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Silver-Catalyzed Dynamic Systemic Resolution of α-Iminonitriles in a 1,3-Dipolar Cycloaddition Process

Lei Hu and Olof Ramström*

A dynamic azomethine ylide system was established using Sc(OTf)$_3$ and Ag/Taniaphos as catalysts. The system was subsequently kinetically resolved in a tandem 1,3-dipolar cycloaddition process where the silver complex acted as both reaction catalyst and external selector, resulting in the formation of an exclusive pyrrolidine product in good yield and enantiopurity.

Dynamic chemistry at the constitutional level remains one of the most powerful methods for the generation and exploration of complex systems. Based on kinetically labile bonds of covalent or non-covalent nature, the spontaneous generation of systems of interconvertible adducts or complexes can be accomplished under thermodynamic control. Due to the adaptive nature of the systems, the application of internal or external pressures can lead to responsive states, where the constituents are forced to adjust to form the optimal overall arrangement. As a result of this rearrangement process, amplification of the optimal constituent(s) can take place at the expense of less favored combinations, in a primitive sense resulting in a thermodynamically controlled evolutive process.[1–3],[4–22]

Although reversibility is a cornerstone to achieve these effects, the resulting entities are inherently labile. Kinetically controlled steps can however be efficiently coupled to dynamic systems, much in the sense of common natural processes, leading to kinetic resolution of the systems, *i.e.* dynamic systemic resolution (DSR). If the kinetic steps are selective, complete amplification of the best fitting species will occur essentially regardless of the thermodynamic equilibrium.[7,17,23–29]

In addition to developing methods to explore the features and properties of complex systems *per se*, this resolution concept also enable efficient screening and identification of components and conditions of synthetic processes. We have for example more recently explored dynamic systemic resolution for asymmetric heterocycle synthesis using biocatalytic action.[30,31] The efficient construction of enantiopure and structurally diverse heterocycles is one of the most important tasks in synthetic medicinal chemistry. For instance, access to five-membered heterocycles, especially pyrrolidines, is highly desirable because of their wide presence in synthetic building blocks, natural products, and active pharmaceutical ingredients.[32–34] Representative structures include,

e.g., proline, hygrine, the antibiotic (-)-anisomycin, and the anticholinergic agent procyclidine for treatment of parkinsonism and akathisia. Herein, we describe a dynamic systemic resolution protocol to enantioenriched pyrrolidine-2-carbonitrile structures carrying four contiguous chiral centers using a combination of transimination and ylide formation/cycloaddition catalysis (Fig. 1).
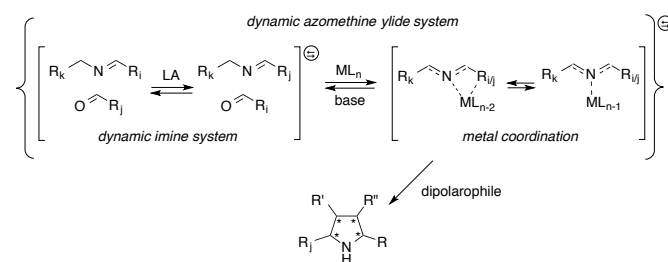

Fig. 1 Dynamic systemic resolution of metal-coordinated azomethine ylide system.

The dynamic system was generated from a sequential reversible process involving imine formation and Ag$^+$-catalyzed azomethine ylide formation in the presence of base. Ag$^+$/Cu$^+$-catalyzed 1,3-dipolar (Huisgen) cycloaddition is in this context considered to be one of the best strategies for the stereoselective synthesis of pyrrolidine derivatives due to the high selectivity with different chiral ligands and its atom-economical property.[35–40] Initially, generation of dynamic α-iminonitrile systems was investigated under Lewis acidic conditions, using glycine methyl ester and four different aldehydes. The systems were thus established using 0.1 equivalents of ZnBr$_2$ or Sc(OTf)$_3$ as transimination catalysts, respectively.[25,41] ZnCl$_2$ and Zn(OTf)$_2$ were in this case also tested, however resulting in lower rates. According to ^{1}H NMR spectroscopy, imine exchange was expectedly observed with both catalysts, where in this case Sc(OTf)$_3$ proved more efficient than ZnBr$_2$, promoting equilibrium formation within two hours. However, imine decomposition was also observed with both catalysts, where the imines were completely decomposed after an additional two hours reaction time in the presence of Sc(OTf)$_3$. The reason for this decomposition is most likely due to polymerization of the glycine
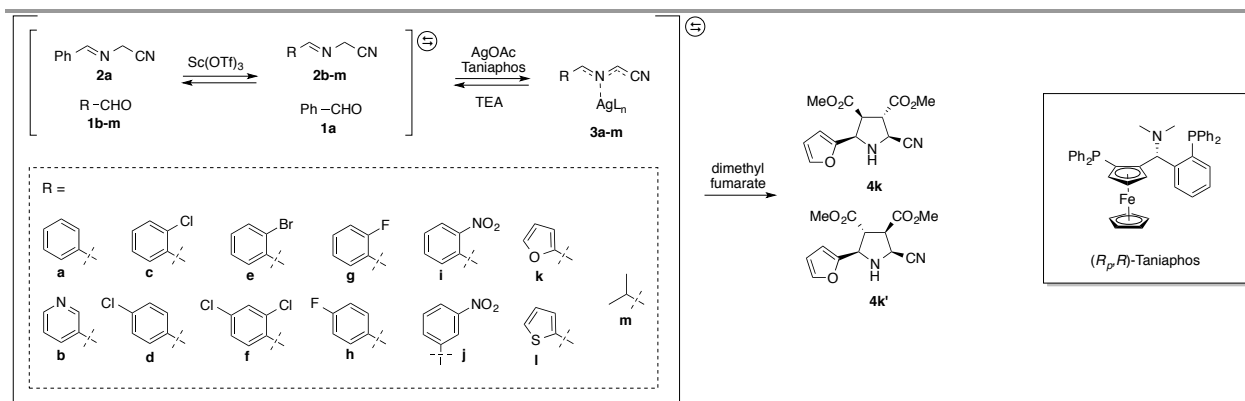
Scheme 1 Silver-catalyzed asymmetric resolution of sequential dynamic system.

methyl ester in the presence of Lewis acid. Less reactive ethyl and isopropyl esters resulted in gradual decomposition overnight, and were also not deemed suitable for the resolution process. In order to avoid any potential polymerization, 2-aminoacetonitrile was instead selected for the process. Besides promoting ylide formation, it is worth noting that 2-cyanopyrrolidine derivatives are compounds that possess important bioactivities.[42,43] The dynamic imine system was thus generated from the 2-(benzylideneamino)acetonitrile (**2a**), mixed with 1 equivalent each of 12 different aldehydes in the presence of 0.05 equivalent of $Sc(OTf)_3$ in $CDCl_3$. The equilibrium was under these conditions attained within 10 minutes, and no decomposition was observed even after overnight reaction. The stabilities of the different imines were also of comparable order, showing relatively isoenergetic behavior (Fig. 3). The dynamic α-iminonitrile system was subsequently subjected to azomethine ylide formation in the presence of triethylamine in dichloromethane in a one-pot process. The Ag(I)/Taniaphos complex,[44] which exhibits high enantioselectivity in similar reactions, was in this case used to generate the dynamic metal coordinated azomethine ylide system and catalyze the ensuing kinetic 1,3-dipolar cycloaddition. Other ligands were also evaluated, however resulting in low enantioselectivities. Upon addition of dimethyl fumarate as dipolarophile, pyrrolidines **4k** (major) and **4k'** (minor) were observed as *the only products* in 54% yield, 69:31 *dr* and 62% *ee* after 6 hours reaction time (Scheme 1).

Since the stereoselective cycloaddition process results from the coordination between the azomethine ylide and the metal/chiral ligand complex, additional coordination sites in the formed complex would potentially produce stronger binding and a more stable transition state. In the α-iminonitrile system, both monodentate and bidentate species could be formed, of which heteroaromatic imines **3b**, **3k** and **3l** in principle provide two coordination sites towards Ag^+, thus potentially enhancing their interactions with the catalyst and resulting in resolution preference in comparison to the other species in the system.

However, among the heteroaromatic imines, only imine **2k** resulted in the corresponding cycloaddition products. This can be rationalized from geometry and electronic effects, favoring metal-coordinated azomethine ylide **3k**. Potential cycloaddition with compound **2b** is thus prevented due to impaired chelation geometry with the metal center. Imines **2k** and **2l** share more similarity in geometry; however the less efficient overlap between the S and Ag^+ orbitals makes compound **2l** less preferred in the following 1,3-dipolar cycloaddition.

In order to improve the dynamic systemic resolution conditions, several reaction parameters were subsequently studied (Table 1). Among the three solvents tested: dichloromethane (DCM), diethyl

ether and THF, THF resulted in better yields and *ee*s, indicating a systemic preference for more polar solvents. NaOAc and triethylamine (TEA) were evaluated as bases, of which TEA proved superior by promoting higher enantioselectivities. The effect of the temperature was also addressed. Lowering the temperature from rt to 0 ^{o}C significantly improved the *dr* to up to 89:11 while the *ee* also increased from 72% to 92%, however requiring longer reaction time (10 h).
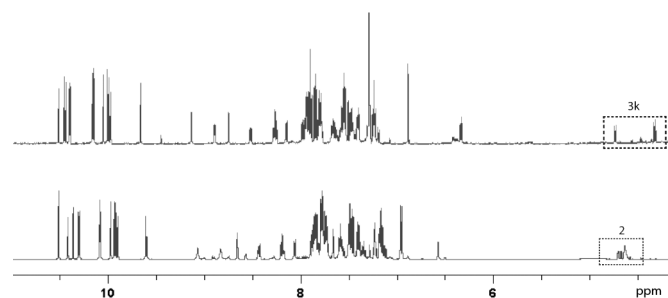
Fig. 3 ^{1}H NMR spectra of the dynamic system: bottom) at imine equilibrium; top) after resolution.

Conclusions

In summary, a sequential, dynamic metal-coordinated azomethine ylide system has been designed and developed, subsequently kinetically resolved through a coupled, silver-catalyzed 1,3-dipolar cycloaddition reaction. The silver complex acted as both reaction catalyst and external selector in the process, where additional coordination sites of the ylide could be used to selectively amplify the constituent with optimal properties. Exclusive formation of chiral 5-furyl-pyrrolidine products was thus obtained, in good yield, *dr* and *ee* following condition screening. This study represents the first example of a dynamic systemic resolution process of an imine system using a coupled, kinetic 1,3-dipolar cycloaddition reaction, thus expanding the reaction scope of DSR and offering a useful method for the selective synthesis of certain pyrrolidine derivatives.

Table 1. Screening of reaction conditions.[a]

Entry	Solvent	T (°C)	Base	Yield (%)[b]	dr (%)[c]	ee (%)[d]
1	DCM	rt	TEA	54	69:31	62
2	Diethyl ether	rt	TEA	61	90:10	82
3	THF	rt	TEA	72	78:22	89
4	THF	rt	NaOAc	76	75:25	76
5	THF	0	TEA	74	89:11	92

[a] Reaction conditions: compound **2a** (0.12 mmol), aldehyde **1b-m** (0.12 mmol), dimethyl fumarate (0.16 mmol), Sc(OTf)₃ (0.006 mmol), AgOAc (0.012 mmol), Taniaphos (0.012 mmol). [b] Isolated yield. [c] Determined by ¹H NMR from the crude **4k/4k'** mixture. [d] Determined by chiral HPLC (Chiralpak OJ column).

Notes and references

KTH - Royal Institute of Technology, Department of Chemistry, Teknikringen 30, Stockholm, Sweden; E-mail: ramstrom@kth.se

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