[b]
OPh	87	0	96	4	51	40	69	23
OCH_2CF_3	82	0	80	0	19	39	17	43
SCN	> 99	0	> 99	0	81	18	43	0[b]
SPh	98	0	95	5	43	52	30	40

[a] All yields were determined by ^1H NMR spectroscopy and confirmed by GC-MS. [b] Decomposition of the functionalized thiophene was observed.



Scheme 4. Functionalization of diaryliodonium salts. (Reductively eliminated aryl iodides are omitted for clarity.)

corresponds to a difference in the Gibbs energies of activation ($\Delta\Delta G^{\ddagger}$) of at least 2.8 kcal mol^{-1}. Thus, the validity of the computational model is confirmed.

To provide context for the SECURE results, arene functionalization by various nucleophiles X in the 4-methoxyphenyl-substituted compound **2** was investigated and revealed a regioselectivity that mirrors that of the cyclophanyl-substituted diaryliodonium salt **1** (Table 1). The 4-methoxyphenyl moiety is the most effective commonly employed directing group in diaryliodonium chemistry,[10,29,30] however perfect regioselectivity for arene functionalization is not observed with this directing group: for the redox-active thiophenoxide and phenoxide nucleophiles, some loss of regiocontrol is evident and functionalized anisoles are formed.

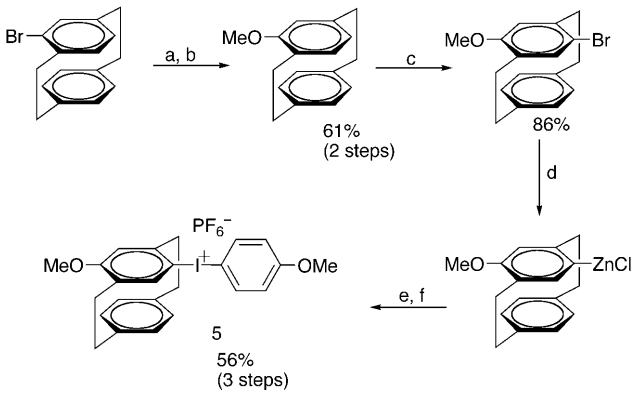
To test the relative directing-group abilities of 4-methoxyphenyl and [2.2]paracyclophan-4-yl substituents, we prepared the unsymmetrical I^{III} derivative **3** from 4-methoxy(diacetoxyiodo)benzene (38% yield) and examined its thermal decomposition chemistry. More vigorous reaction conditions (80 °C, CD_3CN) were necessary to promote speedy carbon–heteroatom bond formation with acetate and thiocyanate from **3** in comparison to **1** or **2**. As can be seen from inspection of Table 1, the directing-group ability of the [2.2]paracyclophanyl ligand is comparable or slightly superior to that of the 4-methoxyphenyl substituent on I^{III}.

The 2-thienyl substituent has been reported to deliver high regioselectivities for the radiofluorination of various electron-rich arenes.[31] We synthesized **4** to examine the relative directing-group abilities of the 2-thienyl and 4-methoxyphenyl substituents under stoichiometric conditions. Inspection of the data in Table 1 indicates that, for the nucleophiles examined here, the directing-group ability of the 2-thienyl moiety is roughly comparable to that of the 4-methoxyphenyl and the [2.2]paracyclophanyl ligands on I^{III}. In all cases, significant amounts of the 4-iodoanisole were generated during the thermal decomposition reactions of **4**, even when 2-functionalized thiophenes are not observed. These data support the assessment of Carroll et al.[32] and the original observations by Yamada and Okawara[33] that the directing-group ability of the 2-thienyl and 4-methoxyphenyl substituents are similar.

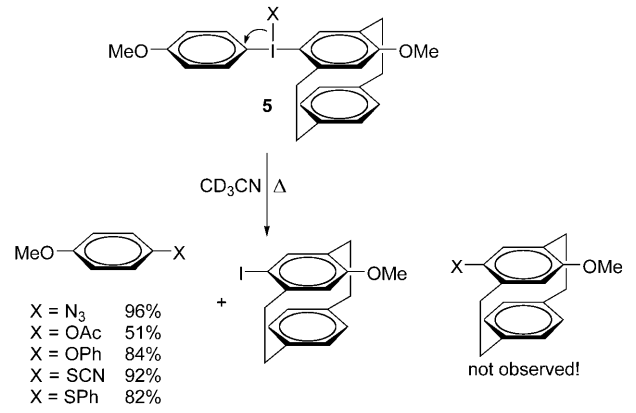
Though the data in Table 1 are limited, it appears that for oxygen or sulfur nucleophiles the directing-group ability of the cyclophane ligand diminishes as nucleophile basicity and the driving force for functionalizing the more electron-poor ring increases. Such a trend is consistent with Hammond's postulate and a concerted, reductive elimination mechanism in which less steric strain is developed at the cyclophane *ipso* carbon atom as the reaction becomes more exergonic.

The kinetics of aryl azide formation from N_3 salts of **1**–**3** were investigated to probe the relative steric and electronic contributions to the observed regioselectivity. The observed rate constants for xylyl azide formation (CD_3CN, 45 °C) were 4.2×10^{-4} s^{-1}, 5.5×10^{-5} s^{-1}, and 3.3×10^{-6} s^{-1}, corresponding to Gibbs energies of activation of 21.7, 22.9, and 24.6 kcal mol^{-1} for the reactions of **1**, **2**, and **3**, respectively. The fact that the rate constant for xylyl azide formation is greater for **1** than for **2** indicates that 4-iodo[2.2]paracyclophane is a significantly better leaving group than 4-iodoanisole. Because leaving-group ability is correlated with the electron density on the iodine atom in the aryl iodide that is being reductively eliminated, these kinetic data show experimentally that the [2.2]paracyclophane ligand is a significantly more electron-poor aryl substituent than the 4-methoxyphenyl ligand and that steric destabilization of the transition state is responsible for the enhanced directing-group ability of the [2.2]paracyclophane ligand.

These initial results validated the SECURE concept, but perfect regiochemical control was still not achievable for functionalizing very electron-rich rings. To address this issue we prepared compound **5**, which features an electron-donating methoxy substituent *para* to the I^{III} center (Scheme 5). The methoxy substituent enhances the solubility of the cyclophanylzinc chloride reagent, leading to improved yield in the I^{III} transfer reaction. We were gratified to find that **5** provided excellent regiochemical control for arene functionalization across the range of nucleophiles investigated. Only anisole substitution was observed after the thermal decomposition of the azide, acetate, phenoxide, thiocyanate, and thiophenoxide salts (Scheme 6). However, a mixture of cyclophane- (30%) and anisole-substituted (60%) products was obtained from the reductive elimination of the 2,2,2-trifluoroethoxide salt of **5**. The reason for the breakdown in regioselectivity is clear from the product analysis, which shows roughly equal amounts of 3- and 4-(2,2,2-trifluoroethoxy)anisole, as well as roughly equal amounts of the two CF_3CH_2O-substituted cyclophane regioisomers. This lack of selectivity and distribution of regioisomers is consistent with a change in mechanism to one involving benzyne intermediates.



Scheme 5. Synthesis of **5**: a) 1. *t*BuLi, Et_2O, −78 °C, 2. $B(OMe)_3$, 3. H_2O_2, NaOH, H_2O; b) K_2CO_3, CH_3I, CH_3CN, 80 °C; c) NBS, CH_2Cl_2; d) 1. *t*BuLi, Et_2O, −78 °C, 2. $ZnCl_2$; e) 1. 4-$MeOC_6H_4I(OAc)_2$, CH_3CN, −40 °C, f) $NaPF_6$, H_2O.



Scheme 6. Anisole functionalization by thermal decomposition of **5** in CD_3CN.

For this basic nucleophile, the strategy of raising the transition state energy for reductive elimination of the aryl iodide enables the benzyne reaction manifold to be competitive.

In summary, computational and experimental data show that an increase in steric demand above the plane of the aromatic ring destabilizes a reductive-elimination transition state. This effect is sufficiently large to provide stereoelectronic control of unidirectional reductive elimination. A number of examples are provided to show that the intrinsic electronic bias in reductive elimination reactions of I^{III} compounds can be overcome. Significantly, even 4-methoxyphenyl groups can be functionalized regiospecifically. Moreover, since the approach is a general one, it is anticipated that it will be useful for controlling reductive elimination from a variety of high-valent main-group and transition metal ions.

Experimental Section

Preparation of **5**: 7-Bromo-4-methoxy[2.2]paracyclophane (1.26 mmol, 400.6 mg) was dissolved in 25 mL of distilled ether and cooled to −78 °C in a 100 mL Schlenk tube. 1.7 M *tert*-butyl lithium (3.16 mmol, 1.85 mL) was added dropwise to the cooled solution and the mixture was stirred at −78 °C for 1 h. A solution of anhydrous zinc chloride (1.51 mmol, 206.1 mg) in 10 mL of diethyl ether was added dropwise to the cooled solution. The mixture was allowed to warm to room temperature, and the solvent was removed under reduced pressure. The residual solid (organozinc chloride reagent and lithium salts) was taken up in anhydrous acetonitrile and cooled to −40 °C before a solution of 4-methoxy(diacetoxyiodo)benzene (1.89 mmol, 665.5 mg) in acetonitrile (10 mL) was added in a dropwise fashion. After 1 h at −40 °C, the mixture was warmed to room temperature and the solvent was removed under reduced pressure. Deionized water and sodium hexafluorophosphate (410 mg) were added, followed by 50 mL of dichloromethane. The mixture was transferred to a separating funnel and the organic phase was separated. The solvent was removed by rotary evaporation and the remaining solid was dissolved in 5 mL of dichloromethane and dripped into 150 mL of hexanes. The precipitate was aged for 1 h, collected by gravity filtration, and dried in vacuo to yield a colorless salt (55.6%, 431.7 mg). **5**: ^{1}H NMR (CD_3CN, 400 MHz, 25 °C): $\delta = 8.01$ (d, $J =$ 9.2 Hz, 2H), 7.25 (s, 1H), 7.07 (d, $J = 9.2$ Hz, 2H), 6.81 (dd, $J = 7.8$, 1.8 Hz, 1H), 6.62 (dd, $J = 7.9$, 1.9 Hz, 1H), 6.29 (dd, $J = 7.9$, 1.6 Hz, 1H), 6.12 (dd, $J = 8.0$, 2.0 Hz, 1H), 6.02 (s, 1H), 3.83 (s, 1H), 3.74 (s, 1H), 2.99–3.34 (m, 7H), 2.64–2.72 ppm (m, 1H). ^{13}C NMR (CD_3CN, 100 MHz, 25 °C): $\delta = 163.3$, 161.6, 146.4, 140.5, 139.9, 137.9, 137.4, 133.2, 132.4, 131.4, 131.3, 128.8, 119.8, 118.2, 107.4, 101.1, 55.8, 24.9, 37.2, 34.5, 32.9, 30.7 ppm. ^{19}F NMR (CD_3CN, 376 MHz, 25 °C): $\delta =$ −72.7 ppm (d, $J = 706.7$ Hz, 6F). HRMS: (HR-FAB) calcd. for $C_{24}H_{24}IO_2$ ($[M]^+$) 471.082107 (100%), 472.085462 (26%); found 471.082206 (100%), 472.085606 (23%).

General procedure for reductive elimination reactions: In a N_2-charged glove box, 0.025 mmol of **2**–**5** was dissolved in 0.3 mL of dry [D_3]acetonitrile. The solution was combined with 0.3 mL [D_3]acetonitrile solution of 1 equivalent of the appropriate salt ($TBAN_3$ (7.1 mg), TBASPh (8.8 mg), NaOPh (2.9 mg), or $NaOCH_2CF_3$ (3.1 mg)). The mixture was transferred into a J-Young NMR tube, sealed, taken out of the glove box, and an initial NMR spectrum was taken. The NMR tube was wrapped with aluminum foil and put into an oil bath at 45 °C. (For acetate and thiocyanate, more vigorous conditions were required: the solutions containing TBAOAc (15 mg) or TBASCN (7.5 mg) were heated at 80 °C in an oil bath.) The progress of the reaction was monitored by ^{1}H NMR spectroscopy until no I^{III} species was left. Product analysis was performed by ^{1}H NMR spectroscopy and GC-MS.

Detailed experimental procedures and characterization data are available in the Supporting Information.

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