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Chemoselective Hydrogenation of Carbonyl Compounds and Acceptorless Dehydrogenative Coupling of Alcohols

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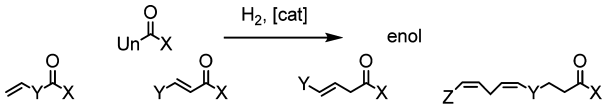
Supporting Information

ABSTRACT: OsHCl(CO)[κ^3-PyCH$_2$NHC$_2$H$_4$NHP*t*Bu$_2$] is the first efficient catalyst for chemoselective reduction of challenging unsaturated esters to enols and for acceptorless coupling of amines with MeOH and EtOH affording formamides and acetamides. The NMR, ESI-MS, and DFT data indicate a mechanism proceeding in the metal coordination sphere and producing no free organic intermediates.

Efficiency and sustainability play increasingly important roles in chemistry, thus calling for development of practical green synthetic methods. The use of hydrogen together with an appropriate catalyst is a clean economic approach toward reduction of carbonyl compounds.[1] Development of robust H_2 hydrogenation catalysts with excellent carbonyl selectivity is a long-standing challenge, especially for applications with low catalyst loadings. Many of the unsaturated carbonyls shown in Scheme 1 are vulnerable to C=C bond hydrogenation and isomerization under the C=O hydrogenation conditions. These include important synthetic and natural chemicals, flavor and fragrances, and fatty acid derivatives of plant oils.[2]

Scheme 1. Catalytic Hydrogenation and Challenging Substrates[a]

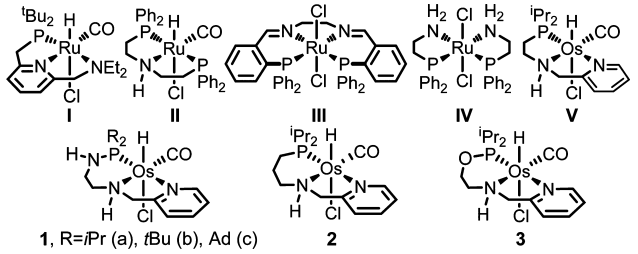


[a]Un = olefin group; X = H, R, OR; Y, Z, R = organic fragment or group.

In the 1990s, Noyori and co-workers discovered catalysts for chemoselective hydrogenation of enals and enones, comprising six-coordinate species with phosphorus and nitrogen donors: RuCl$_2$(P)$_2$(N)$_2$.[3] However, chemoselectivity proved very challenging to achieve in ester hydrogenation where efficient catalysts have only recently become available.[4] Hydrogenation of methyl 10-undecenoate, derived from castor oil, is an instructive example. The desirable product, 10-undecenol, is a valuable material for polymers and perfumery products. Results of hydrogenation of methyl 10-undecenoate with some of today's best catalysts **I**–**V** (Scheme 2) are collected in Table 1.

Milstein's catalyst **I**[4a,b] affords mostly the saturated alcohol together with a small amount of 9-undecenol. The industrial

Scheme 2. Prominent Ester Hydrogenation Catalysts I–V and New Complexes 1–3



catalysts **II** (Ru-MACHO, Takasago),[4d] **III** and **IV** (Firmenich)[4c] hydrogenate the C=O and C=C bonds of methyl 10-undecenoate at similar rates; C-10 to C-9 C=C bond migration is a problem. The performance of the osmium catalyst **V** from our group[4e] is also unsatisfactory. Herein we report new complexes **1**–**3** (Scheme 2) based on the PyCH$_2$NHC$_2$H$_4$XPR$_2$ ligands (NNXP-R, X = CH$_2$, NH, O). In this group, OsHCl(CO)(NNNP-*t*Bu) (**1b**) emerged as a successful catalyst for chemoselective reduction of 10-undecenoate. Further testing confirmed that **1b** is a robust, practical, and highly efficient H_2 hydrogenation catalyst with excellent carbonyl selectivity, also possessing useful and unique activity for acceptorless dehydrogenative coupling of alcohols to esters and amides.

The air-stable **1b** is prepared according to Scheme 3. The related dihydride OsH$_2$(CO)(NNNP-*t*Bu) (**6**) forms when **1b** is treated in THF with Li[HBEt$_3$], or with base under H_2 (via the 16-e$^-$ amido species **5**). The dihydride exists as a mixture of isomers in solution (*trans*/*cis* = 4/1, THF). The reaction of **5** with H_2 to give **6** is reversible, and ca. 17% of **5** is formed when **6** is dissolved in THF (see SI for details).

The hydrogenation results are organized in Table 2. Among the substrates, the nonconjugated compounds that are not base-sensitive (E1, E2, E5, E9) are most efficiently hydrogenated with **1b** and 1–2% NaOMe, preferably without solvent. Moderately base-sensitive compounds that react with metal alkoxides (e.g., E4, E6–8, K1–3) are selectively reduced with **1b** and a carbonate base, optionally neat or in 2-propanol. The use of 0.2 mol% K$_2$CO$_3$ in 2-propanol is particularly recommended. The more base-sensitive substrates, as some of the α,β-unsaturated aldehydes and ketones, are best hydro-

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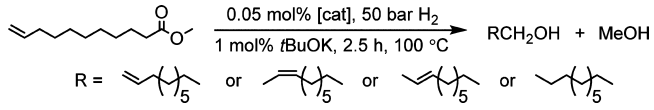
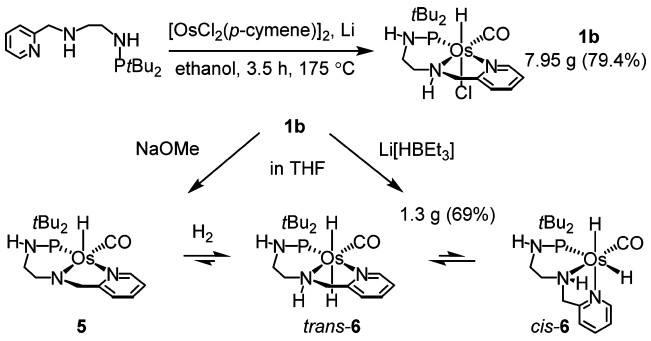
Table 1. Reduction of Methyl 10-Undecenoate[a]



	catalyst									
	I	II	III	IV	V	1a	1b	1c	2	3
conv.[b]	77	18	100[c]	70	74	94	95	97	40	5
select.[d]	10	89	36	22	63	97	98	98	92	85
%C-9[e]	100	3	–[f]	39	<1	<1	<1	<1	<1	1

[a]20 mmol in 7 mL of THF. [b]Conversion to C-11 alcohols, %. [c]With 5 mol% NaOMe.[4c] [d]Selectivity, as total % olefins after hydrogenation (100% when no C=C hydrogenation). [e]%C-9 olefins formed = 100 × [C-9]/([C-9]+[C-10]). [f]Not determined in ref 4c.

Scheme 3. Preparation of Complexes 1b, 5, and 6



genated with **1b** and a carbonate base in a nonpolar solvent. In the case of 10-undecenal, the best selectivity was achieved with 0.2% CsF in 2-propanol. Selective catalytic hydrogenation of α,β-unsaturated esters (E10–13) remains an elusive target. This is surprising, considering that the closely related ketones and aldehydes are hydrogenated selectively with **1b** (cf. A4 and K3). Based on the results of Table 2, **1b** appears to be today's most successful and broadly applicable catalyst with unmatched selectivity for C=O vs C=C bond hydrogenation of unsaturated carbonyl compounds.

Acceptorless dehydrogenative coupling (ADC) of alcohols is the reverse of ester hydrogenation.[5] Indeed, refluxing ethanol with **6** at 90 °C gave a turnover number (TON) of 9000 to ethyl acetate (Table 3). With **1b** and NaOEt, the ADC of ethanol was complicated by formation of ethyl butyrate (1.9%) and traces of unidentified organic compounds. The ADC reactions of propanol and 10-undecenol are efficiently catalyzed by **6**. NMR analyses of the reaction solutions found no observable aldehyde intermediates in reactions 1–4 in Table 3.

Heating ethanol with butylamine or benzylamine with **1b** and base (Table 3, entries 7 and 8) selectively produced *N*-butylacetamide and *N*-benzylacetamide, respectively. Methanol gave the corresponding formamides, at a slower rate (Table 3, entries 5 and 6), together with *N*,*N*′-dibutylurea and *N*,*N*′-dibenzylurea byproducts. *N*-Benzylpropionamide and *N*-benzyl-undec-10-enamide formed selectively in reactions 11 and 12 in Table 3. However, propanol and 10-undecenol with butylamine gave mixtures of the corresponding amide and imine products, in low yields (Table 3, entries 9, 10, 13, and 14). The experimental evidence is indicative of competing catalytic pathways, where the more efficient path leads to amides, whereas the imine formation might be inhibiting the catalyst.

We note the complementarity of **1b** to the Milstein catalyst for direct synthesis of amides from alcohols and amines.[5d] Milstein's method requires heating "under a flow of argon in refluxing toluene" and thus not applicable to volatile substrates (MeOH, EtOH, PrOH, or $BuNH_2$). Complex **1b** efficiently operates at relatively low temperatures (e.g., in ethanol, bp = 78 °C) without solvent and without a flow of Ar. Entries 5 and 6 in Table 3 are the first preparative examples of ADC of MeOH with amines, affording formamides.[6]

Through the rest of this paper, we shall discuss experiments performed in order to gain mechanistic information relevant to the catalytic reactions of Tables 2 and 3. The dihydride **6** rapidly hydrogenates neat esters at room temperature, under 50 bar H_2; e.g., 0.01 mol% **6** in 0.1 mol of methyl formate gave TON = 1570 to methanol in 1 h. The importance of this process for CO hydrogenation has been recently highlighted by Milstein.[4b] Hydrogenations of neat methyl acetate, ethyl acetate, and ethyl butyrate with 0.05 mol% **6** gave TON = 730, 715, and 530, respectively, in 1 h. Hydrogenation of ethyl acetate with **6** and 1 mol% NaOMe gave TON = 740, whereas a 1 h long experiment without base at 40 °C increased TON to 1315. We thus conclude that **6** is a competent ester hydrogenation catalyst, operating equally efficiently with and without base. None of the above reactions produced NMR-observable aldehyde or hemiacetal intermediates.

Surprisingly, negligible (<2%) hydrogenation of neat butyraldehyde and 10-undecenal was observed with 0.05 mol % **6** at room temperature. Hydrogenations of a 1:1 mixture of ethyl acetate and acetaldehyde also failed with 0.05 and 0.1 mol % **6**, suggesting catalyst deactivation. The reasons for this are not clear. The aldehydes could be hydrogenated with **1b** and base, at 100 °C. Independent 1 h long experiments gave TON = 1030 for butyraldehyde vs ca. 100 for ethyl butyrate (with 1 mol% K_2CO_3 in THF) and TON = 1800 for 10-undecenal vs ca. 90 for methyl 10-undecenoate (with 0.2 mol% CsF in 2-propanol). In agreement with the different rates, hydrogenation of a 2000:2000:8:1 mixture of 10-undecenal, methyl 10-undecenoate, CsF, and **1b** gave a 1:1 mixture of 10-undecenol and methyl 10-undecenoate in 1 h at 100 °C, in 2-propanol.

We attempted characterization of reaction intermediates of ADC of ethanol (Table 3, entry 1) with the help of in situ ESI-MS, using the pressurized sample infusion (PSI) technique.[7a,b] Crucial information gathered by the ESI-MS was the observation of intact intermediates as Na^+ ion adducts. Formation of **5**, $OsH(OEt)(CO)(PyCH_2NHC_2H_4PtBu_2)$ (MS**1**) and $OsH(C_4H_9O_2)(CO)(PyCH_2NHC_2H_4PtBu_2)$ (MS**2**) was established by ESI-MS on the basis of their m/z values, isotopic patterns and fragmentation upon collision-induced dissociation (CID) conditions. Under the catalytic conditions, species **5** and MS**1** were detected early, whereas MS**2** appeared after ca. 30 min (Figure S8). The proposed formulation of MS**1** is consistent with the elimination of

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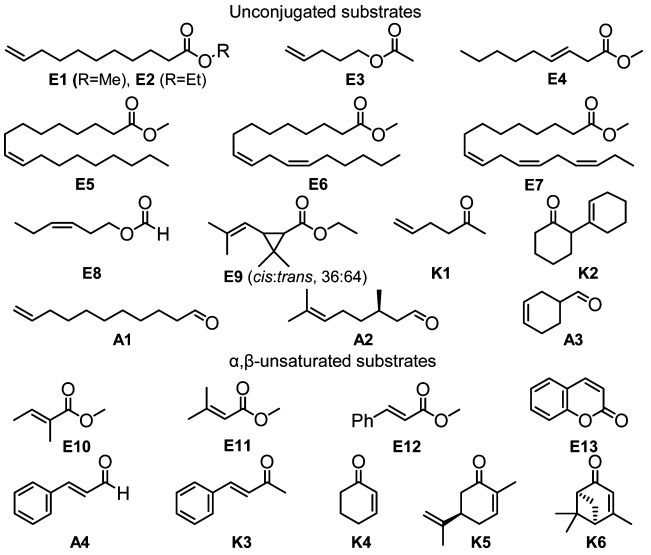
Table 2. Catalytic Hydrogenation with 1b[a]

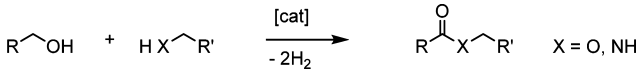


sub.[b]	cat.[c]	t, h	solv	base[d]	select.[e]	conv.[f]
E1, 100	0.01	5	neat	NaOMe, 2	98	98
E2, 100	0.01	4	neat	NaOMe, 2	96	97
E3, 40	0.05	2	*i*PrOH	K_2CO_3, 0.2	98	100
E4, 40	0.05	2	*i*PrOH	K_2CO_3, 0.2	99	99
E5, 40	0.01	4	neat	NaOMe, 2	100	98
E6, 40	0.05	3	neat	Cs_2CO_3, 1.5	100	98
E7, 40	0.05	3	neat	Cs_2CO_3, 1.5	100	>99
E8, 40	0.02	2	*i*PrOH	K_2CO_3, 0.2	100	100
E9, 40	0.05	24	neat	NaOMe, 2	100	98[g]
E10, 40	0.05	1.5	*i*PrOH	Cs_2CO_3, 0.2	0	57
E11, 40	0.05	2	PhMe	Cs_2CO_3, 1.5	0	61
E12, 40	0.02	2	*i*PrOH	K_2CO_3, 0.2	0	98
E12, 20	0.05	2.5	THF	K_2CO_3, 1	91	0
E13, 40	0.02	2	*i*PrOH	K_2CO_3, 0.2	0	100
K1, 80	0.01	2	neat	K_2CO_3, 0.2	98	100
K2, 40	0.02	1	*i*PrOH	K_2CO_3, 0.2	100	100
K3, 20	0.01	12	*i*PrOH	Na_2CO_3, 1	98	100[h]
K4, 20	0.014	2	THF	Na_2CO_3, 1	92	100
K5, 20	0.01	9	THF	Na_2CO_3, 1	100	99
K6, 20	0.05	12	*i*PrOH	Na_2CO_3, 1	100	100[i]
A1, 40	0.05	1	*i*PrOH	CsF, 0.2	>99	100
A2, 20	0.05	2	THF	Cs_2CO_3, 1	100	100
A3, 20	0.05	3	THF	K_2CO_3, 3	100	100
A4, 20	0.05	2.5	THF	K_2CO_3, 1	>99	>99[j]

[a] $p(H_2)$ = 50 bar, at 100 °C. [b] Substrate, mmol. [c] Catalyst, mol%. [d] Base, mol%. [e] Selectivity (100% when no C=C hydrogenation). [f] Total (saturated + unsaturated) conversion to alcohol. [g] *Cis/trans* = 37/63. [h] At 23 °C. [i] At 60 °C. [j] At 80 °C.

NaOEt in the CID mass spectrum of [MS**1** + Na]$^+$. Remarkably, CID of [MS**2** + Na]$^+$ (Figure 1) produced sodium 1-ethoxyethanolate, ethyl acetate, and acetaldehyde (fragment ions at *m*/*z* 516.2, 540.1, and 584.1, respectively) together with the product ions at *m*/*z* 538.1 and 582.2, resulting from subsequent H_2 liberation from the ions at *m*/*z* 540.1 and 584.1. These observations suggest that MS**2** is a key intermediate en route to ethyl acetate, possessing a 1-ethoxyethoxide ligand,[7b] analogous to the hemiacetaloxide documented by Bergens in the reaction of *trans*-RuH_2((*R*)-BINAP)((*R*,*R*)-dpen) with γ-butyrolactone.[8]

Table 3. Coupling to Esters and Amides at 90 °C



no.	sub.[a]	cat.[b]	t, h	base[c]	conv.[d]
1	EtOH, 200	**1b**, 0.01	24	NaOEt, 1	82
2	EtOH, 200	**6**, 0.01	24	none	90
3	PrOH, 150	**6**, 0.01	21	none	69[e]
4	$C_{11}H_{21}OH$, 60	**6**, 0.02	18	none	94[f]
5	MeOH+$BuNH_2$, 90/80	**1b**, 1.0	19	NaOMe, 2	78[g]
6	MeOH+$BnNH_2$, 90/80	**1b**, 1.0	16	NaOMe, 2	68[h]
7	EtOH+$BuNH_2$, 80/80	**1b**, 0.05	17	NaOEt, 1	90
8	EtOH+$BnNH_2$, 80/80	**1b**, 0.05	17	NaOEt, 1	96
9	PrOH+$BuNH_2$, 60/60	**1b**, 0.05	17	KO*t*Bu, 1	43[i]
10	PrOH+$BuNH_2$, 60/60	**6**, 0.05	16	none	39[i]
11	PrOH+$BnNH_2$, 60/60	**1b**, 0.05	17	KO*t*Bu, 1	90
12	$C_{11}H_{21}OH$+$BnNH_2$, 40/40	**6**, 0.05	18	none	88[j]
13	$C_{11}H_{21}OH$+$BuNH_2$, 40/40	**1b**, 0.05	16	NaOMe, 1	15[k]
14	$C_{11}H_{21}OH$+$BuNH_2$, 40/40	**6**, 0.05	22	none	19[k]

[a] Substrates (mmol): Bu = *n*-butyl, Bn = benzyl, $C_{11}H_{21}$ = undec-10-enyl. [b] Catalyst, mol%. [c] Base, mol%. [d] Conversion to ester or amide. [e] At 100 °C. [f] *P* = 2 Torr, 1.5% C-10 to C-9 olefin isomerization. [g] Plus 18% *N*,*N*′-dibutylurea; distilled *N*-butylformamide yield = 6.1 g (75%). [h] Plus 12% *N*,*N*′-dibenzylurea, distilled *N*-benzylformamide yield = 5.5 g (51%). [i] Plus 6% of the imine. [j] *P* = 11 Torr, isolated amide yield = 9.1 g (83%), 3.5% C-10 to C-9 olefin isomerization. [k] Plus ca. 5% of the imine.

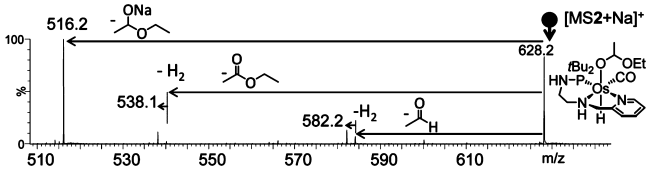
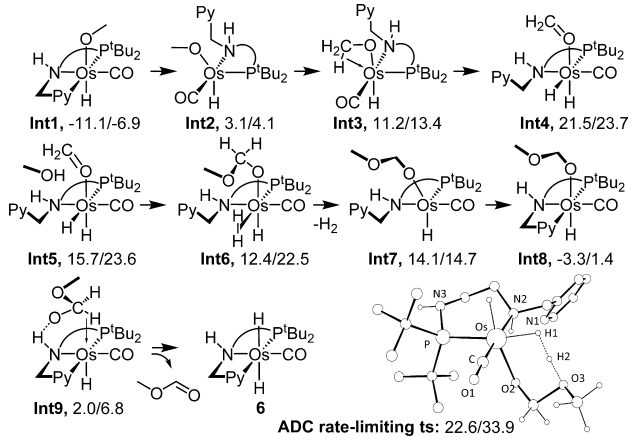


Figure 1. CID mass spectrum of mass-selected [MS**2** + Na]$^+$ ($CE_{Elaboratory}$ = 15 eV).

We performed density functional theory (DFT) calculations to reconstruct the key events of ADC of methanol and ethanol. The results with MeOH are summarized in Scheme 4. Addition of MeOH to **5** gives the methoxide, **Int1**. Stability of the methoxide might be somewhat exaggerated by DFT; however,

Scheme 4. M06L Calculations on ADC of MeOH[a]



[a] The Δ*H*/Δ*G* values (kcal/mol) are relative to **5** + MeOH···OHMe, in MeOH.

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the calculated barrier for methanol loss from **Int1** is $\Delta G^{\ddagger}$ = 10.8 kcal/mol, in agreement with the labile nature of this species. Pyridine decoordination from **Int1** gives the 16-e$^-$ **Int2**, followed by formation of an agostic methoxide **Int3** and β-H elimination to give the aldehyde intermediate **Int4**. Since **Int4** is solvated and hydrogen-bonded by the alcohol (**Int5**), the aldehyde undergoes a nucleophilic attack by MeOH, accompanied by protonation of the neighboring hydride to give the dihydrogen methoxymethoxide **Int6**. This transformation proceeds via a single transition state, shown in Scheme 4, and is the ADC rate-limiting step. Although the barrier for ADC of methanol is not known, the calculated values of $\Delta G^{\ddagger}$ = 33.9 kcal/mol in MeOH (or 30.4 kcal/mol without solvation) are not unreasonable. H_2 elimination from **Int6** via **Int7** gives[9] the relatively stable methoxymethoxide **Int8**, analogous to MS**2** detected by the ESI-MS. In the final steps, **Int8** rearranges into an agostic methoxymethoxide structure **Int9** (via a transition state, $\Delta G^{\ddagger}$ = 12.3 kcal/mol) that readily un-inserts methyl formate (via another transition state, $\Delta G^{\ddagger}$ = 10.4 kcal/mol). A possible but unfavorable side reaction of **Int8** is elimination of methoxymethanol (ΔG = 9.6 kcal/mol, to give **5** from **Int8**). We note that MeOH-assisted splitting of methoxymethanol[10] to release formaldehyde has a barrier of $\Delta G^{\ddagger}$ = 28.5 kcal/mol, calculated at the mPW1k/6-311++g(d,p) level in MeOH (or $\Delta G^{\ddagger}$ = 30.5 kcal/mol without solvation, Figure S12). Therefore, neither methoxymethanol nor formaldehyde is expected to be NMR-observable.

In ethanol, the rate-limiting nucleophilic addition of EtOH to acetaldehyde on Os has a calculated barrier of $\Delta G^{\ddagger}$ = 31.9 kcal/mol (27.8 kcal/mol without solvation), in a qualitative agreement with the relative ease of dehydrogenative coupling of EtOH in Table 3.

In conclusion, this Communication reports the preparation and testing of a practical catalytic system for hydrogenation of a wide range of unsaturated carbonyl compounds and acceptorless dehydrogenative coupling of alcohols, operating preferably without solvent, under mild conditions and distinguished by excellent efficiency, chemoselectivity, and tolerance toward base-sensitive substrates. The mechanistic studies of this work advance our understanding of catalytic ester hydrogenation and ADC reactions.

■ ASSOCIATED CONTENT

Supporting Information

Experimental and computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(7) (a) See SI for details. (b) Yunker, L. P. E.; Stoddard, R. L.; McIndoe, J. S. *J. Mass Spectrom.* **2014**, *49*, 1−8. (c) The formula $Os(C_4H_{10}O_2)(CO)(PyCH_2NHC_2H_4PtBu_2)$ (MS**2**) also agrees with structures possessing two ethoxo ligands, or coordinated EtOH and acetaldehyde ligands. We reject these interpretations on the basis of the absence of liberation of NaOEt from MS**2** in the CID mass spectra.

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(9) The 16-e$^-$ **Int7** can rearrange into an 18-e$^-$ η^2-methoxymethoxide that is more stable by −1.2 kcal/mol. This intermediate can eliminate formaldehyde to give **Int2**: Hasanayn, F.; Baroudi, A. *Organometallics* **2013**, *32*, 2493−2496.

(10) (a) Azofra, L. M.; Alkorta, I.; Elguero, J. *J. Phys. Org. Chem.* **2012**, *25*, 1286−1292. (b) Ethanol-assisted splitting of 1-ethoxyethanol to release acetaldehyde has the barrier $\Delta G^{\ddagger}$ = 28.4 kcal/mol calculated in EtOAc (or $\Delta G^{\ddagger}$ = 29.9 kcal/mol without solvation, see Figure S13).

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