ENISOCOC

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1. INTRODUCTION: Cooperatively Catalysed Isocyanoacetate ketimine Mannich Reaction

2-Imidazolines form the structural core of many biologically active compounds,[1] and are useful building blocks for the synthesis of cyclopalladated complexes, asymmetric catalysts and chiral solvating agents.[2] In addition, through hydrolytic or reductive manipulation, these heterocycles are intermediates for the synthesis of biologically significant and highly versatile α,β-diaminoacids.[3] For these and other reasons, the asymmetric synthesis of 2-imidazolines has been the focus of a number of research groups in recent years. A direct route is the catalytic asymmetric Mannich-type addition / cyclization of isocyanoacetate pronucleophiles with imine electrophiles. Highly stereoselective examples using both metal-rich and metal-free catalysts have been reported using imines derived from aldehydes (aldimines).[4] To date, however, there has been no report of the analogous but much more challenging reaction with the significantly less reactive ketone-derived imines (ketimines) despite its potential to provide a unique route to chiral 2-imidazolines possessing vicinal stereogenic centres, including a fully substituted β-carbon.

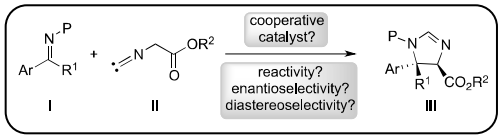


Figure 1. Concept of the Catalytic Isocyanoacetate Ketimine Mannich Reaction.

2. OBJECTIVES OF THE PROJECT

Recently, we reported the highly enantio- and diastereoselective synthesis of oxazolines[5] from isocyanoacetate pronucleophiles and aldehydes using cooperative combinations of cinchona-derived amino-phosphine precatalysts **I** and Ag(I) salts. This new binary catalyst system arose from a generally applicable design introduced by us to overcome poor reactivity profiles in numerous pronucleophile / electrophile addition reactions under bifunctional organocatalyst control. A true test of the capability of this flexible and tunable cooperative catalyst design was in attaining new reactivity and absolute and relative stereocontrol in reactions where previously there was no precedent. The catalytic asymmetric Mannich-type addition / cyclization of isocyanoacetate pronucleophiles **I** with ketimines **II** to afford imidazolines **III** indeed provided this opportunity and herein we wish to present our solution.

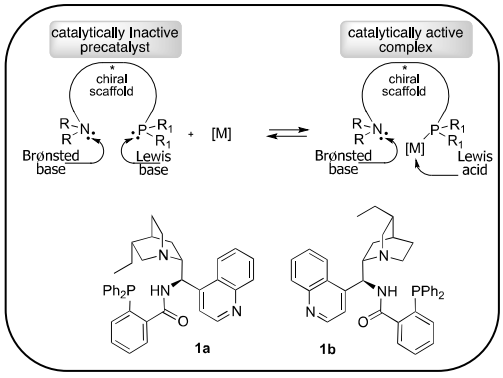


Figure 2. Concept of the Catalytic Isocyanoacetate Ketimine Mannich Reaction.

3. RESULTS

Proof of concept studies were performed on acetophenone-derived imine **3a** bearing the *N*-diphenylphosphinoyl (DPP) protecting group. Such imines are readily prepared from the parent ketone and cleavage of the DPP group from the product imidazolines **4** was anticipated to be facile under mildly acidic conditions. The sterically demanding diphenylmethylisocyanoacetate **2a** was chosen as the pro-nucleophilic component in alignment with our previous studies where stereocontrol correlated with the size of the ester substituent.

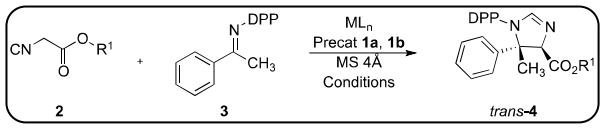


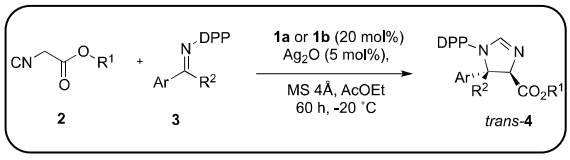
Table 1. Optimization studies.

entry	precat	ML_n(mol %)	R^1	**2**	T (°C)	solvent	Time (h)	**4**	yield(%)[a]	dr(t:c) [b]	ee [c]
1	**1a**	Ag_2O (5)	$CH(Ph)_2$	**2a**	r.t.	CH_2Cl_2	48 h	**4a**	70	71:29	72
2	**1a**	AuCl (10)	$CH(Ph)_2$	**2a**	r.t.	CH_2Cl_2	48 h	**4a**	20	14:86	2
3	**1a**	CuCl (10)	$CH(Ph)_2$	**2a**	r.t.	CH_2Cl_2	48 h	**4a**	23	43:57	2
4	**1a**	Ag_2O (5)	$CH(Ph)_2$	**2a**	r.t.	TBME	24 h	**4a**	44	37:63	70
5	**1a**	Ag_2O (5)	$CH(Ph)_2$	**2a**	r.t.	EtOAc	24 h	**4a**	68	83:17	78
6	**1a**	Ag_2O (5)	$CH(Ph)_2$	**2a**	–20	EtOAc	60 h	**4a**	70	84:16	83
7	**1b**	Ag_2O (5)	$CH(Ph)_2$	**2a**	–20	EtOAc	60 h	**4a**	78	89:11	94
8	**1a**	Ag_2O (5)	^{t}Bu	**2b**	–20	EtOAc	60 h	**4b**	89	88:12	89
9	**1a**	Ag_2O (5)	CH_3	**2c**	–20	EtOAc	60 h	**4c**	94	91:9	74
10	**1a**	-	$CH(Ph)_2$	**2a**	–20	EtOAc	120 h	**4a**	0	---	---
11	-	Ag_2O (5)	$CH(Ph)_2$	**2a**	–20	EtOAc	120 h	**4a**	83	18:82	0

[a] Combined yield of both diastereomers after FCC. [b] Diastereomeric ratio (dr) was determined by ^{1}H NMR analysis of the crude reaction mixture.

[c] Enantiomeric ratio (ee) of major diastereomer determined by chiral HPLC analysis after deprotection

Initially, a silver oxide (5 mol%) / cinchonine-derived amino-phosphine **1a** (20 mol%) catalyst system was examined in dichloromethane as solvent at room temperature. A 2:1 ratio of precatalyst to metal ion ratio was chosen to minimize any competing background reaction.[5] Pleasingly the *trans*-imidazoline product, *(4S,5R)*-**4a**, was obtained with significant diastereo- and enantiocontrol (Table 1, entry 1; 71:29 dr, 72% ee). A metal[6,7] salt screen confirmed silver (rather than gold or copper) to be the best match for **1a** (Table 1, entries 1-3). A solvent survey revealed ethyl acetate as the preferred choice in terms of both diastereo- and enantiocontrol (Table 1, entries 1, 4 and 5). Lowering the temperature of the reaction to –20 °C was found to be beneficial for enantioselectivity (Table 1, entry 6; 84:16 dr, 83% ee) and employment of pseudoenantiomeric **1b** in lieu of **1a** afforded the enantiomeric product *(4R,5S)*-**4a**, as expected, but pleasingly with enhanced enantio- and diastereoselectivity (Table 1, entry 7; 89:11 dr, 94% ee). The bulky *tert*-butylisocyanoacetate was also reactive and afforded the major *trans*-imidazoline product *(4S,5R)*-**4b** in better yield and enantioselectivity (Table 1, entry 8; 89% yield, 88:12 dr, 89% ee). In contrast, use of methyl isocyanoacetate **2c** resulted in diminished enantioselectivity for the major *trans*-diastereomer *(4S,5R)*-**4c** (Table 1, entry 9; 94 % yield, 91:9 dr, 74% ee). Finally, control experiments confirmed the importance of *the combination of both silver salt and aminophosphine precatalyst*; without the silver salt there was no reaction (Table 1, entry 10); without the precatalyst, enantiocontrol was (naturally) absent, the reaction was significantly slower and diastereoselectivity in favour of the *cis*-diastereomer predominated (Table 1, entry 11, 18:82 dr).



With the optimized reaction conditions established, the scope of the reaction was assessed by probing changes to both the aryl and alkyl groups of the ketimine in reactions with bulky isocyanoacetates **2a** and **2b** (Table 2).

With *tert*-butylisocyanoacetate pronucleophile **2b** in the presence of cinchonidine-derived amino phosphine precatalyst **1b**, good to excellent diastereoselectivities and excellent enantioselectivities (94-99% ee) were observed for DPP-protected *para*-substituted arylmethyl ketimines possessing both electron-withdrawing and electron-releasing groups (Table 2, entries 2-6). With the same set of electrophiles under the control of cinchonine-derived amino phosphine precatalyst **1a** enantiomeric imidazoline products were obtained as anticipated but the magnitude of the enantioselectivity was diminished across the series. Importantly, ethyl phenyl ketone-derived imine **3f** was also an excellent substrate and afforded the *trans*-imidazoline product

Table 2. Scope of the reaction.

entry[a]	Ar	R^2	2	4	yield (%)[b]	dr[c],[c] t:c	ee [d]
1	Ph	CH_3	2a	a	70(78)	84:16(89:11)	94(83)
2	Ph	CH_3	2b	b	92(89)	99:1(88:12)	96(89)
3	*p*-NO_2Ph	CH_3	2b	d	87(89)	8:2(99:1)	95(73)
4	*p*-ClPh	CH_3	2b	e	96(80)	96:4(95:5)	93(79)
5	*p*-CH_3Ph	CH_3	2b	f	78(88)	9:1(96:4)	98(75)
6	*p*-OCH_3Ph	CH_3	2b	g	87(81)	75:25(94:6)	99(70)
7	Ph	Et	2b	h	85(89)	88:12(97:3)	97(82)
8	*p*-NO_2Ph	CH_3	2a	i	97(88)	6:4(86:14)	88(75)
9	*p*-ClPh	CH_3	2a	j	83(81)	86:14(94:6)	97(89)
10	*p*-CH_3Ph	CH_3	2a	k	96(89)	95:5(91:9)	96(88)
11	*p*-OCH_3Ph	CH_3	2a	l	96(84)	73:27(88:12)	98(88)
12	Ph	Et	2a	m	80(93)	81:19(88:12)	90(58)
13	*m*-OCH_3Ph	CH_3	2a	n	82(72)	74:26(75:25)	96(96)
14	*o*-OCH_3Ph	CH_3	2a	o	96(79)	8:2(77:23)	97(96)
15	*p*-Ph-Ph	CH_3	2a	p	97(88)	9:1(82:18)	97(85)
16	*o*-BrPh	CH_3	2a	q	97(74)	99:1(99:1)	96(89)
17	*p*-BrPh	CH_3	2a	r	98(84)	78:22(82:18)	94(88)
18	*o*-FPh	CH_3	2a	s	95(98)	84:16(8:2)	96(86)
19	*p*-FPh	CH_3	2a	t	95(74)	83:17(91:9)	96(91)
20	3,5-$(CF_3)_2$Ph	CH_3	2a	u	81(91)	78:22(83:17)	86(75)
21	3,4-Cl_2Ph	CH_3	2a	v	84(91)	85:15(86:14)	95(84)

[a] The data in parentheses refer to reactions performed with precatalyst **1a**. [b] Combined yield of both diastereomers after flash column chromatography. [c] Diastereomeric ratio (dr) was determined by ^{1}H NMR analysis of the crude reaction mixture. [d] Enantiomeric ratio (ee) of the major diastereomer determined by chiral HPLC analysis after DPP removal.

4h in high yield and good diastereoselectivity (Table 2, entry 7). With catalyst **1b** the major *trans*-diastereomer was obtained with an excellent ee of 97% whereas the antipode was afforded with 82% ee using precatalyst **1a**.

Using diphenylmethylisocyanoacetate pronucleophile **2a** a wide range of ketimines with various electron-donating and electron-withdrawing substituents in *ortho*, *meta* and *para* positions were good substrates. As with the *tert*-butylisocyanoacetate pronucleophile, enantioselectivities for the major *trans*-diastereoisomer with precatalyst **lb** were superior (typically between 5-15 ee percentage points) to those obtained with precatalyst **1a** and ranged from 88% ee with *p*-nitrophenylmethyl ketimine (table 2, entry 8) to 98% ee with DPP-protected *p*-methoxyphenylmethylketimine (table 2, entry 11). DPP-protected phenylethyl ketimine was reactive and gave the reaction product **4m** in 80% yield, 81:19 dr and in 90% ee for the major *trans*-diastereoisomer under the control of **1b**. In total 14 substrates proved effective, giving rise to excellent enantio- and good diastereoselectivities for the *trans*-diastereomers when amino phosphine precatalyst **1b** was used with silver oxide (Table 2, entries 8-21).

Although 20 mol% loading of the precatalyst was found to be convenient for assessing substrate scope, in a further demonstration of the practicability of this reaction precatalyst **1b** loading was reduced from 20 mol% to 10 mol%, 5 mol% and 1 mol% at –20 °C (Table 3, entries 1-3). The observed diastereo- and enantioselectivities, were comparable to those obtained at 20 mol% loading, however the reaction speeds became prohibitively slow. In order to reduce the reaction time, the temperature was increased to 0 °C. Pleasingly this was possible without significant detriment to either enantio- or diastereocontrol (Table 3, entries 4-6).

Table 3. Catalyst loading studies.

entry	**1b** (mol%)	Ag_2O(mol%)	T(ºC)	time(h)	yield(%)[a]	dr[b] t:c	ee[c]
1	10	2.5	–20	60	87	94:6	96
2	5	1.25	–20	120	78	93:7	96
3	1	0.25	–20	160	77	92:8	95
4	10	2.5	0	24	89	89:11	95
5	5	1.25	0	60	87	86:14	93
6	1	0.25	0	60	58	87:13	94

[a] Combined yield of both diastereomers after FCC. [b] The dr was determined by ^{1}H NMR analysis of the crude. [c] The ee of major diastereomer determined by chiral HPLC analysis after deprotection.

In addition to the high yields and stereoselectivities, the advantage of our described method lies in the simple and efficient synthetic manipulation of the direct Mannich products into desirable building blocks and motifs. Protecting group-free 2-imidazolines were obtained by the efficient cleavage of the diphenylphosphoryl group[8] using a 1.0 M solution of HCl in dichloromethane at room temperature (Table 4, entries 1-21). The deprotection was effected without compromise to either diastereo- or enantiopurity. Importantly, the absolute stereochemistry of the imidazolines was confirmed by single crystal X-ray analysis of **5w**, a *N*-4-bromophenylsulphonyl derivative of **5r**.

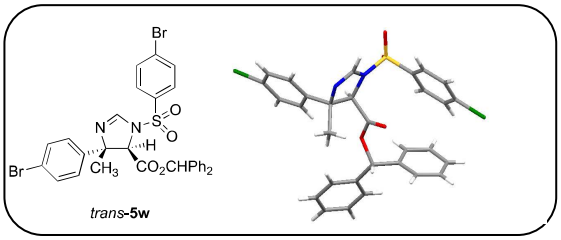
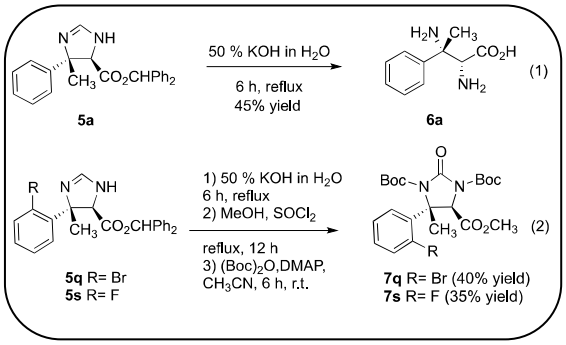


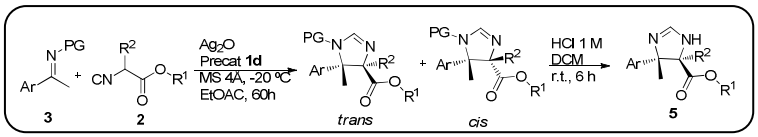
Figure 3. X-Ray of compound **5w**



Furthermore, treatment of the unprotected 2-imidazoline **5a** with a 50% aqueous solution of potassium hydroxide gave α,β-diaminoacid[9] **6a** without compromising stereochemistry (Scheme 2, Eq (1)). To probe the relative configuration of the α,β-diaminoacid, the 1,2-diamine of compounds **5q** and **5s** were transformed into the cyclic urea derivatives **7q** and **7s** using excess Boc_2O and DMAP (Scheme 2, Eq (2)). Absolute stereochemistry was confirmed by single crystal X-Ray analysis of **7q.**

For more challenging, we decided to study the synthesis of imidazolines with two contiguous quaternaries stereocenters. A variety of aromatic ketimines, including heteroaromatic ketimines proved effective, giving rise to excellent enantio- and diastereoselectivities for *trans* diastereomers (entries 1-12, table 4), aliphatic ketimines were also well tolerated giving the best result in terms of enantioselectivity (entry 13, table 4). When cyclic ketimines were used, imidazolines including a spiro function were obtained in good enantioselectivity and excellent diastereoselectivity (entries 14-16, table 4). In order to generalize the reaction, it was performed with bulkiers aryl and alkyl groups in the side chain of the isocyanate. In this study, was observed that ethyl and bencyl group were well-tolerated giving same range values in terms of diastereoselectivity and slightly lower enantioselectivities than the alanine analogue (entries 17-22, table 4). In the other hand, with phenyl group *cis* diastereomer was obtained as the major one, and enantiselectivity dropped to 77 (entry 23, table 4).

Table 4. Scope of the reaction.



entry	precat	ML_n	R^1	R^2	Ar	T(ºC)	Solvent	Time(h)	Yield(%)	Dr(t:c) [a]	Ee [b]
1	1d	Ag_2O	*t*Bu	CH_3	*p*-Ph-Ph	-20	EtOAc	60 h	60 / 88	100:0	88
2	1d	Ag_2O	*t*Bu	CH_3	*p*-F-Ph	-20	EtOAc	60 h	99 / 84	100:0	89
3	1d	Ag_2O	*t*Bu	CH_3	*o*-F-Ph	-20	EtOAc	60 h	95 / 62	100:0	88
4	1d	Ag_2O	*t*Bu	CH_3	*p*-Cl-Ph	-20	EtOAc	60 h	94 / 71	100:0	86
5	1d	Ag_2O	*t*Bu	CH_3	*p*-NO_2-Ph	-20	EtOAc	60 h	84 / 79	100:0	72
6	1d	Ag_2O	*t*Bu	CH_3	*p*-Br-Ph	-20	EtOAc	60 h	89 / 74	97:3	86
7	1d	Ag_2O	*t*Bu	CH_3	*p*-OCH_3-Ph	-20	EtOAc	60 h	91 / 75	100:0	90
8	1d	Ag_2O	*t*Bu	CH_3	*o*-OCH_3-Ph	-20	EtOAc	60 h	30 / 67	100:0	85
9	1d	Ag_2O	*t*Bu	CH_3	3-pyridinyl	-20	EtOAc	60 h	80 / 85	100:0	85
10	1d	Ag_2O	*t*Bu	CH_3	2-pyridinyl	-20	EtOAc	60 h	92 / 67	100:0	86
11	1d	Ag_2O	*t*Bu	CH_3	2-furyl	-20	EtOAc	60 h	87 / 84	100:0	88
12	1d	Ag_2O	*t*Bu	CH_3	2-tiophenyl	-20	EtOAc	60 h	40 / 89	100:0	83

13	1d	Ag_2O	*t*Bu	CH_3	Cyclohexyl	0	EtOAc	60 h	64 / 76	100:0	98
14	1d	Ag_2O	*t*Bu	CH_3		-20	EtOAc	60 h	67 / 94	100:0	75
15	1d	Ag_2O	*t*Bu	CH_3		-20	EtOAc	60 h	96 / 92	100:0	81
16	1d	Ag_2O	*t*Bu	CH_3		-20	EtOAc	60 h	98 / 77	100:0	84
17	1d	Ag_2O	CH_3	Bn	Ph	-20	EtOAc	60 h	80 / 75	98:2	81
18	1d	Ag_2O	*i*Pr	Bn	Ph	-20	EtOAc	60 h	92 / 78	98:2	71
19	1d	Ag_2O	*t*Bu	Bn	Ph	-20	EtOAc	60 h	75 / 86	100:0	80
20	1d	Ag_2O	Bn	Et	Ph	-20	EtOAc	60 h	89 / 84	99:1	84
21	1d	Ag_2O	*i*Pr	Et	Ph	-20	EtOAc	60 h	80 / 84	100:0	84
22	1d	Ag_2O	*t*Bu	Et	Ph	-20	EtOAc	60 h	75 / 79	100:0	90
23	1d	Ag_2O	CH_3	Ph	Ph	-20	EtOAc	60 h	62 / 92	18:82	77

[a] Diastereomer ratio (Dr) was determined by ^1H NMR analysis.; [b] Determined by chiral HPLC analysis after conversion to *N*-deprotected-2-imidazoline.

In order to postulate the catalyst activation code and to further understand the role of precatalyst **1d**, we carried out modifications on **1d** in the amide function and the phosphine group. During these studies, when free-amide function was changed to an ester function or *N*-methyl-amide no reaction was observed (entries 2 and 3, table 5); with this we can conclude that the presence of a hydrogen bond is essential for the reactivity. When phosphine group was removed, reaction was not observed neither (entry 4, table 5), however when an external source of phosphine was added in the reaction, imidazoline was observed but in lower yield and very poor enantioseletivity (entry 5, table 11); this indicates that the presence of phosphine in the pre-catalyst is very important for reactivity and enantioselectivity. Finally, the relative stereochemistry at C-8 and C-9 was investigated. For this purpose precatalys **5,** with the inverted stereochemistry at C-9 (with respect to **1d**) was prepared; notably, a very poor yield and poor enantioselectivity was observed (entry 6, table 5) probing that the relative orientation of chiral pocket between the bridgehead nitrogen and the amide has a very important role in terms of enantioselectivity and reactivity (figure 4).

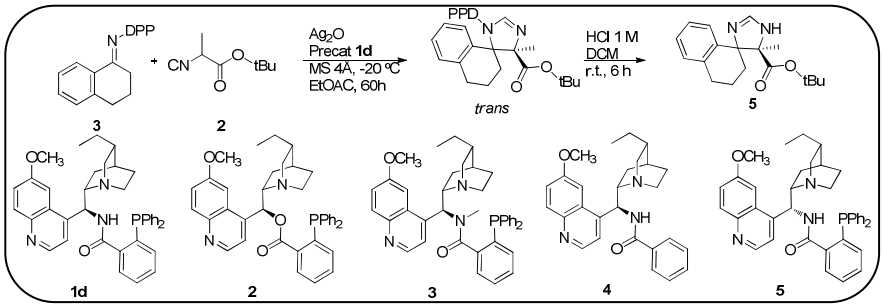


Table 5. Catalyst activation code study.

entry	precat	ML_n	T (ºC)	Solvent	Time (h)	Yield(%)	Dr(t:c) [a]	Ee [b]
1	1d	Ag_2O	-20	EtOAc	60 h	88	100:0	75
2	2	Ag_2O	-20	EtOAc	96 h	n.r.	---	--
3	3	Ag_2O	-20	EtOAc	96 h	n.r.	---	--
4	4	Ag_2O	-20	EtOAc	72 h	n.r.	---	--
5	**4**+PPh_3	Ag_2O	-20	EtOAc	72 h	40	100:0	6
6	5	Ag_2O	-20	EtOAc	72 h	5	100:0	30

[a] Diastereomer ratio (Dr) was determined by ^1H NMR analysis.; [b] Determined by chiral HPLC analysis after conversion to *N*-deprotected-2-imidazoline.

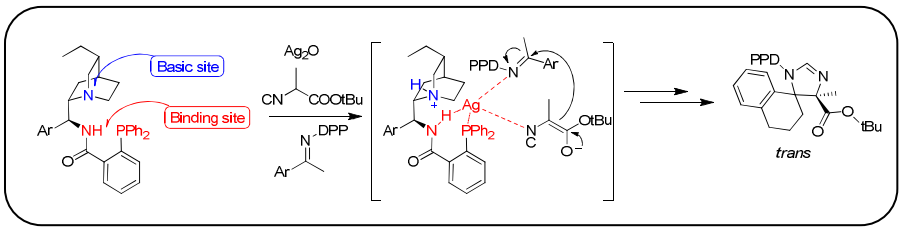


Figure 4. Postulated catalyst activation code.

4. CONCLUSIONS

In conclusion, in this project we have developed an efficient and general, diastereo- and enantioselective method for the synthesis of highly functionalised 2-imidazolines, possessing a fully substituted β-stereocenter through a Mannich type reaction of isocyanoacetate pronucleophiles and ketimines using a silver and aminophosphine binary and cooperative catalyst system. Furthermore, highly functionalised 2-imidazolines two contiguous quaternary centers have been achieved. We have also demonstrated that chiral unprotected 2-imidazolines and α,β-diaminoacids can be easily obtained from the protected 2-imidazoline reaction products. Further investigations to extend this study to the asymmetric synthesis of oxazolines with at least one quaternary centers have been started and are underway.

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