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Highly Enantioselective Michael Additions of Indole to Benzylidene Malonate Using Simple Bis(oxazoline) Ligands: Importance of Metal/Ligand Ratio

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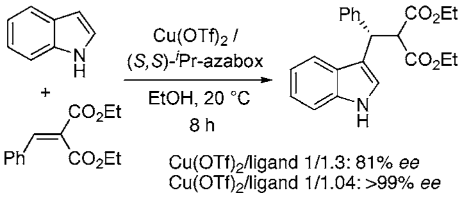
ABSTRACT



Simple bis(oxazoline) ligands, especially azabis(oxazolines), can catalyze the copper-catalyzed addition of indoles to benzylidene malonates in up to >99% ee, provided that *excess of chiral ligand* is avoided. The paradigm followed in many asymmetric catalyses that an excess of chiral ligand with respect to the metal should improve enantioselectivity because a background reaction by free metal is suppressed, is not applicable here, which might call for revisiting some of the many copper(II)–bis(oxazoline)-catalyzed processes known.

Asymmetric Friedel−Crafts alkylations of indoles have been recently of great interest[1] due to the high relevance of indole derivatives as privileged structures in pharmaceutical drugs. Among them, the copper−bis(oxazoline)-catalyzed enantioselective 1,4-addition of indoles to α,β-unsaturated carbonyl compounds plays a prominent role, representing a facile, catalytic asymmetric process for this transformation.[2−5] While in the pioneering work of Jørgensen and co-workers it was demonstrated that copper(II) complexes with bis(oxazolines) **1a** can catalyze the asymmetric addition of indoles to α,β-unsaturated ketoesters with enantioselectivities of >99% ee,[2a] using benzylidene malonates as substrates only proceeded with moderate selectivities (up to 69% ee) under the same reaction conditions.[2b] Subsequently, Tang and co-workers reported some improvements of the latter reaction with bis(oxazoline) ligand **1b** (Table 1, entry 2)[3] but most importantly demonstrated in a number of elegant studies that tris(oxazoline) ligands such as **3** were superior ligands for this process, giving the adduct **8a** with improved yields and selectivities up to 93% ee (Table 1, entry 4).[4] A pentacoordinated copper(II) complex **A** was postulated as the decisive intermediate to account for the high selectivity. In summary, it was concluded from these studies that bis(oxazolines) are unsuitable ligands for the title reaction.

We report here that the ligand/copper ratio is crucial for the selectivity of the title reaction and that under optimized reaction conditions conjugate additions with benzylidene

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(1) Leading review: Bandini, M.; Melloni, A.; Tommasi, S.; Umani-Ronchi, A. *Synlett* **2005**, 1199.

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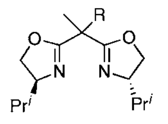
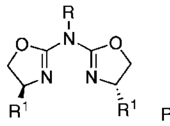
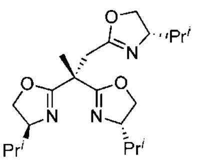


1a: R = Me
1b: R = H



2a: R = Me, R^1 = ^{i}Pr
2b: R = H, R^1 = ^{i}Pr
2c: R = H, R^1 = Bn



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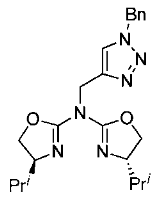

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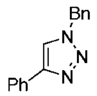

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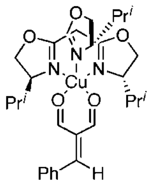
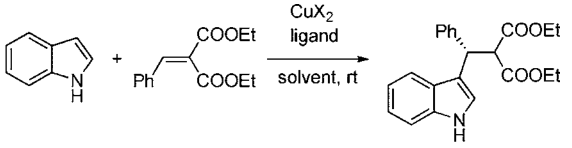


A

malonates can be performed with copper complexes of simple bis(oxazoline) and azabis(oxazoline) ligands in up to 99% ee.

Our investigation began with the finding that under standard conditions (5 mol % of $Cu(ClO_4)_2$, 5.5 mol % of ligand in an alcoholic solvent), azabis(oxazoline) **4**,[6] having a triazole side arm, was able to catalyze under commonly employed conditions the transformation of indole **6a** to **8a** with significantly higher enantioselectivity than that of the parent ligand **2b**[7] or its corresponding N-methylated derivative **2a** (Table 1, entries 4−7), and it also exceeded the best values obtained with any tris(oxazoline) so far. This was unexpected since the rigid aza(bisoxazoline) framework should not allow tridentate coordination involving the triazole moiety. This hypothesis was confirmed by the X-ray structure of copper complex $CuCl_2$·**4** (Figure 1), proving that the centralized sp^2 nitrogen turns the triazole side arm out of reach for coordination to the copper center. However, the X-ray structure of the complex obtained from **4** with $Cu(ClO_4)_2$ in acetonitrile revealed the ability of the triazole unit to coordinate copper in an intermolecular fashion via a second ligand molecule, resulting in a polymeric ligand structure bridged by copper atoms.

Table 1. Dependence of Enantioselectivity on Copper(II)/Metal Ratios in the Asymmetric 1,4-Addition to Benzylidene Malonates



6a **7a** **8a**

entry	X in CuX_2	ligand	Cu/ligand ratio	Cu/ligand mol %	solvent	yield (%)	ee (%)[a]
1[b]	OTf	**1a**	1/1.2	10/12	*i*-BuOH	85	79
2[c]	OTf	**1b**	1/1.1	10/11	*i*-BuOH	99	82[d]
3[c]	OTf	**1b**	1/1.1	10/11	EtOH	94	76
4[b]	OTf	**3**	1/1.2	10/12	*i*-BuOH	90	93
5	ClO_4	**4**	1/1.1	4.5/5.0	EtOH	93	95
6	ClO_4	**2a**	1/1.1	4.5/5.0	EtOH	88	70
7	ClO_4	**2b**	1/1.1	4.5/5.0	EtOH	85	66
8[e]	ClO_4	**2b**	1/1.1	4.5/5.0	EtOH	92	81
9	ClO_4	**2c**	1/1.3	3.8/5.0	EtOH	90	87
10	ClO_4	**2c**	1/1.04	4.8/5.0	EtOH	96	95
11	OTf	**2b**	1/1.3	3.8/5.0	EtOH	98	81
12	OTf	**2b**	1/1.1	4.5/5.0	EtOH	93	85
13[f]	OTf	**2b**	1/1.04	4.8/5.0	EtOH	97	>99
14	OTf	**2b**	1/1	5.0/5.0	EtOH	90	98
15	OTf	**2b**	1.1/1	5.5/5.0	EtOH	96	98
16	OTf	**2b**	1.3/1	6.5/5.0	EtOH	95	91
17	OTf			7.5/0	EtOH	90	0
18	OTf	**1a**	1/1.04	4.8/5.0	EtOH	89	99

[a] Determined by HPLC. [b] Taken from ref 4d. [c] Taken from ref 4c. [d] 75% yield, 93% ee at −25 °C. [e] 5.5 mol % of triazole **5** was employed as an additive. [f] Obtained in three independent runs.

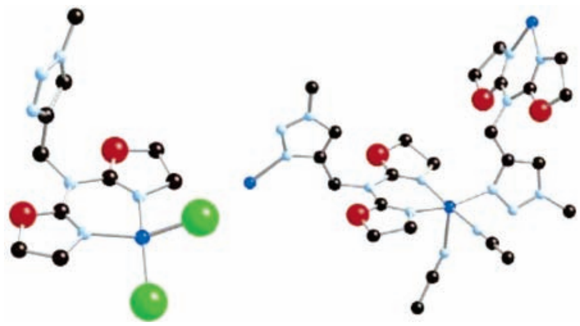


Figure 1. X-ray structures of $CuCl_2$·**4** (left) and $[Cu(ClO_4)_2(CH_3CN)_2·\mathbf{4}]_n$ (right); *i*-Pr, Ph, and ClO_4 groups are omitted for clarity.

Consequently, we concluded that a bidentate bis(oxazoline) in combination with an external ligand such as a triazole should be sufficient to provide an effective chiral environment for the asymmetric addition of indoles to benzylidene malonates.

However, employing 1.1 equiv (based on copper) of triazole **5** as an additive in combination with ligand **2b**, while showing some benefit compared to ligand **2b** alone (entries 7 and 8), could not equalize the result obtained with ligand **4** (entry 5).

This observation suggested an alternative mechanism for the title reaction: While coordination by three nitrogen ligands to copper might represent a resting state of the catalyst, to reach the active species one of the nitrogen ligands has to dissociate off first. If bis(oxazoline) ligands are employed (Table 1, entries 1, 2, and 4−6), the excess ligand used might provide a third oxazoline moiety for coordination, and if subsequent dissociation of one of the chelating oxazoline moieties occurs to create a species such as **B**, selectivity should be low (Figure 2). Having weaker coordinating triazole moieties present would favor dissociation of that moiety, resulting in a species such as **C** that gives rise to high selectivity.

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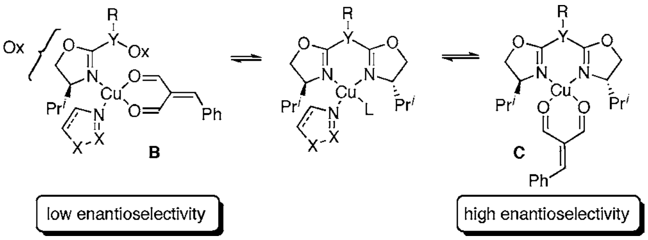


Figure 2. Mechanistic model for the asymmetric 1,4-addition to benzylidene malonates.

Following this line of argument, the superior results obtained with C_3-symmetrical tris(oxazoline) **3** in comparison with bis(oxazolines) can also easily be understood since dissociation of any of the three oxazoline moieties should result in a species of type **C**.

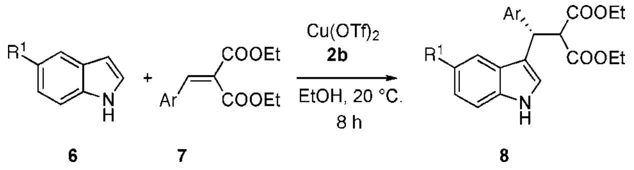
With ligand **4**, coordination of a third oxazoline moiety by the excess of ligand might be prevented due to steric effects, which is exhibited by the benzyl substituent on the triazole unit, again resulting in a species of type **C** giving rise to the high selectivity observed in contrast to employing ligand **2b** with an external triazole additive.

The rationale put forward above suggests that the ligand/copper ratio might have a decisive influence on the selectivity of the title reaction and, especially, that any *excess of ligand* might be detrimental. This is quite in contrast to the usual observation in asymmetric catalysis that an excess of chiral ligand is beneficial in order to avoid background reactions by uncomplexed metal. Indeed, variation of the ratio of **2b**/copper showed a dramatic dependence on the enantioselectivity of **8a**, with the optimum being found when a ligand to copper ratio of 1.04/1 is used (Table 1, entries 11−16). Even employing an excess of copper (entries 15 and 16) still gives respectable but somewhat inferior selectivities, giving further credit to the hypothesis of an intermediate **C** as the decisive species for the catalytic process. A control experiment (entry 17) showed that the reaction proceeds well also in the absence of ligand, clearly demonstrating that the overall process is ligand accelerated. While we noticed a similar trend employing $Cu(ClO_4)_2$ as the copper source (entries 9 and 10), using $Cu(OTf)_2$ gave better results and was therefore used for all subsequent reactions. Finally, although we generally obtain somewhat better results with the aza-(bisoxazoline) ligands, employing a copper/ligand ratio of 1/1.04 also gives very high selectivities with bis(oxazoline) **1a** (entry 18, cf. entries 1 and 3).

Applying this protocol for the reaction between other indoles and benzylidene malonates also gave good results, and with the exception of the strongly electron-deficient *p*-nitro derivative (entry 5), presumably an especially weak coordinating substrate for the copper−ligand complex, equaling or exceeding the selectivities obtained with tris-(oxazolines)[4a] (Table 2).

In conclusion, simple copper(II)−bis(oxazoline) complexes are excellent catalysts for the asymmetric addition of indoles to benzylidene malonates provided that *excess of ligand with respect to copper metal employed is avoided*. This observation could also be significant for related asymmetric copper(II)− and other metal−bis(oxazoline) processes known[8] that follow the paradigm that a slight excess of chiral ligands is advantageous to achieve higher asymmetric inductions. Especially in cases of reactions with substrates that only weakly coordinate to the metal complex, making binding of an oxazoline moiety from a second ligand a competitive process suggests that metal/ligand ratios must be carefully assessed. On the other hand, excess of bis(oxazoline) ligands in metal-catalyzed reactions is clearly not always detrimental to selectivity. For example, the copper(II)−azabis(oxazoline)-

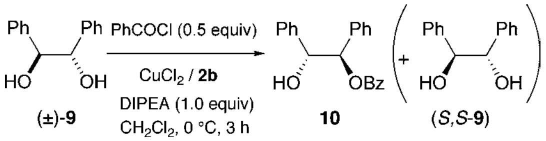
Table 2. Asymmetric Conjugate Addition between Indoles **6** and Benzylidene Malonates **7** at Room Temperature[a]



entry	Ar	R^1	yield (%)	ee (%)[b]
1	Ph	H	97	99
2	*p*-Me−Ph	H	80	93
3	*p*-Cl−Ph	H	91	98
4	*o*-Br−Ph	H	89	85
5	*p*-NO_2-Ph	H	94	80
6	Ph	OMe	80	90

[a] 4.8 mol % of $Cu(OTf)_2$, 5.0 mol % of **2b**. [b] Determined by HPLC.

Table 3. Dependence of Enantioselectivity on Copper(II)/Metal Ratios in the Asymmetric Benzoylation of Diol (±)-**9**



entry	Cu/ligand ratio	Cu/ligand mol %	**10** yield (%)[a]	**10** ee (%)[b]
1	1.5/1.0	7.5/5.0	46	84
2	1.1/1.0	5.5/5.0	44	88
3	1.0/1.0	5.0/5.0	48	88
4	1.0/1.04	4.8/5.0	43	85
5	1.0/1.1	4.5/5.0	49	87
6	1.0/1.5	3.3/5.0	46	85

[a] Isolated yield based on (±)-**9** (theoretical maximum yield 50%). [b] Determined by HPLC.

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catalyzed[6] asymmetric benzoylation of 1,2-diols[9] seems to be indifferent both to excess ligand as well as to excess metal (Table 3).

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Supporting Information Available: Experimental procedures, details on the X-ray structures, copies of ^{1}H and ^{13}C spectra, and HPLC traces of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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