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A catalytic, highly stereoselective aldehyde olefination reaction

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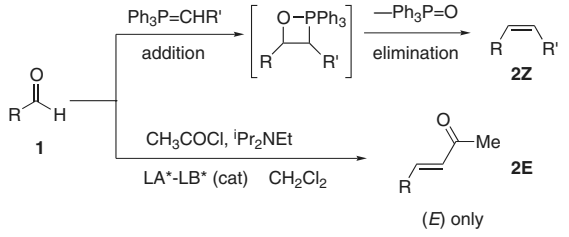
Abstract—A catalytic aldehyde olefination reaction has been discovered. A Cu(II) complex (5 mol %) derived from a salen-quinine mixed ligand catalyzed the reaction between aldehydes and two molecules of acetyl chloride to produce trans C–C double bonds exclusively. The new catalytic aldehyde alkenation reaction presumably goes through a C-3 acylated β-lactone intermediate that loses one molecule of CO_2.

First introduced by Wittig in 1953,[1] the Wittig olefination reaction employing phosphonium ylides has become an indispensible organic reaction.[2] The Wittig reaction efficiently converts the carbonyl groups of aldehydes and ketones into C–C double bonds, an ubiquitous reaction in chemical synthesis. The Wittig reaction is initiated by the addition of a phosphonium ylide carbanion to an electrophilic aldehyde **1** (Scheme 1). The addition–elimination Wittig mechanism proceeds through a betaine intermediate that collapses to form a four-membered oxaphosphetane ring.[2,3] Elimination of triphenylphosphine oxide from the oxaphosphetane intermediate favors the formation of *cis*-alkenes **2Z**. Shortly after Wittig's seminal report, Horner introduced phosphonate-stabilized carbanions that are more nucleophilic than the corresponding nonstabilized Wittig reagents.[4a] In contrast to the Wittig reaction, the HWE (Horner–Wadsworth–Emmons) olefination reaction gives predominantly *trans*-alkenes.[2–5] In spite of the need to remove triphenylphosphine oxide formed in the Wittig reaction, the Wittig and the HWE olefination reactions are invaluable synthetic tools. However, the development of catalytic olefination reactions is significantly lacking.[6,7]



Scheme 1. The Wittig reaction and the new catalytic, stereoselective aldehyde olefination reaction.

Herein, we report the discovery of a catalytic, highly stereoselective aldehyde olefination reaction catalyzed by a Cu(II) complex, using *only* acetyl chloride and Hunig's base as the reagents (Scheme 1, **1** to **2E**). Discovered serendipitously during the Lewis acid (LA), Lewis base (LB) bifunctional catalytic activity screening process, the Cu(II) complex converts the aldehyde carbonyl group into the C–C double bond. Without pre-generating a stabilized carbanion nucleophile, this new catalytic olefination reaction affords *trans*-alkenes **2E** from aldehydes **1** and acetyl chloride in a highly stereoselective fashion.

Using a combination of rational design and catalytic activity screening, we recently reported the design and synthesis of a new mixed ligand **3**, from which a remarkably active Lewis acid–Lewis base (LA*–LB*, * denotes chirality) bifunctional catalyst **4A** (M = Co(II)) was discovered (Fig. 1).[8a] Using the asymmetric Wynberg reaction[9] between 2-benzyloxyacetaldehyde **5** and ketene as the proof-of-principle reaction, we have also established that asymmetric bifunctional catalysis occurs intramolecularly through control experiments. In our initial catalytic activity screening studies, we employed ketene

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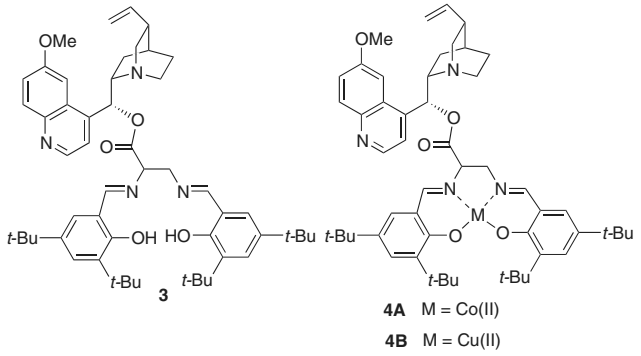
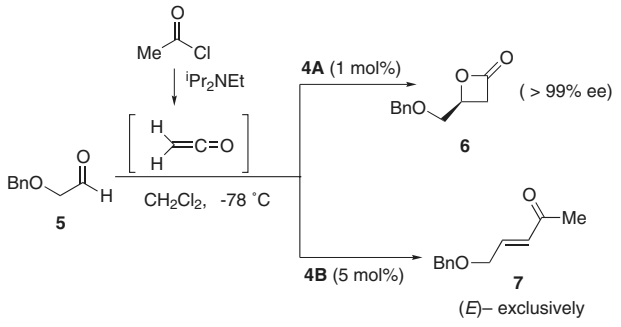


Figure 1. Salen-quinine mixed ligand and Lewis acid–Lewis base bifunctional catalysts.

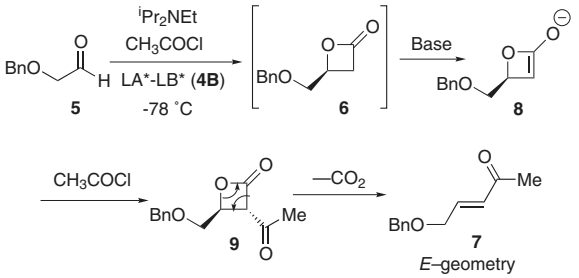
generated in situ from a large excess of acetyl chloride and Hunig's base at −78 °C,[10] as a prelude to the optimized reaction conditions that requires only 1 mol % of the catalyst **4A** for the asymmetric Wynberg reaction to furnish β-lactone **6** in >99% ee (Scheme 2).[8a]

Interestingly, when 5 mol % of Cu(II) complex (**4B**, Fig. 1) was employed as the catalyst in the screening process, the test reaction produced no β-lactone **6** at −78 °C, but with complete consumption of aldehyde **5** within 2 h. After an aqueous workup and subsequent silica gel flash column chromatography separation, a new product was isolated in good mass recovery. Subsequent structural determination established that the unexpected product was indeed enone **7** in 63% yield, having the *E*-stereochemistry. In 2001, in order to determine the absolute configuration of the NADH-fumarate reductase specific inhibitor nafuredin, Omura synthesized enone (*E*)-**7** from aldehyde **5**, employing a standard carbanion-stabilized Wittig reagent.[11]

Without pre-forming a stabilized carbanion nucleophile, the exclusive formation of enone **7** from aldehyde **5** constitutes the first example of a catalytic aldehyde olefination reaction employing only acetyl chloride/Hunig's base as the reagents, catalyzed by Cu(II) complex **4B**. This new catalytic reaction utilizes acetyl chloride as the source of the vinyl carbon in the olefination reaction (i.e., phosphine- and phosphonate-based reagents free). Thus, the mechanism of this highly stereoselective reaction must be fundamentally different from those of other aldehyde olefination reactions.



Scheme 2. Two structurally analogous complexes having different catalytic activity.



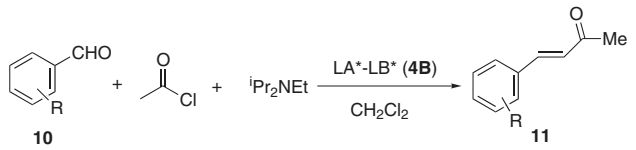
Scheme 3. A possible reaction mechanism for the stereoselective aldehyde olefination reaction.

Mechanistic considerations led us to speculate a possible reaction mechanism for this new aldehyde olefination reaction (Scheme 3). When the Cu(II) catalyst **4B** was employed in the reaction between aldehyde **5** and ketene, although not isolated, β-lactone **6** would most likely be the intermediate produced, because the same reaction catalyzed by the Co(II) analog **4A** afforded β-lactone **6** in excellent yield.[8] This assumption is highly plausible, especially when taking into account the structural similarities between catalysts **4A** and **4B**.

In the presence of the Cu(II) catalyst **4B** and Hunig's base, enolization of β-lactone **6** formed in situ would furnish enolate **8**. Enolization of β-lactone **6** is most likely catalyzed by the LA*–LB* catalyst **4B**, because Hunig's base (pKa ∼ 11) alone would be difficult to deprotonate β-lactone **6**. Subsequent acylation of enolate **8** by acetyl chloride approaching from the less hindered side (i.e., *anti* to the C-4 substituent) would furnish β-keto lactone **9**, placing the acetyl group trans to the C-4 alkyl group. The *anti* acylation thus sets the stereochemistry for enone **7**. Although intermediate **9** was not isolated in our studies, similar C-3 acylated β-lactones were previously isolated.[12] Decarboxylation of the *trans* 3,4-disubstituted β-lactone **9** (a strained β-keto ester) would release the ring strain and furnish (*E*)-enone **7**. The exclusive formation of the trans stereoisomer suggests a concerted elimination mechanism from lactone **9** to enone **7**. The Cu(II) catalyst **4B** might be responsible for the elimination reaction to occur at −78 °C, because Mulzer was able to purify β-lactones *via* vacuum distillation without expulsion of CO_2.[12a]

This new aldehyde olefination reaction constitutes the first catalytic, highly stereoselective synthesis of an *E* enone from an aldehyde, using acetyl chloride as the source of the other vinyl carbon. In addition to the water soluble by-product that can be readily removed during the aqueous workup, this new reaction offers a catalytic alternative to converting the aldehyde carbonyl group to the trans C–C double bond exclusively. The prospect of developing a general catalytic olefination reaction, coupled with the synthetic significance of enones (e.g., as Michael acceptors) prompted us to examine the substrate scope of this catalytic reaction.

Table 1. The substrate scope of the catalytic, stereoselective aldehyde olefination reaction



Entry	ArCHO **10** (R–)	Cat **4B** (mol %)	Temp (°C)	Time (h)	*E*-Enone **11** (% yield)[a]
1	H	10	−78	20	~10[b]
2	4-Br	10	−78	>20	0[c]
3	4-Br	10	−20	20	20
4	2-NO_2	5	−20	15	53
5	3-NO_2	5	−20	16	48
6	4-NO_2	5	−20	15	51
7	2-Cl	5	−20	48	34
8	2-F	5	−20	48	29
9	4-Cl	5	−20	42	15[d]
10	4-NO_2	10	−78	20	60
11	4-NO_2	2	−20	20	50
12	4-NO_2	0	−20	>72	<2

[a] Isolated yield.
[b] Average yield from multiple attempts.
[c] 95% recovery of aldehyde **10** (R = 4-Br).
[d] 70% recovery of aldehyde **10** (R = 4-Cl).

The substrate scope of this new olefination reaction was subsequently investigated (Table 1). Initial studies employing benzaldehyde **10** (R = H) afforded the expected enone **11** (R = H) in poor yields, inspite of many attempts and under various conditions (entry 1). In order to gauge the percent recovery of the starting material, the nonvolatile 4-bromobenzaldehyde was employed to replace benzaldehyde as the substrate for this reaction. Treatment of 4-bromobenzaldehyde **10** (R = 4-Br) with 10 mol % of catalyst **4B** afforded no enone at −78 °C, but with 95% recovery of aldehyde **10** (R = 4-Br, entry 2). Increasing the reaction temperature to −20 °C furnished the expected (*E*)-enone **11** (R = 4-Br) in 20% yield (entry 3). However, increasing the reaction temperature further did not improve the reaction, presumably due to ketene dimerizations.

At −20 °C, aromatic aldehydes having strong electron withdrawing groups are particularly good substrates for this catalytic aldehyde olefination reaction. For nitrobenzaldehydes **10** (R = NO_2), 5 mol % of catalyst **4B** was sufficient for the reaction. Regardless of the steric properties of the aldehyde carbonyl groups, their corresponding *trans* enones **11** (R = NO_2) were produced exclusively in good yields (entries 4–6). In contrast, halogenated benzaldehydes **10** (R = X) required longer reaction time. Their corresponding enones **11** (R = X) were produced in poor yields (entries 3, 7–9). The structure–reactivity relationship of the substrates suggests that the electronic, rather than the steric property of the carbonyl group plays a more important role in this catalytic olefination reaction.

Among the aromatic aldehydes we examined, 4-nitrobenzaldehyde **10** (R = 4-NO_2) was the most reactive substrate for this new reaction. The olefination of 4-nitrobenzaldehyde can be carried out either at a lower temperature (−78 °C, entry 10), or with less catalyst loading at −20 °C (entry 11) to furnish *E*-enone **11** (R = 4-NO_2) in good yields. Thus, we employed 4-nitrobenzaldehyde as the substrate in the control reaction, which was designed to determine the necessity of catalyst **4B**. Indeed, in the absence of catalyst **4B**, the reaction was very slow at −20 °C (entry 12). Less than 2% of enone **11** (R = 4-NO_2) was isolated in more than 72 h.

In summary, we have discovered a new catalytic reaction for converting aldehydes into *E* enones exclusively, using acetyl chloride as a latent vinylating reagent for this olefination reaction. The new Cu(II) catalyst formally converts two molecules of acetyl chloride into the synthetic equivalent of an 'acetyl vinyl' group that olefinates aldehyde carbonyl groups. The required Cu(II) complex for this new olefination reaction is easy to prepare and not air/moisture sensitive. Compared to triphenylphosphine oxide by-product from the Wittig reaction, the trialkyl ammonium chloride generated in this reaction is more environmental friendly and water soluble that facilitates product purification. Mechanistic studies of this new catalytic reaction and expanding its substrate scope to other enolizable aldehydes and ketones are the ongoing research effort in our laboratory.

Acknowledgments

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Supplementary data

Experimental procedures, spectral data, and NMR spectra. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.05.163.

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