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Can a Ketone be More Reactive than an Aldehyde? Catalytic Asymmetric Synthesis of Substituted Tetrahydrofurans

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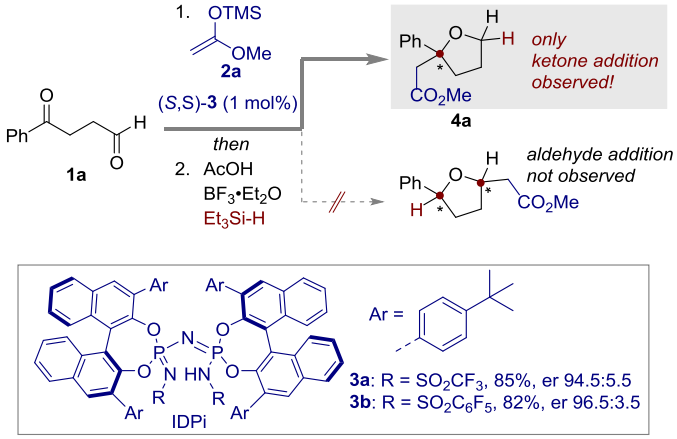
Abstract: *O*-heterocycles bearing tetrasubstituted stereogenic centers are prepared via catalytic chemo- and enantioselective nucleophilic additions to ketoaldehydes, in which the ketone reacts preferentially over the aldehyde. 5- and 6-membered rings with both aromatic and aliphatic substituents, as well as an alkynyl substituent, are obtained. Moreover, 2,2,5-trisubstitued and 2,2,5,5-tetrasubstituted tetrahydrofurans were synthesized with excellent stereoselectivities. Additionally, the synthetic utility of the described method has been demonstrated with a three-step synthesis of the side chain of anhydroharringtonine.

Aldehydes are generally more electrophilic and therefore more reactive toward nucleophilic additions than ketones.[1] This is also true with ketoaldehydes, in which the aldehydic functional group typically reacts preferentially with a nucleophile.[2] However the question arises if this tendency can be reversed upon Lewis acid activation.[3] In this case, the ketone may react first with an external nucleophile, either because it is preferentially activated by the Lewis acid or, as has been suggested by Molander,[4] by virtue of a neighboring group participation. Within the context of our program on asymmetric Lewis acid catalysis with a silylium ion equivalent/chiral anion pair (Si-ACDC),[5] we became interested in exploring this type of reactivity. Specifically, we were keen on developing methodology in which ketoaldehydes undergo asymmetric Lewis acid catalyzed C−C bond forming cyclization reactions that are accomplished by preferential nucleophilic addition to the activated ketone (Scheme 1). Here we report the fruition of these studies with the development of a broadly applicable catalytic and enantioselective approach to highly substituted tetrahydrofurans (THFs) from the corresponding 1,4-ketoaldehydes.

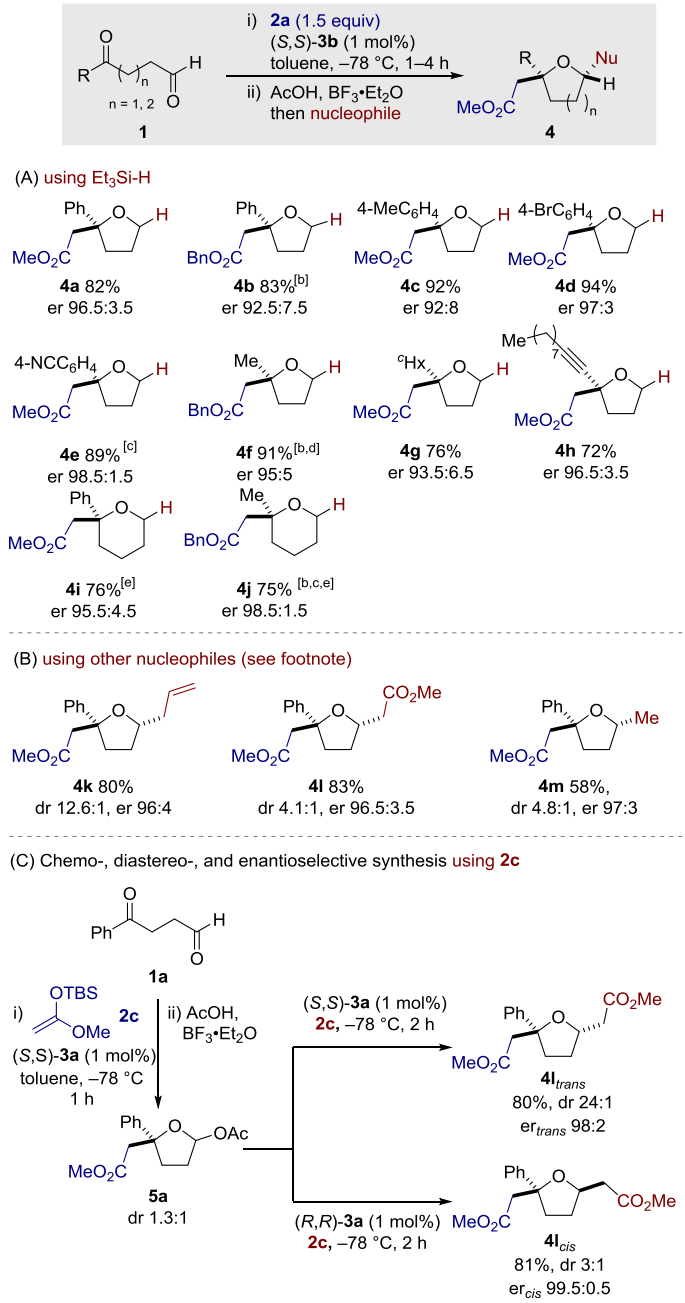
Tetrahydrofurans are frequently appearing structures in natural products and biologically active molecules.[6] Consequently, numerous methods have been developed for the enantioselective construction of these important heterocycles.[7] However, there is a limited number of synthetic methods that provide 2,2-disubstituted analogs with tetrasubstituted steterogenic centers, despite the known biological potency of this motif against multiple targets.[8] In fact, only a few methods aiming at such targets have been reported including oxidative Wacker-type cyclizations,[9] carboalkoxylations,[10] an hydroalkoxylation,[11] and others. [12] In most cases, the stereoselective preparation of the starting tri- and tetrasubstituted olefins is considered the major limitation.



Scheme 1. Initial observations of nucleophilic addition of **2a** to ketoaldehyde **1a** catalysed by IDPi **3**

Recently, the Watson group reported an alkynylation of 2-aryl substituted cyclic oxocarbenium ions using a Cu(I)-complex for the synthesis of diaryl, tetrasubstituted stereogenic centers.[13] Though cyclic oxocarbenium ions are extensively exploited in glycosylations and natural product syntheses, their application in asymmetric synthesis is scarce.[14] This mainly originates from their capricious stability, which largely depends on the amount and size of substituents, as well as the absence of a strong coordinating site. Following our first success on the enantioselective functionalization of *in situ* generated cyclic oxocarbenium ions,[14q] we envisioned that imidodiphosphorimidates (IDPis)[11, 14q, 15] would be efficient catalysts for the formation of tetrasubstituted stereogenic centers by controlling stereochemically more challenging, yet more stable, 2-

Table 1. Substrate scope using ketoaldehydes.[a]



[a] Reactions were conducted with substrate **1** (0.2 mmol, 1.0 equiv), **2a** (0.3 mmol, 1.5 equiv), and catalyst **3b** (1.0 mol%) in toluene (0.1 M) at –78 °C. After full consumption of starting material, 2.0 equiv of AcOH and 3.0 equiv of BF_3·Et_2O were added, followed by addition of 3.0 equiv of the second nucleophile, i.e. Et_3SiH, allyltrimethylsilane, **2c**, or Me_3Al. For details, see the Supporting Information. [b] using 1-(trimethylsilyloxy)-1-benzyloxyethene **2b** instead of **2a** [c] at –40 °C [d] at –95 °C [e] using (*S*,*S*)-**3a**

substituted cyclic oxocarbenium ions via asymmetric counteranion directed catalysis (ACDC).[16]

To test our hypothesis, 4-oxo-4-phenylbutanal **1a** was reacted with silyl ketene acetal **2a** in toluene at –78 °C (Scheme 1). The reaction was complete within 1 hour using only 1 mol% of (*S*,*S*)-IDPi **3a** and gave product **4a** in 94.5:5.5 er with *in situ* reduction of the acetal intermediate.[17]

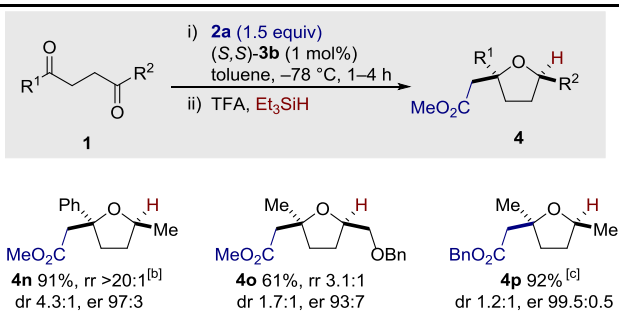
Remarkably, only the product resulting from the attack of the nucleophile on the ketone was observed. Similar to our previous findings on the catalyst design,[11] modifying the electron withdrawing group of the sulfonamide from a CF_3 group to more sterically demanding C_6F_5 group increased the enantioselectivity to 96.5:3.5 with full conversion of the starting material within 1 h (Scheme 1).

With the optimized catalyst in hand, we investigated the reaction scope (Table 1). The steric bulk of the nucleophile could be increased without significant deterioration in yield and enantioselectivty (**4b**, **4f**, and **4j**). Moreover, changes in the electronic nature of phenyl ring were well tolerated (**4c**, **4d**, and **4e**). Both methyl and cyclohexyl ketones **1e** and **1f** showed excellent chemo- and enantioselectivities, as well as alkynyl ketone **1g.** Gratifyingly, when 5-ketoaldehydes were employed, tetrahydropyrans with a tetrasubstituted stereogenic center (**4i** and **4j**) were obtained in high yields and enantioselectivities.

The introduction of carbon nucleophiles in the second step provides a useful procedure to generate 2,2,5-trisubstituted tetrahydrofuran rings, which occasionally appear in natural products (Table 1B). Allylation and alkylations using silylated nucleophiles, such as allyltrimethylsilane and silyl ketene acetal **2c**, resulted in high enantioselectivities and moderate diastereoselectivities of the corresponding trisubstituted products **4k** and **4l**. A simple methyl substitution using Me_3Al was also possible, giving the same level of enantioselectivity (**4m**).

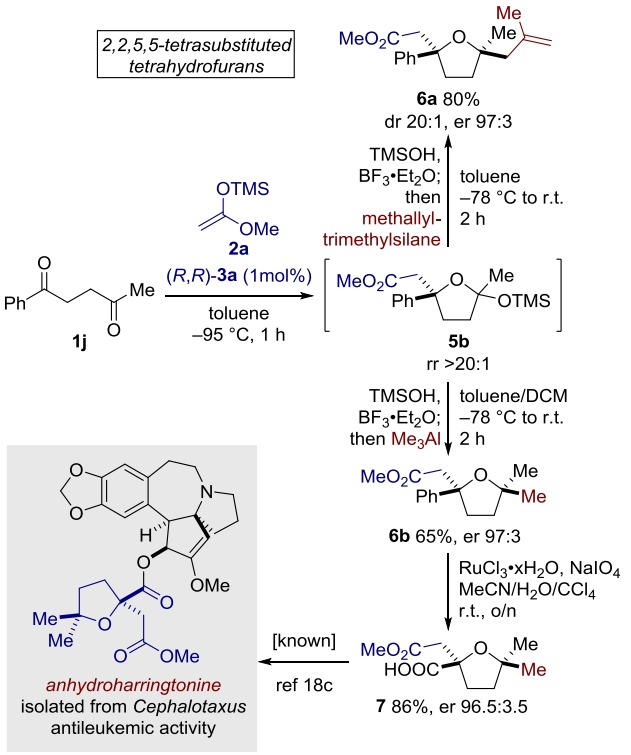
The current method enables the selective formation of either the *cis*- or *trans*-isomer of a 2,2,5-trisubstituted tetrahydrofuran ring, overcoming the intrinsic preference (Table 1C). Namely, after the formation of TBS protected acetal using (*S*,*S*)-IDPi **3a**, treatment with acetic acid and BF_3·Et_2O afforded lactol acetate **5a** with moderate diastereomeric ratio (1.3:1). Remarkably, when the same enantiomer of catalyst was applied in the second C−C bond forming step, the *trans*-selectivity was enhanced to 24:1. In sharp contrast, the other enantiomer of the catalyst, (*R*,*R*)-**3a,** furnished the *cis*-isomer as the major product in superb er and moderate dr within 2 h.

Table 2. Substrate scope using 1,4-diketones.[a]



[a] Reactions were conducted with 1.0 equiv of substrate **1**, 1.5 equiv of **2**, and 1.0 mol% catalyst **3** in toluene (0.1 M) at –78 °C. After full consumption of starting material, 5.0 equiv of trifluoroacetic acid and 5.0 equiv of Et_3SiH were added. For details, see the Supporting Information. [b] at –95 °C [c] using **2b** instead of **2a**

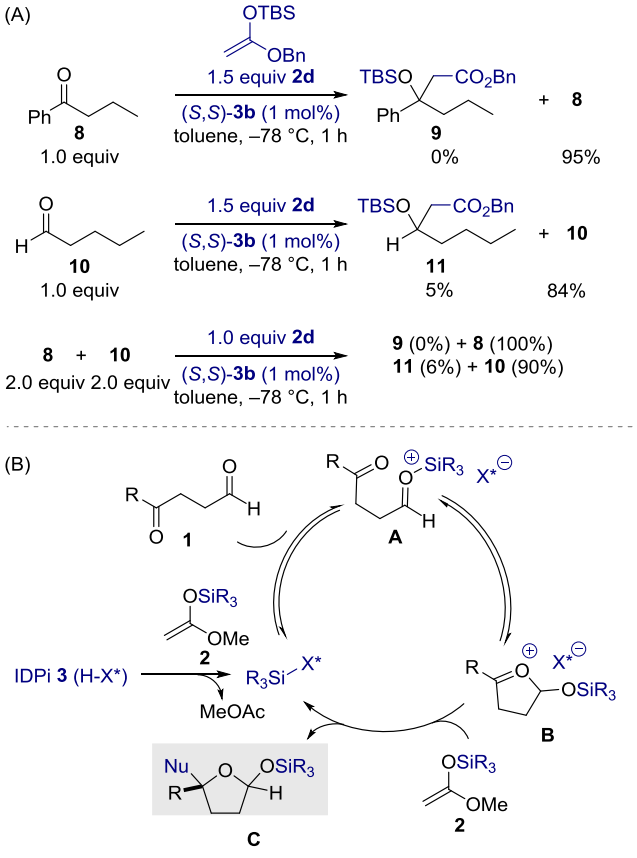
The differentiation between two ketones is also possible (Table 2). When 1-phenylpentane-1,4-dione **1j** was treated with **2a** in the presence of 1 mol% (*S*,*S*)-**3a**, a nucleophilic attack was accomplished on the side of the sterically more hindered carbonyl site, giving 97:3 enantioselectivity at –95 °C, providing **4n**, a diastereomer of **4m**. Interestingly, the regioselectivity can be altered by the substitution of a benzyloxy coordinating group, i.e. ketone **1k** afforded the tetrasubstituted stereogenic center on the side of methyl ketone (**4o**) with er of 93:7. Desymmetrization of a symmetric diketone, hexane-2,5-dione, could be achieved with excellent enantioselectivity, albeit with only a moderate diastereomeric ratio (**4p**).



Scheme 2. Synthesis of enantioenriched 2,2,5,5-tetrasubstituted tetrahydrofurans and the side chain of anhydroharringtonine

The synthetic utility of this method can be highlighted by the straightforward preparation of enantioenriched 2,2,5,5-tetrasubstutited tetrahydrofurans (Scheme 2). When intermediate **5b**, which is generated from the reaction between **1j** and **2a** in the presence of 1 mol% (*R*,*R*)-**3a** at –95 °C, was reacted further with methylallyltrimethylsilane, the corresponding *O*-heterocycles **6a** were afforded with high yield and excellent regio-, diastereo- and enantioselectivity. With the same intermediate **5b**, the side chain of anhydroharrintonine,[18] which is isolated from the genus *Cephalotaxus* and known for antileukemic activity, was synthesized. A methylation of **5b** using trimethylaluminum, followed by catalytic oxidation of phenyl group using $RuCl_3 \cdot xH_2O$, allowed us to obtain the corresponding acid **7** in three steps.

To gain insight on the reaction mechanism, we have investigated the reactivity of 1-phenyl-1-butanone **8** and pentanal **10** under the identical reaction conditions (Scheme 3A). Interestingly, only 5% of product **11** was observed when aldehyde **10** was used as starting material, while no desired aldol adduct was observed using ketone **8**.[19] In addition, an equal molar mixture of ketone **8** and aldehyde **10** gave the same low conversion. These results contrast with the full conversion of ketoaldehyde **1a** and clearly imply that dicarbonyl structures are essential in our reactions and the highly reactive cyclic oxocarbenium ions are involved. Our results also suggest that the reaction does not precede through the direct nucleophilic addition of the silyl ketene acetals onto ketones which can generate the same products by sequential cyclization of silyl ether towards aldehydes. Based on these observations, we propose the following mechanism. First, the *in situ* formed silylium ion pair catalyst coordinates to the sterically less hindered aldehyde (**A**), and invokes an intramolecular cyclization to afford a highly active cyclic oxocarbenium ion intermediate **B** (Scheme 3B). At this point, the counteranion of IDPi **3** can direct the approach of external nucleophiles by discriminating the enantiofaces of a multisubstituted cyclic aliphatic oxocarbenium ion. Subsequently, formation of the highly substituted heterocycle **C** and regeneration of the silylium ion pair complete the catalytic cycle.



Scheme 3. (A) Reactivity comparison between aldehyde and ketone (B) Plausible catalytic cycle

In conclusion, we have developed a regio- and enantioselective catalytic method which affords highly substituted tetrahydrofurans and tetrahydropyrans starting from 1,4- and 1,5-dicarbonyl compounds using IDPis as

catalysts. The selective addition of nucleophiles toward ketones over aldehydes was observed. The efficiency of the method was demonstrated by the chemo-, diastereo- and enantioselective construction of 2,2,5-trisubsituted furans. Moreover, 2,2,5,5-tetrasubstituted tetrahydrofurans can be readily synthesized using the described method.

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Keywords: enantioselective nucleophilic addition, silylium Lewis acid catalysis, imidodiphosphorimidates, *O*-heterocycles, tetrasubstituted stereogenic centers

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