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A Versatile Methodology for the Regioselective C^8-Metalation of Purine Bases

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Supporting Information

ABSTRACT: Purine nucleobases are excellent ligands for metal ions, forming normally coordinative Werner-type bonds by utilizing the N donor atoms of the nucleobase skeleton. Here we show that purines such as 8-chlorocaffeine and 8-bromo-9-methyladenine react with [Pt(PPh$_3$)$_4$] under oxidative addition of the C^8–halogen bond to the metal center. The resulting Pt^{II} complexes feature a C^8-bound ylidene ligand. Protonation of the ylidene at the N$^{7/9}$-atom yields complexes bearing a protic N-heterocyclic carbene ligand derived from the purine base with an NMe,NH-substitution pattern.

Not only are purine nucleobases the building blocks for DNA and RNA, but at the same time they are also excellent ligands for metal ions and provide important binding sites in nucleic acids. A detailed understanding of the coordination chemistry of purines is currently the subject of intensive studies[1] due to the key role metal complexes play in cancer chemotherapy.[2] Significant efforts have been directed toward nucleobase Pt(II) coordination compounds, with the aim to investigate the mechanism of interaction between *cis*-platinum and DNA.[3] Today, it is well known that the N^7-position of N^9-blocked but otherwise unsubstituted purine nucleobases is the preferred binding site for transition metal ions, including Pt(II) antitumor agents.[1a,b] Almost all known complexes involving atoms of the unsubstituted purine skeleton **I** (Figure 1) feature interactions between a Lewis acidic metal ion and nitrogen donor atoms (N^1, N^3, N^7, or N^9) of the purine bicyclus. However, substitution of the purine skeleton, like C^6-arylation, allowed the isolation of chelate complexes with an N^1-metalated purine skeleton and an exocyclic orthometalated phenyl ring.[4]

We became interested in the metalation of purine nucleobases like N^9-methyladenine **II** at the C^8-atom, which would lead to organometallic complexes of unsubstituted purines with an endocyclic M–C bond. The C^8-metalation of **II**, however, poses several challenges, like the regioselective deprotonation at the C^8-atom and the binding of a metal atom at this position. Formation of C-metalated nucleosides and nucleotides (C2, C6, or C8) as intermediates in metal-catalyzed C–C or C–N coupling reactions involving the purine skeleton was described,[5] but to our knowledge none of these intermediates has been isolated and fully characterized yet.

The five-membered diaminoheterocycle of 9-methyladenine resembles that of neutral *N*-alkylimidazoles **III** (Figure 1). While deprotonation and regioselective C^2-metalation of simple neutral

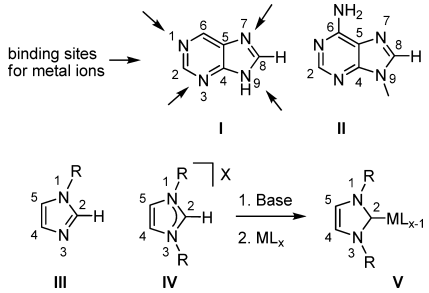
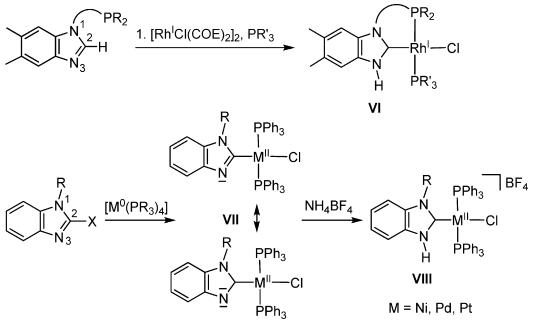


Figure 1. Purine **I**, 9-methyladenine **II**, *N*-alkylimidazole **III**, and metalation of **IV** to give the NHC complex **V**.

Scheme 1. C–H and C–X Oxidative Addition of Neutral Azoles to Transition Metals



type **III** *N*-alkylazoles is rarely mentioned in the literature,[6] deprotonation and C^2-metalation of the related *N*,*N*′-dialkylimidazolium cation in **IV** is standard for the synthesis of complexes **V** bearing N-heterocyclic carbenes (NHCs).[7] Recently, the C^2-metalation of *N*-alkylenephosphine-tethered benzimidazoles with Ru^{II} and Rh^I (Scheme 1) by an oxidative addition/reductive elimination procedure[8] to give type **VI** complexes was described. Subsequently, it was shown that neutral 2-halogenoazoles such as 2-chloro-*N*-methylbenzimidazole also react with transition metal complexes [M^0(PR$_3$)$_4$] (M = Ni, Pd, Pt), giving initially type **VII** complexes (Scheme 1).[9] Protonation yields type **VIII** complexes bearing an NR,NH-NHC ligand. Type **VII** complexes tend to dimerize via intermolecular M–N interactions to give dinuclear species.[9a,c]

The C–X oxidative addition appears to be the method of choice for the regioselective C^8-metalation of N$^{7/9}$-blocked and

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otherwise unsubstituted purine bases. C^8-Halogeno-$N^{7/9}$-methylpurines feature an *N*-methylimidazole heterocycle which is very likely capable of oxidative addition to $[Pt(PPh_3)_4]$. In addition, $[Pt(PPh_3)_4]$ is not Lewis acidic enough for binding to the N donors of the purine skeleton. Here we describe the reaction of C^8-chlorocaffeine and C^8-bromo-N^9-methyladenine with $[Pt(PPh_3)_4]$, leading to regioselective C^8-metalation of the purine bases and formation of isolable ylidene complexes.

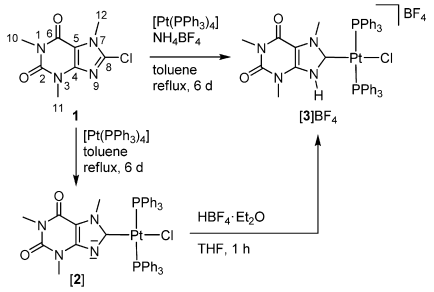
Based on the observation that the initial reaction products of the oxidative addition of 2-halogenobenzimidazoles to Pt^0 tend to form intermolecular Pt−N interactions,[9a,c] we decided to start our studies on the oxidative addition of C^8-halogenated purines with an electron-poor derivative. We were hoping to prevent dimerization after the initial oxidative addition of the C^8−X bond. The 8-chlorocaffeine derivative **1** (8-chloro-1,3,7-trimethyl-3,7-dihydro-1*H*-purine-2,8-dione) was selected for the initial studies. A related N^7,N^9-dimethylated cationic derivative of caffeine, 1,3,7,9-tetramethylxanthinium, was previously C^8-metalated by the classical reaction sequence for the synthesis of NHC complexes (C^8-deprotonation followed by metal coordination).[10]

8-Chlorocaffeine **1** was obtained from 8-chlorotheophylline by N^7-methylation following a published procedure.[11] Reaction of **1** with $[Pt(PPh_3)_4]$ led to the colorless complex [**2**] in 54% yield (Scheme 2). A related Co(I) complex bearing a caffeine-derived ylidene ligand was obtained by the acid/base reaction of caffeine with $[CoMe(PMe_3)_4]$.[12] [**2**] was completely characterized by NMR. The $^{13}C\{^1H\}$ NMR spectrum showed a resonance at δ (ppm) = 150.3 (t, $^2J_{C,P}$ = 10.4 Hz) indicative of C^8-binding of the caffeine and coordination of the two PPh_3 donors to the same Pt atom in *trans* positions. The chemical shift for the C^8-resonance compares well to the chemical shift observed for the C^2-atom in the benzimidazolin-2-ylidene complex **VII** (δ = 149.4, t, $^2J_{C,P}$ = 9.4 Hz).[9c] The $^{31}P\{^1H\}$ NMR spectrum shows a resonance at δ = 19.3 (s, Pt satellites, $^1J_{Pt,P}$ = 2795 Hz) for the two chemically equivalent P atoms in [**2**], confirming their *trans* arrangement. No indications for dimerization of [**2**] were found, which we attribute to the reduced electron density of the unsubstituted ring-N atom due to the electron-withdrawing backbone of the caffeine molecule in addition to steric reasons.

Crystals of [**2**]·$2CH_2Cl_2$ were obtained by slow diffusion of diethyl ether into a saturated dichloromethane (DCM) solution of [**2**]. X-ray diffraction (XRD) analysis of these crystals confirmed the formation of the *trans*-configured caffeine−ylidene complex (Figure 2). The Pt atom is surrounded in a square-planar fashion by the caffeine C^8-atom, the two phosphine donors, and a chloro ligand. Equivalent metric parameters in [**2**] and **VII** are similar or even identical within experimental error. An exception are the $N-C_{NHC}$ distances, which differ for **VII** by 0.07 Å (N1−C2 1.389(2) Å, N3−C2 1.319(3) Å), while they are identical within experimental error in [**2**] (N7−C8 1.360(3) Å, N9−C8 1.352(3) Å). This observation is in accord with a reduced negative charge at the N^9-atom in [**2**] compared to the N^3-atom in **VII**, with concurrent reduction of the electrostatic interaction between N^9 and C^8.

Next, 8-chlorocaffeine **1** was reacted with $[Pt(PPh_3)_4]$ in toluene in the presence of an excess of the proton source NH_4BF_4. After a reaction time of 6 d, [**3**]BF_4 bearing an N^9-protonated NMe,NH-NHC ligand was isolated as a colorless solid in 63% yield (Scheme 2). ^1H NMR confirmed the N^9-protonation of the coordinated caffeine-derived ylidene ligand (δ = 10.89 for N^9−H). The resonance for the C^8-atom could not be detected in the $^{13}C\{^1H\}$ NMR spectrum, while the resonances

Scheme 2. Regioselective C^8-Metalation of Caffeine



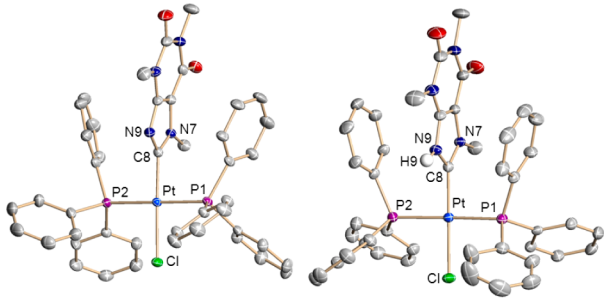


Figure 2. Molecular structures of [**2**] in [**2**]·$2CH_2Cl_2$ (left) and [**3**]$^+$ in [**3**]BF_4·$0.5H_2O$ (right) (nonrelevant H atoms and solvent molecules are omitted for clarity, 50% probability ellipsoids). Selected bond distances (Å) and angles (deg): for [**2**], Pt−Cl 2.3763(6), Pt−P1 2.3100(7), Pt−P2 2.3101(7), Pt−C8 1.980(3), N7−C8 1.360(3), N9−C8 1.352(3), Cl−Pt−P1 89.23(2), Cl−Pt−P2 90.94(2), Cl−Pt−C8 177.28(7), P1−Pt−P2 179.38(2), P1−Pt−C8 88.25(7), P2−Pt−C8 91.59(7), N7−C8−N9 110.6(2); for [**3**]$^+$, Pt−Cl 2.3489(7), Pt−P1 2.3235(7), Pt−P2 2.3246(7), Pt−C8 1.967(3), N7−C8 1.342(3), N9−C8 1.373(3), Cl−Pt−P1 89.99(3), Cl−Pt−P2 89.52(2), Cl−Pt−C8 178.72(7), P1−Pt−P2 174.19(2), P1−Pt−C8 89.39(8), P2−Pt−C8 90.99(8), N7−C8−N9 106.1(2).

for all other C atoms were identified and assigned. The $^{31}P\{^1H\}$ NMR spectrum features the resonance for the two chemically equivalent P atoms in *trans* configuration slightly upfield compared to that of [**2**] at δ = 17.4 (s, Pt satellites, $^1J_{Pt,P}$ = 2483 Hz). The upfield shift of the $^{31}P\{^1H\}$ resonance upon protonation is in line with a decreased donor ability of the NMe,NH-NHC ligand, and this effect was discussed in the literature.[13]

Formation of cation [**3**]$^+$ was also indicated by HRMS spectrometry (ESI, positive ions), with a strong peak at m/z = 949.1969 (calcd for [**3**]$^+$ 949.1967). [**3**]BF_4 can also be obtained by reaction of [**2**] with HBF_4·Et_2O in THF, but the direct synthesis from 8-chlorocaffeine **1**, $[Pt(PPh_3)_4]$, and NH_4BF_4 is more convenient, as it circumvents the isolation of [**2**].

The molecular structure of [**3**]BF_4 was established by an XRD study with crystals of [**3**]BF_4·$0.5H_2O$ obtained by slow diffusion of diethyl ether into a saturated DCM solution of [**3**]BF_4. Structure analysis confirmed the formation of the square-planar complex cation [**3**]$^+$ (Figure 2). Metric parameters of [**2**] and [**3**]$^+$ are rather similar. Most surprisingly, the $N^{7/9}$−C^8 distances in [**3**]$^+$ bearing the protic carbene ligand (N7−C8 1.342(3) Å, N9−C8 1.373(3) Å) differ by 0.03 Å, while they are identical within experimental error for [**2**]. The N7−C8−N9 angle in cation [**3**]$^+$ (106.1(2)°) is significantly smaller than in [**2**] (110.6(2)°). A similar reduction of the N^7−C^8−N^9 angle was observed upon deprotonation of the 1,3,7,9-tetramethylxanthinium cation and coordination of the resulting caffeine-

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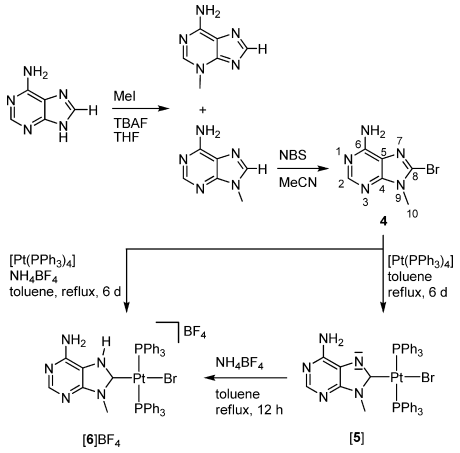
Scheme 3. Regioselective C^8-Metalation of 9-Methyladenine



derived ylidene ligand to Ag(I) and Rh(I).[10b] Generally, the metric parameters found for the caffeine–ylidene ligand in $[\mathbf{3}]^+$ compare well with the metric parameters observed in type **VIII** complexes, and this allows to conclude that the carbon-bound ligand in $[\mathbf{3}]^+$ behaves overall as a classical protic NHC ligand.

After demonstrating that purine derivatives such as 8-chlorocaffeine **1** can be converted into protic NHC ligands by an oxidative addition reaction without prior alkylation of both N atoms of the five-membered heterocycle, we turned to the C^8-metalation of adenine. 9-Methyladenine was prepared together with 3-methyladenine by *N*-alkylation of adenine with methyl iodide.[14] Chromatographic separation of the isomers and reaction of 9-methyladenine with *N*-bromosuccinimide in acetonitrile gave 8-bromo-9-methyladenine **4** as a beige powder (Scheme 3).[15] **4** was reacted with $[Pt(PPh_3)_4]$ in toluene to give $[\mathbf{5}]$ as an off-white powder in 68% yield. Formation of $[\mathbf{5}]$ was confirmed by NMR. The ^{1}H NMR spectrum features the expected resonances for the adenine-derived ylidene and the phenyl groups. More information can be drawn from the $^{13}C\{^1H\}$ NMR spectrum, showing the resonance for the C^8-atom at δ = 149.9, downfield shifted when compared to the C^8-resonance for **4** at δ = 127.0. The $^{31}P\{^1H\}$ NMR spectrum features only one resonance at δ = 18.0 (s, Pt satellites, $^1J_{Pt,P}$ = 2801 Hz), indicative for the arrangement of two phosphine ligands in *trans* positions. In addition, an intensive peak at m/z = 948.1344 (calcd for $[\mathbf{5}+H]^+$ 948.1348) was detected in the HRMS spectrum, and microanalytical data also confirmed the formation of a complex with the composition of $[\mathbf{5}]$.

Crystals of $[\mathbf{5}]\cdot 2C_6H_6$ were obtained by slow evaporation of the solvents from a benzene/DCM solution of $[\mathbf{5}]$ at ambient temperature. The XRD structure analysis (Figure 3) with these crystals confirmed the overall composition and geometry of $[\mathbf{5}]$ as indicated from the spectroscopic data. While the majority of comparable metric parameters of $[\mathbf{2}]$ and $[\mathbf{5}]$ are almost identical, the $N^{7/9}$–C^8 distances in $[\mathbf{5}]$ differ by 0.06 Å, with the short separation found for the N7–C8 bond (1.323(3) Å) and a longer separation found for the N9–C8 bond (1.385(3) Å). This could be the result of an enhanced accumulation of negative charge at the N^7-atom of $[\mathbf{5}]$ leading to a stronger electrostatic interaction between N^7 and C^8 due to the less electron-withdrawing ligand backbone compared to the caffeine-derived ligand in $[\mathbf{2}]$. As was observed for $[\mathbf{2}]$, the N7–C8–N9 angle in $[\mathbf{5}]$ (111.7(2)°) is larger than in classical benzannulated NHC ligands.

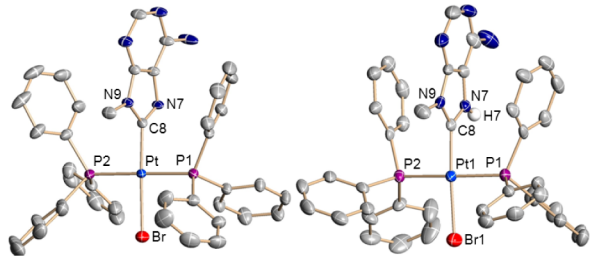


Figure 3. Molecular structures of $[\mathbf{5}]$ in $[\mathbf{5}]\cdot 2C_6H_6$ (left) and of $[\mathbf{6}]^+$ in $[\mathbf{6}]BF_4\cdot 0.5CH_2Cl_2$ (right) (nonrelevant H atoms and solvent molecules are omitted for clarity, 50% probability ellipsoids). The asymmetric unit of $[\mathbf{6}]BF_4\cdot 0.5CH_2Cl_2$ contains two formula units. The metric parameters of the two cations $[\mathbf{6}]^+$ in the asymmetric unit are identical within experimental error, so only one cation $[\mathbf{6}]^+$ is depicted here. Selected bond distances (Å) and angles (deg): for $[\mathbf{5}]$, Pt–Br 2.4987(3), Pt–P1 2.3183(6), Pt–P2 2.3131(6), Pt–C8 1.996(2), N7–C8 1.323(3), N9–C8 1.385(3), Br–Pt–P1 88.16(2), Br–Pt–P2 91.12(2), Br–Pt–C8 177.88(7), P1–Pt–P2 179.07(2), P1–Pt–C8 89.79(7), P2–Pt–C8 90.93(7), N7–C8–N9 111.7(2); for $[\mathbf{6}]^+$, Pt1–Br1 2.4678(7), Pt1–P1 2.3086(15), Pt1–P2 2.3174(15), Pt1–C8 1.979(6), N7–C8 1.327(7), N9–C8 1.359(7), Br1–Pt1–P1 89.45(4), Br1–Pt1–P2 88.86(4), Brl–Pt1–C8 178.68(16), P1–Pt1–P2 174.60(5), P1–Pt1–C8 91.80(16), P2–Pt1–C8 89.93(16), N7–C8–N9 107.0(5).

Reaction of **4** with $[Pt(PPh_3)_4]$ in the presence of the proton acid NH_4BF_4 yielded $[\mathbf{6}]BF_4$ bearing a protic NR,NH-NHC ligand derived from 9-methyladenine. $[\mathbf{6}]BF_4$ was identified by the typical resonance for the carbene C^8-atom at δ = 155.2 in the ^{1}H,^{13}C-HMBC NMR spectrum. The chemical shift of this resonance corresponds well with chemical shifts observed for protic (benz)imidazolin-2-ylidenes coordinated to Pt(II).[9a,16] In addition, the ^{1}H NMR spectrum features a resonance at δ = 12.57 for the N^7–H proton. Only one resonance at δ = 16.5 (s, Pt satellites, $^1J_{Pt,P}$ = 2484 Hz) was observed in the $^{31}P\{^1H\}$ NMR spectrum, indicating the *trans* arrangement of the phosphine donors.

The conclusions drawn from NMR were confirmed by an XRD study with crystals of composition $[\mathbf{6}]BF_4\cdot 0.5CH_2Cl_2$ obtained by slow evaporation of the solvent from a DCM solution of $[\mathbf{6}]BF_4$. The structure analysis shows complex cation $[\mathbf{6}]^+$ surrounded in a slightly distorted square-planar coordination geometry by the 9-methyladenine-derived carbene ligand, the two phosphine donors in *trans* positions, and a bromo ligand (Figure 3). All bond distances involving the Pt atom in cation $[\mathbf{6}]^+$ are slightly shorter than comparable distances in the neutral complex $[\mathbf{5}]$ bearing the unprotonated adenine-derived ylidene ligand. This is very likely to result from the different charges in $[\mathbf{5}]$ and $[\mathbf{6}]^+$. The bond parameters within the five-membered heterocycle in $[\mathbf{5}]$ and $[\mathbf{6}]^+$ also differ slightly. Upon N^7-protonation of $[\mathbf{5}]$ to $[\mathbf{6}]^+$, the $N^{7/9}$–C^8 distances become more equal (N7–C8 1.327(7) Å, N9–C8 1.359(7) Å), and the difference between the two $N^{7/9}$–C^8 distances is reduced from 0.06 Å for $[\mathbf{5}]$ to 0.03 Å for $[\mathbf{6}]^+$. As previously observed with the caffeine-derived NHC ligands, the N7–C8–N9 angle in $[\mathbf{5}]$ (111.7(2)°) shrinks upon protonation of the free ring-nitrogen atom N^7 to 107.0(5)° in $[\mathbf{6}]^+$, in accord with the expectations for a protic NHC ligand.[17]

Only one report on the molecular structure of a C^8-metalated N^9-blocked adenine has appeared so far.[18] An ethylenediamine-tethered adenine was observed to react with a Ru(III) complex to give a C^8-metalated Ru^{II} complex. No proposal for the formation of this complex and for the reduction of Ru^{III} to Ru^{II} during the

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reaction has been put forward. Based on subsequent investigations, it can be assumed that the reaction proceeds by oxidative addition of the C^8–H bond to Ru(II) followed by reductive elimination of a proton from the formed hydride complex. This proton or protons from the solvent can then protonate the N^7-atom of the adenine moiety. The chelating diamine tether is essential for the observed reactivity, and in the absence of the tether, the typical metal coordination at the N^7-atom of the nucleobase occurs.[19] Related reactivity was observed during the reaction of phosphine-tethered neutral benzimidazoles with Ru(II)[8a] and Rh(I)[8b] (Scheme 1).

We present a facile, straightforward method for the regioselective C^8-metalation of N^7- or N^9-blocked but otherwise unsubstituted purine bases by oxidative addition of the C^8–halogen bond to Pt^0 complexes. Both electron-deficient 8-chlorocaffeine and 8-bromo-9-methyladenine react in the oxidative addition reaction to give, in the absence of a proton source, the ylidene complexes with an unsubstituted ring-nitrogen atom. In the presence of a proton source, complexes bearing NMe,NH-NHC ligands are obtained from both the caffeine- and the adenine-derived ligand precursors. The oxidative addition reaction is not affected by basic functionalities of the purine bases. C^8-Metalation of adenine with selected metals in the absence of a proton source gives access to stable ylidene complexes, which possibly can be further metalated instead of protonated at the ring-nitrogen N^7-atom.[20] Such double metalation might lead to interesting building blocks for supramolecular structures and even to novel base-pairings via metal–nitrogen interactions. In addition, the use of water-soluble phosphine complexes possibly enables oxidative addition in water and subsequent incorporation of the metalated adenine into DNA, thereby generating DNA regioselectively metalated at C^8 atoms instead of at N atoms.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details for the synthesis of all compounds and X-ray crystallographic files (in CIF format) for [**2**]·$2CH_2Cl_2$, [**3**]BF_4·$0.5H_2O$, [**5**]·$2C_6H_6$, and [**6**]BF_4·$0.5CH_2Cl_2$. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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