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Reversible carbon–carbon bond formation between carbonyl compounds and a ruthenium pincer complex†

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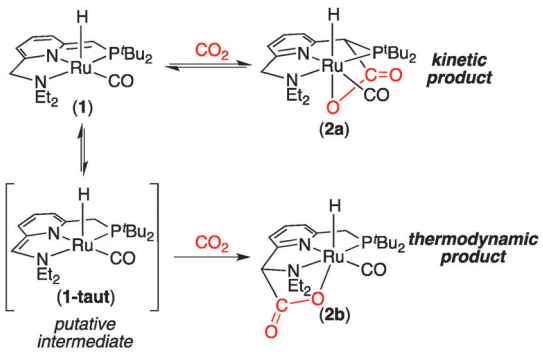
This communication describes the reversible reaction of a ruthenium pincer complex with a variety of carbonyl compounds. Both NMR spectroscopic and X-ray crystallographic characterization of isomeric carbonyl adducts are reported, and the equilibrium constants for carbonyl binding have been determined.

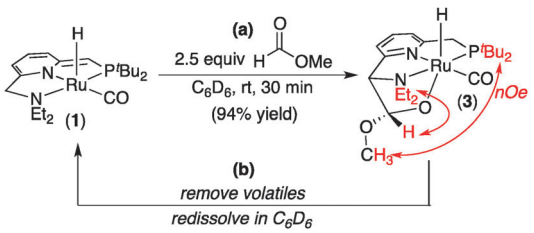
Ruthenium pincer complexes such as (PNN)Ru(H)(CO) (**1**; PNN = 6-(di-*tert*-butylphosphinomethylene)-2-(*N*,*N*-diethylaminomethyl)-1,6-dihydropyridine) are promising catalysts for the hydrogenation of traditionally unreactive carbonyl substrates such as esters, amides, carbonates, and carbamides.[1] Seminal studies by Milstein and coworkers have shown that the unsaturated arm of the pincer ligand plays a critical role in these transformations. Specifically, the ligand accepts a proton during the heterolytic cleavage of H_2 and subsequently delivers this proton to the reduced substrate.[1e,2] Our group became interested in **1** as a catalyst for the hydrogenation of methyl formate during the cascade conversion of CO_2 to CH_3OH.[3] In the course of our investigations of this system, we discovered that the unsaturated pincer ligand arm of **1** can also add to the electrophilic carbon of CO_2.[4] As shown in Scheme 1, this addition initially yields kinetic product **2a**, which rapidly converts to thermodynamic product **2b**. Milstein reported an analogous reversible reaction between CO_2 and the symmetric pincer complex (PNP)Ru(H)CO (PNP = 2,6-bis-(di-*tert*-butylphosphinomethyl)-pyridine-1,6-dihydropyridine).[5,6]

We hypothesized that **1** might react in a similar fashion with other carbonyl compounds like esters, amides, ketones, and/or aldehydes. Such reactions would be of significant interest because these molecules are also substrates for hydrogenation reactions catalyzed by **1**.[1] Our hypothesis about this reactivity was predicated on a key observation made during our studies of the hydrogenation of methyl formate with catalyst **1**.[3] We observed a distinctive color change from brown to yellow upon combining **1** and methyl formate, suggesting that a reaction occurs between these two species. We also noted a recent report by Milstein demonstrating that (PNP)Ru(H)CO reacts with aldehydes at −50 °C.[7,8] The products were characterized by low temperature NMR spectroscopy and were reported to be unstable at room temperature. We report herein that the PNN complex **1** reacts reversibly with formate esters as well as aldehydes and ketones to generate room temperature stable addition products. Detailed investigations of these transformations (using both NMR spectroscopy and X-ray crystallography) show that up to three isomeric products are formed and ultimately equilibrate to a single major stereoisomer.



Scheme 1 CO_2 activation at pincer complex **1**.

Initial studies focused on the reaction of **1** with 2.5 equivalents of methyl formate in C_6D_6 at 25 °C (Scheme 2a). NMR spectroscopic analysis of the crude reaction mixture shows signals consistent with a product in which the pincer ligand has added to methyl



Scheme 2 Reversible reaction of **1** with methyl formate.

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† Electronic supplementary information (ESI) available: Text, tables, figures, and spectral details for the synthesis and characterization of new compounds; crystallographic data for **3**, **5**, **6B-i** and **6B-ii**. CCDC 936845–936848. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3cc43517b

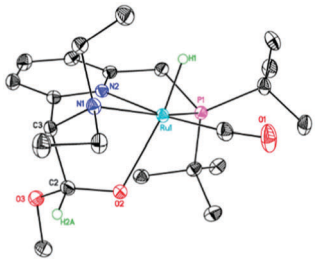


Fig. 1 ORTEP diagram (50% probability level) of the molecular drawing of **3**. All H atoms (other than Ru–H and H–COOMe) have been omitted for clarity. Selected bond lengths (Å) and angles (deg): Ru1–O2 = 2.2022(9), C2–C3 = 1.5678(17), O2–C2 = 1.3409(15), Ru1–H1 = 1.526(19); Ru1–O2–C2 = 112.65(7), O2–C2–C3 = 112.50(10).

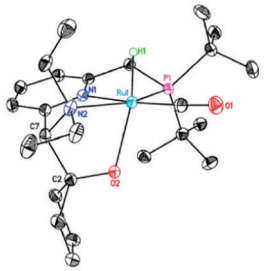


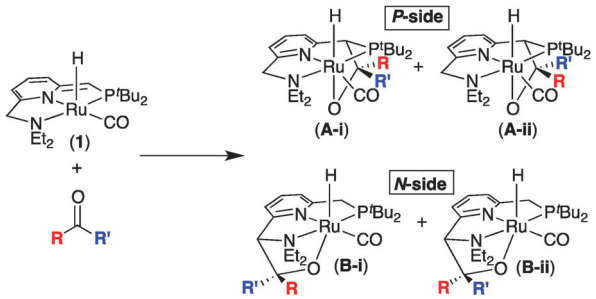
Fig. 2 ORTEP diagram (50% probability level) of the molecular drawing of **5**. All H atoms (other than Ru–H) have been omitted for clarity. Selected bond lengths (Å) and angles (deg): Ru1–O2 = 2.1991(9), C2–C7 = 1.5816(17), O2–C2 = 1.3867(14), Ru1–H1 = 1.534(19); Ru1–O2–C2 = 113.59(7), O2–C2–C7 = 109.79(9).

formate to form a single detectable product, **3**. Removal of the volatiles from this mixture under high vacuum resulted in clean regeneration of complex **1**, indicating that the reaction is fully reversible. Analytically pure samples were obtained in 94% yield by slow evaporation of solvent from a solution of **3** in methyl formate.

^{1}H and ^{13}C NMR spectroscopic experiments clearly show that **3** contains a C–C bond between the carbonyl carbon of methyl formate and the nitrogen arm of the pincer ligand (see ESI† for full details). As highlighted in red, NOESY NMR analysis shows cross-peaks consistent with the stereoisomer depicted in Scheme 2. X-ray quality crystals were obtained by crystallization from a mixture of methyl formate and pentane, and the solid state structure of **3** is shown in Fig. 1. The X-ray structure shows the same stereoisomer as that characterized in solution *via* NMR analysis.

A survey of carbonyl compounds revealed that other formate esters (*e.g.*, ethyl formate) as well as ketones and aldehydes (*e.g.*, cyclopentanone and benzaldehyde) undergo analogous reactions with **1** (Scheme 3). In most cases these transformations were reversible, and removal of the volatiles followed by redissolution in C_6D_6 resulted in clean regeneration of **1**.[9] Products **4–6** were isolated in 65–88% yield *via* an analogous procedure to that described for **3** (see ESI† for full details). Complex **5** was also characterized by X-ray crystallography (Fig. 2).

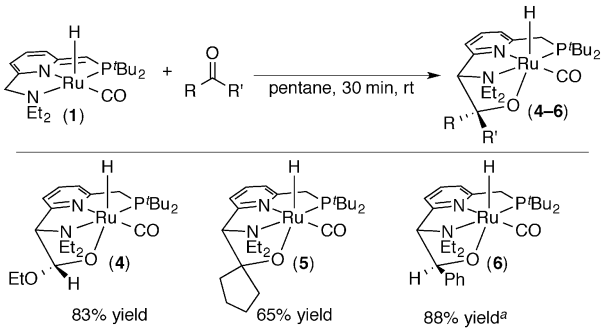
The reaction of **1** with unsymmetrical carbonyl compounds could, in principle, lead to four products (Scheme 4). These include two pairs of regioisomers [**A** (P-side)/**B** (N-side)], with each pair being a set of diastereomers (**A-i**/**A-ii** and **B-i**/**B-ii**). Despite this potential complexity, products **3–5** were formed as >95% of the isomer reported in Schemes 2 and 3 under the



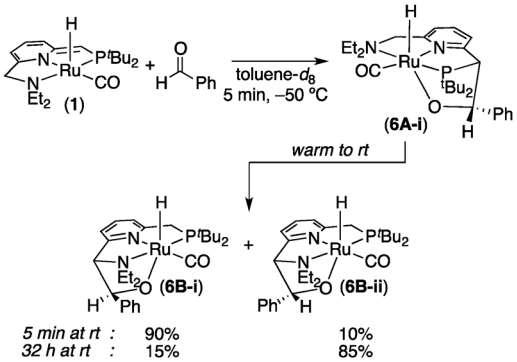
Scheme 4 Four possible isomeric products from the reaction of **1** with unsymmetrical carbonyl compounds.

standard conditions (30 min, rt). In contrast, the reaction of **1** with benzaldehyde at rt yielded **6** as an ~85 : 15 mixture of two isomeric products. As a result, a more detailed investigation of the latter transformation was conducted.

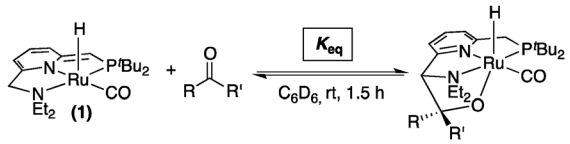
When the reaction of Ru complex **1** with benzaldehyde was conducted at −50 °C for 5 min in toluene-d_8, the P-side adduct, **6A-i**, was formed as a single diastereomer (Scheme 5).[10] Warming this mixture to room temperature and allowing it to equilibrate for 5 min resulted in complete disappearance of **6A-i** along with the formation of a 90 : 10 mixture of the two N-side diastereomers **6B-i** : **6B-ii**. Finally, allowing this solution to stand for 24 h at rt resulted in a 15 : 85 ratio of **6B-i** : **6B-ii**. This ratio did not change further after longer times at room temperature, suggesting that it represents the equilibrium isomer mixture. All of the isomeric products were completely characterized *via* NMR spectroscopic experiments, and the full details are described in the ESI.†



Scheme 3 Reaction of **1** with different carbonyl compounds.



Scheme 5 Reactivity of **1** with benzaldehyde.



Carbonyl Compound	Major Product	K_{eq}
	**3**	2.7×10^2
	**4**	1.5×10^2
	**5**	5.0×10^1
	**6**[a]	$>10^3$
	trace	$< 10^{-2}$
	nd[b]	$< 10^{-3}$
	nd[b]	$< 10^{-3}$

[a] Mixture of diastereomers **6B-i** and **6B-ii**. [b] nd = products were not detected

Scheme 6 K_{eq} for reaction of **1** with carbonyl compounds.

Additionally, both **6B-i** and **6B-ii** were characterized by X-ray crystallography.[11] Overall this system exemplifies the potential complexity of the reactions of **1** with unsymmetrical carbonyl compounds.[12]

The equilibrium constants (K_{eq}) for the reactions of **1** with all of the carbonyl substrates were determined *via* ^{1}H NMR integration (Scheme 6). K_{eq} appears to be particularly sensitive to the steric properties of the carbonyl substrate. For example, K_{eq} drops from 2.7×10^2 to 1.5×10^2 upon moving from methyl to ethyl formate, likely reflecting the increased size of the ethyl substituent. Electronic effects also play an important role in this equilibrium. For example, aldehydes are similar in size to formate esters but have a significantly more electrophilic carbonyl carbon. This results in a large value of K_{eq} for the reaction of **1** with benzaldehyde ($K_{eq} > 10^3$ at rt). Ketones are also more electrophilic than formate esters, but the carbonyl carbon is more sterically encumbered. With these substrates, steric factors appear to dominate the binding equilibrium. For example, K_{eq} for cyclopentanone is 5.0×10^1, while acetone (which does not have the alkyl groups tied back in a ring) barely reacts (K_{eq} estimated to be $<10^{-2}$ at rt). Similarly, no product was detected in the presence of up to 20 equivalents of methyl acetate or *N*,*N*-dimethylformamide, indicating that K_{eq} for these substrates is $<10^{-3}$.

Overall, the work described in this communication shows that the reactivity of **1** with carbonyl compounds is more complex than was previously appreciated. While prior work focused primarily on **1** as a catalyst for the hydrogenation of C=O derivatives, this report describes the first example of the addition of a Ru-bound pincer ligand to a carbonyl compound at room temperature. The observed C–C bond and Ru–O bond forming reactions are reversible. Numerous isomeric products can be formed, but they eventually equilibrate to a single major isomer in all cases examined. This study reveals that there is a rich complexation chemistry of **1** that competes with H_2 addition and may impact hydrogenation catalysis. Further investigations to probe the role of these reactions in catalysis are underway.

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9 The reaction with benzaldehyde was the only reaction that was not reversible by this method.

10 The other P-side isomer (**6A-ii**) was not detected. We hypothesize that this is due to the sterically large nature of the *tert*-butyl groups attached to the phosphine. Notably, Milstein reported a single isomeric product in the low temperature reaction of (PNP)Ru(H)CO with benzaldehyde.

11 The crystal structure of **6B-ii** was also obtained and details can be found in ESI†.

12 The P side regioisomer of **5** was also fully characterized by NMR spectroscopy at −40 °C (**5A**). See ESI† for more details.