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Iridium Pincer-Catalyzed Dehydrogenation of Ethers Featuring Ethylene as the Hydrogen Acceptor

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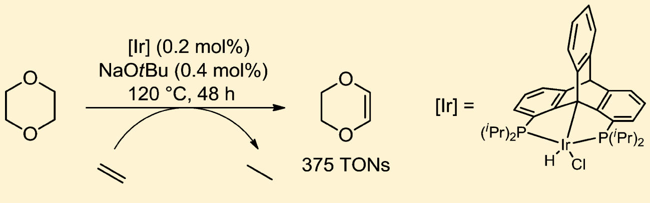
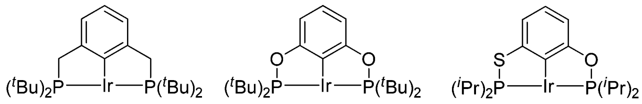
ABSTRACT: We describe efficient methods to dehydrogenate ethers by using iridium pincer complexes (^{iPr4}Anthraphos)-Ir(H)(Cl), **4**, ^{iPr4}PC(sp^3)P–Ir(H)(Cl), **5**, and (^{iPr4}PCP)-Ir(H)(Cl), **6**. At 120 °C, cyclic ethers were dehydrogenated with *tert*-butylethylene as the hydrogen acceptor with high turnover numbers (over 400 in many cases). Acyclic ethers such as diethyl ether can also be dehydrogenated catalytically with TONs up to 90. The efficient dehydrogenation of cyclic and acyclic ethers using ethylene as a more practical hydrogen acceptor has been demonstrated for the first time.



INTRODUCTION

The selective dehydrogenation of inexpensive and abundant alkanes to form higher value alkenes is an attractive, but challenging task. Such alkenes are widely used as raw materials in the synthesis of fine chemicals and polymers. Heterogeneous dehydrogenation is used on a large scale in the petroleum industry but requires high temperatures (~500 °C), often resulting in low selectivity.[1] Since the initial reports of alkane dehydrogenation by Crabtree and Felkin,[2] numerous homogeneous alkane dehydrogenation catalysts have been developed capable of dehydrogenation under milder conditions (150–250 °C) with excellent TONs (~6000).[3] The most active of these catalysts utilize an Ir "pincer" framework for stability and robustness. Among the earliest designs are the complexes (^{tBu4}PCP)-Ir, **1**, and (^{tBu4}POCOP)-Ir, **2**, which provide high TONs for a number of alkane dehydrogenations (Figure 1).



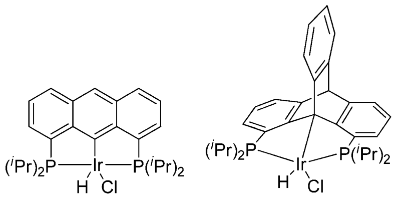
1 **2** **3**

Figure 1. Examples of active iridium pincer complexes for alkane dehydrogenation.

More recently, modified pincer iridium complexes, including those based on anthraphos[4] and triptycene[5] backbones, have demonstrated significantly increased thermal stability in dehydrogenation reactions.

Despite the large number of highly active catalysts for alkane dehydrogenation, surprisingly little work has been extended to functionalized substrates. An early report by Jensen and Kaska showed modest reactivity (TON ~57) using **1** for the dehydrogenation of THF.[6] Related reactivity was demonstrated by Goldman in the dehydrogenation of tertiary amines, again with modest TONs.[7] In the context of hydrogen storage, acceptorless dehydrogenation of perhydrocarbazole derivatives was reported by Jensen.[8] Only recently, Huang has demonstrated a much broader scope of heterocycle dehydrogenations using a novel (^{iPr4}PSCOP)-Ir catalyst, **3**.[9]

Developing new protocols for the dehydrogenation of functionalized substrates such as ethers could provide novel strategies for the functionalization of organic molecules including late-stage functionalization of natural products and postpolymerization modification of polyethers. With this in mind, we chose to explore some of the most active Ir-pincer complexes in alkane dehydrogenation reactions for the dehydrogenation of ether substrates (Figure 2). Importantly, each features diisopropyl-substituted phosphines, which have demonstrated high reactivity in related dehydrogenation reactions.



4 **5** **6**

Figure 2. Iridium pincer complexes used in this study.

Previous dehydrogenation reactions with Ir-pincer complexes have relied on specialized alkenes as a sacrificial hydrogen acceptor, including *tert*-butyl ethylene (TBE) and norbornene (NBE). Recently, our group has successfully used ethylene as a hydrogen acceptor in alkane dehydrogenation in conjunction with **4** as a catalyst.[4b,c] Thus, we sought to develop new methods for the dehydrogenation of functionalized substrates using ethylene as an inexpensive, readily available, and easily separable hydrogen acceptor. Herein we describe our efforts to develop efficient methods for the dehydrogenation of ethers

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with TBE as well as the first report of ether dehydrogenations using ethylene as the hydrogen acceptor.

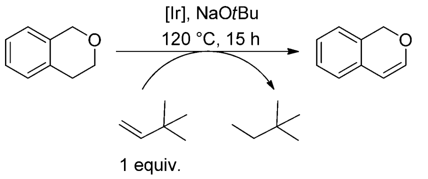
■ RESULTS AND DISCUSSION

Dehydrogenation with TBE as a Hydrogen Acceptor.

The dehydrogenation of ether substrates with TBE is thermodynamically quite favorable since the heat of hydrogenation of TBE, $\Delta H°$, of −126 kJ/mol is significantly greater than the heat of hydrogenation of most vinyl ethers, for example, vinyl ethyl ether ($\Delta H°$ = −111 kJ/mol) or 2,3-dihydrofuran ($\Delta H°$ = −107 kJ/mol).[10] However, strong coordination of the vinyl ether product to iridium can significantly retard the rate of dehydrogenation. We began our studies by exploring the dehydrogenation of isochroman with TBE as the hydrogen acceptor. Isochroman is a desirable model substrate for these studies because it contains a single site for dehydrogenation, produces a conjugated product, and has a high boiling point. Using reaction conditions similar to those reported by Huang,[9] we screened the three catalysts for their reactivity in dehydrogenation at different catalyst loadings. Active catalysts were generated *in situ* by dehydrohalogenating the iridium hydrochlorides with sodium *tert*-butoxide.

As shown in Table 1, all three Ir-pincer complexes were capable of high TONs using TBE as the hydrogen acceptor.

Table 1. Initial Catalyst Screening with Isochroman[a]



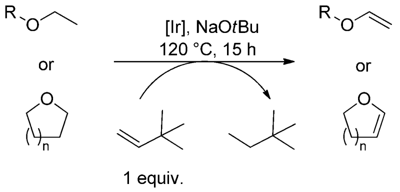
entry	cat	loading (mol %)	TON	yield (%)[b]
1	4	0.5	185	93
2	4	0.2	425	85
3	4	0.1	210	21
4	5	0.5	180	90
5	5	0.2	300	60
6	5	0.1	480	48
7	6	0.5	192	96
8	6	0.2	460	92
9	6	0.1	670	67

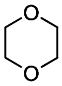
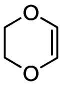
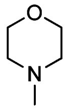
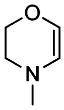
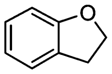
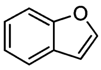
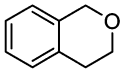
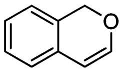
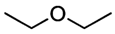
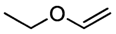
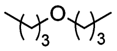
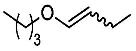
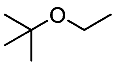
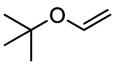
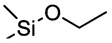
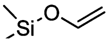
[a] Reaction conditions: isochroman (1.7 mmol), *tert*-butylethylene (1.7 mmol), [Ir] (0.1−0.5 mol %), NaO*t*Bu (0.2−1 mol %), 120 °C, 15 h. [b] Yield determined by GC.

Using 0.5 mol % catalyst loading and 1 equiv of TBE at 120 °C, complex **6** provided the highest conversion at 96% and highest TON (entry 7). However, both **4** and **5** provided high conversions under similar conditions (entries 1, 4). With catalyst loadings of 0.1 mol % all three catalysts gave acceptable conversions (entries 2, 5, 8). Even at 0.1% catalyst loading, catalyst **6** exhibited a TON of 670 and 67% conversion (entry 9).

With the success of all three complexes in the dehydrogenation of isochroman, we explored the scope of ether dehydrogenation with a series of cyclic and acyclic substrates. The results in Table 2 show that all three pincer complexes are capable of catalyzing the dehydrogenation of a variety of ethers. All reactions were carried out at 120 °C for 15 h using 1 equiv of TBE unless otherwise noted. In the presence of 0.2 mol % Ir and 2 equiv of TBE, tetrahydrofuran was dehydrogenated

Table 2. Dehydrogenation of Cyclic and Acyclic Ethers with TBE[a]



Entry	Substrate	Product	Catalyst (mol%)	TON	Yield (%)[b]
1			**4** (0.2)	660	66[c]
2			**5** (0.2)	580	58[c]
3			**5** (1)	188	94[c]
4			**6** (0.2)	300	30[c]
5			**4**(0.2)	446	89
6			**5** (0.2)	400	80
7			**6** (0.2)	324	65
8			**4** (0.2)	325	65
9			**5** (0.2)	275	55
10			**5** (0.5)	156	78
11			**6** (0.2)	265	53
12			**4** (0.2)	452	90
13			**5** (0.2)	500	>99
14			**6** (0.2)	410	89
15			**4** (0.2)	425	85
16			**5** (0.2)	300	60
17			**5** (0.5)	180	90
18			**6** (0.2)	460	92
19			**4** (0.2)	54	11
20			**5** (0.2)	90	18
21			**5** (2)	24	47
22			**6** (0.2)	50	10
23			**4** (0.2)	25	5
24			**5** (0.2)	50	10
25			**6** (0.2)	20	4
26			**4** (0.2)	55	11
27			**5** (0.2)	85	17
28			**5** (2)	25	50
29			**6** (0.2)	55	11
30			**4** (0.2)[d]	60	12
31			**4** (2)[d]	28	55

[a] Reaction conditions: substrate (3.4 mmol), *tert*-butylethylene (3.4 mmol), [Ir] (0.2−2 mol %), NaO*t*Bu (0.4−4 mol %), 120 °C, 15 h. [b] Yield determined by GC. [c] 2 equiv of TBE. [d] Using ^{iPr4}PC(sp^3)P−Ir(ethylene).

readily to furan with 66% conversion and a TON of 660 using **4** (entry 1). Increasing the catalyst loading to 1% of **5** provided near-complete conversion (entry 3).

These results compare favorably to previous reports of THF dehydrogenation using complexes (^{tBu4}PCP)-Ir, **1**, or (^{iPr4}PSCOP)-Ir, **3**, each of which used higher catalyst loadings with corresponding lower TONs.[6,9] Under the standard conditions of 0.2 mol % catalyst, we achieved higher conversion with 1,4-dioxane. Both **4** and **5** provide high conversion (89% and 80%, respectively, entries 5, 6) and selectivity for the monodehydrogenated ether. The Ir-PCP catalyst **6** provided slightly lower conversions (65%, entry 7). No bis-dehydrogenated ether was observed under these reaction conditions using **4**−**6**. In an effort to synthesize the bis-dehydrogenated ether, we screened a range of conditions with higher TBE loadings (up to 10 equiv), but no evidence for a diene product was observed. Similar results were obtained using norbornene as the hydrogen acceptor in place of TBE.[11] *N*-Methylmorpholine was also successfully dehydrogenated under the standard conditions. With 0.2 mol % catalyst loading, **4** was superior, giving 65% conversion (entry 8) vs 55% with **5** (entry 9) and 53% with **6** (entry 11). An increased catalyst loading of **5** resulted in higher conversion (entry 10). The dehydrogenation of 2,3-dihydrobenzofuran proceeded with excellent conversion with 0.2 mol % of catalysts **4**−**6** to give benzofuran in high yield (89−99%, entries 12−14). As previously noted, isochroman was readily dehydrogenated to benzofuran in good yields with low catalyst loadings (entries 15−18).

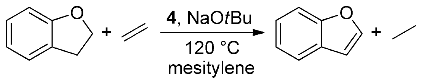
Acyclic ethers represent a more challenging class of substrates. The small, electron-rich alkene products are strong ligands for Ir(I) complexes and thus readily inhibit catalysis. While stoichiometric dehydrogenation of diethyl ether by iridium pincer complexes has been reported and a stable vinyl ether complex was isolated as product,[12] this report appears to be the first case of catalytic dehydrogenation of an acyclic ether. Diethyl ether was dehydrogenated with all three catalysts, although **5** gave the best result, providing a TON of 90 with 0.2 mol % loading (entry 20). Higher catalyst loading provided higher conversion (47%, entry 21). Dibutyl ether was dehydrogenated with similar efficiency to give a mixture of alkene isomers (entries 23−25). The more sterically bulky *tert*-butyl ethyl ether was dehydrogenated with a maximum TON of 87 using **5** (entry 27). Ethoxytrimethylsilane was dehydrogenated with the ethylene derivative of complex **5**, ^{iPr4}PC(sp^3)-P−Ir(ethylene) (0.2 mol %), giving a TON of 60 (entry 30).

Dehydrogenation with Ethylene as a Hydrogen Acceptor. Alkane and heterocycle dehydrogenations with Ir-pincer catalysts have utilized a sterically bulky sacrificial alkene as the hydrogen acceptor, most commonly TBE or NBE. While effective as a hydrogen acceptor, these specialized olefins are costly and may require distillation to separate the acceptor and hydrogenated acceptor from the product alkene. Ethylene is a more desirable hydrogen acceptor because it is inexpensive and readily available, and the saturated product, ethane, can be easily separated from liquid phase reactions. Previously, our group has successfully used ethylene as a hydrogen acceptor in alkane dehydrogenation for the synthesis of *para*-xylene[4b] and toluene.[4c] Thus, we sought to explore ethylene as a hydrogen acceptor in the dehydrogenation of ethers.

The transfer dehydrogenation reactions using ethylene as hydrogen acceptor (heat of hydrogenation ($\Delta H°(H_2)$ = −136 kJ/mol) are even more thermodynamically favored than those using TBE ($\Delta H°(H_2)$ = −126 kJ/mol).[10] However, the thermodynamic benefit of ethylene is counterbalanced by its strong coordination to iridium; thus use of low pressures of ethylene give higher turnover frequencies. In this study, we found that the dehydrogenation of ethers using 1 atm (2−3 equiv) of ethylene resulted in high TONs, comparable to those obtained with TBE.

We began our studies by using 2,3-dihydrobenzofuran as a model substrate under 1 atm of ethylene (Table 3). Initial experiments were performed in a sealed Kontes flask (100 mL) with sufficient head space to provide an excess of ethylene (~3 equiv) at 120 °C using mesitylene as a cosolvent and catalyst **4**. Our initial catalyst loading of 0.2 mol % provided promising results with 18% yield after 48 h (entry 3). An optimal catalyst loading of 0.5 mol % led to near-quantitative conversion of 2,3-dihydrobenzofuran to benzofuran (entry 6).

Table 3. Dehydrogenation of 2,3-Dihydrobenzofuran with Ethylene as Hydrogen Acceptor[a]



entry	loading (mol %)	time (h)	TON	yield (%)[b]
1	0.2	12	18	9
2	0.2	24	24	12
3	0.2	48	36	18
4	0.5	12	160	80
5	0.5	24	192	96
6	0.5	48	196	98

[a]Reaction conditions: 2,3-dihydrobenzofuran (1.7 mmol), ethylene (1 atm), mesitylene (200 μL), [Ir] (0.2−0.5 mol %), NaO*t*Bu (0.4−1 mol %), 120 °C, 12−48 h in a 100 mL Kontes flask. Flask recharged with ethylene after each sampling. [b]Yield determined by GC.

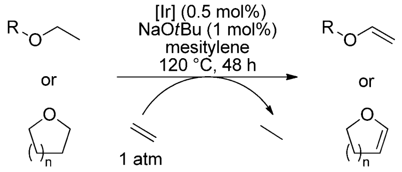
With these promising results in hand, we pursued the dehydrogenation of a series of cyclic and acyclic ethers using ethylene as the hydrogen acceptor, again using catalysts **4**−**6**. In these cases reactions were done in mesitylene at 120 °C by employing a closed system with a reflux condenser, a procedure similar to that reported by Goldman for keeping lower boiling substrates in solution.[13] The results are summarized in Table 4.

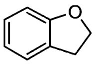
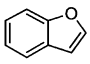
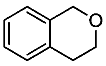
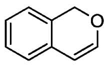
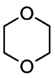
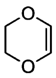
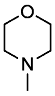
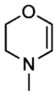
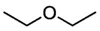
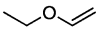
All catalysts surveyed provided near-quantitative dehydrogenation of 2,3-dihydrobenzofuran (entries 1−3). Similar results were also obtained with isochroman, giving between 68% and 85% yield (entries 4−6). Tetrahydrofuran could also be dehydrogenated using ethylene as the hydrogen acceptor. Surprisingly, **5** performed notably better than catalysts **4** and **6**, giving 71% yield (entry 8 vs 7 and 9). 1,4-Dioxane was successfully dehydrogenated using **5** in 97% yield (entry 11). The catalyst loading with this substrate could be lowered to 0.2 mol % with only a modest decrease in yield (75%, entry 12). *N*-Methylmorpholine was dehydrogenated in good yield using **5** as the catalyst (57%, entry 15). Finally, a yield of 44% was obtained when using diethyl ether with 2 mol % of catalyst **5** (entry 18). The differences in conversions for these substrates are unexpected, and work is ongoing to understand these results.

■ CONCLUSION

We have shown three previously reported alkane dehydrogenation catalysts, (^{iPr4}Anthraphos)-Ir(H)(Cl), **4**, ^{iPr4}PC(sp^3)P−Ir(H)(Cl), **5**, and ^{iPr4}PCP-Ir(H)(Cl), **6**, to be effective, after activation with NaO*t*Bu, for the dehydrogenation of acyclic

Table 4. Dehydrogenation of Cyclic and Acyclic Ethers with Ethylene as Acceptor[a]



Entry	Substrate	Product	Catalyst	TON	Yield (%)[b]
1			**4**	196	98
2			**5**	195	98
3			**6**	192	96
4			**4**	135	68
5			**5**	170	85
6			**6**	140	70
7			**4**	16	4
8			**5**	284	71
9			**6**	136	34
10			**4**	20	10
11			**5**	194	97
12			**5**[c]	375	75
13			**6**	67	33
14			**4**	18	9
15			**5**	114	57
16			**6**	90	45
17			**4**	1	2
18			**5**	22	44
19			**6**	7	14

[a] Reaction conditions: substrate (0.7 mmol), ethylene (1 atm), mesitylene (200 μL), [Ir] (0.5 mol %), NaO*t*Bu (1 mol %), 120 °C, 48 h in a 20 mL closed system with a reflux condenser. [b] Yield determined by GC. [c] [Ir] (0.2 mol %), NaO*t*Bu (0.4 mol %).

ethers using TBE as a hydrogen acceptor. In many cases, these results are superior to previously reported methods. In particular, **4** is capable of TONs of 660 in the conversion of tetrahydrofuran to furan. We have also been successful in dehydrogenating acyclic ethers, which shows promise for the conversion of this prevalent moiety into more functionalized products.

The dehydrogenation of cyclic and acyclic ethers using ethylene as the hydrogen acceptor has been demonstrated for the first time. Under relatively mild conditions (120 °C), a series of ethers can be dehydrogenated with high TONs, producing ethane as the hydrogenated product, which is readily separated from the reaction mixture. Complex **5** is particularly active in this protocol, producing good yields for all the substrates surveyed. While low catalyst loadings have been emphasized here to test the limits of these catalytic systems, high conversions should be achievable using higher catalyst loadings, as demonstrated by several entries in the tables and by the fact that there are no byproducts produced. These results with ethylene represent a significant advance in practical development of dehydrogenation chemistry. The further development of this methodology could provide new approaches for the late-stage modification of natural products and pharmaceutical candidates.

■ EXPERIMENTAL SECTION

General Procedures. All manipulations were carried out under an argon atmosphere using standard Schlenk techniques or in an argon-filled drybox. Argon was purified by passing it through columns of BASF R3-11 catalyst (Chemalog) and 4 Å molecular sieves. All substrates were purified by distillation from sodium, then degassed by three freeze−pump−thaw cycles and stored in Kontes flasks. TBE was purchased from Aldrich, dried over sodium, and collected by vacuum transfer. Ethylene (polymer purity) was purchased from Airgas National Welders and used as received. Pincer complexes **4**,[4a] **5**,[5] and **6**[4a] were synthesized according to literature methods. An Agilent Technologies 6850 having a fused silica capillary column (100 m length × 0.25 mm i.d. × 0.50 μm film thicknesses) was used for gas chromatographic analysis using the following method: FID detector, temp = 300 °C; initial temperature, 40 °C; final temperature, 250 °C; oven program, 40 °C, hold for 20 min; ramp 1: 85 °C/min to 150 °C, hold for 5 min; ramp 2: 10 °C/min to 250 °C, hold for 20 min. All the ether dehydrogenation reactions were repeated three times. Yields (average of the 3 runs) were obtained by GC via the use of an internal standard. All the products were verified by comparison with authentic samples.

Typical Procedure for the Dehydrogenation of Cyclic and Acyclic Ethers with TBE. In an argon-filled glovebox, a 4 mL Kontes vial equipped with a Teflon screw-cap was charged with the complex (**4**, **5**, or **6**, 0.2 mol %, 6.8 μmol) followed by NaO*t*Bu (0.4 mol %, 13.6 μmol, 1.3 mg), dissolved in a solution of ether (3.4 mmol) and TBE (3.4 mmol), sealed, and heated in a preheated oil-bath at 120 °C while the solution was stirred. After 15 h, the tube was cooled to room temperature, and a sample was analyzed by gas chromatography.

Typical Procedure for the Dehydrogenation of Cyclic and Acyclic Ethers with Ethylene. In an argon-filled glovebox, the catalyst (**4**, **5**, or **6**, 0.5 mol %, 3.5 μmol) and NaO*t*Bu (1 mol %, 7 μmol, 0.7 mg) were added in a reactor consisting of a 5 mL round-bottom cylindrical flask fused to a water-jacketed condenser (ca. 15 cm). The top of the condenser was fused to two Kontes high-vacuum valves. A solution of mesitylene (200 μL) and ether (0.7 mmol) was added, the contents were cooled under liquid nitrogen, and the solution was degassed via two freeze−pump−thaw cycles and then brought to room temperature and charged with ethylene (1 atm). The flask was sealed and heated in a preheated oil bath at 120 °C while the solution was stirred. After 48 h, the tube was cooled to room temperature and a sample was analyzed by gas chromatography.

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Notes

The authors declare no competing financial interest.

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