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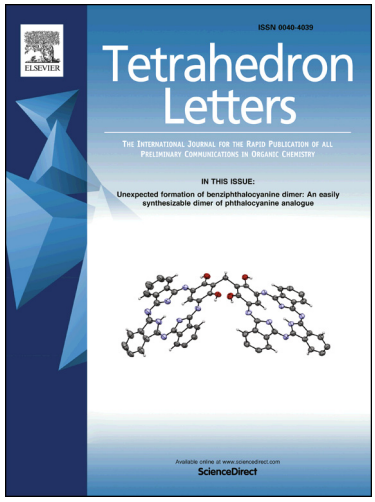

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Cu^{II}-catalysed asymmetric 1,3-dipolar cycloaddition of azomethine ylides with a chiral ferrocene-derived P,N-Ligand

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ABSTRACT

A ferrocene-derived P,N-heterodonor ligand was effectively used in a $Cu(OAc)_2.H_2O$-catalysed asymmetric 1,3-dipolar cycloaddition of azomethine ylides with maleate derivatives, affording cycloadducts with high yields (up to 96%), diastreoselectivities (>99 dr), and enantioslectivities (up to 99% ee).

1. Introduction

The addition of 1,3-dipoles to dipolarophiles for the synthesis of five member rings is considered one of the most efficient and powerful approaches for the preparation of different heterocycles.[1] Over the past decades, among heterocycles, pyrrolidine derivatives have received a great deal of capital attention. The reaction between azomethine ylides and α,β-unsaturated carboxylic acid derivatives constitutes a reliable approach to the straightforward synthesis of highly substituted pyrrolidine derivatives.[2] Since the pioneering work of Grigg in which methyl acrylate was used as the first α,β-unsaturated carboxylic acid derivative in an enantioselective 1,3-dipolar cycloaddition (1,3-DCA),[3] various dipolarophiles have been extensively investigated for the 1,3-DCA, varying from standard mono- or double-activated α,β-unsaturated carboxylic acid derivatives (such as acrylates, vinyl sulfones, maleates, fumarates, fumarodinitriles, and maleimides) to more complicated and challenging alkenes, paving the way to the synthesis of structurally diverse pyrrolidine derivatives.[4]

The reaction of azomethine ylides generated from α-iminoesters **1** and maleate ester derivatives is a useful strategy to generate pyrrolidines bearing up to three ester groups and four stereogenic centres. The regioselectivity of this reaction has been fully studied; *endo* selectivities were reported by the groups of Zhou,[5a] Hu,[5b] Zheng,[5c] Wang,[5d] Cossío,[5e] Gao,[5f] Legault,[5g] and Carretero[5h] using Ag(I)/P,S-ligands, Cu(I)/ImiferroS/Et_3N, Ag(I)/PPFAPhos/Et_3N, Ag(I)/CA-AA-AmidPhos, Cu(I)/PF-L-Proline/Et_3N, Cu(I)/TF-BiphamPhos/Et_3N, Ag(I)/*N*-acyl iminoimidazolium ylide proligands and Cu(I)/Fesulphos/Et_3N complexes respectively; on the other hand, the groups of Kobayashi,[6a] Raghunath,[6b] and Cossío[5e] reported high *exo* selectivities using AgHMDS/(*R*)-DTBM-SEGPHOS, Cu(I)/N,P-ligands/DBU and Cu(I)/PF-D-Proline/Et_3N complexes, respectively.

Recently, our group has synthesised new chiral N,P oxazolinylferrocene ligand **L1** (siloxane-FOXAP) and used it in the asymmetric 1,3-dipolar cycloaddition of azomethine ylides with β-CF_3-β,β-disubstituted nitroalkenes affording *exo*-trifluoromethylated pyrrolidine derivatives in excellent diastereo and enantioselectivities (>98:2 dr and >99.9 ee, respectively).[7] We have reported that Cu(II)/K_2CO_3/**L1** is an efficient chiral catalytic system for the asymmetric 1,3-DCA of azomethine ylides with alkylidene malonates

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and that *endo* tricarboxylated pyrrolidine analogues are obtained in excellent enantioselectivities (up to 99 %ee).[8] We intended to investigate

the performance of different ferrocene ligands including **L1** in the asymmetric catalysed 1,3-DCA of azomethine ylides with fumarate **2a** and maleate **2b-c** ester derivatives(Fig. 1).

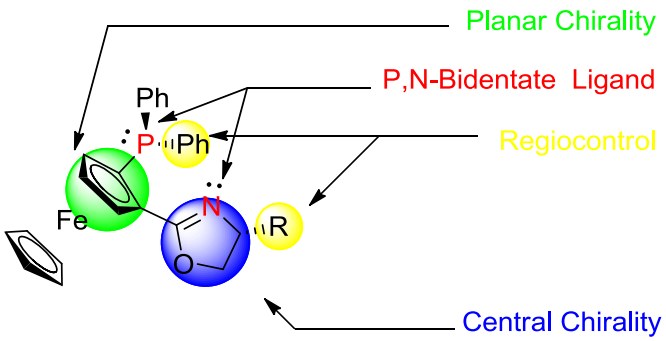


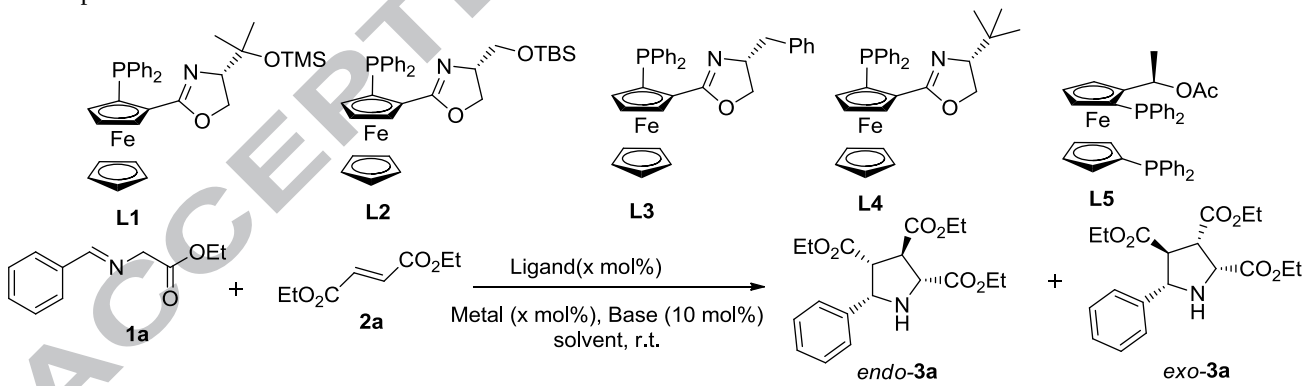
Figure 1. Structure of N,P oxazolinylferrocene ligands

2. Results and discussion

First, we investigated the 1,3-DCA of benzaldehyde Schiff base derivatives of glycine ethyl ester (**1a**) with diethyl fumarate (**2a**) in the presence of the chiral complex (10 mol%) prepared from $Cu(OAc)_2.H_2O$ and different ferrocene ligands, using diisopropylethylamine (DIPEA) as base in THF at room temperature. Our investigation revealed that the reaction afforded quantitatively the desirable cycloadduct in the presence of **L1**, albeit with moderate stereoselectivities (entry 1, Table 1). Encouraged by these promising results, siloxane-FOXAP **L1** was selected as the ligand of choice for further metal, solvent and base screening.

Copper salts showed a significant effect on the reaction; in the presence of $Cu(OAc)_2.6H_2O$, a mixture of diastereomers (*endo/exo*=9:1) was obtained in 95% yield and low enantioselectivity [40% ee (*endo*)] (entry 1, Table 1). The nature of the solvent used in the 1,3-DCA reaction proved to have a remarkable influence in both catalytic activity and enantioselectivity. Thus, the yields dropped dramatically when ether and acetonitrile were used as solvents (entries 9 and 10, Table 1) and cycloadduct **3a** was not detected when the reaction was performed in toluene (entry 11, Table 1). Instead, the reaction proceeded smoothly in dry DCM at room temperature and both diastereomers were obtained equally ($dr_{endo/exo}$= 1:1) in good yield, and with excellent enantioselectivity for the *endo*-cycloadduct **3a** (*endo*-**3a** 92% ee, entry 8, Table 1).

Table 1. Optimisation of the reaction conditions[a]



Entry	Ligand/Metal	x (mol%)	Solvent	Base (10 mol%)	T (°C)	Yield (%)[b]	dr[c]	ee (%)[d]	
								endo	*exo*
1	**L1**/$Cu(OAc)_2.H_2O$	10	THF	DIPEA	r.t.	95	9:1	40	0
2	**L2**/$Cu(OAc)_2.H_2O$	10	THF	DIPEA	r.t.	n.r.	-	-	-
3	**L3**/$Cu(OAc)_2.H_2O$	10	THF	DIPEA	r.t.	23	1:1	29	15
4	**L4**/$Cu(OAc)_2.H_2O$	10	THF	DIPEA	r.t.	45	2:1	39	3
5	**L5**/$Cu(OAc)_2.H_2O$	10	THF	DIPEA	r.t.	n.r.	-	-	-
6	**L1**/$CuBF_4$	10	THF	DIPEA	r.t.	55	1:1	35	5
7	**L1**/$Cu(ClO_4)_2.6H_2O$	10	THF	DIPEA	r.t.	54	1:1	30	0
8	**L1**/$Cu(CH_3CN)_4ClO_4$	10	THF	DIPEA	r.t	79	1:1	50	10
9	**L1**/$Cu(CH_3CN)_4ClO_4$	10	Ether	DIPEA	r.t.	35	1:1	−72	−10
10	**L1**/$Cu(CH_3CN)_4ClO_4$	10	CH_3CN	DIPEA	r.t.	45	4:1	−63	−48
11	**L1**/$Cu(CH_3CN)_4ClO_4$	10	Toluene	DIPEA	r.t.	n.r.	-	-	-

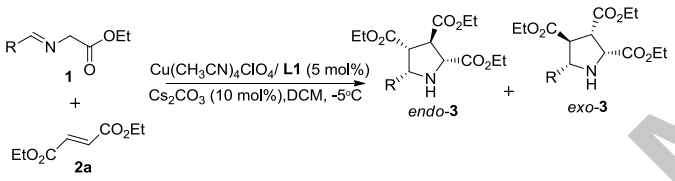
12	**L1**/$Cu(CH_3CN)_4ClO_4$	10	DCM	DIPEA	r.t.	75	1:1	92	50
13	**L1**/$Cu(CH_3CN)_4ClO_4$	10	DCM	K_2CO_3	r.t	80	1:1	86	29
14	**L1**/$Cu(CH_3CN)_4ClO_4$	10	DCM	CH_3CO_2Na	r.t	20	1:1	90	45
15	**L1**/$Cu(CH_3CN)_4ClO_4$	10	DCM	Cs_2CO_3	r.t	65	1:1	94	29
16	**L1**/$Cu(CH_3CN)_4ClO_4$	5	DCM	Cs_2CO_3	r.t	66	1:1	95	30
17	**L1**/$Cu(CH_3CN)_4ClO_4$	5 (4)[e]	DCM	Cs_2CO_3	-5	71 (69)[e]	1:1 (1:1)[e]	96 (93)[e]	30(30)[e]
18	**L1**/$Cu(OAc)_2.H_2O$	5	DCM	TEA	-5	70	3:1	91	73

[a]Reaction conditions: **1a** (0.8 mmol), **2a** (1.2 mmol), ligand **1** (10 mol%) and base (10 mol%) in 2.0 mL solvent at room temperature overnight.

[b]Isolated yield. [c]Determined by chiral HPLC. [d]Determined by chiral HPLC. [e]Catalyst loading (4 mol%)

We next investigated the effect of base additives. Cs_2CO_3 was found to be the best base additive, superior to all other organic and inorganic bases tested, such as DIPEA, K_2CO_3, and CH_3CO_2Na (entries 12–15, Table 1). Lowering the amount of catalyst loading to 5 mol% did not affect significantly the yield or enantioselectivity of the reaction (entry 16, Table1). However, reducing both the catalyst loading (5 mol%) and the temperature of the reaction (−5 °C), slightly increased the yield (71%) and enantioselectivity (96% ee) of *endo*-cycloadduct **3a** (entry 17, Table 1). Instead, we observed that Schiff base derived from 2-naphthaldehyde provided good to excellent enantioselectivities for both *endo*- and *exo*-**3e** diasteromers (98% and 70% ee, respectively)**,** albeit with low diastereoselectivity (dr $_{endo/exo}$= 1:1, entry 3, Table 2). Similarly, low diastereoselectivities were previously reported by the teams of Gao[9b] and Kobayashi[9a] when fumarate ester derivatives were used as activated olefins. After column chromatography separation of the diastereomeric mixtures of **3b** and **3e**, their stereochemistry was confirmed by comparing to spectroscopic (^{1}H NMR, *J* values and NOESY spectrum) and chromatographic data already well-established in the literature (see the Supporting Information).[10-11]

Table 2. Asymmetric 1,3-DCA of **1** with diethyl fumarate **2a**[a]



Entry	Substrate (R)	Product	Yield[b] (%)	dr[c]	ee (%)[d] *endo*	ee (%)[d] *exo*
1	**1b** (*p*-BrC_6H_4)	**3b**	94	1:1	83	19
2	**1c** (*p*-Me C_6H_4)	**3c**	86	1:1	81	-
3	**1d** (2-naphthyl)	**3e**	91	1:1	98	70

[a]Reaction conditions: **1a** (0.8 mmol), **2a** (1.2 mmol), $Cu(CH_3CN)_4ClO_4$ (5 mol%), ligand **L1** (5mol%) and Cs_2CO_3 (10 mol%) in 2.0 mL DCM at −5 ℃.

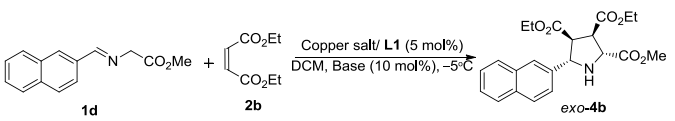
[b]Isolated yield.

[c]Determined by ^{1}H NMR spectroscopy of the crude product.

[d]Determined by chiral HPLC.

Following the unsuccessful attempts to improve the diastereoselectivities, we continued our investigation by switching the nature of the dipolarophile from diethyl fumarate (**2a**) to diethyl maleate (**2b**) (Table 3). The results in the Table 1 indicate that $Cu(OAc)_2.H_2O$ exhibits better diastereoselectivity (dr$_{endo/exo}$= 9:1) than $Cu(CH_3CN)_4ClO_4$ (entries 1 and 4, Table 1). Based on the observation that the nature of copper salt influences drastically the stereoselectivities, the reaction of **1d** and **2b** gave exclusively the *exo*-cycloadduct **4b** (dr$_{exo/endo}$ >99, entries 3 and 5, Table 3) when $Cu(OAc)_2.H_2O$ was used as salt instead of $Cu(CH_3CN)_4ClO_4$. The reaction proved to be highly sensitive to the base additive. Thus, the use of DIPEA and *t*BuOK resulted in decreased yields and enantioselectivities (54−85% and 63−65% ee, respectively, entries 4 and 5, Table 3). Instead, in the presence of Et_3N (entry 3, Table 3), **4b** was obtained in excellent yield and diastereo- and enantioselectivity (96%, dr$_{exo/endo}$ >99 and 96% ee, respectively).

Table 3. Optimization of 1,3-DCA between **1d** and diethyl maleate **2b**[a]



Entry	Metal	Base	Yield[b] (%)	dr[c]	ee (%) (*exo*)[d,e]
1	$Cu(CH_3CN)_4ClO_4$	Cs_2CO_3	90	65:35	75
2	$Cu(OAc)_2.H_2O$	Cs_2CO_3	91	90:10	84
3	$Cu(OAc)_2.H_2O$	Et_3N	96	>99:<1	96
4	$Cu(OAc)_2.H_2O$	*t*BuOK	85	20:1	63

5	$Cu(OAc)_2.H_2O$	DIPEA	54	>99:<1	65

[a]Reaction conditions: **1d** (0.8 mmol), **2b** (1.2 mmol), copper salt (5 mol%), ligand **1** (5mol%) and base (10 mol%) in 2.0 mL DCM at −5 ℃.

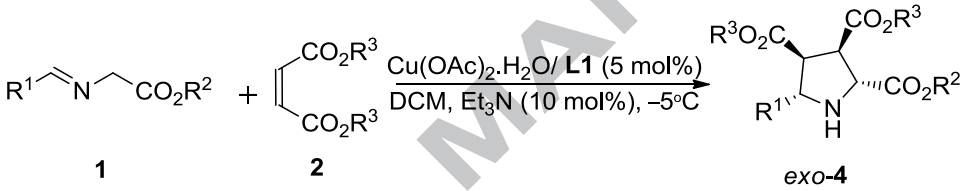
[b]Isolated yield.

[c]Determined by ^{1}H NMR spectroscopy.

[d] Determined by chiral HPLC.

With the optimal reaction conditions in hand, we examined the scope of the substrates and the results are summarised in Table 4. First, several Schiff bases derivatives of glycine methyl ester were screened against diethyl maleate (**2b**) in the presence of Cu(II)/**L1** complex. High to excellent yields of exclusive *exo*-adducts were obtained exclusively in most cases (except for entries1 and 11: $dr_{exo/endo}$ =20:1, Table 4). The nature and the position of the substituents on the phenyl group of the Schiff base proved to have a remarkable influence in both catalytic activities and stereoselectivities. Thus, electron-withdrawing substituents in *para*- or *meta*-positions on the aromatic ring, such as halogens or amino groups, gave almost identical results to iminoester **1a**, and the desired products were obtained quantitatively in excellent enantio and diastereoselectivities (89−95% yield, 91−95% ee and >99 dr, respectively; entries 2, 4, 6, 10 and 12, Table 4). On the other hand, under the same reaction conditions the reactions did not reach completion when bromo, methoxy and chloro *meta*-substituted substrates were used, and the corresponding cycloadducts **4hb**, **4ib**, and **4lb** were obtained in lower yields (40−65%; entries 7, 8, and 11, Table 4). 2-Naphthyl and 1-bromo-2-naphthyl substituted substrates **1d** and **1f** performed well, giving *exo*-pyrrolidine derivatives in high yields and enantioselectivities (75−96% and 91−96% ee, respectively; entries 3, 5 and 16, Table 4). The highest ee (99%) was obtained with *N*-(4-nitrobenzylidene) glycine methyl ester **1o** (entry 14, Table 4). Unfortunately, Schiff bases derived from salicylic aldehyde derivatives (**1q-s**) were not suitable for the 1,3-DCA reaction, probably because the free hydroxyl group inhibits the catalytic activity of the chiral complex.

.**Table 4**: Cu-catalysed asymmetric 1,3-DCA: scope of azomethine ylides and maleate ester derivatives[a]



1 **2** *exo*-**4**

Entry	R^1/ R^2	R^3	Adduct	Yield[b] (%)	dr[c]	ee[d] (%)
1	Ph/Me (**1a**)	Et (**2b**)	**4ab**	63	20: 1	91
2	*p*-Br C_6H_4/Me (**1b**)	Et (**2b**)	**4bb**	90	>99:<1	91
3	2-naphthyl/Me (**1d**)	Et (**2b**)	**4db**	96	>99:<1	96
4	*p*-F C_6H_4/Me (**1e**)	Et (**2b**)	**4eb**	94	>99:<1	91
5	1-Br-2-naphthyl/Me (**1f**)	Et (**2b**)	**4fb**	81	>99:<1	91
6	*p*-ClC_6H_4/Me (**1g**)	Et (**2b**)	**4gb**	90	>99:<1	90
7	2,4-di-ClC_6H_3/Me (**1h**)	Et (**2b**)	**4hb**	65	>99:<1	82
8	*o*-Br C_6H_4/Me (**1i**)	Et (**2b**)	**4ib**	55	>99:<1	92
9	2,4-di-F-C_6H_4/Me **(1j)**	Et (**2b**)	**4jb**	91	>99:<1	95
10	*m*-BrPh /Me **(1k)**	Et (**2b**)	**4kb**	95	>99:<1	81
11	2,3-di-MeO-C_6H_3/Me **(1l)**	Et (**2b**)	**4lb**	40	20:1	83
12	*p*-$N(CH_3)_2C_6H_4$/Et **(1m)**	Me(**2c**)	**4mc**	89	>99:<1	95
13	Ph/Et **(1n)**	Me(**2c**)	**4nc**	65	>99:<1	92
14	*p*-$NO_2C_6H_4$/Et **(1o)**	Me(**2c**)	**4oc**	95	>99:<1	>99
15	Ph/Me **(1p)**	Me(**2c**)	**4pc**	60	>99:<1	65
16	2-naphthyl/Me **(1d)**	Me(**2c**)	**4dc**	75	20: 1	91
17	*o*-OHC_6H_4/Me (**1q**)	Et (**2b**)	—	n.r.	—	—
18	3-Br-2-OH-C_6H_3/Me (**1r**)	Et (**2b**)	—	n.r.	—	—
19	3-NO_2-2-OH- C_6H_3/Me (**1s**)	Et (**2b**)	—	n.r.	—	—

[a]All the reactions were carried out under the optimised reaction conditions: 5 mol % of $Cu(OAc)_2.H_2O$, 5 mol % of **L1**, and 10 mol % of Et_3N in DCM at −5 °C overnight.

[b]Isolated yields after column chromatography.

[c]Determined by ^{1}H NMR spectroscopic analysis of the crude product.

[d] Determined by chiral HPLC.

We rationalised the regioselectivity of this reaction, based on our previously proposed computational model.[8]

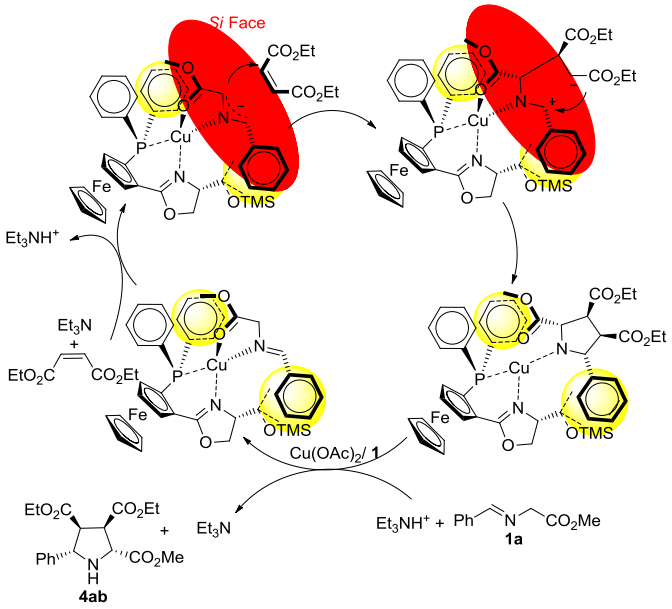


Figure 2. Proposed transition state leading to the major *exo* product **4**

The azomethine ylide, generated from the α-imino ester, coordinates to the Cu(II) catalyst in a distorted tetrahedral geometry. In this complex, the ylide adopts an orientation in which the electrostatic and steric repulsion between the phenyl rings linked to the phosphorus atom and the aromatic ring of the azomethine ylide are minimized as shown in Fig. 2. In the adopted geometry, the *Re* face of the azomethine ylide is shielded by the phenyl and trimethylsilyl groups (shown in yellow). Therefore, we postulated that the *Si* face is more accessible for the nucleophilic attack on the activated alkene **2b** affording exclusively the *exo*- pyrrolidine derivatives **4.**

3. Conclusion

In conclusion, $Cu(OAc)_2.H_2O$ siloxane-FOXAP complex was found to be an efficient catalyst for the asymmetric 1,3-dipolar cycloadditon of azomethine ylides with dimethyl maleate giving the cycloadducts in high *exo*-selectivities (up to >99 dr) and good to excellent enantioselectivities (up to 99% ee). Studies regarding further applications of these ferrocenyl P,N-ligands in other type of asymmetric reactions are currently in progress.

4. Experimental

4.1. General methods

All reactions were performed under an atmosphere of argon using oven-dried glassware. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Bruker Avance DRX 500 spectrometer. ^{1}H chemical shifts are reported in □ ppm relative to $CHCl_3$ (7.26 ppm), ^{13}C chemical shifts are reported relative to the central peak of $CDCl_3$ (77.0 ppm). Data are reported either as: s = singlet, d = doublet, dd =double doublet, t = triplet, q = quartet, m = multiplet, br = broad, coupling constants are given in Hz. High resolution mass spectra (HRMS) experiments were performed on an Agilent 6520 UHD Accurate-Mass Q-TOF LC/MS system. IR spectra were recorded on a Bruker Alpha-p spectrometer. Reactions were monitored by thin layer chromatography (TLC) using silica gel plates. Flash column chromatography was performed over silica gel (200-300 mesh).

The enantiomeric excess (ee) of the products was determined by HPLC using Daicel Chiralpak OJ-H, AD-H and ChiralcelOD-H columns with 2-propanol/hexane as eluent

4.2. General procedure for the Cu(II)-catalysed 1,3-DCA reactions

$Cu(OAc)_2.H_2O$ (7.9 mg, 0.04 mmol) and Ligand **1** (23.4 mg, 0.04 mmol) were added under argon to a 10 mL Schlenk tube, containing activated 4 Å MS. Freshly distilled anhydrous DCM (1 mL) was added into the tube and the resulting mixture was stirred for 60 min at room temperature. The reaction mixture was cooled to 0 °C and α-imino ester **1** (0.8 mmol), olefins **2b** or **2c** (1.2 mmol) and Et_3N (10 µL, 0.08 mmol) were added subsequently. The reaction mixture was stirred overnight at −5 °C. The reaction was monitor by TLC and upon completion the mixture was passed through a short column of silica gel and the diastereomeric ratio (*exo/endo*) was determined by ^{1}H NMR spectroscopic analysis of the crude product. The pure adducts were then purified by column chromatography on silica gel (200-300 mesh).

4.3. Characterization data of product

All the products were characterized by ^{1}H NMR, ^{13}C NMR, HRMS
(ESI) and IR. The copies of NMR and HRMS charts were reported in Supplementary Data.

*4.3.1. (2R,3R,4S,5S)-3,4-diethyl2-methyl 5-phenylpyrrolidine-2,3,4-tricarboxylate (**4ab**)*

Yellow sticky oil: Yield 63%; ee = 91%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (d, *J* = 7.4 Hz, 2H), 7.32 (t, *J* = 7.3 Hz, 2H), 7.26 (q, *J* = 7.1 Hz, 1H), 4.68 (d, *J* = 6.6 Hz, 1H), 4.38 (s, 1H), 4.16 (dd, *J* = 13.9, 6.9 Hz, 2H), 4.10 (q, *J* = 7.1 Hz, 2H), 3.79 (s, 3H), 3.60 (dd, *J* = 6.9, 3.8 Hz, 1H), 3.24 (t, *J* = 7.9 Hz, 1H), 2.77 (br, 1H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.21 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.10, 171.16, 171.09, 128.50, 127.70,

126.98, 64.67, 61.95, 61.30, 60.96, 54.42, 52.52, 49.89, 14.05. IR (KBr) υ 2982, 1731, 1439, 1372, 1267, 1178, 911, 729, 700 cm^{-1}. HRMS Calcd. For $C18H24NO6^+$ $[M+H]^+$:350.1604; found: 350.1588. HPLC (Chiralpak AD-H column, hexane/2-propanol = 70/30, flow rate = 1 mL/min) t_R = 9.48 min, 12.98 min.

4.3.2 (2R,3R,4S,5S)-3,4-diethyl2-methyl 5-(4-bromophenyl) pyrrolidine-2,3,4-tricarboxylate (**4bb**)

Brown sticky oil: Yield 90%; ee = 91%; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.4 Hz, 2H), 7.35 (d, *J* = 8.4 Hz, 2H), 4.63 (d, *J* = 7.6 Hz, 1H), 4.32 (d, *J* = 5.1 Hz, 1H), 4.14 (qd, *J* = 7.1, 3.7 Hz, 2H), 4.08 (qd, *J* = 7.1, 1.4 Hz, 2H), 3.76 (s, 3H), 3.56 (dd, *J* = 8.5, 5.6 Hz, 1H), 3.15 (t, *J* = 8.2 Hz, 1H), 2.75 (br, 1H)1.23 (t, *J* = 7.1 Hz, 3H), 1.18 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.05, 171.00, 170.81, 140.85, 131.47, 128.84, 121.43, 63.75, 61.76, 61.33, 61.02, 54.29, 52.49, 49.70, 14.05. IR (KBr) υ 2982, 1730, 1486, 1439, 1373, 1176, 1009, 910, 729 cm^{-1}. HRMS Calcd. For $C18H23BrNO6^+$ $[M+H]^+$:428.0709; found: 428.0690. HPLC (Chiralpak AD-H column, hexane/2-propanol = 70/30, flow rate = 1 mL/min) t_R = 13.15 min, 14.38 min.

4.3.3 (2R,3R,4S,5S)-3,4-diethyl2-methyl 5-(naphthalen-2-yl) pyrrolidine-2,3,4-tricarboxylate (**4db**)

Colorless oil: Yield 96%; ee = 96%; ^1H NMR (500 MHz, $CDCl_3$) δ 7.97 – 7.41 (m, 7H), 4.58 (d, *J* = 12.4 Hz, 1H), 4.31 (d, *J* = 6.8 Hz, 1H), 4.36 – 4.05 (m, 4H), 3.81 (s, 3H), 3.64 (dd, *J* = 41.9, 9.6 Hz, 1H), 3.53 (s, 1H),, 2.94 (s, 1H), 1.29 (t, *J* = 6.3 Hz, 3H), 1.15 (t, *J* = 6.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.13, 172.09, 171.22, 135.40, 133.10, 132.97, 127.98, 127.89, 127.56, 126.22, 126.05, 125.63, 65.49, 63.34, 61.56, 60.76, 53.71, 52.65, 51.13, 14.19, 13.42. IR (KBr) υ 2962, 1732, 1433, 1368, 1203, 1013, 818, 741, 551cm^{-1}. HRMS Calcd. For $C22H26NO6^+$ $[M+H]^+$:400.1760 ; found: 400.1680. HPLC (Chiralpak OD-H column, hexane/2-propanol = 80/20, flow rate = 0.5 mL/min) t_R = 31.11 min, 34.46 min.

4.3.4 (*2R,3R,4S,5S*)-3,4-diethyl2-methyl 5-(4-fluorophenyl) pyrrolidine-2,3,4-tricarboxylate (**4eb**)

Light yellow oil: Yield 94%; ee = 90.6%; ^1H NMR (500 MHz, $CDCl_3$) δ 7.45 – 7.39 (m, 2H), 6.97 (t, *J* = 8.3 Hz, 2H), 4.64 (d, *J* = 7.3 Hz, 1H), 4.31 (d, *J* = 3.2 Hz, 1H), 4.16 – 4.11 (m, 2H), 4.07 (dd, *J* = 13.9, 6.8 Hz, 2H), 3.76 (s, 3H), 3.58 – 3.53 (m, 1H), 3.15 (t, *J* = 8.1 Hz, 1H), 2.75 (br, 1H), 1.23 (t, *J* = 7.1 Hz, 3H), 1.17 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.10, 172.11, 171.07, 163.20, 161.24, 137.40, 128.71, 128.65, 115.26, 115.09, 63.77, 63.77, 61.76, 61.76, 54.39, 52.45, 49.74, 13.99. IR (KBr) υ 2983, 1730, 1605, 1509, 1373, 1179, 1094, 1016, 836, 731 cm^{-1}. HRMS Calcd. For $C18H23FNO6^+$ $[M+H]^+$:368.1509; found: 368.1342. HPLC (Chiralpak OJ-H column, hexane/2-propanol = 70/30, flow rate = 1 mL/min) t_R = 9.08 min, 14.31 min.

4.3.5 (*2R,3R,4S,5S*)-3,4-diethyl 2-methyl5-(1-bromonaphthalen-2-yl) pyrrolidine-2,3,4-tricarboxylate (**4fb**)

Brown oil: Yield 81%; ee = 90.6%; ^1H NMR (500 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.4 Hz, 1H), 7.90 (d, *J* = 8.4 Hz, 1H), 7.78 (dd, *J* = 13.3, 8.4 Hz, 2H), 7.54 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.2 Hz, 1H), 5.42 (s, 1H), 4.55 (d, *J* = 5.1 Hz, 1H), 4.16 (dt, *J* = 13.2, 6.6 Hz, 4H), 3.81 (s, 3H), 3.60 (t, *J* = 8.2 Hz, 1H), 3.34 (dd, *J* = 7.5, 4.0 Hz, 1H), 2.91 (br, 1H), 1.22 (dd, *J* = 10.7, 6.8 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.13, 171.76, 170.44, 139.85, 132.16, 128.15, 128.03, 127.44, 127.35, 126.53, 125.62, 122.99, 64.36, 61.93, 61.21, 53.97, 52.47, 48.89, 14.07. IR (KBr) υ 2982, 1731, 1438, 1373, 1259, 1179, 1027, 908, 819, 513 cm^{-1}. HRMS Calcd. For $C22H25BrNO6^+$ $[M+H]^+$:480.0845; found: 480.0825. HPLC (Chiralpak AD-H column, hexane/2-propanol = 70/30, flow rate = 1 mL/min) t_R = 11.73 min, 17.70 min.

4.3.6 (2R,3R,4S,5S)-3,4-diethyl2-methyl 5-(4-chlorophenyl) pyrrolidine-2,3,4-tricarboxylate (**4gb**)

Yellow oil: Yield 90%; ee = 90.4%; ^1H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.2 Hz, 1H), 7.26 (d, *J* = 8.2 Hz, 1H), 4.64 (d, *J* = 7.2 Hz, 1H), 4.32 (d, *J* = 2.7 Hz, 1H), 4.18 – 4.11 (m, 1H), 4.11 – 4.04 (m, 1H), 3.77 (s, 1H), 3.56 (dd, *J* = 8.2, 5.2 Hz, 1H), 3.15 (t, *J* = 8.1 Hz, 1H), 2.70 (br, 1H), 1.24 (t, *J* = 7.1 Hz, 2H), 1.19 (t, *J* = 7.1 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.09, 171.05, 170.86, 128.53, 128.49, 63.73, 61.78, 61.34, 61.02, 54.36, 53.52, 52.50, 49.73, 14.03. IR (KBr) υ 2983, 1729, 1603, 1506, 1365, 116, 1084, 1009, 820 cm^{-1}. HRMS Calcd. For $C18H23ClNO6^+$ $[M+H]^+$:384.1214; found: 384.1196. HPLC (Chiralpak AD-H column, hexane/2-propanol = 70/30, flow rate = 1 mL/min) t_R = 17.63 min, 21.36 min.

4.3.7 (2R,3R,4S,5S)-3,4-diethyl2-methyl 5-(2,4-dichlorophenyl) pyrrolidine-2,3,4-tricarboxylate (**4hb**)

Orange sticky oil: Yield 65%; ee = 81.8%; ^1H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.4 Hz, 1H), 7.32 (s, 1H), 7.24 (d, *J* = 8.3 Hz, 1H), 5.01 (d, *J* = 3.1 Hz, 1H), 4.45 (d, *J* = 8.7 Hz, 1H), 4.19 – 4.07 (m, 4H), 3.78 (s, 3H), 3.46 (t, *J* = 8.3 Hz, 1H), 3.20 (dd, *J* = 7.6, 3.6 Hz, 1H), 2.76 (br, 1H), 1.22 (q, *J* = 7.2 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.13, 171.61, 170.24, 139.05, 133.63, 133.18, 129.77, 129.07, 127.31, 61.57, 61.23, 60.91, 53.40, 52.45, 48.50, 14.01. . IR (KBr) υ 2982, 1730, 1588, 1466, 1373, 1179, 1096, 1047, 911, 825, 730 cm^{-1}. HRMS Calcd. For $C18H22Cl2NO6^+$ $[M+H]^+$:418.0824; found: 418.0807. HPLC (Chiralpak AD-H column, hexane/2-propanol = 70/30, flow rate = 1 mL/min) t_R = 8.36 min, 10.68 min.

4.3.8 (2R,3R,4S,5S)-3,4-diethyl2-methyl 5-(2-bromophenyl) pyrrolidine-2,3,4-tricarboxylate (**4ib**)

Colorless sticky oil: Yield = 55%; ee = 91.6%; ^1H NMR (500 MHz, $CDCl_3$) δ 7.77 – 7.74 (m, 1H), 7.51 (d, *J* = 7.8 Hz, 1H), 7.32 (t, *J* = 7.5 Hz, 1H), 7.14 – 7.09 (m, 1H), 5.05 (d, *J* = 3.6 Hz, 1H), 4.49 (d, *J* = 9.0 Hz, 1H), 4.22 – 4.10 (m, 4H), 3.80 (s, 3H), 3.51 (t, *J* = 8.5 Hz, 1H), 3.26 (dd, *J* = 8.0, 3.7 Hz, 1H), 2.88 (br, 1H), 1.24 (q, *J* = 7.3 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.11, 171.79, 170.32, 141.75, 132.72, 128.97, 128.90, 127.70, 63.54, 61.75, 61.19, 53.63, 52.44, 48.46, 14.11, 14.05. IR (KBr) υ 2982, 1730, 1483, 1439, 1372, 1178, 1021, 911, 728, 647 cm^{-1}. HRMS Calcd. For $C18H23BrNO6^+$ $[M+H]^+$:428.0709; found: 428..0690. HPLC (Chiralpak AD-H column, hexane/2-propanol = 70/30, flow rate = 1 mL/min) t_R = 8.56 min, 12.06 min.

4.3.9 (2R,3R,4S,5S)-3,4-diethyl2-methyl 5-(2,4-difluorophenyl) pyrrolidine-2,3,4-tricarboxylate (**4jb**)
Light yellow oil: Yield = 91%; ee = 94.6%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63 (dd, *J* = 15.2, 8.5 Hz, 1H), 6.87 (dd, *J* = 11.6, 4.8 Hz, 1H), 6.80 – 6.75 (m, 1H), 4.92 (d, *J* = 4.3 Hz, 1H), 4.39 (d, *J* = 5.6 Hz, 1H), 4.16 (ddd, *J* = 16.8, 7.1, 2.3 Hz, 3H), 3.81 (s, 3H), 3.57 (dd, *J* = 13.7, 6.8 Hz, 1H), 3.28 (dd, *J* = 8.1, 6.5 Hz, 1H), 2.83 (br, 1H), 1.25 (dt, *J* = 14.4, 7.1 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.36 (d, J_{CF} = 12.1 Hz), 161.35 (dd, J_{CF} = 12.0, 8.4 Hz), 159.34 (d, J_{CF} = 11.9 Hz), 129.80 (dd, J_{CF} = 9.6, 5.7 Hz), 111.41 (d, J_{CF}= 3.5 Hz), 111.24 (d, J_{CF} = 3.5 Hz), 103.71 (t, J_{CF}= 25.6 Hz), 61.73, 61.32, 61.17, 58.27, 53.38, 52.54, 49.28, 14.04, 13.99. IR (KBr) υ 2983, 1732, 1616, 1502, 1435, 1373, 1180, 1026, 965, 013, 848, 816, 713 cm^{-1}. HRMS Calcd. For $C18H22F2NO6^+$ $[M+H]^+$:386.1415; found: 386.1398. HPLC (Chiralpak AD-H column, hexane/2-propanol = 80/20, flow rate = 1 mL/min) t_R = 11.75 min, 18.46 min.

4.3.9 (2R,3R,4S,5S)-3,4-diethyl 2-methyl 5-(3-bromophenyl) pyrrolidine-2,3,4-tricarboxylate (**4kb**).

Colorless oil: Yield = 95%; ee = 81.2%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (s, 1H), 7.52 (dd, *J* = 11.7, 5.3 Hz, 1H), 7.29 (dd, *J* = 8.6, 6.1 Hz, 1H), 7.20 (t, *J* = 7.8 Hz, 1H), 4.68 (d, *J* = 6.8 Hz, 1H), 4.47 (d, *J* = 6.0 Hz, 1H), 4.20 – 4.10 (m, 4H), 3.82 (s, 3H), 3.25 (dd, *J* = 11.8, 4.9 Hz, 1H), 3.24 – 3.20 (m, 1H), 1.27 (t, *J* = 7.2 Hz, 3H), 1.24 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.97, 171.04, 170.52, 144.28, 131.23, 130.76, 130.04, 126.77, 126.31, 122.59, 63.81, 61.84, 61.40, 61.14, 52.62, 51.44, 47.61, 14.08. IR (KBr) υ 2982, 1731, 1594 1570, 1434, 1176, 1023, 997, 909, 784, 694 cm^{-1}. HRMS Calcd. For $C18H23BrNO6^+$ $[M+H]^+$:428.0709; found: 428.0686. HPLC (Chiralpak AD-H column, hexane/2-propanol = 90/10, flow rate = 1 mL/min) t_R =17.43 min, 27.57 min.

4.3.10 (2R,3R,4S,5S)-3,4-diethyl 2-methyl 5-(2,3-dimethoxyphenyl) pyrrolidine-2,3,4-tricarboxylate (**4lb**).

Light red oil: Yield = 40%; ee = 83.2%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 – 7.09 (m, 1H), 7.04 (t, *J* = 7.9 Hz, 1H), 6.88 (dt, *J* = 8.1, 4.0 Hz, 1H), 4.93 (d, *J* = 6.0 Hz, 1H), 4.47 (d, *J* = 8.1 Hz, 1H), 4.13 (ddd, *J* = 14.3, 8.8, 5.3 Hz, 4H), 4.00 (s, 3H), 3.92 (s, 3H), 3.57 (t, *J* = 8.5 Hz, 1H), 3.36 (dd, *J* = 8.9, 6.0 Hz, 1H), 3.06 (s, 3H), 1.25 (t, *J* = 3.6 Hz, 3H), 1.23 (t, *J* = 5.1 Hz, 3H).^{13}C NMR (126 MHz, $CDCl_3$) δ 172.71, 171.73, 170.65, 152.48, 146.63, 124.17, 119.20, 118.11, 62.36, 61.96, 61.23, 61.00, 60.69, 56.05, 55.81, 53.37, 52.55, 49.64, 14.07, 14.05. . IR (KBr) υ 2981, 1733, 1690, 1585, 1480, 1376, 1263, 1173, 1065, 1000, 910, 748cm^{-1}. HRMS Calcd. For $C20H28NO8^+$ $[M+H]^+$:410.1815; found: 410.1797. HPLC (Chiralpak column, hexane/2-propanol = 70/30, flow rate = 1 mL/min) t_R = 11.03min, 15.03min.

4.3.11 (2R,3R,4S,5S)-2-ethyl 3,4-dimethyl 5-(4-(dimethylamino)phenyl) pyrrolidine-2,3,4-tricarboxylate (**4mc**)

Dark red oil: Yield = 89%; ee = 95.2%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.7 Hz, 2H), 6.71 (d, *J* = 8.7 Hz, 2H), 4.58 (d, *J* = 8.2 Hz, 1H), 4.33 (d, *J* = 3.7 Hz, 1H), 4.26 (ddd, *J* = 9.2, 7.6, 2.6 Hz, 2H), 3.73 (s, 3H), 3.64 (s, 3H), 3.59 (dd, *J* = 10.5, 5.5 Hz, 1H), 3.23 (t, *J* = 8.7 Hz, 1H), 3.09 (s, 1H), 2.94 (s, 3H), 2.93 (s, 3H), 1.32 (d, *J* = 6.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.78, 172.54, 171.85, 171.71, 150.21, 127.79, 127.65, 112.62, 112.26, 64.47, 62.02, 61.58, 52.37, 52.04, 51.69, 50.25, 40.64, 40.56, 14.18. (KBr) υ 2951, 1732, 1614, 1523, 1435, 1347, 1165, 1036, 946, 805 cm^{-1}. HRMS Calcd. For $C19H27N2O6^+$ $[M+H]^+$:379.1869; found: 410.1849. HPLC (Chiralpak AD-H column, hexane/2-propanol = 70/30, flow rate = 1 mL/min) t_R = 11.43 min, 25.81 min.

4.3.12 (2R,3R,4S,5S)-2-ethyl 3,4-dimethyl phenylpyrrolidine-2,3,4-tricarboxylate (**4nc**)

Ligh yellow oil: Yield = 65%; ee = 92.4%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, *J* = 7.3 Hz, 2H), 7.31 (t, *J* = 7.5 Hz, 2H), 7.25 (d, *J* = 7.3 Hz, 1H), 4.66 (s, 1H), 4.34 (d, *J* = 1.9 Hz, 1H), 4.24 (qd, *J* = 7.1, 2.8 Hz, 2H), 3.70 (s, 3H), 3.63 (s, 3H), 3.62 – 3.58 (m, 1H), 3.24 (t, *J* = 8.3 Hz, 1H), 2.78 (br, 1H), 1.30 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.48, 171.61, 141.31, 128.52, 127.76, 126.96, 64.51, 62.01, 61.53, 54.33, 52.38, 52.09, 49.92, 14.16. (KBr) υ 2982, 1732, 1440, 1370, 1265, 1170, 910, 715 cm^{-1}. HRMS Calcd. For $C17H22NO6^+$ $[M+H]^+$:336.1444; found: 336.1428. HPLC (Chiralpak AD-H column, hexane/2-propanol = 90/10, flow rate = 1 mL/min) t_R = 11.90 min, 19.93 min.

4.3.13 (2R,3R,4S,5S)-2-ethyl 3,4-dimethyl 5-(4-nitrophenyl)pyrrolidine-2,3,4-tricarboxylate (**4oc**)

Dark red sticky oil: Yield 95%; ee = 99.8%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, *J* = 8.7 Hz, 2H), 7.72 (d, *J* = 8.7 Hz, 2H), 4.84 (d, *J* = 8.0 Hz, 1H), 4.35 (d, *J* = 4.5 Hz, 1H), 4.26 (q, *J* = 7.1 Hz, 2H), 3.74 (s, 3H), 3.67 (s, 3H), 3.63 (dd, *J* = 8.2, 5.0 Hz, 1H), 3.25 (dd, *J* = 9.7, 6.4 Hz, 1H), 2.91 (br, 1H), 1.32 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.43, 171.48, 170.99, 149.55, 129.00, 128.16, 123.65 (s), 61.93 (s), 61.71, 54.24, 52.57, 52.12, 49.70, 14.17. (KBr) υ 2955, 1730, 1600, 1519, 1436, 1345, 1196, 1014, 853, 699 cm^{-1}. HRMS Calcd. For $C17H21N2O8^+$ $[M+H]^+$:381.1298; found: 381.1277. HPLC (Chiralpak AD-H column, hexane/2-propanol = 70/30, flow rate = 1 mL/min) t_R = 16.28 min, 20.03 min.

4.3.14 (2R,3R,4S,5S)-trimethyl 5-phenylpyrrolidine-2,3,4-tricarboxylate (**4pc**).

Ligh yellow oil: Yield = 60%; ee = 65.8%; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 (d, *J* = 7.3 Hz, 2H), 7.24 (t, *J* = 7.4 Hz, 2H), 7.18 (d, *J* = 7.5 Hz, 1H), 4.58 (d, *J* = 7.6 Hz, 1H), 4.29 (d, *J* = 5.9 Hz, 1H), 3.71 (br, 3H), 3.63 (s, 3H), 3.56 (s, 3H), 3.55 – 3.52 (m, 1H), 3.17 (dd, *J* = 10.7, 6.0 Hz, 1H), 2.62 (s, 1H).^{13}C NMR (101 MHz, $CDCl_3$) δ 171.97, 170.60, 170.55, 140.28, 127.53, 126.75, 125.90, 63.55, 60.80, 53.34, 51.52, 51.37, 51.07, 48.79. (KBr) υ 2982, 1730, 1436, 1265, 1180, 1025, 908, 705 cm^{-1}.HRMS Calcd. For $C16H20NO6^+$ $[M+H]^+$:322.1291; found: 322.1271. HPLC (Chiralpak AD-H column, hexane/2-propanol = 70/30, flow rate = 1 mL/min) t_R = 10.23 min, 12.81 min.

4.3.15 *(2R,3R,4S,5S)-trimethyl 5-(naphthalen-2-yl)pyrrolidine -2,3,4-tricarboxylate* (**4dc**).

Colorless oil: Yield = 75%; ee = 91.2%; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (s, 1H), 7.84 (dd, *J* = 9.0, 5.4 Hz, 3H), 7.60 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.50 – 7.47 (m, 2H), 4.87 (d, *J* = 7.8 Hz, 1H), 4.48 (d, *J* = 6.1 Hz, 1H), 3.85 (s, 3H), 3.76 (s, 3H), 3.71 (dd, *J* = 8.9, 6.1 Hz, 1H), 3.68 (s, 3H), 3.40 (t, *J* = 8.2 1H), 2.94 (br, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.96, 171.63, 171.57, 138.45, 133.28, 133.12, 128.47, 128.06, 127.64, 126.17, 126.10, 125.99, 124.79, 64.76, 61.87, 54.24, 52.64, 52.48, 52.18, 49.79. (KBr) υ 2952, 1730, 1620, 1508, 1434, 1359, 1198, 1173, 1015, 820, 747, 478 cm^{-1}. HRMS Calcd. For $C20H22NO6^+$ $[M+H]^+$:372.1447; found: 372.1442. . HPLC (Chiralpak AD-H column, hexane/2-propanol = 70/30, flow rate = 1 mL/min) t_R = 16.35 min, 18.20 min.

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Highlights

- The regioselectivity is controlled by stepwise cis-cycloaddition pathway.
- The diastereoselectivities are sensitive to the nature of Copper salt.
- The stereoselectivities of 1,3-DCA reaction are sensitive to the structure of oxazoline ring

Cu^{II}-catalysed asymmetric 1,3-dipolar cycloaddition of azomethine ylides with a chiral ferrocene-derived P,N-Ligand

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