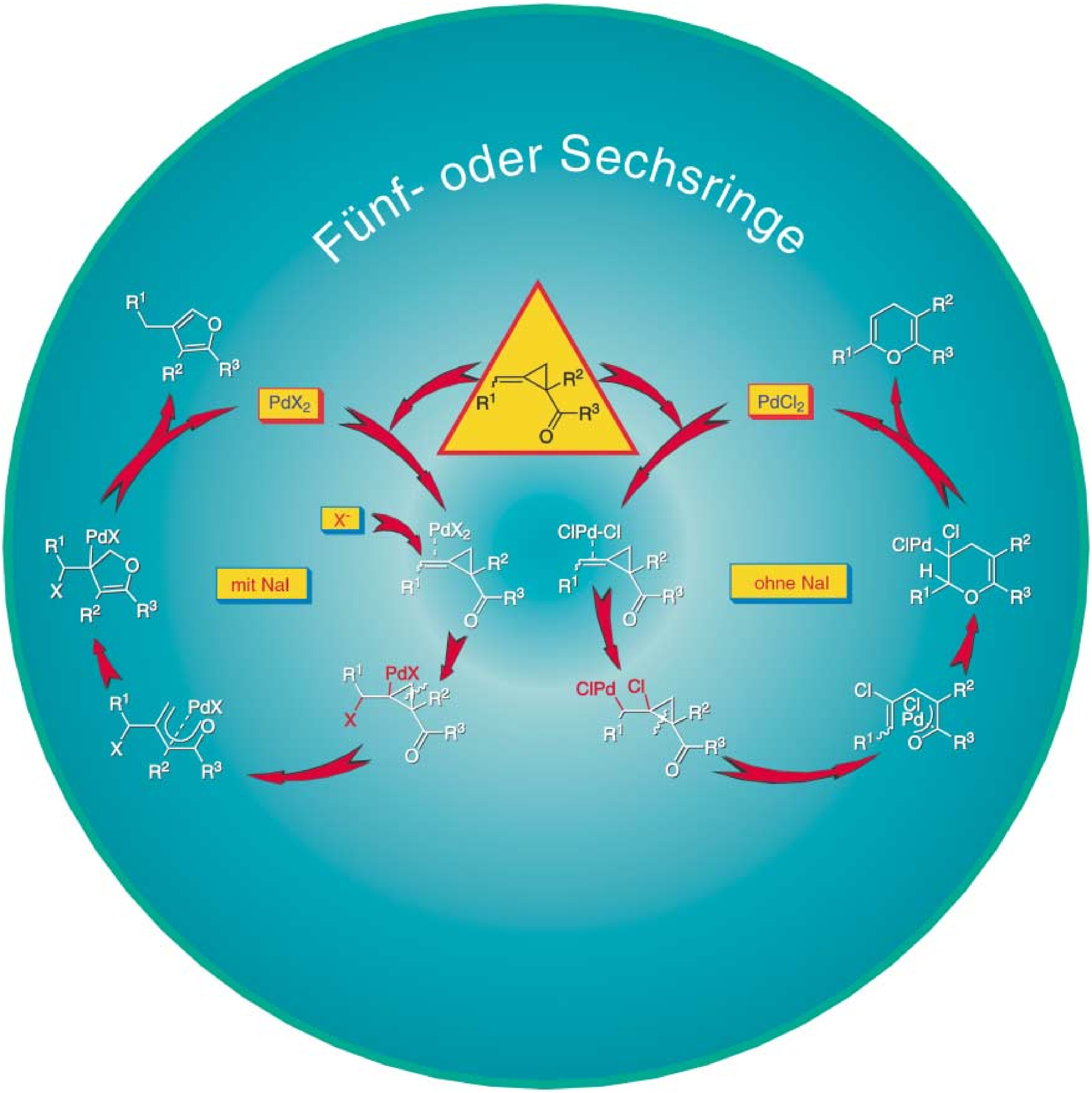
Zuschriften



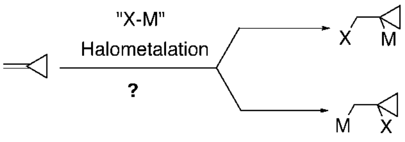
Ausgehend von Alkylidencyclopropylketonen lassen sich in Abhängigkeit von den Reaktionsbedingungen zwei Arten nützlicher organischer Synthesebausteine regioselektiv herstellen, Furane und 4*H*-Pyrane. Details erfahren Sie auf den nächsten Seiten im Beitrag von S. Ma und J. Zhang.

Regioselective Cyclization

Tuning the Regioselectivity in the Palladium(II)-Catalyzed Isomerization of Alkylidene Cyclopropyl Ketones: A Dramatic Salt Effect**

Shengming Ma and Junliang Zhang*

In the last three decades, methylenecyclopropanes (MCPs) have been studied with numerous mechanistic,[1] biological[2] and synthetic interests.[3] Especially, mounting attention has been paid to the transition-metal-catalyzed reactions of MCPs.[4,5] Various reaction pathways, including oxidative addition of the distal or proximal C–C bond[4,6] and regioselective hydrometalation[7,8] or carbometalation[9,10] of the C=C bond, have been observed in the transition-metal-catalyzed reactions of MCPs. Although the chloropalladation reaction of MCPs with stoichiometric [PdCl$_2$(PhCN)$_2$] has been studied,[11] no catalyzed reaction has been reported (Scheme 1). During our systematic study of allene chemistry,[12] we have been interested in the chemistry of its analogues, MCPs. Herein, we disclose a dramatic salt effect[13] in the palladium(II)-catalyzed regioselective cycloisomerization reaction of the alkylidene cyclopropyl ketones **1** giving the corresponding furan or 4*H*-pyran derivatives initiated with the regioselective halopalladation of the C=C bond of MCPs.



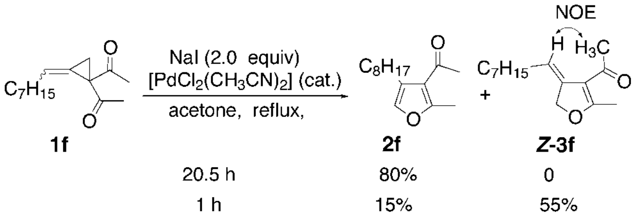
Scheme 1. Two possible modes of halometalation reactions of MCPs.

We initially examined the reaction of the methylenecyclopropyl ketone **1a**[14] in the presence of a catalytic amount of [PdCl$_2$(CH$_3$CN)$_2$]. After numerous trial and error attempts, fortunately we observed the [PdCl$_2$(CH$_3$CN)$_2$]-catalyzed regioselctive isomerization of **1a** with two equivalents of sodium iodide in THF afforded 2-phenyl-4-methylfuran **2a**[15] in 51 % yield (entry 2, Table 1). The reaction can also be carried out in CH$_3$CN or DMF to afford the product in very low yields (entries 3 and 4, Table 1). The best results were obtained using two equivalents of sodium iodide as the additive in refluxing acetone, under the catalysis of 5 mol % [PdCl$_2$(CH$_3$CN)$_2$] (Conditions A; entry 5, Table 1). Other salts such as tetra(*n*-butyl)ammonium iodide, tetra(*n*-butyl)ammonium bromide, and lithium bromide also showed a similar effect, albeit that **2a** was formed in lower yields (entries 6–8, Table 1).

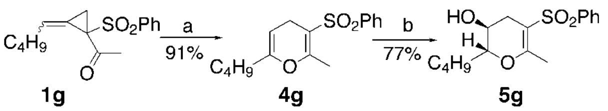
This transformation is general and some of the typical results are summarized in Table 2. The reactions of **1** under Conditions A afforded the corresponding polysubstituted furans **2** in good yields (Table 2). The reaction of **1d** with 20 mol % of sodium iodide afforded the corresponding product **2d** in a lower yield (compare entries 3 and 4, Table 2). The reaction of **1f** for 20.5 h afforded the furan **2f** in 80 % yield, while 4-octylidene-4, 5-dihydrofuran *Z*-**3f** was formed in 55 % yield together with **2f** (15 %; Scheme 2) within 1 h, which indicates that the reaction proceeded through the intermediacy of **3f**. The stereochemistry of *Z*-**3f** was determined by an NOE study.

Furthermore, it is surprising for us to observe that the [PdCl$_2$(CH$_3$CN)$_2$]-catalyzed reaction of **1g** in acetone at RT *in the absence of NaI* (Conditions B) afforded the 4*H*-pyran **4g** in 91 % yield (Scheme 3), of which the structure was determined by a X-ray diffraction study of the corresponding hydroboration–oxidation product **5g**.[16]

This transformation is also general and the results are summarized in Table 3. In the presence of 5 mol % [PdCl$_2$(CH$_3$CN)$_2$], the reaction of the alkylidene cyclopropyl ketone **1b** at RT in acetone gave the 4*H*-pyran **4b** in 80 % yield (entry 1, Table 3). In some cases, benzene is a better solvent. For example, the reaction of **1d** in benzene afforded **4d** in 80 % yield, while the same reaction in acetone afforded **4d** in 69 % yield (entries 3 and 4, Table 3). The reaction of **1e**, which contains the TBS-protected hydroxy group (TBS = *tert*-butyldimethylsilyl), gave **4e** in 85 % yield in benzene (entry 5, Table 3). The presence of the electron-withdrawing group R^2



Scheme 2. The Pd^{II}-catalyzed cycloisomerization reaction of **1f** under Conditions A.



Scheme 3. The Pd^{II}-catalyzed isomerization reaction of **1g** under Conditions B and the subsequent hydroboration–oxidation reaction. a) 5 mol % [PdCl$_2$(CH$_3$CN)$_2$], acetone, RT, 15 min; b) 1. BH$_3$·SMe$_2$, THF, 0 °C→RT, 1 h; 2. NaOH–H$_2$O$_2$, 0 °C→RT, 6 h.

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[**] Financial support from the National Science Foundation of China, the Major State Basic Research Development Program (Grant No. G2000077500), the Chinese Academy of Sciences, and the Shanghai Municipal Committee of Science and Technology are greatly appreciated. S.M. is the recipient of the 1999 Qiu Shi Award for Young Chinese Scientific Workers issued by the Hong Kong Qiu Shi Foundation of Science and Technology (1999–2003)

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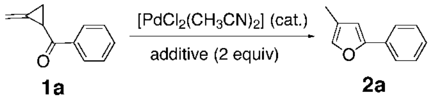
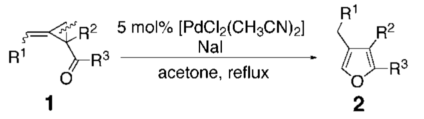
Table 1: Palladium(II)-catalyzed regioselective isomerization of **1a** into **2a**.



Entry	Additive	Solvent	*T* [°C]	*t* [h]	Yield [%][a]
1	LiCl	CH_2Cl_2	RT	5	0
2	NaI	THF	reflux	10	51
3	NaI	CH_3CN	70	10	5
4	NaI	DMF	70	10	9
5	NaI	acetone	reflux	9	80
6	Bu_4NI	acetone	reflux	10	61[b]
7	Bu_4NBr	acetone	reflux	10	57[b]
8	LiBr	acetone	reflux	10	63

[a] 5 mol% of catalyst was used. [b] 10 mol% of catalyst was used.

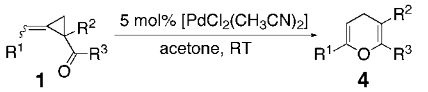
Table 2: Palladium(II)-catalyzed regioselective isomerization of ketones **1**, which leads to furans **2**.[a]



Entry	**1**			*t*	Yield of **2**
	R^1	R^2	R^3	[h]	[%]
1	C_7H_{15}	CO_2Et	Me (**1b**)	10	74 (**2b**)
2	C_4H_9	CO_2Et	Me (**1c**)	14	74 (**2c**)
3	Bn	CO_2Et	Me (**1d**)	13.5	78 (**2d**)
4		**1d**		24	65(**2d**)[b]
5	TBSO$(CH_2)_3$	CO_2Et	Me (**1e**)	26	82 (**2e**)
6	C_7H_{15}	COMe	Me (**1f**)	20.5	80 (**2f**)[c]
7	H	H	$C_6H_5(CH_2)_2$ (**1h**)	12	77 (**2h**)

[a] Unless otherwise specified, the reaction was carried out using **1** (0.25–1.5 mmol) in the presence of 5 mol% [PdCl$_2$(CH$_3$CN)$_2$] and 2 equiv of sodium iodide in 2 mL of acetone under reflux (Conditions A). [b] The reaction was carried out in the presence of 0.2 equiv of sodium iodide in 0.5 mL of acetone under reflux. [c] See the text.

Table 3: Palladium(II)-catalyzed regioselective isomerization of the ketones **1**, which leads to the 4*H*-pyrans **4**.[a]



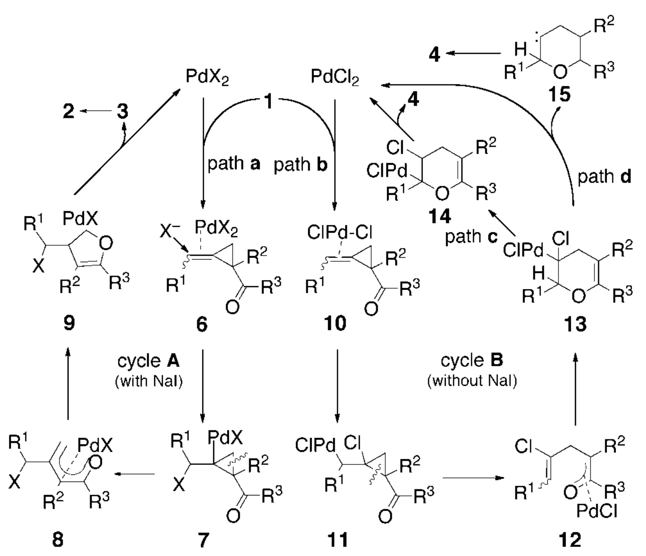
Entry	**1**			*t*	Yield of **4**
	R^1	R^2	R^3	[min]	[%]
1	C_7H_{15}	CO_2Et	Me (**1b**)	15	80 (**4b**)
2	C_4H_9	CO_2Et	Me (**1c**)	15	75 (**4c**)
3	Bn	CO_2Et	Me (**1d**)	15	69 (**4d**)
4		**1d**		10	80 (**4d**)[b]
5	TBSO$(CH_2)_3$	CO_2Et	Me (**1e**)	10	85 (**4e**)[b]
6	C_7H_{15}	COMe	Me (**1f**)	40	60 (**4f**)
7	C_4H_9	SO_2Ph	Me (**1g**)	15	91 (**4g**)
8	C_8H_{17}	H	Ph (**1i**)	15	70 (**4i**)[b]

[a] Unless otherwise specified, all reactions were carried out using **1** (0.5 mmol) in the presence of 5 mol% [PdCl$_2$(CH$_3$CN)$_2$] in 2 mL of acetone at RT (Conditions B). [b] The solvent used was benzene.

is not necessary because the reaction of **1i** was also good, affording **4i** in 70% yield (entry 8, Table 3).

A plausible rationale for the dramatic salt effect of NaI in the palladium(II)-catalyzed regioselective cycloisomerization of **1** is shown in Scheme 4. In the presence of NaI, the iodide anion (I$^-$) attacks the palladium(II)-coordinated C=C bond to afford the palladium intermediate **7** (path **a**), then β decarbopalladation involving the proximal C–C bond of the complex **7** would give the delocalized intermediate **8,** which would undergo the intramolecular *endo*-mode insertion of the C=C bond into the oxy-palladium bond followed by β halide elimination to produce the catalytically active palladium(II) species and **3**, which would furnish the furan **2** upon aromatization (cycle **A**). In the absence of NaI the reaction would go through cycle **B**. The regioselective chloropalladation[11] of the C=C bond of the alkylidene cyclopropane ketone **1** (path **b**) would afford the palladium intermediate **11**, which would undergo β decarbopalladation to afford the delocalized intermediate **12**. Subsequent intramolecular *endo*-mode insertion of the C=C bond into the oxygen–palladium bond of the intermediate **12** would afford a cyclic palladium intermediate **13**, which would undergo β-hydride elimination–hydropalladation with an opposite regioselectivity to afford the palladium intermediate **14**. Finally, β-halide elimination of **14** would produce the 4*H*-pyran **4** and regenerate the palladium(II) species (path **c**). The intermediate **13** might also undergo α-halide elimination[17] to afford a carbene intermediate **15** and regenerate palladium(II) species (path **d**). The carbene intermediate **15** would undergo intramolecular 1, 2-migration of hydrogen to afford the 4*H*-pyran **4**.

In conclusion, a dramatic salt effect was observed in the palladium(II)-catalyzed regioselective cycloisomerization of alkylidene cyclopropyl ketones **1**. In the presence of two equivalents of sodium iodide or other salts the reaction provides the furans **2** through distal-bond cleavage, while in the absence of salt, the polysubstituted 4*H*-pyrans **4** were formed by proximal-bond cleavage. Further studies into the scope, mechanism, and synthetic applications of this reaction are being carried out in our laboratory.



Scheme 4. A plausible mechanism for the Pd^{II}-catalyzed isomerization reaction of **1**.

Experimental Section

Conditions A; synthesis of **2b**: [PdCl$_2$(MeCN)$_2$] (17 mg, 0.65 mmol) was added to a solution of **1b** (356 mg, 1.3 mmol) and sodium iodide (400 mg, 2.7 mmol) in acetone (5 mL). The mixture was then stirred under reflux for 14 h. Evaporation of the solvent and chromatography on silica gel (petroleum ether/ether 100:1) afforded pure **2b** (256 mg, 74 %) as a liquid. ^{1}H NMR (300 MHz, C$_6$D$_6$): $\delta = 6.81$ (s, 1 H), 4.03 (q, $J = 7.2$ Hz, 2 H), 2.61 (t, $J = 7.5$ Hz, 2 H), 2.37 (s, 3 H), 1.60–1.46 (m, 2 H), 1.38–1.10 (m, 10 H), 0.97 (t, $J = 7.2$ Hz, 3 H), 0.84 ppm (t, $J = 7.$ 2 Hz, 3 H); ^{13}C NMR (75.4 MHz, C$_6$D$_6$): $\delta = 164.10$, 160.06, 137.63, 126.76, 113.51, 59.57, 32.25, 30.08, 29.96, 29.87, 29.73, 25.17. 23.03, 14.31, 14.26, 14.24 ppm; MS (70 eV): m/z (%): 266 (1.14) [M^+], 168 (100) [$M^+ - C_7H_{14}$]; IR (neat): $\tilde{\nu} = 1716$, 1607, 1559 cm^{-1}; HRMS calcd for $C_{16}H_{26}O_3$: 266.18819, found: 266.18641.

Conditions B; synthesis of **4b**: [PdCl$_2$(MeCN)$_2$] (6 mg, 5 mol %) was added to a solution of **1b** (133 mg, 0.50 mmol) in acetone (2 mL). The mixture was then stirred at RT for 15 min. Evaporation of the solvent and chromatography on silica gel (petroleum ether/ether 100:1) afforded pure **4b** (106 mg, 80 %) as an air-sensitive liquid. ^{1}H NMR (300 MHz, CDCl$_3$): $\delta = 4.65$ (t, $J = 3.6$ Hz, 1 H), 4.14 (q, $J = 6.9$ Hz, 2 H), 2.90–2.80 (m, 2 H), 2.20 (t, $J = 0.9$ Hz, 3 H), 1.99 (t, $J = 6.9$ Hz, 2 H), 1.50–1.30 (m, 2 H), 1.30–1.20 (m, 8 H), 1.25 (t, $J = 6.9$ Hz, 3 H), 0.87 ppm (t, $J = 6.6$ Hz, 3 H); ^{13}C NMR (75.4 MHz, CDCl$_3$): $\delta = 168.16$, 160.95, 150.23, 100.27, 97.33, 59.81, 32.58, 31.76, 29.04, 28.94, 26.35, 22.62, 21.92, 19.13, 14.31, 14.05 ppm; MS (70 eV): m/z (%): 266 (7.89) [M^+], 43 (100) [$C_3H_7^+$]; IR (neat): $\tilde{\nu} = 1720$, 1637, 761 cm^{-1}; HRMS calcd for $C_{16}H_{26}O_3$: 266.18819, found 266.1857.

Received: July 29, 2002 [Z19842]

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[16] X-ray data for compound **5g**: $C_{16}H_{22}O_4S$, $M_r = 310.40$, monoclinic, space group $P2(1)/c$, $Mo_{K\alpha}$, final R indices [$I > 2\sigma(I)$], $R1 = 0.0553$, $wR2 = 0.1280$, $a = 17.931(4)$, $b = 8.4053(16)$, $c = 10.938(2)$ Å, $\alpha = 90$, $\beta = 94.494(3)$, $\gamma = 90°$, $V = 1643.5(5)$ Å^3,

$T = 293$ K, $Z = 4$, reflections collected/unique: 9438/3824 ($R_{\text{int}} = 0.0457$), no observation [$I > 2\sigma(I)$] 3824, parameters 257. CCDC-190370 (**5g**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit @ccdc.cam.ac.uk).

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Electrochemical Sensors

Mono-Tetrathiafulvalene Calix[4]pyrrole in the Electrochemical Sensing of Anions**

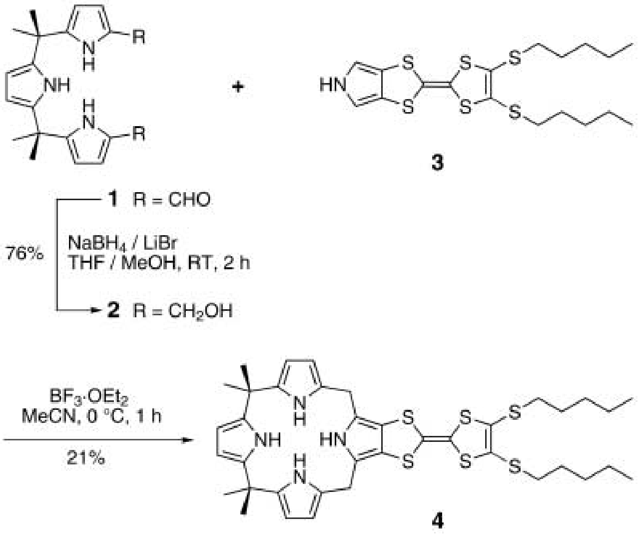
Kent A. Nielsen, Jan O. Jeppesen, Eric Levillain, and Jan Becher**

Dedicated to Professor J. Fraser Stoddart
on the occasion of his 60th birthday

The advent of supramolecular chemistry[1] has stimulated the contemporary chemist's interest in the development of chemosensors capable of recognizing specific chemical species.[2] Calix[4]pyrroles[3]—first synthesized in the 19th Century by Baeyer[4]—contain four pyrrole–NH hydrogen-bond functionalities and have recently been studied for possible use as receptors for anionic and neutral substrates.[5] They have been used to prepare optical anion sensors[6] and anion-selective high-performance liquid-chromatography (HPLC) supports.[7] However, only a few electrochemically active sensors based on calix[4]pyrroles have been reported.[8] Electrochemically active sensors, designed to permit the detection of substrates by binding-induced changes in the redox properties, are generally composed of a receptor unit, which works by the covalent association of a substrate-recognition functionality, and an electrochemical-signaling capacity (redox-active unit). The redox-active tetrathiafulvalene[9] (TTF) unit can exist in three stable redox states (TTF^0, $\text{TTF}^{+\bullet}$, and TTF^{2+}) and for this reason TTF derivatives have found widespread use in materials chemistry.[9] Progress in synthetic TTF chemistry[9] has revolutionized the possibilities for the incorporation of TTF into macrocyclic, molecular, and supramolecular structures and has transformed complicated systems, such as TTF cyclophanes,[9] TTF catenanes,[9] and TTF rotaxanes/pseudorotaxanes[9,10] from chemical curiosities into a vibrant area of modern-day research. In the context of electrochemically active sensors, TTF has already been used as the redox-active unit in a number of cation responsive receptors.[11] However, to our knowledge, no anion receptor incorporating TTF as the redox-active unit has been reported. We have recently developed an efficient synthesis of the parent pyrrolo[3,4-*d*]TTF-ring system.[12] With this building block in hand, we have prepared the first example of a single molecule in which the anion-receptor abilities of the calix[4]pyrrole system were coupled to the favorable redox properties of the TTF core through direct annulation of one TTF unit to the upper rim of the calix[4]pyrrole skeleton.

Herein, we report the synthesis of the first calix[4]pyrrole incorporating a TTF unit. Furthermore, we describe our ^{1}H NMR spectroscopic and electrochemical studies on the recognition abilities of this novel mono-TTF calix[4]pyrrole **4** system towards anions.

Our preparation of the mono-TTF calix[4]pyrrole **4** is outlined in Scheme 1. The tripyrrane dialdehyde **1** was prepared according to a literature procedure[13] by the condensation of pyrrole and acetone followed by a Clezy formylation. The reduction of the formyl groups with NaBH_4/LiBr in anhydrous THF/MeOH produced the bishydroxymethyltripyrrane **2** in 76% yield. The tripyrrane **2** was used immediately after purification by means of flash column chromatography on account of the low stability of the compound. Treatment of equal quantities of **2** and the newly developed pyrrolo TTF **3** with a catalytic amount of $\text{BF}_3{\cdot}\text{Et}_2\text{O}$ in anhydrous MeCN, gave the mono-TTF calix[4]pyrrole **4** as yellow crystals after purification by means of column chromatography (yield 21%).[14]



Scheme 1. Synthesis of the mono-TTF calix[4]pyrrole **4**.

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[**] We gratefully acknowledge the University of Odense for a Ph.D scholarship to K.A.N., financial support from Carlsbergfondet to J.O.J, and the French Embassy Copenhagen for a travel grant to J.B.