CHEMISTRY
A European Journal

A Journal of
ChemPubSoc Europe

Accepted Article

Title: Nonclassical mechanism in the cyclodehydration of diols catalyzed by a bifunctional iridium complex

Authors: Greco González Miera, Aitor Bermejo López, Elisa Martínez-Castro, Per-Ola Norrby, and Belén Martín-Matute

To be cited as: *Chem. Eur. J.* 10.1002/chem.201805460

Link to VoR: http://dx.doi.org/10.1002/chem.201805460

Supported by
ACES

WILEY-VCH

10.1002/chem.201805460

WILEY-VCH

Nonclassical mechanism in the cyclodehydration of diols catalyzed by a bifunctional iridium complex

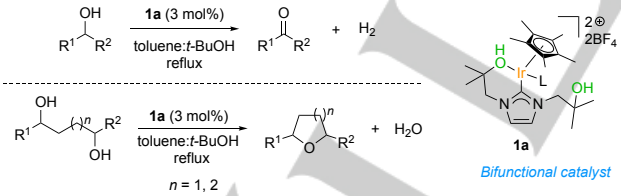
Greco González Miera,#[a] Aitor Bermejo López,#[a] Elisa Martínez-Castro,[a] Per-Ola Norrby,[b] and Belén Martín-Matute*[a]

Abstract: 1,4- and 1,5-Diols undergo cyclodehydration upon treatment with cationic *N*-heterocyclic carbene (NHC) Ir(III) complexes to give tetrahydrofurans and tetrahydropyrans, respectively. The mechanism was investigated, and a metal-hydride-driven pathway is proposed for all substrates, with the exception of very electron-rich ones. This contrasts with the well-established classical pathways involving nucleophilic substitution.

Introduction

NHC-Ir complexes have proven to be excellent catalysts in numerous processes, particularly in dehydrogenations and transfer-hydrogenations.[1,2,3] NHCs can be relatively easily functionalized to provide the desired reactivity. Their versatility has been recently highlighted by Peris in a recent review article,[4] where the author refers to NHCs as “smart ligands”.

We have previously investigated the activity of Ir(III) complexes bearing functionalized NHC ligands (**1**) in C–N bond-forming reactions from anilines and alcohols. Mechanistic investigations indicated that the oxygen functionality on the NHC ligand is involved in proton transfer steps, enabling to perform the reactions under base-free conditions.[3b] The binfunctional nature of the NHC-Ir complexes (**1**) was also explored in the acceptorless dehydrogenation of alcohols [2] (Scheme 1, top). (**1a**). Here we observed that when two 1,4-diols, 1-phenyl-1,4-pentanediol (**2a**) and 1,4-diphenyl-1,4-butanediol (**2j**), were reacted with **1a**, tetrahydrofurans were formed in very good yields (Scheme 1, bottom), instead of the expected products derived from a dehydrogenation process (Scheme 1, bottom).



Scheme 1. Acceptorless dehydrogenation of alcohols (top) and redox cyclization of diols (bottom) catalyzed by **1a**.

[a] Dr. G. González Miera, A. Bermejo López, Dr. E. Martínez-Castro, Prof. B. Martín-Matute
Department of Organic Chemistry
Stockholm University
Stockholm 10691, Sweden
E-mail: belen.martin.matute@su.se
# Equal contribution

[b] Prof. P.-O. Norrby,
Early Product Development, Pharmaceutical Sciences, IMED Biotech Unit, AstraZeneca, Gothenburg, Sweden.

Supporting information for this article is given via a link at the end of the document.

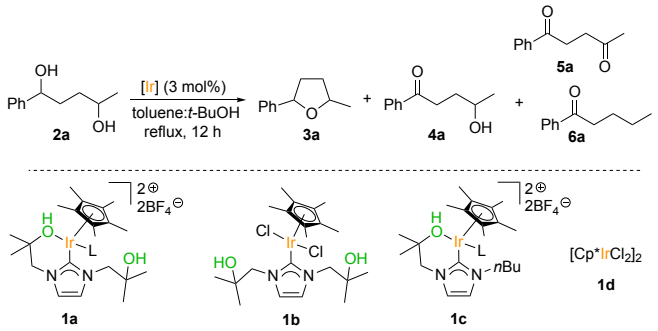
The synthesis of this type of cyclic ethers from diols is a well-established procedure that can be mediated by Brønsted [5] or Lewis acids,[6] and mechanisms involving nucleophilic substitution have been proposed.[7] Cyclizations under basic conditions have also been reported.[8] However, in those cases where transition-metal complexes were used, the possibility that an alternative hydrogen-borrowing (or hydrogen-autotransfer) mechanism could be operating was not investigated; this motivated us to study the mechanism of these formal cyclodehydration reactions.[9] We foundthat the mechanism for the dehydrogenation of benzylic alcohols by **1a** involved an initial hydrogen-transfer step with concomitant formation of an iridium-hydride species.[2] The hydroxy/alkoxide functionality on the carbene ligand participated in proton-transfer steps. We were intrigued by the possibility that a similar hydrogen-transfer mechanism could also be operating in the case of the diols, and we have now studied the cyclodehydration reactions of 1,4- and 1,5-diols catalyzed by NHC–iridium complexes **1a**–**1c**. In this paper, we propose mechanistic pathways that are dependent on the electronic properties of the diols, and also on whether the substrate is a 1,4- or a 1,5-diol.

Results

First, we tested a series of NHC–Ir(III) complexes in the cyclodehydration reaction of 1-phenyl-1,4-pentanediol (**2a**; Table 1).[2] The optimized reaction conditions for the acceptorless alcohol dehydrogenation (AAD) reaction (Scheme 1, top) had previously been tested on **2a** (i.e., iridium complex **1a**, in a mixture of toluene and *t*-butanol (2.6:1, v/v) under reflux), and under these conditions, tetrahydrofuran **3a** was formed in excellent yield (91%, Table 1, entry 1). [2] In contrast, neutral iridium dichloride complex **1b** did not promote the cyclization, and instead, mono- and dioxidized linear compounds **4a** and **5a**, as well as deoxygenated ketone **6a** (see Supporting Information),[10] were detected in the crude mixture at 80% conversion of **2a** (Table 1, entry 2). Biscationic bifunctional catalyst **1c**, which has an NHC ligand with only one hydroxy-functionalized wingtip, gave the tetrahydrofuran product (**3a**) in a low yield of 31%, together with a mixture of oxidized linear compounds (Table 1, entry 3). The commercially available complex $[Cp^*IrCl_2]_2$ (**1d**) was also tested, and this gave **3a** in only 11% yield (Table 1, entry 4), along with higher yields of oxidized linear by-products. In a control experiment carried out in the absence of any iridium complex under otherwise identical reaction conditions, **2a** did not undergo any reaction (Table 1, entry 5). When toluene was used as the sole solvent, the catalytic activity of **1a** towards the formation of **3a** decreased; this product was formed in a lower yield of 70% (Table 1, entry 6 *vs* entry 1).

10.1002/chem.201805460

Table 1. Cyclodehydration of diols catalyzed by Ir(III) complexes.[a]



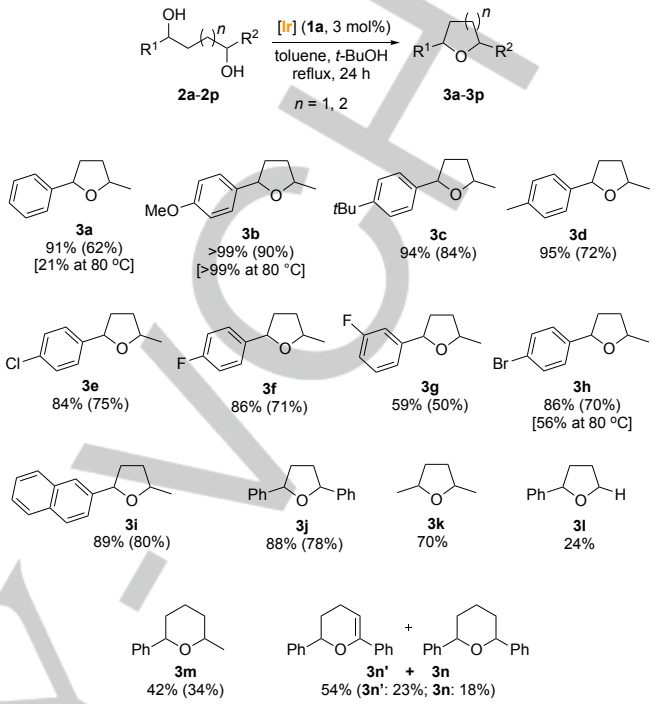
Entry	[Ir]	**2a** [%]	**3a** [%]	**4a** [%]	**5a** [%]	**6a** [%]
1	**1a**	nd[b]	91	5	4	nd[b]
2	**1b**	20	nd	45	13	23
3	**1c**	8	31	30	13	18
4	**1d**	10	17	26	12	35
5	-	>95	nd[b]	nd[b]	nd[b]	nd[b]
6[c]	**1a**	14	70	3	14	nd[b]

[a] Reaction conditions: diol (1 mmol), [Ir] (0.03 mmol, 3 mol%), toluene (2.6 mL), *t*-BuOH (1 mL), 80 °C or reflux, 24 h. Yield determined by ^{1}H NMR spectroscopy. [b] nd = not detected. [c] In toluene as the sole solvent.

Iridium complex **1a** was then used as the catalyst in the cyclodehydration of a series of 1,4-diols (**2a**–**2l**) and 1,5-diols (**2m**–**2n**) using the conditions of Table 1, entry 1 (Table 2). For 1,4-diols containing only *sec*-alcohols, the corresponding tetrahydrofurans **3a**–**3k** were formed in good to excellent yields. The ^{1}H NMR spectra of the products indicated the presence of diastereomeric mixtures (see Supporting Information). The reaction even worked well for aliphatic biomass-derived 2,5-hexanediol (**2k**), which gave 2,5-dimethyltetrahydrofuran (**3k**), an important industrial additive.[11]

When 1,4-diol **2l**, which contains a *sec*- and a primary alcohol, was subjected to the reaction conditions, the yield dropped dramatically to only 24%. This is consistent with our observations on the AAD reactions of primary alcohols catalyzed by **1a**.[2] Unsaturated diols did not yield cyclic ether derivatives, but mixtures of diketones and deoxygenated ketones (see the Supporting Information). Importantly, when the reaction was tested under milder reaction conditions (80 °C), good yields were only obtained for the very electron-rich diol **2b** (to give **3b**; **3a** and **3h** were formed in lower yields). Interestingly, 1,5-diol substrates (**2m** and **2n**) reached full conversions to give mixtures of products; the major products were six-membered-ring compounds; both saturated cyclic ethers (**3m** and **3n**) and 2,3-dihydropyrans (**3m'** and **3n'**) were observed. The presence of the unsaturated products suggests a net loss of dihydrogen for this family of substrates. Dihydropyran **3m'** was transformed into the corresponding tetrahydropyran **3m** in a subsequent hydrogenation step (see Supporting Information).

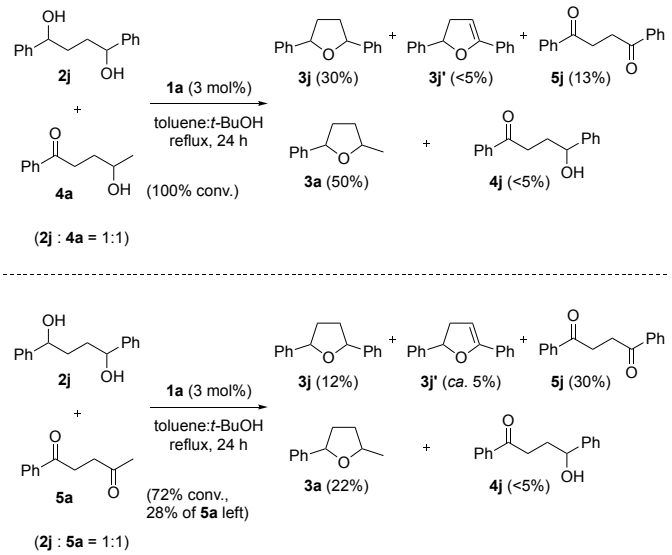
Table 2. Cyclodehydration of diols catalyzed by **1a**.[a]



[a] Reaction conditions: diol (1 mmol), **1a** (0.03 mmol, 3 mol%), toluene (2.6 mL), *t*-BuOH (1 mL), 80 °C or reflux, 24 h. Yield determined by ^{1}H NMR spectroscopy. Isolated yields in parentheses.

Crossover experiments were carried out to gain some insight into the overall redox-neutral reaction of diols. When a 1:1 mixture of **2j** and ketoalcohol **4a** was subjected to the reaction conditions, cyclic structures **3j** and **3a** were both obtained (Scheme 2, top). The reaction mixture also contained oxidized intermediates 2,3-dihydrofuran **3j'**, ketoalcohol **4j**, and diketone **5j**. Similarly, a 1:1 mixture of **2j** and diketone **5a** was subjected to the reaction conditions (Scheme 2, bottom), and after 24 h, tetrahydrofurans **3j** and **3a** were obtained, along with the corresponding oxidized intermediates **3j'**, **4j**, and **5j**.

Hammett studies on the cyclization of five different *para*-functionalized 1-aryl-1,4-pentanediol substrates are shown in Figure 1: 1-phenyl-1,4-pentanediol (**2a**), *p*-methoxyphenyl-1,4-pentanediol (**2b**), *p*-*tert*-butylphenyl-1,4-pentanediol (**2c**), *p*-tolyl-1,4-pentanediol (**2d**), *p*-chlorophenyl-1,4-pentanediol (**2e**), and *p*-fluorophenyl-1,4-pentanediol (**2f**) (see also the Supporting Information).[12] The conversions were monitored by *in situ* ^{1}H NMR spectroscopy. For electron-poor 1,4-diols and for 1,4-diols with moderately electron-rich substituents, plots of [log(k_X/k_H)] *vs* σ (Figure 1a) show a linear relationship with a negative slope of -1.73 ± 0.22. The electron-rich *para*-methoxy-substituted diol **2b** deviates from this Hammett correlation, as it reacted *ca*. 10^4 times faster than extrapolated (Figure 1a).[13]



Scheme 2. Crossover experiments for the cyclization of 1,4-diol **2j** in the presence of ketoalcohol **4a** (top) or diketone **5a** (bottom).

Figure 1b also shows a plot of [log(k_X/k_H)] *vs* the Hammett–Brown σ^+ constants instead of the σ constants (see the Supporting Information).[14]

Kinetic isotope effect (KIE) studies were then carried out.[15] The cyclodehydration rate of **2a** was compared to that of **2a**-d_2, and a KIE of 2.94 ± 0.14 was observed (see Supporting Information). This value suggests that the cleavage of the C−H(D) bond at the benzylic position occurs in the rate determining step. In contrast, a negligible KIE of 1.14 ± 0.08 was obtained for the *p*-methoxy-substituted diols, **2b** and **2b**-d_2 (see the Supporting Information).

Discussion

Two possible mechanistic pathways are shown in Scheme 3. Scheme 3a shows a mechanism that proceeds through acid catalysis,[16] and that involves nucleophilic substitution (S_N1 or S_N2). Scheme 3b shows a redox-neutral mechanism with carbonyl compounds and iridium hydrides as key intermediates. The functionalized NHC ligand of **1a** participates in proton-shuffling steps.[3] The iridium complex acts in the first instance as an acid catalyst, and in the second as a hydrogen-transfer catalyst. When we investigated the scope of this reaction (*vide supra*, Table 2), we found that diol **2b**, which has an electron-rich *p*-MeOC_6H_4 subtituent, gave the tetrahydrofuran product **3b** in excellent yield, even when a lower temperature of 80 °C was used. Neither **2a** nor **2b** gave any product when the reaction was carried out in the absence of an iridium catalyst (*vide supra*, Table 1, entry 5), under otherwise identical reaction conditions.

The Hammett plots (Figure 1a and 1b) clearly show that the *p*-MeO-substituted substrate (**2b**) reacts at a rate that is orders of magnitude higher than what would be predicted based on the log(k_X/k_H) of the other substrates. Due to the excellent fitting of

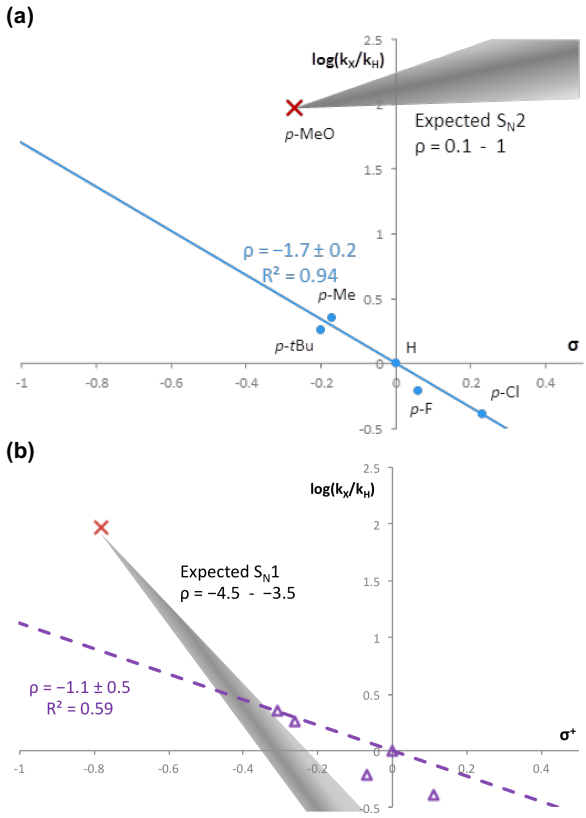


Figure 1. Hammett plots for the cyclodehydration of diols **2a**–**2f**. (a) log(k_X/k_H) versus σ, log(k_X/k_H) = (−1.7±0.2)σ, R^2 = 0.94. (b) log(k_X/k_H) versus σ^+, log(k_X/k_H) = (−1.1±0.5)σ^+, R^2 = 0.59. The shaded regions show the expected areas for log(k_X/k_H) if the substrates were to follow an S_N2 (top, a) or an S_N1 (bottom, b) mechanism. Each point corresponds to an average of three experiments. Note: **2b** (red cross) is not used for the correlations, see text.

all substrates, excluding **2b,** in the Hammett plot (Figure 1a, substituent constants σ, R^2 = 0.94) compared with the Hammett-Brown plot (Figure 1b, substituent constants σ+, R^2 = 0.59), the S_N1 pathway (i.e. through a fully developed positive charge in direct conjugation with the *para* substituent) can already be ruled out for these substrates. Closer analysis of Figure 1b gives further support to the absence of an S_N1 pathway for **2a**, and **2c**–**2f**; In general, for an S_N1 mechanism, we would expect a linear fit with the σ^+ values, and a ρ value of around −4.[14] In Figure 1b, the shaded area shows the range of gradients for typical ρ values in S_N1 reactions, ranging from −3.5 to −4.5 (using the data point of **2b** as a reference point). If diols **2a**, **2c**–**2f** followed an S_N1 pathway, their data points would fall within this shaded region (Figure 1b), and this is in clear disagreement with the experimental data; All substrates except **2b** lie above the expected S_N1 plot bracket based on **2b** (Figure 1b, shaded region). In short, we can conclude that all the substrates except *p*-MeO diol **2b** follow a faster neutral pathway instead of the alternative S_N1 mechanism.

Thus, we now have to consider which of the alternative neutral mechanisms, the S_N2 and redox pathways (Scheme 3), is operating for **2a**, and for **2c**–**2f**. If the reaction followed an S_N2 mechanism, we would expect to see a correlation with σ with a

small positive ρ value (typical ρ values for S_N2 reactions range from 0.1 to 1; Figure 1a, shaded area, using the data point of **2b** as a reference point).[14] Thus, **2a**, **2c**–**2f** would all be expected to have reactivities equal to or higher than that of *p*-MeO diol **2b** (i.e., a positive ρ value, with substrates with electron-withdrawing substituents having higher rates). This is once again in clear disagreement with the observed results. In fact, excluding cyclic ether **3b**, which is obviously formed by a different mechanism (c.f., KIE), the opposite reactivity trend is observed, as the data fit well to standard Hammett σ values (Figure 1a) with a negative ρ value of −1.7. This is very similar to what we reported before for a rate-limiting Ir-catalyzed hydrogen transfer from benzylic alcohols.[3b]

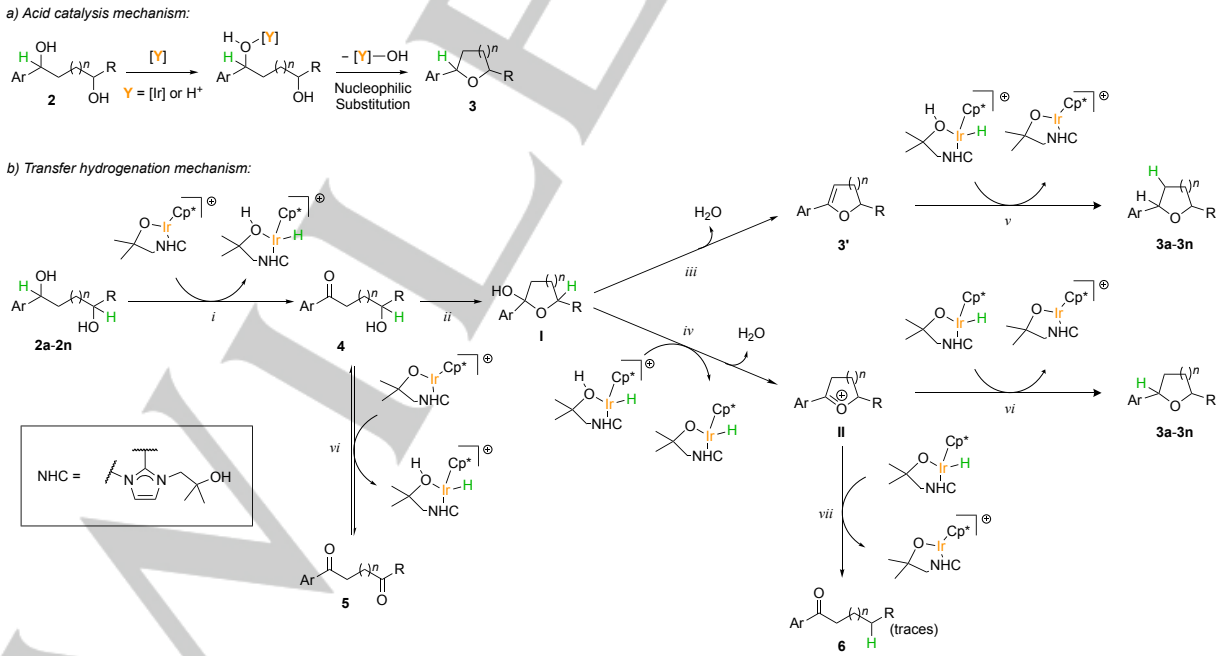
We may therefore conclude that there are two competing mechanisms. Normally, this situation results in a Hammett plot with two linear regions showing an upwards break, a so-called "V" shape.[17] In the peculiar case described here, this should instead be represented with two different Hammett plots, as the S_N1 pathway correlates with σ^+ values, and the neutral-redox pathway with the neutral substituent constants σ. The inflection point can be estimated by looking into Figure 1b, at a σ^+ value of around −0.3 to −0.4, at the intersection between the shaded region representing an S_N1 mechanism from **2b** and the experimental Hammett–Brown plot (purple dashed line constructed from **2a**, **2c**–**2f**).

The substantial difference obtained in the KIE studies on diol **2a** *vs* diol **2b** (2.94 ± 0.14 *vs* 1.14 ± 0.08, respectively) also supports the operation of two distinct mechanistic pathways, depending on the electronic properties of the substrates. Thus, in the case of **2a**, the C–H bond is broken in the rate determining step, in contrast to **2b**.

Further support for the redox pathway (Scheme 3b) for substrate **2a** was obtained in the crossover experiments (Scheme 2), as hydrogen was transferred between the diol substrates and the diketone or ketoalcohol additives. Furthermore, the cyclodehydration of 1,5-diols **2m**–**2n** gave mixtures of 2,3-dihydropyrans **3'** and tetrahydropyrans **3**. The former type of products (**3'**) could only be formed through a mechanism involving hydrogen transfer.[18]

In an attempt to obtain further evidence for the formation of carbocationic species in the cyclodehydration of **2b**, we carried out a number of experiments in the presence of nucleophiles (see Supporting Information).[19] With **2b** as a substrate, these experiments only resulted in the formation of **3b**. However, when a model alcohol with identical electronic properties that is unable to undergo intramolecular cyclization, namely (1-(*p*-methoxyphenyl)-1-pentanol, **13b**), was subjected to the same reaction conditions, this substrate did react with the added nucleophiles (e.g., MeOH, 5 equiv.). This result clearly supports the idea of carbocationic intermediates in the cyclization of **2b**.

In summary, we have reported the acid- and base-free cyclodehydration of 1,4- and 1,5-diols catalyzed by NHC–iridium(III) complex **1a**. Supported by Hammett studies, KIE investigations, and crossover and trapping experiments, we found that the mechanism of the cyclization is highly dependent on the electronic properties of the diol substrates. Very electron-rich aromatic substrates follow an acid-catalyzed mechanistic pathway, whereas substrates with no substituents on the aromatic ring, or electron-withdrawing substituents, follow a hydrogen-transfer mechanism. Both mechanisms may be operating simultaneously for moderately electron-rich



Scheme 3. Proposed mechanism for the formation of cyclic ethers **3** (*n* = 1,2).

substrates. From a synthetic point of view, the protocol reported here using bifunctional NHC-iridium(III) complexes can be used for the preparation of functionalized 2,6-disubstituted dihydropyran or 2,5-disubstituted tetrahydrofuran building blocks from diols under neutral reaction conditions.

Experimental Section

Synthesis of 1,4-diols: Commercially available 1,4-diols **2k** and **2l** were purchased from Sigma–Aldrich, and were used as received. Non-commercially-available 1,4-diols were obtained by reduction of 1,4-diketone precursors. Commercially available 1,4-diketones **5a** and **5j**, precursors of 1,4-diols **2a** and **2j**, respectively, were purchased from Sigma–Aldrich, and were used as received. Non-commercially-available 1,4-diketones **5** were synthesized following reported procedures:

(a) $Cu(OTf)_2$ (5 mol%), $MnCl_2{\cdot}4H_2O$ (5 mol%), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU; 7.5 mmol, 1.5 equiv) and aqueous *tert*-butyl hydroperoxide (TBHP; 20 mmol, 4 equiv; 70% in water) were added to a round-bottom flask equipped with a condenser containing a mixture of the corresponding vinylarene (**7**, 5 mmol) and acetone (**8**, 30 mL). The reaction mixture was stirred at reflux, and the reaction progress was monitored by TLC. When the reaction was complete, the mixture was diluted with CH_2Cl_2 (125 mL), and washed with water.The aqueous phase was further extracted with CH_2Cl_2. The combined organic phases were dried with $MgSO_4$, filtered, and concentrated under vacuum. The residue was purified by column chromatography using petroleum ether and ethyl acetate (9:1, v/v) as eluent to give the desired diketone **5**.[20]

(b) In a sealed glass tube equipped with a stirrer bar, the corresponding precursor benzaldehyde (**9**, 0.09 mol), triethylamine (19.5 mL, 0.14 mol), methyl vinyl ketone (**10**, 0.09 mol), and 3-ethyl-5-(2-hydroxyethyl)-4-methylthiazolium bromide (**11**, 3.53 g, 0.014 mol) were mixed together. The flask was heated in the cavity of a microwave reactor for 15 min (150 W, internal temperature 70 °C, and internal pressure 60 psi). After this time, the resulting mixture was stirred with aqueous HCl (2 M; 10 mL) for 30 min. The mixture was extracted with EtOAc. The organic layers were washed with aqueous sodium bicarbonate and brine. The organic fractions were dried over Na_2SO_4, filtered, and concentrated to give a crude orange liquid. Column chromatography (cyclohexane/ethyl acetate, 3:1, v/v) gave the desired diketone (**5**).[21]

Synthesis of 1,5-diols: 1,5-Diols **2m** and **2n** were obtained by reduction of 1,5-diketones **5m** and **5n**, respectively. 1,5-Diketone **5n** is commercially available, and was used as received from Sigma–Aldrich. The synthesis of 1,5-diketone **5m** was carried out following a reported procedure.[22] Methyl vinyl ketone **10** and iodine were added to a solution of the corresponding silyl enol ether **12m** in acetonitrile. When the reaction was complete, methanol and sodium thiosulfate were added. The mixture was extracted with EtOAc, and the crude product was purified by column chromatography to give 1,5-diol **2m**.

General procedure for the cyclodehydration of diols: An oven-dried microwave vial containing **1a** (0.03 mmol) was flushed with a stream of argon. Toluene (2.6 mL), *tert*-butanol (1 mL), and the corresponding diol **2** (1 mmol) were added. The reaction mixture was stirred and heated at reflux for 24 h. After this time, the mixture was cooled down. The yield was quantified by ^{1}H NMR spectroscopic analysis of the crude mixture or after purification by column chromatography. For 1,5-diol substrates **2m** and **2n**, an additional independent hydrogenation step with Pd/C was carried out to give the tetrahydropyrans (see the Supporting Information).

General procedure for NMR-scale experiments: Iridium complex **1b** (0.045 mmol, 27.5 mg) and anhydrous and degassed CH_2Cl_2 (4 mL) were added to a vial containing $AgBF_4$ (0.0945 mmol, 18.4 mg). The reaction mixture was stirred for 2 h at room temperature. The mixture was filtered through a pad of Celite® to remove the AgCl precipitate, and the filtrate was distributed into 20 NMR tubes. The solvent was evaporated under vacuum, and the NMR tubes could then be stored under an inert atmosphere. Toluene-d_8 (0.2 mL), *tert*-butanol (0.05 mL), and a stock solution of a 1,4-diol **2** (0.075 mmol) were added to an NMR tube containing **1a** (0.00225 mmol). The NMR tube was then put into an NMR spectrometer preheated to 100 °C. ^{1}H NMR spectra were recorded every 2 min.

Acknowledgements

This project was generously supported by the Swedish Research Council through Vetenskapsrådet (VR), and by the Knut and Alice Wallenberg Foundation. The Wenner-Gren foundation is gratefully acknowledged for a postdoctoral grant to E.M.-C.

Keywords: Hydrogen Transfer • Hammett-Brown • Kinetic Isotope Effect • Cyclodehydration • Hydride

References

[1] Selected examples on the use of [Ir-NHC] complexes in catalysis: a) A. Bunrit, C. Dahlstrand, S. K. Olsson, P. Srifa, G. Huang, A. Orthaber, P. J. R. Sjöberg, S. Biswas, F. Himo, J. S. M. Samec, *J. Am. Chem. Soc.* **2015**, *137*, 4646–4649; b) J.-E. Bäckvall, S. E. Byström, R. E. Nordberg, *J. Org. Chem.* **1984**, *49*, 4619–4631; c) J. L. Princival, S. M. G. de Barros, J. V. Comasseto, A. A. Dos Santos, *Tetrahedron Lett.* **2005**, *46*, 4423–4425; d) R. R. Muslukhov, A. K. Shayakhmetova, M. P. Yakovleva, O. V. Shitikova, G. Yu. Ishmuratov, G. A. Tolstikov, *Russ. J. Org. Chem.* **2008**, *44*, 1130–1133; e) R. S. Harvey, E. G. Mackay, L. Roger, M. N. Paddon-Row, M. S. Sherburn, A. L. Lawrence, *Angew. Chem.* **2015**, *127*, 1815–1818; *Angew. Chem., Int. Ed.* **2015**, *54*, 1795–1798.

[2] G. González Miera, E. Martínez-Castro, B. Martín-Matute, *Organometallics* **2018**, *37*, 636–644.

[3] a) A. Bartoszewicz, R. Marcos, S. Sahoo, A. K. Inge, X. Zou, B. Martín-Matute, *Chem. Eur. J.* **2012**, *18*, 14510−14519; b) A. Bartoszewicz, G. González Miera, R. Marcos, P.-O. Norrby, B. Martín-Matute, *ACS Catal.* **2015**, *5*, 3704–3716.

[4] E. Peris, *Chem. Rev.* **2018**, *118*, 9988-10031

[5] a) A. Bunrit, C. Dahlstrand, S. K. Olsson, P. Srifa, G. Huang, A. Orthaber, P. J. R. Sjöberg, S. Biswas, F. Himo, J. S. M. Samec, *J. Am. Chem. Soc.* **2015**, *137*, 4646–4649; b) J.-E. Bäckvall, S. E. Byström, R. E. Nordberg, *J. Org. Chem.* **1984**, *49*, 4619–4631; c) J. L. Princival, S. M. G. de Barros, J. V. Comasseto, A. A. Dos Santos, *Tetrahedron Lett.* **2005**, *46*, 4423–4425; d) R. R. Muslukhov, A. K. Shayakhmetova, M. P. Yakovleva, O. V. Shitikova, G. Yu. Ishmuratov, G. A. Tolstikov, *Russ. J. Org. Chem.* **2008**, *44*, 1130–1133; e) R. S. Harvey, E. G. Mackay, L. Roger, M. N. Paddon-Row, M. S. Sherburn, A. L. Lawrence, *Angew. Chem.* **2015**, *127*, 1815–1818; *Angew. Chem., Int. Ed.* **2015**, *54*, 1795–1798.

[6] a) T. Shibata, R. Fujiwara, Y. Ueno, *Synlett* **2005**, *1*, 152–154; b) X. Jiang, E. K. London, D. J. Morris, G. J. Clarkson, M. Wills, *Tetrahedron* **2010**, *66*, 9828–9834; c) I. Čorić, J. H. Kim, T. Vlaar, M. Patil, W. Thiel,

B. List, *Angew. Chem.* **2013**, *125*, 3574–3577; *Angew. Chem., Int. Ed.* **2013**, *52*, 3490–3493; d) J. Kim, D.-H. Lee, N. Kalutharage, C. S. Yi, *ACS Catal.* **2014**, *4*, 3881–3885; e) M. Hellal, F. C. Falk, E. Wolf, M. Dryzhakov, J. Moran, *Org. Biomol. Chem.* **2014**, *12*, 5990–5994; f) G. V. M. Sharma, K. R. Kumar, P. Sreenivas, P. R. Krishna, M. S. Chorghade, *Tetrahedron Asymmetry* **2002**, *13*, 687–690; g) S. Nagashima, T. Sasaki, S. Kamiguchi, T. Chihara, *Chem. Lett.* **2015**, *44*, 764–766.

[7] a) H. Aikawa, S. Tago, K. Umetsu, N. Haginiwa, N. Asao, *Tetrahedron* **2009**, *65*, 1774–1784; b) K. Yoshikawa, T. Nagata, T. Yoshino, Y. Nakamoto, N. Haginoya, R. Muto, A. Mochizuki, H. Kanno, T. Ohta, *Heterocycles* **2012**, *85*, 1711–1720; c) B. D. Kelly, T. H. Lambert, *Org. Lett.* **2011**, *13*, 740–743; d) P. H. Huy, A. M. P. Koskinen, *Org. Lett.* **2013**, *15*, 5178–5181.

[8] a) F. Aricò, P. Tundo, A. Maranzana, G. Tonachini, *ChemSusChem* **2012**, *5*, 1578–1586; b) F. Aricò, P. Tundo, *J. Chin. Chem. Soc.* **2012**, *59*, 1375–1384; c) F. Aricò, S. Evaristo, P. Tundo, *Green Chem.* **2015**, *17*, 1176–1185.

[9] a) A. Yamaguchi, N. Hiyoshi, O. Sato, M. Shirai, *ACS Catal.* **2011**, *1*, 67–69; b) B. Liu, Z. Zhang, *ChemSusChem* **2016**, *9*, 2015−2036.

[10] R. F. Perez, M. A. Fraga, *Green Chem.* **2014**, *16*, 3942–3950.

[11] H. Li, Z. Fang, R. L. Smith, S. Yang, *Prog. Energy Combust. Sci.* **2016**, *55*, 98–194.

[12] a) L. P. Hammett, *J. Am. Chem. Soc.* **1937**, *59*, 96−103; b) C. K. Ingold, F. R. Shaw, *J. Chem. Soc.* **1927**, *0*, 2918−2926.

[13] T. B. Phan, C. Nolte, S. Kobayashi, A. R. Ofial, H. Mayr, *J. Am. Chem. Soc.* **2009**, *131*, 11392–11401

[14] H. H. Jaffé, *Chem. Rev.* **1953**, *53*, 191–261.

[15] a) E. M. Simmons, J. F. Hartwig, *Angew. Chem.* **2012**, *124*, 3120–3126; *Angew. Chem., Int. Ed.* **2012**, *51*, 3066−3072; b) M. Gómez-Gallego, M. A. Sierra, *Chem. Rev.* **2011**, *111*, 4857−4963.

[16] Diol cyclizations on carbohydrate substrates follow purely S_N2 pathways due to the very electron-poor nature of these substrates. See: a) R. Cribiù, K. E. Borbas, I. Cumpstey, *Tetrahedron* **2009**, *65*, 2022–2031; b) R. Cribiù, I. Cumpstey, *Chem. Commun.* **2008**, 1246–1248.

[17] J. Clayden, N. Greeves, and S. Warren. *Organic Chemistry*, *2nd Edition*, Oxford University Press, Oxford, **2012**, pp. 1029−1068.

[18] R. J. Sullivan, E. Latifi, B. K.-M. Chung, D. V. Soldatov, M. Schlaf, *ACS Catal.* **2014**, *4*, 4116–4128.

[19] a) R. Ortiz, A. Koukouras, E. Marqués-López, R. P. Herrera, *Arabian J. Chem.* **2018**, DOI: 10.1016/j.arabjc.2018.01.022; b) R. Ortiz, R. P. Herrera, *Molecules* **2017**, *22*, 574.

[20] X.-W. Lan, N.-X. Wang, W. Zhang, J.-L. Wen, C.-B. Bai, Y. Xing, Y.-H. Li, *Org. Lett.* **2015**, *17*, 4460–4463.

[21] G. Poce, M. Cocozza, S. Alfonso, S. Consalvi, G. Venditti, R. Fernandez-Menendez, R. H. Bates, D. Barros Aguirre, L. Ballell, A. De Logu, G. Vistoli, M. Biava, *Eur. J. Med. Chem.* **2018**, *145*, 539–550.

[22] S. Deuri, P. Phukan, *J. Phys. Org. Chem.* **2012**, *25*, 1228–1235.

10.1002/chem.201805460

WILEY-VCH

FULL PAPER

Hydrogen transfer vs acid catalysis: Mechanistic studies on the iridium-catalyzed cyclodehydration of a series of diols have been carried out. Hammett and Hammett–Brown analyses of the reactivity data are compared, along with kinetic isotope effect and crossover experiments. In this way, we were able to elucidate the reaction mechanisms, which were found to be dependent on the electronic properties of the substrates.

*Greco González Miera, Aitor Bermejo López, Elisa Martínez-Castro, Per-Ola Norrby, and Belén Martín-Matute**

Page No. – Page No.

Nonclassical mechanism in the cyclodehydration of diols catalyzed by a bifunctional iridium complex