tal analysis (%) calcd for $C_{21}H_{15}N_3O_3Ni$: C 60.62, H 3.63, N 10.10; found: C 60.58, H 3.60, N 10.05; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 3.80$ (s, 2H, CH_2), 6.8–8.9 (m, 13H, ArH); UV (CH_2Cl_2, lgε (λ_{max})): 4.60 (354 nm); IR: $\tilde{\nu} =$ 1685, 1610 (amide), 1650 cm^{-1} (C=N).

Asymmetric alkylation of **3** under PTC conditions (described for RX = BnBr): Finely ground NaOH (2.0 g, 50 mmol), substrate **3** (2.1 g, 5 mmol), and (*R*)-NOBIN (0.14 g, 0.5 mmol) in anhydrous CH_2Cl_2 (30 mL) were stirred under Ar for 3 min at 15–20 °C. Then BnBr (1 g, 5.8 mmol) was added under Ar, and the mixture was stirred for an additional 8 min. The reaction mixture was quenched by the addition of 10 mL of aqueous AcOH and diluted with CH_2Cl_2 (30 mL). The organic layer was separated, and a small part of it was used to determine the *ee* (97% *R*) of the crude Phe (Table 1, entry 5). The residue was purified by flash chromatography on silica gel (to remove unconsumed **3**) with $CHCl_3$/acetone as eluent to give **5** (2.3 g, 4.5 mmol, 90% yield, 97% *ee* according to GLC analysis of the corresponding (*R*)-amino acid). The crude complex was crystallized from C_6H_6/acetone to give the enantiomerically pure product **5** (R = Bn; 1.9 g, 3.7 mmol, 74% yield); m.p. 276 °C, $[\alpha]_D^{25} = -3605°$ ($c = 1$, $CHCl_3$/MeOH), *ee* > 99.8% (*R*) according to GLC on the amino acid (ref. [9]: for **5** (R = Bn) with *ee* 13% (*S*): $[\alpha]_D^{25} = +370°$ ($c = 1$, $CHCl_3$/MeOH)). Elemental analysis (%) calculated for $C_{28}H_{21}N_3O_3Ni$: C 66.40, H 4.15, N 8.30; found: C 66.63, H 4.28, N 8.11; ^{1}H NMR (200 MHz, $CDCl_3$): $\delta = 2.86$, 3.13 (ABX system, $J_{A,B} = 13.4$ Hz, 2H, CH_2), 4.36 (ABX system, $J_{A,X} = 2.9$, $J_{B,X} =$ 5.65 Hz, 1H, CH), 6.80–7.90 (m, 18H, Ar); UV ($CHCl_3$, lgε (λ_{max})): 2.80 (256), 3.79 (351), 3.68 (455 nm). IR: $\tilde{\nu} = 1685$, 1615 (amide), 1660 cm^{-1} (C=N).

Recovery of amino acids, as illustrated for Phe: The crystallized complex **5** (R = Bn, 1.8 g, 3.5 mmol) was decomposed by refluxing a suspension in a mixture of aqueous 6 N HCl (5 mL) and MeOH (6 mL) for a few minutes until the red color of the solution disappeared, as described previously.[9] The solution was evaporated to dryness, water was added to the residue, and the insoluble material was filtered off, washed with water, and dried to afford **4**·HCl. The aqueous layer was adjusted to pH 8 with aqueous ammonia solution, and the mixture was extracted with $CHCl_3$ (3 × 10 mL) to remove small amounts of remaining **4**. Phe was recovered from the aqueous solution by the ion-exchange technique (DOWEX-50, H^+ form). (*R*)-Phe (0.40 g, yield 68%) was analyzed by chiral GLC (*ee* > 99.8%); m.p. 288–290 °C (decomp), $[\alpha]_D^{25} = +33.2$ ($c = 2$, H_2O), [ref. [10]: (*S*)-Phe $[\alpha]_D^{25} = -33.4$ ($c = 1.3$, H_2O)]. Elemental analysis (%) calcd for $C_9H_{11}NO_2$: C 65.44, H 6.71, N 8.48; found: C 65.36, H 6.78, N 8.44.

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[1] A. Nelson, *Angew. Chem.* **1999**, *111*, 1685–1687; *Angew. Chem. Int. Ed.* **1999**, *38*, 1583–1585.

[2] a) M. J. O'Donnell, W. D. Bennett, S. Wu, *J. Am. Chem. Soc.* **1989**, *111*, 2353–2355; M. J. O'Donnell, F. Delgano, C. Hostettler, R. Schwesinger, *Tetrahedron Lett.* **1998**, *39*, 8775–8778; b) U.-H. Dolling, P. Davis, E. J. J. Grabowski, *J. Am. Chem. Soc.* **1984**, *106*, 446–447; c) E. Corey, F. Xu, M. Noe, *J. Am. Chem. Soc.* **1997**, *119*, 12414–12415; E. Corey, M. Noe, F. Xu, *Tetrahedron Lett.* **1998**, *39*, 5347–5350; E. Corey, Y. Bo, J. Busch-Petersen, *J. Am. Chem. Soc.* **1998**, *120*, 13000–13001; d) B. Lygo, J. Crosby, T. R. Lowdon, P. G. Wainwright, *Tetrahedron Lett.* **1997**, *38*, 2343–2345; B. Lygo, P. G. Wainwright, *Tetrahedron Lett.* **1997**, *38*, 8595–8598; B. Lygo, P. G. Wainwright, *Tetrahedron Lett.* **1998**, *39*, 1599–1602; B. Lygo, J. Crosby, J. A. Peterson, *Tetrahedron Lett.* **1999**, *40*, 8671–8674; e) R. Chinchilla, P. Mazon, C. Najera, *Tetrahedron: Asymmetry* **2000**, *11*, 3277–3281.

[3] T. Ooi, M. Kameda, K. Maruoka, *J. Am. Chem. Soc.* **1999**, *121*, 6519–6520; T. Ooi, M. Takeuchi, M. Kameda, K. Maruoka, *J. Am. Chem. Soc.* **2000**, *122*, 5228–5229.

[4] Yu. N. Belokon, K. A. Kochetkov, T. D. Churkina, N. S. Ikonnikov, A. A. Chesnokov, O. V. Larionov, I. Singh, V. S. Parmar, Š. Vyskočil, H. B. Kagan, *J. Org. Chem.* **2000**, *65*, 7041–7048.

[5] Yu. N. Belokon, K. A. Kochetkov, T. D. Churkina, N. S. Ikonnikov, S. A. Orlova, V. V. Smirnov, A. A. Chesnokov, *Mendeleev Commun.* **1997**, 137–138.

[6] a) C. Girard, H. B. Kagan, *Angew. Chem.* **1998**, *110*, 3088–3127; *Angew. Chem. Int. Ed.* **1998**, *37*, 2922–2959; b) K. Mikami, M. Terada, T. Korenaga, Y. Matsumoto, M. Ueki, R. Angelaud, *Angew. Chem.* **2000**, *112*, 3676–3701; *Angew. Chem. Int. Ed.* **2000**, *39*, 3532–3556.

[7] M. Smrčina, J. Polákova, Š. Vyskočil, P. Kočovský, *J. Org. Chem.* **1993**, *58*, 4534–4538; M. Smrčina, Š. Vyskočil, J. Polívková, J. Poláková, P. Kočovský *Collect. Czech. Chem. Commun.* **1996**, *61*, 1520; H. Mahmound, Y. Han, B. Segal, L. Cai, *Tetrahedron: Asymmetry* **1998**, *9*, 2035–2045; K. Ding, Y. Wang, H. Yun, J. Liu, Y. Wu, M. Terada, Y. Okubo, K. Mikami, *Chem. Eur. J.* **1999**, *5*, 1734–1737.

[8] S. Makaparskin, P. Birrel, E. Gil-av, I. Oro, *J. Chromatogr. Sci.* **1970**, *8*, 177.

[9] Yu. N. Belokon, V. I. Maleev, T. Ph. Savel'eva, N. S. Garbalinskaya, M. B. Saporovskaya, V. I. Bakhmutov, V. M. Belikov, *Izv. Akad. Nauk SSSR Ser. Khim.* **1989**, *47*, 631–635; *Bull. Acad. Sci. USSR Div. Chem. Sci.* **1989**, *37*, 557–562.

[10] J. P. Greenstein, M. Winitz, *Chemistry of the Amino Acids*, *Vol. 1*, Wiley, New York, **1961**, p. 116.

Synthesis and Characterization of a Metallabenzyne**

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Interesting organometallic compounds can often be obtained by replacement of (hydro)carbon groups of organic compounds with isolobal transition metal fragments.[1] For example, the CH_2 group in CH_2=CHR can be replaced by 16-electron transition metal fragments [L_nM] to give carbene complexes [L_nM=CHR], the CH group in HC≡CR can be replaced by 15-electron transition metal fragments [L_nM] to give carbyne complexes [$L_nM \equiv$ CR], and a CH group in benzene can be replaced by 15-electron transition metal fragments to give metallabenzenes.[2] In principle, a carbon atom in benzyne could also be replaced by 14-electron transition metal fragments to give metallabenzynes. However, such a possibility has not previously been realized. Here we describe the synthesis and characterization of the first metallabenzyne.

Treatment of [$OsCl_2(PPh_3)_3$] (**1**)[3] with an excess of HC≡CSiMe$_3$ in wet benzene produced a yellow precipitate and a brown solution. The yellow precipitate was identified as

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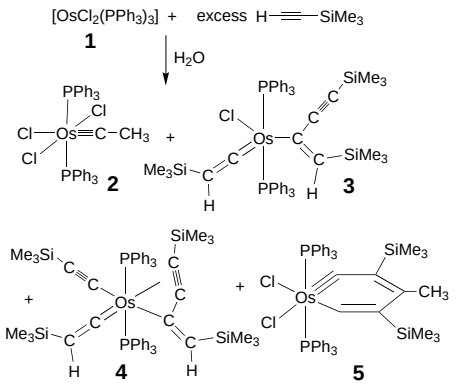
the carbyne complex $[OsCl_3(\equiv CCH_3)(PPh_3)_2]$ (**2**). From the brown solution, complexes **3**, **4**, and the metallacyclic **5** were isolated in 22, 4.5, and 30% yield, respectively (Scheme 1).



Scheme 1. Reaction of **1** with $HC\equiv CSiMe_3$.

All new complexes were characterized by elemental analysis and multinuclear NMR spectroscopy. The structures of **4** and **5** were also confirmed by X-ray diffraction analysis (Figures 1 and 2).[4] Formation of complexes **2** and **3** from the

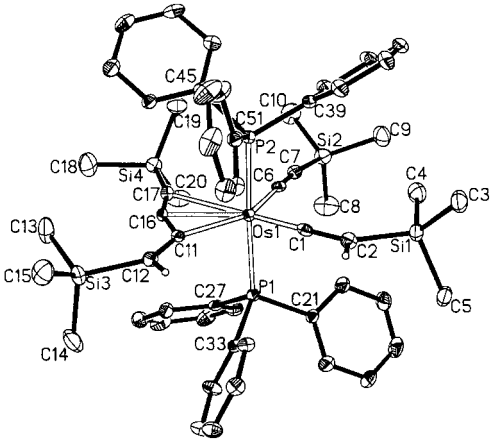


Figure 1. Molecular structure of **4**. Selected bond lengths [Å] and angles [°]: Os1-P1 2.3821(14), Os1-P2 2.3722(14), Os1-C1 1.803(6), Os1-C6 2.060(5), Os1-C11 2.126(5), Os1-C16 2.341(5), Os1-C17 2.685(5), C1-C2, 1.332(7), C6-C7 1.218(6), C11-C12 1.321(7), C11-C16 1.406(7), C16-C17 1.223(7); C2-C1-Os1 179.1(5), C1-C2-Si1 128.7(5), C7-C6-Os1 177.6(5), C6-C7-Si2 172.8(5), C12-C11-Os1 150.6(4), C11-C12-Si3 126.9(4), C16-C11-Os1 80.2(3), C16-C17-Si4 161.5(5), C11-C16-Os1, 63.5(3), C17-C16-Os1 92.3(4), C12-C11-C16 129.1(5), C17-C16-C11 155.8(5), Si4-C17-Os1 137.87(26), P2-Os1-P1 171.41(5).

reaction of **1** with an excess of $HC\equiv CSiMe_3$ can be understood, as the similar products $[OsCl_3(\equiv CCH_2CMe_3)(PPh_3)_2]$ and $[OsCl(=C=CHCMe_3)\{C(C\equiv CCMe_3)=CHCMe_3\}(PPh_3)_2]$ were obtained from the reaction of **1** with an excess of $HC\equiv CCMe_3$ via the intermediate $[OsCl_2(=C=CHCMe_3)(PPh_3)_2]$.[5] Thus one might expect that $[OsCl_3(\equiv CCH_2SiMe_3)(PPh_3)_2]$ and **3** could also be produced from the reaction of **1** with $HC\equiv CSiMe_3$ via the intermediate $[OsCl_2(=C=CHSiMe_3)(PPh_3)_2]$. However, desilylation apparently occurred in the formation of **2** as a result of hydrolysis of the $C-SiMe_3$ bond. There are many reports that reactions of

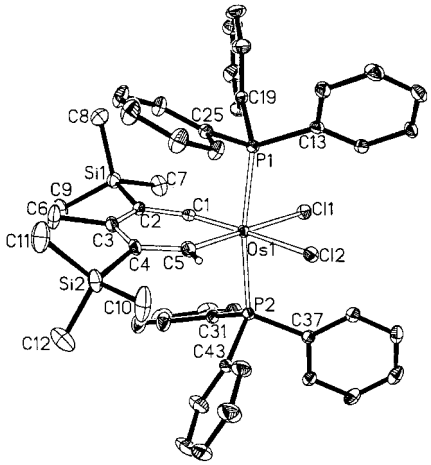
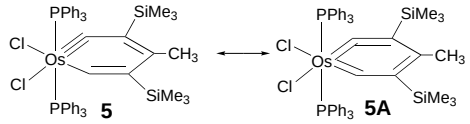


Figure 2. Molecular structure of **5**. Selected bond lengths [Å] and angles [°]: Os1-P1 2.4103(9), Os1-P2 2.4117(10), Os1-Cl1 2.4798(9), Os1-Cl2 2.4811(10), Os1-C1 1.815(4), Os1-C5 1.939(5), C1-C2 1.376(5), C2-C3 1.420(5), C3-C4 1.416(6), C4-C5 1.378(6), C3-C6 1.515(7); P1-Os1-P2 171.21(3), C1-Os1-C5 78.1(2), C4-C3-C2 124.0(4), C2-C1-Os1 148.7(3), C4-C5-Os1 138.6(5), C1-C2-C3 112.4(4), C5-C4-C3 117.7(4), C1-C2-Si1 120.0(3), C5-C4-Si2 118.8(4), C3-C2-Si1 127.6(3), C3-C4-Si2 123.4(3), C2-C3-C6 117.4(5), C4-C3-C6 118.6(5).

silylated alkynes with low-valent transition metal complexes in the presence of water can lead to hydrolysis of C–Si bonds to give C–H bonds.[6, 7] Complex **4** is presumably formed by the reaction of **3** with $HC\equiv CSiMe_3$ and elimination of HCl.

The most unusual complex formed in the reaction of **1** with an excess of $HC\equiv CSiMe_3$ is **5**. As confirmed by X-ray diffraction analysis, it contains an essentially planar six-membered metallacycle (Figure 2). The maximum deviation from the least-squares plane through Os1 and C1 – C5 is 0.047 Å for C1. The C1–C2 distance (1.376(5) Å) is comparable to that of C4–C5 (1.378(6) Å), and the C2–C3 distance (1.420(5) Å) is similar to that of C3–C4 (1.416(6) Å). The Os–C1 bond length (1.815(4) Å) is slightly longer than those observed for typical Os≡C bonds[6, 8] and is at the lower end of those found for Os=C=CRR′ complexes.[9] The Os–C5 bond length (1.939(5) Å) is slightly shorter than those observed for typical Os–C(vinyl) bonds[10] and is within the range of those reported for Os–C(carbene) bonds.[11] The Os–C and C–C bond lengths within the six-membered ring, together with its planar nature, indicate that the six-membered metallacycle has a delocalized structure with contributions from the resonance structures **5** and **5A**. The Os1-C1-C2 angle



(148.7(3)°) is significantly smaller than that expected for a carbyne or vinylidene complex owing to the constraint of the six-membered ring. Consistent with the solid-state structure, the $^{13}C\{^1H\}$ NMR spectrum of **5** displayed signals for Os≡C and Os–CH at $\delta = 306.6$ and 227.8, respectively. Since the structure of **5** is closely related to that of benzyne, complex **5** can be regarded as a metallabenzyne.

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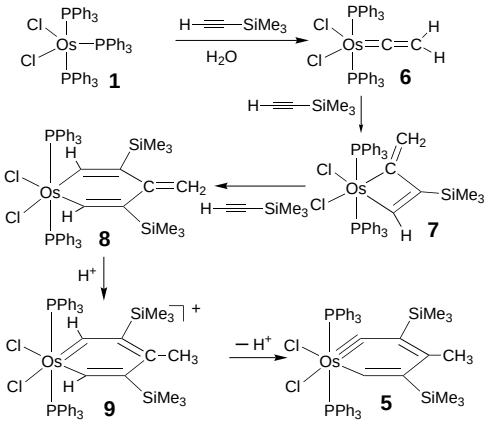
Although many metallabenzenes are known,[2] complex **5** appears to be the first well characterized example of a metallabenzyne. Benzynes[12] are important intermediates which have been widely used in organic and organometallic synthesis and mechanistic studies. However, it is difficult to isolate free benzynes because of their low thermal stability and high reactivity. To our knowledge, no X-ray structures of free benzynes have previously been determined.

Scheme 2 shows a plausible mechanism for the formation of **5**. Reaction of $[OsCl_2(PPh_3)_3]$ (**1**) with $HC{\equiv}CSiMe_3$ could initially produce the vinylidene intermediate $[OsCl_2(=C=CHSiMe_3)(PPh_3)_2]$ which can undergo desilylation in



Scheme 2. A proposed mechanism for the formation of **5**.

the presence of water to give **6**. Related ruthenium vinylidene complexes $[RuCl_2(=C=CHR)(PPh_3)_2]$ were prepared from the reactions of $[RuCl_2(PPh_3)_3]$ with $HC{\equiv}CR$.[13] Intermediate **6** can react with additional $HC{\equiv}CSiMe_3$ to give **7** and **8**. Complex **8** could then rearrange to the osmabenzyne **5** by an acid-catalyzed reaction, i.e., protonation of the $=CH_2$ carbon atom of **8** to give **9** followed by deprotonation of an α-CH proton of **9**. The protonation/deprotonation process could be mediated by any proton donor (e.g., the carbyne complex **3** or H_2O) present in the reaction mixture. Consistent with the mechanism, it was shown that deuterium is incorporated into the methyl group of **5** when the reaction is carried out in the presence of D_2O.

In summary, we have synthesized the first metallabenzyne **5** from the reaction of $[OsCl_2(PPh_3)_3]$ (**1**) with $HC{\equiv}CSiMe_3$. We are currently preparing other metallabenzynes and investigating the chemistry of this novel class of compounds.

Experimental Section

A mixture of **1** (1.0 g, 0.95 mmol) and $HC{\equiv}CSiMe_3$ (1.1 mL, 7.6 mmol) in benzene (15 mL) was stirred at room temperature (RT) for 5 d to give a yellow microcrystalline solid and a brown solution. The volume of the reaction mixture was reduced to ca. 5 mL, and it was filtered. The yellow solid was washed with benzene (3 mL) and diethyl ether (2×10 mL) and dried under vacuum to give **2** (0.11 g, 14%). The filtrate was concentrated to ca. 1 mL, and hexane (30 mL) was added slowly with stirring to give a brownish green precipitate and a brownish red solution, which were separated by filtration. The solvent of the brownish red filtrate was removed under vacuum, and the residue was extracted with 10 mL of hexane and filtered. The brownish red extract was allowed to stand at $-8\,^{\circ}C$ for several days to give **4** as yellow microcrystalline needles, which were collected by filtration and washed with hexane (3 mL) and dried under vacuum (0.047 g, 4.5%). Further storage of the mother liquid at $-8\,^{\circ}C$ after concentration to 5 mL gave **3** as brownish red blade crystals, which were collected by filtration, washed with hexane (5 mL) and dried under vacuum (0.22 g, 22%). The brownish green solid obtained above was washed with hexane (15 mL), dried, and redissolved in 2 mL of CH_2Cl_2. A greenish blue solid formed when hexane (30 mL) was added with stirring. The solid was collected by filtration, washed with diethyl ether (2×10 mL) and hexane (2×20 mL), and dried under vacuum to give **5** (0.29 g, 30%).

2: $^{31}P\{^1H\}$ NMR (121.5 MHz, CD_2Cl_2): $\delta = -13.5$ (s); ^1H NMR (300.13 MHz, CD_2Cl_2): $\delta = 0.042$ (t, $^4J(P,H) = 2.5$ Hz, 3H, CH_3), 7.36–7.43 (m, 18H, PPh_3), 7.89–7.96 (m, 12H, PPh_3); $^{13}C\{^1H\}$ NMR (100.40 MHz, CD_2Cl_2): $\delta = 283.7$ (t, $^2J(P,C) = 12.3$ Hz, Os≡C), 135.1–127.9 (m, PPh_3), 36.9 (s, CH_3); elemental analysis (%): calcd for $C_{38}H_{33}Cl_3OsP_2$: C 53.81, H 3.92; found: C 53.60, H 4.18.

3: $^{31}P\{^1H\}$ NMR (121.5 MHz, CD_2Cl_2, 298 K): $\delta = 13.6$ (brs); ^1H NMR (300.13 MHz, CD_2Cl_2, 298 K): $\delta = -0.38$ (s, 9H, $SiMe_3$), -0.33 (s, 9H, $SiMe_3$), 0.02 (t, $^4J(P,H) = 3.6$ Hz, 1H, Os=C=CH), 0.08 (s, 9H, $SiMe_3$), 4.68 (brs, 1H, Os-C=CH), 7.32–7.40 (m, 18H, PPh_3), 7.62–7.67 (m, 12H, PPh_3); $^{13}C\{^1H\}$ NMR (100.40 MHz, CD_2Cl_2, 298 K): $\delta = 272.7$ (brs, Os=C), 144.8 (brs, Os*C*=CH), 143.3 (brs, Os-C=*C*H), 136.2–128.7 (m, other aromatic C and C≡C), 91.9 (brs, Os=C=*C*H), 1.9 (s, $SiMe_3$), 0.0 (s, $SiMe_3$), -0.1 (brs, $SiMe_3$); elemental analysis (%): calcd for $C_{51}H_{59}ClOsP_2Si_3$: C 58.68, H 5.70; found: C 58.79, H 5.87.

4: $^{31}P\{^1H\}$ NMR (121.5 MHz, CD_2Cl_2, 298 K): $\delta = 3.1$ (brs); ^1H NMR (300.13 MHz, CD_2Cl_2, 298 K): $\delta = -0.51$ (s, 9H, $SiMe_3$), -0.26 (brs, 18H, $2 \times SiMe_3$), -0.02 (s, 9H, $SiMe_3$), 0.48 (t, $^4J(P,H) = 3.7$ Hz, 1H, Os=C=CH), 5.47 (brs, 1H, OsC=CH), 7.28–7.32 (m, 18H, PPh_3), 7.68–7.84 (m, 12H, PPh_3); $^{13}C\{^1H\}$ NMR (100.40 MHz, CD_2Cl_2, 298 K): $\delta = 275.1$ (t, $^2J(P,C) = 11.9$ Hz, Os=C), 161.9 (t, $^2J(P,C) = 6.7$ Hz, Os*C*=CH), 140.2 (s, OsC=*C*H), 135.7–127.4 (m, other aromatic C and C≡C), 116.7 (s, OsC(*C*≡CSiMe_3)=CH$SiMe_3$), 93.9 (t, $^3J(P,C) = 3.7$ Hz, Os=C=*C*H), 83.5 (s, Os-C≡*C*$SiMe_3$), 1.2 (s, Si$(CH_3)_3$), 1.0 (s, $SiMe_3$), -1.0 (s, $SiMe_3$), -1.1 (s, $SiMe_3$); elemental analysis (%): calcd for $C_{56}H_{68}OsP_2Si_4$: C 60.84, H 6.20; found: C 60.81, H 6.30.

5: $^{31}P\{^1H\}$ NMR (121.5 MHz, CD_2Cl_2): $\delta = -3.3$ (s); ^1H NMR (300.13 MHz, CD_2Cl_2): $\delta = -0.14$ (s, 9H, $SiMe_3$), 0.06 (s, 9H, $SiMe_3$), 2.27 (s, 3H, CH_3), 7.27–7.38 (m, 18H, PPh_3), 7.62–7.68 (m, 12H, PPh_3), 13.83 (s, 1H, OsCH); $^{13}C\{^1H\}$ NMR (100.40 MHz, CD_2Cl_2): $\delta = 306.6$ (t, $^2J(P,C) = 10.1$ Hz, Os≡C), 227.8 (t, $^2J(P,C) = 6.5$ Hz, OsCH), 188.6 (s, *C*CH_3), 136.1 (s, *C*$SiMe_3$), 135.0 (t, $J(P,C) = 4.6$ Hz, *m*-PPh_3), 132.6 (t, $J(P,C) = 26.8$ Hz, *ipso*-PPh_3), 130.5 (s, *p*-PPh_3), 127.9 (t, $J(P,C) = 4.6$ Hz, *o*-PPh_3), 113.0 (s, *C*$SiMe_3$), 27.1 (s, CH_3), 1.7 (s, $SiMe_3$), 0.9 (s, $SiMe_3$); elemental analysis (%): calcd for $C_{48}H_{52}Cl_2OsP_2Si_2$: C 57.19, H 5.20; found: C 57.38, H 5.38.

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[1] R. H. Crabtree, *The Organometallic Chemistry of the Transition Metals*, 2nd ed., Wiley, New York, **1994**, p. 348.

[2] See for example: a) C. E. F. Rickard, W. R. Roper, S. D. Woodgate, L. J. Wright, *Angew Chem.* **2000**, *112*, 766; *Angew Chem. Int. Ed.* **2000**, *39*, 750; b) R. D. Gilbertson, T. J. R. Weakley, M. M. Haley, *J. Am. Chem. Soc.* **1999**, *121*, 2597; c) U. Englert, F. Podewils, I. Schiffers, A. Salzer, *Angew Chem.* **1998**, *110*, 2196; *Angew Chem. Int. Ed.* **1998**, *37*, 2134; d) J. R. Bleeke, R. Behm, *J. Am. Chem. Soc.* **1997**, *119*, 8503; e) J. R. Bleeke, R. Behm, Y. F. Xie, M. Y. Chiang, K. D. Robinson, A. M. Beatty, *Organometallics* **1997**, *16*, 606, and references therein; f) G. P. Elliott, W. R. Roper, J. M. Waters, *J. Chem. Soc. Chem. Commun.* **1982**, 811.

[3] P. R. Hoffman, K. G. Caulton, *J. Am. Chem. Soc.* **1975**, *97*, 4221.

[4] All the intensity data were collected on a Bruker SMART CCD Area Detector with graphite-monochromated $Mo_{K\alpha}$ radiation at room temperature. All structures were solved by direct methods, expanded by difference Fourier syntheses, and refined by full-matrix least-squares methods on F^2 by using the Bruker SHELXTL (Version 5.10) program package. Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were placed in ideal positions and refined as

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riding atoms. Crystal data for **4**: $C_{56}H_{68}OsP_2Si_4 \cdot C_6H_6$, $M_r = 1183.71$; triclinic, space group $P\bar{1}$; $a = 12.5486(16)$, $b = 13.5107(18)$, $c = 20.905(3)$ Å, $\alpha = 90.187(3)$, $\beta = 104.815(3)$, $\gamma = 116.824(2)^\circ$, $V = 3028.7(7)$ Å^3; $Z = 2$, $\rho_{calcd} = 1.298$ g cm^{-3}; 20888 reflections, 13820 independent reflections ($R_{int} = 0.0454$); $R_1 = 0.0502$, $wR_2 = 0.0736$ for 630 parameters and 8304 reflections with $I > 2\sigma(I)$. The two protons H2A and H12A attached to the vinyl carbon atoms were located in the difference Fourier maps and refined isotropically. Crystal data for **5**: $C_{48}H_{52}Cl_2OsP_2Si_2$, $M_r = 1008.12$; monoclinic, space group $P2_1/n$; $a = 12.7613(4)$, $b = 17.4260(6)$, $c = 21.4826(7)$ Å, $\beta = 104.1100(10)^\circ$, $V = 4633.1(3)$ Å^3; $Z = 4$, $\rho_{calcd} = 1.445$ g cm^{-3}; 30794 reflections, 11178 independent reflections ($R_{int} = 0.0478$); $R_1 = 0.0327$, $wR_2 = 0.0566$ for 512 parameters and 7697 reflections with $I > 2\sigma(I)$. The protons attached to C5 and C6 were located from the difference Fourier maps and refined with isotropic thermal parameters. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-155319 (**4**) and CCDC-155320 (**5**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

[5] T. B. Wen, S. Y. Yang, Z. Y. Zhou, Z. Lin, C. P. Lau, G. Jia, *Organometallics* **2000**, *19*, 3757.

[6] H. Werner, S. Jung, B. Webernörfer, J. Wolf, *Eur. J. Inorg. Chem.* **1999**, 951.

[7] See, for example, a) C. Bianchini, A. Marchi, L. Marvelli, M. Peruzzini, A. Romerosa, R. Rossi, *Organometallics* **1996**, *15*, 3804; b) M. L. Buil, O. Eisenstein, M. A. Esteruelas, C. Garcîa-Yebra, E. Gutiérrez-Puebla, M. Oliván, E. Oñate, N. Ruiz, M. A. Tajada, *Organometallics* **1999**, *18*, 4949; c) Y. Kawata, M. Sato, *Organometallics* **1997**, *16*, 1093.

[8] M. A. Esteruelas, M. Oliván, E. Oñate, N. Ruiz, M. A. Tajada, *Organometallics* **1999**, *18*, 2953.

[9] a) D. Huang, M. Oliván, J. C. Huffman, O. Eisenstein, K. G. Caulton, *Organometallics* **1998**, *17*, 4700; b) B. Weber, P. Steinert, B. Windmüller, J. Wolf, H. Werner, *J. Chem. Soc. Chem. Commun.* **1994**, 2595; c) L. J. Baker, C. E. F. Rickard, W. R. Roper, S. D. Woodgate, L. J. Wright, *J. Organomet. Chem.* **1998**, *565*, 153.

[10] a) C. Bohanna, B. Callejas, A. J. Edwards, M. A. Esteruelas, F. J. Lahoz, L. A. Oro, N. Ruiz, C. Valero, *Organometallics* **1998**, *17*, 373; b) H. Werner, M. A. Esteruelas, H. Otto, *Organometallics* **1986**, *5*, 2295.

[11] a) H. Werner, W. Stüer, N. Laubender, C. Lahmann, R. Herbst-Irmer, *Organometallics* **1997**, *16*, 2236; b) M. A. Esteruelas, F. J. Lahoz, E. Oñate, L. A. Oro, C. Valero, B. Zeier, *J. Am. Chem. Soc.* **1995**, *117*, 7935.

[12] For recent work on benzynes in organic/organometallic synthesis, see a) E. Yoshikawa, K. V. Radhakrishnan, Y. Yamamoto, *J. Am. Chem. Soc.* **2000**, *122*, 7280; b) M. A. Bennett, C. J. Cobley, A. D. Rae, E. Wenger, A. C. Willis, *Organometallics* **2000**, *19*, 1533; c) S. Tripathy, R. LeBlanc, T. Durst, *Org. Lett.* **1999**, *1*, 1973; d) T. Kitamura, M. Yamane, K. Inoue, M. Todaka, N. Fukatsu, Z. Meng, Y. Fujiwara, *J. Am. Chem. Soc.* **1999**, *121*, 11674; e) M. Frid, D. Pérez, A. J. Peat, S. L. Buchwald, *J. Am. Chem. Soc.* **1999**, *121*, 9469.

[13] Y. Wakatsuki, N. Koga, H. Yamazaki, K. Morokuma, *J. Am. Chem. Soc.* **1994**, *116*, 8105.

Characterization of the Alkylation Product of Heme by the Antimalarial Drug Artemisinin**

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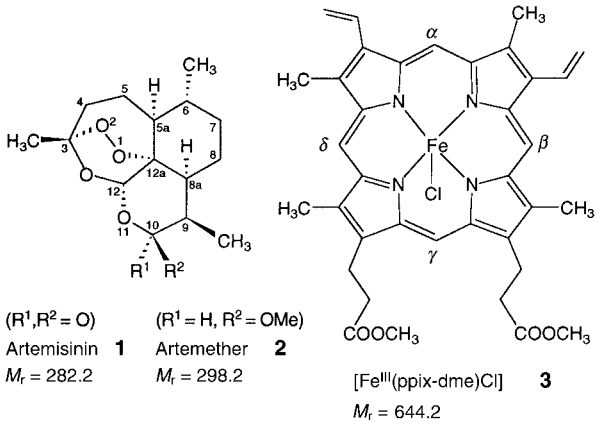
Artemisinin **1** and its hemi-synthetic derivatives such as artemether **2** are increasingly used to treat *Plasmodium falciparum* drug-resistant malaria, which causes between one and three million deaths annually.[1] The stable endoperoxide bridge of these compounds is required for their antimalarial



activity. The activity of artemisinin is dependent on the cleavage of the endoperoxide by intraparasitic heme, which is generated by the digestion of hemoglobin within infected red blood cells.[2–5] In fact, the reductive activation by Fe^{II}–heme results in the homolytic cleavage of the endoperoxide bond and the subsequent formation of drug-derived carbon-centered radicals, which act as alkylating agents toward either heme or vital parasite proteins. The alkylation of proteins[6] or heme[7] was observed after the incubation of parasites with pharmacologically relevant concentrations of artemisinin derivatives but no heme–artemisinin or protein–artemisinin adducts had been characterized up to now. Herein we report the first characterized adduct produced by the alkylation of heme by the antimalarial artemisinin.

The alkylation of a synthetic metalloporphyrin heme model, manganese(II) tetraphenylporphyrin, by artemisinin,[8] artemether, and other synthetic pharmacologically active trioxanes[9] has been reported in recent years. Herein, the "true" target of artemisinin, heme, was used. Artemisinin was incubated under an argon atmosphere with the dimethyl ester of hemin, [Fe^{III}(ppix-dme)Cl] (**3**), in dichloromethane in the presence of 2,3-dimethylhydroquinone to reduce hemin to

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