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Stereodefined Acyclic Polysubstituted Silyl Ketene Aminals: Asymmetric Formation of Aldol Products with Quaternary Carbon Stereocenters

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Dedicated to Professor Jochanan Blum on the occasion of his birthday

Abstract: *The regio- and stereoselective formation of stereodefined polysubstituted silyl ketene aminals is easily achieved through selective combined carbometalation–oxidation–silylation reactions. These substrates are ideal candidates for Mukaiyama aldol reactions with aliphatic aldehydes as they give the aldol products with a quaternary carbon stereocenter α to the carbonyl groups in outstanding diastereoselectivities.*

The aldol reaction is one of the most important methods for forming carbon–carbon bonds and has been extensively used over the years to construct polyketide fragments.[1] The power of this approach results from the plethora of stereoselective variants that have been developed over the last few decades and lead to almost all desired substructures.[1,2] However, the formation of a quaternary carbon stereocenter at the α-position to carbonyl groups remains elusive and has been the focus of only a few studies.[3] The main problem that limits the formation of this stereocenter is the difficulty to prepare stereodefined trisubstituted enolates with different alkyl groups in an acyclic system (Figure 1).[4]

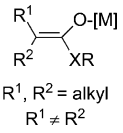
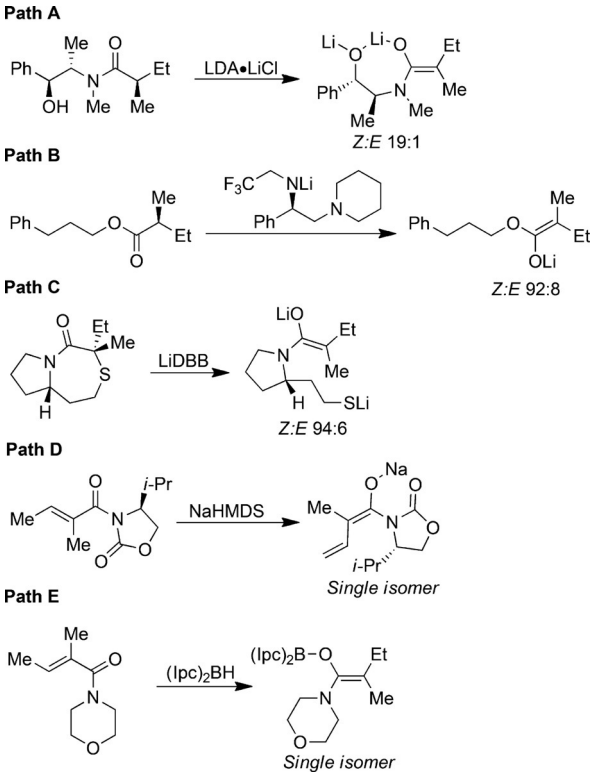


Figure 1. Stereodefined trisubstituted enolates with two different alkyl groups in an acyclic system. X: N, O; R: alkyl, acyl.

The most prominent examples reported to date for the formation of disubstituted enolates of amides and esters, although rarely used for aldol transformations, are the stereospecific enolization of enantiomerically enriched starting materials such as acyclic α-alkylbutyramides (path A, Scheme 1),[5] the double stereodifferentiation in the deprotonation of enantiomerically enriched α-branched esters with enantiomerically pure chiral lithium amides (path B, Scheme 1),[6] and ring-opening of chiral bicyclic thioglycolate lactams (path C, Scheme 1).[7] These three original methods require the preparation of enantiomerically pure sp^3 stereocenters that are subsequently enolized into stereodefined disubstituted enolates of amides and esters. The conjugate addition (not shown) or the deprotonation of α,β-unsaturated amides (path D, Scheme 1)[5c,8] and the 1,4-hydroboration reaction of α,β-unsaturated morpholine carboxamides (path E, Scheme 1)[9] constitute alternative approaches to prepare stereodefined disubstituted enolates of amides.



Scheme 1. General approach to stereodefined trisubstituted enolates. LDA: lithium diisopropylamide; LiDBB: lithium di-*tert*-butylbiphenyl; NaHMDS: sodium bis(trimethylsilyl)amide; $(Ipc)_2BH$: (−)-diisopinocamphenylborane.

It should be noted that only one report describes the formation of trisubstituted enolates of ketones (Figure 1, XR: alkyl) as intermediates on the way to aldol products with the required quaternary carbon stereocenter (in racemic form) by reaction of a nucleophile with the in situ generated ketene intermediates.[10] A different approach that avoids the issues

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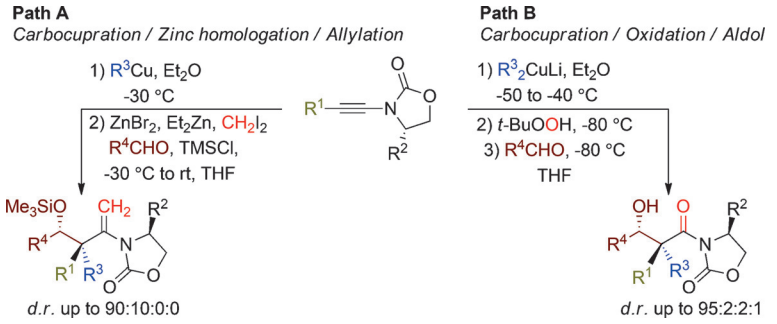
associated with enolate geometry is the use of silyl ketene imines that successfully leads to aldol surrogates.[11] Although there are many methods for the preparation of these enolates, their application to aldol additions to aldehydes as the equivalent of tetrasubstituted double bonds is rare due to retro-aldol processes. In the context of developing strategies that could answer such challenging problems while improving efficiency in synthesis, we have initially reported the combined carbometalation, zinc homologation, and allylation reaction of ynamides[12] as an aldol-surrogate approach (Scheme 2, path A) that was subsequently replaced by a sequence of carbometalation and oxidation followed by an aldol reaction (Scheme 2, path B).[13]

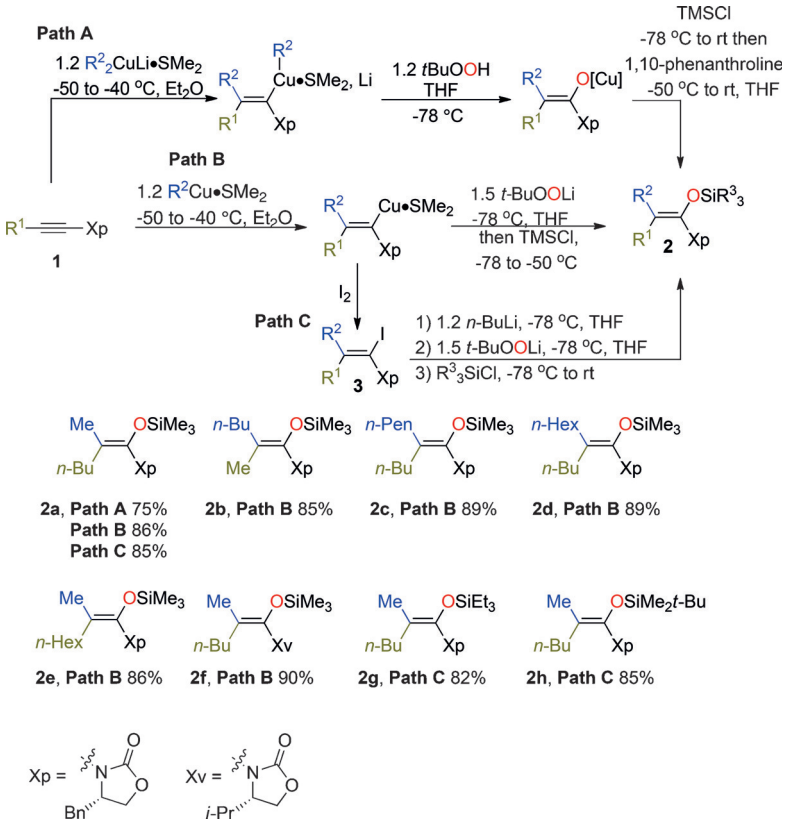
Although these strategies proved that challenging motifs such as quaternary carbon stereocenters in acyclic systems could be prepared from simple α-heterosubstituted alkynes in a single-pot operation with the concomitant creation of several new bonds,[14] the aldol reaction with aliphatic aldehydes proceeded sluggishly with only low diastereomeric ratios. Whereas Lewis base catalyzed additions of silyl ketene imines to aliphatic aldehydes proceed with good results,[15] in all other cases, useful yields and diastereoselectivities were only achieved by using α,β-unsaturated aldehydes which could eventually serve as surrogates for saturated aldehyde substrates through hydrogenation.[7,9,13] The development of a new approach to aldol products by reaction of stereodefined trisubstituted acyclic enolates with aliphatic aldehydes leading to the expected quaternary carbon stereocenters was therefore needed.

In this Communication, we report the missing piece for the diastereo- and enantioselective formation of quaternary carbon stereocenters α to carbonyl groups through an aldol reaction with aliphatic aldehydes[16] by using stereodefined disubstituted silyl ketene aminals[17] for the Mukaiyama aldol reaction.[18]

As the formation of acyclic stereodefined disubstituted silyl ketene aminals **2** (Scheme 3) represents a challenging issue by itself,[17] our first goal was to develop simple and reliable stereoselective approaches to such entities.[19] Stereodefined polysubstituted double bonds were obtained by addition of an organocuprate[20] ($R^2_2CuLi{\cdot}Me_2S$, $R^2 = Me$) to ynamide **1a** ($R^1 = Bu$)[21] and treatment of the resulting dissymmetric organometallic species with *t*BuOOH (path A, Scheme 3). As the methyl group on copper is more basic than the vinyl group, the addition of *t*BuOOH led to an in situ deprotonation of the peroxide by the methyl group, with liberation of methane and concomitant formation of a heterocuprate that underwent a 1,2-metalate rearrangement[22] to give a stereodefined copper enolate ($R^1 = Bu$, $R^2 = Me$).[13] Simple addition of TMSCl exclusively formed the expected silyl ketene aminal **2a** in 75% yield as a single isomer. It should be noted that such silyl ketene aminals are rather sensitive in the presence of copper salts and undergo decomposition when standing at room temperature. Therefore, addition of a copper scavenger such as 1,10-phenanthroline to the reaction mixture before work-up drastically improved stability and yield (see the Supporting Information). Alternatively, the carbometalation reaction can be achieved by addition of an organocopper species ($R^2Cu{\cdot}SMe_2$) that can be directly oxidized with freshly prepared *t*BuOOLi[23] to give the copper enolate that subsequently reacts with TMSCl to give the same silyl ketene aminal **2a** in a slightly better yield (86% on path B versus 75% on path A; Scheme 3).[24] By exchanging the alkyl



Scheme 2. Formation of aldol products from ynamides.

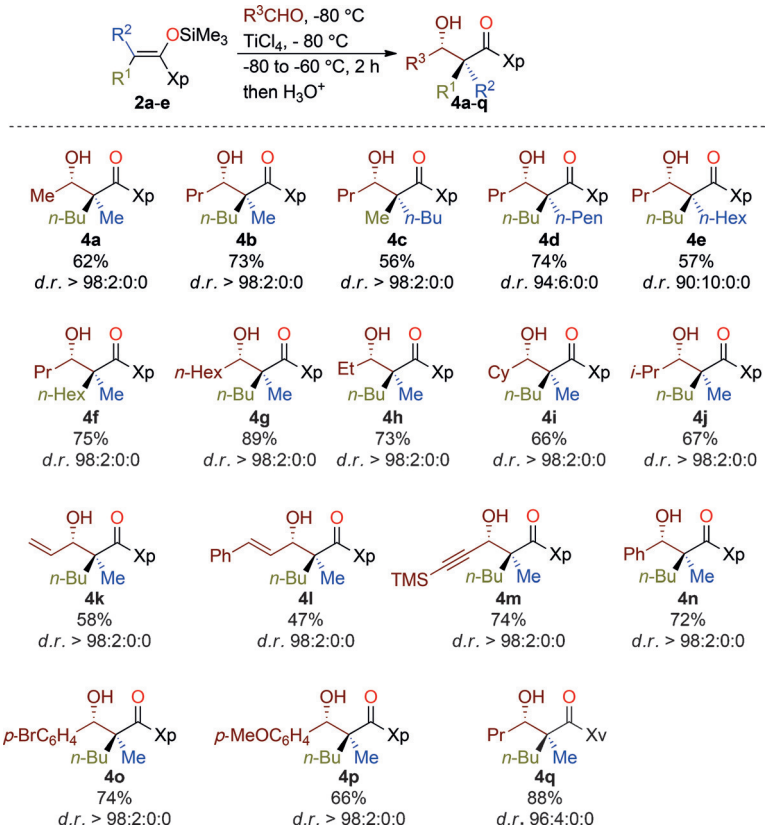


Scheme 3. Formation of stereodefined disubstituted silyl ketene aminals **2a–h**. TMSCl: trimethylsilylchloride.

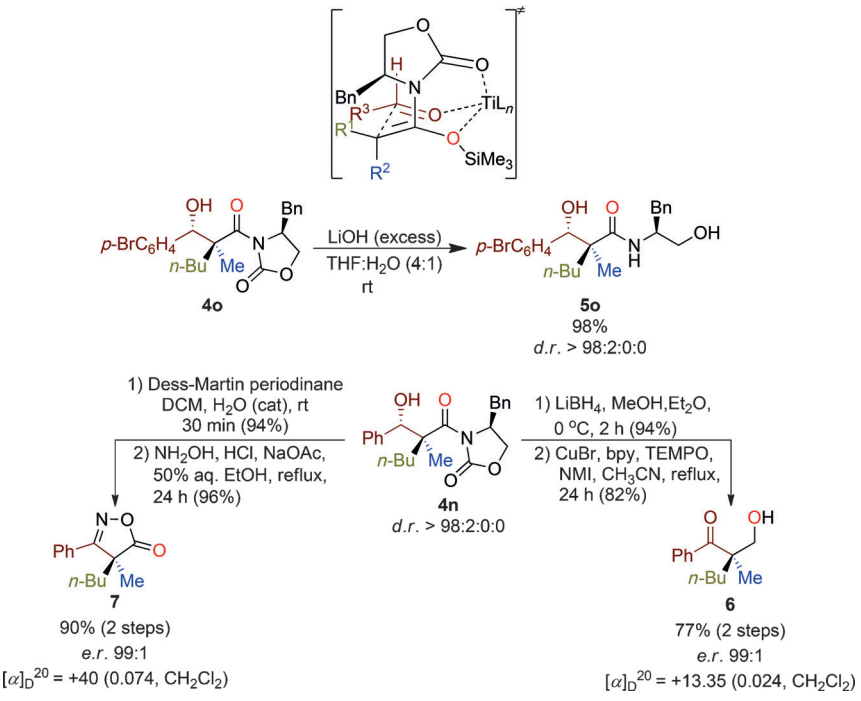
groups R^1 and R^2 present on the alkyne and the organocopper compound, respectively, and performing the same combined carbometalation–oxidation–silylation reactions, the opposite diastereomer **2b** was obtained in identical yield, still as a single isomer. Therefore, both isomers of fully substituted silyl ketene aminals **2** are easily accessible by this single-pot combined protocol and several substrates were prepared (**2a–e**) independent of the nature of the chiral ynamide **1** (as demonstrated by the formation of **2f**). When a less reactive silyl chloride such as triethylsilylchloride or *tert*-butyldimethylsilylchloride was added to the copper enolate, low yields were obtained. Therefore, more reactive stereodefined trisubstituted lithium enolates were prepared by addition of *t*BuOOLi[23] to vinyl lithium species easily obtained from **3** through iodine–lithium exchange (path C, Scheme 3).[25] In this case, trimethylsilyl ketene aminal **2a** as well as silyl ketene aminals with bulkier groups on silicon (**2g**,**h**) were obtained as single isomers in excellent yields.

Having at hand different stereodefined disubstituted silyl ketene aminals (**2a–h**), the Mukaiyama aldol reaction was tested by addition of one equivalent of $TiCl_4$ at low temperature to aliphatic aldehydes such as acetaldehyde followed by the addition of silyl ketene aminal **2a** in CH_2Cl_2 (Scheme 4).[26] To our delight, the reaction proceeded smoothly at −60 °C to give the desired aldol product **4a** with a quaternary carbon stereocenter in 62 % yield and an outstanding diastereomeric ratio of > 98:2:0:0 as determined by ^1H and ^{13}C NMR analysis of the crude reaction mixture.[27] As both diastereomers **4b** and **4c** can be easily prepared by adding either silyl ketene aminal **2a** or **2b** to butanal, we suggest that the reaction proceeds through a cyclic transition state. Various primary aliphatic aldehydes were then tested and excellent diastereoselectivities were obtained (**4a–h**; Scheme 4).

Interestingly, the longer alkyl chain R^2 is, the lower is the diastereoselectivity[28] (compare **4b**, **4d**, and **4e**), whereas the nature of R^1 and of the alkyl substituent of the aliphatic aldehyde (R^3) has no effect on the diastereoselectivity of the reaction (compare **4f**,**g**). Even α-branched aldehydes (cyclohexanecarboxaldehyde or isobutyraldehyde) or very reactive unsaturated aldehydes such as acrolein, cinnamaldehyde or 3-trimethylsilylpropynal led to the aldol products with a quaternary stereocenter in high diastereoselectivities and good chemical yields illustrating the mild conditions



Scheme 4. Formation of aldol products with quaternary carbon stereocenters. For Xp and Xv see Scheme 3.



Scheme 5. Zimmerman–Traxler transition state (top) and elimination of the oxazolidinone ring from products **4**. DCM: dichloromethane; bpy: 2,2′-bipyridine; NMI: *N*-methylimidazole.

used for this transformation (formation of **4i,j** and **4k–m**, respectively; Scheme 4). When aromatic aldehydes were treated under this Mukaiyama-type condition, aldol products (**4n–p**) were obtained with similar diastereoselectivities as previously reported.[13] When a different oxazolidinone-based chiral moiety was used (Xv instead of Xp), ratios and yields were comparable (compare **4b** with **4q**). The reaction can also be performed with a sub-stoichiometric amount of Lewis acid (20 mol%) and aldol products were obtained with similar diastereoselectivities but yields were usually lower (12–20% less). The TES and TBS silyl ketene aminals **2g,h** failed to react under our experimental conditions.

The absolute configuration of the Mukaiyama aldol products was determined by chemical correlation with an authentic sample of **4n** and by X-ray analysis of **5o**,[29] easily obtained by basic hydrolysis of the aldol adduct **4o** with LiOH (see the Supporting Information and Scheme 5), and assigned by analogy for all other products. A Zimmerman–Traxler transition state with the benzyl group of the oxazolidinone unit shielding one face of the six-membered chelate ring and the incoming aldehyde group occupying a pseudo-equatorial position can rationalize the configuration of the major isomer (Scheme 5, top).[30] Increasing the size of the alkyl group R^2 occupying a pseudo-axial position may indeed decrease the diastereoselectivity of the process as discussed in the analysis of the results shown in Scheme 4. Cleavage of the oxazolidinone moiety of **4** could be performed using reliable high-yielding transformations (Scheme 5). For instance, reduction of **4n** with $LiBH_4$, followed by a Stahl oxidation[31] of the resulting diol, provided the enantiopure ketol **6** whereas oxidation of the secondary alcohol,[32] followed by treatment with hydroxylamine, led to the chiral isoxazolone **7** with complete recovery of the chiral auxiliary in both cases.[33] The aldol product (not shown) could also be prepared through classical transformations.[13]

In conclusion, the regio- and stereoselective formation of stereodefined disubstituted silyl ketene aminals could be easily achieved through selective one-pot carbometalation–oxidation–silylation reactions. These substrates are ideal candidates for Mukaiyama aldol reactions with aliphatic aldehydes as they lead to aldol products with a quaternary carbon stereocenter α to the carbonyl group in outstanding diastereoselectivities.

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Keywords: aldols · Mukaiyama reaction · one-pot reactions · quaternary carbon stereocenters · silyl ketene aminals

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