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Dependence of Enantioselectivity on the Ligand/Metal Ratio in the Asymmetric Michael Addition of Indole to Benzylidene Malonates: Electronic Influence of Substrates

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Abstract: Simple bis(oxazoline) ligands, especially azabis(oxazolines), can promote the copper(II)-catalyzed Michael addition of indoles to benzylidene malonates with up to >99% *ee* (*ee* = enantiomeric excess), provided that the ligand/metal ratio is tuned meticulously with particular regard to the electronic properties of the substrate. Despite a common paradigm followed in many asymmetric catalyses, an excess of chiral ligand is not always beneficial. In fact any excess of ligand has to be avoided to reach excellent enantioselectivities when electron-rich benzylidene malonates are used. On the contrary, malonates carrying an electron-withdrawing group require an excess of ligand for an optimum *ee* value. A correlation of optical yields versus the σ_I values of several *para* substituents shows a sigmoid trajectory. In the presence of an additive, such as triflate, the significance of the ligand/metal ratio vanishes and very good enantioselectivities are achieved at any rate—no matter whether electron-donating or withdrawing substituents are present.

Keywords: asymmetric catalysis · enantioselectivity · homogeneous catalysis · Michael addition · oxazoline ligands

Introduction

Determination of the optimum ligand/metal ratio has been an issue in many pioneering works in the field of asymmetric catalysis with chiral oxazoline ligands. An early example was reported by Brunner and co-workers, in which they demonstrated that, in general, the rhodium/ligand ratio in the enantioselective hydrosilylation of acetophenone with $[RhCl(cod)]_2$ (cod = 1,5-cyclooctadiene) by using pyridineoxazoline ligands as cocatalysts is crucial for asymmetric induction.[1] An excess of rhodium was found to be as detrimental as an equimolar ratio of ligand to metal, whereas a fivefold ligand surplus was found to give the best optical induction. The same group showed that the $Cu(OAc)_2$-catalyzed monophenylation of *meso*-diols with $Ph_3Bi(OAc)_2$ can be rendered enantioselective with an even higher excess of pyridineoxazoline.[2] Indeed, it appears reasonable to assume that at least a small excess of ligand is required to suppress a background reaction promoted by ligand-free and, therefore, unselective metal centers. Consequently, a slight excess of ligand was applied in various asymmetric catalyses ever since. Evans[3] and Pfaltz[4] have developed highly enantioselective processes for the copper(I)-catalyzed cyclopropanation of olefins by utilizing bis(oxazolines) and semicorrines, respectively, in small overspill, the latter also applied at a ligand/copper ratio of two, but accompanied by a diminutive loss of selectivity. The same ligands proved to be very efficient in palladium-catalyzed allylic alkylations at a ligand/Pd ratio of 1.25.[4b]

However, we found the stereoelectronic outcome of the asymmetric monobenzolyation of 1,2-diols to be affected by neither an excess of copper(II) nor bis(oxazoline) ligands,[5] which raised the question as to if these catalyses might even be negatively influenced in their optical yields by a ligand surplus. Indeed, we observed such a detrimental effect on the enantioselective Michael addition of indole to benzylidene malonate, which gave rise to selectivities that were not achieved with simple bis(oxazoline) ligands heretofore.[6] This unprecedented effect was subsequently validated in the copper(I)-catalyzed alkynylation of an α-amino ester with arylacetylenes, which responds to any excess of pybox (pybox = pyridine-2,6-bis(oxazoline)) with a significant decrease in enantiofacial selection to the point that even a reversal of enantioselectivity can be achieved.[7]

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Herein, we present complementary results, which indicate that the title reaction shows a unique behavior towards the ligand/metal ratio. The different electronic parameters of substituted benzylidene malonates highly influence not only the sensitivity towards the ligand/metal ratio, but also whether an excess of ligand is detrimental or beneficial. Furthermore, the role of certain additives, such as triflate, is discussed. Especially in the presence of an excess of triflate, the enantioselectivity of the reaction is decoupled from its aboriginal strong dependence to the ligand/copper ratio.

Results and Discussion

The Friedel–Crafts reaction is one of the most powerful methods for the formation of carbon–carbon bonds[8] and has, therefore, gained a lot of attention during the past decades, which has included the development of enantioselective variants.[9] The copper(II)-catalyzed 1,4-addition of indole (**4**) to benzylidene malonate **5a** is known to proceed in the presence of bis(oxazoline) **1a** with moderate selectivities (up to 69% *ee*; *ee* = enantiomeric excess) under standard reaction conditions (ligand/copper ratio 1.1–1.2 in alcoholic solvents at ambient temperature and atmosphere) as reported by Jørgensen et al.[10] Although some improvement was achieved by Tang et al.[11] (up to 82% *ee*) they reasoned that simple C_2-symmetric bis(oxazolines) were unsuitable ligands to form a highly stereodiscriminating environment for the copper complex, a prerequisite to achieve high enantioselectivities. An elegant alternative was proposed with the development of tris(oxazoline) ligand **3**, which is able to coordinate in a tridentate fashion to the copper center. A pentacoordinated complex of type **B** (Figure 1), in which one oxazoline moiety necessarily has to be in an apical position, was postulated to account for enhanced stereochemical induction. Indeed, employing **3** resulted in highly improved selectivities of up to 93% *ee* for the adduct **6a**.[12]

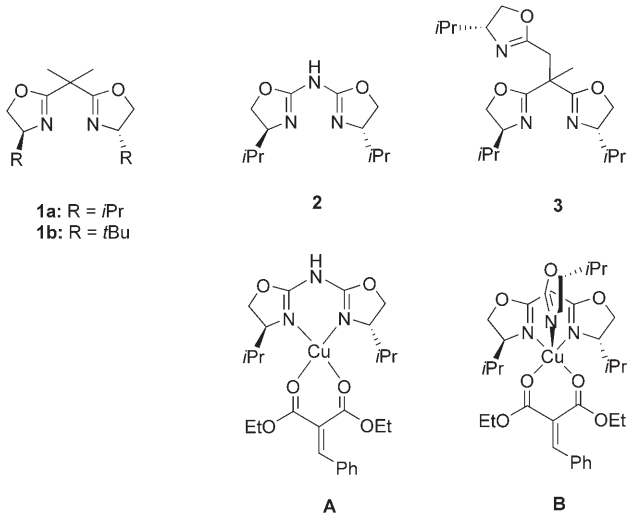
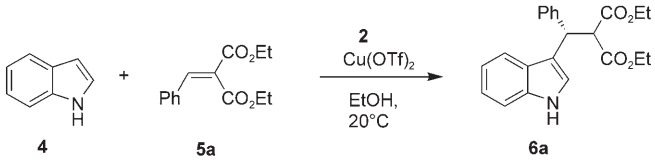


Figure 1. Ligands and binding modes in copper complexes with benzylidene malonate **4a**.

However, we found that a species of type **B** might not necessarily be required to create highly stereoselective complexes. Seemingly inferior bidentate bis(oxazolines) were found to be applicable for the highly enantioselective addition of indole (**4**) to benzylidene malonate **5a**.[6] If any excess of ligand is avoided and the ligand/copper ratio carefully adjusted to 1.04, excellent enantioselectivities (> 99% *ee*) are obtained by using both, bis(oxazoline) **1a** or azabis(oxazoline)[13] **2**, the latter resulting in somewhat higher yields (entry 3, Table 1). Even if the **2**/copper ratio is shifted towards a slight excess of copper (entry 5), the selectivity remains respectable and clearly superior to the one obtained if the self-same ligand surplus is employed (entry 2).

Table 1. Dependence of enantioselectivity on the ligand/metal ratio in the asymmetric 1,4-addition of indole (**4**) to benzylidene malonate **5a**.[6][a]



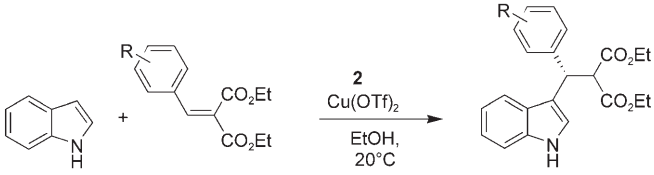
Entry	Ligand/metal ratio	Yield [%]	*ee* [%][b]
1	1.3:1.0	98	81
2	1.1:1.0	93	85
3	1.04:1.0	97	> 99
4	1.0:1.0	90	98
5	1.0:1.1	96	98
6	1.0:1.3	95	91

[a] Reagents and conditions: indole (1.2 mmol), malonate (1.0 mmol), **2** (5 mol%), $Cu(OTf)_2$ according to the metal/ligand ratio, 20 °C, 8 h; solvent: EtOH (4 mL). [b] Determined by HPLC.

This is quite in contrast to the usual observation in asymmetric catalysis that an excess of chiral ligand is beneficial to avoid background reactions by uncomplexed metal. A square-planar species of type **A** is assumed to give the same high enantioselectivity as its five-membered counterpart **B** if bis(oxazoline) ligands **1** or **2** are employed. A resting state of the catalyst might be entered by coordination of a third oxazoline moiety to copper, as suggested by Gade et al.[14] if an excess of ligand is provided. To reach an active species, one of the nitrogen moieties has to leave the coordination sphere, which should be the apical oxazoline if ligand **3** is employed. An excess of external ligand might, however, compete for an equatorial position, which could result in low enantioselectivity. In this study, we provide evidence for such a mechanistic model.

When a number of substituted benzylidene malonates were examined for the reaction with indole at ligand/metal ratios of 1.05 and 1.3, a surprising dependence of the latter with the electronic nature of the substituent was revealed. We found that comparatively electron-rich compounds, especially **5a** and **5b** (entries 1–4, Table 2), formed adducts

Table 2. Dependence of enantioselectivity on the ligand/metal ratio in the 1,4-addition of indole (**4**) to substituted benzylidene malonates **5a–h**: electronic effects of different malonates.[a]



4 **5a-h** **6a-h**

Entry	Ligand/metal ratio	R	Yield [%]	*ee* [%][b]
1	1.04:1.0	H (**5a**)	97	>99[c]
2	1.3:1.0	H (**5a**)	98	81[c]
3	1.04:1.0	4-Me (**5b**)	80	93
4	1.3:1.0	4-Me (**5b**)	78	76
5	1.05:1.0	4-OMe (**5c**)	75	84
6	1.3:1.0	4-OMe (**5c**)	69	70
7	1.05:1.0	4-CF_3 (**5d**)	95	90
8	1.3:1.0	4-CF_3 (**5d**)	93	81
9	1.05:1.0	2-Br (**5e**)	89	85
10	1.3:1.0	2-Br (**5e**)	86	86
11	1.05:1.0	4-Br (**5f**)	97	75
12	1.3:1.0	4-Br (**5f**)	95	82
13	1.05:1.0	4-NO_2 (**5g**)	92	82[c]
14	1.3:1.0	4-NO_2 (**5g**)	83	94[c]
15	1.05:1.0	4-NMe_2 (**5h**)	–	–

[a] Reagents and conditions: indole (1.2 mmol), malonate (1.0 mmol), **2** (5 mol%), 20°C, 8 h; solvent: EtOH (4 mL). [b] Determined by HPLC. [c] Obtained by at least two independent runs.

with indole (**4**) in high optical yields if any excess of ligand is prevented. On the contrary, the strongly electron-deficient 4-nitro-derivative **5g** pales in this respect (entry 13). Surprisingly, very good enantioselectivities were achieved for **5g** if an excess of ligand (**2**/copper ratio 1.3) was applied, which was found to be highly disadvantageous for the electron-rich counterparts (entry 2 and 14). In addition, we found that the sensitivity of enantioselectivity towards ligand excess vanishes with the decreasing inductive contribution of the substituent until it is reversed: Best results for compounds **5c** and **5d** are still found at nearly an equimolar ratio of ligand and copper (entries 5–8), although both, selectivities and ligand dependence are somewhat lower relative to **5a** and **5b**. Whereas the 2-bromo-derivative **5e** appears to be rather insensitive to the influence of the ligand/copper ratio, 4-bromo-benzylidene malonate **5f** marks the turnaround with maximum *ee* at a ligand/metal ratio of 1.3 (entries 9–12). As mentioned above, the reversed sensitivity towards ligand excess culminates for 4-nitro-derivative **5g**. A further rise in the ligand/metal ratio did not increase the selectivity. Strongly electron-donating substituents, such as the dimethylamino group, oppress the reactivity of the substrate completely (entry 15).

Hence, we supposed this different behavior to be associated with the different electronic parameters of the derivatives. A semi-logarithmic plot of optical yields at the two different ligand/metal ratios (1.05 and 1.3) versus the σ_I values[15] of all *para*-substituted benzylidene malonates gave a sigmoid trajectory (Figure 2).

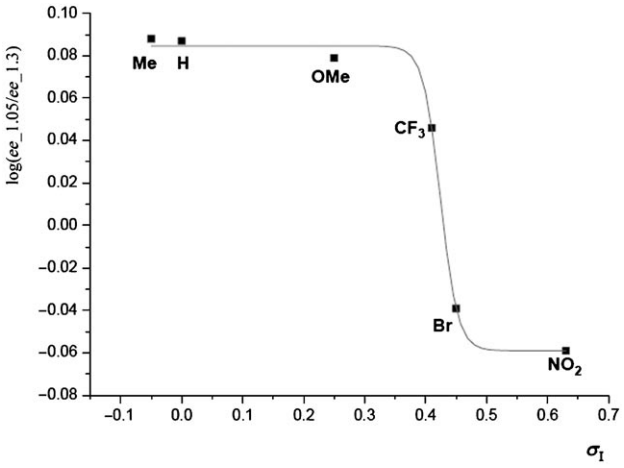
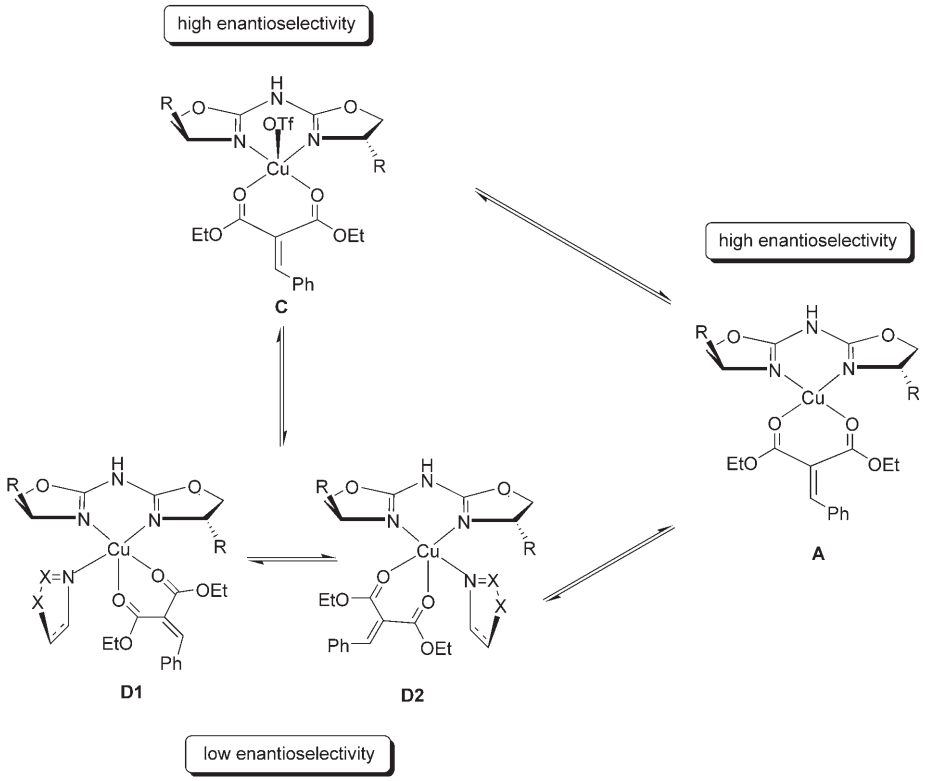


Figure 2. Semi-logarithmic correlation of optical yield ratio versus σ_I values of *para* substituents in the reaction of indole (**4**) with substituted benzylidene malonates **5a–d**,**f**,**g**.

To obtain a deeper insight into the proposed interplay of tetra- and pentacoordinated copper–oxazoline complexes, we investigated the use of lithium triflate for the title reaction, an additive that is supposed to have an influence on the enantioselectivity by coordination of triflate on the copper center in an apical position.[12b] We speculated that a pentacoordinated complex of type **C** might be less affected by ligand excess (Scheme 1). In contrast to the likewise square-pyramidal species **B** (Figure 1), no additional stereochemical information is provided by coordination of the triflate counterion.

Studies were carried out at different **2**/copper ratios and with benzylidene malonates **5a**, **5e**, and **5g**, each representing a varied inductive contribution and, therefore, different sensitivity towards ligand excess. Changing the amount of indole (**4**) in the reaction with **5a** from 1.2 to 5.0 mmol at a ligand/metal ratio of 1.04 had no influence on either enantioselectivity or yield (entry 1, Table 3), thus indicating a minor role played by indole (**4**) as a ligand for coordination of copper.[16] An addition of 25 mol% (equal to 5 equiv with respect to the copper–aza(bisoxazoline) complexes) of lithium triflate to the already highly selective reaction of indole (**4**) with **5a** in the absence of additives at a ligand/metal ratio of 1.04 had some negative effects on enantioselectivity, whereas the same amount of additive at the disadvantageous **2**/copper ratio of 1.3 annihilates the negative influence of ligand excess to a large part. The enantioselectivity thus obtained is almost comparable to the one at a meticulously adjusted ligand/metal ratio (entries 1–4).

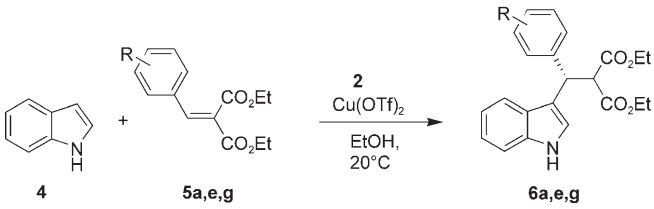
At the present time, we cannot offer a satisfactory explanation for the observed electronic differences of the substrates with respect to ligand ratio and enantioselectivity. Our finding with regard to employing additives can be, however, explained if a five-membered square-pyramidal complex is taken into consideration, which is widely accepted to persist additionally to the distorted square-planar complex of type **A** during catalysis with bis(oxazoline) complexes,[17]



Scheme 1. Mechanistic model for the asymmetric 1,4-addition of benzylidene malonate **5a**.

malonate: it might be bound in the plain of the oxazolines with either both carboxyl moieties or with one in an equatorial and the other in an apical position. The latter binding fashion is most popular for pyridinebis(oxazolines),[18] but was also discussed for bis(oxazolines).[17b,19] With an excess of ligand present competing with benzylidene malonate for coordination space, the benzylidene malonate might be driven in the less-enantioselective binding mode **D** (Scheme 1), which provides the sterically more demanding oxazoline surplus with an equatorial position. In this case, nonidentical alternatives for coordination at the equatorial position would probably arise, accounting for the drop in selectivity. In fact we have a hint that triazole moieties, although sterically less demanding than their oxazoline counterparts, are bound in a square-pyramidal copper complex in an equatorial rather than in an apical position (Figure 3). With a considerable excess of triflate applied (5 equiv with respect to **2**), competing with a rather small ligand surplus for the fifth coordination site, triflate might cover this position due to plain spillover. However, it is unlikely by means of steric and electronic demand that triflate would occupy

Table 3. Dependence of enantioselectivity on the ligand/metal ratio in the 1,4-addition of indole (**4**) to benzylidene malonates **5a**,**e**,**g**: influence of triflate as an additive.[a]



4 5a,e,g 6a,e,g

Entry	Ligand/metal ratio	R	Li(OTf)/**2**	Yield [%]	*ee* [%][b]
1	1.04:1.0	H (**5a**)	–	97	>99[c]
2	1.05:1.0	H (**5a**)	5	90	93
3	1.3:1.0	H (**5a**)	–	98	81[c]
4	1.3:1.0	H (**5a**)	5	97	96
5	1.04:1.0	2-Br (**5e**)	–	89	85
6	1.05:1.0	2-Br (**5e**)	5	84	82
7	1.3:1.0	2-Br (**5e**)	–	86	86
8	1.3:1.0	2-Br (**5e**)	5	78	85
9	1.05:1.0	4-NO_2 (**5g**)	–	92	82[c]
10	1.05:1.0	4-NO_2 (**5g**)	5	89	96
11	1.3:1.0	4-NO_2 (**5g**)	–	83	94[c]
12	1.3:1.0	4-NO_2 (**5g**)	5	73	93

[a] Reagents and conditions: indole (1.2 mmol), malonate (1.0 mmol), **2** (5 mol%), 20°C, 8 h; solvent: EtOH (4 mL). [b] Determined by HPLC. [c] Obtained by at least two independent runs.

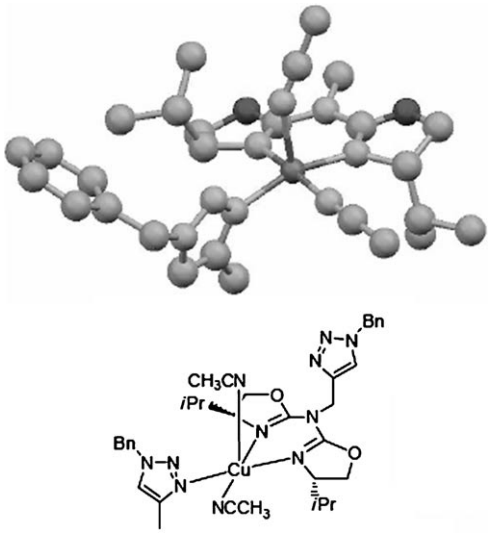


Figure 3. X-ray structure of a polymeric ligand structure bridged by a copper atom. Triazole moieties are coordinated at the equatorial position.[6]

whereas the catalytic activity of such intermediates remains an unsettled issue. This square-pyramidal complex offers two possible modes for the coordination of the benzylidene

an equatorial position rather than benzylidene malonate. Moreover, structures of type **C**, in which triflate is bound in an apical position have been disclosed previously.[12b,17c] Such a complex geometry would provide the same high enantioselectivity as the tetracoordinated species of type **A**, for which also an example has been reported[17d] (Figure 4). After all, a mechanistic model involving a five-membered intermediate is rather capable of explaining both the effect of ligand excess and our novel findings concerning the addition of triflate than aboriginal considerations that propose a four-membered resting state. However, coordination of a third oxazoline moiety would, in this model, not result in a deactivation of the complex due to reduced Lewis acidity as proposed by Gade et al.,[14] but in less enantioselective 19e-species **D1** and **D2**. Pentacoordinated copper–bis(oxazoline) complexes with equatorial/apical-coordinated α-ketoesters[20] or (benzyloxy) acetaldehyde[17a] as electrophilic substrates have been proposed as catalytically relevant species before.

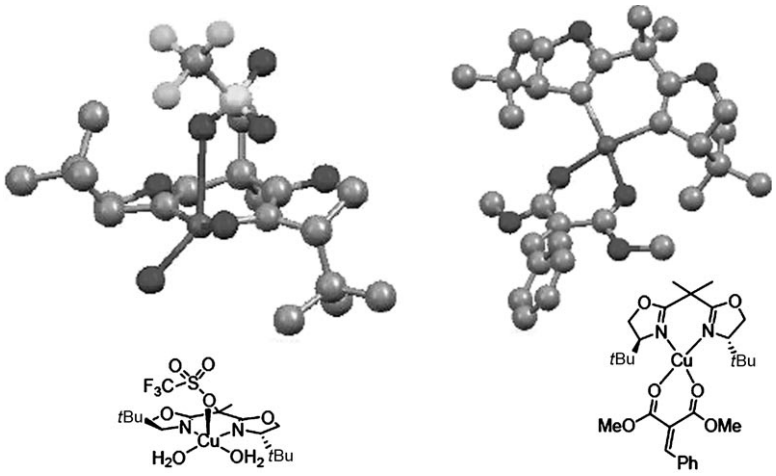


Figure 4. X-ray structure of $[Cu(\mathbf{1b})(H_2O)_2]\cdot(OTf)_2$[17c] (left) and $[Cu(\mathbf{1b})(Ph(CH)_2(CO_2Me)_2)]\cdot(SbF_6)_2$[17d] (right); non-coordinating counterions are omitted for clarity.

As expected, the addition of triflate does not increase the selectivity if the reaction itself is insensitive towards the ligand/copper ratio, as is the case for the alkylation of indole (**4**) with **5e** (entries 5–7, Table 3). The enantioselectivity obtained with the 4-nitro-derivative **5g** at optimum reaction conditions, that is, at a **2**/copper ratio of 1.3, is likewise indiscernible from the result without additive. However, if the disfavored ligand/metal ratio is applied for substrate **5g**, its detrimental influence vanishes after addition of triflate, which leads in this case to the highest enantioselectivities ever obtained for **6g**, either by using bis- or tris(oxazoline) ligands (entries 9–11).[12a] Lithium triflate seems to act as a decoupling agent for the ligand/metal ratio by stabilizing a pentacoordinated complex of type **C**, which is supposed to be less susceptible to this effect.

Conclusion

We report that simple C_2-symmetric bis(oxazoline) ligands, especially azabis(oxazolines), can promote the copper(II)-catalyzed Michael addition of indoles to a broad scope of benzylidene malonates with up to >99% *ee* provided that the ligand/metal ratio is tuned meticulously. Explicit attention has to be paid to the electronic parameters of the derivatives. If comparatively electron-rich benzylidene malonates are used, any excess of ligand has to be avoided to reach high enantioselectivities, which is in contradiction to a common paradigm in asymmetric catalysis that calls for an excess of ligand to suppress a background reaction promoted by metal centers in a ligand-free, that is, achiral environment.

In addition, we found that the sensitivity of enantioselectivity towards ligand excess vanishes with decreasing inductive contribution of the substituent. This trend is even reversed for strong electron acceptors, which require an excess of ligand for maximum *ee*. A semi-logarithmic plot of optical yields at two different ligand/metal ratios versus the σ_I values of the substituted benzylidene malonates results in a sigmoid trajectory.

In the presence of an excess of triflate, the significance of the ligand/metal ratio vanishes, giving rise to equal or even superior enantioselectivities at any ligand/metal ratio employed.

Experimental Section

General methods: Reactions were carried out in Schlenk tube under a nitrogen atmosphere, unless otherwise stated. EtOH was dried by distillation over Mg and stored over molecular sieves 3 Å. Diethylbenzylidene malonates were synthesized by classical Aldol reaction conditions and the crude products were distilled to obtain the pure compounds. Silica gel 60 (Merck, 0.063–0.200 mm) was used for column purification. TLC analysis was performed on silica gel 60 F254 (Merck) coated on aluminum sheets. ^{1}H (300 MHz) and ^{13}C NMR (75.5 MHz) spectra were recorded on a Bruker Avance 300 spectrometer in $CDCl_3$ with $CHCl_3$ (δ = 7.27 ppm for ^{1}H, δ = 77 ppm for ^{13}C) as a standard. Mass spectrometry (Finnigan ThermoQuest TSQ 7000) was done by the Central Analytical Laboratory (Universität Regensburg). Optical rotations were measured on a Perkin–Elmer 241 Polarimeter.

General procedure for the catalytic asymmetric Michael additions: Ligand **2a** (12.0 mg, 0.05 mmol) and $Cu(OTf)_2$ (18.1 mg, 0.05 mmol) were added to a Schlenk tube under air. Ethanol (2 mL) was added and the mixture was stirred for 1 h at room temperature (20–25 °C). Malonate (1 mmol, 1.0 equiv) in EtOH (2 mL) was added to the resulting blue–green solution and stirring was continued for 20 min before the indole (1.2 mmol, 1.2 equiv) was added. After stirring for 8 h at room temperature, the red-colored solution was concentrated under reduced pressure.

The crude product was purified by column chromatography (performed with hexanes/CH_2Cl_2 1:1, followed by CH_2Cl_2).

(*S*)-Ethyl-2-ethoxycarbonyl-3-(3-indolyl)-3-phenylpropanoate (6a): The reaction was conducted according to the general procedure and the crude product purified by column chromatography (performed with hexanes/CH_2Cl_2 1:1, followed by CH_2Cl_2) to afford the pure product as a white solid. M.p. 174–176 °C; $[\alpha]_D^{20} = +65.4$ (20 mg/2 mL in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.93$–1.06 (m, 6H), 3.93–4.06 (m, 4H), 4.30 (d, $J =$ 11.8 Hz, 1H), 5.09 (d, $J = 11.8$ Hz, 1H), 7.00–7.07 (m, 1H), 7.09–7.31 (m, 6H), 7.37 (d, $J = 7.4$ Hz, 2H), 7.56 (d, $J = 8.0$ Hz, 1H), 8.07 ppm (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 168.1$, 167.9, 141.4, 136.2, 128.4, 128.2, 126.8, 126.7, 122.3, 120.9, 119.5, 119.4, 117.0, 111.0, 61.5, 61.4, 58.4, 42.9, 13.8, 13.8 ppm; MS (CI): *m*/*z* (%): 383 (89) $[M+NH_4]^+$, 366 (3) $[M+H]^+$, 206 (100), 178 (5); HPLC analysis (Chiralcel OD/OD-H, 10% *i*PrOH/*n*-hexane, 0.5 mL min^{-1}, 254 nm; t_r(minor) = 26.67, t_r (major) = 31.40 min): > 99% *ee*.

(*S*)-Ethyl-2-ethoxycarbonyl-3-(3-indolyl)-3-(*p*-methylphenyl)propanoate (6b): The reaction was conducted according to the general procedure and the crude product was purified by column chromatography (performed with hexanes/CH_2Cl_2 1:1, followed by CH_2Cl_2) to afford the pure product as a white solid. M.p. 140–142 °C; $[\alpha]_D^{20} = +26.7$ (10 mg/2 mL in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.98$ (t, $J = 7.1$ Hz, 3H), 1.04 (t, $J = 7.1$ Hz, 3H), 2.24 (s, 3H), 3.94–4.05 (m, 4H), 4.27 (d, $J = 11.8$ Hz, 1H), 5.04 (d, $J = 11.8$ Hz, 1H), 6.99–7.06 (m, 3H), 7.08–7.18 (m, 2H), 7.22–7.31 (m, 3H), 7.55 (d, $J = 8.0$ Hz, 1H), 7.99 ppm (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 168.1$, 167.9, 138.4, 136.2, 136.2, 129.0, 128.0, 126.7, 122.2, 120.8, 119.5, 119.5, 117.3, 110.9, 61.4, 61.4, 58.4, 42.4, 21.0, 13.8, 13.8 ppm; MS (CI): *m*/*z* (%): 397 (73) $[M+NH_4]^+$, 379 (2), 220 (100), 178 (7); HPLC analysis (Chiralcel OD/OD-H, 10% *i*PrOH/*n*-hexane, 0.5 mL min^{-1}, 254 nm; t_r(major) = 22.12, t_r(minor) = 25.47 min): > 94% *ee*.

(*S*)-Ethyl-2-ethoxycarbonyl-3-(3-indolyl)-3-(p-methyoxyphenyl)propanoate (6c): The reaction was conducted according to the general procedure and the crude product was purified by column chromatography (performed with hexanes/CH_2Cl_2 1:1, followed by CH_2Cl_2) to afford the pure product as a white solid. M.p. 168–170 °C; $[\alpha]_D^{20} = +53.3$ (20 mg/2 mL in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.97$–1.07 (m, 6H), 3.73 (s, 3H), 3.95–4.04 (m, 4H), 4.23 (d, $J = 11.7$ Hz, 1H), 5.03 (d, $J =$ 11.8 Hz, 1H), 6.73–6.78 (m, 2H), 6.98–7.31 (m, 6H), 7.52 (d, $J = 7.8$ Hz, 1H), 8.01 ppm (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 167.9$, 158.3, 136.3, 133.5, 129.2, 126.7, 122.3, 120.7, 119.5, 117.4, 113.7, 110.9, 61.4, 58.6, 55.3, 42.1, 13.8 ppm; MS (CI): *m*/*z* (%): 413 (31) $[M+NH_4]^+$, 395 (5), 236 (100), 178 (11); HPLC analysis (Chiralcel OD/OD-H, 10% *i*PrOH/*n*-hexane, 0.5 mL min^{-1}, 254 nm; t_r(minor) = 48.38, t_r(major) = 53.71 min): > 84% *ee*.

(*S*)-Ethyl-2-ethoxycarbonyl-3-(3-indolyl)-3-(*p*-trifluoromethylphenyl)propanoate (6d): The reaction was conducted according to the general procedure and the crude product was purified by column chromatography (performed with hexanes/CH_2Cl_2 1:1, followed by CH_2Cl_2) to afford the pure product as a white solid. M.p. 152–154 °C; $[\alpha]_D^{20} = +15.2$ (10 mg/2 mL in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.02$ (m, 6H), 3.95–4.05 (m, 4H), 4.29 (d, $J = 11.7$ Hz, 1H), 5.14 (d, $J = 11.7$ Hz, 1H), 7.01–7.22 (m, 3H), 7.29–7.33 (m, 1H), 7.50–7.52 (m, 4H), 8.05 ppm (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 167.6$, 167.5, 145.6, 136.2, 128.6, 126.4, 125.3, 122.6, 121.0, 119.1, 116.1, 111.1, 61.7, 61.6, 57.9, 42.5, 13.7 ppm; MS (CI): *m*/*z* (%): 451 (100) $[M+NH_4]^+$, 433 (12), 274 (78), 178 (9); HPLC analysis (Chiralcel OJ/OJ-H, 10% *i*PrOH/*n*-hexane, 0.5 mL min^{-1}, 254 nm; t_r(minor) = 40.78, t_r(major) = 47.98 min): > 90% *ee*.

(*S*)-Ethyl-2-ethoxycarbonyl-3-(3-indolyl)-3-(o-bromophenyl)propanoate (6e): The reaction was conducted according to the general procedure and the crude product was purified by column chromatography (performed with hexanes/CH_2Cl_2 1:1, followed by CH_2Cl_2) to afford the pure product as a brown gummy solid. $[\alpha]_D^{20} = +48.5$ (20 mg/2 mL in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.96$ (t, $J = 7.1$ Hz, 3H), 1.03 (t, $J = 7.1$ Hz, 3H), 3.92–4.07 (m, 4H), 4.37 (d, $J = 11.5$ Hz, 1H), 5.64 (d, $J = 11.5$ Hz, 1H), 6.97–7.31 (m, 5H), 7.41 (dd, $J = 8.0$, 1.6 Hz, 1H), 7.53 (dd, $J = 8.0$, 1.4 Hz, 1H), 7.72 (d, $J = 7.7$ Hz, 1H), 8.08 ppm (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 168.0$, 167.7, 140.8, 136.1, 133.2, 129.1, 128.2, 127.6, 126.7, 124.9, 122.3, 122.2, 119.7, 115.6, 111.2, 61.6, 58.0, 41.8, 41.4, 14.1, 13.8, 13.7 ppm; MS (CI): *m*/*z* (%): 461 (100) $[M+NH_4]^+$, 444 (4) $[M+H]^+$, 284 (58), 206 (3), 178 (12); HPLC analysis (Chiralcel OD/OD-H, 10% *i*PrOH/*n*-hexane, 0.5 mL min^{-1}, 254 nm; t_r(minor) = 24.30, t_r(major) = 37.42 min): > 85% *ee*.

(*S*)-Ethyl-2-ethoxycarbonyl-3-(3-indolyl)-3-(*p*-bromophenyl)propanoate (6f): The reaction was conducted according to the general procedure and the crude product was purified by column chromatography (performed with hexanes/CH_2Cl_2 1:1, followed by CH_2Cl_2) to afford the pure product as a white solid. M.p. 148–150 °C; $[\alpha]_D^{20} = +24.4$ (20 mg/2 mL in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.00$ (t, $J = 7.1$ Hz, 3H), 1.06 (t, $J =$ 7.1 Hz, 3H), 4.02 (m, $J = 7.13$ Hz, 4H), 4.24 (d, $J = 11.7$ Hz, 1H), 5.04 (d, $J = 11.7$ Hz, 1H), 6.99–7.38 (m, 8H), 7.49 (d, $J = 7.9$ Hz, 1H), 8.02 ppm (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 167.7$, 167.6, 140.5, 136.2, 131.4, 129.9, 126.5, 122.8, 120.6, 119.7, 119.2, 116.5, 111.0, 61.6, 58.0, 42.2, 13.8, 13.7 ppm; MS (CI): *m*/*z* (%): 461 $[M+NH_4]^+$, 66), 443 (9), 284 (100), 178 (7); HPLC analysis (Chiralcel OD/OD-H, 10% *i*PrOH/*n*-hexane, 0.5 mL min^{-1}, 254 nm; t_r(minor) = 29.17, t_r(major) = 31.86 min): > 82% *ee*.

(*S*)-Ethyl-2-ethoxycarbonyl-3-(3-indolyl)-3-(*p*-nitrophenyl)propanoate (6g): The reaction was conducted according to the general procedure and the crude product was purified by column chromatography (performed with hexanes/CH_2Cl_2 1:1, followed by CH_2Cl_2) to afford the pure product as a yellow solid. M.p. 105–107 °C; $[\alpha]_D^{20} = +8.3$ (20 mg/2 mL in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 1.01$ (t, $J = 7.1$ Hz, 3H), 1.07 (t, $J =$ 7.1 Hz, 3H), 3.97–4.08 (m, 4H), 4.32 (d, $J = 11.8$ Hz, 1H), 5.20 (d, $J =$ 11.5 Hz, 1H), 7.05 (m, 1H), 7.16 (m, 1H), 7.21 (d, $J = 2.5$ Hz, 1H), 7.32 (d, $J = 8.2$ Hz, 1H), 7.47 (d, $J = 8.0$ Hz, 1H), 7.55 (m, 2H), 8.10 (m, 2H), 8.15 ppm (brs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 167.5$, 167.4, 149.3, 146.7, 136.2, 129.2, 126.3, 123.7, 122.7, 121.3, 119.9, 118.9, 115.4, 111.3, 61.8, 57.7, 42.5, 13.9, 13.8 ppm; MS (CI): *m*/*z* (%): 428 (100) $[M+NH_4]^+$, 410 (2), 398 (7), 251 (25), 221 (22), 178 (11); HPLC analysis (Chiralcel AS, 15% *i*PrOH/*n*-hexane, 0.5 mL min^{-1}, 254 nm; t_r(minor) = 29.13, t_r(major) = 39.83 min): > 96% *ee*.

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