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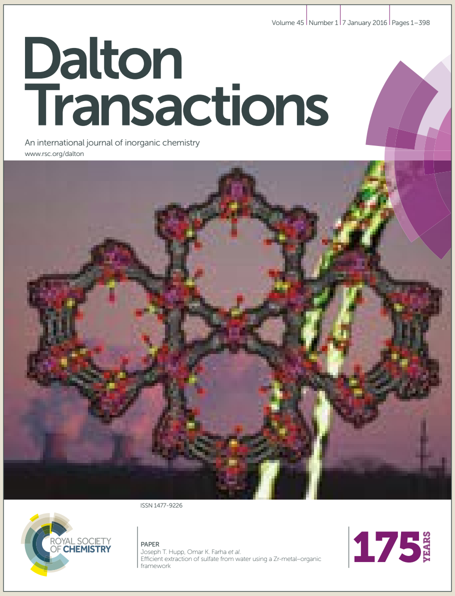

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1,5-Cyclooctadienyl alcohols and ketones generate a new class of COD Pt complexes

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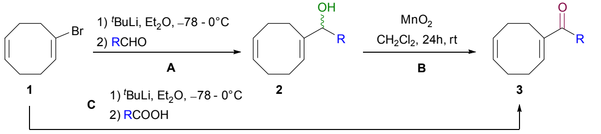
A variety of new racemic alcohol and ketone cyclooctadiene derivatives was prepared for their complexation with platinum to generate a new class of platinum(II) complexes.

Platinum(II)[1-6] and other metal[7-9] complexes with unsubstituted 1,5-cyclooctadiene (COD) are very common as building blocks for the creation of other mono- and polynuclear platinum(II) complexes.[10-16] Besides that platinum compounds have been used in catalysis[17-19] and material science,[20, 21] they also have shown interesting cytotoxic properties.[3, 6, 22-24] Recently we have discovered new organometallic platinum(II) compounds with monosubstituted 1,5-cyclooctadiene ligands and performed their detailed NMR characterization and toxicological studies.[12] However, there are virtually no reports on the effect of additional coordinating groups, so there is still plenty of room for investigation.

In this work we elaborate the synthesis of oxygen-functionalized cyclooctadienyl derivatives inspired by the work of Matier *et al.*[25] (Scheme 1) and the discovery of new platinum complexes with monosubstituted 1,5-cyclooctadiene units. Recently, we disclosed a route using palladium-catalyzed lithium cross-coupling reactions using cyclooctadienyl lithium as the building block of choice.



Scheme 1: Synthesis of 1,5-cyclooctadienyl alcohols **2** and ketones **3**.

Herein we presented the optimization of the lithiation of COD (see SI). This step expresses the most crucial step for the work we describe in this paper.[26] In order to obtain the desired building blocks, two pathways turned out to be feasible (Scheme 1).

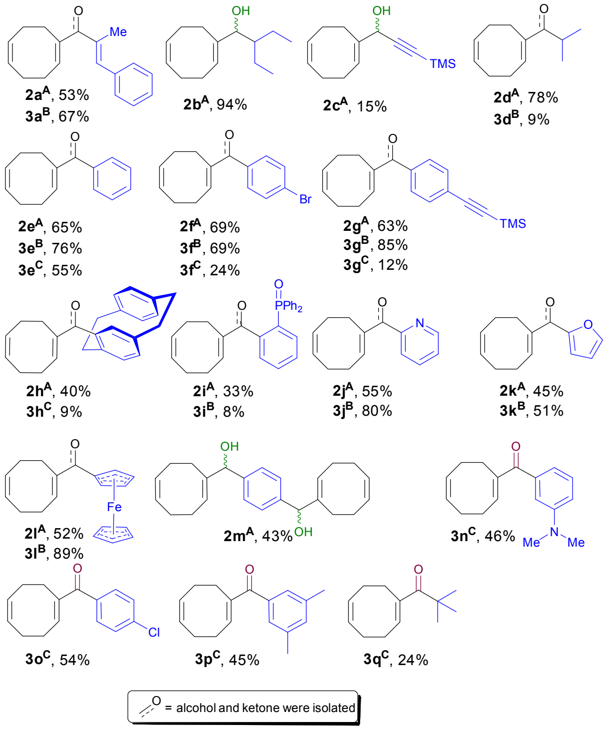


Figure 1: Synthesized COD derivatives. (^{A}: yield of the alcohol; ^{B}: yield of the ketone via Method B; ^{C}: yield of the ketone via Method C; isolated yields)

The two-step method A/B started from the lithiated species which was treated with the corresponding aldehydes to form the alcohols **2a**-**2m** and then oxidized with manganese dioxide to yield compounds **3a**, **3d**-**3g** and **3i**-**3l** (for the molecular structure of **3f**, see SI).

Specifically, the alcohol derivatives were isolated in moderate (**2i**; 33%) to excellent yields (**2b**; 94%). Alcohol **2c** was obtained in a yield of 15%. Over a time-period of a few days the mass of the starting material could not be detected *via* GC-MS, that aggravates the performance of the second step, the oxidation.

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Electronic Supplementary Information (ESI) available: Crystallographic data of **3f** (CCDC 1812128) and **5e** (CCDC 1812129) in cif-format.

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Phosphine **2i** was synthesized starting from 2-(diphenylphosphino)benzaldehyde.

Our motivation was to build up ligands with two interesting coordination sides for the synthesis of bimetallic complexes. The COD derivative **2i** contains the diene moiety for coordination of one metal and the phosphine and an alcohol moiety as bidentate coordination for the second metal. Unfortunately, it turned out that the phosphorous was easily oxidized during the reaction, following by the formation of unknown byproducts, which reduces the yield of the unexpected but still attractive product.

Paracyclophane derivative **2h** was produced as a single diastereomer, the relative configuration was assumed to be R_P/S and R_p/R. Terephthaldehyde gave a mixture of *meso*- and *rac*-**2m**.

Oxidation of the alcohols **2a, 2d-2g** and **2i-2l** by manganese dioxide[27] delivered the ketones **3a, 3d-3g** and **3i-3l** in good to very good yields (51-89%) with two exceptions (**3d**/9%; **3i**/8%). For the synthesis of compound **3d** it is necessary to use another conditions with stronger oxidative reagents, e.g. pyridinium chlorochromate in order to increase the reaction yield.[28] On closer examination, the molecule **2b** exhibits similar structural properties like **2d**, so stronger oxidative conditions are necessary to obtain the corresponding ketone in a good yield, therefore the experiment was not carried out.

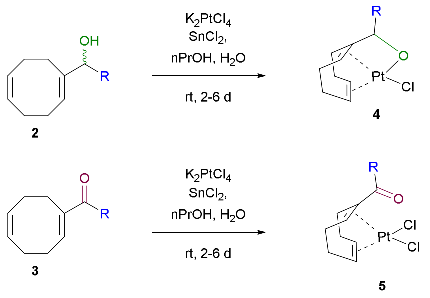
Phosphineoxide **3i** was isolated in low yields for reasons described above.

Finally, the ketones **3e-h** and **3n-q** can be prepared directly in one step starting from COD-Li and carboxylic acids in low to moderate yields (9-55%). In general, benzoic acid derivatives are suitable for this method, while the reaction is not compatible with enolizable compounds. For example, the ketone **3d** was synthesized via Method B, but could not be formed by Method C. Lithiated COD acts as a base and enolates the isobutyric acid, therefore the desired product cannot be obtained by this method. In summary the two-step route A/B is more versatile than the direct method supported by the fact of the use of a high excess of lithiated specie.

Nearly all products were obtained in high yields. The compounds shown in Figure 1 are unknown, except of **2a** and **3a**.[25]

With these new substances in hand we performed the synthesis of platinum(II) complexes starting from these novel ligand classes. Platinum(II) complexes were synthesized based on the protocols which were reported by us previously[12] following the procedure developed by Wen[29] and Clark.[30] Using Clark`s protocol, we were able to isolate monometallic platinum(II) complexes starting from our newly synthesized alcohols and ketones (Scheme 2, Figure 2).

Complexes **4d**, **4h**, **5d** and **5e** were obtained in good yields (Figure 2). The gross formula of complexes **4f** and **4e** were corroborated by EI-Mass and HRMS but the structure could not fully investigated via NMR spectroscopy (vide infra).



Scheme 2. Synthesis of platinum (II) complexes **4,5** starting from alcohol **2** and ketone **3** derivatives, respectively.

For **4f** the corresponding alcohol **2f** is just slightly soluble in all solvents which can be used for the reaction system. So, the resulting solid product was isolated as a mixture of the newly formed complex **4f** and the starting material **2f**. Also heating up the reaction mixture for a couple of hours did not change the conformation turnover. Interestingly, the complex **4e** was insoluble in all commercial available deuterated solvents.

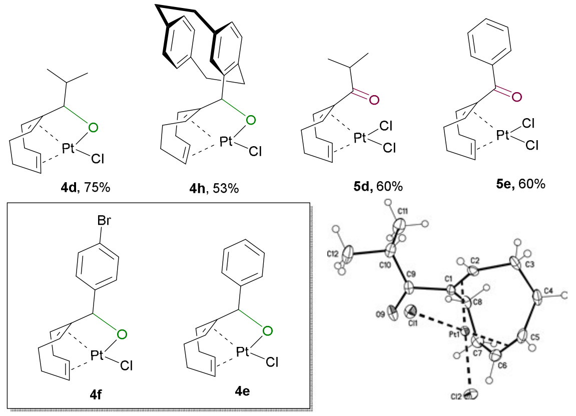


Figure 2. First examples for intramolecular COD alkoxide and acyl platinum(II) complexes; molecular structure of complex **5d** (displacement parameters are drawn at 50% probability level).

For complex **5d** we obtained a molecular structure which confirms the proposed conformation (Figure 2). The acyl complexes **5** show hemi-labile behavior – the mass spectra shows the fast release of one chloride ion (see SI).

The performance of the synthesis of the complexes starting from the alcohols is a lot easier to realize. Most of the alcohols are oils which are soluble in *n*propanol. The handling of paracyclophanes can be difficult. Using Method C gave cyclooctadiene **3h** in a low yield of 9%. So, we decided to focus on the formation of the complex **4h**. Further, we developed the synthesis of compound **2m** because of our high interest to yield directly a bimetallic Pt-complex. Unfortunately, the reaction was not successful.

These complexes **4** and **5** represent a new class of platinum(II) complexes. We showed that a 1-substituted cyclooctadiene derivative can be used to coordinate a metal-atom with its two coordination sides: two double bonds and its donor functional group. In case of the complexes with the ketone as a ligand it is quite remarkable that it was possible to build the

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dichloroplatinum(II) complexes, were the metal center faces the carbonyl group close-by.

Structural analysis of some complexes was performed in detail by multinuclear Platinum-195 NMR spectroscopy. Chemical shifts and coupling constant data are summarized in Table 1. Chemical shifts are in the expected range of Pt(II) complexes (−5500 to −1500 ppm).[31] Compared to the unsubstituted COD ligand, the residue *R* increases chemical shift by a small value (up to 150 ppm). In previous studies using alkane substituents smaller shift differences were observed.[12]

As shown previously,[14, 32-35] the strength of the $^{2}J_{PtH}$ coupling constant to the olefinic protons is dependent on the substituent *trans* to the olefinic bond and the effect is called *trans* influence.[30] Strong ligands such as methyl groups reduce the $^{2}J_{PtH}$ coupling constant to 30 or 40 Hz, while weaker ligands like chlorine yield coupling constants of 60 to 70 Hz. All measured coupling constants confirm the idea of a weak ligand in *trans* position.

Proton spectra acquired at 9.4 and 14.1 T field strength revealed a small field dependence of the $^{2}J_{PtH}$ splitting. While *J*-coupling constants are not field-dependent, the observed splitting is influenced by T_1 relaxation.

For ^{195}Pt this is attributed to CSA relaxation and can even lead to the disappearance of ^{195}Pt satellites as has been described in literature.[31] For the complex **5e**, satellites were visible, platinum coherences, however, could not be observed directly, hinting at an apparent increase in T_2 relaxation, possibly caused by rapid ligand exchange.

Table 1. Pt-NMR chemical shift and $^{2}J_{PtH}$ coupling constants. Samples were measured in $CDCl_3$ at 14.1 T field strength. Some remote coupling constants could be estimated and are listed in the supporting information. For **4h**, olefinic protons could not be evaluated due to peak overlap. **6**: COD($PtCl_2$)

No	$\delta(^{195}Pt)$ /ppm	$\Delta\delta(^{195}Pt)$ to *R* = H	$\delta(^{1}H)$ /ppm, $^{2}J_{PtH}$ /Hz 1		2		3	
6	−3331	0	5.63	*67*				
4d	−3333	−2	5.41	*66*	5.66	*69*	5.71	*62*
4h	−3313	+28	--		--		--	
5d	−3185	+146	5.72	*62*	5.89	*75*	6.19	*62*
5e	−3211	+120	5.84	*70*	6.14	*60*	6.34	*58*

In this work, we have demonstrated a robust synthesis of 1-functionalized cyclooctadienes. Starting from two different protocols we isolated a variety of 1,5-cyclooctadienylalcohols **2a**-**2m** and 1,5-cyclooctadienylketones **3a**, **3d**-**3l** and **3n**-**3q**. Almost all compounds were obtained in high selectivity and good yields. Some of these dienes were used in the synthesis of novel alkoxy and hemilabile acyl platinum(II) complexes which were characterized *via* Pt NMR and X-ray crystallography. The investigation of their biological effects is on-going.

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Conflicts of interest

"There are no conflicts to declare".

Notes and references

CCDC 1812128 (**3f**) and 1812129 (**5e**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

1. A. Koppaka, V. Yempally, L. Zhu, G. C. Fortman, M. Temprado, C. D. Hoff and B. Captain, *Inorg. Chem.*, 2015, **55**, 307-321.
2. A. Klein, M. Neugebauer, A. Krest, A. Lüning, S. Garbe, N. Arefyeva and N. Schlörer, *Inorganics*, 2015, **3**, 118-138.
3. V. Lingen, A. Lüning, A. Krest, G. B. Deacon, J. Schur, I. Ott, I. Pantenburg, G. Meyer and A. Klein, *J. Inorg. Biochem.*, 2016, **165**, 119-127.
4. Y. Suzaki, M. Kiho and K. Osakada, *Organometallics*, 2017, **36**, 1391-1397.
5. L. M. Alluhaibi, A. K. Brisdon and R. G. Pritchard, *J. Fluorine Chem.*, 2017, **203**, 146-154.
6. M. Frik, J. Fernández-Gallardo, O. Gonzalo, V. Mangas-Sanjuan, M. González-Alvarez, A. Serrano del Valle, C. Hu, I. González-Alvarez, M. Bermejo and I. Marzo, *J. Med. Chem.*, 2015, **58**, 5825-5841.
7. M. W. Drover, E. G. Bowes, J. A. Love and L. L. Schafer, *Organometallics*, 2016, **36**, 331-341.
8. T. Nakamura, K. Suzuki and M. Yamashita, *J. Am. Chem. Soc.*, 2017.
9. G. Smits, B. Audic, M. Wodrich, C. Corminboeuf and N. Cramer, *Chem. Sci.*, 2017, **8**, 7174-7179.
10. G. Annibale, M. Brandolisio and B. Pitteri, *Polyhedron*, 1995, **14**, 451-453.
11. J. W. Ellis, K. N. Harrison, P. A. Hoye, A. G. Orpen, P. G. Pringle and M. B. Smith, *Inorg. Chem.*, 1992, **31**, 3026-3033.
12. M. Enders, B. Görling, A. B. Braun, J. E. Seltenreich, L. F. Reichenbach, K. Rissanen, M. Nieger, B. Luy, U. Schepers and S. Bräse, *Organometallics*, 2014, **33**, 4027-4034.
13. S. Fallis, G. K. Anderson and N. P. Rath, *Organometallics*, 1991, **10**, 3180-3184.
14. A. Lüning, J. Schur, L. Hamel, I. Ott and A. Klein, *Organometallics*, 2013, **32**, 3662-3672.
15. S. Otsuka, T. Yoshida, M. Matsumoto and K. Nakatsu, *J. Am. Chem. Soc.*, 1976, **98**, 5850-5858.
16. F. G. A. Stone, *Accounts Chem. Res.*, 1981, **14**, 318-325.
17. G. Mann, K. D. John and R. T. Baker, *Org. Let.*, 2000, **2**, 2105-2108.
18. L. N. Lewis and N. Lewis, *J. Am. Chem. Soc.*, 1986, **108**, 7228-7231.
19. C. N. Iverson and M. R. Smith, *Organometallics*, 1997, **16**, 2757-2759.
20. J.-C. Hierso, P. Serp, R. Feurer and P. Kalck, 1998.
21. S. D. Cummings and R. Eisenberg, *Inorg. Chem.*, 1995, **34**, 2007-2014.
22. M. Cleare, P. Hydes, B. Malerbi and D. Watkins, *Biochemie*, 1978, **60**, 835-850.

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DOI: 10.1039/C8DT00075A

23. T. Connors, M. Cleare and K. Harrap, *Structure-activity relationships of the antitumor platinum coordination complexes*, 1979.
24. A. Lüning, M. Neugebauer, V. Lingen, A. Krest, K. Stirnat, G. B. Deacon, P. R. Drago, I. Ott, J. Schur and I. Pantenburg, *European Journal of Inorganic Chemistry*, 2015, **2015**, 226-239.
25. C. D. Matier, Y. Kwon and F. West, *Can. J. Chem.*, 2013, **92**, 58-61.
26. A. E. Wandler and S. Bräse, *Adv. Synth. Catal.*, 2016, **358**, 4125-4128.
27. L.-Y. Zhu, Z. Lou, J. Lin, W. Zheng, C. Zhang and J.-D. Lou, *Res. Chem. Intermediat*, 2013, **39**, 4287-4292.
28. P. Kraft, K. Popaj and A. Abate, *Synthesis*, 2005, **2005**, 2798-2809.
29. F. Wen, H. Bönnemann, J. Jiang, D. Lu, Y. Wang and Z. Jin, *Appl. Organomet. Chem.*, 2005, **19**, 81-89.
30. H.-C. Clark and L. Manzer, *J. Organomet. Chem.*, 1973, **59**, 411-428.
31. B. M. Still, P. A. Kumar, J. R. Aldrich-Wright and W. S. Price, *Chem. Soc. Rev.*, 2007, **36**, 665-686.
32. A. Klein, T. Schurr, H. Scherer and N. S. Gupta, *Organometallics*, 2007, **26**, 230-233.
33. A. Klein, K.-W. Klinkhammer and T. Scheiring, *J. Organomet. Chem.*, 1999, **592**, 128-135.
34. A. Klein, A. Lüning, I. Ott, L. Hamel, M. Neugebauer, K. Butsch, V. Lingen, F. Heinrich and S. Elmas, *J. Organomet. Chem.*, 2010, **695**, 1898-1905.
35. K. Butsch, S. Elmas, N. S. Gupta, R. Gust, F. Heinrich, A. Klein, Y. von Mering, M. Neugebauer, I. Ott and M. Schäfer, *Organometallics*, 2009, **28**, 3906-3915.