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A versatile catalyst for asymmetric reactions of carbonyl groups working purely by activation through hydrogen bonding: Mukaiyama-aldol, hetero Diels–Alder and Friedel–Crafts reactions

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Bis-sulfonamides are demonstrated to be promising candidates for the efficient activation of carbonyl compounds through hydrogen bonding. Exemplified by three carbonyl addition reactions: Mukaiyama-aldol, hetero Diels–Alder and Friedel–Crafts reactions we show that bis-triflamides or bis-nonaflamides of commercially available chiral diamines act as chiral Brønsted-acid catalysts, leading to the optically active products in moderate to excellent yields and with enantioselectivities up to 73% ee.

Introduction

A recent interest in asymmetric catalysis is the use of chiral Brønsted acids to activate π-electrophiles towards nucleophilic attack.[1] Although this area is still very much in its infancy, many enantioselective addition reactions to imines have already occurred covering Strecker,[2] Mannich,[3] aza-Friedel–Crafts,[4] hydrophosphonylation,[5] acyl-Pictet–Spengler[6] and aza-Henry reactions.[7] However, successful applications of this concept to reactions involving carbonyl electrophiles have so far remained more elusive[1,8]—although the work of especially Rawal *et al.* convincingly demonstrates that highly enantioselective processes are possible.[9] Due to the bifunctional nature of some of the catalysts employed in the studies mentioned above, the role of the Brønsted-acid for substrate activation and/or enantioinduction cannot be unambiguously determined.

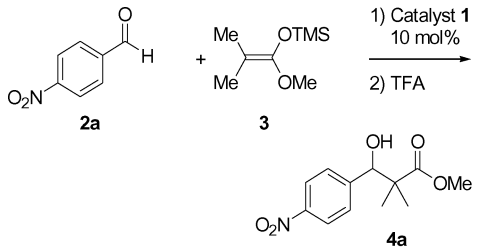
Although the importance of bifunctional catalyst design is obvious, the development of Brønsted-acid catalysts working purely by activation through hydrogen-bonding is appealing due to their inherent simplicity. This concept might also afford simpler alternatives to chiral Lewis-acid complexes and the rather strict demands their use sometimes make on reaction conditions. Although Brønsted-acid catalyzed addition reactions of carbonyl groups are among the most studied reactions in organic chemistry there lies considerable challenge in the development of asymmetric versions due to the difficult balance of achieving sufficient activation of the substrate while maintaining the structural rigidity of the catalyst–substrate complex necessary for enantioinduction.

We previously reported that bis-sulfonamides could activate nitroolefins towards nucleophilic attack *via* a hydrogen bonding interaction.[10] In the following, we demonstrate the use of bis-sulfonamides as chiral hydrogen bond donors (HBD's) in nucleophilic addition reactions to carbonyl compounds exemplified by three different enantioselective transformations: Mukaiyama-aldol, hetero Diels–Alder with Danishefsky's diene, and Friedel–Crafts reactions. To the best of our knowledge, the present study provides the first examples of chiral Brønsted-acid catalysis within these fundamental reactions of carbonyl compounds.

Results and discussion

Mukaiyama-aldol reactions

The addition of enol-silanes to carbonyl compounds—the Mukaiyama-aldol reaction—has been subject of extensive investigation[11] due to the usefulness of products containing one new C–C bond and up to two new stereogenic centres. Many successful examples employing chiral metal-complexes have been developed as have organocatalytic reactions with chiral fluoride-donor catalysts.[12] Our interest in the development of an asymmetric Mukaiyama-aldol reaction by the use of, preferably, catalytic amounts of a chiral HBD was stimulated by the finding that addition of stoichiometric amounts of optically active BINOL greatly increased the rate of the reaction between 2-pyridine carboxaldehyde and silyl ketene acetals. Importantly, the product aldol was optically active and up to 69% ee could be obtained. However, efficient catalyst turnover was not possible due to the formation of silylated derivatives of the catalyst.[13] It was our belief, that substrate activation was achieved by hydrogen bonding of the naphtholic hydroxyl groups to the aldehyde carbonyl group leading to an energetic lowering of the LUMO orbital. Our search for a general chiral scaffold that would place two hydrogens of acidity comparable to the phenolic hydroxyl groups without having a strong affinity for silicon then lead to the bis-sulfonamide derivatives **1** of vicinal diamines—compounds having a successful history as ligands in various metal-catalyzed reactions.[14] As a model reaction we chose *p*-nitrobenzaldehyde (**2a**) and silyl ketene acetal **3** [eqn. (1)] and the initial results are shown in Table 1.



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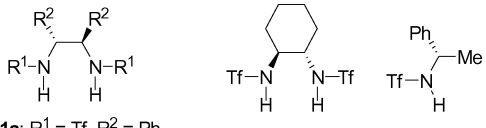

1a: R^1 = Tf, R^2 = Ph
1b: R^1 = Tf, R^2 = *t*-Bu
1c: R^1 = Tf, R^2 = cyclohexyl
1d: R^1 = Nf, R^2 = Ph
1e: R^1 = Ts, R^2 = Ph
1f: R^1 = Ms, R^2 = Ph
1g: R^1 = *p*-NO_2-$PhSO_2$, R^2 = Ph

1h **1i**

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Table 1 Results for the catalytic enantioselective Mukaiyama-aldol reaction of *p*-nitrobenzaldehyde (**2a**) with silyl ketene acetal **3** catalyzed by bis-sulfonamides **1** under various reaction conditions[a]

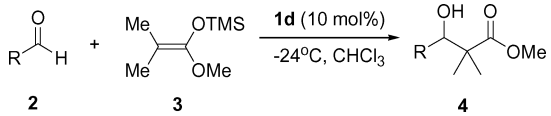
Entry	Catalyst	Solvent	Temp./°C	Time/h	Conv (%)[b]	Ee (%)[c]
1	—	toluene	rt	24	0	—
2	BINOL	toluene	rt	24	0	—
3	TADDOL	toluene	rt	24	0	—
4	**1a**	toluene	−24	24	65	31
5	**1a**	CH_2Cl_2	−24	24	86	22
6	**1a**		−24	24	49	37
7	**1a**	CH_3CN	−24	12	87	24
8	**1a**	$CHCl_3$	−24	24	79	33
9	**1a**	$CHCl_3$	−50	40	100	37
10	**1b**	toluene	−24	40	17	17
11	**1c**	toluene	−24	16	39	9
12	**1d**	$CHCl_3$	−24	19	91	43
13	**1e**	toluene	−24	24	0	—
14	**1f**	toluene	−24	24	28	3
15	**1h**	toluene	−24	24	0	—
16	**1i**	toluene	−24	24	0	—

[a] Reaction performed at 0.25 mmol scale of aldehyde **2a** and 1.5 equiv. of silyl ketene acetal **3** in 1 mL solvent. After the time indicated in the table, 4 mL 5% TFA in CH_2Cl_2 was added and the reaction mixture was stirred for 1 h at room temperature. The solvent was removed *in vacuo* to give the corresponding crude product. [b] Determined by ^{1}H NMR. [c] Determined on the crude sample by chiral stationary phase HPLC. [d] TBME = *tert*-butyl methyl ether.

The presence of HBD's carrying hydroxyl groups (entries 2, 3) did not lead to any conversion, and in the case of BINOL significant silylation of the catalyst was observed within the reaction time. The presence of bis-triflamide **1a** (10 mol%) (entries 4–9), however, greatly increased the reaction rate, and within 24 h at −24 °C moderate to high conversion to the Mukaiyama-aldol product **4a** was observed, depending on the solvent employed. Interestingly, the product also possessed low to moderate enantiomeric excess, indicating a rigid complex between catalyst **1a** and aldehyde **2a**.

To probe the structural elements necessary for substrate activation, we replaced the triflyl-groups with tosyl-groups (entry 13), but no conversion was observed.[15] Realising the importance of the triflamide group, we then evaluated mono-triflamide **1i** as the activator, however, no conversion was observed (entry 16). This finding clearly shows that catalyst function involves both sulfonamide groups, and, as will be discussed below, a chelated structure where the catalyst interacts *via* two hydrogen bonds to the carbonyl oxygen atom would be in accordance with recent observations.[1b] Further structural variation of the general diamine scaffold, while maintaining the two triflamide groups, demonstrated surprising differences in reactivity. For instance changing the two phenyl groups to *tert*-butyl or cyclohexyl (entries 10, 11) led both to lower conversion and impaired enantioselectivity. This difference in reactivity underscores the importance of suitable catalyst geometry for achieving substrate activation—by changing the substituents (*e.g.* phenyl to *tert*-butyl) the dihedral angle between the substituents is changed, which leads to a repositioning of the sulfonamide hydrogens and a change in their ability to associate with the carbonyl oxygen atom (see discussion below). This effect is emphasized even further in the fact the bis-triflamide of cyclohexane diamine shows no catalytic activity (entry 15). Finally, we chose to investigate the effect of replacing the triflyl-group with the longer chain nonaflyl-group (CF_3-$(CF_2)_3$-SO_2-), which afforded a slightly more active catalyst (91% conversion within 19 h) and an increase in the enantiomeric excess to 43% (entry 12).

Different aldehydes were then applied in the Mukaiyama-aldol reaction catalyzed by 10 mol% of **1d** [eqn. (2)] and the results are presented in Table 2. *p*-Nitrobenzaldehyde (**2a**) reacted with silyl ketene acetal **3** to give aldol **4a** in 90% yield after hydrolysis and 43% ee (entry 1). For benzaldehyde (**2b**) a moderate yield (43%) and enantioselectivity (30%) were obtained (entry 2). The Mukaiyama-aldol reaction also performed well for heteroaromatic aldehydes as both 2- and 4-pyridinecarboxaldehyde **2c,d** reacted with **3** to give the aldol products in high yields and up to 56% ee (entries 3, 4).



2 3 4 (2)

Table 2 Results for the catalytic enantioselective Mukaiyama-aldol reaction of aldehydes **2a–d** with silyl ketene acetal **3** in the presence of 10 mol% bis-nonaflamide **1d** as the catalyst[a]

Entry	Substrate	R	Time/h	Yield (%)[b]	Ee (%)[c]
1	**2a**	*p*-NO_2-Ph	16	**4a**-90	43
2	**2b**	Ph	40	**4b**-41	30 (*R*)
3	**2c**	2-pyridine	16	**4c**-87	30
4	**2d**	4-pyridine	16	**4d**-85	56

[a] Reaction performed at 0.25 mmol scale of aldehyde **2** and 1.5 equiv. of silyl ketene acetal **3** in 1 mL $CHCl_3$ at −24 °C. After the time indicated in the table, 4 mL 5% TFA in CH_2Cl_2 was added and the reaction mixture was stirred for 1 h at room temperature. The solvent was removed *in vacuo* to give the corresponding crude product. [b] Isolated yield. [c] Ee of the isolated product determined by chiral stationary phase HPLC.

Hetero Diels–Alder reactions

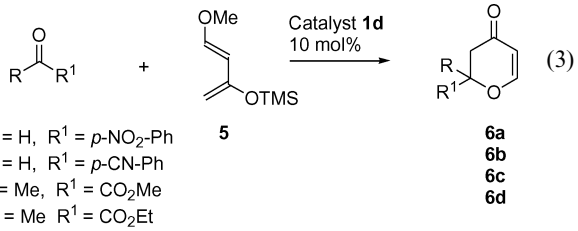
Mechanistically closely related to the Mukaiyama-aldol reaction is the formal hetero Diels–Alder reaction of *trans*-1-methoxy-3-trimethylsiloxy-1,3-butadiene—Danishefsky's diene—(**5**) with carbonyl compounds to give tetrahydropyranones after ring closure under acidic conditions. Although, the hetero Diels–Alder reaction of carbonyl compounds has already been subject to attention within the concept of chiral Brønsted-acid catalysis, the impressive examples[9a,c,d] demonstrated so far has utilized highly reactive dienes for achieving sufficient reactivity. An important extension of the concept would be to introduce Danishefsky's diene—being commercially available—as an alternative diene for chiral Brønsted-acid catalyzed hetero Diels–Alder reactions. Due to the mechanistic resemblance and similar reactivity[16] of silyl ketene acetals and **5** we reasoned that the bis-sulfonamide catalysts might display sufficient substrate activation to afford a chiral Brønsted-acid alternative to the well-established chiral metal-complexes, that so far have dominated asymmetric hetero Diels–Alder methodology.[17] Gratifyingly, this reasoning proved successful and we therefore evaluated

Table 3 Results for the catalytic enantioselective hetero Diels–Alder reaction of carbonyl compound (**2a,e,f–g**) with Danishefsky's diene (**5**) in the presence of 10 mol% **1d** as the catalyst[a]

Entry	R	R^1	Solvent	Temp./°C	Yield (%)[b]	Ee (%)[c]
1	H	*p*-NO_2-Ph	$CHCl_3$	−24	**6a**-76	50 (*S*)
2	H	*p*-CN–Ph	$CHCl_3$	−40	**6b**-74	49
3	Me	CO_2Me	toluene	−40	**6c**-44	65 (*S*)
4	Me	CO_2Et	toluene	−40	**6d**-49	73 (*S*)

[a] Reaction performed at 0.25 mmole scale of aldehyde or ketone **2** and 1.5 equiv. of Danishefsky's diene **5** in 1 mL solvent at the temperature indicated in the table. After 16 h, 4 mL 5% TFA in CH_2Cl_2 was added and the reaction mixture was stirred for 1 h at room temperature. The solvent was removed *in vacuo* to give the corresponding crude product. [b] Isolated yield. [c] Ee of the isolated product determined by chiral stationary phase HPLC.

different carbonyl compounds as dienophiles in hetero Diels–Alder reactions with Danishefsky's diene catalyzed by 10 mol% of bis-nonaflamide **1d** [eqn. (3)]. The results are shown in Table 3.



2a: R = H, R^1 = *p*-NO_2-Ph
2e: R = H, R^1 = *p*-CN-Ph
2f: R = Me, R^1 = CO_2Me
2g: R = Me R^1 = CO_2Et

5

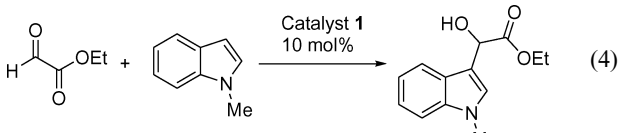
6a
6b
6c
6d

Both mono- and α-dicarbonyl compounds could be applied as electrophilic partners, and after ring closure with TFA the optically active tetrahydropyranones **6** could be isolated in moderate to good yields. In the case of *para*-substituted benzaldehydes (entries 1, 2) moderate enantioselectivities of up to 50% ee were observed, when catalyst **1d** was employed with $CHCl_3$ as the solvent. Slightly altered reaction conditions were found optimal for the application alkyl pyruvates as dienophiles (entries 3, 4), and the combination of catalyst **1d** in toluene at −40 °C lead to an increase in enantioselectivity to 73% ee for ethyl pyruvate (**2g**).

The successful activation of α-dicarbonyl compounds by catalyst **1d** prompted us to investigate other reactions of these important electrophiles in organic synthesis, and in particular we wished to evaluate reactions having a different mechanistic profile compared to the ones mentioned above.

Friedel–Crafts reactions

A candidate meeting these demands is the Friedel–Crafts reaction of indoles with α-dicarbonyl compounds. The possibility offered by this electrophilic aromatic substitution reaction for producing highly attractive optically active building blocks have already attracted the attention of many research groups.[18] Utilizing Lewis acids such as $Cu(OTf)_2$ complexed with chiral ligands catalytic asymmetric versions of this reaction have been devised. In this context we were pleased to find that the reaction also could be efficiently facilitated by the presence of catalytic amounts of the bis-sulfonamides **1**. Due to the different reaction profile we decided to re-optimize the reaction conditions and chose as a model reaction that between ethyl glyoxylate (**2h**) and *N*-methyl indole (**7a**) [eqn. (4)]. The results of these initial investigations are displayed in Table 4.



2h **7a** **8a**

First it is worth noticing that even without the presence of the catalyst, ethyl glyoxylate reacted with *N*-methyl indole at −24 °C smoothly. Trying to employ catalytic amounts of established chiral Brønsted acids (entries 1, 2) afforded essentially racemic products and no significant acceleration of the reaction compared to the racemic background reaction. However, the presence of bis-triflamide **1a** afforded again significant acceleration of the reaction and after 16 h at −24 °C compound **8a** was obtained in nearly quantitative yield and with 43% ee. Changing of the catalyst loading did not affect the enantioselectivity of the reaction (entries 3–5). Varying the reaction conditions (entries 6,7) revealed CH_2Cl_2 as an optimal solvent in terms of enantioselectivity. Curiously, a further decrease in reaction temperature (entry 8) did not lead to significant change in the enantioselectivity. Other bis-sulfonamides were also tested in this reaction (entries 9–12). A change of the phenyl-groups to *tert*-butyl lead to both a decrease in enantioselectivity and activity (entry 9). Contrary to the Mukaiyama-aldol reaction, the presence of catalysts **1h** and **1g** (entries 11, 12) accelerated the Friedel–Crafts reaction, but unfortunately the products were

Table 4 Results for the catalytic enantioselective Friedel–Crafts reaction of ethyl glyoxylate (**2h**) with *N*-methyl indole (**7a**) catalyzed by bis-sulfonamides **1** under various reaction conditions[a]

Entry	Catalyst	Solvent	Temp./°C	Time/h	Yield (%)[b]	Ee (%)[c]
1	(*R*)-BINOL	CH_2Cl_2	−24	16	55	3
2	TADDOL	CH_2Cl_2	−24	16	58	0
3	**1a**	CH_2Cl_2	−24	16	96	43
4[d]	**1a**	CH_2Cl_2	−24	16	99	43
5[e]	**1a**	CH_2Cl_2	−24	16	84	42
6	**1a**	$CHCl_3$	−24	16	98	33
7	**1a**	toluene	−24	16	85	30
8	**1a**	$CHCl_3$	−40	40	92	31
9	**1b**	CH_2Cl_2	−24	16	51	20
10	**1d**	CH_2Cl_2	−24	16	99	48
11	**1h**	CH_2Cl_2	−24	16	90	0
12	**1g**	CH_2Cl_2	−24	16	69	0

[a] Reaction performed at 0.25 mmol scale of *N*-methyl indole **7a** and 2.0 equiv. of ethyl glyoxylate (**2h**) in 1 mL solvent at the temperature indicated in the table. [b] Isolated yield. [c] Ee of the isolated product determined by chiral stationary phase HPLC. [d] 20 mol% **1a** was used as catalyst. [e] 5 mol% **1a** was used as catalyst.

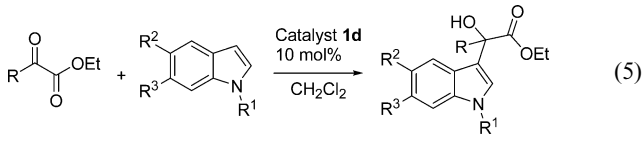
Table 5 Results for the catalytic enantioselective Friedel–Crafts reaction of α-dicarbonyl compounds **2** with indoles **7** in the presence of 10 mol% **1d** as the catalyst[a]

Entry	R	R^1	R^2	R^3	Temp./°C	Yield (%)[b]	Ee (%)[c]
1	H-**2h**	Me	H	H	−24	**8a**-99	48
2	H-**2h**	Me	OMe	H	−40	**8b**-98	63
3	H-**2h**	Me	H	Cl	−24	**8c**-73	46
4	H-**2h**	H	H	H	0	**8d**-73	33
5[d]	CF_3-**2i**	Me	H	H	−24	**8e**-99	23 (*R*)

[a] Reaction performed at 0.25 mmol scale of indole **7** and 2.0 equiv. of ethyl glyoxylate (**2h**) in 1 mL CH_2Cl_2 at the temperature indicated in the table. [b] Isolated yield. [c] Ee of the isolated product determined by chiral stationary phase HPLC. [d] 10 mol% **1a** was used as catalyst.

obtained as racemates. As was the case in the reactions involving silylated nucleophiles, catalyst **1d** (entry 8) performed better than catalyst **1a**, and after 16 h at −24 °C Friedel–Crafts product **8a** was isolated in nearly quantitative yield with an enantiomeric excess of 48%.

Different indoles (**7**) can be employed in the Friedel–Crafts reaction with α-dicarbonyl compounds [eqn. (5)] and Table 5 shows some of the results.



(5)

2 **7** **8**

a: R = H, R^1 = Me, R^2 = R^3 = H
b: R = H, R^1 = Me R^2 = OMe, R^3 = H
c: R = H, R^1 = Me R^2 = H, R^3 = Cl
d: R = R^1 = R^2 = R^3 = H
e: R = CF_3, R^1 = Me, R^2 = R^3 = H

Substituting the indole nucleus with either electron-releasing or mildly electron-withdrawing substituents afforded the products in good to excellent yields (entries 2, 3). In the case 5-methoxy *N*-methyl indole (**7b**) the Friedel–Crafts product **8b** was obtained in 63% ee, which to the best of our knowledge is comparable to the enantioselectivity obtained from chiral Lewis-acid complex catalyzed Friedel–Crafts reactions.[19] The use of an unprotected indole (entry 4) also afforded the Friedel–Crafts product in good yield, however, the optical purity was decreased to 33% ee (entry 4). Due to the importance of organofluorine compounds in several scientific disciplines,[20] ethyl trifluoropyruvate was applied in the Friedel–Crafts reaction catalyzed by 10 mol% **1a** and the corresponding product was obtained in quantitative yield (99%) with low enantiomeric excess (23%).

As is apparent from the results above, bis-sulfonamides **1a** and **1d** are efficient catalysts for carbonyl-addition reactions. It is also worth to notice that in the three different studies above the catalysts are consistently affording the products in an enantiomeric excess of *ca.* 40–50%—a fact implying a well defined catalyst–substrate complex leading to substrate activation. Inspection of the X-ray crystal structure[21] (Fig. 1) of catalyst **1a** does not directly reveal a possible explanation for the catalytic activity.

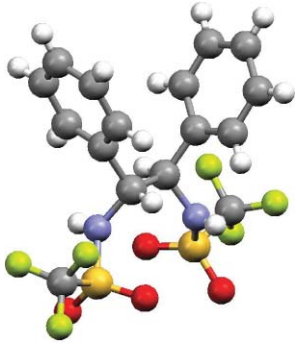


Fig. 1 X-Ray crystal structure of catalyst **1a**.[10]

In the solid state both sulfonamide hydrogens are engaged in hydrogen bonds to the sulfonyl-oxygen atom of a neighboring molecule (not shown in Fig. 1) but they are positioned on opposite sides of the plane defined by the phenyl rings and the C–N bonds, as is obvious from Fig. 1. As clearly indicated by the results above, the presence of both hydrogens is demanded to maintain catalytic activity. We therefore suggest that the catalyst in solution may adopt a conformation allowing for a double hydrogen-bonding interaction with a substrate carbonyl-group (Fig. 2). Inspection of molecular models of catalyst **1** clearly shows that rotational flexibility in the bond between the two chiral carbon atoms is demanded to minimize severe non-bonded interactions when adopting the conformation as shown in Fig. 2. This may provide an explanation for the fact that **1h** is catalytically inactive in the Mukaiyama-aldol reaction (Table 1, entry 15), as the presence of the cyclohexane ring severely diminishes the rotational freedom of the carbon–carbon bond. Likewise the diminished activity of catalysts **1b** and **1c** (Table 1, entries 10, 11) may be attributed to impaired rotational flexibility of the carbon–carbon bond due to the presence of the more bulky *tert*-butyl- and cyclohexyl-groups.

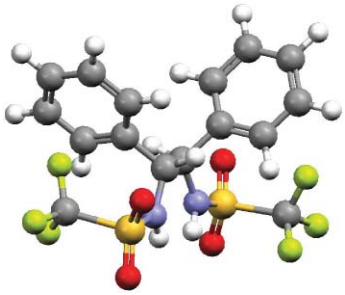


Fig. 2 Molecular model of catalyst **1a** having the sulfonamide hydrogens twisted into a conformation allowing for double hydrogen bonding.

Conclusion

Exemplified by three different carbonyl-addition reactions, Mukaiyama-aldol, hetero Diels–Alder and Friedel–Crafts reactions, we have demonstrated C_2-symmetric chiral bis-sulfonamides to be effective Brønsted-acid catalysts leading to the optically active products in moderate to excellent yields and with moderate enantioinduction. Based on structural studies of different bis-sulfonamides the catalyst function was discussed.

Experimental

General methods

The ^{1}H NMR and ^{13}C NMR spectra were recorded at 400 MHz and 100 MHz, respectively. The chemical shifts are reported in ppm relative to $CHCl_3$ (δ = 7.26) for ^{1}H and relative to the central $CDCl_3$ resonance (δ = 77.0) for ^{13}C NMR. Flash chromatography (FC) was carried out using Merck silica gel 60 (230–400 mesh). Optical rotation was measured on a

Perkin-Elmer 241 polarimeter. The enantiomeric excess (ee) of the products were determined by chiral HPLC using Daicel Chiralpak or Daicel Chiralcel columns with hexane–2-propanol as eluent as indicated in the respective entries.

Materials

Compounds **2a–g**, **2i**, **3**, **5**, **7a,d** are commercially available and were used as received without further purification. Compound **2h** was prepared by ozonolysis of diethyl maleate according to standard procedures[22] and freshly distilled before the use. Bis-sulfonamide catalysts[23] **1a–i**, *N*-protected indoles[24] **7b,c** were prepared according to literature procedures.

General procedure for Mukaiyama-aldol reactions

Aldehyde **2** (0.25 mmol) and 1.5 equiv. of silyl ketene acetal **3** were dissolved in 1 mL solvent and chiral bis-sulfonamides (10 mol%) was added. After the time indicated in the table, 4 mL 5% TFA in CH_2Cl_2 was added and the reaction mixture was stirred for 1 h at room temperature. The solvent was removed *in vacuo* to give the corresponding crude product then purified by column chromatography (Et_2O–CH_2Cl_2 as eluent).

3-Hydroxy-2,2-dimethyl-3-(4-nitro-phenyl)-propionic acid methyl ester (4a)

The ee was determined by HPLC using a Daicel Chiralcel OJ column; (hexane : 2-propanol = 90 : 10, flow rate 1.0 mL min^{-1}, τ_{minor} = 14.3 min; τ_{major} = 16.5 min). $[\alpha]_D^{rt} = -4.8$ (c = 1.4 in $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.18 (d, J = 8.8 Hz, 2H), 7.48 (d, J = 8.8 Hz, 2H), 5.00 (d, J = 4.0 Hz, 1H), 3.73 (s, 3H), 3.40 (d, J = 4.0 Hz, 1H), 1.13 (s, 3H), 1.12 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 177.7, 147.4, 147.2, 128.5 (2C), 122.9 (2C), 77.3, 52.4, 47.6, 22.7, 19.1. HRMS $C_{12}H_{15}NO_5$ [M + Na]$^+$ calculated 276.0848; found 276.0817.

3-Hydroxy-2,2-dimethyl-3-phenyl-propionic acid methyl ester (4b)

The ee was determined by GC on a Chrompak CP-Chirasil Dex CB-column. The temperature program: from 70 °C to 135 °C at a rate of 10 °C min^{-1} and then maintained for 20 min; increasing the temperature at a rate of 10 °C min^{-1} to 150 °C then maintained for 5 min. (τ_{major} = 29.7 min; τ_{minor} = 30.7 min). $[\alpha]_D^{rt} = -0.86$ (c = 0.7 in MeOH); ^{1}H NMR ($CDCl_3$) δ 7.28–7.21 (m, 5H), 4.85 (d, J = 4.0 Hz, 1H), 3.68 (s, 3H), 3.00 (d, J = 4.0 Hz, 1H), 1.10 (s, 3H), 1.07 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 178.2, 139.9, 127.8 (2C), 127.6 (2C), 78.7, 52.1, 47.7, 23.1, 19.0. HRMS $C_{12}H_{16}O_3$ [M + Na]$^+$ calculated 231.0997; found 231.0999.

3-Hydroxy-2,2-dimethyl-3-pyridin-2-yl-propionic acid methyl ester (4c)

The ee was determined by HPLC using a Daicel Chiralpak AS column; (hexane : 2-propanol = 95 : 5, flow rate 1.0 mL min^{-1}, τ_{minor} = 6.95 min; τ_{major} = 8.11 min). $[\alpha]_D^{rt} = +0.77$ (c = 1.3 in $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.53 (d, J = 4.4 Hz, 1H), 7.63 (td, J = 7.6, 1.6 Hz, 1H), 7.15 (d, J = 4.8 Hz, 1H), 7.15 (d, J = 7.6 Hz, 1H), 4.93 (s, 1H), 3.71 (s, 3H), 1.15 (s, 3H), 1.07 (s, 3H); ^{13}C NMR ($CDCl_3$) δ 177.2, 158.3, 148.1, 136.2, 122.9, 122.1, 77.1, 52.0, 48.5, 20.9. HRMS $C_{11}H_{15}NO_3$ [M + Na]$^+$ calculated 232.0950; found 232.0942.

3-Hydroxy-2,2-dimethyl-3-pyridin-4-yl-propionic acid methyl ester (4d)

The ee was determined by HPLC using a Daicel Chiralpak AS column; (hexane : 2-propanol = 80 : 20, flow rate 1.0 mL min^{-1}, τ_{minor} = 5.77 min; τ_{major} = 7.15 min). $[\alpha]_D^{rt} = -13.2$ (c = 1.4 in $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.57 (d, J = 4.8 Hz, 2H), 7.24 (d, J = 4.8 Hz, 2H), 4.88 (d, J = 4.4 Hz, 1H), 3.74 (s, 3H), 3.36 (d, J = 4.4 Hz, 1H), 1.14 (s, 6H); ^{13}C NMR ($CDCl_3$) δ 177.7, 149.2 (2C), 148.9, 122.8 (2C), 52.3, 47.4, 30.2, 22.7, 19.1. HRMS $C_{11}H_{15}NO_3$ [M + H]$^+$ calculated 210.1130; found 210.1135.

General procedure for hetero Diels–Alder reactions

Aldehyde or ketone **2** (0.25 mmol) and 1.5 equiv. of Danishefsky's diene **5** were dissolved in 1 mL solvent and chiral bis-sulfonamides (10 mol%) was added. After the time indicated in the table, 4 mL 5% TFA in CH_2Cl_2 was added and the reaction mixture was stirred for 1 h at room temperature. The solvent was removed *in vacuo* to give the corresponding crude product then purified by column chromatography (EtOAc–pentane as eluent).

2-(4-Nitro-phenyl)-2,3-dihydro-pyran-4-one (6a)

The ee was determined by HPLC using a Daicel Chiralcel OD column; (hexane : 2-propanol = 80 : 20, flow rate 1.0 mL min^{-1}, τ_{major} = 21.7 min; τ_{minor} = 31.3 min). $[\alpha]_D^{rt} = +16.8$ (c = 1.1 in $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.29 (d, J = 8.8 Hz, 2H), 7.60 (d, J = 8.8 Hz, 2H), 7.51 (d, J = 5.6 Hz, 1H), 5.58 (dd, J = 5.6, 1.2 Hz, 1H), 5.55 (dd, J = 14.0, 3.6 Hz, 1H), 2.89–2.70 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 190.7, 162.6, 148.0, 144.8, 126.7 (2C), 124.1 (2C), 107.9, 79.7, 43.3. HRMS $C_{11}H_9NO_4$ [M + H]$^+$ calculated 220.0610; found 220.0611.

4-(4-Oxo-3,4-dihydro-2*H*-pyran-2-yl)-benzonitrile (6b)

The ee was determined by HPLC using a Daicel Chiralcel OD column; (hexane : 2-propanol = 80 : 20, flow rate 1.0 mL min^{-1}, τ_{major} = 15.8 min; τ_{minor} = 19.5 min). $[\alpha]_D^{rt} = +33.5$ (c = 0.9 in $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.73 (d, J = 7.2 Hz, 2H), 7.54–7.49 (m, 3H), 5.57 (d, J = 6.0 Hz, 1H), 5.50 (dd, J = 14.0, 3.6 Hz, 1H), 2.87–2.67 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 190.9, 162.7, 142.9, 132.7 (2C), 126.5 (2C), 118.2, 112.7, 107.8, 79.9, 43.2. HRMS $C_{12}H_9NO_2$ [M + Na]$^+$ calculated 222.0531; found 222.0525.

2-Methyl-4-oxo-3,4-dihydro-2*H*-pyran-2-carboxylic acid methyl ester (6c)

The ee was determined by GC on a Chrompak CP-Chirasil Dex CB-column. The temperature program: from 70 °C to 150 °C at a rate of 10 °C min^{-1} and then maintained for 5 min. τ_{minor} = 9.0 min; τ_{major} = 9.4 min). $[\alpha]_D^{rt} = +48.6$ (c = 1.2 in $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.36 (d, J = 6.0 Hz, 1H), 5.44 (d, J = 6.0 Hz, 1H), 3.78 (s, 3H), 3.01 (d, J = 17.2 Hz, 1H), 2.69 (d, J = 16.8 Hz, 1H), 1.67 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 190.0, 171.4, 161.9, 107.3, 82.8, 53.2, 44.6, 24.2. HRMS $C_8H_{10}O_4$ [M + Na]$^+$ calculated 193.0477; found 193.0469.

2-Methyl-4-oxo-3,4-dihydro-2*H*-pyran-2-carboxylic acid ethyl ester (6d)

The ee was determined by GC on a Chrompak CP-Chirasil Dex CB-column. The temperature program: from 70 °C to 150 °C at a rate of 10 °C min^{-1} and then maintained for 5 min. τ_{minor} = 9.7 min; τ_{major} = 10.2 min). $[\alpha]_D^{rt} = +70.4$ (c = 0.7 in $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.35 (d, J = 6.4 Hz, 1H), 5.41 (d, J = 6.0 Hz, 1H), 4.21 (q, J = 6.8 Hz, 2H), 2.99 (d, J = 16.4 Hz, 1H), 2.67 (d, J = 16.8 Hz, 1H), 1.65 (s, 3H), 1.25 (d, J = 6.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 190.1, 170.9, 161.9, 107.3, 82.8, 62.4, 44.6, 24.1, 14.0. HRMS $C_9H_{12}O_4$ [M + Na]$^+$ calculated 207.0633; found 207.0632.

General procedure for Friedel–Crafts reactions

Indole **7** (0.25 mmol) and 2.0 equiv. of ethyl glyoxylate **2h** were dissolved in 1 mL solvent and chiral bis-sulfonamides (10 mol%) was added. After the time indicated in the table, the reaction mixture was concentrated *in vacuo* and crude product was purified by column chromatography (Et_2O–CH_2Cl_2 as eluent).

Hydroxy-(1-methyl-1*H*-indol-3-yl)-acetic acid ethyl ester (8a)

The ee was determined by HPLC using a Daicel Chiralpak AS column; (hexane : 2-propanol = 90 : 10, flow rate 1.0 mL min^{-1}, τ_{major} = 20.4 min; τ_{minor} = 29.6 min). $[a]_D^{rt}$ = +10.8 (c = 1.4 in $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.67 (d, J = 7.6 Hz, 2H), 7.28 (d, J = 8.0 Hz, 1H), 7.22 (td, J = 8.0, 0.8 Hz, 1H), 7.11 (d, J = 7.6 Hz, 1H), 7.08 (s, 1H), 5.41 (d, J = 6.0 Hz, 1H), 4.27 (dq, J = 10.8, 7.6 Hz, 1H), 4.14 (dq, J = 10.8, 7.6 Hz, 1H), 3.72 (s, 3H), 3.26 (d, J = 5.6 Hz, 1H), 1.20 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 174.1, 137.2, 127.7, 125.8, 122.0, 119.6, 119.5, 112.2, 109.4, 67.1, 62.0, 32.8, 14.1. HRMS $C_{13}H_{15}NO_3$ [M + Na]$^+$ calculated 256.0950; found 256.0946.

Hydroxy-(5-methoxy-1-methyl-1*H*-indol-3-yl)-acetic acid ethyl ester (8b)

The ee was determined by HPLC using a Daicel Chiralpak AS column; (hexane : 2-propanol = 90 : 10, flow rate 1.0 mL min^{-1}, τ_{major} = 22.7 min; τ_{minor} = 34.9 min). $[a]_D^{rt}$ = +18.5 (c = 1.0 in $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.19 (dd, J = 9.2, 3.2 Hz, 1H), 7.13 (t, J = 2.8 Hz, 1H), 7.07 (d, J = 2.8 Hz, 1H), 6.90 (td, J = 8.8, 2.4 Hz, 1H), 5.41 (s, 1H), 4.31 (dq, J = 11.2, 7.2 Hz, 1H), 4.19 (dq, J = 11.2, 7.2 Hz, 1H), 3.85 (s, 3H), 3.73 (s, 3H), 3.21 (br, 1H), 1.25 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 174.1, 154.2, 132.5, 128.1, 126.1, 112.6, 111.7, 110.3, 100.9, 67.1, 62.0, 55.8, 33.0, 14.1. HRMS $C_{14}H_{17}NO_4$ [M + Na]$^+$ calculated 286.1055; found 286.1048.

(6-Chloro-1-methyl-1*H*-indol-3-yl)-hydroxy-acetic acid ethyl ester (8c)

The ee was determined by HPLC using a Daicel Chiralpak AS column; (hexane : 2-propanol = 90 : 10, flow rate 1.0 mL min^{-1}, τ_{major} = 18.6 min; τ_{minor} = 30.1 min). $[a]_D^{rt}$ = +30.7 (c = 1.9 in $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.60 (d, J = 8.4 Hz, 1H), 7.30 (d, J = 0.8 Hz, 1H), 7.11 (s, 1H), 7.09 (d, J = 2.0 Hz, 1H), 5.41 (s, 1H), 4.29 (dq, J = 10.8, 7.2 Hz, 1H), 4.18 (dq, J = 10.8, 7.2 Hz, 1H), 3.73 (s, 3H), 3.31 (br, 1H), 1.22 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 173.9, 137.7, 128.3, 128.2, 124.3, 120.5, 120.4, 112.5, 109.5, 66.9, 62.2, 32.9, 14.1. HRMS $C_{13}H_{14}ClNO_3$ [M + Na]$^+$ calculated 290.0560; found 290.05551.

Hydroxy-(1*H*-indol-3-yl)-acetic acid ethyl ester (8d)

The ee was determined by HPLC using a Daicel Chiralpak AS column; (hexane : 2-propanol = 90 : 10, flow rate 1.0 mL min^{-1}, τ_{major} = 24.4 min; τ_{minor} = 31.9 min). $[a]_D^{rt}$ = +23.0 (c = 1.5 in $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 8.22 (br, 1H), 7.67 (d, J = 7.6 Hz, 1H), 7.29 (d, J = 8.0 Hz, 1H), 7.21–7.09 (m, 3H), 5.42 (s, 1H), 4.25 (dq, J = 10.8, 7.2 Hz, 1H), 4.13 (dq, J = 10.8, 7.2 Hz, 1H), 3.33 (s, 1H), 1.17 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 174.0, 136.4, 125.3, 123.2, 122.5, 120.1, 119.4, 113.8, 111.1, 67.2, 62.1, 53.7, 29.2, 14.1. HRMS $C_{12}H_{13}NO_3$ [M + Na]$^+$ calculated 242.0793; found 242.0787.

3,3,3-Trifluoro-2-hydroxy-2-(1-methyl-1H-indol-3-yl)-propionic acid ethyl ester (8e)

The ee was determined by HPLC using a Daicel Chiralpak AS column; (hexane : 2-propanol = 90 : 10, flow rate 1.0 mL min^{-1}, τ_{major} = 8.8 min; τ_{minor} = 11.1 min). $[a]_D^{rt}$ = −3.8 (c = 1.3 in $CHCl_3$); The spectroscopic data were in agreement with literature values.[25]

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References

1 See *e.g.*: (*a*) P. I. Dalko and L. Moisan, *Angew. Chem., Int. Ed.*, 2004, **43**, 5138; (*b*) P. M. Pihko, *Angew. Chem., Int. Ed.*, 2004, **43**, 2062.
2 M. S. Sigman, P. Vachel and E. N. Jacobsen, *Angew. Chem., Int. Ed.*, 2000, **39**, 1279.
3 (*a*) A. G. Wenzel and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2002, **124**, 12964; (*b*) D. Uraguchi and M. Terada, *J. Am. Chem. Soc.*, 2004, **126**, 5356; (*c*) T. Akiyama, J. Itoh, K. Yokota and K. Fuchibe, *Angew. Chem., Int. Ed.*, 2004, **43**, 1566.
4 D. Uraguchi, K. Sorimachi and M. Terada, *J. Am. Chem. Soc.*, 2004, **126**, 11804.
5 G. D. Joly and E. N. Jacobsen, *J. Am. Chem. Soc.*, 2004, **126**, 4102.
6 M. S. Taylor and E. N. Jacobsen, *J. Am. Chem. Soc*, 2004, **126**, 10558.
7 T. Okino, S. Nakamura, T. Furukawa and Y. Takemoto, *Org. Lett.*, 2004, **6**, 625.
8 For hydrogen-bond accelerated reactions involving carbonyl groups see: (*a*) T. R. Kelly, P. Meghani and V. S. Ekkundi, *Tetrahedron Lett.*, 1990, **31**, 3381; (*b*) D. P. Curran and L. H. Kuo, *J. Org. Chem.*, 1994, **59**, 3259; (*c*) T. Schuster, M. Bauch, G. Dürner and M. W. Göbel, *Org. Lett.*, 2000, **2**, 179; (*d*) P. R. Schreiner and A. Wittkopp, *Org. Lett.*, 2002, **4**, 217; (*e*) P. R. Schreiner, *Chem. Soc. Rev.*, 2003, **32**, 289.
9 (*a*) Y. Huang, A. K. Unni, A. N. Thadani and V. H. Rawal, *Nature*, 2003, **424**, 126; (*b*) A. N. Thadani, A. R. Stankovic and V. H. Rawal, *Proc. Natl. Acad. Sci. USA*, 2004, **101**, 5846; (*c*) A. K. Unni, N. Takenaka, H. Yamamoto and V. H. Rawal, *J. Am. Chem. Soc.*, 2005, **127**, 1336. See also: (*d*) H. Du, D. Zhao and K. Ding, *Chem. Eur. J.*, 2004, **10**, 5964.
10 W. Zhuang, R. G. Hazell and K. A. Jørgensen, *Org. Biomol. Chem.*, 2005, **3**, 2566.
11 For a seminal reference see (*a*) K. Narasaki and T. Mukaiyama, *Chem. Lett*, 1974, 1223. For a review see *e.g.*:; E. M. Carreira, in *Comprehensive Asymmetric Catalysis*, Vol. 3, E. H. Jacobsen, A. Pfaltz, H. Yamamoto, (Eds.), Springer-Verlag, Berlin, 1999, p. 997.
12 For a review see: T. Ooi and K. Maruoka, *Acc. Chem. Res.*, 2004, **37**, 526.
13 Using 40 mol% of BINOL as the catalyst produced only 19% yield of the Mukaiyama-aldol product. T. B. Poulsen, W. Zhuang, K. A. Jørgensen, unpublished results.
14 For a review see: D. Lucet, T. L. Gall and C. Mioskowski, *Angew. Chem., Int. Ed.*, 1998, **37**, 2581.
15 The tosyl-amide (*p*-Me-Ph-SO_2NH_2) has a pK_a-value of *ca.* 16 (DMSO) compared to the triflamide (CF_3-SO_2NH_2) which has *ca.* 10 (DMSO).
16 J. Burfeindt, M. Patz, M. Muller and H. Mayr, *J. Am. Chem. Soc.*, 1998, **120**, 3629.
17 For reviews see *e.g.*: (*a*) K. A. Jørgensen, *Angew. Chem., Int. Ed.*, 2000, **39**, 3558; (*b*) J. S. Johnson and D. A. Evans, *Acc. Chem. Res.*, 2000, **33**, 325; (*c*) K. A. Jørgensen, M. Johannsen, S. Yao, H. Audrain and J. Thorhauge, *Acc. Chem. Res.*, 1999, **32**, 605.
18 For a review see: M. Bandi, A. Melloni and A. Umani-Ronchi, *Angew. Chem., Int. Ed.*, 2004, **43**, 550.
19 Various combinations of Lewis acid and chiral ligand were screened for the catalytic Friedel–Crafts reaction of ethyl glyoxylate with *N*-methyl indole, the best enantiomeric excess of corresponding product was 68% ee.
20 For a review see: P. Lin and J. Jiang, *Tetrahedron*, 2000, **56**, 3635.
21 Several attempts were made to form inclusion complexes between catalysts **1a,d** and different carbonyl compounds, but unfortunately all attempts so far has been without success.
22 W. Zhuang and K. A. Jørgensen, *Chem. Commun.*, 2002, 1336.
23 Synthesis of chiral diamines see *e.g.*:(*a*) E. J. Corey, R. Imwinkelried, S. Pikul and Y. B. Xiang, *J. Am. Chem. Soc.*, 1989, **111**, 5493; (*b*) E. J. Corey, D.-H. Lee and S. Sarshar, *Tetrahedron: Asymmetry*, 1995, **6**, 3; (*c*) S. Roland and P. Mangeney, *Eur. J. Org. Chem*, 2000, 611; (*d*) S. Rolan and P. Mangeney, *Synthesis*, 1999, 228.
24 (*a*) C. A. Merlic, Y. You, D. M. McInnes, A. L. Zechman, M. M. Miller and Q. Deng, *Tetrahedron*, 2001, **57**, 5199; (*b*) P. J. Beswick, C. S. Greenwood, T. J. Mowlem, G. Nechvatal and D. A. Widdowson, *Tetrahedron*, 1988, **44**, 7235.
25 W. Zhuang, N. Gathergood, R. G. Hazel and K. A. Jørgensen, *J. Org. Chem.*, 2001, **66**, 1009.