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Note

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Silver-Catalysed Enantioselective Mannich Reaction of Diazoacetate Esters with *N*-Boc Aldimines

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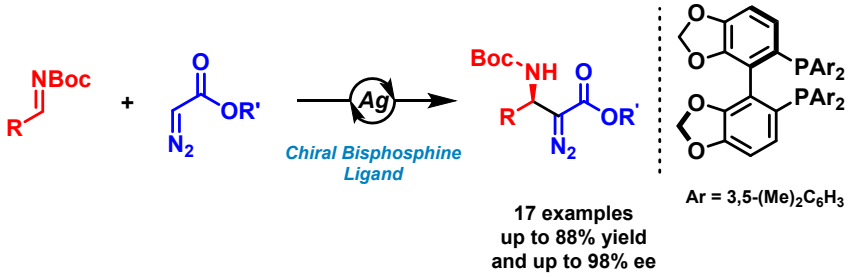
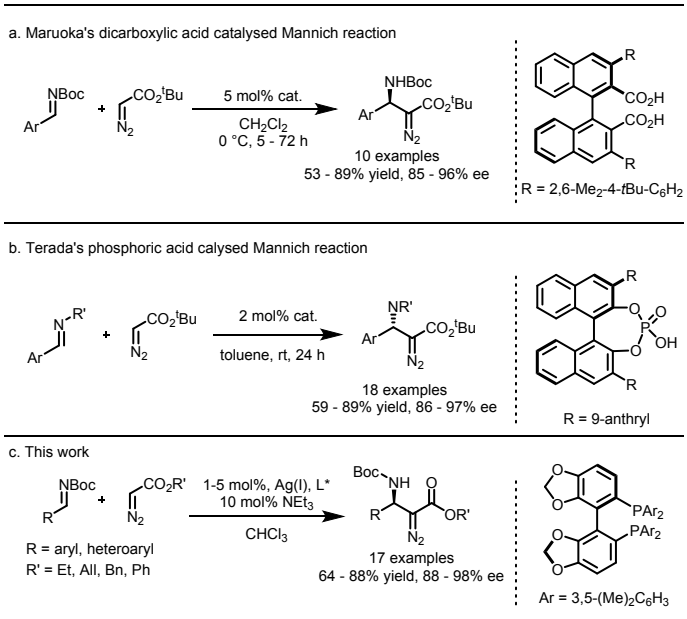


ABSTRACT: The highly enantioselective Mannich reaction of diazoacetate esters with *N*-Boc aldimines catalysed by silver (I) triflate in the presence of (*R*)-DM-SEGPHOS is reported. The reaction is broad in scope with respect to the (hetero)aromatic aldehyde-derived aldimine and tolerates significant variability of the diazoacetate ester component. Yields and enantioselectivities are good to excellent and the reaction can be performed on gram scale with catalyst loadings as low as 1 mol%.

The Mannich reaction is a fundamental two-component coupling reaction in organic chemistry, enabling the ready construction of chiral amine building blocks of significance to the pharmaceutical, agrochemical and fine chemical industries.[1] The reaction, which unites an imine electrophile and a nucleophilic carbonyl component (via an enol, enol derivative or an enolate ion), can be rendered catalytic and with the appropriate catalyst or catalytic system, highly enantioselective. To date a range of enantioselective Mannich-type reactions using a plethora of nucleophilic and electrophilic components have been reported.[2] Despite these advances, considerable opportunities still exist to improve catalyst loading, efficiency, selectivity and most importantly scope of the enantioselective Mannich reaction.

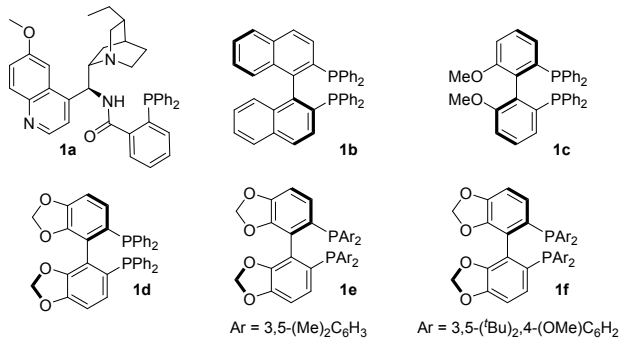
One class of reagent that has received considerable attention within the synthetic community due to its versatility and potential for downstream functionalization reactions is the α-diazo carbonyl compound,[3] of which the chemistry of α-diazoacetate derivatives predominates.[4] The diazo unit enables facile carbene/carbenoid generation under a variety of conditions that can be widely exploited in reactions ranging from CH activation to diversity oriented library generation.[5]

Figure 1. Previous approaches to β-amino acids bearing α-diazo substitution and this work.



Maruoka and Terada independently reported the organocatalytic enantioselective addition of diazoacetate derivatives to aldimines under carboxylic acid[6a] and phosphoric acid catalysis[6b] (Figure 1). Very recently, Wang disclosed the ethyl diazoacetate (EDA) Mannich reaction of cyclic ketimines.[6d]

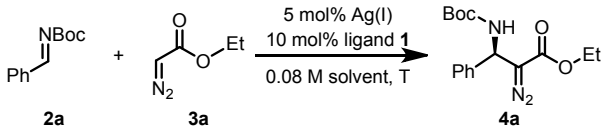
Figure 2. Ligands used in the optimization studies.



We envisaged that the development of a new catalyst system for this reaction which imparted high enantioselectivity whilst tolerating a broad scope with respect to both the aldimine electrophile and the diazoacetate ester would bring synthetic value and potentially advance the field (Figure 1c).[6] As part of our research programme into the development of challenging enantioselective Mannich and Aldol reactions of isocyanoacetate pronucleophiles,[7] aminophosphine **1a** ligated silver(I) salts were identified as a privileged catalytic system for related transformations. Our hope was that such silver(I) complexes could provide the necessary reactivity and selectivity for the first silver catalyzed enantioselective diazoacetate addition to *N*-Boc aldimines and herein we wish to report our findings.

The reaction of benzaldehyde derived *N*-Boc imine **2a** with ethyl diazoacetate (**3a**) was chosen as a model system. Proof of concept was rapidly established when a catalyst system comprising Ag_2O and aminophosphine ligand **1a** (figure 2) was employed in the reaction at room temperature (table 1, entry 1 and Supporting Information). We were delighted to observe product formation and after 15 hours β-amino ester **4a** was isolated in 81% yield and 9% ee. In a search to identify alternative ligands, a bidentate phosphine, BINAP (**1b**), was screened and found to offer improvement to both the reaction time and enantioselectivity in the formation of **4a** (entry 2). The enantioselectivity was further improved by switching to AgOTf (entries 3 & 4) although a slightly diminished reaction yield was returned. Increasing the loading of AgOTf to 20 mol% reduced both the ee and yield in the formation of **4a** (entry 5).

Table 1. Optimization of the silver-catalysed addition of ethyl diazoacetate to *N*-Boc aldimine **2a**.[a]

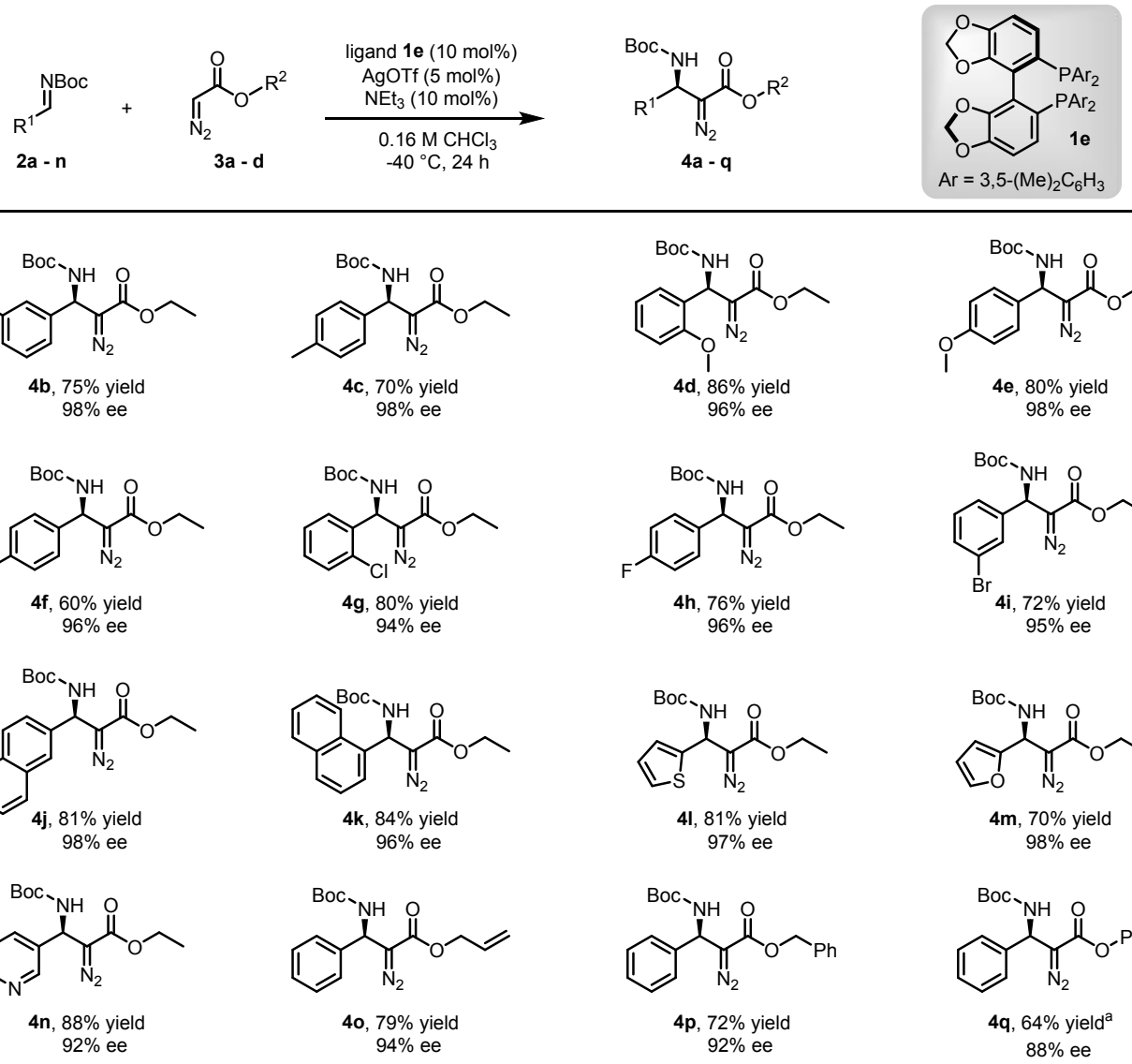


	Ag(I)	1	Solvent	T (°C)	Time (h)	Yield (%)[b]	ee[c]
1	Ag_2O	**a**	EtOAc	rt	15	81	9[d]
2	Ag_2O	**b**	EtOAc	rt	5	87	24[d]
3	AgOTf[e]	**b**	EtOAc	rt	5	74	37[d]
4	AgOTf	**b**	EtOAc	rt	5	71	39[d]
5	AgOTf[f]	**b**	EtOAc	rt	5	52	35[d]
6	AgOTf	**b**	Et_2O	rt	6	28	21[d]
7	AgOTf	**b**	CH_2Cl_2	rt	6	38	49[d]
8[g]	AgOTf	**b**	CH_2Cl_2	rt	4	50	49[d]
9[g]	AgOTf	**c**	CH_2Cl_2	rt	2	68	51
10[g]	AgOTf	**d**	CH_2Cl_2	rt	5	52	59
11[g]	AgOTf	**e**	CH_2Cl_2	rt	5	58	81
12[g]	AgOTf	**f**	CH_2Cl_2	rt	7	58	71
13[g]	AgOTf	**e**	PhCl	rt	6	65	75
14[g]	AgOTf	**e**	$CHCl_3$	rt	6	48	85
15[g]	AgOTf	**e**	$CHCl_3$	-20	24	32	91
16[g,h]	AgOTf	**e**	$CHCl_3$	-20	16	68	88
17[g,h]	AgOTf	**e**	$CHCl_3$	-40	24	77	97
18[g,h]	AgOTf	**e**	$CHCl_3$	-50	24	68	97
19[g,i]	AgOTf	**e**	$CHCl_3$	-40	24	40	95

[a]Reactions performed using 0.10 mmol of **2a** with 1.2 eq **3a**. [b]Isolated yield. [c]Enantiomeric excess (*ee*) determined by chiral HPLC analysis using a chiral stationary phase. [d](*S*)-**4a** obtained. [e]10 mol% Ag used. [f]20 mol% Ag used. [g]10 mol% NEt_3 added. [h]Reaction performed at 0.16 M concentration wrt **2a**. [i]Reaction performed at 0.12 M concentration wrt **2a**.

A brief screen of solvents at this point, revealed that dichloromethane gave the highest enantioselectivity (entries 6 & 7). Interestingly, it was found that the addition of 10 mol% NEt_3 to the reaction increased the yield (entry 8). At this stage, related atropisomeric bisphosphine ligands **1c-f** were evaluated (entries 9 – 12) and yielded **4a** in up to 81% ee (entry 11). Subsequent optimisation studies were performed with ligand **1e** and a solvent switch to chlorobenzene and chloroform improved the enantioselectivity to 75 and 85% ee respectively (entries 13 & 14).

Figure 3. Scope of the silver catalysed enantioselective Mannich reaction of diazoacetate esters with *N*-Boc aldimines.



Reactions were carried out with 0.10 mmol **2** and 0.12 mmol **3**. Yields are isolated yields and enantiomeric excesses were determined by HPLC analysis on a chiral stationary phase. [a]The reaction was quenched after 66 hours.

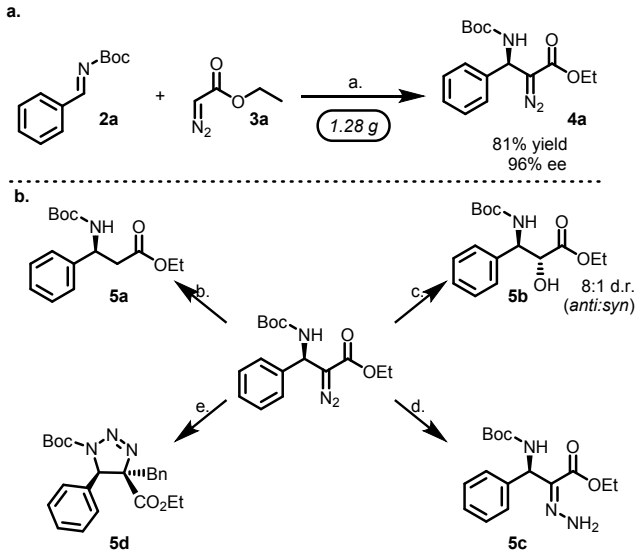
Lowering the reaction temperature to –20 °C improved the enantiomeric excess to 91%, albeit to the detriment of the yield (entry 15). This was circumvented by increasing the reaction concentration to 0.16 M and the reaction time to 24 h which enabled the reaction to be performed at –40 °C (entries 17 & 18). Decreasing the reaction temperature further to –50 °C did not improve the enantioselectivity nor did diluting the reaction to 0.12 M (entries 18 & 19). β-Amino ester **4a** was accordingly synthesised in 77% yield and 97% ee using the optimal conditions as identified in entry 17.

With optimised conditions in hand, the scope of the transformation was investigated (Figure 3). The addition of methyl groups to the aromatic ring in the meta and para position was well-tolerated and afforded both **4b** and **4c** in 98% ee. Simarly the addition of a methoxy group or a chlorine atom in the ortho or para positions of the aromatic imine gave the desired β-amino esters **4d-g** in good yield and with consistently excellent levels of enantioselectivity. Fluorine and bromine substituents on the aromatic ring were also compatible and products **4h** and **4i** were afforded in 96% and 95% ee respectively. Both 1- and 2-naphthaldehyde-derived *N*-Boc aldimines successfully underwent the Mannich reaction to give **4j** and **4k** in good yields and excellent enantiomeric excesses. Having demonstrated the compatibility of 10 π-electron aromatics we next focused on heteroaromatic aldimines and were delighted to observe that both 2-

thiophene and 2-furan substituted imines **4l** and **4m** afforded the desired products with consistently high levels of enantioselectivity. Significantly, the reaction could also be performed with an imine incorporating a pyridine ring and the product **4n** was isolated in 88% yield and 92% ee. After extensive exploration of the imine component we then investigated the scope with respect to the α-diazoacetate ester. Allyl, benzyl and phenolic esters **3b - d** all performed well in the formation of **4o - q**; although the formation of **4q** required an extended reaction time of 66 h to give the product in decent yield.

To further demonstrate the synthetic utility and general applicability of this catalysed reaction we next set about performing the reaction on preparative scale and successfully lowered the catalyst loading to 1 mol% using 5 mmol of **2a** to afford 1.28 g of the addition product **4a** in 81% yield and with 96% ee (scheme 1).

Scheme 1. Preparative synthesis of **4a** and derivatisation.



Conditions: (a) 1 mol% AgOTf, 2 mol% **1e**, 4 mol% NEt_3, $CHCl_3$, 4 Å molecular sieves, -40 °C, 48 h. (b) 10 mol% Pd/C, 1 atm H_2, MeOH, 12 h, 75%, 96% ee. (c) i. Oxone®, $NaHCO_3$, acetone/H_2O (1.5/1.0), CH_2Cl_2, ii. $NaBH_4$, CH_2Cl_2, -78 °C to RT, 58% (over 2 steps), 8 : 1 d.r. (anti:syn) determined by ^{1}H-NMR analysis. (d) P(*n*-Bu)$_3$, Et_2O, rt, 20 min, 88%, 96% ee. (e) 1.2 equiv NaH, 1.2 equiv BnBr, DMF, 0 °C to rt, 30 min, 79%, 96% ee.

In a brief demonstration of the synthetic utility of the reaction products, **4a** was hydrogenated using hydrogen (balloon pressure) over Pd/C which afforded the β-amino ester **5a** without loss of enantiopurity. Oxone® oxidation followed by borohydride reduction of the resulting ketone afforded the alcohol **5b** as an 8: 1, anti : syn mixture of diastereoisomers.[8] The diazo unit was partially reduced to the hydrazone by treatment with tributylphosphine; **5c** was afforded in 88% yield without loss of enantiopurity (96% ee). Finally, treatment of **4a** with NaH and subsequently with benzyl bromide afforded the triazoline **5d** bearing a fully substituted α-carbon in 79% yield as a single diastereomer.[9]

In conclusion, we have developed a silver(I) catalysed enantioselective Mannich reaction of diazoacetate esters with *N*-Boc protected aldimines. The reaction is broad in scope with respect to the (hetero)aryl aldehyde-derived *N*-Boc aldimine and can tolerate variation to the ester of the diazoacetate. The β-amino ester products are formed in typically good yields and with excellent levels of enantioselectivity and the reaction can be performed on gram scale with catalyst loadings as low as 1 mol%. Importantly, the diazo moiety remains intact during the transformation and provides a handle for further downstream modification without erosion of the enantiopurity. Further work focusing on the development of novel catalytic systems and their application to synthetically useful products is ongoing in our group and the results will be disclosed in due course.

EXPERIMENTAL SECTION

General Information

Solvents and Reagents Concentration under reduced pressure was performed by rotary evaporation at the appropriate pressure and temperature. Reagents used were obtained from commercial suppliers or purified according to standard procedures. Petroleum ether refers to distilled light petroleum of fraction 30 - 40 °C. Anhydrous toluene, tetrahydrofuran, dichloromethane and diethyl ether were dried by filtration through activated alumina (powder ~150 mesh, pore size 58 Å, basic, Sigma-Aldrich) columns. Chloroform was bought from Sigma Aldrich in a 2.5 L Winchester, containing 0.5% - 1.0% ethanol as stabilizer and was extracted with water, basified over K_2CO_3, distilled and stored over 4 Å molecular sieves. Deuterated solvents were used as supplied. (*R*)-DM-SEGPHOS was obtained from STREM chemicals. Ethyl diazoacetate was obtained as a 15% stock solution in toluene from Sigma Aldrich.

Chromatography Reactions were monitored by thin layer chromatography (TLC) using Merck silica gel 60 F_{254} plates and visualized by fluorescence quenching under UV light. In addition, TLC plates were stained with potassium permanganate solution. Flash column chromatography (FCC) was performed on VWR 60 silica gel 40 - 63 μm using technical grade solvents that were used as supplied.

Instrumentation Melting points were obtained on a Leica Galen III Hot-stage melting point apparatus and microscope and on a Kofler hot block and are reported uncorrected. NMR spectra were recorded on a Bruker Spectrospin spectrometer operating at 200, 400 or 500 MHz (^{1}H acquisitions), 100 or 125 MHz (^{13}C acquisitions), 377 MHz (^{19}F acquisitions) and 162 MHz (^{31}P acquisitions). Chemical shifts (δ) are reported in ppm with the solvent resonance as the internal standard (e.g. chloroform δ 7.27 ppm for ^{1}H and 77.0 ppm for ^{13}C). Coupling constants (*J*) are reported in hertz (Hz), and rounded to the nearest

0.5 Hz. Data are reported as follows: multiplicity [s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, ddd = doublet of doublets of doublets, td = triplet of doublets, m = multiplet, br = broad], coupling constants in Hz, integration. Two-dimensional spectroscopy (COSY, HSQC and HMBC) was used to assist in the assignment and the data is not reported. High-resolution mass spectra (ESI) were recorded on Bruker µTOF mass spectrometer. Infrared spectra were recorded on a Bruker Tensor 27 FT-IR spectrometer as a thin film. Only selected maximum absorbances are reported. Optical rotations were recorded using a Perkin Elmer 341 polarimeter; $[\alpha]_D^T$ values are reported in 10^{-1} deg cm^2 g^{-1}; concentrations (c) are quoted in g/100 mL; D refers to the D-line of sodium (589 nm); temperatures (T) are given in degrees Celsius (°C). (+) and (–) compound number prefixes indicate the sign of the optical rotation. The enantiomeric excesses were determined by HPLC analysis on an Agilent 1200 Series instrument employing a chiral stationary phase column specified in the individual experiment and by comparing the samples with the appropriate racemic mixtures. -40 °C conditions were achieved using an EK90 cryocooler.

General Procedure for *N*-Boc Aldimine Synthesis (2a – 2n). Step 1: According to a literature procedure,[10] a mixture of aldehyde (37.5 mmol, 1.5 equiv), *N*-Boc-carbamate (2.93 g, 25 mmol, 1.0 equiv) and benzene sulfinic acid sodium salt (8.26 g, 50 mmol, 2.0 equiv) was suspended in MeOH/H_2O (2:1, 75 mL). Formic acid (1.9 mL) was then added and the resulting mixture was then stirred for 72 hours at room temperature whereupon the reaction mixture filtered, the precipitate was washed with water and then Et_2O and dried to afford the desired amidosulfone as a colourless solid. Step 2: a RBF was charged with amidosulfone (10 mmol, 1.0 equiv), potassium carbonate (15.0 equiv) and sodium sulfate (18.0 equiv). Dry THF was added (0.51 mM) under argon and the suspension was heated to 70 °C in an oil bath for 16 hours after which the reaction mixture was passed through a thick pad of Celite© on a glass frit, with washings of CH_2Cl_2. The filtrate was concentrated *in vacuo* to afford the aldimine.

Diazoesters **3b – d** were prepared according to a reported protocol.[11]

General Procedure A for the Ag(I) catalyzed Mannich reaction on 0.10 mmol scale. A reaction tube was charged with silver triflate (1.3 mgs, 0.005 mmol, 5 mol%,) and phosphine ligand (7.2 mgs, 0.010 mmol, 10 mol%). Anhydrous chloroform (0.4 mL, 0.167 *m*M) was added under an atmosphere of argon. The resulting mixture was stirred for 1 hour at room temperature after which triethylamine (1.4 µL, 0.010 mmol, 10 mol%) was added and a faint yellow solution was produced after 15 min of stirring at room temperature. The aldimine was then added (21 mgs, 0.1 mmol in 0.2 mL of $CHCl_3$) and the reaction mixture was cooled to -40 °C and stirred at this temperature for 30 min. Electron-rich aldimines produced a bright yellow colour on addition, no colour change was observed on addition of electron-deficient aldimines. Ethyl diazoacetate (0.10 mL, 0.12 mmol, 1.2 eq, 15% in toluene), which had been pre-cooled was finally added. After a 24 h period, the reaction mixture was passed through a short pad of silica on a glass frit, eluting with diethyl ether. The filtrate was then concentrated *in vacuo* and purified immediately *via* FCC (15 mL of silica) eluting with [100% petroleum ether to 10% diethyl ether] to yield the desired compound as either a yellow oil or yellow solid.

***Ethyl (3R)-3-{[(tert-butoxy)carbonyl]amino}-2-diazo-3-phenylpropanoate* 4a** Prepared according to General Procedure A using aldimine **2a** (20.5 mg, 0.10 mmol) to afford the title compound in 77% isolated yield as a yellow solid (25 mg) and 97% ee [determined by HPLC, Chiralpak AS-H, hexane/isopropanol = 95/5, 1 mL/min, λ = 220 nm, t (minor) = 12.36 min, t (major) = 16.64 min]. **MPT** 78 – 80 °C; $[\alpha]_D^{25}$ = +27.3 (*c* = 1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.27 - 7.41 (m, 5 H, Ar<u>H</u>), 5.66 (d, *J* = 6.6 Hz, 1 H, C<u>H</u>NH), 5.43 (br. s, 1 H, N<u>H</u>CH), 4.21 (q, *J*=7.3 Hz, 2 H, C<u>H</u>$_2$CH$_3$), 1.46 (s, 9 H, OC(C<u>H</u>$_3$)$_3$), 1.25 (t, *J*=7.2 Hz, 3 H, CH$_2$C<u>H</u>$_3$);**^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$), δ ppm 165.9 (O<u>C</u>=O), 154.9 (N<u>C</u>(=O)OC), 139.1 (Ar<u>C</u>), 128.9 (Ar<u>C</u>H), 128.0 (Ar<u>C</u>H), 126.2 (Ar<u>C</u>H), 80.4 (O<u>C</u>(CH$_3$)$_3$), 61.0 (<u>C</u>H$_2$CH$_3$), 51.2 (<u>C</u>HNH), 28.3 (OC(<u>C</u>H$_3$)$_3$), 14.4 (CH$_2$<u>C</u>H$_3$); **IR** ν_{max}/cm^{-1} 3346, 2978, 2095, 1697, 1497, 1167; Data is consistent with that given in the literature.[12]

***Ethyl (3R)-3-{[(tert-butoxy)carbonyl]amino}-2-diazo-3-(3-methylphenyl)propanoate* 4b** Prepared according to the general procedure A using aldimine **2b** (22 mg, 0.10 mmol) to afford the title compound in 75% isolated yield as a yellow oil (25 mg) and 98% ee [determined by HPLC, Chiralpak AD-H, hexane/isopropanol = 95/5, 1 mL/min, λ = 220 nm, t (major) = 14.42 min, t (minor) = 15.84 min]. $[\alpha]_D^{25}$ = +22.3 (c = 1.0, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ ppm 7.33-7.46 (m, 1 H, Ar<u>H</u>), 7.16-7.31 (m, 3 H, Ar<u>H</u>), 5.74 (d, J=7.3 Hz, 1 H, C<u>H</u>NH), 5.47 (br. s., 1 H, N<u>H</u>CH), 4.33 (q, J=7.1 Hz, 2 H, CH$_3$C<u>H</u>$_2$), 2.47 (s, 3 H, ArC<u>H</u>$_3$), 1.57 (s, 9 H, OC(C<u>H</u>$_3$)$_3$), 1.37 (t, J=7.1 Hz, 3 H, CH$_2$<u>C</u>H$_3$); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ ppm 166.1 (O<u>C</u>=O), 155.0 (N<u>C</u>(=O)OC), 139.2 Ar<u>C</u>), 138.8 (Ar<u>C</u>), 129.0 (Ar<u>C</u>H), 128.9 (Ar<u>C</u>H), 127.0 (Ar<u>C</u>H), 123.3 (Ar<u>C</u>H), 80.5 (O<u>C</u>(CH$_3$)$_3$), 61.1 (CH$_3$<u>C</u>H$_2$), 51.3 (<u>C</u>HNH), 28.5 (OC(<u>C</u>H$_3$)$_3$), 21.6 (Ar<u>C</u>H$_3$), 14.5 (CH$_2$<u>C</u>H$_3$); **IR** ν_{max}/cm^{-1} 3351, 2979, 2093, 1698, 1491, 1368, 1163; **HRMS** (ESI-TOF): calcd for [M+Na]$^+$: calcd for $C_{17}H_{23}N_3O_4Na$ [M+Na]$^+$ 356.1581, found 356. 1577. Data is consistent with that given in the literature.[12]

***Ethyl (3R)-3-{[(tert-butoxy)carbonyl]amino}-2-diazo-3-(4-methylphenyl)propanoate* 4c** Prepared according to the general procedure A using aldimine **2c** (22 mg, 0.10 mmol) to afford the title compound as a yellow solid in 70% isolated yield (22 mg) and 98% ee [determined by HPLC, Chiralpak AD-H, hexane/isopropanol = 95/5, 1 mL/min, λ = 220 nm, t (major) = 15.67 min, t (minor) = 16.86 min]. **MPT** 74 – 76 °C; [lit. for the racemate 70.8 – 71.4 °C][12]; $[\alpha]_D^{25}$ = +13.1 (*c* =1.3, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.23 (d, *J*=8.1 Hz, 2 H, Ar<u>H</u>), 7.16 (d, *J*=8.1

Hz, 2 H, ArH), 5.62 (d, *J*=7.5 Hz, 1 H, CHNH), 5.35 (br. s., 1 H, NHCH), 4.21 (q, *J*=7.2 Hz, 2 H, CH_2CH_3), 2.33 (s, 3 H, $ArCH_3$), 1.45 (s, 9 H, $OC(CH_3)_3$), 1.25 (t, *J*=7.1 Hz, 3 H, CH_2CH_3); **^{13}C {^{1}H} NMR** 166.1 (OC=O), 155.0 (NC(=O)OC), 137.9 (ArC), 136.3 (ArC), 129.7 (ArCH), 126.2 (ArCH), 80.3 ($OC(CH_3)_3$), 61.1 (CH_2CH_3), 50.9 (CHNH), 28.5 ($OC(CH_3)_3$), 21.2 ($ArCH_3$), 14.6 (CH_2CH_3); **IR** ν_{max}/cm^{-1} 3353, 2978, 2093, 1697, 1512, 1392, 1167. **HRMS** (ESI-TOF): calcd for $[M+Na]^+$ $C_{17}H_{23}N_3O_4Na$ 356.1581 found 356.1581. Data is consistent with that given in the literature.[12]

***Ethyl (3R)-3-{[(tert-butoxy)carbonyl]amino}-2-diazo-3-(2-methoxyphenyl)propanoate* 4d** Prepared according to the general procedure A using aldimine **2d** (23.5 mg, 0.10 mmol) to afford the title compound in 86% isolated yield as a yellow oil (30 mg) and 96% ee [determined by HPLC, Chiralpak AD-H, hexane/isopropanol = 95/5, 1 mL/min, λ = 220 nm, t (major) = 16.29 min, t (minor) = 19.79 min]. $[\alpha]_D^{25}$ = +4.5 (*c* =1.2, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ ppm 7.23 - 7.37 (m, 2 H, ArH), 6.88 - 6.98 (m, 2 H, ArH), 5.83 (br. s., 2 H, CHNH& NHCH), 4.17 (q, *J*=7.1 Hz, 2 H, CH_2CH_3), 3.87 (s, 3 H, $ArOCH_3$), 1.46 (s, 9 H, $OC(CH_3)_3$), 1.23 (t, *J*=7.1 Hz, 3 H, CH_2CH_3); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ 166.3 (OC=O), 156.8 (ArC), 154.8 (NC(=O)OC)), 129.2 (ArCH), 128.4 (ArCH), 127.4 (ArC), 120.8 (ArCH), 110.7 (ArCH), 80.2 ($OC(CH_3)_3$), 60.9 (CH_3CH_2), 55.4 ($ArOCH_3$), 47.8 (CHNH), 28.4 ($OC(CH_3)_3$), 14.5 (CH_2CH_3); **IR** ν_{max}/cm^{-1} 3353, 2976, 2093, 1695, 1602, 1491, 1392, 1165. **HRMS** (ESI-TOF): calcd for $[M+Na]^+$ for $C_{17}H_{23}N_3O_5Na$ 372.1530, found 372.1527.

***Ethyl (3R)-3-{[(tert-butoxy)carbonyl]amino}-2-diazo-3-(4-methoxyphenyl)propanoate* 4e** Prepared according to the general procedure A using aldimine **2e** (23.5 mg, 0.10 mmol) to afford the title compound in 80% isolated yield as a yellow solid (28 mg) and 98% ee [determined by HPLC, Chiralpak AD-H, hexane/isopropanol = 95/5, 1 mL/min, λ = 220 nm, t (major) = 25.17, t (minor) = 27.78 min]. **MPT** 68 – 70 °C; [lit. for the racemate 97 – 98 °C][12]; $[\alpha]_D^{25}$ = +12.3 (*c* = 1.3, $CHCl_3$). **^{1}H-NMR** (400 MHz, $CDCl_3$) δ ppm 7.28 (d, *J* = 8.6 Hz, 2H, ArH), 6.90 (d, *J*=8.6 Hz, 2H, ArH), 5.62 (d, *J*=7.3 Hz, 1H, CHNH), 5.32 (br.s, 1H, NHCH), 4.25 (q, *J* = 7.1 Hz, 2H, CH_2CH_3), 3.80 (s, 3H, $ArOCH_3$), 1.45 (s, 9H, $OC(CH_3)_3$), 1.27 (t, *J*=7.1 Hz, 3H, CH_2CH_3); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ ppm 166.0 (OC=O), 159.3 (ArCOMe), 154.8 (NC(=O)OC), 131.2 (ArC), 127.4 (ArCH), 114.2 (ArCH), 80.3 ($OC(CH_3)_3$), 61.0 (CH_2CH_3), 55.3 ($ArOCH_3$), 50.7 (CHNH), 28.3 ($OC(CH_3)_3$), 14.4 (CH_2CH_3); **IR** ν_{max}/cm^{-1} 3352, 2978, 2092, 1692, 1511, 1162; **HRMS** (ESI-TOF) : calcd for $[M+Na]^+$ $C_{17}H_{23}N_3O_5Na$ 372.1530, found 372.1532. Data is consistent with that given in the literature.[12]

***Ethyl (3R)-3-{[(tert-butoxy)carbonyl]amino}-3-(4-chlorophenyl)-2-diazopropanoate* 4f** Prepared according to general procedure A using aldimine **2f** (23.9 mg, 0.10 mmol) to afford the title compound in 60% isolated yield as a yellow solid (19 mg) and 96% ee. [determined by HPLC, Chiralpak AD-H, hexane/isopropanol = 95/5, 1 mL/min, λ = 220 nm, t (major) = 15.42 min, t (minor) = 17.49 min]. **MPT** 88-92 °C; [lit. for the racemate 102 – 103 °C][17]; $[\alpha]_D^{25}$ = +32.4 (*c* = 0.75, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.34 (d, *J*=8.5 Hz, 2 H, ArH), 7.30 (d, *J*=8.5 Hz, 2 H, ArH), 5.63 (d, *J*=7.7 Hz, 1 H, CHNH), 5.42 (br. s., 1 H, NHCH), 4.13 - 4.33 (m, 2 H, CH_2CH_3), 1.45 (s, 9 H, $OC(CH_3)_3$), 1.25 (t, *J*=7.1 Hz, 3 H, CH_2CH_3); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ ppm 165.9 (OC=O), 155.0 (NC(=O)OC), 137.9 (ArC), 134.0 (ArC), 129.2 (ArCH), 127.8 (ArCH), 80.7 ($OC(CH_3)_3$), 61.3 (CH_3CH_2), 51.0 (CHNH), 28.4 ($OC(CH_3)_3$), 14.5 (CH_2CH_3); **IR** ν_{max}/cm^{-1} 3343, 2876, 2931, 2095, 1695, 1491, 1392, 1166; **HRMS** (ESI-TOF) : calcd for $[M+Na]^+$ $C_{16}H_{20}ClN_3O_4Na$ 376.1035, found 376.1036. Data is consistent with that given in the literature.[12]

***Ethyl (3R)-3-{[(tert-butoxy)carbonyl]amino}-3-(2-chlorophenyl)-2-diazopropanoate* 4g** Prepared according to general procedure A using aldimine **2g** (23.9 mg, 0.10 mmol) to afford the title compound in 80% isolated yield (28 mg) and 94% ee [determined by HPLC, Chiralpak AD-H, hexane/isopropanol = 95/5, 1 mL/min, λ = 220 nm, t (major) = 16.74 min, t (minor) = 19.41 min]. $[\alpha]_D^{25}$ = +104.9 (*c* =1.0, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.47 (d, *J*=7.3 Hz, 1 H, ArH), 7.38 (dd, *J*=7.6, 1.4 Hz, 1 H, ArH), 7.21 - 7.32 (m, 2 H, ArH), 5.94 (d, *J*=7.7 Hz, 1 H, CHNH), 5.74 (br. s, 1 H, NHCH), 4.01 - 4.37 (m, 2 H, CH_2CH_3), 1.44 (s, 9 H, $C(CH_3)_3$), 1.23 (t, *J*=7.1 Hz, 3 H, CH_2CH_3);**^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ ppm 166.0 (OC=O), 154.8 (NC(=O)OC), 136.8 (ArC), 132.8 (ArC), 130.1 (ArCH), 129.2 (ArCH), 128.2 (ArCH), 127.1 (ArCH), 80.5 ($OC(CH_3)_3$), 61.3 (CH_2CH_3), 49.34 (CHNH), 28.59 ($OC(CH_3)_3$), 14.65 (CH_2CH_3); **IR** ν_{max}/cm^{-1} 3343, 2977, 2360, 2096, 1698, 1476, 1169. **HRMS** (ESI-TOF): calcd for $[M+Na]^+$ $C_{16}H_{20}ClN_3O_4Na$ 376.1035, found 376.1036.

***Ethyl (3R)-3-{[(tert-butoxy)carbonyl]amino}-2-diazo-3-(4-fluorophenyl)propanoate* 4h** Prepared according to general procedure A, using aldimine **2h** (22.3 mg, 0.10 mmol) which afforded the title compound in 76% isolated yield as a yellow solid (25 mg) and 96% ee. [determined by HPLC, Chiralpak AD-H, hexane/isopropanol = 95/5, 1 mL/min, λ = 220 nm, t (major) = 15.31 min, t (minor) = 17.15 min]. **MPT** 82 – 86 °C; $[\alpha]_D^{25}$ = +29.5 (*c* =1.1, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.31-7.34 (m, 2 H, ArH), 7.02-7.06 (m, 2 H, ArH), 5.64 (d, *J*=7.4 Hz, 1 H, CHNH), 5.41 (br. s, 1 H, NHCH), 4.22 (q, *J*=7.1 Hz, 2 H, CH_2CH_3), 1.45 (s, 9 H, $OC(CH_3)_3$), 1.25 (t, *J*=7.1 Hz, 3 H, CH_2CH_3); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ ppm 165.8 (OC=O), 163.6 & 161.1 (d, J_{CF} = 247.2 Hz, ArCF), 154.9 (NC(=O)OC), 134.9 (ArC), 127.9 (ArCH), 127.9 (ArCH), 115.8 (ArCH), 115.6 (ArCH), 80.5 ($OC(CH_3)_3$), 61.1 (CH_2CH_3), 50.8 (CHNH), 28.3 ($OC(CH_3)_3$), 14.4 (CH_2CH_3); **^{19}F NMR** δ -114.3; **IR** ν_{max}/cm^{-1} 3346, 2980, 2095, 1694, 1509, 1158. Data is consistent with that given in the literature.[12]

***Ethyl (3R)-3-(3-bromophenyl)-3-{[(tert-butoxy)carbonyl]amino}-2-diazopropanoate* 4i** Prepared according to the general procedure A using aldimine **2i** (28.4 mg, 0.10 mmol) to afford the title compound as a yellow oil in 72% isolated yield (28 mg) and 95% ee [determined by HPLC, Chiralpak AS-H,

hexane/isopropanol = 95/5, 1 mL/min, λ = 220 nm, t (minor) = 9.65 min, t (major) = 13.11 min]. $[\alpha]_D^{25}$ = +30.5 (*c* =1.3 , $CHCl_3$); **^{1}H NMR**(400 MHz, $CDCl_3$) δ ppm 7.53 (s, 1 H, ArH), 7.46 (d, *J*=7.8 Hz, 1 H, ArH), 7.18 - 7.36 (m, 2 H, ArH), 5.67 (d, *J*=7.6 Hz, 1 H, CHNH), 5.48 (br. s, 1 H, NHCH), 4.18-4.40 (m, 2H, CH_2CH_3), 1.49 (s, 9 H, $OC(CH_3)_3$), 1.27 (t, *J*=7.1 Hz, 3 H, CH_2CH_3); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ ppm 165.8 (OC=O), 155.0 (NC(=O)OC), 141.6 (ArC), 131.3 (ArCH), 130.5 (ArCH), 129.5 (ArCH), 125.0 (ArCH), 123.0 (ArC), 80.8 ($OC(CH_3)_3$), 61.3 (CH_2CH_3), 50.9 (CHNH), 28.4 ($OC(CH_3)_3$), 14.5 (CH_2CH_3); **IR** ν_{max}/cm^{-1} 3341, 2980, 2095, 1695, 1571, 1475, 1369, 1163; **HRMS** (ESI-TOF) : calcd for $[M+Na]^+$ $C_{16}H_{20}BrN_3O_4Na$ 420.0529, found 420.0530.

***Ethyl (3R)-3-{[(tert-butoxy)carbonyl]amino}-2-diazo-3-(naphthalen-2-yl)propanoate* 4j** Prepared according to general procedure A, using aldimine **2j** (25.5 mg, 0.10 mmol) which afforded the desired compound in 81% isolated yield as an amorphous, yellow solid (29 mg) and 98% ee. [determined by HPLC, Chiralpak AD-H, hexane/isopropanol = 95/5, 1 mL/min, λ = 220 nm, t (minor) = 14.66 min, t (major) = 18.32 min]. $[\alpha]_D^{25}$ = +22.9 (*c* = 1.1, $CHCl_3$); **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.77-7.93 (m, 4 H, ArH), 7.41 - 7.55 (m, 3 H, ArH), 5.84 (d, *J*=7.5 Hz, 1 H, CHNH), 5.50 (br. s, 1 H, NHCH), 4.23 (q, *J*=7.1 Hz, 2 H, CH_2CH_3), 1.47 (s, 9 H, $OC(CH_3)_3$), 1.25 (t, *J*=7.1 Hz, 3 H, CH_2CH_3); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ ppm 166.1 (OC=O), 155.1 (NC(=O)OC), 136.6 (ArC), 133.4 (ArC), 133.1 (ArC), 129.0 (ArCH), 128.2 (ArCH), 127.8 (ArCH), 126.6 (ArCH), 126.4 (ArCH), 125.1 (ArCH), 124.3 (ArCH), 80.6 ($OC(CH_3)_3$), 61.2 (CH_2CH_3), 51.6 (CHNH), 28.5 ($OC(CH_3)_3$), 14.5 (CH_2CH_3); **IR** ν_{max}/cm^{-1} 3342, 2978, 2093, 1695, 1506, 1392, 1164. Data is consistent with that given in the literature.[12]

***Ethyl (3R)-3-{[(tert-butoxy)carbonyl]amino}-2-diazo-3-(naphthalen-1-yl)propanoate* 4k** Prepared according to general procedure A using aldimine **2k** (25.5 mg, 0.10 mmol) to afford the desired compound in 84% isolated yield as a yellow oil (31 mg) and 96% ee [determined by HPLC, Chiralpak AD-H, hexane/isopropanol = 95/5, 1 mL/min, λ = 220 nm, t (major) = 21.15 min, t (minor) = 22.85 min]. $[\alpha]_D^{25}$= +46.5 (*c* = 1.4, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 8.02 (d, *J*=8.3 Hz, 1 H, ArH), 7.88 (d, *J*=7.9 Hz, 1 H, ArH), 7.82 (d, *J*=8.2 Hz, 1 H, ArH), 7.49 - 7.60 (m, 3 H, ArH), 7.42 - 7.48 (m, 1 H, ArH), 6.43 (d, *J*=7.0 Hz, 1 H, CHNH), 5.30 (br. s., 1 H, NHCH), 4.25 (q, *J*=7.1 Hz, 2 H, CH_2CH_3), 1.44 (br. s., 9 H, $OC(CH_3)_3$), 1.26 (t, *J*=7.1 Hz, 3 H, CH_2CH_3); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$), δ ppm 165.8 (OC=O), 154.9 (NC(=O)OC), 134.3 (ArC), 134.2 (ArC), 130.4 (ArC), 129.2 (ArCH), 129.1 (ArCH), 127.0 (ArCH), 126.2 (ArCH), 125.3 (ArCH),), 123.8 (ArCH), 122.9 (ArCH), 80.6 ((OC(CH$_3$)$_3$), 61.3 (CH_2CH_3), 48.1 (CHNH), 28.4 ($OC(CH_3)_3$), 14.6 (CH_3CH_2); **IR** ν_{max}/cm^{-1} 3341, 2978, 2094, 1694, 1510, 1368, 1165; **HRMS** (ESI-TOF): calcd for $[M+Na]^+$ $C_{20}H_{23}N_3O_4Na$ $[M+Na]^+$ 392.1581, found 392.1577.

***Ethyl (3S)-3-{[(tert-butoxy)carbonyl]amino}-2-diazo-3-(thiophen-2-yl)propanoate* 4l** Prepared according to General Procedure A using aldimine **2l** (21.1 mg, 0.10 mmol) to afford the title compound in 81% isolated yield as a yellow oil (27 mg), and 97% ee [determined by HPLC, Chiralpak AD-H, hexane/isopropanol = 95/5, 1 mL/min, λ = 220 nm, t (minor) = 11.57 min, t (major) = 16.81 min]. $[\alpha]_D^{25}$ = +8.6 (*c* = 1.1, $CHCl_3$); **^{1}H NMR**(400 MHz, $CDCl_3$) δ ppm 7.21-7.28 (m, ArH), 6.94 - 7.01 (m, 2 H, ArH), 5.87 (d, *J*=7.9 Hz, 1 H, CHNH), 5.49 (br. s., 1 H, NHCH), 4.25 (q, *J*=7.1 Hz, 2 H, CH_2CH_3), 1.47 (s, 9 H, $OC(CH_3)_3$), 1.27 (t, *J*=7.1 Hz, 3 H, CH_2CH_3); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$), δ ppm 165.7 (OC=O), 154.7 (NC(=O)OC), 143.3 (ArC), 127.2 (ArCH), 125.3 (ArCH), 124.9 (ArCH), 80.7 ($OC(CH_3)_3$), 61.2 (CH_2CH_3), 48.1 (CHNH), 28.4 ($OC(CH_3)_3$), 14.5 (CH_2CH_3); **HRMS** (ESI-TOF) : calcd for $[M+Na]^+$ $C_{14}H_{19}N_3O_4SNa$ 348.0988, found 348.0987. Data is consistent with that given in the literature.[12]

***Ethyl (3S)-3-{[(tert-butoxy)carbonyl]amino}-2-diazo-3-(furan-2-yl)propanoate* 4m** Prepared according to general procedure A, using aldimine **2m** (19.5 mg, 0.10 mmol) which afforded the desired compound in 70% isolated yield as a yellow oil (22 mg) and 98% ee. [determined by HPLC, Chiralpak AD-H, hexane/isopropanol = 95/5, 1 mL/min, λ = 220 nm, t (minor) = 9.44 min, t (major) = 13.75 min]. $[\alpha]_D^{25}$ = +12.0 (*c* = 1.0, $CHCl_3$). **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.36 (s, 1 H, ArH), 6.31 - 6.37 (m, 1 H, ArH), 6.28 (d, J = 3.1 Hz, 1H, ArH), 5.70 (d, *J*=7.6 Hz, 1 H, CHNH), 5.39 (br. s, 1 H, NHCH), 4.23 (q, *J*=7.2 Hz, 2 H, CH_2CH_3), 1.46 (s, 9 H, $OC(CH_3)_3$), 1.26 (t, *J*=7.1 Hz, 3 H, CH_3CH_2); **^{13}C {^{1}H} NMR** (101 MHz, $CDCl_3$) δ ppm 165.7 (OC=O), 154.8 (NC(=O)OC), 151.3 (ArC), 142.6 (ArCH), 110.7 (ArCH), 107.2 (ArCH), 80.7 ($OC(CH_3)_3$), 61.2 (CH_2CH_3), 46.2 (CHNH), 28.4 ($OC(CH_3)_3$), 14.6 (CH_2CH_3); **HRMS** (ESI-TOF) : calcd for $[M+Na]^+$ $C_{14}H_{19}N_3O_5Na$ 332.1217, found 332.1216. Data is consistent with that given in the literature.[12]

***Ethyl (3R)-3-{[(tert-butoxy)carbonyl]amino}-2-diazo-3-(pyridin-3-yl)propanoate* 4n** Prepared according to the general procedure A using aldimine **2n** (20.6 mg, 0.10 mmol) to afford the title compound as a yellow oil in 88% isolated yield and 92% ee [determined by HPLC, Chiralpak AD-H, hexane/isopropanol = 95/5, 1 mL/min, λ = 220 nm, t (minor) = 36.21 min, t (major) = 45.04 min]. $[\alpha]_D^{25}$ = +33.8 (*c* =0.145, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 8.62 (d, *J*=1.9 Hz, 1 H, ArH), 8.54 (d, *J*=3.8 Hz, 1 H, ArH), 7.65-7.73 (m, 1 H, ArH), 7.29 (dd, *J*=7.9, 4.8 Hz, 1 H, ArH), 5.70 (br. s., 1 H, CHNH& NHCH), 4.16 - 4.27 (m, 2 H, CH_2CH_3), 1.45 (s, 9 H, $OC(CH_3)_3$), 1.25 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3); **^{13}C {^{1}H} NMR** (126 MHz, $CDCl_3$) δ ppm 165.8 (OC=O), 155.0 (NC(=O)OC), 149.4 (ArCH), 148.2 (ArCH), 135.0 (ArC), 134.1 (ArCH), 123.6 (ArCH), 80.9 ($OC(CH_3)_3$), 61.4 (CH_2CH_3), 49.6 (CHNH), 28.4 ($OC(CH_3)_3$), 14.5 (CH_2CH_3); **IR** ν_{max}/cm^{-1} 3338, 2979, 2925, 2094, 1695, 1513, 1392, 1166; **HRMS** (ESI-TOF) : calcd for $[M+H]^+$ $C_{15}H_{21}N_4O_4$ 321.1557, found 321.1559.

***Prop-2-en-1-yl (3R)-3-{[(tert-butoxy)carbonyl]amino}-2-diazo-3-phenylpropanoate* 4o** Prepared according to

modified general procedure A, using diazoester **3b** (30 mg, 0.24 mmol, 1.2 eq) and aldimine **2a** (41 mg, 0.20 mmol) to afford the title compound in 79% isolated yield (52 mg) as a yellow oil and in 94% ee [determined by HPLC, Chiralpak AS-H, hexane/isopropanol =90/10, 1 mL/min, λ = 220 nm, t (minor) = 9.77 min, t (major) = 13.83 min]. $[\alpha]_D^{25}$ = +30.0 (*c* = 1.2, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.28 - 7.40 (m, 5 H, ArH), 5.93-5.85 (m, 1 H, $CH_2CH=CH_2$), 5.68 (br. s., 1 H, CHNH), 5.37 (br. s, 1 H, NHCH), 5.18 - 5.31 (m, 2 H, $CH_2CH=CH_2$), 4.60 - 4.72 (m, 2 H, $CH_2CH=CH_2$), 1.45 (s, 9 H, $OC(CH_3)_3$); **^{13}C {^{1}H} NMR** (126 MHz, $CDCl_3$) δ ppm 165.7 (OC=O), 155.0 (NC(=O)OC), 139.0 (ArC), 132.1 ($CH_2CH=CH_2$), 129.0 (ArCH), 128.2 (ArCH), 126.3 (ArCH), 118.4 ($CH_2CH=CH_2$), 80.5 ($OC(CH_3)_3$), 65.6 ($CH_2CH=CH_2$), 51.30 (CHNH), 28.38 ($OC(CH_3)_3$); **IR** ν_{max}/cm^{-1} 3323, 2095, 1720, 1495, 1114; **HRMS** (ESI-TOF) : calcd for $[M+Na]^+$ $C_{17}H_{21}N_3O_4Na$ $[M+Na]^+$ 354.1424, found 354.1426.

***Benzyl (3R)-3-{[(tert-butoxy)carbonyl]amino}-2-diazo-3-phenylpropanoate* 4p** Prepared according to modified general procedure A, using diazoester **3c** (42 mg, 0.24 mmol) and aldimine **2a** (41 mg, 0.20 mmol) to afford the title compound **4p** in 72% isolated yield (55 mg) as a yellow oil and in 92% ee [determined by HPLC, Chiralpak IA, hexane/isopropanol =95/5, 1 mL/min, λ = 220 nm, t (major) = 25.56 min, t (minor) = 32.25 min]. $[\alpha]_D^{25}$ = +21.9 (*c* = 1.1, $CHCl_3$); **^{1}H NMR** (400MHz, $CDCl_3$) δ ppm 7.27-7.40 (m, 10 H, ArH), 5.70 (br. s, 1 H, CHNH), 5.42 (br. s, 1 H, NHCH), 5.15-5.27 (m, 2 H, $ArCH_2$), 1.45 (s, 9 H, $(OC(CH_3)_3)$; **^{13}C {^{1}H} NMR** (126 MHz, $CDCl_3$) δ ppm 165.8 (OC=O), 155.0 (NC(=O)OC), 139.0 (ArC), 135.9 (ArC), 129.0 (ArCH), 128.7 (ArCH), 128.4 (ArCH), 128.2 (ArCH), 128.1 (ArCH), 126.3 (ArCH), 80.5 ($OC(CH_3)_3$), 66.7 ($ArCH_2$), 51.3 (CHNH), 28.4 ($OC(CH_3)_3$); **IR** ν_{max}/cm^{-1} 3349, 2094, 1690, 1453, 1165; **HRMS** (ESI-TOF) : calcd for $[M+Na]^+$ $C_{21}H_{23}N_3O_4Na$ $[M+Na]^+$ 404.1581, found 404.1578.

***(3R)-3-{[(tert-butoxy)carbonyl]amino}-2-diazo-3-phenylpropanoate* 4q** Prepared according to modified general procedure A, using diazoester **3d** (39 mg, 0.24 mmol) and aldimine **2a** (41 mg, 0.20 mmol) to afford the title compound **4q** after 66 h, in 64% isolated yield (47 mg) as a pale yellow solid and in 88% ee [determined by HPLC, Chiralpak AS-H, hexane/isopropanol =95/5, 1 mL/min, λ = 220 nm, t (major) = 16.75 min, t (minor) = 22.32 min]. **MPT** 102 – 104 °C; $[\alpha]_D^{25}$ = +29.0 (*c* = 1.1, $CHCl_3$); **^{1}H NMR** 400 MHz, $CDCl_3$) δ ppm 7.30-7.49 (m, 7 H, ArH), 7.19 - 7.24 (m, 1 H, ArH), 7.11 (d, *J*=6.2 Hz, 2 H, ArH), 5.76 (br. s, 1 H, CHNH), 5.48 (br. s, 1 H, NHCH), 1.48 (s, 9 H, $(OC(CH_3)_3)$; **^{13}C {^{1}H} NMR** (126 MHz, $CDCl_3$) δ ppm 164.2 (OC=O), 155.1 (NC(=O)OC), 150.4 (ArC), 138.9 (ArC), 129.5 (ArCH), 129.1 (ArCH), 128.4 (ArCH), 126.4 (ArCH), 125.9 (ArCH), 121.7 (ArCH), 80.7 ($OC(CH_3)_3$), 51.5 (CHNH), 28.4 ($OC(CH_3)_3$); **IR** ν_{max}/cm^{-1} 3327, 2097, 1718, 1453, 1137; **HRMS** (ESI-TOF) : calcd for $[M+Na]^+$ $C_{20}H_{21}N_3O_4Na$ $[M+Na]^+$ 390.1424, found 390.1423.

Preparative synthesis of 4a A reaction tube was charged with silver triflate (12.8 mg, 0.05 mmol, 0.01 eq) and (*R*)-DM-SEGPHOS (72 mg, 0.1 mmol, 0.02 eq). $CHCl_3$ (2.0 mL) was added under argon and the resulting mixture was stirred for 30 minutes at room temperature. Triethylamine (28 µL, 0.20 mmol, 0.04 eq) was added to produce a yellow coloured solution of catalyst. Aldimine **2a** (1.0 g, 5.0 mmol) was then added in $CHCl_3$ (4.0 mL) to produce a brightly coloured yellow solution. 4 Å molecular sieves were added at this point. The resulting mixture was cooled to -40°C and kept at this temperature for 30 minutes after which ethyl diazoacetate (5.2 mL, 6.0 mmol, 1.2 eq) was added. After 48 h, the reaction was quenched by passing it through a short pad of silica on a glass frit, eluting with diethyl ether. The volatiles were removed *in vacuo* and the resulting yellow crude oil was purified by FCC [100% petroleum ether to 2% diethyl ether to 10% diethyl ether] afforded diazo adduct **4a** as a yellow solid (1.28 g) in 81% yield and 96% ee determined by chiral HPLC. All spectroscopic data was consistent with that given previously.

Synthesis of racemates A round bottom flask was charged with aldimine (1.0 equiv, 0.1 mmol), Ag_2O (3.5 mg, 0.015 mmol) was then added and 4 Å molecular sieves. Ethyl acetate (1.0 mL) was added under an atmosphere of argon followed by triethylamine (1.4 µL, 0.01 mmol) and the resulting suspension was stirred for 10 minutes. The diazoester was then added (1.2 equiv) in 0.2 mL of solvent. Stirring was maintained for a 24 h period after which the reaction mixture was filtered through a pad of Celite® on a glass frit, eluting with ethyl acetate. The filtrate was concentrated *in vacuo* and purified by FCC.

***Ethyl (3S)-3-{[(tert-butoxy)carbonyl]amino}-3-phenylpropanoate* 5a** According to a literature procedure,[13] a flask was charged with diazo-adduct **4a** (100 mg, 0.30 mmol) and 10% palladium on carbon (32 mg). Dry methanol (1.25 mL) was added under argon. The flask was flushed with argon 3 times by alternating vacuum and argon filling with a balloon. The argon balloon was replaced with H_2 and stirred at room temperature for 12 hours. The palladium catalyst was then removed by filtration through a pad of Celite® on a glass frit, eluting with methanol. The filtrate was then concentrated *in vacuo* and purified directly by FCC eluting with [100% petroleum ether and ramping to 10% diethyl ether] to yield the desired compound **5a** as a colourless crystalline solid (66 mg), 75% isolated yield, 96% ee [determined by HPLC, Chiralcel OD, hexane/isopropanol = 95/5, 1 mL/min, λ = 220 nm, t (minor) = 15.81 min, t (major) = 19.28 min]. By comparison of peak order elution on the HPLC, the absolute stereochemistry of **5a** was determined to be (*S*).[13] **MPT** 76 - 80°C; $[\alpha]_D^{25}$ = -32.7 (*c* = 1.1, EtOAc) [lit. $[\alpha]_D^{20}$ = -31.6 (*c* = 1.0, EtOAc) for (*S*)-**5a**. From the optical rotation, the absolute configuration was determined to be (*S*)[14]; **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.17 - 7.41 (m, 5 H, ArH), 5.50 (br. s., 1 H, NHCH), 5.10 (br. s., 1 H, CHNH), 4.06 (q, *J*=7.3 Hz, 2 H, CH_2CH_3), 2.70 - 2.99 (m, 2 H, $CHCH_aH_bNH$), 1.41 (br. s., 9 H, $OC(CH_3)_3$), 1.15 (t, *J*=7.1 Hz, 3 H, CH_2CH_3); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$) δ ppm 171.0 (OC=O), 155.1 (NC(=O)OC), 141.2

(ArC), 128.6 (ArCH), 127.5 (ArCH), 126.2 (ArCH), 79.7 ($OC(CH_3)_3$), 60.7 (CH_2CH_3), 51.3 ($CHCH_aH_bNH$), 41.1 ($CHCH_aH_bNH$), 28.4 ($OC(CH_3)_3$), 14.1(CH_2CH_3); **IR** ν_{max}/cm^{-1} 3352, 2978, 2930, 2358, 1728, 1497, 1167. All data reported is in agreement with the literature.[13]

Ethyl (2R,3R)-3-{[(tert-butoxy)carbonyl]amino}-2-hydroxy-3-phenylpropanoate **5b** According to a literature procedure,[15] Oxone® (154 mg, 0.50 mmol, 5.0 equiv) was suspended in acetone/H_2O (3.0 mL:1.5 mL). Sodium hydrogencarbonate was then added (168 mg, 2.0 mmol, 20 equiv) and stirred for 15 min at room temperature, after which the resulting mixture was cooled to 0 °C. Diazo adduct **4a** (32 mg, 0.10 mmol, 1.0 equiv) was then added in 3.0 mL of dichloromethane over a period of 5 minutes. The mixture was then allowed to warm to room temperature and stirred at this temperature for 5 hours. Upon completion, the reaction mixture was diluted with water (3 mL) and extracted with dichloromethane (3 × 5 mL). The organic phase was washed with brine and dried over sodium sulfate and concentrated *in vacuo*. The resulting clear oil was re-dissolved in dry dichloromethane (2.5 mL) under argon which was then cooled to -78°C. Sodium borohydride (8.7 mg, 0.23 mmol, 2.25 equiv) was then added in one portion. The reaction mixture was allowed to warm to room temperature slowly. After 27 hours, the reaction was quenched with sat. NH_4Cl and extracted with dichloromethane (3 × 5 mL). The combined organics were dried over sodium sulfate and concentrated *in vacuo*. Purification by FCC [100% petroleum ether to 50% diethyl ether] afforded the title compound **5b** in 58% isolated yield (18 mgs) as a white, crystalline solid with a 8:1 d.r. (*anti*:*syn*). A round bottom flask was charged with aldimine (1.0 equiv, 0.1 mmol), Ag_2O (3.5 mg, 0.015 mmol) was then added and 4 Å molecular sieves. Ethyl acetate (1.0 mL) was added under an atmosphere of argon followed bytriethylamine (1.4µL, 0.01 mmol) and the resulting suspension was stirred for 10 minutes. The diazoester was then added (1.2 equiv) in 0.2 mL of solvent. Stirring was maintained for a 24 h period after which the reaction mixture was filtered through a pad of Celite® on a glass frit, eluting with ethyl acetate. The filtrate was concentrated *in vacuo* and purified by FCC. *Major diastereoisomer:* **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.12 - 7.34 (m, 5 H, ArH), 5.61 (d, *J*=8.3 Hz, 1 H, NHCH), 5.10 (d, *J* =6.4 Hz, 1 H, CHNH), 4.57 (br.s. 1H, CHOH), 4.09 - 4.17 (m, 2 H, CH_2CH_2), 2.90 (d, *J*=6.4 Hz, 1 H, CHOH), 1.43 (s, 9 H, $OC(CH_3)_3$), 1.24 (t, *J*=7.1 Hz, 3 H, CH_2CH_3); **^{13}C {^{1}H} NMR** (100 MHz, $CDCl_3$) δ ppm 172.0 (OC=O), 155.1 (NC(=O)OC), 136.9 (ArC), 128.5 (ArCH), 128.2 (ArCH), 127.5 (ArCH), 80.0 ($OC(CH_3)_3$), 73.3 (CHOH), 62.2 (CH_2CH_3), 56.7 (CHNH), 28.3 ($OC(CH_3)_3$), 14.1 (CH_2CH_3). All data reported is in agreement with the literature.[12]

Ethyl (2E,3R)-3-{[(tert-butoxy)carbonyl]amino}-2-hydrazinylidene-3-phenylpropanoate **5c** Diazo adduct **4a** (32 mg, 0.10 mmol) was dissolved in diethyl ether (0.30 mL) under argon. Tributylphosphine (75 µL, 3 equiv) was added in one portion. The resulting mixture was stirred at room temperature for 20 minutes upon which the mixture turned from a yellow solution to clear and then solid precipitate was observed. The reaction mixture was diluted with ethyl acetate and washed with saturated sodium hydrogen carbonate solution and brine. The organic phase was dried over sodium sulfate and concentrated *in vacuo*. Purification by FCC [petroleum ether to petroleum ether/ethyl acetate 1/1] to afford the title compound **5c** in 88% isolated yield (27 mgs) as a clear oil and 96% ee [determined by HPLC, Chiralpak AD-H, hexane/isopropanol =80/20, 1 mL/min, λ = 220 nm, t (major) = 7.48 min, t (minor) = 8.37 min]. $[\alpha]_D^{25}$ = -38.2 (*c* = 1.3, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.32-7.35 (m, 2 H, ArH), 7.25-7.28 (m, 3 H, ArH), 6.65 (br. s., 2 H, C=NNH_2), 6.07 (d, *J*=9.5 Hz, 1 H, CHNH), 6.00 (br. s., 1 H, CHNH), 4.16-4.24 (m, 2 H, CH_2CH_3), 1.46 (s, 9 H, $OC(CH_3)_3$), 1.24 (t, *J* = 7.1 Hz, 3 H, CH_2CH_3); **^{13}C {^{1}H} NMR** (126 MHz, $CDCl_3$) δ ppm 164.2 (OC=O), 156.1(NC(=O)OC), 138.5 (C=N-NH_2), 137.8 (ArC), 128.8 (ArCH), 127.6 (ArCH), 125.5 (ArCH), 80.4 ($OC(CH_3)_3$), 61.2 (CH_2CH_3), 47.4 (CHNH), 28.3 ($OC(CH_3)_3$), 14.1 (CH_2CH_3); **IR** ν_{max}/cm^{-1} 3410, 3300, 3236, 2979, 2932, 1696, 1495, 1167; **HRMS** (ESI-TOF) : calcd for $[M+Na]^+$ $C_{16}H_{23}N_3O_4Na$ 344.1581, found 344.1582.

1-tert-Butyl 4-ethyl (4S,5R)-4-benzyl-5-phenyl-4,5-dihydro-1H-1,2,3-triazole-1,4-dicarboxylate **5d** According to a literature procedure,[9] a RBF was charged with sodium hydride (19.1 mg, 0.48 mmol) and cooled to 0 °C with an ice bath under an atmosphere of argon. Dry *N, N*-dimethylformamide was then added (1.0 mL). Diazo adduct **4a** (0.40 mmol, 128 mg) and benzyl bromide (0.48 mmol, 58 µL) were then added in a dropwise manner in DMF (0.44 mL) and the mixture was stirred for 15 min. The resulting suspension was allowed to warm to room temperature and stirred for 30 minutes. A saturated solution of ammonium chloride (2 mL) was then added to produce a yellow suspension and the organic phase was extracted using ethyl acetate, dried over Na_2SO_4 and concentrated *in vacuo*. Purification by FCC [100% petroleum ether to 20% diethyl ether] afforded the title compound in 79% isolated yield as a white solid (129 mg) as a single diastereoisomer, 96% ee [determined by HPLC, Chiralpak IA, hexane/isopropanol =95/5, 1 mL/min, λ = 220 nm, t (major) = 15.79 min, t (minor) = 19.12 min]. **MPT** 160 - 162 °C; $[\alpha]_D^{25}$ = +103.6 (*c* = 0.9, $CHCl_3$); **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.19 - 7.42 (m, 8 H, ArH) 7.05 (br. s., 2 H, ArH) 4.80 (s, 1 H, CHCN(C=O)) 3.57 - 3.72 (m, 2 H, CH_2CH_3) 3.54 (d, *J* = 14.0 Hz, 1 H, $ArCH_aH_bC$) 3.25 (d, *J* = 14.0 Hz, 1 H, $ArCH_aH_bC$) 1.27 (s, 9 H, $OC(CH_3)_3$) 0.83 (t, *J*=7.2 Hz, 3 H, CH_2CH_3); **^{13}C {^{1}H} NMR** (126 MHz, $CDCl_3$) δ ppm 167.2 (OC=O), 148.9 (NC(=O)OC), 136.7 (ArC), 133.4 (ArC), 130.6 (ArCH), 128.5 (ArCH), 128.4 (ArCH), 128.3 (ArCH), 127.6 (ArCH), 126.8 (ArCH), 95.0 ($ArCH_aH_bC$), 83.4 ($OC(CH_3)_3$), 62.9 (CHCN(C=O)), 61.8 (CH_2CH_3), 43.1 ($ArCH_aH_bC$), 27.8 ($OC(CH_3)_3$), 13.5 (CH_2CH_3); **IR** ν_{max}/cm^{-1} 2978, 2358, 1738, 1498, 1336, 1149. All data reported is in agreement with the literature.[9]

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: xx.

Further optimization tables, NMR spectra and HPLC chromatograms (PDF)

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