7-Azaindoline Auxiliary: A Versatile Attachment Facilitating Enantioselective C–C Bond-Forming Catalysis

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Abstract
This short review provides an overview of 7-azaindoline auxiliaries in asymmetric catalysis. 7-Azaindoline serves as a useful attachment to carboxylic acids, and the thus-formed 7-azaindoline amides are amenable to atom-economical C–C bond-forming reactions with high stereoselectivity. The attachment is used for the sake of gaining traction in promoting the reaction of interest and can be easily removed after enantioselective reactions. Both nucleophilic and electrophilic catalyses are realized with broad tolerance for functional groups, showcasing the usefulness of 7-azaindoline auxiliaries for practical and streamlined synthesis of a wide range of acyclic chiral building blocks.

1 Introduction
Given the increased demand for optically active synthons in various research fields, the focus of asymmetric catalysis has shifted from lab-scale demonstration to sophistication with a practical robustness. To access specific enantioenriched synthons of interest with rapid synthesis and overall efficiency, C–C bond-forming reactions furnishing sp3-carbon connectivity with decent control of the stereoselectivity are ideal. Our research group has focused on devising a versatile synthetic tool to access a range of broadly applicable chiral building blocks, in which the designed catalyst is solely responsible for promoting the reactions without the use of reagents. Our continued research in this context over the last 5 years has shown that 7-azaindoline is a versatile substrate attachment that allows for a variety of enantioselective reactions. This short review summarizes the utility of 7-azaindoline units in asymmetric catalysis.

2 7-Azaindoline as a Key Auxiliary
In addition to the obviously important factors, e.g. reactivity and stereoselectivity, chemoselectivity is indispensable for enabling the reaction of interest in the ensemble of chemical species bearing different functional groups. Although chemoselectivity that is solely exerted by a catalyst is ideal, it may diminish control of the chemoselectivity, leading to undesired side reactions. We searched for a substrate ‘attachment’ that: 1. would enable stabilization of the substrate itself to suppress uncontrolled reactions (side-reactions, low stereoselectivity); 2. would switch on a hidden...
3 7-Azaindoline Amide as a Pronucleophile

Based on X-ray crystallography and $^1$H NMR, the 7-azaindoline amides 2 assume an E-conformation as both a solid and in solution phase, respectively (Scheme 2a). The E-amide conformation is readily inverted to the activated form of Z-amide upon the addition of a soft Lewis acidic metal complex. The chelated structure revealed by X-ray crystallography facilitates enolization upon the combined use of a mild Brønsted base as a co-catalyst, efficiently driving direct-type aldol and Mannich-type reactions on the chiral ligand of metal cations in an asymmetric environment.1–2 A notable feature of 7-azaindoline amides 2 as enolate precursors is the wide variety of applicable α-substituents; basically, all the elements [α-alkyl (C), α-fluoroalkyl (R$^f$), α-azido (N), α-benzylxoy (O), α-halo (F, Cl, Br, I), and α-methylsulfanyl (S$^{Me}$)] used in standard organic synthesis can be installed, highlighting its particular utility for providing tailor-made chiral building blocks with the pendant α-substituent of interest. The cooperative catalytic system comprising a soft Lewis acid and Brønsted base has three variants depending on the Brønsted base: Type A: [Cu(CH$_3$CN)$_2$]PF$_6$/chiral P-ligand/Barton’s base; Type B: mesitylcopper$^{10}$/chiral P-ligand; and Type C: mesitylcopper/chiral P-ligand/phenol derivatives (Scheme 2b). Type A is an archetypal catalyst cocktail with broad competency in independent functions of the Cu(I)/P-ligand complex and Barton’s base, allowing for recognition/activation of the 7-azaindoline amide functionality and deprotonation of the activated amide, respectively. The Type B catalyst utilizes oligomeric mesitylcopper as a Brønsted base at the initial trigger of the catalysis to form a ligated Cu(I)-enolate, which undergoes C=C bond formation with C=O (aldehyde)
or C=N(imine) type electrophiles. The thus-formed Cu(I)-aldolates or Cu(I)-amides act as a soft Lewis acid/Bronsted base cooperative catalyst to drive the following catalytic cycle. The addition of phenol derivatives to the Type B catalyst mixture gives the Type C catalyst, which is characterized by a ligated Cu(I)-aryloxide complex.

Scheme 2 (a) 7-Azaindoline amide as an enolate precursor. (b) Variants of the cooperative catalyst used for nucleophilic activation of 7-azaindoline amide; (c) Structures of reagents/ligands.

3.1 α-Carbon-Substituted 7-Azaindoline Amide

The C3 propionate unit is ubiquitously found in a number of biologically active natural products and therapeutic agents. The aldol- and Mannich-type reactions offer a simple, yet powerful method for constructing carbon frameworks containing the propionate unit. The facilatated enolization capability of 7-azaindoline propionamide 2a emerged as a proficient pronucleophile in this regard, allowing for enantioselective coupling with aldehydes 4 and imines 5. The combined use of Lewis acid [chiral Cu(I) complexes] and Bronsted base (Barton’s base or phenoxides) at temperatures ranging from –40 °C to room temperature promoted the catalytic enolization of 2a and subsequent addition to electrophiles. Systematic studies revealed that the privileged ligand depended on subtle changes of the electrophiles, which likely reflects the fact that the open-transition state is operative in this catalysis. The sterics of the amide moiety prefer the formation of a Z-configured Cu(I)–enolate, where Cu(I) is coordinatively saturated and the face-selection of the electrophiles is strongly affected by the chiral ligand used. Although α-sp3 aldehydes and enals were found to be intractable, ynaals 4ynal and aromatic aldehydes 4ar exhibited high reactivity to afford the desired aldol products with high diastereo- and enantioselectivity (Schemes 3 and 4). Due to the likely involvement of the open-transition state, diverted diastereoselectivity is observed by the combination of the chiral ligand and aldehydes. (R)-Trimethoxy-Biphep (L1) was identified as a preferred ligand in the Type C catalyst to steer the high anti- and enantioselectivity to deliver propargylic alcohol 6 containing the synthetically versatile propionate unit (Scheme 3). Intriguingly, with the Type B catalyst using (S,S)-Ph-BPE (L2) as a chiral ligand, aromatic aldehydes 4ar react with 7-azaindoline propionamide 2a to give syn-configured aldol products 7.

The applicability of 7-azaindoline propionamide 2a for a Mannich-type reaction11 expands the accessible chiral building blocks containing the propionate unit. α-sp2 N-Boc imines 5 derived from aromatic aldehydes and enal exhibit good reactivity. The Type A catalyst proved optimal with L1 as a chiral ligand, which is also used in the aldol reaction with ynaals 4ynal producing anti-configured β-amino acid derivatives anti-8 (Scheme 5). The aldol and Mannich adducts share an identical absolute configuration, suggesting that the face selection of the Cu(I)–enolate complex as well as that of C=O or C=N is operative in a similar manner via an open-transition state. By switching the chiral ligand from L1 to Walphos-type ligand L3, syn-adducts syn-8 are obtained as major diastereomers with high enantioselectivity (Scheme 6). Of note, other than C3 propionamide, C2 acetamide and C4 butyramide are also competent in this catalytic Mannich protocol, albeit with somewhat lower reactivity and stereoselectivity.
3.2 α-Nitrogen-Substituted 7-Azaindoline Amide

Given the particular utility of the products as natural and unnatural α-amino acid derivatives, the α-nitrogen-functionalized acetic acid unit has broad synthetic value as a pronucleophile in enolate chemistry. Azido-functionalized 7-azaindoline amide 2b, which exhibits facile enolization capability and minimized steric bias, is best suited for this purpose. The simple Type B catalyst system, comprising mesitylcopper and (R,R)-Ph-BPE (L4), efficiently promotes the aldol reaction of ortho-substituted aromatic aldehydes 4ar-ortho and ynals 4ynal in an anti-selective manner with high enantioselectivity (Scheme 7). Face selection of the approaching aldehydes is highly sensitive to subtle changes in steric factors; aromatic aldehydes without ortho-substituents give a syn-configured product with an identical absolute configuration at the α-position under identical reaction conditions. syn-Adducts of ortho-substituted aromatic aldehydes 4ar-ortho are accessible by switching the chiral ligand from L4 to (R)-xyl-Binap L5 (Scheme 8). The diastereoselectivity is lowest with α-fluorobenzaldehyde, suggesting that the sterics are crucial for the face selection of aldehydes.

α-Trifluoromethyl yrones 10 are also incorporated as applicable electrophiles, affording densely functionalized propargylic tertiary alcohols 11 (Scheme 9). In this particular example, catalyst Types A–C failed to afford products with synthetically useful stereoselectivity, which was addressed by utilizing instead the Cu(II) complex of bisphosphine (BHA) ligands developed by Yamamoto and co-workers. Kinetic studies revealed second-order dependency on the BHA–Cu(II) complex, suggesting that the BHA–Cu(II) complex has a dual role to activate 7-azaindoline amide 2b as a Lewis acid and to deprotonate 7-azaindoline amide 2b as a Brønsted base.
Azido-functionalized 7-azaindoline amide 2b also contributes to the synthesis of 1,2-diamino acid units via a Mannich-type reaction with N-diphenylthiophosphinoyl imines 12. The Type A catalyst with (R)-xyl-Segphos L6 gave the desired Mannich adducts 13 with high anti- and enantioselectivity (Scheme 10). A soft Lewis basic thiophosphinoyl group on the imine nitrogen is essential for high stereoselectivity.

3.4 α-Fluorocarbon-Substituted 7-Azaindoline Amide

Given the established beneficial effects of introducing fluorine into active pharmaceutical ingredients, methods for fluorination have gained increasing attention. The 7-azaindoline attachment has particular utility for providing optically active fluorinated compounds with functional groups. α-Trifluoromethyl 7-azaindoline amide 2d serves as a fluorinated pronucleophile that can be coupled with N-Boc imines 5 via direct and catalytic enolization with a Type A catalyst using (R)-DIPA-Biphep ligand L7 (Scheme 12). In general, β-fluorinated carbonyl compounds are elusive conducted at room temperature using a Type A catalyst, affording syn-adducts 14 with high stereoselectivity. This reaction is particularly useful for the enantioselective synthesis of the side chain of docetaxel and paclitaxel (Ar = Ph), which are highly potent anticancer pharmaceuticals.
enolate precursors due to rapid defluorination, which is effectively circumvented for 7-azaindoline amide 2d by chelate formation with the chiral Cu(I) complex through the pyridyl nitrogen.

The Mannich reaction of α-trifluoromethyl 7-azaindoline amide with N-Boc imines 5 affords β-amino acid derivative 15 bearing an α-trifluoromethyl group at the stereogenic carbon. The identical catalytic system is competent to engage more fluorinated 7-azaindoline amide 2e in the Mannich-type reaction. The thus-produced enantioenriched adducts 16 contain the fully fluorinated propionate unit, a compound not so easily accessed by other methods (Scheme 13). It is worth noting that α-pentafluoroethyl and α-(bromo)tetrafluoroethyl groups are also tolerated in this enantioselective Mannich reaction protocol by switching chiral ligand from L7 to L6.

Although aldehydes are intractable electrophiles in the reaction with α-trifluoromethyl 7-azaindoline amide 2d, the aldol reaction with aryglyoxylic hydrates 17 proceeds smoothly to give dicarbonyl products 18 (Scheme 14).

### 3.5 α-Halogen-Substituted 7-Azaindoline Amide

The features of the 7-azaindoline enolate surrogate are best represented by α-halo 7-azaindoline amide 2f. The C-halogen bond next to the carbonyl functionality is generally labile and frequently undergoes uncontrolled dehalogenation.

Due to the stable nature of 7-azaindoline amides, the C-halogen bond of 2f and Mannich adducts 19 is intrinsically stable and undesired dehalogenation is not observed, even under the reaction conditions (Schemes 15 and 16). N-Boc imines 5 are the most suitable electrophiles in this Mannich-type reaction, which is efficiently promoted by the Type A catalyst with Walphos-type ligand L3. Similarly, face selection of aromatic imines is diverted by the presence of ortho-substituents; ortho-substituted imines prefer syn-products syn-19 and others give anti-configured products anti-19 with high enantioslectivity (Scheme 15). Aliphatic imines are successfully incorporated with a different ligand L1, albeit with slightly lower diastereoselectivity (Scheme 16).
3.6 α-Sulfur-Substituted 7-Azaindoline Amide

The remaining indispensable element commonly found in biologically active natural products and therapeutics is sulfur. α-Methylsulfanyl 7-azaindoline acetamide 2g is accommodated in direct enolization chemistry and produces sulfur-containing, optically active chiral building blocks (Scheme 17).8 Likely due to the soft Lewis basic character of the sulfur atom, a distinct catalytic system employing Ag(I) cation as a Lewis acid was identified in this specific reaction. While Ag(I)/(R,R)-Ph-BPE L4 gives an insoluble complex in THF, the addition of LiOTf leads to a homogeneous mixture containing a dimeric complex, Ag2L42(OTf)2, as the dominant species, as characterized by NMR and X-ray crystallographic analysis. The dimeric complex is in equilibrium with monomeric species, which is facilitated by the addition of the soft Lewis basic substrate α-methylsulfanyl 7-azaindoline acetamide 2g, as evidenced by ESI-MS. Interaction of the monomeric Ag(I) complex and 2g enhances the acidity of 2g en route to catalytic deprotonation by Li(OC6H4-p-OMe). The aldol reaction with aliphatic aldehydes 4 proceeds in a syn-selective fashion with high enantioselectivity, showcasing its highly chemoselective nature to in situ generate the amide enolate exclusively. Of note, this aldol protocol tolerates the reaction using aromatic aldehydes 4α, and inverted diastereoselectivity (anti) is observed (Scheme 18). The reaction proceeds much faster than with aliphatic aldehydes, and simple application of the optimal conditions results in significantly lower enantioselectivity due to an extensive retro-aldol reaction. 2-(Methylthio)ethanol (21) was identified as an effective additive that acts as a dummy product to suppress the re-entry of the product anti-20 into the catalytic cycle. With a 10-fold excess of 21 in relation to the catalyst, anti-aldol adducts anti-20 are obtained reliably with high stereoselectivity.

4 7-Azaindoline Amide as an Electrophile

4.1 Conjugate Addition of Butenolides

Besides the facilitated enolization capability driven by chelate activation through the azaindoline attachment summarized in Section 3, the identical activation mode is effective for electrophilic activation of α,β-unsaturated 7-azaindoline amide 22 (Scheme 19).16 In a similar manner, 22 prefers the E-amide conformation, as confirmed by X-ray crystallographic analysis. This conformation is also favored in solution phase, as evidenced by the unusually downfielded α-proton (Hα) due to hydrogen-bonding interactions with the pyridyl nitrogen. The switch to the Z-amide conformation is realized by the addition of the Cu(I) complex, which is now used to enhance the electrophilicity of the β-carbon in an unsaturated framework. Barton’s base in the Type A catalyst allows for deprotonative activation of pronucleophiles, and butanolides 23 bearing a variety of substituents are widely applicable for catalytic coupling with α,β-unsaturated 7-azaindoline amide 22. While (R)-xyl-Binap L5 is optimal for bulkier butanolides 23 (R ≠ H), less sterically demanding 23 (R = H) requires bulkier ligand (R)-DTBM-Segphos L9 to realize efficient traction on stereoselectivity.
4.2 1,3-Dipolar Cycloaddition Of Nitrones

Chelation of the 7-azaindoline unit to metal cations elicits enhanced reactivity of the neighboring unsaturated bond as a dipolarophile. In the 1,3-dipolar cycloaddition of nitrones 26,17 α,β-unsaturated 7-azaindoline amide 22 exhibits metal cation accelerated reactivity (Scheme 20).18 Although both Cu(II) and In(III) complexes promote the reaction, the latter using BHA ligands emerged as more effective promoters.

The subtle change in the nitrone structure affects the preferred ligand structure; aromatic nitrones afford the best stereoselectivity with saturated diphenyl-type BHA ligand 2, while unsaturated version BHA ligand 3 outperforms in the reaction with aliphatic nitrones.

5 Transformation of 7-Azaindoline Amide

From a synthetic point of view, facile removal of the 7-azaindoline attachment is critical (Figure 1). Indeed, divergent transformation is another advantage of the 7-azaindoline amide in the synthesis of versatile chiral building blocks. Reliable transformation into ketones and aldehydes by simple treatment with organometallic reagents and typical hydride reductants is also particularly important because amides sometimes suffer from undesired overalkylation or overreduction. 7-Azaindoline harnesses its chelating ability in stabilizing the tetrahedral intermediate in alklylation and reduction in a similar manner as Weinreb’s amide.19 Hydrolysis as well as solvolysis are applied via protic or Lewis acidic (CuCl) conditions to give the corresponding acids and esters for further elaboration to meet the synthetic needs.
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