

Fig. 2 ^1H NMR spectra of the dynamic system: (bottom) at imine equilibrium; (top) after resolution.

were in this case also tested, however, resulting in lower rates. According to ^1H NMR spectroscopy, imine exchange was expectedly observed in both catalysts, where in this case $\text{Sc}(\text{OTf})_3$ 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 $\text{Sc}(\text{OTf})_3$. The reason for this decomposition is most likely due to polymerization of the glycine methyl ester in the presence of Lewis acid. Less reactive ethyl and isopropyl esters resulted in gradual decomposition overnight, and were also deemed not suitable for the resolution process. In order to avoid any potential polymerization, 2-aminoacetonitrile was selected instead 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 equivalents of $\text{Sc}(\text{OTf})_3$ in CDCl_3 . The equilibrium under these conditions was 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. 2). 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 $\text{Ag}(\text{I})$ -Taniaphos complex,⁴⁴ which exhibits high enantioselectivity in similar reactions, was in this case

Table 1 Screening of reaction conditions^a

Entry	Solvent	T ($^\circ\text{C}$)	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

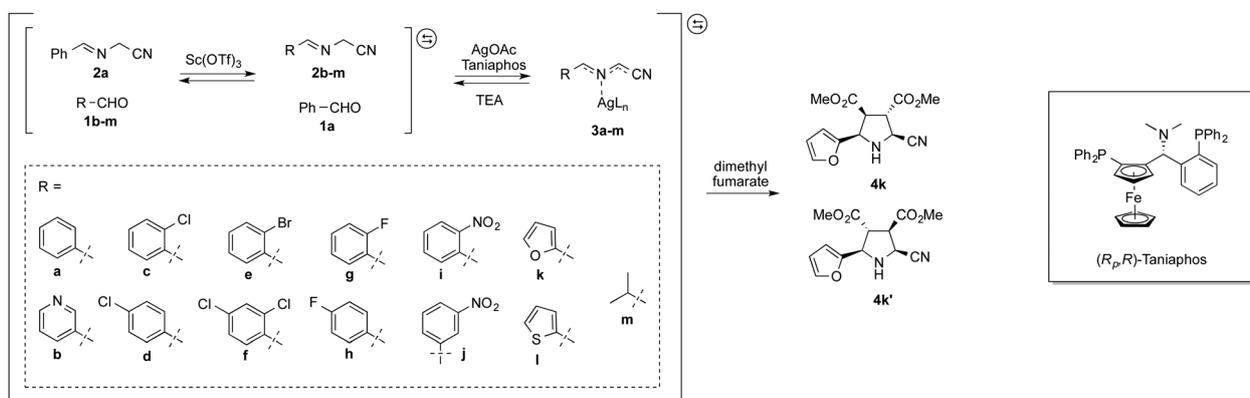
^a Reaction conditions: compound **2a** (0.12 mmol), aldehyde **1b-m** (0.12 mmol), dimethyl fumarate (0.16 mmol), $\text{Sc}(\text{OTf})_3$ (0.006 mmol), AgOAc (0.012 mmol), Taniaphos (0.012 mmol). ^b Isolated yield. ^c Determined by ^1H NMR from the crude **4k-4k'** mixture. ^d Determined by chiral HPLC (Chiralpak OJ column).

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 of 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 the geometry; however, the less efficient overlapping 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).



Scheme 1 Silver-catalyzed asymmetric resolution of sequential dynamic system.



Among the three solvents tested: dichloromethane (DCM), diethyl ether and THF, THF provided better yields and ees, 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 °C significantly improved the dr to up to 89:11 while the ee also increased from 72% to 92%, however, requiring a longer reaction time (10 h).

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 a reaction catalyst and an 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.

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Notes and references

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