Available online at www.sciencedirect.com
SCIENCE DIRECT®
Electrochemistry Communications 7 (2005) 1013–1020
electrochemistry communications
www.elsevier.com/locate/elecom

Combinatorial micro electrochemistry. Part 4: Cyclic voltammetric redox screening of homogeneous ruthenium(II) hydrogenation catalysts ☆

Ekkehard Lindner [a], Zhong-Lin Lu [a,1], Hermann A. Mayer [a], Bernd Speiser [b,*], Carsten Tittel [b], Ismail Warad [a]

[a] Universität Tübingen, Institut für Anorganische Chemie, Auf der Morgenstelle 18, D-72076 Tübingen, Germany
[b] Universität Tübingen, Institut für Organische Chemie, Auf der Morgenstelle 18, D-72076 Tübingen, Germany

Received 23 June 2005; accepted 7 July 2005
Available online 10 August 2005

Abstract

Organometallic ruthenium(II) complexes, which act as homogeneous hydrogenation catalysts, are characterized electrochemically with respect to their redox properties by means of a new screening technique (''redox screening''). Samples of the complexes are dissolved in an electrolyte and placed in the wells of microtiter plates. Electrode bundles are moved under computer control between these wells, and cyclic voltammograms are automatically recorded. Analysis of the current/potential curves shows a relation between the voltammogram shape or position and the catalytic activity of the complexes. Thus, the technique proves well suited as an electrochemistry-based high-throughput method.

Keywords: Redox screening; Compound collections; Redox active catalysts; Cyclic voltammetry

1. Introduction

The analytical screening of ''compound collections'' or ''chemical libraries'' [3] by the use of high-throughput methods [4] is a main task of combinatorial chemistry [5] in material [6,7] and life sciences [8,9]. Chemical properties of the individual library elements are determined sequentially or in parallel. In typical scenarios, the compounds are arranged spatially separated in a matrix, for example in the wells of microtiter plates [10] or deposited on a surface [11]. Popular screening protocols depend on spectroscopic methods such as IR [12] and NMR [13], mass spectrometry [14] or the use of bioassays [15], and provide information on structure, molecular mass or biochemical activities of the individual elements, respectively.

Although redox properties of molecules represent an extraordinarily important aspect of their chemical behavior, screening by use of electrochemical methods has not yet become very common. Some earlier approaches involve ''electrode arrays'' [16,17] to identify methanol oxidation catalysts [18] and electrocatalysts for oxygen reduction [19] as well as parallel detection systems for immunoassays [15] and heavy metal stripping analysis [20]. Recently, the microtiter plate hosted investigation of the relationship between structure and redox potentials of quater-3-arylthiophenes [21] and instrumentation using robotic techniques for automated

☆ Part 3: see, Ref. [1]; also part 12 of the series ''Electrochemistry of Transition Metal Catalysts'', part 11, see [2].

* Corresponding author. Tel.: +49 7071 2976205; fax: +49 7071 295518.
E-mail address: bernd.speiser@uni-tuebingen.de (B. Speiser).
[1] Present address: Department of Chemistry, Queen's University, Kingston, Ont., Canada K7L 3N6.

1388-2481/$ - see front matter © 2005 Elsevier B.V. All rights reserved.
doi:10.1016/j.elecom.2005.07.002

electrochemical measurements with dissolved species [22] introduced a convenient format to apply potentiostatic control. In this automatic protocol, bundles of three or four electrodes are moved in all three spatial dimensions by use of stepper motors and inserted into the microtiter plate wells (e.g., 96 wells arranged in 8 columns of 12 wells each, with well volumes of 300 μl).

In a previous paper [23] of this series, we discussed the application of such an arrangement for the electrosynthesis of localized (spatially separated) compound collections. Cyclic voltammetry was used in this context for the determination of electrolysis potentials and monitoring of the reaction [1].

Here, we report on the rapid determination of the redox properties of electroactive diamine(phosphine) ruthenium(II) complexes by multiple automated cyclic voltammetry in microtiter plates. We propose to denote this procedure applied to a compound collection as ''redox screening''.

2. Results and discussion

Ruthenium(II) complexes **1, 2** with diamine, phosphine and two chloro ligands ($N_2P_2Cl_2$ ligand set) and a structure similar to that of the Noyori complexes (e.g. **3** [24]) proved to be highly active and selective catalysts in the hydrogenation of unsaturated ketones under mild conditions (in the presence of a co-catalyst, a base, and 2-propanol) [25–29]. Variability in the ligand set and immobilization of the complexes in a polymeric ''interphase'' matrix [30] open the way to optimize their catalytic properties. One particular information, which could be useful in the optimization, is the complexes' redox potential E^0. Moreover, electrochemical redox processes potentially activate transition metal catalysts [31,32]. Consequently, the determination of the electrochemical properties for an extended series of complexes **1** and **2** is of high interest and comprises a combinatorial problem.

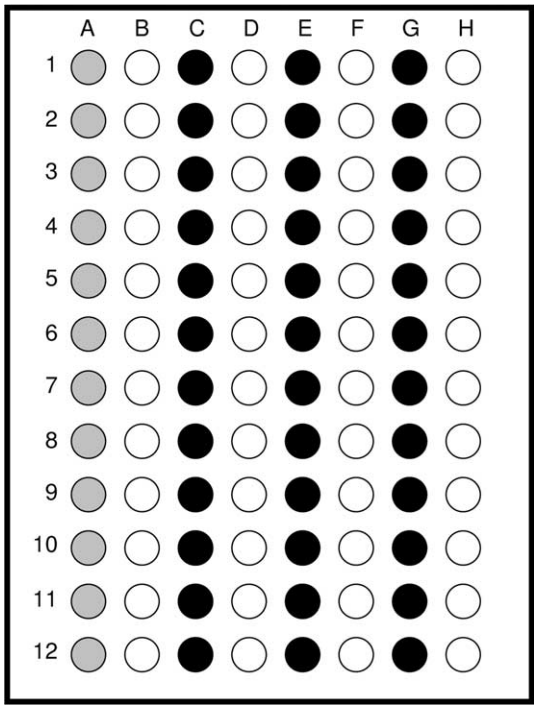
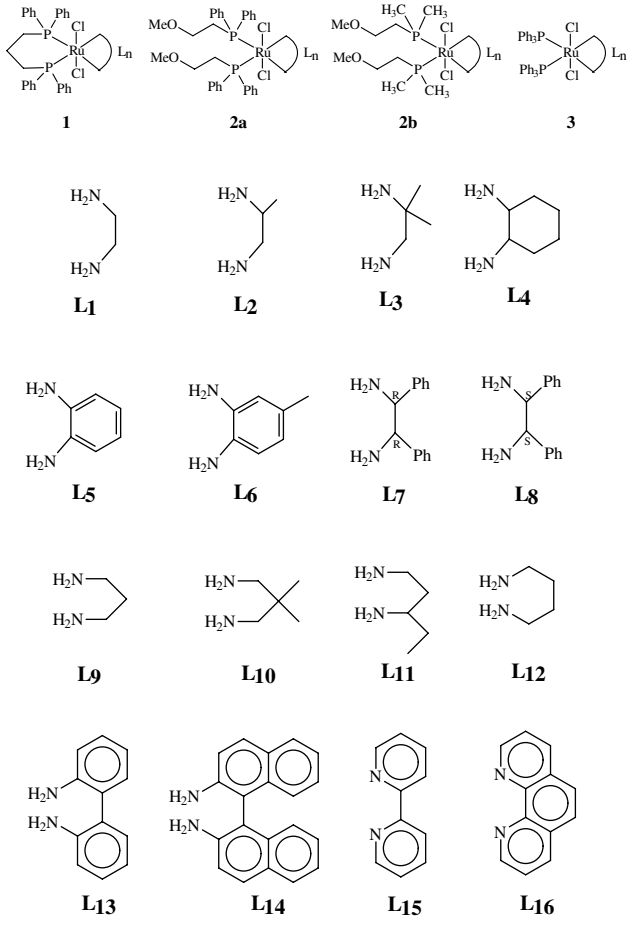


Fig. 1. Charging of a 96-well microtiter plate for cyclic voltammetric redox screening of ruthenium(II) complexes **1**, **2**; light grey: reference wells; open circles: wash wells; black: sample wells.



For cyclic voltammetric redox screening experiments with **1** and **2** a 96-well microtiter plate is typically charged with solutions as shown in Fig. 1. The minaturized and bundled electrodes [23] are moved between the wells row by row.

The following aspects were taken into consideration when assigning the wells: First, the potential of the pseudo-reference electrode in the bundle (chloridized silver wire; see Section 3) might shift with time during the screening experiment. To detect and correct such referencing artifacts, all wells of column A (''reference wells'') were filled with a ferrocene (fc) standard solution. While scanning the plate, the fc/fc^+ potential is

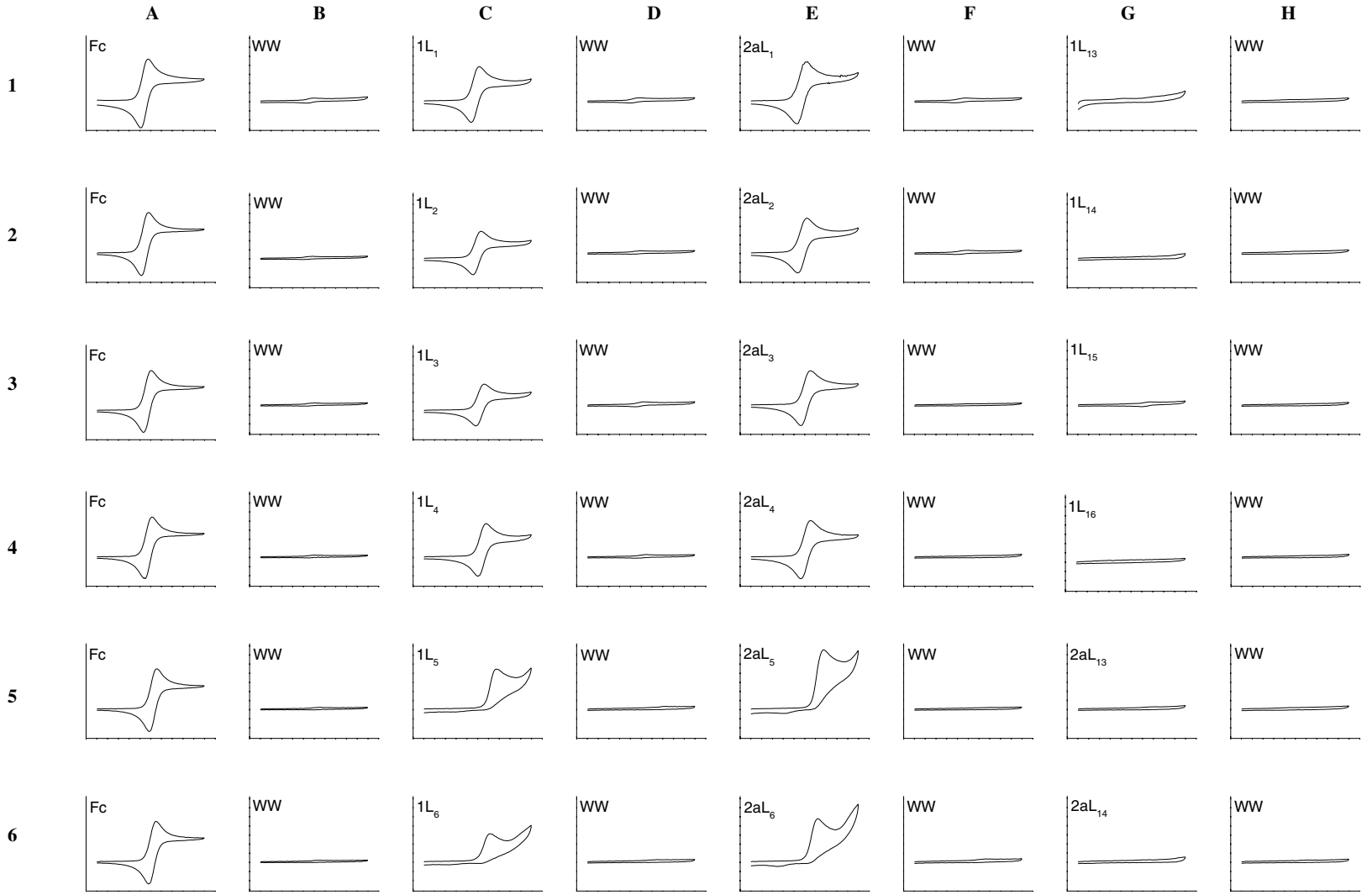


Fig. 2 Cyclic voltammetric array (potential axes range from −0.1 to 1.1 V vs. Ag/AgCl, current axes range from −80 to 180 nA) of samples in a microtiter plate as shown in Fig. 1; potential scan rate $v = 0.5\ \mathrm{V\ s^{-1}}$, all wells with 0.1 M NBu_4PF_6/CH_3CN electrolyte; reference wells with 0.5 mM fc solution; sample wells with ≈0.5 mM complex solution; wash wells (WW): electrolyte without redox active species; 200 μm Pt disc electrode.

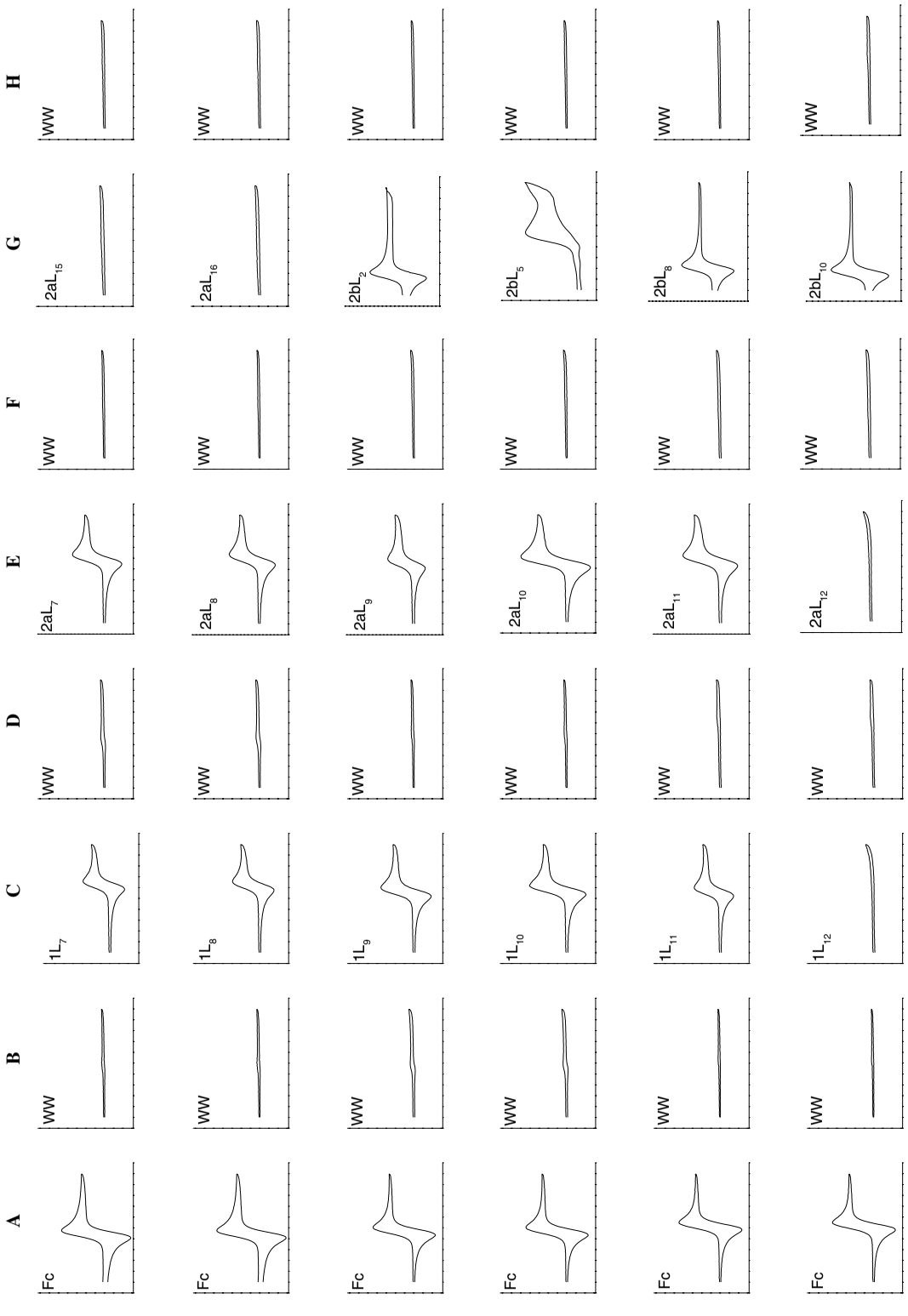


Fig. 2 (*continued*)

thus checked in regular intervals. The position of the fc/fc^+ redox peaks on the potential scale provides a stability measure for the reference electrode. Moreover, all potentials are easily rescaled to the external fc/fc^+ standard potential [33] after the experiment. Second, to avoid cross contamination between the wells, the electrode bundle is cleaned after each contact with a solution containing redox-active material in ''wash wells'', filled with electrolyte in the absence of any redox-active species (columns B, D, F, and H). Recording of cyclic voltammograms in the wash wells enables us to check the effectiveness of the cleaning procedure. Occurrence of redox signals instead of smooth background currents would indicate that cleaning was not yet sufficient. For species not adsorbing at the electrode surface, such as the ruthenium complexes investigated here, one wash well ensures reproducible cleaning [22].

Finally, for the investigation of analytes, columns C, E, and G with ''sample wells'' remain. Thus, data for up to 36 complexes can be generated within one scan across the 96-well microtiter plate. Such a complete screening scan lasts between 20 and 120 min, depending on the potential range and scan rate v.

After recording a cyclic voltammogram in each well, a ''voltammetric array'' (Fig. 2) results, where the current/potential curves are arranged as generated during the plate scan. In addition to the typical pattern based on the charging of the wells, the large amount of data

Table 2
Electrochemical redox chemistry of $RuN_2P_2Cl_2$ complexes **2b** and catalytic transfer hydrogenation[a] of acetophenone

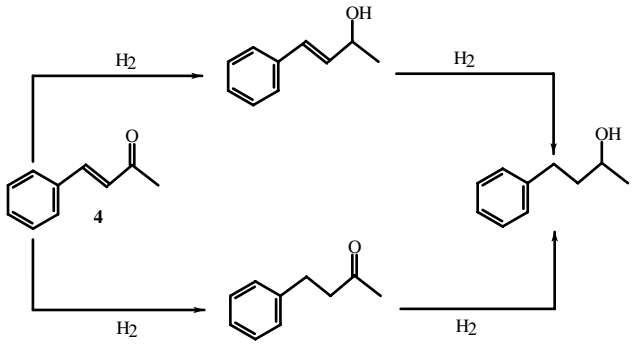
Complex	E^0 or (E_p^{ox}) (mV)[c]	Class	Product yield (%)[b]
2bL$_2$	−331	IVa	95
2bL$_5$	(12)	IVb	90
2bL$_8$	−305	IVa	94
2bL$_{10}$	−353	IVa	98

[a] Some catalytic data taken from earlier work [28].
[b] Hydrogenation of 0.75 ml acetophenone at 82 °C in 15 ml 2-propanol; [Ru]:[KOH]:[substrate] = 1:10:500; reaction time 4 h; yields determined by GC.
[c] E vs. fc/fc^+; $v = 0.5$ V s^{-1}; $c \approx 0.5$ mM; 0.1 M NBu_4PF_6/CH_3CN; 200 μm diameter Pt disc electrode.

Table 1
Electrochemical redox chemistry of catalytically active $RuN_2P_2Cl_2$ complexes **1** and **2a** and homogeneous hydrogenation[a] of *trans*-4-phenyl-3-butene-2-one **4**

Complex	E^0 or (E_p^{ox}) (mV)[c]	Class	Product yield (%)[b]	TOF[d]	Selectivity (%)[b]	
					C=O	C=C
1L$_1$	46	I	100	1080	100	0
1L$_2$	69	I	90	776	100	0
1L$_3$	66	I	54	540	100	0
1L$_4$	74	I	100	1210	100	0
1L$_5$	(124)	II	28[f]	18	0	100
1L$_6$	(93)	II	0[e]	0	0	0
1L$_7$	106	I	100	1490	100	0
1L$_8$	117	I	100	1724	100	0
1L$_9$	38	I	100	926	100	0
1L$_{10}$	22	I	92	920	100	0
1L$_{11}$	61	I	100	2000	100	0
1L$_{12}$	–	III	25[f]	17	45	55
2aL$_1$	29	I	90	1120	100	0
2aL$_2$	59	I	80	936	100	0
2aL$_3$	46	I	67	673	100	0
2aL$_4$	36	I	100	1587	100	0
2aL$_5$	(113)	II	10[g]	9	0	100
2aL$_6$	(91)	II	17[g]	15	0	100
2aL$_7$	63	I	100	1240	100	0
2aL$_8$	82	I	100	2439	100	0
2aL$_9$	33	I	100	1500	79.5	20.5
2aL$_{10}$	−3	I	97	1429	82.4	17.6
2aL$_{11}$	82	I	100	1000	71.6	23.4
2aL$_{12}$	–	III	27[f]	18	43	57

[a] Some catalytic data taken from earlier work [25,26].
[b] Hydrogenation of 3–5 g *trans*-4-phenyl-3-butene-2-one at 35 °C in 50–80 ml 2-propanol; [Ru]:[KOH]:[substrate] = 1:10:1000; reaction time 1–2 h; yields and selectivities determined by GC.
[c] E vs. fc/fc^+; $v = 0.5$ V s^{-1}; $c \approx 0.5$ mM; 0.1 M NBu_4PF_6/CH_3CN; 200 μm diameter Pt disc electrode.
[d] Turnover frequency in $mol_{substrate}\ mol^{-1}_{catalyst}\ h^{-1}$.
[e] Overnight reaction.
[f] Reaction time 15 h.
[g] Reaction time 11 h.



Scheme 1. Hydrogenation routes of *trans*-4-phenyl-3-butene-2-one **4** with homogeneous hydrogenation catalysts.

collected during the experiment can easily be acknowledged.

The ferrocene voltammograms in wells of column A show negligible shifts of the mean value E^0(fc) of the oxidation and reduction peak potentials, which indicates stability of the reference electrode under the conditions of this work. We assign the origin of the potential scale vs. the fc/fc$^+$ standard redox couple to E^0(fc). Curves in columns B, D, F, and H (wash wells) prove the success of the cleaning procedure. Compared to voltammograms in wells containing redox active compounds, the curves recorded in these wells show negligible deviations from the background currents.

Voltammograms of ruthenium complexes in columns C, E and G exhibit three different shapes. Some complexes (wells C1–C4, C7–C11, E1–E4, and E7–E11 – class I and G9, G11, G12 – class IVa) show reversible behavior, assigned to an electron transfer process between ruthenium(II) and ruthenium(III) in analogy to [34]. Class I compounds differ from class IVa complexes by their redox potential with those of class IVa being much easier to oxidize than those of class I. Other species (wells C5–C6, E5–E6 – class II; well G10 – class IVb) are oxidized irreversibly to ruthenium(III). Again, classes II and IVb differ in the potential where the signal occurs. The third group of compounds (wells C12, E12, and G1–G8; class III) shows no redox activity in the investigated potential range. Formal (classes I or IVa) or peak (classes II or IVb) potentials of the investigated complexes are given in Tables 1 and 2.

The different classes of voltammograms correlate with the catalytic activity of the complexes with respect to the hydrogenation of carbonyl compounds (Tables 1 and 2). Two different sites are possible for hydrogenation of α,β-unsaturated ketones, i.e., the C=C and/or C=O double bonds as in the direct hydrogenation of *trans*-4-phenyl-3-butene-2-one **4** which served as a test example (Scheme 1) [31].

Class I complexes are effective direct hydrogenation catalysts for substrate **4**. This is evident from high values of the turnover-frequency (TOF; Table 1). Additionally, they show a high selectivity towards hydrogenation of the carbonyl double bond. In contrast, class IV compounds catalyze the reaction of the carbonyl group of, e.g. acetophenone (Table 2) via transfer hydrogenation (see, e.g. [35]) with 2-propanol as hydrogen source [28].

Complexes with irreversible oxidation peaks (class II), on the other hand, exhibit low TOF values and are less effective catalysts. Conversion is low even after prolonged reaction (Table 1). Interestingly, selectivity changes towards hydrogenation of the olefinic double bond.

As NMR studies show [25,26], class III complexes are not stable in solution under the experimental conditions, which explains both the lack of a cyclic voltammetric signal and their poor catalytic activity and selectivity.

These results are compatible with the different mechanisms discussed for the hydrogenation of carbonyl groups [24,36,37]. Formation of a ruthenium hydride intermediate in the presence of a co-catalyst initiates the reaction. This central intermediate is re-formed during the catalytic cycle. As the screening results indicate, efficient catalysis based on this recycling seems to be related to the reversibility of the Ru(II)/Ru(III) redox system. A complex proves useful as catalyst only if the oxidation is reversible in order to allow re-formation of the intermediate during catalysis.

Chemical irreversibility of the oxidation, on the other hand, leads to low TOF numbers. This correspondence is valid for all active catalysts, with the only exception of **2bL**$_5$, which catalyses the transfer hydrogenation without showing a reversible electron transfer.

The evident potential shift between class I or II complexes on the one hand and class IVa,b compounds on the other hand is easily explained by the change from the essentially "electron-neutral" phenyl to the electron-donating methyl substituents at the ligand phosphorus atoms. The electron density at the ruthenium central atom is directly influenced by this variation. Concomitant with this shift in the redox potential, a change in the catalytic mechanism (direct vs. transfer hydrogenation) is observed, while the high activity is maintained. As pointed out earlier, the coordination of H_2 to ruthenium(II) and its subsequent heterolytic splitting requires a well balanced electron density at the metal center [28,37]. Obviously, the dimethylphosphine ligands donate too much electron density which leads to repulsion of the H_2 molecule when it approaches the ruthenium(II) center. Thus, the activation of H_2 is reduced and only transfer hydrogenation remains operative. Class II complexes are provided with aromatic ligands **L**$_5$ or **L**$_6$, respectively. Owing to the stiffness of the ligands these complexes are not able to attain the required conformation for an effective heterolytic splitting of the η^2-H_2 ligand [36,37]. Consequently, no C=O hydrogenation is possible.

Redox screening of prospective homogeneous catalysts thus proves to be a successful method to elucidate behavioral patterns for electrochemical properties within the compound collection **1**, **2**. The electrochemical current/potential curves are paralleled by the catalytic behavior. The multiple cyclic voltammetric experiment with the computer controlled instrument is very fast as compared to the effort needed to check, in the present example, catalytic activity of the large number of complexes in a classical way by chemical reaction and product analysis (see Tables 1 and 2). Alternative charging patterns of the microtiter plate are possible, with less reference and wash wells, resulting in even more information generated from a single screening run. In the present approach, the voltammetric data are necessarily limited to curves at a single scan rate to keep the time expenditure at a minimum. As the ruthenium complex example shows, however, mechanistic conclusions are already possible with this fast experiment. If a higher effort is accepted, scan rate variation is easily implemented. Consequently, this technique provides a useful high-throughput method for compound libraries, based on electrochemical principles, resulting in a simple screening of properties related to redox activity.

3. Experimental

3.1. Chemicals

Purified acetonitrile [38] was used as solvent with tetra-*n*-butylammoniumhexa-fluorophosphate [38] as supporting electrolyte (NBu_4PF_6, $c = 0.1$ M). Before use, the electrolyte solution was degassed by bubbling with argon for about 30 min.

Ruthenium(II) complexes were prepared according to previously published procedures [25,26,28].

3.2. Screening experiments

Within an instrument as described earlier [22,23] the wells of the microtiter plate were charged according to Fig. 1 with 250 μl of analyte solution (sample wells), ferrocene solution (reference wells) as standard or pure electrolyte (wash wells). Additional solvent was filled in glass containers located around the microtiter plate, in order to saturate the atmosphere above the plate with solvent vapor and to minimize evaporation of solvent from the wells. The arrangement was placed in an aluminium trough, covered with a glass plate and the atmosphere was flushed with argon. The trough could be moved by two stepper motors in the horizontal *x*- and *y*-directions. An electrode bundle (200 μm Pt disc electrode, Pt wire counter electrode, Ag/AgCl reference electrode) was fixed at a third stepper motor for vertical *z* movement and placed in the first well. Under computer control, the bundle was moved into every well through a hole in the covering glass plate and cyclic voltammograms were recorded.

Control of the experiments was performed by a Microsoft Visual Basic 3.0 program [22]. Automated screening scans were executed after defining the positions of the wells and the respective experimental parameters in a script language [22].

Acknowledgements

We thank the Deutsche Forschungsgemeinschaft, Bonn-Bad Godesberg, Germany (collaborative project "Kombinatorische Microelektrochemie" and the Graduiertenkolleg 441 "Chemie in Interphasen") for financial support and fellowships for Z.L. and I.W. We also thank the Max-Buchner-Forschungsstiftung, Frankfurt/Main, Germany, and the Alexander von Humboldt-Stiftung for providing fellowships for C.T. and Z.L., respectively. We are greateful to M. Gloria Quintanilla, Universidad de Alcala, Spain, for preliminary mechanistic discussions.

References

[1] W. Märkle, B. Speiser, Electrochim. Acta., in press, doi:10.1016/j.electacta.2005.01.052.
[2] F. Novak, B. Speiser, E. Lindner, Z.-L. Lu, H.A. Mayer, Angew. Chem. 116 (2004) 2059–2062;
Angew. Chem. Int. Ed. 43 (2004) 2025–2028.
[3] D. Maclean, J.J. Baldwin, V.T. Iwanov, Y. Kato, A. Shaw, P. Schneider, E.M. Gordon, Pure Appl. Chem. 71 (1999) 2349–2365.
[4] N. Sepetov, O. Issakova, Analytical characterization of synthetic organic libraries, in: S. Miertus, G. Fassina (Eds.), Combinatorial Chemistry and Technology. Principles, Methods and Applications, Marcel Dekker, New York, 1999, pp. 169–203.
[5] G. Jung (Ed.), Combinatorial Chemistry. Synthesis, Analysis, Screening, Wiley-VCH, Weinheim, 1999.
[6] J.J. Hanak, J. Mater. Sci. 5 (1970) 964–971.
[7] E. Reddington, A. Sapienza, B. Gurau, R. Viswanathan, S. Sarangapani, E.S. Smotkin, T.E. Mallouk, Science 280 (1998) 1735–1737.
[8] S.A. Sundberg, Curr. Opin. Biotechnol. 11 (2000) 47–53.
[9] C.D. Bevan, R.S. Lloyd, Anal. Chem. 72 (2000) 1781–1787.
[10] In [5], p. 7.
[11] In [5], p. 9.
[12] B. Yan, H. Gstach, Tetrahedron Lett. 37 (1996) 8325–8328.
[13] G.C. Look, C.P. Holmes, J.P. Chinn, M.A. Gallop, J. Org. Chem. 59 (1994) 7588–7590.
[14] B.J. Egner, G.J. Langley, M. Bradley, J. Org. Chem. 60 (1995) 2652–2653.
[15] T.-C. Tang, A. Deng, H.-J. Huang, Anal. Chem. 74 (2002) 2617–2621.
[16] M.G. Sullivan, H. Utomo, P.J. Fagan, M.D. Ward, Anal. Chem. 71 (1999) 4369–4375.
[17] R. Feeney, S.P. Kounaves, Electroanalysis 12 (2000) 677–684.
[18] R. Jiang, D. Chu, J. Electroanal. Chem. 527 (2002) 137–142.

[19] J.L. Fernandez, D.A. Walsh, A.J. Bard, J. Am. Chem. Soc. 127 (2005) 357–365.
[20] M. Dřevínek, F. Trojánek, Chem. Listy 95 (2001) 231–233.
[21] C.A. Briehn, M.-S. Schiedel, E.M. Bonsen, W. Schuhmann, P. Bäuerle, Angew. Chem. 113 (2001) 4817–4820;
Angew. Chem. Int. Ed. 40 (2001) 4680–4683.
[22] T. Erichsen, S. Reiter, W. Märkle, C. Tittel, V. Ryabova, E.M. Bonsen, G. Jung, B. Speiser, W. Schuhmann, Rev. Sci. Instrum. 76 (2005) 062204-1–062204-11.
[23] W. Märkle, B. Speiser, C. Tittel, M. Vollmer, Electrochim. Acta 50 (2005) 2753–2762.
[24] R. Noyori, T. Ohkuma, Angew. Chem. 113 (2001) 40–75;
Angew. Chem. Int. Ed. 40 (2001) 40–73.
[25] E. Lindner, I. Warad, K. Eichele, H.A. Mayer, Inorg. Chim. Acta 350 (2003) 49–56.
[26] E. Lindner, H.A. Mayer, I. Warad, K. Eichele, J. Organomet. Chem. 665 (2003) 176–185.
[27] E. Lindner, A. Ghanem, I. Warad, K. Eichele, H.A. Mayer, V. Schurig, Tetrahedron-Asymmet. 14 (2003) 1045–1053.
[28] Z.-L. Lu, K. Eichele, I. Warad, H.A. Mayer, E. Lindner, Z.-j. Jiang, V. Schurig, Z. Anorg. Allg. Chem. 629 (2003) 1308–1315.
[29] C. Nachtigal, S. Al-Gharabli, K. Eichele, E. Lindner, H.A. Mayer, Organometallics 21 (2002) 105–112.
[30] E. Lindner, T. Schneller, F. Auer, H.A. Mayer, Angew. Chem. 111 (1999) 2288–2309;
Angew. Chem. Int. Ed. 38 (1999) 2154–2174.
[31] H.A.Y. Mohammad, J.C. Grimm, K. Eichele, H.-G. Mack, B. Speiser, F. Novak, M.G. Quintanilla, W.C. Kaska, H.A. Mayer, Organometallics 21 (2002) 5775–5784.
[32] F. Novak, B. Speiser, H.A.Y. Mohammad, H.A. Mayer, Electrochim. Acta 49 (2004) 3841–3853.
[33] G. Gritzner, J. Kůta, Pure Appl. Chem. 56 (1984) 461–466.
[34] A.A. Batista, L.A.C. Cordeiro, G. Oliva, O.R. Nascimento, Inorg. Chim. Acta 258 (1997) 131–137.
[35] A.M. Hayes, D.J. Morris, G.J. Clarkson, M. Wills, J. Am. Chem. Soc. 127 (2005) 7318–7319.
[36] S.E. Clapham, A. Hadzovic, R.H. Morris, Coord. Chem. Rev. 248 (2004) 2201–2237.
[37] R. Hartmann, P. Chen, Angew. Chem. 113 (2001) 3693–3697;
Angew. Chem. Int. Ed. 40 (2001) 3581–3585.
[38] S. Dümmling, E. Eichhorn, S. Schneider, B. Speiser, M. Würde, Curr. Sep. 15 (1996) 53–56.