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Regiospecific reductive elimination from diaryliodonium salts

Bijia Wang, **Joseph W. Graskemper**, **Linlin Qin**, and **Stephen G. DiMagno***

Abstract

StereoElectronic Control of Unidirectional Reductive Elimination (*SECURE*) is provided by the cyclophane substituent on iodine(III). Computational and experimental studies demonstrate that out of plane steric bulk strongly destabilizes the reductive elimination transition state, and leads to regiochemical control. This approach should be general for high valent main group and transition metal ions.

Keywords

reductive elimination; stereoelectronic effects; regiochemistry; iodanes; cyclophanes

Diaryliodonium salts are useful precursors for arylation of diverse carbon and heteroatom nucleophiles.[1–4] In practice, poor regioselectivity for reductive elimination narrows the synthetic scope of diaryliodonium 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 to prepare the symmetrical diaryliodonium salt is often a significant challenge, and purification of the functionalized product from the reductively eliminated aryl iodide can prove difficult.

In the thermal decomposition of unsymmetrical diaryliodonium salts, the identity of the aryl iodide reductively eliminated 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. Since electronic effects cannot be used exclusively to achieve this end, steric and/or stereoelectronic effects must be exploited to gain regiocontrol of reductive elimination. Here we show that the use of cyclophane-derived iodonium salts permits regiospecific reductive elimination (Scheme 2).

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) the more sterically demanding aromatic ring prefers an equatorial position syn to the nucleophile, and 2) the ortho-substituted aromatic is more likely to prefer a conformation in which the p-system is more likely to align with the incoming nucleophile.[13–15] In an exception to this rule, Ochiai and coworkers 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 iodine 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 *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 since 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 *p*-xylene and [2.2]paracyclophane. Inspection of Scheme 3 shows that movement from the ground state to the transition state geometries 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 free energy of activation for reductive elimination of HI from the *p*-xylene salt is 13.7 kcal/mol, while the barrier for the cyclophane derivative is 4.8 kcal/mol higher. Armed with an "in silico" justification for the *SECURE* concept, we sought its empirical validation.

To compare the directing effects of the electronically similar *p*-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** was formed in 18% yield. (Though organolithium,[23, 24] organoboron,[25] organosilicon,[26] and organotin[27] compounds have been used for diaryliodonium salt synthesis, to our knowledge this is the first example of the preparation of a diaryliodonium salt from an arylzinc chloride. The unusual reaction conditions used here 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.)

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The hexafluorophosphate salt of **1** is particularly convenient because a wide range of nucleophiles may be introduced via their tetraalkylammonium or sodium salts. Accordingly, when compound **1** was treated with $TBAN_3$ and heated at 45 °C in CD_3CN (0.04 M), conversion of the diaryliodonium azide was complete within a few hours. 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) corresponds to a difference in the free energies of activation ($DDG^{‡}$) of at least 2.8 kcal/mol. Thus, the validity of the computational model is confirmed.

To provide context for the *SECURE* results, arene functionalization by various nucleophiles (X) in compound **2** was investigated. The regioselectivity observed during the reductive elimination of cyclophanyl-substituted diaryliodonium salts mirrors that of 4-methoxyphenyl derivatives (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]paracyclophane 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 2-thienyl moiety's directing group ability is roughly comparable to the 4-methoxyphenyl and [2.2]paracyclophane ligands on I(III). In all cases significant amounts of the 4-iodoanisole are generated during the thermal decomposition reactions of **4**, even when 2-functionalized thiophenes are not observed. These data support Carroll's assessment[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 sulphur nucleophiles the directing group ability of the cyclophane ligand diminishes as nucleophile basicity and the driving force for functionalizing the more electron-poor ring increase. 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**, **2** and **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 free energies of activation of 21.7, 22.9, and 24.6 kcal/mol for the reactions of **1**, **2** and **3,** respectively. The fact that the rate constant for formation of azidoxylene is greater for **1** than **2** indicates that 4-iodo-[2.2]paracyclophane is a

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significantly better leaving group than 4-iodoanisole. Since leaving group ability is correlated with the electron density on iodine in the aryl iodide being reductively eliminated, these kinetic data show experimentally that the [2.2]paracyclophane ligand is a significantly more electron-poor aryl substituent than 4-methoxyphenyl 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 available 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 cyclophane organozinc chloride reagent, leading to improved yield in the I(III) transfer reaction. We were gratified to find that **5** provides excellent regiochemical control for arene functionalization across the range of nucleophiles investigated here. 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. 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 (*SECURE*); 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 *SECURE* will be useful for controlling reductive elimination from a variety of high valent main group and transition metal ions.

Experimental Section

Preparation of **5**: In a 100 mL Schlenk tube, 4-methoxy-7-bromo[2.2]paracyclophane (1.26 mmol, 400.6 mg) was dissolved in 25 mL of distilled ether and cooled to −78 °C. To the cooled solution, 1.7M t-butyl lithium (3.16 mmol, 1.85 mL) was added dropwise and the stirred solution was held at −78 °C for 1 hour. 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 hour 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 separatory 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 hexanes. The precipitate was aged for one

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hour, 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): δ 8.01 (d, J = 9.2 Hz, 2 H), 7.25 (s, 1 H), 7.07 (d, J = 9.2 Hz, 2 H), 6.81 (dd, J = 7.8, 1.8 Hz, 1 H), 6.62 (dd, J = 7.9, 1.9 Hz, 1 H), 6.29 (dd, J = 7.9, 1.6 Hz, 1 H), 6.12 (dd, J = 8.0, 2.0 Hz, 1 H), 6.02 (s, 1 H), 3.83 (s, 1 H), 3.74 (s, 1 H), 2.99 – 3.34 (m, 7 H), 2.64 – 2.72 (m, 1 H). ^{13}C NMR (CD_3CN, 100 MHz, 25 °C): δ 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. ^{19}F NMR (CD_3CN, 376 MHz, 25 °C): δ −72.7 (d, J = 706.7 Hz, 6 F). HRMS: (HRFAB) calcd. for C24H24IO2 [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 equiv. of the appropriate salt ($TBAN_3$ (7.1 mg), TBASPh (8.8 mg), NaOPh (2.9 mg) $NaOCH_2CF_3$ (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 a 45 °C oil bath. (For acetate and thiocyanate, more vigorous conditions were required. The solutions containing TBAOAc (15 mg) and TBASCN (7.5 mg) were heated in an 80 °C oil bath.) The progress of the reaction was monitored by ^{1}H NMR until no I(III) species was left. Product analysis was performed by ^{1}H NMR and GC-MS.

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

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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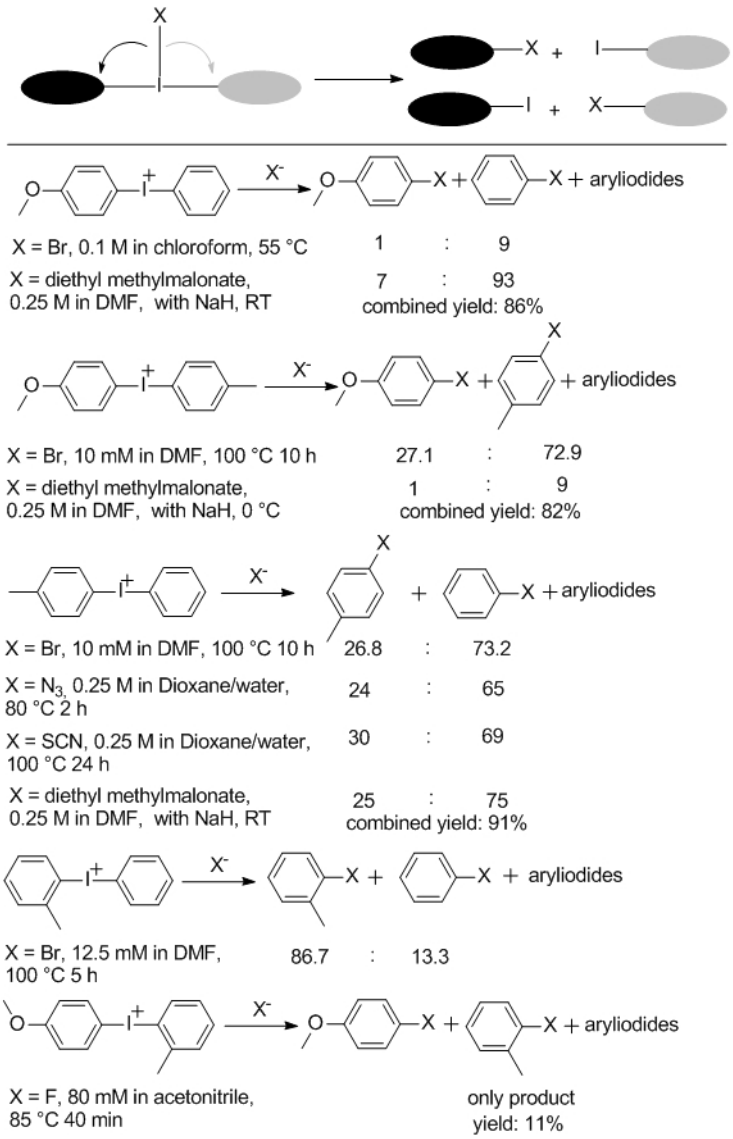

Scheme 1.

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

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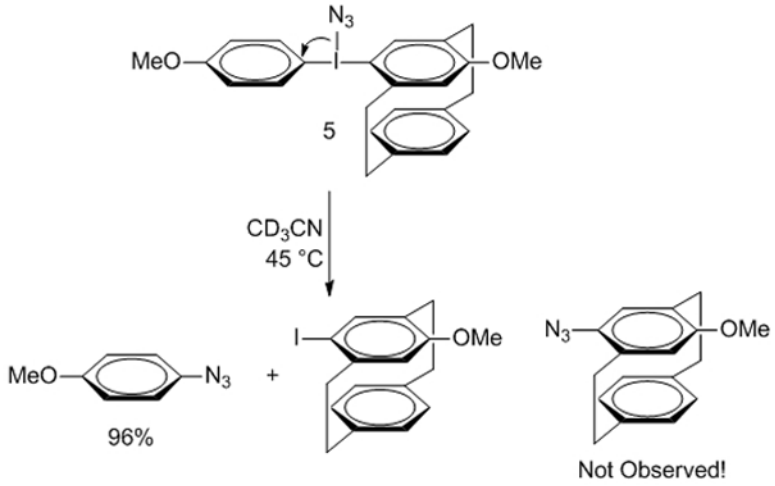

Scheme 2.
Regiochemically controlled reductive elimination of an electron-rich, cyclophane-derived diaryliodonium salt.

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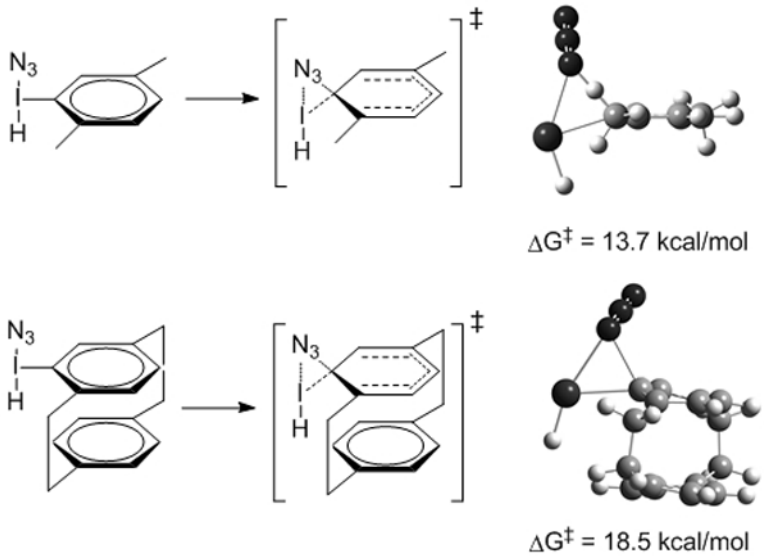

Scheme 3.
Calculated TS structures and activation barriers for (2,5-dimethylphenyl) and [2.2]paracyclophan-4-yl iodonium salts.

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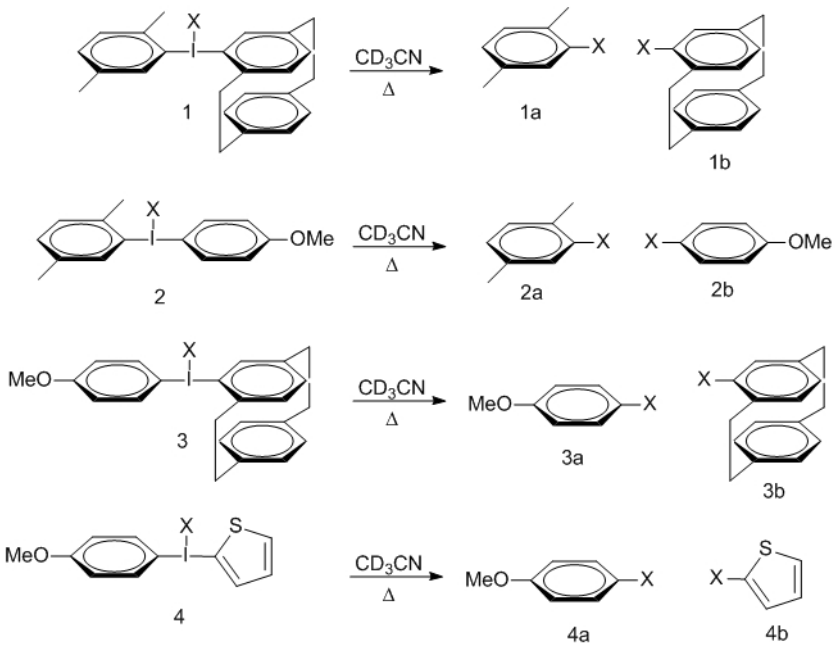

Scheme 4.

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

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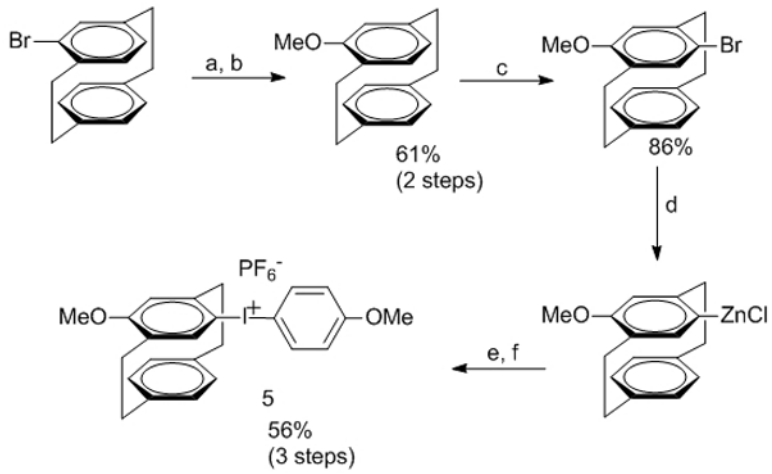

Scheme 5.

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.)

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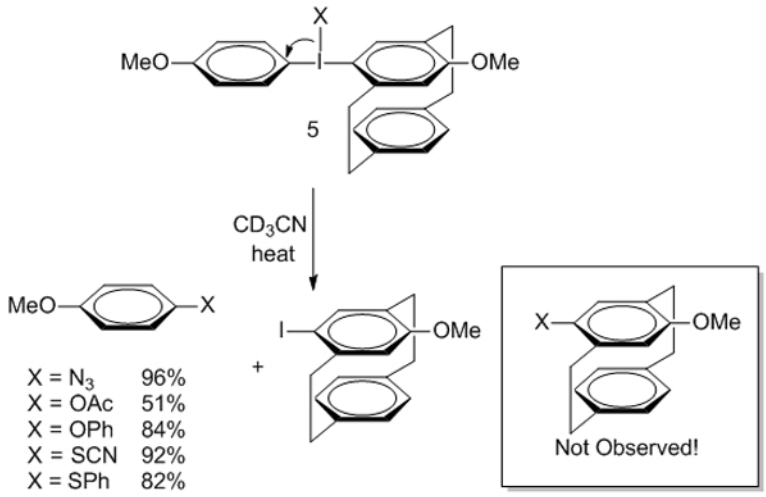

Scheme 6.
Anisole functionalization by thermal decomposition of **5** in CD_3CN.

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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 ^{1}H NMR spectroscopy and confirmed by GC-MS.

[b] Decomposition of the functionalized thiophene was observed.

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