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Z-Enolate Geometry in the Thioamide Aldol Reaction Illuminated by the 7-Azaindoline Auxiliary

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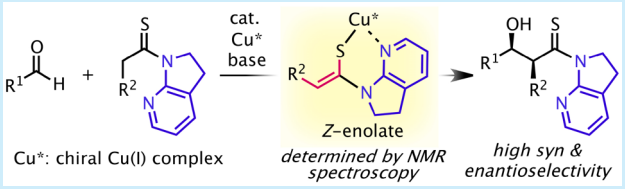
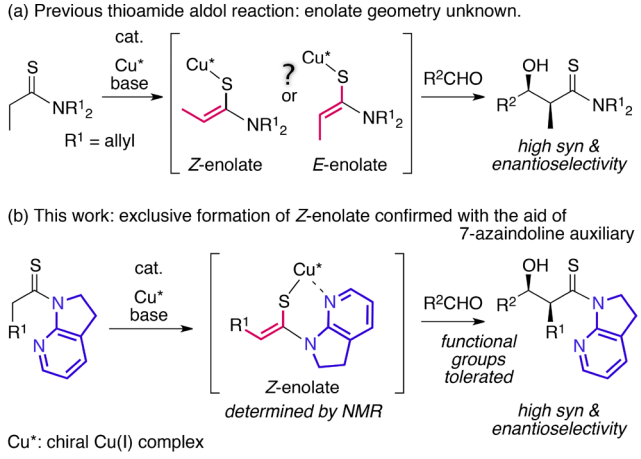
Supporting Information

ABSTRACT: *Z* or *E* enolate geometry is the primary determinant of diastereoselectivity in the aldol reaction. Although amide and thioamide enolates are anticipated to have predominantly the *E* geometry because of the intrinsic steric demand, spectroscopic confirmation of the geometry in solution has remained elusive, particularly in the realm of highly stereoselective catalytic asymmetric aldol reactions. Herein we demonstrate that the 7-azaindoline auxiliary enables direct observation of the exclusive formation of the *Z*-enolate of the thioamide en route to a highly *syn*-selective aldol reaction.



The aldol reaction, which involves coupling of acceptor carbonyls (often aldehydes) and donor carbonyls, provides ready access to synthetically versatile β-hydroxycarbonyl units.[1−3] Significant advances in the last two decades have rendered this particular reaction asymmetric, catalytic, and direct.[4,5] A direct aldol reaction, although difficult to attain, enables the direct use of donor substrates without reagent-driven preactivation processes, thus enhancing the reaction efficiency. Our group has been working to develop direct catalytic asymmetric aldol reactions using weakly acidic carbonyl compounds as aldol donors. In 2011, we disclosed thioamides as competent aldol donors incorporated in cooperative catalytic systems[6] to deliver *syn*-aldols with high enantioselectivity (Scheme 1a).[7,8] Our continuous efforts in this field later led us to identify that the 7-azaindoline auxiliary engages amides in the direct aldol reaction with high stereoselectivity.[9] Although there has been substantial progress in amide and thioamide aldol reactions from a synthetic standpoint,[10] the geometry of in situ-generated enolate species under catalytic conditions is underexplored. Direct observation of the amide enolate in solution by spectroscopic means remains elusive,[11] and determination of the enolate geometry under specific conditions with a chiral catalyst is a formidable task. Herein we report that combining thioamide chemistry with the 7-azaindoline auxiliary provided explicit evidence of the involvement of the *Z*-configured thioamide enolate in delivering *syn*-aldols (Scheme 1b). The 7-azaindoline thioamide donor accommodates various α-substituents with sufficient reactivity, thereby expanding the scope of the direct catalytic asymmetric aldol reactions of weakly acidic donors.

Scheme 1. Prior Art of the Thioamide Aldol Reaction and Confirmation of *Z*-Enolate Formation with the 7-Azaindoline Auxiliary



In the direct catalytic asymmetric aldol reaction of *N*,*N*-diallylthiopropionamide (**1**), a cooperative catalytic system comprising a chiral Cu(I) complex and LiOAr was effective, with the former activating the thiocarbonyl functionality as a soft Lewis acid and the latter deprotonating the α-proton for enolization (Scheme 2).[7] Ph-BPE is a privileged ligand in this specific reaction and uniquely competent to afford high enantioselectivity. We reasoned that thiopropionamide **2a** bearing a 7-azaindoline unit could stabilize the enolate intermediate by additional chelation to Cu(I) to dissect the geometry of the enolate.[12] 7-Azaindolinyl thiopropionamide **2a** was obtained from the parent 7-azaindolinyl amide via a standard protocol using Lawesson's reagent.[13] The initial trial of the direct aldol reaction of **2a** and hydrocinnamaldehyde (**3a**) under standard catalytic conditions ($[Cu(CH_3CN)_4]PF_6$/(*S*,*S*)-Ph-BPE/LiOAr) confirmed that **2a** shares similar reactivity with **1**, as the corresponding product **5a** was obtained with high stereoselectivity and an identical absolute configuration.

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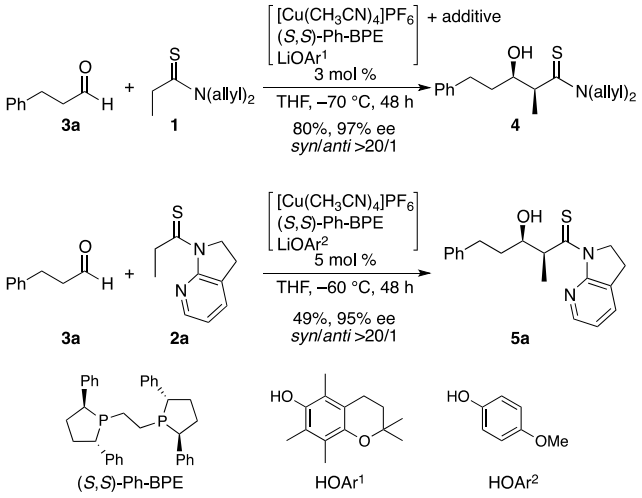
Scheme 2. Prior Art of the Thioamide Aldol Reaction and Confirmation of *Z*-Enolate Formation with the 7-Azaindoline Auxiliary



Having confirmed **2a** as a competent thioamide model with chelation capability, we next probed its interaction with the Cu(I)/(*S*,*S*)-Ph-BPE complex and the subsequent enolization process by NMR spectroscopy (Figure 1). The addition of

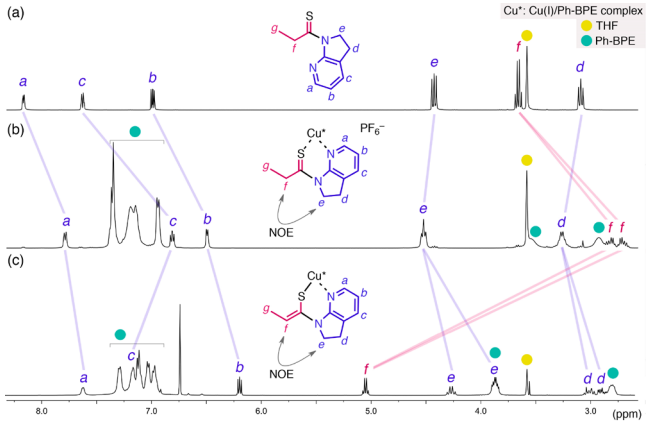


Figure 1. ^{1}H NMR spectra of 7-azaindolinyl thiopropionamide **2a** and Cu(I) complexes in THF-d_8: (a) **2a** only; (b) 1/1/1 **2a**/[Cu(CH$_3$CN)$_4$]PF$_6$/(*S*,*S*)-Ph-BPE = 1/1/1 mixture. (c) 1/1.1/1.1 **2a**/mesitylcopper/(*S*,*S*)-Ph-BPE mixture.

[Cu(CH$_3$CN)$_4$]PF$_6$ and (*S*,*S*)-Ph-BPE to a THF-d_8 solution of **2a** induced significant changes in the chemical shift that correspond to the conformational flipping of the 7-azaindoline unit for chelation to the Cu(I) complex (Figure 1a,b). The characteristic upfield shift of the α-protons (H$_f$) indicates the lack of intramolecular hydrogen bonding with the pyridyl nitrogen, which was confirmed by the NOE with the protons on the pyrroline unit (H$_e$). Subsequent addition of Li(OC$_6$H$_4$-*p*-OMe) to the thioamide **2a**/Cu(I) complex barely changed the ^{1}H NMR spectrum, presumably because enolization/reprotonation is in equilibrium and the enolate species is significantly less populated. To address this issue, irreversible enolization was attempted with mesitylcopper[14] as a highly basic Cu(I) source. In contrast to the case with Li(OC$_6$H$_4$-*p*-OMe), the thioamide **2a**/mesitylcopper/(*S*,*S*)-Ph-BPE mixture gave a different spectral pattern from the **2a**/[Cu(CH$_3$CN)$_4$]-PF$_6$/(*S*,*S*)-Ph-BPE mixture (Figure 1b,c). Indeed, the newly appearing quartet at 5.05 ppm (H$_f$) is the signature of the olefinic proton corresponding to the formation of the copper(I) enolate. Only one species was detected from the clear spectral pattern, and prominent NOE signals between the olefinic proton (H$_f$) and the protons on the pyrroline unit (H$_e$) confirmed the exclusive formation of the *Z*-configured enolate.[15] The 7-azaindoline auxiliary played a pivotal role in stabilizing the enolate and preventing the rotation of the C–N single bond, which rendered the enolate discernible by NMR spectroscopy even at room temperature.[16] The *Z*-enolate generated from mesitylcopper reacted with aldehyde **3a** at −60 °C to reproduce comparable stereoselectivity (*syn*/*anti* > 20/1, 86% ee) in the catalytic system comprising [Cu(CH$_3$CN)$_4$]-PF$_6$/(*S*,*S*)-Ph-BPE/LiOAr.[15] This observation supports the general involvement of the *Z*-enolate and a cyclic transition state to deliver *syn*-aldols in Cu(I)-catalyzed thioamide aldol reactions.[17]

7-Azaindolinyl thiopropionamide **2a** displayed a synthetically useful substrate scope (Figure 2).[18] Further optimization

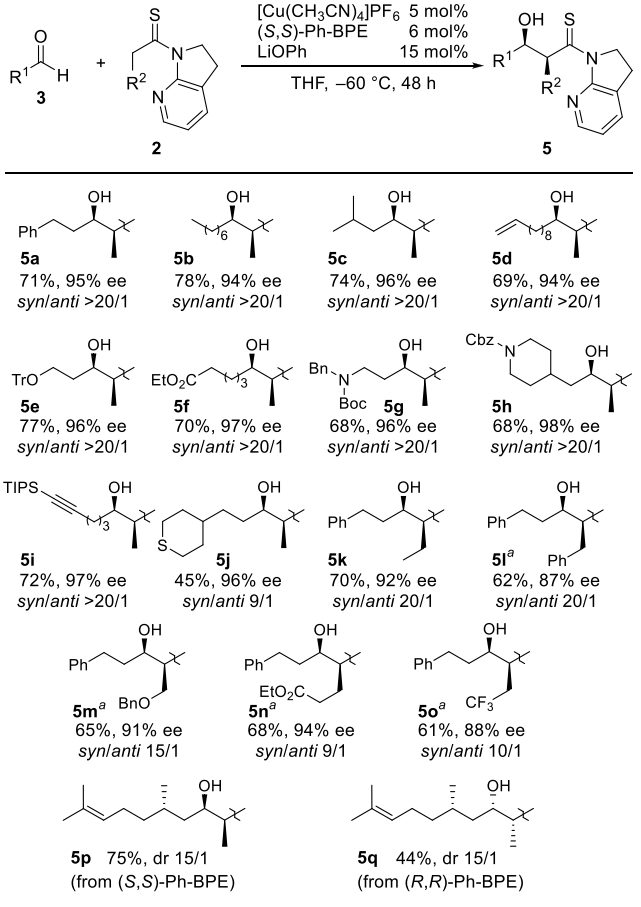


Figure 2. Substrate generality of the direct aldol reaction using 7-azaindolinyl thioamide **2**. Isolated yields are shown. [a]Reaction at −78 °C.

revealed that a slight excess of the base PhOLi with respect to the Cu(I) complex provided a better yield.[15] α-Nonsubstituted aldehydes, which are generally prone to undesired self-aldol reactions, gave *syn*-aldols **5a**–**d** without the formation of self-aldol products. Aldehydes bearing Lewis acid-sensitive or base-sensitive functionalities are applicable to the present catalysis, and an alkynyl group was tolerated (**5e**–**i**). An aldehyde with a

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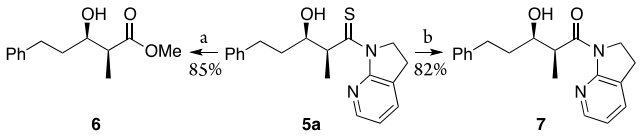
fully saturated thiopyran, a soft Lewis base that could competitively coordinate to Cu(I) complex to disturb the catalysis, was accommodated to give product **5j** with high enantioselectivity but a slightly lower yield and *syn* selectivity. The advantage of 7-azaindolinyl thioamide **2a** compared with *N,N*-diallylthioamide **1** is the engagement of various α-substituted donors in direct aldol reactions. Along with nonfunctionalized thiopropionamide and thiobutyramide (**5k** and **5l**), thioamides with an ether, ester, or trifluoromethyl group were tractable donor substrates to deliver *syn*-aldol products (**5m**–**o**).[19] The stereoselectivity was slightly eroded, but this was somewhat addressed by lowering the reaction temperature to −78 °C. The reaction with (−)-citronellal afforded the products **5p** and **5q** with similar diastereoselectivity irrespective of the *R*/*S* sense of the catalyst, indicating that the stereoselection was determined by the asymmetric environment of the catalyst via high-fidelity formation of the *Z*-enolate.[20] It is worthy of note that simple treatment of aldol product **5a** with 2 N HCl in MeOH at 60 °C converted it to the corresponding methyl ester **6** without epimerization (Scheme 3). Desulfurization with H_2O_2 in the presence of $ZrCl_4$ was another option to give 7-azaindolinyl amide **7**,[21] which is amenable to diverse functional group transformations.[12]

Scheme 3. Transformation of the Product[a]



[a]Reagents and conditions: (a) 2 N HCl/MeOH, 60 °C, 8 h, 85%; (b) $ZrCl_4$, 30% H_2O_2, rt, 1 h, 82%.

In summary, we utilized the 7-azaindoline auxiliary to probe the enolate geometry in a direct catalytic asymmetric aldol reaction of thioamides. The 7-azaindoline unit played a key role in detecting the copper(I) enolate even at room temperature, revealing the exclusive formation of a *Z*-configured enolate. Considering the generally high *syn* diastereoselectivity, a cyclic transition state is likely operative in the C–C bond-forming process with aldehydes. A range of α-substituted 7-azaindolinyl thioamides proved to be tractable latent enolates, expanding the scope of direct aldol chemistry.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04120.

Experimental procedures, spectroscopic data for new compounds, crystallographic data for **2a** and **5a′**, and NMR spectra (PDF)

Accession Codes

CCDC 1966091 and 1966092 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by e-mailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, U.K.; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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(15) See the Supporting Information for details.
(16) NMR experiments using *N*,*N*-diallylthioamide **1** resulted in complicated spectra.
(17) In view of the identical absolute configurations of aldol products **4** and **5a**, the chelated *Z*-enolate presumably dissociates prior to the aldol addition step, thereby forming a cyclic transition state with an incoming aldehyde.
(18) The absolute configuration was determined by X-ray crystallographic analysis after conversion of the product into the 3,5-dichlorobenzoate ester. See the Supporting Information for details.
(19) The geometries of the enolates derived from thioamides **2e** and **2f** (for products **5n** and **5o**) were determined to be *Z* in the same manner as in Figure 1. See the Supporting Information for details.
(20) The reaction using α-branched aldehydes was sluggish and failed to give reasonable amount of aldol products.
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