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## Author Manuscript

*Organometallics*. Author manuscript; available in PMC 2012 May 9.

Published in final edited form as:

*Organometallics*. 2011 May 9; 30(9): 2457–2460. doi:10.1021/om2001958.

## Driving Catalyst Reoxidation in Wacker Cyclizations with Acetal-Based Metal-Hydride Abstractors

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### Summary

In traditional Wacker processes, Pd(II) becomes reduced to Pd(0) after C-O bond formation and  $\beta$ -H elimination and must be reoxidized to the electrophilic Pd(II) state via a stoichiometric oxidant like benzoquinone, CuCl<sub>2</sub>, or O<sub>2</sub>. We report herein a Pt-catalyzed Wacker-type process that regenerates the electrophilic Pt<sup>2+</sup> state by H<sup>-</sup> abstraction from a [Pt]-H using an oxocarbenium ion generated from an acetal or ketal under acidic conditions.

Wacker-like oxidative cyclization reactions have provided net-dehydrogenative routes to a broad variety of heterocycles.<sup>1</sup> The sequence of elementary steps leading to these products typically involve activation of an alkene by an electrophilic metal center, attack of a carbon or hetero-nucleophile (e.g. H<sub>2</sub>O, H<sub>2</sub>NAr), and  $\beta$ -H elimination of the resulting alkyl complex to yield a metal hydride and product alkene. The challenge in rendering these processes catalytic has been to return the catalyst to its electrophilic state. In the case of Pd(II) catalysts, the resulting [Pd]-H typically undergoes reductive elimination (deprotonation) to generate Pd(0), which is reoxidized to Pd(II).<sup>1,2</sup> Early variants of these catalysts relied on oxidants such as CuCl<sub>2</sub> or benzoquinone, though recent advances have shown that O<sub>2</sub> may also be used.<sup>1e,2</sup>

While Pt complexes display many of the same reactivity profiles as Pd complexes, they have typically not been used for Wacker-type transformations.<sup>3</sup> The reasons include a lower acidity of the platinum hydride, and the higher binding strength of Pt(II) to counterions like Cl<sup>-</sup>, which poison its electrophilic character. Previous efforts in our group on electrophilic dicationic Pt(II) complexes demonstrated that Wacker-like activity could be achieved with polyene substrates that propagate via cation-olefin pathways.<sup>4</sup> A terminating regioselective  $\beta$ -H elimination subsequently gave polycyclic structures with control of elimination regiochemistry.<sup>3a,5b,c</sup> Returning the resulting [Pt]-H cations to the electrophilic Pt-dicationic state, however, was not achievable using conventional oxidants. Fortunately, trityl cation [Ph<sub>3</sub>C<sup>+</sup>][BF<sub>4</sub><sup>-</sup>] was found to efficiently abstract the hydride to form Ph<sub>3</sub>CH and regenerate Pt<sup>2+</sup> free of coordinating anions.<sup>5b,c,6</sup>

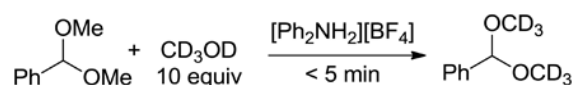
Use of Ph<sub>3</sub>C<sup>+</sup> thus provides an approach to Pt(II) Wacker-type catalysts and access to new transformations not available to Pd variants.<sup>3a,5b,c,7</sup> Most convenient in this first-generation approach was the use of Ph<sub>3</sub>COMe which, upon reacting with H<sup>+</sup> (the by-product of the electrophilic activation), liberated MeOH and the active Ph<sub>3</sub>C<sup>+</sup>. This served to keep the concentration of the reactive species at relatively low levels and ultimately enabled the development of catalytic, enantio- and regioselective oxidative cascade cyclizations.

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Supporting Information Available. Synthesis of metal complexes and experimental information are available in the supporting information free of charge via the internet at <http://pubs.acs.org>.

One disadvantage of this approach, however, was the consequent generation of a full equivalent of  $\text{Ph}_3\text{CH}$ , which, combined with unreacted  $\text{Ph}_3\text{COMe}$ , makes workup cumbersome. Resin bound variants of the  $\text{Ph}_3\text{COMe}$  were effective, but batch to batch variability was observed along with some reduction in activity. To circumvent these issues we sought alternative “oxidants” that could similarly abstract  $\text{H}^-$ , but were more atom economical and conveniently removed from products. To this end, we considered the possibility that acetals, ketals, and ortho-esters might be capable of hydride abstraction under acidic conditions (Scheme 1). Supporting this hypothesis were data reported by Bullock demonstrating that acetals in combination with strong acids could abstract hydrides from  $[\text{Mo}]\text{-H}$  complexes.<sup>8</sup>

Since most  $\text{P}_2\text{Pt}^{2+}$ -catalyzed polyene cyclization reactions are buffered with  $\text{Ph}_2\text{NH}$ , we first tested whether its conjugate acid,  $\text{Ph}_2\text{NH}_2^+$ , could generate the putative oxocarbenium ion. Benzaldehyde dimethyl acetal was therefore combined with  $\text{CD}_3\text{OD}$  and in <5 min complete exchange gives  $\text{PhCH}(\text{OCD}_3)_2$ , which was observed by  $^1\text{H}$  NMR spectroscopy (Eq. 1). This suggested that the putative oxocarbenium ion, **1**, was readily accessible under conditions known to be compatible with the substrates for  $\text{P}_2\text{Pt}^{2+}$ -catalyzed cyclizations.



(1)

The ability of reactive intermediate, **1**, to abstract hydride from a catalytic  $[\text{P}_2\text{Pt-H}]^+$  intermediate was examined using a close mimic of this intermediate in our reaction mechanism,  $[(\text{xylyl-phanephos})\text{Pt}(\text{H})(\text{NCC}(\text{CH}_3)_3)][\text{BF}_4]$ , **2**. Complex **2** could be generated *in situ* from the corresponding  $\text{P}_2\text{Pt}(\text{H})$  by iodide abstraction with  $\text{AgBF}_4$  in the presence of 2 equivalents of  $\text{NCC}(\text{CH}_3)_3$ .  $\text{P}_2\text{PtI}(\text{H})$  was obtained from the reaction of  $\text{P}_2\text{PtI}_2$  with polystyrene-bound triacetoxymethylborohydride (see Supporting Information).

To look for hydride abstraction activity, a stoichiometric amount of **2** was added to a premixed solution of a 1:1 ratio of benzaldehyde dimethyl acetal and  $[\text{Ph}_2\text{NH}_2][\text{BF}_4]$  in  $\text{CD}_3\text{NO}_2$ , the solvent of choice for catalysis (Scheme 2). Over the course of 5 h, **2** cleanly converted to  $[(\text{xylyl-phanephos})\text{Pt}(\text{NCC}(\text{CH}_3)_3)_2][(\text{BF}_4)_2]$ , **3**; no intermediates were observed by  $^1\text{H}$  and  $^{31}\text{P}$  NMR spectroscopy. The predicted byproducts of hydride abstraction, benzyl methyl ether and MeOH were confirmed by  $^1\text{H}$  NMR spectroscopy and GC-MS (BnOMe), consistent with Scheme 1. Under identical conditions, reactions of  $\text{Ph}_3\text{COMe}$  with a stoichiometric amount of  $[\text{Ph}_2\text{NH}_2][\text{BF}_4]$  and **2** resulted in > 95% conversion to **3**, and as expected,  $\text{Ph}_3\text{CH}$  was observed as the only byproduct ( $^1\text{H}$  NMR and GCMS). These baseline experiments were slightly faster than the acetal abstraction experiments.

With a reliable protocol in hand for testing the viability of acetal-based hydride abstraction, other convenient commercially available aromatic, cyclic and aliphatic acetals and ketals were tested. As shown in Table 1, the most successful aromatic hydride abstractor candidates included benzaldehyde dimethyl acetal and 4-methoxy benzaldehyde dimethyl acetal, each giving > 95% conversion to **3** within 24 h. Noteworthy is the observation that benzaldehyde itself was equally effective and presumably paralleled the protonated carbonyl reactivity reported by Bullock, Tilset, Norton and others.<sup>8a,b,d,9,10,11</sup>

Aliphatic acetals were also examined and found to be viable (entries 7–11). Bullock has previously noted that secondary carbenium ions are more reactive than tertiary ions, a trend

followed by these aliphatic hydride abstractor candidates (see Table 1).<sup>8d,12,13</sup> Trioxane was not particularly effective, perhaps because fast reclosure results in a low steady concentration of the oxocarbenium ion (entry 7). By contrast, the doubly stabilized dioxocarbenium ion derived from trimethylorthoformate likely suffers from a slow abstraction rate (entry 8). Encouraging were results obtained from the acetals derived from formaldehyde and acetaldehyde, especially dimethoxymethane, which generated **2** in high yields. Since both the reaction products and dimethoxymethane are volatile, workup using this reoxidant is particularly attractive.

Tilset has previously demonstrated that hydride abstraction by triflic acid in acetone is proportional to the steady state concentration of  $(\text{CH}_3)_2\text{C}=\text{OH}^+$ .<sup>10</sup> This observation reasonably suggests that the rate of the reactions described in Table 1 depend on a combination of factors including the steady state concentration of the oxocarbenium ion along with its electrophilicity. More electrophilic ions will be present at lower concentrations than stabilized ions, but would compensate with higher reactivities. In the event, the balance of forces tended to favor the more stabilized oxocarbenium ions (entries 2–4 and 9–10). Although no intermediates were observed during the reaction in Scheme 2, both Bullock and Tilset have shown that hydride abstraction by protonated ketones proceed through a pathway wherein oxygen coordination to the metal immediately follows M-H breakage and yields alcohol adducts as the kinetic product.<sup>8a,b,d,9,10,14</sup>

Based on the reaction profiles displayed in Table 1, the most efficient hydride abstractor candidates were submitted to catalytic reaction conditions using a biaryl xylyl-MeO-BIPHEP based Pt(II) catalyst, (Table 2).<sup>5a,b</sup> Our working mechanism for this new protocol is thus shown in Scheme 3; the  $\text{P}_2\text{Pt}$  dication coordinates to the least substituted alkene and initiates the cyclization of **4** to give an alkyl cation that regioselectively  $\beta$ -H eliminates to generate **5**. Hydride abstraction by transiently generated oxocarbenium ions thus turn the catalytic cycle over by regenerating the electrophilic  $\text{P}_2\text{Pt}^{2+}$  initiator.<sup>15</sup> Even with  $\text{Ph}_2\text{NH}$  as a buffer, acid buildup can initiate a Brønsted cyclization to generate **6**. As shown in Table 2, the acetals, while generally more sluggish than  $\text{Ph}_3\text{COMe}$ , were also less likely to generate Brønsted products. Dimethoxymethane was especially selective, giving a high preponderance of the desired **5** over **6**. Enantioselectivities were unchanged compared to experiments using  $\text{Ph}_3\text{COMe}$ .<sup>5b</sup> Product isolation of **5** for entry 5 (Table 2) simply involved running the reaction mixture through a plug of silica gel to remove the catalyst, followed by removal of the methanol and dimethylether byproducts via vacuum concentration.

In summary, these data indicate that the model hydride abstraction studies outlined in Table 1 reliably track the catalytic efficiency of our oxidative cascade cyclizations. To our knowledge, these results demonstrate that acetals can, for the first time, serve as stoichiometric oxidants in Wacker-type catalysis with concomitant improvements in atom efficiency and ease of use over alternative oxidants (e.g. benzoquinone and  $\text{Ph}_3\text{COMe}$ ).

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

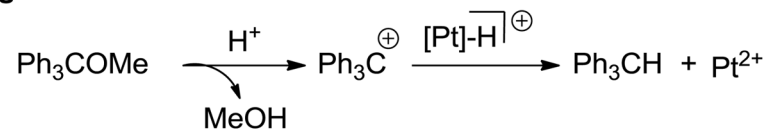
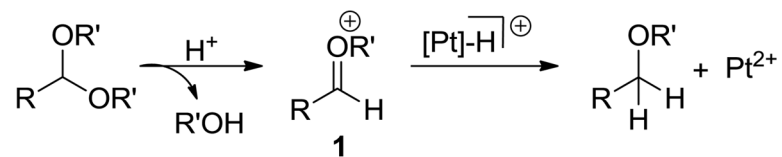
## Acknowledgments

We thank the National Institute of General Medical Sciences for generous support (Grant GM-60578).

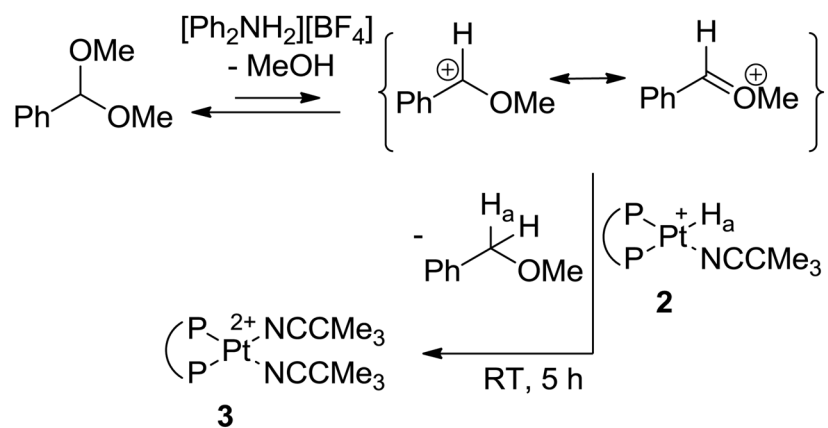
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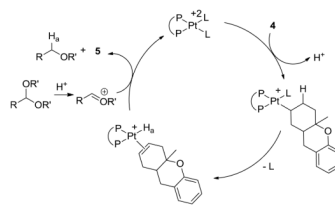
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  15. It is worth noting that in contrast to typical Pd-Wacker cyclizations, Pt undergoes no redox changes through the cycle.

**Original Work:****This work:**

**Scheme 1.**  
Hydride abstraction reactions with  $[\text{Pt}\text{-H}]^{\oplus}$ .

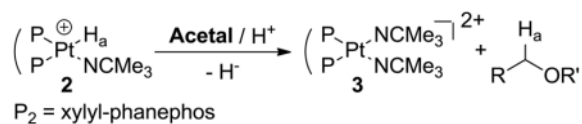
**Scheme 2.**

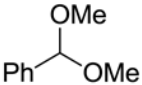
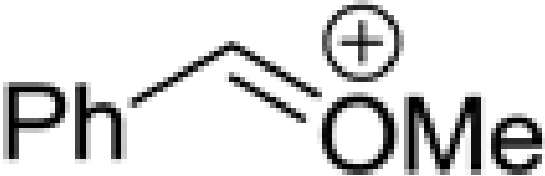
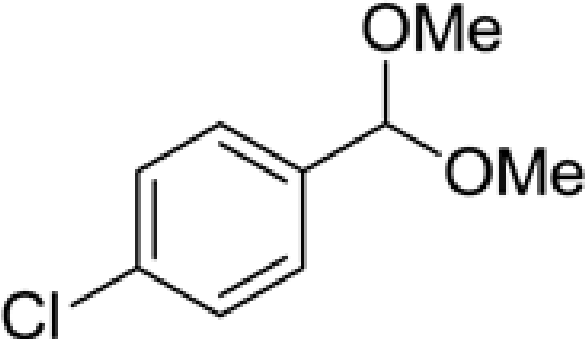
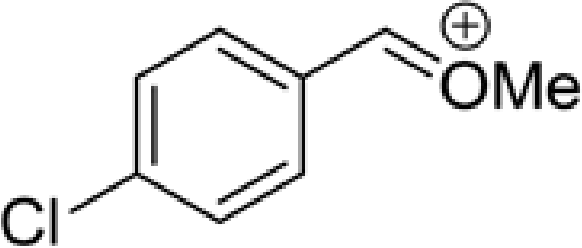
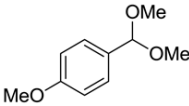
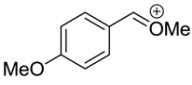
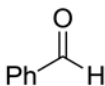
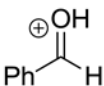
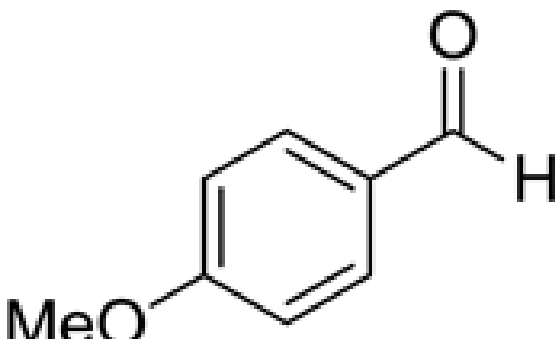
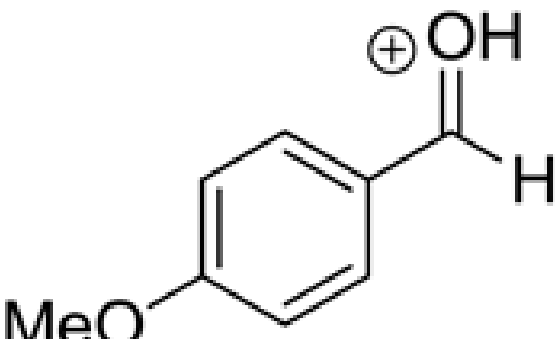
Predicted pathway for hydride abstraction with benzaldehyde dimethyl acetal.



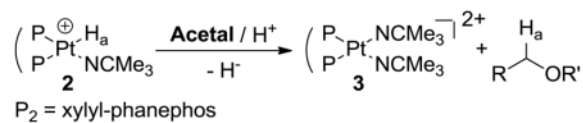
**Scheme 3.**  
Proposed catalytic cycle for oxocarbenium hydride abstractor.

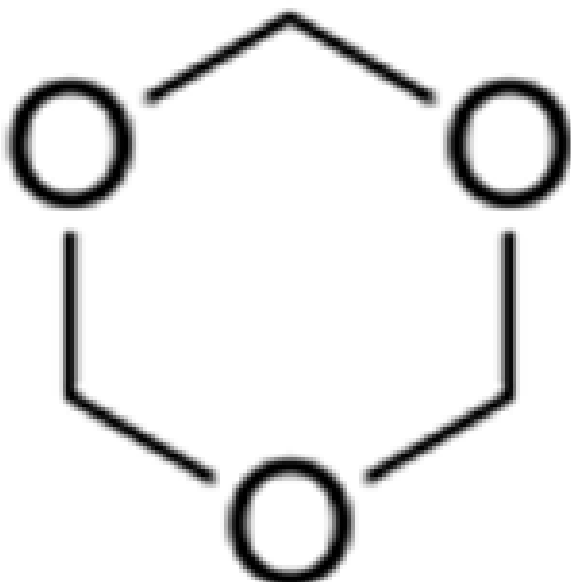
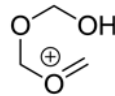
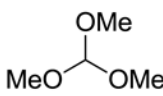
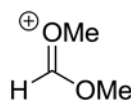
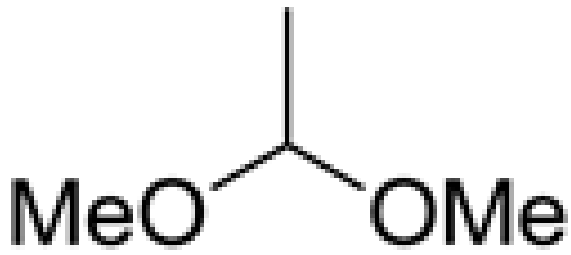
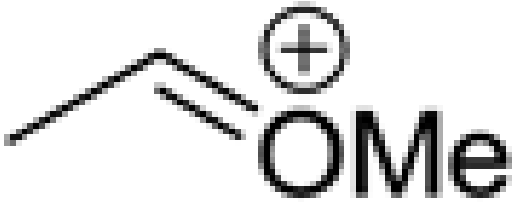

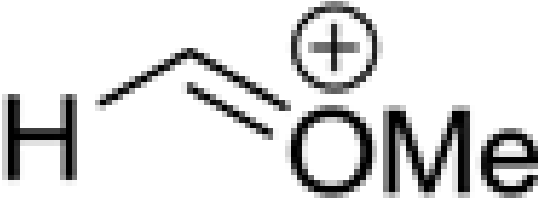
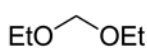
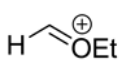
Table 1

Stoichiometric Pt-H abstractor candidates.<sup>a</sup>

Entry	Acetal	Hydride Abstractor	% <sup>3a</sup>
1	Ph <sub>3</sub> COMe	Ph <sub>3</sub> C <sup>⊕</sup>	>95%
2			>95%
3			39%
4			>95%
5			>95%
6			61%

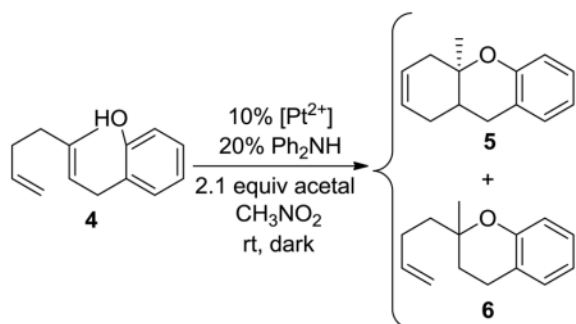




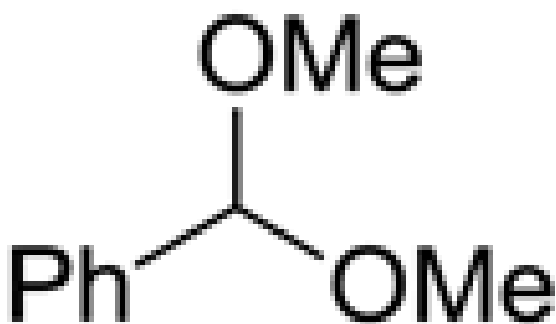
Entry	Acetal	Hydride Abstractor	% <sup>3a</sup>
7			52%
8			18%
9			71%
10			>95%
11			83%

<sup>a</sup> Acetal added to [Ph<sub>2</sub>NH<sub>2</sub>][BF<sub>4</sub>] in 0.1 mL CD<sub>3</sub>NO<sub>2</sub> for 5 min at RT, subsequently [Pt] in 0.2 mL CD<sub>2</sub>Cl<sub>2</sub>/0.3 mL CD<sub>3</sub>NO<sub>2</sub> was added.

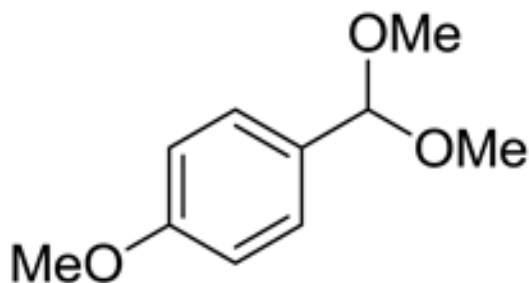
<sup>b</sup> % conversion to **3** after 24 h as determined by <sup>31</sup>P NMR spectroscopy.

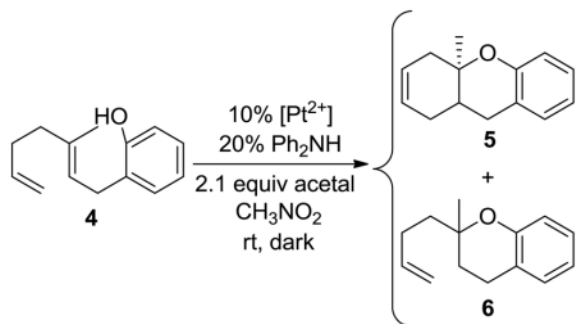
**Table 2**Catalytic results using alternative hydride abstractors.<sup>a</sup>

Entry	Acetal	% <b>5</b> (ee) <sup>b</sup>	% <b>6</b> <sup>b</sup>
1	$Ph_3COMe$	67 (36)	33
2		35 (35)	3



3		7 (38)	0.4
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Entry	Acetal	% <b>5</b> (ee) <sup>b</sup>	% <b>6</b> <sup>b</sup>
4		48 (38)	20
5 <sup>c</sup>		50 (37)	4

<sup>a</sup> All reactions performed under standard catalytic conditions with 13 mM solution of 10 mol% [(R)-(xylyl-MeO-BIPHEP)]Pt<sub>2</sub>, 25 mol% AgBF<sub>4</sub>, 20 mol% Ph<sub>2</sub>NH, 2.1 equiv acetal in CH<sub>3</sub>NO<sub>2</sub>.

<sup>b</sup> Yields and % ee determined by chiral GC after 24 h. The mass balance was unreacted **4**.

<sup>c</sup> Results after 48 h.