Asymmetric Friedel–Crafts Reactions: Catalytic Enantioselective Addition of Aromatic and Heteroaromatic C–H Bonds to Activated Alkenes, Carbonyl Compounds, and Imines

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Received 4 February 2003

Abstract: The development and scope of catalytic enantioselective addition of aromatic and heteroaromatic C–H bonds to α,β-unsaturated alkenes, carbonyl compounds, and imines are presented. α,β-Unsaturated alkenes, 4-substituted 2-oxo-3-butenoate esters and alkylidene malonates react with indoles, furans and electron-rich aromatic compounds in the presence of chiral bisoxazoline-copper(II) complexes to give the Friedel–Crafts alkylation adduct in moderate to high yields and with up to >99.5% ee. Chiral bisoxazoline-copper(II) complexes can also catalyze the enantioselective addition of especially electron-rich aromatic compounds to activated carbonyl compounds such as glyoxylates and trifluoropyruvate to give e.g. optically active aromatic mandelic acid esters in good yields and enantioselectivities. Electron-rich aromatic compounds and heteroaromatic compounds react in an enantioselective fashion with activated *N*-protected α-imino esters to give optically active aromatic and heteroaromatic α-amino acid derivatives using chiral BINAP-copper(I) complexes as the catalyst.

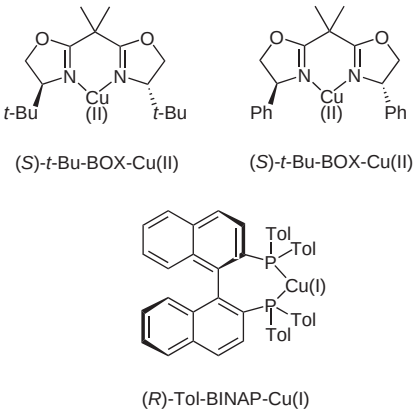
Key words: asymmetric catalysis, Friedel–Crafts reactions, alkenes, carbonyl compounds, imines

Friedel–Crafts reactions are fundamental transformations in organic chemistry and have been widely used for the synthesis of many different compounds in academia and industry.[1] Depending on the substrates used, alkenes, carbonyl compounds, or imines, different types of catalytic activation can be applied to these substrates, Brønsted and Lewis acids are among the most frequently used catalysts.

One of the challenges in organic chemistry is the development of synthetic procedures, which allow the formation of optically active compounds using chiral Lewis acids as catalysts. Until recently, for the catalytic enantioselective Friedel–Crafts reactions only a very limited number of reactions have been developed.[2]

In this feature article our recent developments in the field of catalytic enantioselective Friedel–Crafts-type addition reactions of aromatic and heteroaromatic C–H bonds to activated alkenes, carbonyl compounds, and imines are presented. Our approach to these reactions has been to try to develop transformations, which use easy-available chiral ligands in combination with Lewis acids as the catalysts.

The chiral bisoxazoline-copper(II) and BINAP-copper(I) complexes (see Figure 1) have been found to be useful catalysts for the enantioselective addition of electron-rich aromatic and heteroaromatic compounds to activated alkenes, carbonyl compounds, and imines.



(*S*)-*t*-Bu-BOX-Cu(II) (*S*)-*t*-Bu-BOX-Cu(II)

(*R*)-Tol-BINAP-Cu(I)

Figure 1

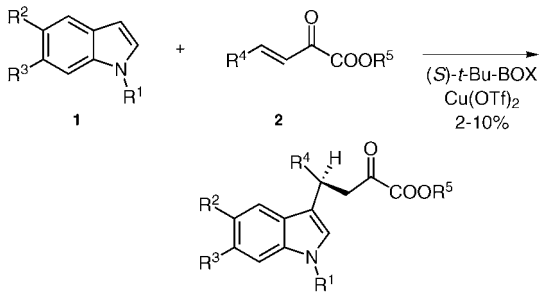
1 Catalytic Enantioselective Addition to Activated Alkenes

Chiral bisoxazoline[3] (BOX)-copper(II) complexes (Figure 1) have been found to be useful catalysts for a variety of different organic transformations including the enantioselective Friedel–Crafts alkylation of heteroaromatic and aromatic compounds to various types of α,β-unsaturated activated compounds. In order to apply the (BOX)-copper(II) complexes as the catalyst for these reactions, a substrate which can coordinate to the catalyst in a bidentate fashion has to be used. The reactions to be presented here are addition reactions to β,γ-unsaturated α-keto esters (4-substituted 2-oxo-3-butenoate esters) and alkylidene malonates, which can coordinate to the (BOX)-copper(II) complex in a bidentate fashion. These reactions might also be considered as asymmetric Michael-type reactions.

The (*S*)-*t*-Bu-BOX-Cu(II) and (*S*)-Ph-BOX-Cu(II) complexes catalyse an enantioselective addition of heteroaromatic and aromatic C–H bonds to β,γ-unsaturated α-ketoesters.[4] Substituted indoles **1** reacted with 4-substituted 2-oxo-3-butenoate esters **2** to give the Friedel–Crafts alkylation adducts **3**. A screening of the (*S*)-*t*-Bu-BOX-Cu(II) and (*S*)-Ph-BOX-Cu(II) in various solvents, using

Synthesis 2003, No. 7, Print: 20 05 2003.
Art Id.1437-210X,E;2003,0,07,1117,1125,ftx,en;Z01703SS.pdf.

different counterions and reaction conditions revealed that the combination of (*S*)-*t*-Bu-BOX and $Cu(OTf)_2$ in Et_2O as the solvent gave the best results in terms of yield and enantiomeric excess of **3** (Equation 1 and Table 1).



3a: R^1-R^3 = H, R^4 = Ph, R^5 = Me
3b: R^1 = Me, R^2 = R^3 = H, R^4 = Ph, R^5 = Me
3c: R^1 = R^3 = H, R^2 = OMe, R^4 = Ph, R^5 = Me
3d: R^1 = R^2 = H, R^3 = Cl, R^4 = Ph, R^5 = Me
3e: R^1-R^3 = H, R^4 = Me, R^5 = Et
3f: R^1 = R^3 = H, R^2 = OMe, R^4 = Me, R^5 = Et
3g: R^1 = R^3 = H, R^2 = OMe, R^4 = CH_2OBn, R^5 = Et

Equation 1

Table 1 Catalytic Enantioselective Friedel–Crafts Reactions of Indoles **1** with 4-Substituted 2-Oxo-3-butenoate Esters **2**[a,4]

Entry	Reaction Time (h)	Product	Yield (%)	ee (%)
1	64	**3a**	77	99.5
2	48	**3b**	98	96
3	1	**3c**	95	>99.5
4	16	**3d**	69	97
5	16	**3e**	96	95
6	1	**3f**	95	>99.5
7	1	**3g**	98	95

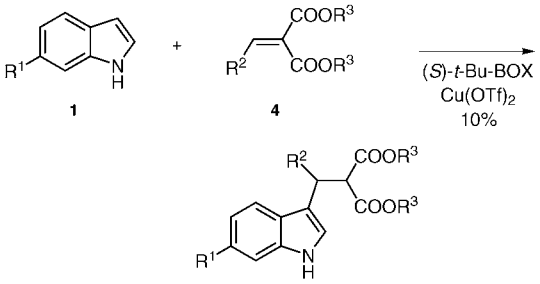
[a] Catalyzed by (*S*)-*t*-Bu-BOX-$Cu(OTf)_2$ (2–10 mol%) in Et_2O.

The results in Table 1 show that (*S*)-*t*-Bu-BOX-$Cu(OTf)_2$ catalyses a highly enantioselective addition of indoles **1** with both electron-donating (entries 3,6,7) and electron-withdrawing (entry 4) substituents on the 4-substituted 2-oxo-3-butenoate esters **2**.

The Friedel–Crafts alkylation of the 4-substituted 2-oxo-3-butenoate esters **2** proceeded well also for other heteroaromatic compounds, e.g. 2-methyl-furan in the presence of (*S*)-*t*-Bu-BOX-$Cu(OTf)_2$ (10 mol%) as the catalyst in Et_2O. The corresponding Friedel–Crafts adducts (the reaction takes place selectivity at 5-position of 2-methyl furan) were obtained in very high yields (>90%) and with >79% ee. Quite similar results were obtained for electron-rich aromatic compounds, e.g. reaction of 1,3-dimethoxy benzene with the 2-oxo-3-butenoate esters **2** gave 60–89% ee.

The absolute configuration of the Friedel–Crafts alkylation adducts was assigned using X-ray analysis. The absolute configuration of the chiral carbon atom formed in the indole derived adduct **3d** was found to be (*R*).

The chiral bisoxazoline-copper(II) complexes have also been shown to be useful chiral catalysts for other Friedel–Crafts alkylation reactions. Indoles **1** reacted with alkylidene malonates **4** in an enantioselective reaction (Equation 2).[5] The reaction proceeded at room temperature in THF and some representative results are given in Table 2.



5a: R^1 = H, R^2 = Ph, R^3 = Et
5b: R^1 = H, R^2 = 4-NO_2-Ph, R^3 = Me
5c: R^1 = H, R^2 = 2-Cl-Ph, R^3 = Et
5d: R^1 = OMe, R^2 = Ph, R^3 = Me

Equation 2

Compared to the reaction of 4-substituted 2-oxo-3-butenoate esters **2**, the reactions of alkylidene malonates **4** with indoles, catalysed by (*S*)-*t*-Bu-BOX-$Cu(OTf)_2$ pro-

Biographical Sketch

Karl Anker Jørgensen (b. 1955) is a Professor at the Danish National Research Foundation: Center for Catalysis. Following a PhD from Aarhus University 1984 and a post-doctoral period with R. Hoffmann, Cornell University he joined the Aarhus University faculty. The development and understanding of catalytic reactions in chemistry is the main goal of his research.

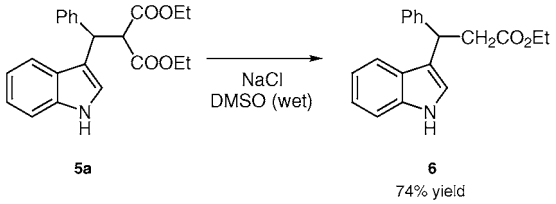
Table 2 Catalytic Enantioselective Friedel–Crafts Alkylation Reactions of Alkylidene Malonates **4** with Indoles **1**[a,5]

Entry	Product	Yield (%)	Ee (%)
1	**5a**	73	60 (92)[b]
2	**5b**	92	56
3	**5c**	87	69
4	**5d**	99	58

[a] Catalyzed by (*S*)-*t*-Bu-BOX-Cu(OTf)$_2$ (10 mol%) in THF.
[b] Ee after recrystallisation.

ceeded with lower enantioselectivity as shown in Table 2. However, the enantiomeric excess of the Friedel–Crafts adduct can be improved to >90% ee by crystallisation. The catalytic enantioselective Friedel–Crafts alkylation of the alkylidene malonates could also be achieved for heteroaromatic compounds, i.e. pyrroles and indoles. For these heteroaromatic compounds the isolated yields of the Friedel–Crafts adducts were >95%, however, the enantiomeric excess was low to moderate.

The optically active Friedel–Crafts adducts obtained by the addition of indoles to alkylidene malonates can undergo a decarboxylation reaction[6] to give mono ester **6** in 74% isolated yield (Equation 3). The product (**6**) obtained by this reaction is in principle the optically active Friedel–Crafts adduct obtained from the reaction of indole with cinnamic acid ethyl ester.



Equation 3

Recently, Tang et al. have developed the Friedel–Crafts alkylation/Michael addition of alkylidene malonates with indoles as a highly enantioselective reaction as a further development of the chiral bisoxazoline ligand.[7] The use of the C_3-trisoxazoline ligand (Figure 2) in combination with $Cu(ClO_4)_2$ as the Lewis acid gave the optically active adducts **5** in high yields and very high enantioselectivity (up to 93% ee)

An interesting new dimension to the catalytic enantioselective addition of aromatic and heteroaromatic compounds to activated alkenes has also recently been presented by MacMillan et al.[8] By using organocatalysis they have developed the enantioselective addition of pyrroles, indoles and anilines to α,β-unsaturated aldehydes. These reactions proceed in good yield and with very high enantioselectivities.

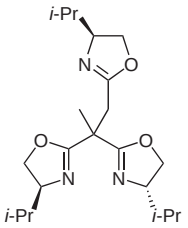
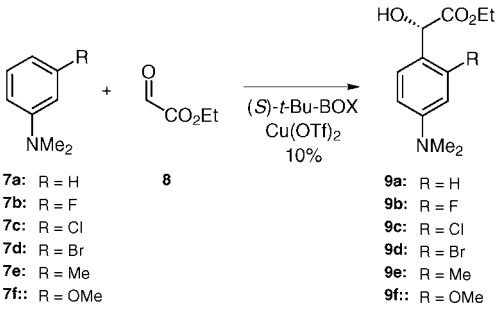


Figure 2

2 Catalytic Enantioselective Addition to Carbonyl Compounds

Catalytic enantioselective Friedel–Crafts reactions have been found for the reaction of chloral with anisole derivatives catalysed by chiral aluminium complexes.[9] Mikami et al. have also studied the catalytic enantioselective reactions of chloral using BINOL-TiX_2 as the catalyst.[10] Furthermore, a chiral zirconium complex has been shown to catalyse the enantioselective addition of 1-napthol to pyruvate.[11]

We have found that especially the (*S*)-*t*-Bu-BOX-Cu(II) complex also is an effective catalyst for the addition of electron-rich aromatic compounds to activated carbonyl compounds such as glyoxylate and trifluoropyruvate.[12] The catalytic enantioselective Friedel–Crafts reaction proceeds well for *meta*-substituted *N*,*N*-dimethyl-anilines **7** reacting with ethyl glyoxylate **8** in the presence of (*S*)-*t*-Bu-BOX-Cu(OTf)$_2$ (10 mol%) as the catalyst in a variety of solvents (Equation 4). Table 3 shows the results for the reaction of **7** with **8** in CH_2Cl_2 and THF as the solvents.



Equation 4

The catalytic enantioselective Friedel–Crafts reactions of *meta*-substituted *N*,*N*-dimethylanilines **7** with ethyl glyoxylate **8** proceeded when both electron-donating and electron-withdrawing substituents were attached to the aromatic nucleus. The results in Table 3 show that the reactions can proceed in both CH_2Cl_2 and THF. The yields of the optically active mandelic acid derivatives range from low (entry 6) to high (entry 3) depending on the aromatic substituent. The highest yields were found for aromatic compounds substituted with electron-withdrawing

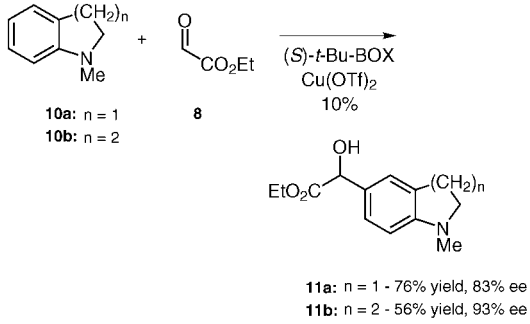
Table 3 Catalytic Enantioselective Friedel–Crafts reactions of *N*,*N*-Dimethylanilines **7** with Ethyl Glyoxylate **8**[a,12]

Entry	Reaction Time (d)	Product	Yield (%) CH_2Cl_2/THF	ee (%) CH_2Cl_2/THF
1	1	**9a**	81/71	80/90
2	1	**9b**	80/58	85/81
3	2	**9c**	84/41	93/95
4	2	**9d**	68/36	88/89
5	1	**9e**	77/76	80/92
6	1	**9f**	21/19	77/86

[a] Catalyzed by (*S*)-*t*-Bu-BOX-Cu(OTf)$_2$ (10 mol%) in CH_2Cl_2 and THF.

groups. It should be noted that the enantioselectivity is relatively independent of the electronic properties of the substituent and the solvent.

N-Methylindoline (**10a**) and *N*-methyltetrahydroquinoline (**10b**) reacted smoothly with ethyl glyoxylate **8** using (*S*)-*t*-Bu-BOX-Cu(OTf)$_2$ (10 mol%) as the catalyst (Equation 5).[12] The reaction of **10a** gave **11a** as the only isomer in good yield and enantiomeric excess (83% ee), while the yield of **10b** was slightly lower, however, the enantiomeric excess improved to 93% ee.



Equation 5

The Friedel–Crafts reactions of *N*-methylindoline **10a** and *N*-methyltetrahydroquinoline **10b** can give attractive products, which by oxidation of the unsaturated ring produced optically active indoles and quinolines, substituted in the aromatic ring with chiral α-hydroxy ester functionalities.

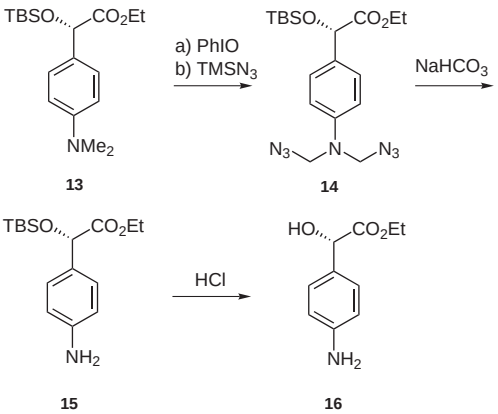
Other aromatic compounds such as julolidine, *N*,*N*-dimethylamino-1-naphthalene, *N*,*N*-dimethylamino-1-anthracene and 2-substituted furans all reacted with ethyl glyoxylate to give the corresponding optically active Friedel–Crafts adducts in moderate to good yield and up to 89% ee.

The highly activated carbonyl compound, trifluoropyruvate, can also be used as the substrate for these Friedel–Crafts reactions of activated aromatic and heteroaromatic compounds using (*S*)-*t*-Bu-BOX-Cu(OTf)$_2$ as the catalyst.[12b] Substituted indoles, pyrroles, furans, thiophenes and electron-rich aromatic compounds react with ethyl trifluoropyruvate in low (for the thiophenes) to high yields and with up to 93% ee for the optically active aromatic and heteroaromatic hydroxy trifluoromethyl esters formed.

The chiral bisoxazoline catalyst was covalently anchored to silica and mesoporous MCM-41 to obtain a heterogeneous catalyst.[13] The Ph-BOX ligand was used for this purpose and the chiral Ph-BOX-Cu(II) solid support catalyst displayed a high enantioselectivity in the Friedel–Crafts hydroxyalkylation of 1,3-dimethoxybenzene with trifluoropyruvate. The enantiomeric excess was higher than those obtained with the unsupported (*S*)-*t*-Bu-BOX-Cu(OTf)$_2$ complex in solution.

The Friedel–Crafts reactions using the chiral bisoxazoline catalyst are restricted to activated carbonyl compounds. However, using other 2-keto esters, such as ethyl pyruvate, as the substrate for the reaction with *N*,*N*-dimethylaniline in the presence of (*S*)-*t*-Bu-BOX-Cu(OTf)$_2$ as the catalyst gave the homo-aldol, rather that the Friedel–Crafts adduct.[14]

An important synthetically useful aspect of the catalytic enantioselective Friedel–Crafts reactions is that the corresponding anilines can easily be prepared from optically active adducts obtained in these reactions. Scheme 1 shows the *N*,*N*-demethylation of the Friedel–Crafts adduct obtained from the reaction of ethyl glyoxylate with *N*,*N*-dimethylaniline.[12a] The *N*,*N*-demethylation of the TBS-protected alcohol **13** proceeds in good yield with the free amine **16** and a variety of different optically active *para*-substituted mandelic acid derivatives can be prepared.

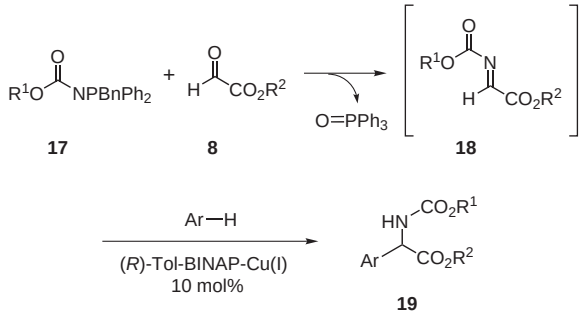


Scheme 1

The catalytic enantioselective hydroxyalkylation reaction of carbonyl compounds with aromatic compounds seems to be a much more difficult reaction to achieve. We have shown that pyridinecarbaldehydes can react with the aromatic C–H bond in aldehydes mediated by chiral BINOL-aluminium complexes to give the corresponding alcohols in moderate yields and enantioselectivities.[15]

3 Catalytic Enantioselective Addition to Imines

Optically active non-natural aromatic and heteroaromatic α-amino acid derivatives can be prepared from aza-Friedel–Crafts reactions of aromatic or heteroaromatic compounds with α-imino esters using the (*R*)-Tol-BINAP-Cu(I) complex (Figure 1) as the catalyst.[16] Starting from readily available starting materials the optically active products are formed with an easily removal N-protecting groups. The α-imino ester electrophiles are generated in situ by an aza-Wititig reaction followed by the catalytic enantioselective addition of the aromatic or heteroaromatic C–H bond to the *N*-protected α-imino ester **18** (Scheme 2).



Scheme 2

Optimisation of the aza-Wititig reaction, the formation of *N*-protected α-imino ester **18** (Scheme 2), revealed that the best results were obtained for $R^1 = R^2 = Me$ and some representative results for the aza-Friedel–Crafts reaction of some aromatic and heteroaromatic compounds are presented in Table 4.[16b]

Table 4[16] Catalytic Enantioselective aza-Friedel–Crafts Reactions of some Aromatic and Heteroaromartic Compounds with *N*-Moc α-Imino Ester **18**[a]

Entry	Aromatic	Product	Yield (%)	ee (%)
1	**7a**	**19a**	80	98
2	**7f**	**19b**	81	96
3	**10a**	**19c**	56	97
4	**10b**	**19d**	86	88
5	2-Me-furan	**19e**	59	89
6	2-Bn-furan	**19f**	40	95
7	2-MeO-furan	**19g**	63	96
8	2-MeO-thiophene	**19h**	75	94

[a] $R^1 = R^2 = Me$, catalyzed by (*R*)-Tol-BINAP-Cu(ClO_4) (10 mol%).

The activated anilines, *N*,*N*-dimethylaniline **7a** and *m*-methoxy-*N*,*N*-dimethylaniline **7f**, and the cyclic amines *N*-*m*ethylindoline **10a** and *N*-methyltetrahydroquinoline **10b**, all reacted all with the *N*-Moc α-imino ester ($R^1 = R^2 = Me$) **19** in the presence of (*R*)-Tol-BINAP-Cu(ClO_4) (10 mol%) as the catalyst to give a highly regioselective and enantioselective aza-Fridel–Crafts reaction. Only one regioisomer (in the *para*-position relative to the nitrogen substituent in the aromatic compound) of the optically active aromatic α-amino acid derivatives was obtained with very high enantioselectivities (Table 4, entries 1–4). For the reactions of the heteroaromatic compounds presented in Table 4, the reaction takes place selectively at 5-position relative to the substituent on the reagent. For the furans presented the yield of the corresponding furfuryl-α-amino acid derivatives is moderate, however, very high enantiomeric excesses are obtained (entries 5–7). 2-Methoxythiophene (entry 8), as well as other thiophenes, also react in a highly enantioselective reaction with good yield of the corresponding thiophene-α-amino acid derivative. Naphthalene and anthracene derived α-amino acids can also be obtained when 2-*N*,*N*-dimethylnaphtalene and 2-*N*,*N*-dimethyl anthracene were used as substrates (92% ee and 89% ee, respectively, were obtained for these reactions).

The two amino functionalities can be selectively deprotected and further transformations can be carried out.[16b] The *N*,*N*-demethylation proceeds well using the procedure described above for the optically active aromatic α-amino acid obtained by reaction of *N*,*N*-dimethylaniline **7a** reaction with iodosobenzene and $TMSN_3$, and subsequent hydrolysis of the bis-azide formed, gave the unprotected aniline derivative in 83% yield. It was demonstrated that the aromatic amino group could be removed by diazotisation and subsequent copper-catalysed decomposition of the diazonium salt in saturated aqueous H_3PO_2. A variety of synthetic procedures are available for the transformation of diazonium salts into halogens or hydroxyl groups and transformations provide the access to versatile optically active building blocks.

It was also demonstrated the *N*-Moc protecting groups, as well as other *N*-carbamate groups, could easily be removed by standard procedure.[16]

4 Conclusion

This feature article has demonstrated that chiral Lewis acids catalyse highly enantioselective addition of aromatic and heteroaromatic C–H bonds to β,γ-unsaturated α-keto esters, activated carbonyl compounds and *N*-protected α-imino esters. The reactions take place in moderate to high yields and with high enantioselectivities. These new catalytic processes give access to new classes of optically active compounds.

All reactions were carried out under an atmosphere of N_2 using anhydrous solvent and flame-dried glassware. Commercially available compounds were used without further purification. Solvents were dried according to standard procedures. Purification of the products, when necessary, was carried out by flash chromatography

(FC) using Merck silica gel 60 (230–400 mesh). TLC was performed using Merck silica gel 60 F254 plates and visualized with blue stain. Optical rotations were measured on a Perkin–Elmer 241 polarimeter. ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz respectively, using $CDCl_3$ as the solvent, and are reported in ppm downfield from TMS (δ = 0) for ^{1}H NMR and relative to the central $CDCl_3$ resonance (δ = 77.0) for ^{13}C NMR.

Catalytic Enantioselective Addition of Indoles 1 to 4-Substituted 2-Oxo-3-butenoate Esters 2; General Procedure (Table 1)[4]

To a flame dried Schlenk tube were added $Cu(OTf)_2$ (14.46 mg, 0.04 mmol) and the ligand 2,2′-isopropylidene bis[(4*S*)-4-*tert*-butyl-2-oxazoline] (*S*)-*t*-Bu-BOX (12.96 mg, 0.044 mmol) under a stream of N_2. The mixture was dried under vacuum for 1–2 h, the anhydrous solvent (2.0 mL) was added, and the resulting suspension was stirred vigorously for 1–2 h. The catalyst is green and heterogeneous in Et_2O whereas it is homogeneous in other solvents. To the catalyst in solution was added the 4-substituted 2-oxo-3-butenoate ester **2** (0.8 mmol). The solution was stirred at r.t. for 15 min, then cooled to the desired reaction temperature, where the appropriate indole **1** (0.8 mmol) was added. The solution was then stirred at –78 °C for 1–64 h depending on the substrate (see Table 1). Pentane (1.0 mL) was added to the reaction mixture. The heterogeneous mixture was filtered through a 40 mm plug of silica gel. The silica was washed with of 60% pentane in Et_2O (5–10 mL) followed by CH_2Cl_2 (5–10 mL) and the combined fractions were evaporated. The crude product **3a**–**g** exists both in keto and enol form, however this equilibrium shifts towards the keto form in MeOH at r.t. The keto form of **3a**–**g** was purified by FC. In many cases the last purification is not necessary as the reaction is very clean.

3a[4]

Yield: 77%; mp 98 °C; 99.5% ee; HPLC (Chiralcel OD-R column, MeOH, 0.5 mL/min) t_R 8.9 min (minor), t_R 10.1 min (major); $[\alpha]_D^{r.t.}$ –23.9 (*c* 0.0100, $CHCl_3$).

^{1}H NMR: δ = 8.00 (br s, 1H), 7.44–7.01 (m, 10 H), 4.93 (t, *J* = 7.6 Hz, 1 H), 3.77 (s, 3 H), 3.69 (dd, *J* = 16.8, 7.6 Hz, 1 H), 3.60 (dd, *J* = 16.8, 7.6 Hz, 1 H).

^{13}C NMR: δ = 37.7, 45.6, 52.9, 111.1, 118.3, 119.4, 119.5, 121.4, 122.3, 126.4, 126.6, 127.7, 128.5, 136.5, 143.1, 161.3, 192.6.

HRMS: *m*/*z* calcd for calcd for $C_{19}H_{17}NNaO_3$ $[M + Na]^+$, 330.1106; found, 330.1108.

3b[4]

Yield: 98% yield; mp 100 °C; 96% ee; HPLC (Chiralcel OD-R column, MeOH, 0.5 mL/min) t_R 10.5 min (minor), t_R 11.8 min (major), $[\alpha]_D^{r.t.}$ –26.6 (*c* 0.0100, $CHCl_3$).

^{1}H NMR: δ = 6.88–7.44 (m, 10 H), 4.93 (t, *J* = 8.0. Hz, 1 H), 3.77 (s, 3 H), 3.74 (s, 3 H), 3.68 (dd, *J* = 17.2, 8.0 Hz, 1 H), 3.60 (dd, *J* = 17.2, 8.0 Hz, 1 H).

^{13}C NMR: δ = 32.7, 37.6, 45.7, 52.9, 109.2, 116.7, 118.9, 119.4, 121.8, 126.3, 126.5, 126.7, 127.7, 128.5, 137.2, 143.3, 161.2, 192.6.

HRMS: *m*/*z* calcd for $C_{21}H_{23}NNaO_4$ $[M + Na + MeOH]^+$, 376.1525; found, 376.1515.

3c[4]

Yield: 95%; semi-crystalline oil; 95% ee; HPLC (Chiralcel OD column, hexane–*i*-PrOH, 85:15, 0.5 mL/min) t_R 13.1 min (minor), t_R 15.6 min (major); $[\alpha]_D^{r.t.}$ +5.2 (*c* 0.0100, $CHCl_3$).

^{1}H NMR: δ = 7.92 (br s, 1 H), 7.29–6.75 (m, 9 H), 4.82 (t, *J* = 8.0. Hz, 1 H), 3.71 (s, 3 H), 3.70 (s, 3 H), 3.62 (dd, *J* = 16.8, 8.0 Hz, 1 H), 3.54 (dd, *J* = 16.8, 8.0 Hz, 1 H).

^{13}C NMR: δ = 37.6, 45.5, 52.9, 55.7, 101.2, 111.8, 112.2, 117.9, 122.2, 126.6, 126.7, 127.7, 128.5, 131.6, 143.1, 153.8, 161.2, 192.6.

HRMS: *m*/*z* calcd for $C_{21}H_{23}NNaO_5$ $[M + Na + MeOH]^+$, 392.1474; found, 392.1476.

3d[4]

Yield: 69% yield; mp 158 °C; 97% ee; HPLC (Chiralcel OD column, hexane–*i*-PrOH, 85:15, 0.5 mL/min) t_R 15.4 min (major), t_R 19.6 min (minor); $[\alpha]_D^{r.t.}$ –18.5 (*c* 0.0100, $CHCl_3$).

^{1}H NMR: δ = 7.95 (br s, 1 H), 7.23–6.89 (m, 9 H), 4.80 (t, *J* = 7.2 Hz, 1 H), 3.71 (s, 3 H), 3.59 (dd, *J* = 16.8, 7.2 Hz, 1 H), 3.50 (dd, *J* = 16.8, 7.2 Hz, 1 H).

^{13}C NMR: δ = 37.5, 45.5, 53.0, 111.1, 118.5, 120.3, 120.3, 122.0, 125.0, 126.7, 127.7, 128.3, 128.6, 136.9, 142.9, 161.2, 192.4.

HRMS: *m*/*z* calcd for $C_{20}H_{20}ClNNaO_4$ $[M + Na + MeOH]^+$, 396.0979; found, 396.0983.

3e[4]

Yield: 96%; yellow oil; 95% ee; HPLC (Chiralcel OB column, hexane–*i*-PrOH, 98:2, 0.5 mL/min) t_R 26.1 min (major), t_R 33.1 min (minor); $[\alpha]_D^{r.t.}$ –1.7 (*c* 0.0100 g/mL, $CHCl_3$).

^{1}H NMR: δ = 7.95 (br s, 1 H), 7.67 (d, *J* = 7.2 Hz, 1 H), 7.36 (d, *J* = 8.0 Hz, 1 H), 7.18 (t, *J* = 6.8 Hz, 1 H), 7.13 (t, *J* = 6.8 Hz, 1 H), 7.02 (s, 1 H), 4.23 (q, *J* = 6.8 Hz, 2 H), 3.71 (m, 1 H), 3.36 (dd, *J* = 16.8, 6.0 Hz, 1 H), 3.12 (dd, *J* = 16.8, 8.4 Hz, 1 H), 1.44 (d, *J* = 6.8 Hz, 3 H), 1.30 (t, *J* = 7.6 Hz, 3 H).

^{13}C NMR: δ = 13.8, 20.9, 26.6, 46.8, 62.4, 111.2, 119.0, 119.3, 120.1, 120.4, 122.0, 126.1, 136.4, 161.1, 194.1.

HRMS: *m*/*z* calcd for $C_{15}H_{19}NNaO_4$ $[M + Na + H_2O]^+$, 300.1212; found, 300.1200.

3f[4]

Yield: 95%; yellow oil; >99.5% ee; HPLC (Chiralcel OJ column, hexane–*i*-PrOH, 85:15, 0.5 mL/min) t_R 26.5 min (minor), t_R 37.2 min (major); $[\alpha]_D^{r.t.}$ –10.4 (*c* 0.0100, $CHCl_3$).

^{1}H NMR: δ = 7.89 (br s, 1 H), 7.23 (d, *J* = 9.2 Hz, 1 H), 7.09 (d, *J* = 2.4 Hz, 1 H), 6.98 (d, *J* = 2.8 Hz, 1 H), 6.86 (dd, *J* = 9.2, 2.4 Hz, 1 H), 4.23 (q, *J* = 7.2 Hz, 2 H), 3.65 (m, 1 H), 3.88 (s, 3 H), 3.33 (dd, *J* = 16.8, 6.0 Hz, 1 H), 3.09 (dd, *J* = 16.8, 8.0 Hz, 1 H), 1.41 (d, *J* = 6.8 Hz, 3 H), 1.29 (t, *J* = 7.6 Hz, 3 H).

^{13}C NMR: δ = 13.9, 20.9, 26.5, 46.8, 56.0, 62.4, 101.0, 111.9, 112.2, 120.1, 121.1, 126.5, 131.6, 153.9, 161.1, 194.1.

HRMS: *m*/*z* calcd for $C_{16}H_{21}NNaO_5$ $[M + Na + H_2O]^+$, 330.1317; found, 330.1320.

3g[4]

Yield: 98%, yellow oil; 95% ee; HPLC, Chiralcel OJ column (hexane–*i*-PrOH 85:15, 0.5 mL/min) t_R 45.2 min (minor), t_R 51.0 min (major), $[\alpha]_D^{r.t.}$ 23.0 (*c* 0.0100, $CHCl_3$).

^{1}H NMR: δ = 7.93 (br s, 1 H), 7.36–7.23 (m, 6 H), 7.09 (d, *J* = 2.4 Hz, 1 H), 7.03 (d, *J* = 2.4 Hz, 1 H), 6.86 (dd, *J* = 9.6, 2.4 Hz, 1 H), 4.50 (s, 2 H), 4.19 (m, 2 H), 3.97 (m, 1 H), 3.86 (s, 3 H), 3.81 (dd, *J* = 9.2, 4.4 Hz, 1 H), 3.63 (t, *J* = 9.2 Hz, 1 H), 3.43 (dd, *J* = 15.6, 8.4 Hz, 1 H), 3.19 (dd, *J* = 15.6, 6.4 Hz, 1 H), 1.26 (t, *J* = 6.8 Hz, 3 H).

^{13}C NMR: δ = 13.9, 34.0, 42.8, 55.9, 62.2, 72.9, 73.5, 100.7, 111.9, 112.5, 115.3, 122.0, 126.8, 127.6, 127.6, 128.3, 131.2, 137.9, 154.0, 161.0, 193.2.

HRMS: *m*/*z* calcd for $C_{23}H_{27}NNaO_6$ $[M + Na + H_2O]^+$, 436.1736; found, 436.1738.

Catalytic Friedel–Crafts Reactions of *N*,*N*-Dimethylanilines 7 with Ethyl Glyoxylate; General Procedure[12a]

To a flame dried Schlenk tube was added $Cu(OTf)_2$ (18.1 mg, 0.05 mmol, 10 mol%) and (*S*)-*t*-Bu-BOX (15.5 mg, 0.055 mmol, 11

mol%). The mixture was dried under vacuum for 1–2 h and freshly distilled anhyd CH_2Cl_2 (2.0 mL) was added and the solution was stirred for 0.5–1 h. Freshly distilled ethyl glyoxylate (255 mg, 2.5 mmol) and *N*,*N*-dimethylaniline (0.5 mmol, 1 equiv) were added. After stirring at r.t. for the appropriate amount of time (Table 3), the reaction mixture was filtered through a pad of silica, which was eluted with Et_2O, the eluent was concentrated in vacuo, and the product was purified by FC.

9a[12a]

Yield: 81% yield; mp 101–103 °C; 80% ee; GC (column Astec B-PM, initial T = 80 °C, 20 °C/min to 135 °C, 1 °C/min to 145 °C, 0.2 °C to 158 °C) t_R 38.5 min (major), t_R 39.2 min (minor); $[\alpha]_D^{r.t.}$ +98.7 (*c* 0.023, $CHCl_3$).

^{1}H NMR: δ = 7.28–7.23 (m, 2 H), 6.73–6.68 (m, 2 H), 5.07 (d, *J* = 6.0 Hz, 1 H), 4.27 (dq, *J* = 10.5, 7.2 Hz, 1 H), 4.15 (dq, *J* = 10.5, 7.2 Hz, 1 H), 3.33 (d, *J* = 6.0 Hz, 1 H), 2.96 (s, 6 H), 1.23 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR: δ =174.4, 150.8, 127.8, 126.4, 112.6, 73.0, 62.2, 40.7, 14.3.

HRMS: *m*/*z* calcd for $C_{12}H_{17}NO_3$ $[M]^+$, 223.1208; found, 223.1207.

9b[12]

Yield: 80%; colorless oil; 85% ee; GC (column Astec B-PM, initial T = 80 °C, 10 °C/min to 140 °C, hold 60 min, 0.5 °C/min to 155 °C) t_R 76.3 min (minor), t_R 77.0 min (major); $[\alpha]_D^{r.t.}$ +85.3 (*c* 0.008, $CHCl_3$).

^{1}H NMR: δ = 7.14 (dd, $J_{H\text{-}F}$ = 8.8 Hz, $J_{H\text{-}H}$ = 8.8 Hz, 1 H), 6.44 (dd, $J_{H\text{-}F}$ = 8.8 Hz, $J_{H\text{-}H}$ = 2.6 Hz, 1 H), 6.36 (dd, $J_{H\text{-}F}$ = 14.0 Hz, $J_{H\text{-}H}$ = 2.6 Hz, 1 H), 5.25 (d, *J* = 5.6 Hz, 1 H), 4.26 (dq, *J* = 10.4, 6.8 Hz, 1 H), 4.19 (dq, *J* = 10.4, 6.8 Hz, 1 H), 3.42 (d, *J* = 5.6 Hz, 1 H), 2.94 (s, 6 H), 1.22 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR: δ = 174.1, 161.8 (d, $J_{C\text{-}F}$ = 243.0 Hz), 152.4 (d, $J_{C\text{-}F}$ = 10.7 Hz), 129.4 (d, $J_{C\text{-}F}$ = 6.1 Hz), 113.1 (d, $J_{C\text{-}F}$ = 15.2 Hz), 108.1 (d, $J_{C\text{-}F}$ = 23.0 Hz), 99.3 (d, $J_{C\text{-}F}$ = 26.0 Hz), 66.8 (d, $J_{C\text{-}F}$ = 2.3 Hz), 62.3, 40.5, 14.3.

HRMS: *m*/*z* calcd for $C_{12}H_{16}FNO_3$ $[M]^+$, 241.1114; found, 241.1120.

9c[12]

Yield: 84%; colorless oil; 93% ee; GC (column Astec B-PM, initial T = 80 °C, 20 °C/min to 135 °C, hold 120 min, 0.05 °C/min to 140 °C) t_R 146.9 min (major), t_R 149.9 min (minor); $[\alpha]_D^{r.t.}$ +117.6 (*c* 0.0047, $CHCl_3$).

^{1}H NMR: δ = 7.17 (d, *J* = 8.8 Hz, 1 H), 6.68 (d, *J* = 2.4 Hz, 1 H), 6.58 (dd, *J* = 8.8, 2.4 Hz, 1 H), 5.42 (d, *J* = 5.6 Hz, 1 H), 4.26 (dq, *J* = 10.4, 7.2 Hz, 1 H), 4.20 (dq, *J* = 10.4, 7.2 Hz, 1 H), 3.40 (d, *J* = 5.6 Hz, 1 H), 2.95 (s, 6 H), 1.23 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR: δ = 174.2, 151.8, 134.6, 129.5, 123.4, 113.0, 111.1, 70.5, 62.4, 40.5, 14.3.

HRMS: *m*/*z* calcd for $C_{12}H_{16}ClNO_3$ $[M]^+$, 257.0819; found, 257.0814.

9d[12]

Yield: 68%; colorless oil; 88% ee; HPLC (Chiralpak OD column, hexane–*i*-PrOH 95:5, 0.5 mL/min) t_R 23 min (minor), t_R 29 min (major), $[\alpha]_D^{r.t.}$ +110.0 (*c* 0.011, $CHCl_3$).

^{1}H NMR: δ = 7.08 (d, *J* = 8.4 Hz, 1 H), 6.79 (d, *J* = 2.5 Hz, 1 H), 6.55 (dd, *J* = 8.4, 2.5 Hz, 1 H), 5.37 (d, *J* = 5.2 Hz, 1 H), 4.20 (dq, *J* = 10.4, 6.8 Hz, 1 H), 4.12 (dq, *J* = 10.4, 6.8 Hz, 1 H), 3.32 (d, *J* = 5.2 Hz, 1 H), 2.88 (s, 6 H), 1.17 (t, *J* = 6.8 Hz, 3 H)

^{13}C NMR: δ = 174.2, 151.4, 129.3, 125.0, 124.8, 116.2, 111.7, 72.5, 62.4, 40.5, 14.3.

HRMS: *m*/*z* calcd for $C_{13}H_{16}BrNO_3$ $[M]^+$, 301.0314; found, 301.0316.

9e[12]

Yield: 77%; yellow oil; 80% ee; GC (column Astec B-PM, initial T = 80 °C, 20 °C/min to 135 °C, 1 °C/min to 140 °C, 1 °C to 160 °C, 0.2 °C/min to 170 °C) t_R 38.1 min (major), t_R 38.8 min (minor); $[\alpha]_D^{r.t.}$ +124.4 (*c* 8.9, $CHCl_3$).

^{1}H NMR: δ = 7.12 (d, *J* = 8.0 Hz, 1 H), 6.57–6.52 (m, 2 H), 5.27 (d, *J* = 6.8 Hz, 1 H), 4.28 (dq, *J* = 10.4, 7.2 Hz, 1 H), 4.20 (dq, *J* = 10.4, 7.2 Hz, 1 H), 3.22 (d, *J* = 6.8 Hz, 1 H), 2.94 (s, 6 H), 2.40 (s, 3 H), 1.24 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR: δ = 175.0, 150.7, 137.5, 128.0, 125.0, 114.7, 110.4, 70.5, 62.1, 40.67, 20.0, 14.4.

HRMS: *m*/*z* calcd for $C_{13}H_{19}NO_3$ $[M]^+$, 237.1365; found, 237.1368.

9f[12]

Yield: 21%; colorless oil; 77% ee; HPLC (Chiralpak OD column, hexane–*i*-PrOH, 85:15, 0.5 mL/min) t_R 24 min (major), t_R 28 min (minor), $[\alpha]_D^{r.t.}$ +85.4 (*c* 0.0048, $CHCl_3$).

^{1}H NMR: δ = 7.08 (d, *J* = 8.4 Hz, 1 H), 6.27 (dd, *J* = 8.4, 2.4 Hz, 1 H), 6.21 (d, *J* = 2.4 Hz, 1 H), 5.16 (d, *J* = 6.8 Hz, 1 H), 4.25 (dq, *J* = 9.2, 7.2 Hz, 1 H), 4.19 (dq, *J* = 9.2, 7.2 Hz, 1 H), 3.82 (s, 3 H), 3.40 (d, *J* = 6.8 Hz, 1 H), 2.96 (s, 6 H), 1.22 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR: δ = 174.6, 158.4, 152.4, 130.3, 115.4, 104.7, 96.1, 70.3, 61.8, 55.5, 40.8, 14.4.

HRMS $[M]^+$ calc. for $C_{13}H_{19}NO_4$ 253.1314, found 253.1320.

Catalytic aza-Friedel–Crafts Reactions of Aromatic and Heteroaromatic Compounds to the *N*-Moc α-Imino Ester 18; General Procedure[16]

To a flame dried Schlenk tube equipped with a magnetic stirring bar was added the aza-ylide **17** (R^1 = Me) (0.40 mmol), which was dried under vacuum at r.t. for 1 h before toluene (0.66 mL) was added by syringe. After stirring for 10 min, the suspension was added to a 0.42 M solution of methyl glyoxylate **8** (R^2 = Me) in toluene (1.14 mL, 0.48 mmol) and stirred for another 15 min at ambient temperature before the white milky slurry was cooled to –78 °C (complete imine formation was checked by ^{1}H NMR spectroscopy, as full conversion of the aza-ylide is crucial to achieving good results). A catalyst solution was prepared by drying $CuPF_6$·4MeCN (15 mg, 0.040 mmol) and (*R*)-Tol-BINAP (30 mg, 0.044 mmol) in a flame dried Schlenk tube under vacuum for 1 h, this mixture was then dissolved in a mixture of CH_2Cl_2 (0.20 mL) and toluene (2.0 mL) and added via syringe. The resulting mixture was stirred for 30 s, the aromatic or heteroaromatic substrate (0.80 mmol) was added in one portion. After 44 h the reaction mixture was filtered through a plug of silica and eluted with Et_2O (50 mL). The crude product was concentrated in vacuo and purified by FC to give directly protected aromatic or heteroaromatic α-amino acid derivative.

19a[16]

Yield: 80%; 98% ee; HPLC (Daciel Chiralcel OD, hexane–*i*-PrOH, 90:10, 1 mL/min) t_R 17.2 min (minor), t_R 22.8 min (major); $[\alpha]_D^{r.t.}$ –146.3 (*c* 0.8, $CHCl_3$).

^{1}H NMR: δ = 7.18 (d, *J* = 8.6 Hz, 2 H), 6.65 (d, *J* = 8.6 Hz, 2 H), 5.61 (br d, *J* = 5.8 Hz, 1 H), 5.22 (d, *J* = 7.0 Hz, 1 H), 3.68 (s, 3 H), 3.64 (s, 3 H), 2.91 (s, 6 H).

^{13}C NMR: δ = 171.9, 155.9, 150.4, 127.9, 123.6, 112.3, 57.3, 52.5, 52.2, 40.3.

HRMS: *m*/z calcd for $C_{13}H_{18}N_2O_4$ $[M + Na]^+$, 289.1164; found, 289.1168.

19b[16]

Yield: 81%; mp 124–126 °C; 96% ee; HPLC (Daciel Chiralcel OD, hexane–*i*-PrOH, 85:15) 1 mL/min t_R 14.5 min (minor), t_R 34.1 min (major); $[\alpha]_D^{r.t.}$ –131.0 (*c* 1, $CHCl_3$).

^{1}H NMR: δ = 7.11 (d, *J* = 8.5 Hz, 1 H), 6.23 (dd, *J* = 8.5, 2.3 Hz, 1 H), 6.17 (d, *J* = 2.3 Hz, 1 H) 5.76 (br d, *J* = 8.5 Hz, 1 H), 5.36 (d, *J* = 8.5 Hz, 1 H), 3.78 (s, 3 H), 3.65 (s, 3 H), 3.63 (s, 3 H), 2.93 (s, 6 H).

^{13}C NMR: δ = 172.3, 169.8, 157.7, 156.4, 152.0, 130.6, 113.2, 104.3, 95.6, 55.2, 54.4, 53.1, 52.5, 40.4.

HRMS: *m*/*z* $[M + Na]^+$ calcd for $C_{14}H_{20}N_2O_5$, 319.1270; found, 319.1266.

19d[16]

Yield: 86%; 92% ee; HPLC (Daciel Chiralcel OD, hexane–*i*-PrOH, 85:15, 1 mL/min) t_R 11.4 min (minor), t_R 17.2 min (major); $[\alpha]_D^{r.t.}$ –130.1 (*c* 1, $CHCl_3$).

^{1}H NMR: δ = 7.00 (d, *J* = 8.6 Hz, 1 H), 6.89 (s, 1 H), 6.49 (d, *J* = 8.6 Hz, 1 H), 5.58 (br d, *J* = 7.0 Hz, 1 H), 5.16 (d, *J* = 7.0 Hz, 1 H), 3.69 (s, 3 H), 3.64 (s, 3 H), 3.19 (t, *J* = 5.6 Hz, 2 H), 2.84 (s, 3 H), 2.71 (t, *J* = 6.2 Hz, 2 H), 1.95–1.82 (m, 2 H).

^{13}C NMR: δ = 172.0, 155.9, 146.8, 127.5, 125.9, 123.7, 122.9, 110.7, 57.4, 52.5, 52.2, 51.0, 38.8, 27.6, 22.0.

HRMS: *m*/*z* calcd for $C_{15}H_{20}N_2O_4$ $[M + Na]^+$, 315.1321; found, 315.1326.

19e[16]

Yield: 59%; 89% ee; HPLC (Daicel Chiralpak AS, hexane–*i*-PrOH, 97:3, 1 mL/min) t_R 19.2 min (minor), t_R 25.2 min (major); $[\alpha]_D^{r.t.}$ –123.0 (*c* 1, $CHCl_3$).

^{1}H NMR: δ = 6.21 (d, *J* = 3.2 Hz, 1 H), 5.91–5.90 (m, 1 H), 5.69 (br d, *J* = 6.9 Hz, 1 H), 5.42 (d, *J* = 8.2 Hz, 1 H) 3.75 (s, 3 H), 3.68 (s, 3 H), 2.24 (s, 3 H).

^{13}C NMR: δ = 169.6, 156.0, 152.7, 146.6, 109.4, 106.5, 52.9, 52.4, 51.9, 13.4.

HRMS: *m*/*z* calcd for $C_{10}H_{13}NO_5$ $[M+Na]^+$, 250.0691; found, 250.0692.

19f[16]

Yield: 40% yield; 95% ee; HPLC (Daicel Chiralpak AS, hexane–*i*-PrOH, 95:5, 1 mL/min) t_R 18.3 min (minor), t_R 25.7 min (major), $[\alpha]_D^{r.t.}$ –132.0 (*c* 1, $CHCl_3$).

^{1}H NMR: δ = 7.32–7.19 (m, 5 H), 6.25 (d, *J* = 3.2 Hz, 1 H), 5.91 (d, *J* = 3.0 Hz, 1 H), 5.64 (br d, *J* = 7.5 Hz, 1 H) 5.46 (d, *J* = 8.3 Hz, 1 H), 3.93 (s, 2 H), 3.75 (s, 3 H), 3.69 (s, 3 H).

^{13}C NMR: δ = 169.5, 156.0, 155.3, 147.3, 137.5, 128.7, 128.5, 126.6, 109.4, 107.3, 52.9, 52.5, 52.0, 34.4.

HRMS: *m*/*z* calcd for $C_{16}H_{17}NO_5$ $[M+Na]^+$, 326.1004; found, 326.1005.

19g[16]

Yield: 63% yield; 95% ee; HPLC (Daicel Chiralpak AS, hexane–*i*-PrOH 90/10, 1 mL/min) t_R 23.9 min (minor), t_R 28.7 min (major); $[\alpha]_D^{r.t.}$ –114 (*c* 1, $CHCl_3$).

^{1}H NMR: δ = 6.21 (d, *J* = 3.1 Hz, 1 H), 5.69 (br d, *J* = 8.2 Hz, 1 H), 5.34 (d, *J* = 8.2 Hz, 1 H), 5.07 (d, *J* = 3.44 Hz, 1 H), 3.79 (s, 3 H), 3.74 (s, 3 H), 3.66 (s, 3 H).

^{13}C NMR: δ = 169.3, 161.5, 156.0, 138.3, 110.2, 80.2, 57.7, 52.9, 52.4, 51.9.

HRMS: *m*/*z* calcd for $C_{10}H_{13}NO_6$ $[M + Na]^+$, 266.0641; found, 266.0633.

19h[16]

Yield: 75%; 94% ee; HPLC (Daicel Chiralpak AS, hexane–*i*-PrOH, 90:10, 1 mL/min) t_R 21.8 min (minor), t_R 43.1 min (major): $[\alpha]_D^{r.t.}$ –131 (*c* 1, $CHCl_3$).

^{1}H NMR: δ = 6.65 (d, *J* = 3.7 Hz, 1 H), 5.07 (d, *J* = 4.3 Hz, 1 H), 5.71 (br d, *J* = 7.1 Hz, 1 H), 5.43 (d, *J* = 7.7 Hz, 1 H), 3.83 (s, 3 H), 3.76 (s, 3 H), 3.67 (s, 3 H)

^{13}C NMR: δ = 170.5, 166.5, 155.8, 124.1, 124.0, 103.2, 60.1, 53.9, 52.9, 52.4.

HRMS: *m*/*z* calcd for $C_{10}H_{13}NO_5S$ $[M + Na]^+$, 282.0412; found, 282.0416.

Acknowledgements

This work was made possible by a grant from Danish National Research Foundation. The work presented in this feature article were performed by a series of dedicated co-workers: Kim B. Jensen, Jacob Thorhauge, Rita G. Hazell, Wei Zhuang, Tore Hansen, Nicolas Gathergood, Aase S. Gothelf, Steen Saaby, Xiangming Fang, Pau Bayón and Pompiliu Aburel. Their contributions to our development of new catalytic enantioselective reactions are highly acknowledged.

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