Pincer Ligands

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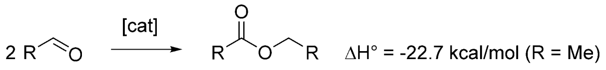
Rethinking the Claisen–Tishchenko Reaction

*Stacey A. Morris and Dmitry G. Gusev**

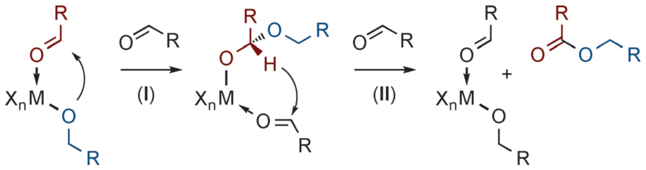
***Abstract:** Pincer-type complexes $[OsH_2(CO)\{PyCH_2NHCH_2CH_2NHPtBu_2\}]$ and $[OsH_2(CO)\{HN(CH_2CH_2PiPr_2)_2\}]$ catalyze the disproportionation reaction of aldehydes via an outer-sphere bifunctional mechanism achieving turnover frequencies up to 14000 h^{-1}. The N–H group of the catalysts is a key player in this process, elucidated with the help of DFT calculations.*

The Claisen–Tishchenko reaction (Scheme 1) is an atom-efficient method of producing esters from aldehydes.[1] The aldehyde disproportionation was first reported in 1887 by Claisen who obtained benzyl benzoate by treating benzaldehyde with sodium ethoxide in ethanol.[2] Subsequently, Tishchenko developed the general catalytic approach of Scheme 1 using aluminum and magnesium alkoxides.[3] Modern catalysts achieve up to 200 turnovers,[4] although turnover numbers (TONs) under 100 and the use of up to 5 mol% catalyst are more common.[1]



Scheme 1. The Claisen–Tishchenko reaction.

The Claisen–Tishchenko reaction has been comprehensively reviewed.[1] The generally accepted mechanism of the aldehyde disproportionation is summarized in Scheme 2. The key steps of the C–O bond formation and the hydride transfer occur in the coordination sphere of the metal. Step II of the Claisen–Tishchenko reaction is analogous to the hydride transfer step of the Meerwein–Pondorf–Verley (MPV) reaction.[5]

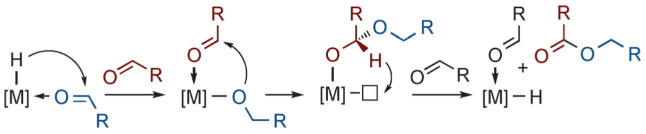


Scheme 2. Key intermediates of the Claisen–Tishchenko reaction (M = metal from Main Groups I–III).

The use of d-block metals for the ester synthesis of Scheme 1 is relatively uncommon.[6] $[RuH_2(PPh_3)_4]$ was the first complex discovered to catalyze the disproportionation of aldehydes by Yamamoto in 1982.[6a] Other prominent d-metal systems include the Shvo catalyst,[6d] $[OsH_6(PiPr_3)_2]$,[6e] and $[RhH_2(NCMe)(PhB(CH_2PPh_2)_3)]$.[6k] With the exception of the Shvo catalyst, the d-metal compounds tested afforded TON = 100–200 and thus little incentive for replacing the main-group catalysts. This is somewhat surprising, considering how dramatically the mechanistically related MPV reaction was transformed by the development of the bifunctional ruthenium catalysts.[7]

Different reaction mechanisms have been considered with the d-metals. The prevalent thought is that vacant coordination sites on the metal and substrate coordination are important. Aldehyde insertion into a M–H bond to give a metal alkoxide is another key mechanistic event.

Yamamoto originally proposed that the coordinated aldehyde undergoes β-H elimination to give a metal acyl hydride intermediate, then a second molecule of the aldehyde inserts into the Ru–H bond to form an alkoxide. Ultimately, the C–O coupling of the acyl with the alkoxide affords the ester.[6a] The mechanism of Tejel[6k] (Scheme 3) resembles the classical mechanism (Scheme 2), except that the final hydride transfer is to the metal. In yet another mechanism, Shvo proposed that the aldehyde is first hydrogenated to produce the primary alcohol and a 16-electron metal intermediate.[6d] The alcohol further reacts with the substrate in solution to give the hemiacetal. This hemiacetal is dehydrogenated by the 16-electron catalyst intermediate to afford the final product. Both the hydrogenation and dehydrogenation events with the Shvo catalyst were envisaged to occur in an outer-sphere fashion.



Scheme 3. A mechanism of the d-metal-catalyzed ester synthesis.

The experimental and computational work presented here establish that the C–O bond formation of the Claisen–Tishchenko reaction can be an outer-sphere process. Thus, the mechanism does not require a vacant coordination site, and the disproportionation of aldehydes is most efficiently promoted by thermally robust 18-electron bifunctional catalysts affording turnover frequencies on the order of 10^4 h^{-1}. These findings provide insights into the unusual role of the

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[*] S. A. Morris, Prof. Dr. D. G. Gusev
Department of Chemistry and Biochemistry
Wilfrid Laurier University
75 University Ave. W., Waterloo ON N2L 3C5 (Canada)
E-mail: dgoussev@wlu.ca

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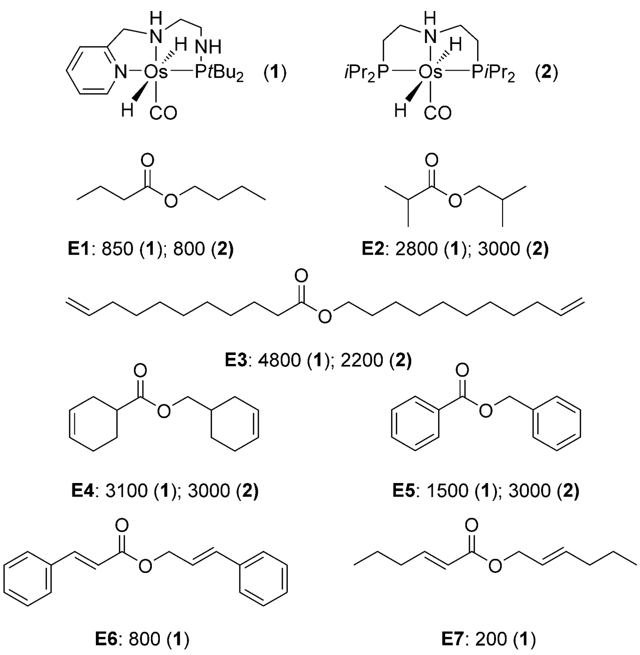


Scheme 4. Disproportionation products and turnover numbers of the tested aldehydes (3 M for 10-undecenal and 5 M for the other substrates in toluene) with **1** and **2** (for details see the Supporting Information, Table S1, and Figures S1–S7).

N–H group in the reactions promoted by the bifunctional catalysts.

We tested complexes **1**[8a] and **2**[8b] (Scheme 4) with representative substrates: enolizable (butyraldehyde, *iso*-butyraldehyde, 10-undecenal, 3-cyclohexene-1-carboxaldehyde) and non-enolizable aldehydes (benzaldehyde, *trans*-cinnamaldehyde, and *trans*-2-hexenal). The catalytic solutions in toluene were stirred at room temperature for 10 min, then the first NMR spectra of the reaction solutions were collected in 5–7 minutes. The ^{1}H and ^{13}C NMR spectra of the product esters **E1**–**E7** are provided with the Supporting Information (Figures S1–S7).

The Claisen–Tishchenko reaction generates a considerable amount of heat. The reactions of Scheme 4 toward **E1**–**E5** were fast, with the temperature reaching 60–75 °C on the surface, registered by an IR thermometer. The corresponding turnovers of Scheme 4 are at 100 % conversion, with the reaction times being ≤ 20 min. Formation of **E6** and **E7** was less rapid and required 1–2 h to give $> 99\,\%$ conversion and the turnovers of Scheme 4. The non-enolizable substrates afforded the product esters **E5**, **E6**, and **E7** selectively, while the formation of **E1**–**E4** was accompanied by a trace byproduct tentatively identified as a primary alcohol (see Figures S1–S7 for details). Using **2** produced slightly more of this byproduct whose origin is uncertain.

The turnovers of Scheme 4 are the limiting numbers, and increasing the S/C ratio resulted in product mixtures with the unreacted substrates. Larger turnover numbers could be achieved for **E3**, **E5**, and **E6** with **1** by allowing longer reaction times. For example, using S/C = 7000 gave 98 % conversion of 10-undecenal in 6 h, S/C = 5000 gave 88 % conversion of benzaldehyde in 7 h, and S/C = 1000 gave 98 % conversion of *trans*-cinnamaldehyde in 3 h. This behavior is indicative of some catalyst deactivation that can be due to a reaction with the substrate or due to a reaction with a trace impurity.

The results of Scheme 4 present several salient points. Both **1** and **2** are outstanding catalysts (TOF up to $14\,000\ \mathrm{h}^{-1}$), one to two orders of magnitude more efficient than the known catalysts developed in the past 100 years. Only the Shvo catalyst, tested with heating at 65 °C for several hours, afforded comparable initial turnover frequencies reaching $5000\ \mathrm{h}^{-1}$. We note that **1**, **2**, and the Shvo complex are bifunctional carbonyl hydrides; the significance of this observation should become clear when we discuss the reaction mechanism. Catalysts **1** and **2** well tolerate the sterically more hindered and extended substrates.

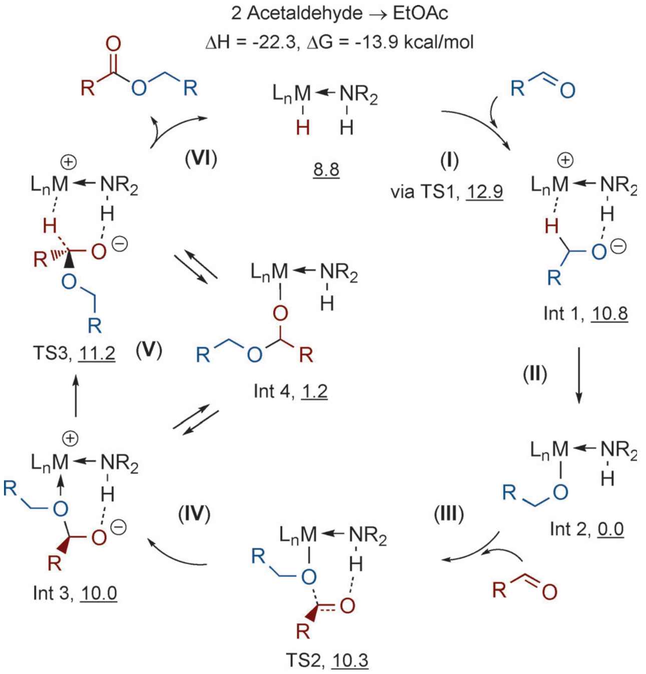
A special feature of **1** is the ability to catalyze the Claisen–Tishchenko reaction of α,β-unsaturated aldehydes, which are very challenging substrates with the existing catalysts. The near quantitative formation of **E6** and **E7** from cinnamaldehyde and 2-hexenal, respectively (Scheme 4), is unprecedented. Generally, the C=C bonds of the unsaturated substrates seem to be unaffected by **1** and are retained in the products (**E3** and **E4**, Scheme 4). Complex **2** proved to be inactive toward **E6** and **E7**.

Complex **1** and especially **2** are thermally robust species. We propose that the reactions leading to the esters of Scheme 4 involve 18-electron intermediates and outer-sphere steps utilizing the bifunctional nature of **1** and **2**. The elucidation of the mechanism was guided by DFT (M06L-D3) calculations, using the disproportionation of acetaldehyde to ethyl acetate as the model reaction.

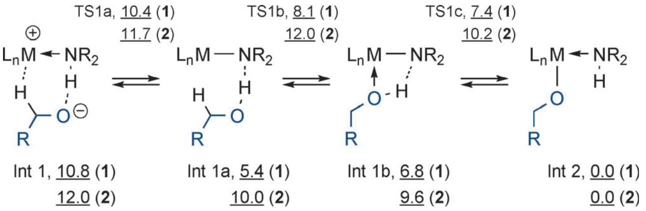
The proposed catalytic cycle (Scheme 5) starts by an outer-sphere hydride transfer from **1** or **2** to the substrate, followed by a rearrangement of the intermediate alkoxide to give Int 2. This transformation is downhill with acetaldehyde: $\Delta G = -8.8$ and $-6.4\ \mathrm{kcal\,mol^{-1}}$ with **1** and **2**, respectively. Int 2 is the ground-state species of the reaction mixture. A second molecule of the aldehyde reacts with Int 2 in an outer-sphere fashion; the C–O bond is fully formed in Int 3. Step **III** can be viewed as a nucleophilic addition of the alkoxide onto the carbonyl, facilitated by the C=O···H–N hydrogen bonding. A similar mechanistic event is part of the dehydrogenative homocoupling of alcohols, while the reverse of step **III** occurs in catalytic ester hydrogenation.[9]

For the product ester of Scheme 5 to form, Int 3 should rearrange to TS3. It is likely that this involves Int 4, which is the thermodynamic "sink" in step **V**. The relevant 1-ethoxyethanolate complex was documented by ESI-MS in ethanol dehydrogenation to ethyl acetate catalyzed by **1**, and the collision-induced dissociation experiments demonstrated formation of ethyl acetate from this species in the gas phase.[10]

The calculations suggest that step **II** of Scheme 5 is unexpectedly complex and involves formation of the alcohol RCH_2OH in the coordination sphere of the metal (Scheme 6). From Int 1, formation of the O–H bond in Int 1a is downhill. The alcohol of Int 1a rearranges easily to give the 18-electron complex Int 1b. Finally, the O–H proton returns to the nitrogen to give the alkoxide Int 2. All of the steps of



Scheme 5. d-Metal-catalyzed ester synthesis. The origin of the M06L-D3 free energies for the formation of ethyl acetate (underlined values, kcal mol^{-1}, in toluene at 298.15 K) is $OsH(OEt)(CO)[PyCH_2NHCH_2CH_2NHPtBu_2]$ (int 2) with CH_3CHO. Mass balance is ensured throughout.

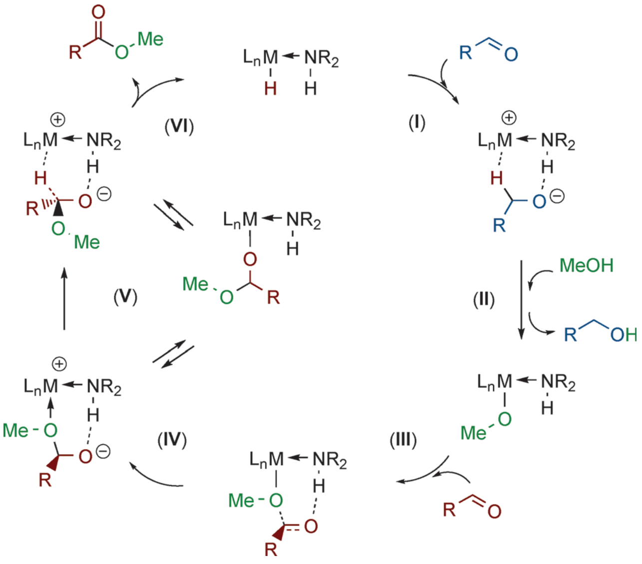


Scheme 6. A path connecting Int 1 and Int 2. The M06L-D3 free energies (kcal mol^{-1}) are for the reactions of **1** and **2** in toluene (R = Me, M = Os).

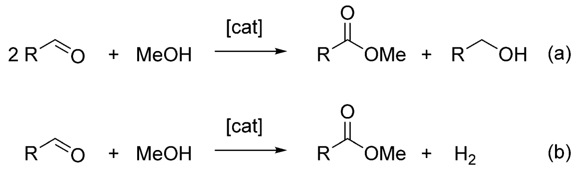
Scheme 6 leading to TS1c proceed on a relatively flat, practically barrier-less free energy surface. We note that Scheme 6 also explains formation of Ru-alkoxides as the kinetic products observed by Bergens in the reactions of ketones with the Noyori catalyst, *trans*-[Ru((*R*)-BINAP)(H)$_2$((*R*,*R*)-dpen)].[11] When considering the reverse process of Scheme 6, it is clear that the N−H group should be instrumental in repositioning the alkoxide from Int 2 to Int 1 in the dehydrogenation reactions of alcohols catalyzed by **1**.[8a,9d,10]

16-Electron intermediates have become a mechanistic staple in the catalytic cycles constructed based on the ideas of metal–ligand cooperation (MLC). Considering Int 1a, it is intriguing to see no free alcohol RCH_2OH released in step **II** along with formation of the 16-electron amido complexes $[OsH(CO)\{PyCH_2NCH_2CH_2NHPtBu_2\}]$ (**3**, from **1**), or $[OsH(CO)\{N(CH_2CH_2PiPr_2)_2\}]$ (**4**, from **2**). Our DFT calculations suggest that the alcohol elimination is unfavorable versus Int 2 in toluene. For example, addition of EtOH to **3** and **4** to give the corresponding ethoxides is exoergic by $\Delta G = -4.0$ and -12.9 kcal mol^{-1}, respectively.[12] Thus, the catalytic reaction of Scheme 5 proceeds with net retention of the N−H bond. Dub and Gordon recently proposed a revised mechanism for the Noyori hydrogenation, suggesting retention of the N−H bond of the catalyst in that reaction as well.[13]

The use of a non-protic solvent is crucial for the ester synthesis of Scheme 5. For example, the outcome of the reaction changes when toluene is replaced by methanol. When a 2 M solution of butyraldehyde in MeOH was treated with **1** or **2** (S/C = 900), the ensuing rapid reaction afforded a mixture of butanol and methyl butyrate (Figure S8). This observation is easily rationalized by formation of the methoxide intermediate in step **II** of Scheme 7 and the outer-sphere coupling of the methoxide with butyraldehyde. The overall reaction is that of Scheme 8 a. It is interesting whether catalysts and/or reaction conditions can be developed to circumvent the insertion step **I** of Scheme 7 by allowing rapid H_2 elimination from the hydride intermediate, to produce the methyl ester selectively per reaction of Scheme 8 b.



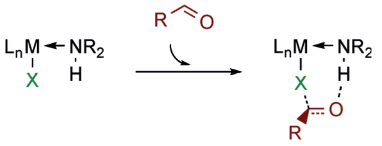
Scheme 7. d-Metal-catalyzed methyl ester synthesis in methanol.



Scheme 8. Methyl ester formation in methanol.

One can reasonably expect that a reaction with water, analogous to Scheme 7, should afford an osmium hydroxide and ultimately a stable carboxylate complex[14] that can be detrimental to the ester synthesis. The presence of water is inhibitory to the classical Tishchenko reaction catalyzed by aluminum alkoxides.[1d] Another practical point related to the catalyst stability is the well-known tendency of aldehydes to decarbonylation with d-metal complexes.[6e] This unwanted side-reaction can be minimized by employing 4 or 5d-metal carbonyls, such as **1**, **2**, and the Shvo catalyst, where the formation of di- or polycarbonyls is relatively unfavorable.

In conclusion, this paper broadens the scope of the catalytic bifunctional outer-sphere reactions. Clearly, M−X nucleophiles other than $\mathrm{X}=\mathrm{H}^-$ can be usefully coupled with the carbonyls (Scheme 9). The N−H group of the bifunctional catalyst is a key player in this process. The N−H is directing and activating the carbonyl substrate toward the nucleophile X^- through the C=O···H−N hydrogen bonds. More intriguingly, the N−H can "shuttle" an alkoxide in and out of the metal coordination sphere, thus allowing facile heterolytic C−H activation in systems where β-H elimination is not feasible. The latter removes the mechanistic need for opening a coordination site through elimination of an ancillary ligand and allows working with thermally stable, electronically and coordinatively saturated d-metal catalysts.



Scheme 9. Outer-sphere bifunctional reactions of carbonyls.

The metal complexes tested in this work, particularly complex **1**, by a large margin outperform all of the known catalysts for the Claisen–Tishchenko reaction developed in the last 100 years. The selective and efficient ester formation with **1** and **2** makes the homocoupling of aldehydes a useful contribution to the library of "click" reactions.[15] The chemistry of Scheme 7 is promising for the development of a catalytic approach toward coupling aldehydes with alcohols for the synthesis of the corresponding mixed esters.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: aldehyde disproportionation · bifunctional catalysts · ester synthesis · metal–ligand cooperation · pincer complexes

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Communications

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S. A. Morris, D. G. Gusev* ——— ■■■–■■■

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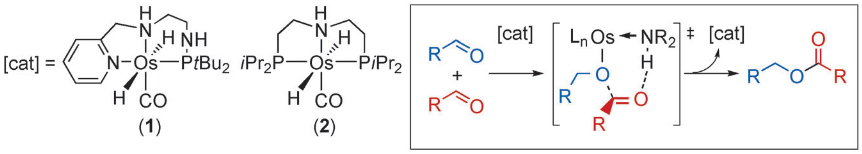

Think again: Pincer-type complexes **1** and **2** catalyze the homocoupling of aldehydes via an outer-sphere bifunctional mechanism achieving turnover frequency of up to 14 000 h^{-1}.