**Organocatalysis**

**The Cyclohexa-2,5-dienyl Group as a Placeholder for Hydrogen: Organocatalytic Michael Addition of an Acetaldehyde Surrogate**

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**Abstract:** An aldehyde with a cyclohexa-2,5-dienyl group in the α-position is introduced as a storable surrogate of highly reactive acetaldehyde. The cyclohexa-2,5-dienyl unit is compatible with enantioselective Michael addition to nitroalkenes promoted by a Hayashi–Jørgensen catalyst and can be removed by a boron Lewis acid mediated C–C bond cleavage. The robust two-step sequence does not require a large excess of the aldehyde component that is typically needed when directly using acetaldehyde.

The direct use of readily available acetaldehyde (1) as a C₂ building block is synthetically attractive. [1] However, a low boiling point (bp. 20 °C) together with severe toxicity complicates handling of this highly reactive chemical. It is therefore particularly impressive that 1 can be engaged as the nucleophilic reactant in various enantioselective transformations catalyzed by proline or congeners such as Hayashi–Jørgensen catalysts. [2-4] For example, List [4a] as well as Hayashi [4b] independently reported Michael additions with nitroalkenes to yield γ-nitroaldehydes with excellent enantiocontrol. Poelarends and co-workers had similar success with a proline-based tautomerase as catalyst. [4c,e] To avoid the delicate manipulation of volatile 1, Pericás and co-workers turned toward employing liquid paraldehyde (2; bp. 124 °C) that hydrolyzes in acidic medium. With a sulfonic acid resin, high enantioselectivities were obtained in the aforementioned reaction in the presence of a polystyrene-supported Hayashi–Jørgensen catalyst. [5] Despite these important advances, alternative methods that bypass the use of 1 and 2 are still in demand.

We introduce here the new user-friendly acetaldehyde surrogate 3 (Scheme 1, top). The design of 3 emerges from observations made during our investigations of boron Lewis acid catalyzed ionic transfer processes with cyclohexadiene-based reagents. [6] To be precise, we had shown that nucleofugal carbon groups attached to one of the saturated positions of the cyclohexadiene can be abstracted by certain boron Lewis acids with cleavage of a C=C bond. [7] The outcome is an ion pair composed of a boron ate complex and a Brønsted acidic Wheland intermediate that can either react with itself or with an added reaction partner. By this, alkene hydrofunctionalizations such as transfer hydrocyanation [7d] and hydromethallation [7f] have been accomplished. We anticipated that a cyclohexa-2,5-dienyl unit α to a carbonyl group could be degraded the same way (5→6), hoping that it would also be compatible with an organocatalytic Michael reaction (4→5; Scheme 1, bottom). Being part of the carbon skeleton, the cyclohexa-2,5-dienyl substituent nevertheless fulfills the role of a placeholder for a hydrogen atom.

Acetaldehyde surrogate 3 was prepared on gram scale by metatation of cyclohexa-1,4-diene followed by electrophilic substitution with 2-bromo-1,1-dimethoxethane and subsequent acidic hydrolysis of the acetal (see the Supporting Information for the detailed procedure). Despite being an aldehyde, 3 can be stored in the freezer for months with no sign of decomposition. Treatment of 3 with BF₃·OEt₂ resulted in the desired degradation into acetaldehyde (1) and benzene (not shown).

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shown), thereby verifying the validity of the strategy outlined above. The Michael addition did not require much optimization. Starting from List’s and Hayashi’s reaction conditions with (S)-7[10] as catalyst,[14,15] we found that, depending on the scale of the reaction, either no solvent or just a few drops of CH2Cl2 are needed and that the reaction can be run open to air.[10] Moreover, the key difference to the known protocols was that 2.0 equiv of 3 were sufficient to reach high conversion within 24 h at room temperature. With freshly distilled acetaldehyde, a 5.0-fold excess[16] (stock solution of 1) or a 10-fold excess[16] (neat 1) were required. The model reaction afforded the product in 80% yield with 99% ee and moderate diastereoselection[10] (4a—5a; Scheme 2). Purification by flash chromatography on silica gel improved the diastereomeric ratio from 82:18 to 96:4, and this enantio- and diastereenriched sample allowed for growing single crystals suitable for X-ray diffraction,[11] the relative configuration is as shown (see the Supporting Information). The model reaction on a 5.0 mmol scale afforded 82% yield with 99% ee and d.r. = 87:13.

This Michael addition turned out to be broadly applicable with superb functional-group tolerance (Scheme 2). The majorities of the reactions were run at high concentration in CH2Cl2. Nitroalkenes 4b–e with a methoxy or methyl group at the aryl substituent in the β position and mono- and trihalogenated 4f–j gave consistently high yields and enantiomeric excesses. A β-naphthyl and a fur-3-yl group as in 4k and 4l were also compatible. Electron-withdrawing substituents in aryl-substituted nitroalkenes 4m–q were tolerated, including carboxy, cyano, and nitro groups as well as a boronate pinacol ester. Likewise, alkyl-substituted nitroalkenes 4r–t showed excellent enantioselectivities and good yields. These Michael adducts were chemically stable for extended periods of time when kept in the freezer.

The deprotection step, that is the removal of the cyclohexa-2,5-dienyl unit, by acid-promoted C–C bond cleavage did work as planned (5a–6a; Table 1). However, treatment of the model compound with B(C6F5)3, the boron Lewis acid typically used in our transfer chemistry,[6,7] required 18 h for completion (entry 1). Conversely, the reaction was significantly faster with BF3·OEt2, and full conversion was reached within 2 h (entry 2). Unlike the boron Lewis acid catalyzed transfer reactions, stoichiometric amounts of either B(C6F5)3 or BF3·OEt2 were necessary. We explain this by the presence of the nitro group. Hence, substoichiometric quantities of BF3·OEt2 led to prolonged reaction times (entry 3) while overstoichiometric amounts furnished the desired aldehyde within minutes (entry 4). A Brønsted acid such as TFOH as a promoter was also possible but caused partial decomposition (entry 5).

The standard protocol with 1.5 equiv of BF3·OEt2 was then applied to the whole range of Michael adducts 5 (Scheme 2). The BF3·OEt2-mediated C–C bond cleavage was successful for

![Scheme 2. Michael addition of the acetaldehyde surrogate to nitroalkenes catalyzed by a Hayashi–Jørgensen catalyst. All reactions were performed on a 0.10 to 0.20 mmol scale with the isolated yield determined after flash chromatography on silica gel. Diastereomeric ratios (d.r.) estimated by 1H NMR analysis after purification (those of the crude product in parentheses), and enantiomeric excesses (ee) determined by HPLC analysis on chiral stationary phases. (a) Reaction time of 62 h. (b) 4.0 equiv of 3 and reaction time of 48 h. (c) Reaction time of 39 h. (d) Aldehyde reduced to the corresponding alcohol prior to HPLC analysis. pin = pinacolato.](Image 288x610)

![Table 1. Selected examples of the optimization of the acid-promoted C–C bond cleavage.[h](Table 2)](Image 128x256)

| Entry | Acid (equiv) | t (h) | Conversion[a] |
|-------|-------------|------|---------------|
| 1     | B(C6F5)3 (1.0) | 18   | full          |
| 2     | BF3·OEt2 (1.0) | 2    | full          |
| 3     | BF3·OEt2 (0.20) | 48   | full          |
| 4     | BF3·OEt2 (1.5) | 1/4  | full          |
| 5     | TFOH (1.0) | 1    | full          |

[a] A solution of the Michael adduct (0.04 mmol) in CD2Cl2 (0.5 mL) was treated with the indicated acid at room temperature until full conversion was reached. (b) Estimated by 1H NMR analysis. (c) Impurities observed. TF = trifluoromethanesulfonyle.
the majority of substrates (5 → 6; Scheme 3). Electron-rich aryl groups in 5 were an exception, and anisyl-substituted 5b and 5c as well as furyl derivative 5l decomposed independent of the acid employed. The aliphatic substrates 5r-t participated with similar success. No loss of the stereochemical information was seen in any of these reactions. The NMR spectroscopic characterization of aldehydes 6 was done immediately after their preparation, including the measurement of the optical rotation. However, the carbonyl group was converted into the corresponding dihydroxy alcohol by acatalization with alcohol or borohydride reduction for the HPLC analysis. The absolute configuration was assigned by comparison with literature-known optical rotations and retention times (see the Supporting Information for details).

Scheme 3. BF3·OEt2-mediated C=C bond cleavage for the release of the acetaldehyde-derived Michael adducts. All reactions were performed on a 0.05 to 0.15 mmol scale with the isolated yield determined after work-up and the removal of solvents. [a] Compound converted into the corresponding dihydroxy alcohol prior to the measurement of the enantiomeric excess by HPLC analysis on a chiral stationary phase. [b] Compound reduced to the corresponding alcohol prior to the measurement of the enantiomeric excess by HPLC analysis on a chiral stationary phase. [c] Enantiomeric excesses determined by HPLC analysis on a chiral stationary phase.

We presented here an alternative preparation of Michael adducts formally derived from nitroalkanes and acetaldehyde. The approach is based on a acetaldehyde surrogate with a cyclohexa-2,5-dienyl substituent α to the carbonyl group as a placeholder for a hydrogen atom. The two-step sequence consists of a highly enantioselective Michael addition of that surrogate promoted by a Hayashi–Jörgensen catalyst and a mild removal of the ‘protecting group’ by C=C bond cleavage with BF3·OEt2. Aside from broad functional-group tolerance, the main advantages are a favorable stoichiometry of the reactants (2.0 equiv of the surrogate instead of n-fold excess of highly reactive acetaldehyde) and avoidance of toxic acetaldehyde as a whole.

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Conflict of interest

The authors declare no conflict of interest.

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We note here that related surrogates with a quaternary carbon atom in the C1 position of the cyclohexa-2,5-dienyl unit did not react. Apparently, aldehydes with a neopentylic α-carbon atom are sterically too hindered. The preparation of these surrogates is outlined in the Supporting Information.