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In-depth structure–selectivity investigations on asymmetric, copper-catalyzed oxidative biaryl couplings in the presence of 5-*cis*-substituted prolinamines †

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13 new and 25 known prolinamines carrying an additional 5-*cis* substituent were evaluated as the chiral ligands in asymmetric copper-catalyzed, oxidative biaryl couplings of 3-hydroxy-2-naphthoates. Comprehensive structure–selectivity investigations revealed that a phenyl group in 5-*cis* position and a small substituent at the pyrrolidine nitrogen (e.g., Me) are essential for high levels of chirality transfer. The sense of the asymmetric induction depends on the steric demand of the exocyclic amino function. In the coupling of methyl 2-hydroxy-3-naphthoate, a primary amino group permitted up to 36% ee in favor of the *P*-enantiomer, while up to 64% ee in favor of the *M*-enantiomer was reached with secondary and tertiary amino functions (e.g. NMe_2, (*S*)-NHCH(Me)Ph). A fully linear relationship between the enantiomeric excess of the prolinamine and the binaphthol was observed. A mechanism consistent with all stereochemical findings is proposed, indicating that 3-hydroxy-2-naphthoates with bulkier ester groups should permit better stereocontrol. And indeed, the enantiomeric excess was raised to good 87% when *tert*-butyl 3-hydroxy-2-naphthoate was used as the substrate.

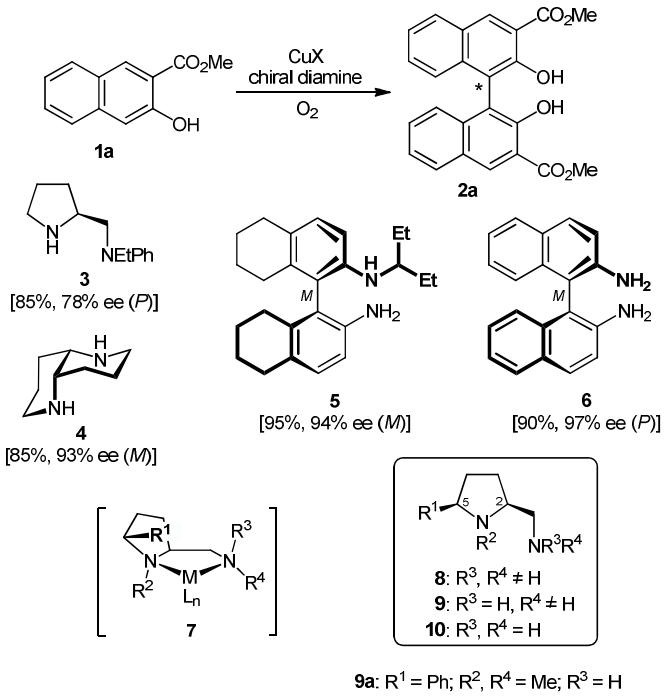
Introduction

A chiral biaryl axis is the characteristic and dominating feature of a wide variety of bioactive natural products[1] and privileged ligands for enantioselective synthesis.[2] During the past three decades, many efficient and strategically diverse methods for the stereoselective construction of chiral biaryl bonds have been developed, reaching from the desymmetrization of achiral, but rotationally hindered biaryls and the stereochemical fixation of configurationally labile ones through the atroposelective construction of aromatic rings to diastereo- and enantioselective biaryl coupling reactions.[3,4]

Among the latter approaches, oxidative couplings of 2-naphthols[3c] in the presence of chirally modified copper catalysts have received particular attention,[5–7] since these reactions offer a direct access to the important class of axially chiral 1,1'-binaphthol derivatives.[2] A first breakthrough in this field was achieved by Nakajima et al. in 1995.[8–10] The oxidative coupling of the naphthol **1a**, catalyzed by 10 mol% of a complex generated from CuCl and the prolinamine **3**, provided the 1,1'-binaphthyl-2,2'-ol **2a** in good 85% yield and 78% ee (Scheme 1). As for most copper–diamine catalysts developed so far, the additional ester group at C2 (or another coordinating electron-withdrawing group allowing a bidentate binding) is crucial for a high level of enantioselection.[11] Further seminal work was done by Kozlowski et al. introducing the C_2-symmetric 1,5-diaza-*cis*-decalin **4**.[12,13] The CuI complex of **4** proved to be a highly enantioselective catalyst, providing, for example, the model biaryl **2a** in good 85% yield and excellent 93% ee.[12] This system was successfully applied in the total synthesis of several axially chiral biaryl natural products.[13] Among all other diamines evaluated so far in the enantioselective, copper-catalyzed oxidative coupling of **1a**,[14] only the CuCl complex of Ha's C_1-symmetric BINAM (1,1'-binaphthyl-2,2'-diamine) derivative **5** was able to provide binaphthol **2a** in comparable 94% ee.[15] The highest level of asymmetric induction (97% ee) was recently reported by Sekar et al., using a 2:1 ratio of C_2-symmetric BINAM (**6**) and CuCl in combination with the stable radical additive TEMPO (2,2,6,6-tetramethylpiperidin-1-yloxyl).[16]

In the course of our investigations on conformationally rigid diamines[17] we became interested in prolinamines of general types **8**–**10**, which possess, as compared to other proline derived ligands, an additional substituent R^1 in 5-*cis* position. Upon chelation of a metal (see complex **7**), this substituent R^1 should shield the upper left face, which might result in enhanced levels of stereocontrol in asymmetric synthesis. This assumption was recently corroborated by copper-catalyzed, enantioselective Henry reactions[18] of nitromethane with a series

of aromatic, heteroaromatic, vinylic, and aliphatic aldehydes.[19] The $CuCl_2$ and $CuBr_2$ complexes of the simple prolinamine **9a** (R^1 = Ph; R^2, R^4 = Me; R^3 = H) provided the corresponding ß-nitro alcohols with 99% ee in all cases (36 examples). This successful application and the structural similarity of **8**–**10** with Nakajima's diamine **3** prompted us to study the performance of **8**–**10** in the enantioselective, copper-catalyzed oxidative biaryl coupling of **1** to **2**. With the broad variety of derivatives available, in-depth investigations on structure–selectivity relationships should be possible.



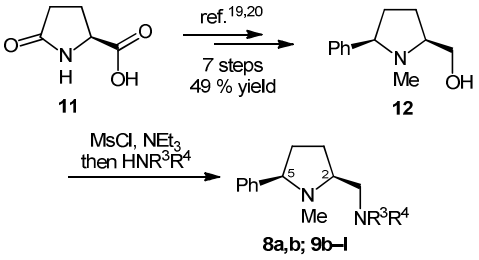
Scheme 1 The oxidative biaryl coupling of **1a** to **2a**, a selection of successfully used chiral diamines (**3**–**6**), the metal complex **7** and the new 5-*cis*-substituted prolinamines **8**–**10**.

Results and discussion

Synthesis of the prolinamines

We recently developed three tailor-made routes to prolinamines of type **8**–**10** that all start from cheap L-pyroglutamic acid (**11**), but differ in the order of introduction of the substituent at 5-*cis* position (R^1), at the pyrrolidine nitrogen atom (R^2), and at the exocyclic aminomethyl function (R^3, R^4).[20] The high flexibility and applicability of these approaches was demonstrated in the preparation of more than 25 derivatives with widely varying substitution patterns. Some of these compounds were used in this study. The new prolinamines **8a**,**b** and **9b**–**l** (Table 1) were all synthesized from the amino alcohol **12**, which is available from **11** in seven steps and 49% overall yield[19,20] and possesses a 5-*cis*-phenyl substituent and an *N*-methyl group at the pyrrolidine. Activation of the hydroxy function of **12** by mesylation and subsequent treatment with an excess of the respective amine HNR^3R^4 afforded the target prolinamines in one pot operations.[21] Two bulky tertiary amines (**8a**,**b**), ten secondary amines (**9b**–**k**) with varying steric demand and, in part, additional stereogenic centers, and one anilinyl substituent (**9l**) were thus introduced in acceptable to good 47–78% yield.

Table 1 Preparation of the prolinamines **8a**,**b** and **9b**–**l** from **12**



Entry	Cmpd.	R^3	R^4	Yield[a] (%)
1	**8a**	Me	*t*Bu	72
2	**8b**	Me	Ph	66
3	**9b**	H	Et	62
4	**9c**	H	CH_2*t*Bu	78
5	**9d**	H	*i*Pr	53
6	**9e**	H	3-pentyl	55
7	**9f**	H	(*S*)-CH(Me)Ph	74
8	**9g**	H	(*S*)-CH(Et)Ph	65
9	**9h**	H	(*S*)-CH(Me)*t*Bu	52
10	**9i**	H	(*R*)-CH(Me)Ph	62
11	**9j**	H	*t*Bu	65
12	**9k**	H	$C(CH_2OBn)_3$	47
13	**9l**	H	Ph	73

[a] Isolated yield.

Validation of the enantiomer analysis

Initially, an accurate determination of the enantiomeric excess of the stereochemically enriched binaphthyl **2a** by HPLC on chiral phase proved to be difficult.[22] Just picking a small sample from the product, which was obtained as a slightly yellowish solid after column chromatography, and dissolving it in the HPLC solvent led to huge derivations in the ee measured. For example, the ee-values of a scalemic sample with 63% ee varied between 27% and 80%, depending on the position the material was taken from. Thus, the solid material of **2a** is not stereochemically homogeneous, but a conglomerate of areas with different enantiopurities. Furthermore, the low solubility of **2a** in typical HPLC solvents such as hexane, isopropanol, ethanol, or methanol in connection with the high tendency of **2a** to form racemic (micro)crystals[8b] bears the risk of an exaggerated enantiomeric excess in the solution to be measured.

We solved these problems by using the following procedure for sample preparation: The complete material of **2a** gathered from column chromatography was dissolved in dichloromethane (ca. 1 mL/10 mg) giving a homogeneous, clear solution. A small aliquot was taken, evaporated, and dissolved in methanol (ca. 50 µg/mL) under ultra-sonification and warming. The resulting solution was directly injected into HPLC, providing reliably and reproducibly ee-values ($\Delta ee \leq 1\%$) as checked by several control measurements.

Optimization of the reaction conditions

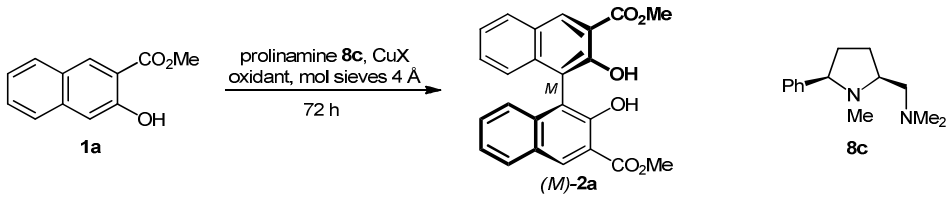
All copper–diamine complexes were freshly prepared prior to use by stirring a solution of the copper salt and the respective 5-*cis*-substituted prolinamine **8–10** in acetonitrile–dichloromethane 0.9:1 for 20 min. After evaporation, the residue was dissolved in the reaction solvent, providing a clear green solution.

The reaction conditions were optimized using the simple prolinamine **8c** (R^1 = Ph, R^2–R^4 = Me) as the chiral ligand (Table 2). Because of the close structural relationship of **8c** with diamine **3**,[8b] we initially choose Nakajima's conditions (entry 1), but added mol sieves 4Å, which is known[12a] to be beneficial to the reaction rate and yield. After 72 h at 20 °C, the oxidative coupling of naphthol **1a** afforded binaphthol **2a** in high 91% yield and acceptable 61% ee in favor of the *M*-Enantiomer. In agreement with literature,[8b] the enantiomeric excess of **2a** was easily raised by trituration in ethyl acetate, giving highly enriched (*M*)-**2a** (96% ee) in the mother liquor.

Variation of the reaction parameters showed that chlorinated hydrocarbons and mol sieves 4Å are essential for high yields and enantioselectivities (entries 1–6). Small changes in the relative stoichiometry CuCl/**8c** (1.2:1–0.9:1) had no measureable effect on the chirality transfer (entries 7 and 8). 9 Mol% of catalyst were required; lower loadings resulted in significantly reduced yields (entries 9–11). CuI was not suited as the metal salt because of the formation of side-products (entries 12 and 13). $CuCl_2$•$2H_2O$ (entry 14) and CuCl gave comparable results, as expected from the redox process Cu(I) ⇄ Cu(II) in the catalytic cycle, in which both oxidation states are involved. The enantioselectivity of the oxidative biaryl coupling can be enhanced to 75% ee by lowering the temperature from 20 °C to 0 °C (entry 16), albeit at the price of a reduced yield (65% within 72 h). At -20 °C, a drastic breakdown of the reaction rate was observed (56% yield after 7 d in the presence of 18 mol% catalyst), in combination with just a poor further gain in chirality control (77% ee, entry 17). The dilution had no significant effect on the chirality transfer, although the best result at 20 °C (91% yield, 64% ee) was obtained at higher concentration (c = 0.5 M, entry 19). As the oxidant, air can be used instead of oxygen, but the reaction rate slows somewhat down (entry 20). *t*BuOOH and AgCl afforded lower yields and diminished enantioselectivities, while no biaryl coupling was observed with DDQ (entries 21–23).

The optimum conditions with respect to reaction rate, yield, and stereoselectivity, which were used in the following diamine screening, are thus as follows: diamine (10 mol%), CuCl (9 mol%), O_2 (1 bar), CH_2Cl_2 (c = 0.5 M), mol sieves 4Å, 20 °C, 72 h (entry 19).

Table 2 Optimization of the reaction conditions for the oxidative biaryl coupling of **1a** to **2a** in the presence of **8c**



Entry	Solvent	Conc. (M)	**8c** (mol%)	CuX (mol%)	Temp. (° C)	Oxidant	Yield (%)[a]	ee (%)[b]
1	CH_2Cl_2	0.1	10	CuCl (10)	20	O_2	91	61 (96)[c]
2	$(CH_2Cl)_2$	0.1	10	CuCl (10)	20	O_2	80	61
3	$CHCl_3$	0.1	10	CuCl (10)	20	O_2	83	62
4	MeCN	0.1	10	CuCl (10)	20	O_2	45	25
5	Et_2O[d]	0.1	10	CuCl (10)	20	O_2	22	28
6[e]	CH_2Cl_2	0.1	10	CuCl (10)	20	O_2	67	62
7	CH_2Cl_2	0.1	10	CuCl (12)	20	O_2	87	61
8	CH_2Cl_2	0.1	10	CuCl (9)	20	O_2	94	62
9	CH_2Cl_2	0.1	20	CuCl (18)	20	O_2	94	62
10	CH_2Cl_2	0.1	5	CuCl (4.5)	20	O_2	59	61
11	CH_2Cl_2	0.1	1	CuCl (0.9)	20	O_2	23	55
12	CH_2Cl_2	0.1	10	CuI (9)	20	O_2	43[f]	59
13	MeCN	0.1	10	CuI (9)	20	O_2	55[f]	19
14	CH_2Cl_2	0.1	10	$CuCl_2$•H_2O (9)	20	O_2	81	63
15	$(CH_2Cl)_2$	0.1	10	CuCl (9)	40	O_2	78[g]	53
16	CH_2Cl_2	0.1	10	CuCl (9)	0	O_2	65	75
17	CH_2Cl_2	0.5	20	CuCl (18)	-20	O_2	56[h]	77
18	CH_2Cl_2	0.05	10	CuCl (9)	20	O_2	85	63
19	**CH_2Cl_2**	**0.5**	**10**	**CuCl (9)**	**20**	**O_2**	**91**	**64**
20	CH_2Cl_2	0.5	10	CuCl (9)	20	air	84	63
21	CH_2Cl_2	0.5	10	CuCl (9)	20	*t*BuOOH	12	55
22	CH_2Cl_2	0.5	10	CuCl (9)	20	AgCl	77	56
23	CH_2Cl_2	0.5	10	CuCl (9)	20	DDQ	0	---

[a] Isolated yield. [b] Determined by HPLC on chiral phase. [c] After trituration with ethyl acetate. [d] Suspension. [e] Without mol sieves 4Å. [f] Side products formed. [g] Reaction time: 18 h. [h] Reaction time: 7 d.

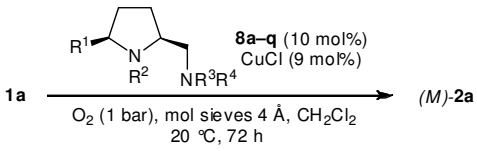
Structure–selectivity studies

The facile and modular access to various prolinamines of type **8–10** permitted in-depth investigations on the structure–enantioselectivity relationship. All four substituents R^1–R^4 were separately varied and their influence on the chirality transfer was studied.

Prolinamines **8**, which are characterized by a tertiary exocyclic amino function (R^3, $R^4 \neq H$), were screened first (Table 3). The bulkiness of the 5-*cis* substituent R^1 was found to exert a profound influence on the chirality transfer (entries 1–8). The enantiomeric excess of **2a** rose from low 4% to acceptable 62–64% by increasing the steric demand of R^1 from H (**8d**) to 4-methoxyphenyl (**8h**) and phenyl (**8c**). Larger substituents R^1 such as 3,5-(bistrifluoromethyl)phenyl in **8i** and 1-naphthyl in **8j**, however, resulted in a deterioration of the chirality transfer (48% and 25% ee, respectively).

The *N*-methyl group at the pyrrolidine nitrogen atom is essential since all variations of R^2 (**8k–m**, R^2 = H, Et, Bn) led to lower enantioselectivities (15–28% ee, entries 9–11). A similar small substituent tolerance was observed for R^3 and R^4 at the exocyclic amino function (entries 12–17). Good enantioselectivities (63–64% ee) were only reached with model diamine **8c** (R^3, R^4 = Me) and the pyrrolidine derivative **8o**. Even a slight increase of the steric demand of one or both substituents at the NR^3R^4 group as, for example, in **8q** (NR^3R^4 = NEt_2) and **8p** (NR^3R^4 = piperidinyl) resulted in drastically reduced enantioselectivities (6–42% ee). Finally, it should be noted that the formation of the *M*-atropoenantiomer of **2a** was favored in all coupling reactions in the presence of a diamine **8**.

Table 3 Oxidative biaryl couplings of **1a** in the presence of the tertiary prolinamines **8**

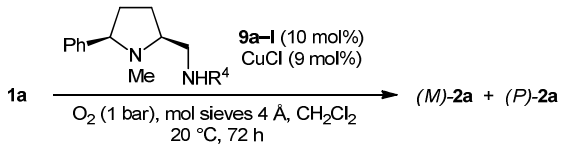


Entry	8	R^1	R^2	R^3	R^4	Yield (%)[a]	ee (%)[b]
1	**d**	H	Me	Me	Me	95	4
2	**e**	Me	Me	Me	Me	95	7
3	**f**	Bn	Me	Me	Me	95	22
4	**g**	*i*Pr	Me	Me	Me	73	28
5	**h**	4-MeOC_6H_5	Me	Me	Me	98	62
6[c]	**c**	Ph	Me	Me	Me	91	64
7	**i**	3,5-$(CF_3)_2C_6H_3$	Me	Me	Me	74	48
8	**j**	1-naphthyl	Me	Me	Me	59	25
9	**k**	Ph	H	Me	Me	64	15
10	**l**	Ph	Et	Me	Me	81	28
11	**m**	Ph	Bn	Me	Me	93	19
12	**n**	Ph	Me	Me	Bn	74	12
13	**a**	Ph	Me	Me	*t*Bu	46	10
14	**b**	Ph	Me	Me	Ph	20	10
15	**o**	Ph	Me	–$(CH_2)_4$–		77	63
16	**p**	Ph	Me	–$(CH_2)_5$–		54	42
17	**q**	Ph	Me	Et	Et	73	6

[a] Isolated yield. [b] Determined by HPLC on chiral phase. [c] See Table 2, entry 19.

In the screening of the secondary prolinamines **9** (R^3 = H), we first kept the optimized substituents R^1 = Ph and R^2 = Me and varied R^4 at the exocyclic amino group (Table 4). To our surprise and in contrast to the results with all tertiary diamines **8** (see Table 3), the *P*-atropoenantiomer of **2a** was preferentially formed (19% ee) in the presence of **9a**, which possesses the sterically least hindered secondary aminomethyl function (R^4 = Me, entry 1). Even a slight increase in the bulkiness of R^4 deteriorated the *P*-preference and a racemic mixture was obtained with **9b** (R^4 = Et, entry 2). More demanding α-branched substituents R^4 tilted the sense of stereoinduction in favor of the *M*-enantiomer. A broad maximum plateau in the range of 58–61% ee was reached for R^4 = 3-pentyl, (*S*)-1-phenylethyl, (*S*)-1-phenylpropyl, and (*S*)-3,3-dimethylbutan-2-yl (**9e–h**, entries 5–8). The configuration of the stereocenter in α-position in **9f–h** was also of importance, as seen on the reaction with **9i**, which carries, compared to **9f**, the enantiomeric (*R*)-1-phenylethyl side chain, and provided (*M*)-**2a** in lower 49% ee (entry 9). A further increase of the steric demand in R^4 was not favorable. With bulky α-tertiary substituents such as *t*Bu (**9j**) and $C(CH_2OBn)_3$ (**9k**), the stereoinduction sharply dropped to 42% and 22% ee, respectively (entries 10 and 11). The reactions rates, which roughly correspond to the isolated yields after 72 h, also decreased with rising steric demand of R^4. The aniline derivative **9l** failed to induce a good chirality transfer (38% ee, entry 12).

Table 4 Oxidative biaryl couplings of **1a** in the presence of the secondary prolinamines **9a–l**



Entry	9	R^4	Yield (%)[a]	ee (%)[b]	Config.
1	**a**	Me	96	19	*P*
2	**b**	Et	99	0	---
3	**c**	CH_2tBu	60	42	*M*
4	**d**	*i*Pr	81	47	*M*
5	**e**	3-pentyl	64	58	*M*
6	**f**	(*S*)-CH(Me)Ph	72	61	*M*
7	**g**	(*S*)-CH(Et)Ph	73	61	*M*
8	**h**	(*S*)-CH(Me)*t*Bu	77	61	*M*
9	**i**	(*R*)-CH(Me)Ph	68	49	*M*
10	**j**	*t*Bu	61	42	*M*
11	**k**	$C(CH_2OBn)_3$	38	22	*M*
12	**l**	Ph	49	38	*M*

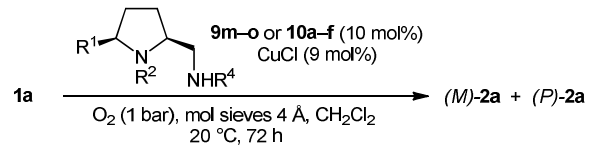
[a] Isolated yield. [b] Determined by HPLC on chiral phase.

Curious by the reversed stereoinduction observed with the prolinamine **9a**, we wondered whether the *P*-preference could be raised by appropriate choice of the substituents. Since an increase of the size of R^2 at the pyrrolidine nitrogen atom had led to a loss of chirality transfer with the *M*-selective prolinamines **8l** and **8m** (see Table 3, entries 10 and 11), we anticipated that the opposite effect, an enhanced *P*-selectivity, should occur with the analogous derivatives of **9a**. However, just slightly higher 24% ee (vs. 19% ee for **9a**) were found for the

N-ethyl diamine **9m**, whereas the sense of stereoinduction switched back to *M* for **9n** and **9o** carrying the lager *N*-benzyl and *N*-isopropyl groups (Table 5, entries 1–3).

An increase in *P*-selectivity might also result if the steric demand at the exocyclic NR^3R^4 group is minimized, as in the primary diamines **10a–f** ($NR^3R^4 = NH_2$, entries 4–9). And indeed, derivative **10e** delivered, compared to corresponding secondary amine **9a**, the binaphthol (*P*)-**2a** with an improved *P*-selectivity (36% ee vs. 19% ee for **9a**). Increasing the size of R^1 as in **10f** (R^1 = 1-naphthyl) as well as decreasing it as in **10b–10d** (R^1 = *i*Pr, Bn, Me) resulted in diminished enantioselectivities, while the formation of the *M*-atropoisomer was slightly favored for the 5-*cis*-unsubstituted prolinamine **10a** (R^1 = H, 8% ee).

Table 5 Oxidative biaryl couplings of **1a** in the presence of the primary and secondary prolinamines **9m–o** and **10a–f**



Entry	Diamine	R^1	R^2	R^4	Yield (%)[a]	ee (%)[b]	Config.
1	**9m**	Ph	Et	Me	96	24	*P*
2	**9n**	Ph	Bn	Me	90	3	*M*
3	**9o**	Ph	*i*Pr	Me	74	15	*M*
4	**10a**	H	Me	H	90	8	*M*
5	**10b**	Me	Me	H	91	19	*P*
6	**10c**	Bn	Me	H	89	29	*P*
7	**10d**	*i*Pr	Me	H	93	33	*P*
8	**10e**	Ph	Me	H	85	36	*P*
9	**10f**	naph[c]	Me	H	82	19	*P*

[a] Isolated yield. [b] Determined by HPLC on chiral phase. [c] naph = 1-naphthyl.

The structure–enantioselectivity relationships found show that there is a complex interplay between the relative and absolute steric bulk of the substituents R^1–R^4. Significant findings are: (i) The catalyst system is highly sensitive to steric overcrowding. In particular at the positions R^2 and R^3, only small substituents (R^2 = Me and R^3 = Me, H) are tolerated. (ii) The stereoselection rises with an enhanced steric demand of R^1. This accounts for the *M*-selective prolinamines as well as for the *P*-selective ones. (iii) In the prolinamine series with R^1 = Ph and R^2 = Me (**8a–c**,**n–q**, **9a–l** and **10e**), the sense of stereoinduction can be steered by the size and degree of substitution of the exocyclic NR^3R^4 group. Tertiary diamines of type **8** generally provide the *M*-enantiomer of **2a**, but good levels of enantioselection require small substituents as in **8c** and **8o** ($NR^3R^4 = NMe_2$, pyrrolidinyl). Roughly the same chirality transfer is achieved with the secondary diamines **9e–h** possessing a sterically more demanding, α-branched alkyl substituent R^4. (iv) *P*-configured **2a** is preferentially formed, albeit with lower stereocontrol, if an NHMe group as in **9a** and **9m** or a primary NH_2 group as in **10b–f** is present. (v) A hydrogen bridging between the catalyst and the naphthols to be coupled can be excluded for the *M*-selective prolinamines since the best ligand, **8c**, does not possess an acidic proton; for the *P*-selective ligands **9a**,**m** and **10b–f** ($NR^3R^4 = NH_2$), however, such an additional prefixation might be possible.

Furthermore, the screening revealed that there are significant differences between our prolinamines and the known diamines **3**[8] and **4**.[12] For example, both latter ligands require at least one secondary amino function for high levels of asymmetric induction, while **8c** has just tertiary ones. In addition, the optimum reaction conditions elaborated for diamine **4** (CuI, solvent MeCN) gave only unsatisfying results with our prolinamine **8c** (see Table 2, entries 4, 12, and 13).

Mechanistic and stereochemical considerations

Kozlowski et al.[12] did extensive studies on the mechanism of enantioselective, oxidative biaryl couplings[23] in the presence of their catalyst CuI•**4**, finding first order dependences on the oxygen and catalyst concentrations.[12d] Rate determining step of the catalytic cycle is the reoxidation of the catalyst by O_2,[12d] which presumably involves several oxygenated dimeric or oligomeric species.[24,25] The stereochemically decisive formation of the biaryl axis is proposed to proceed in two consecutive steps, a face-selective coupling of two naphthyl radicals,[26] of which at least one is chelated to a tetrahedral diamine–Cu-complex, followed by a central-to-axial chirality transfer upon rearomatization.[12c,27] Since the counter ion has no effect on the stereoselection, it is likely that the reaction takes place at a cationic metal complex.[12b] Finally, a positive nonlinear effect[28] was observed, hinting at dimeric or oligomeric catalyst species in solution.[12b] This assumption was furthermore corroborated by VPO measurements.[12b]

Our mechanistic studies started with the proof that the 64% ee in the product (*M*)-**2a**, as achieved with the catalyst CuCl•**8c**, is based on a stereodifferentiating coupling step, and not, as observed for couplings with stoichiometric amounts of chirally modified Cu-complexes,[9] on a non-stereoselective coupling followed by resolution or deracemization of the primarily formed, racemic biaryl. A mere diastereoselective crystallization of CuCl•**8c**•(*M*)-**2** can safely be excluded because the amount of (*M*)-**2** isolated was by far larger than the amount of catalyst used. A subsequent deracemization by atropodiastereomerization of configurationally unstable copper complexes, namely of CuCl•**8c**•(*M/P*)-**2** to CuCl•**8c**•(*M*)-**2**, can be ruled out since there was no change in the optical purity if scalemic or racemic **2a** were treated with the catalyst for several days.

A fully linear relationship between the enantiomeric excess of the prolinamine **8c** and the product **2a** was found (Figure 1). The absence of a nonlinear effect[28] makes the existence of dimeric or oligomeric catalyst species as well as a participation of two molecules of the catalyst in the stereochemically decisive biaryl coupling step unlikely (although both possibilities cannot fully be ruled out).

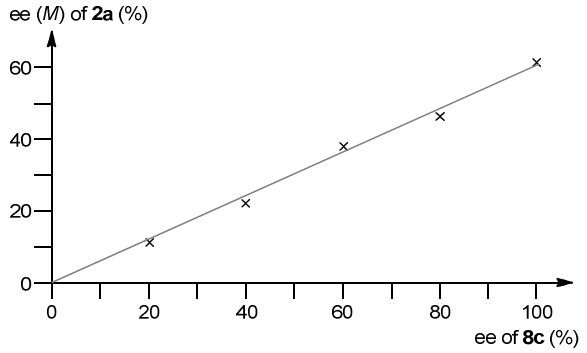
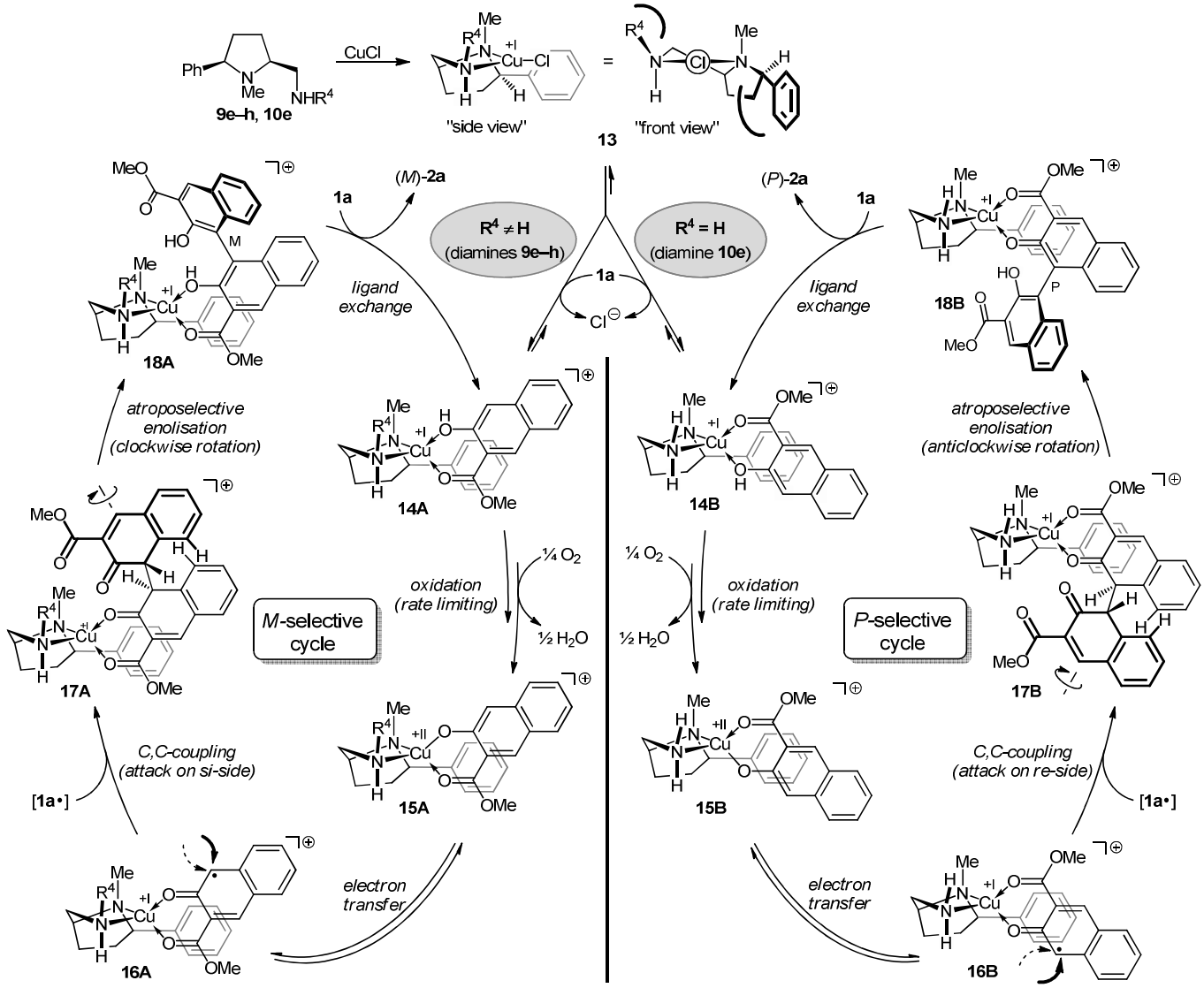


Fig. 1 Fully linear relationship between the enantiomeric excess of the prolinamine **8c** and the binaphthol **2a**.

Based on the aforementioned mechanistic investigations and our studies we propose the following mechanism for the oxidative biaryl couplings of **1a** in the presence of our prolinamine-derived copper catalysts (Scheme 2). For a simplification of the discussion, a phenyl group in 5-*cis* position (R^1 = Ph) and an *N*-methyl group at the pyrrolidine nitrogen atom (R^2 = Me), which are both essential for good levels of stereoselection, and a secondary or primary exocyclic amino function are set. The ligands **9e–h** (NR^3R^4 = NHR^4; R^4 = secondary alkyl, 58–61% ee in favor of *M*) and **10e** (NR^3R^4 = NH_2, 36% ee in favor of *P*) fulfill these premises. Taking the relative and absolute steric demands of the substituents R^1–R^4 into account, this mechanism can be extended to all prolinamines that provided significant levels of asymmetric induction.



Scheme 2 Proposed mechanism for the *M*- and *P*-selective oxidative biaryl couplings of **1a** in the presence of the prolinamines **9e–h** and **10e**.

Initial chelation of the chiral prolinamine to CuCl provides the bicyclic, C_1-symmetric complex **13**, to which the naphthol **1a** principally can bind in two different orientations, as illustrated in the tetrahedral[29] complexes **14A** and **14B**.[30] The preference for one or the other is controlled by steric factors. On side of the naphthol **1a**, the methoxy group of the ester function is more demanding than the two carbon atoms C-4 and C-4a of the aryl ring. On side of the chiral catalyst, it is reasonable that, in the energetically most favored conformation, the larger substituents at the two nitrogen atoms (R^4 and the annelated pyrrolidine) occupy opposite positions with respect to the central copper heterocycle and align pseudo-equatorially, as well as the phenyl group does. As a consequence of this arrangement depicted in **13**, the lower right quadrant is shielded by the phenyl group and the upper left one by R^4 (see "front view"). In the case of **10e** with R^4 = H, only the repulsion by the phenyl group exists, thus favoring the formation of **14B**, while in the cases of **9e–h** (R^4 = secondary alkyl), the higher steric demand of R^4 dominates, thus favoring the orientation shown in **14A**.

The following steps are identical for both catalytic cycles. Multistage[24] and rate-limiting[12d,25] oxidation of the copper(I) atom in **14** by O_2 affords the copper(II) complexes **15**, which can undergo electron transfer from the naphthol to the copper atom to give the naphthyl radicals **16**. In both complexes, the backside of the naphthyl radical is efficiently shielded by the phenyl group, possibly supported by some π-stacking, which directs the attack of a second naphthyl radical [**1a**•] to the front side, thus leading to **17**. It should be noted that the true nature of [**1a**•] is still unclear,[26] although the observed absence of a nonlinear effect (see Figure 2) makes a complexation of [**1a**•] to a second, chirally modified copper atom and, thus, a coupling between two molecules of **16**, unlikely.

During the rearomatization process via twofold ketoenol tautomerism, the two (pre)aromatic moieties have to rotate in order to reach the orthogonal alignment in biaryls. This rotation follows the pathway of the least steric hindrance, which means that the carbonyl groups pass each other and not the aromatic rings (repulsion of the *peri*-H).[12c,27] Consequently, the rotation is clockwise in **17A**, leading to *M*-configuration at the newly created biaryl axis in **18A**, whereas an anticlockwise rotation takes place in **17B**, creating the *P*-configured biaryl axis in **18B**. Final exchange of the binaphthol **2a** against naphthol **1a** completes the catalytic cycle. For the orientation of **1a** upon complexation, the very same steric arguments apply as in the chelation of **1a** to **13** giving **14A** and **14B**, respectively.

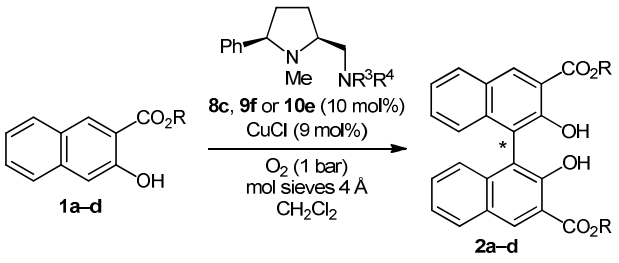
Since most of the prolinamines **8**–**10** used in this study favored the formation of (*M*)-**2a**, the top faces of the respective copper complexes must be more strongly shielded than the bottom faces, which forces the incoming naphthol **1a** to bind in the fashion shown in **14A**. This also means that the steric demand of the annelated, R^1-substituted pyrrolidine cannot be high, probably due to its pseudo-equatorial orientation with respect to the central copper heterocycle. The size of R^1 at this ring, however, exerts a drastic effect on the level of stereoselection. Since the same trends – decreasing the bulkiness of R^1 led to a reduced chirality transfer (see **8d**–**j**, Table 3, and **10a**–**f**, Table 5) – were observed for the *M*- and the *P*-directing prolinamines, this substituent cannot play an important role in the binding of **1a**, but must be decisive in the shielding of the backside of the complexed naphthyl radical in **16A** and **16B** (see Scheme 2), which is in good agreement with the mechanism proposed.

Consequences of the mechanism

Under the assumption that the backside-shielding in **16** and the central-to-axial chirality transfer occur highly selective, the resulting enantiomeric excess in the binaphthol **2a** is thus determined by the orientation of **1a** during binding to **18** (and **13** in the starting sequence). As a consequence, the enantioselection of the *M*-selective catalysts should increase if the steric differentiation in the naphthol substrate is more pronounced, which can be achieved by raising the steric bulk of the ester group at C-2. In order to consolidate this theory, we synthesized the naphthol esters **1b–d** and subjected these compounds to the coupling procedures (Table 6). And indeed, the levels of stereoselection significantly increased by using the sterically more hindered esters. The binaphthol **2d** (R = *t*Bu) was produced in good 78% and 75% ee with the prolinamines **8c** and **9f** as the chiral ligands (entries 4 and 8). This trend is in sharp contrast to the observations made in other oxidative biaryl couplings in the presence of diamine–copper catalysts, in which the chirality transfer dropped when the size of the ester group was increased.[8b,12c,14a,16] By lowering the reaction temperature to 0 °C, the enantiomeric excess in the CuCl•**8c** catalyzed coupling of **1d** to **2d** was further improved to 87%, without any noticeable loss in yield (96%, entry 9). The latter result is the best asymmetric induction so far reached with the naphthyl ester **1d**.

For the *P*-selective catalyst CuCl•**10e**, the enantioselection achieved with the methyl ester **1a** and the *t*-butyl ester **1d** was virtually identical (entries 10 and 11). This result is also in good agreement with the proposed catalytic cycle, since the interaction between the ester group and the chiral backbone is just weak (see **14b**, Scheme 2).

Table 6 Oxidative biaryl couplings of **1b–d** in the presence of the prolinamines **8c**, **9f** and **10e**



8c: $NR^3R^4 = NMe_2$; **9f**: NR^3R^4 = (*S*)-NHCH(Me)Ph; **10e**: $NR^3R^4 = NH_2$

Entry	Biaryl **1**, **2**	R	Diamine	Temp. (°C)	t (d)	Yield (%)[a]	ee (%)[b]	Config.
1[c]	**a**	Me	**8c**	20	3	91	64	*M*
2	**b**	*i*Pr	**8c**	20	3	94	69	*M*
3	**c**	Bn	**8c**	20	3	93	73	*M*
4	**d**	*t*Bu	**8c**	20	6	99	78	*M*
5[d]	**a**	Me	**9f**	20	3	72	61	*M*
6	**b**	*i*Pr	**9f**	20	5	94	75	*M*
7	**c**	Bn	**9f**	20	5	99	72	*M*
8	**d**	*t*Bu	**9f**	20	7	94	75	*M*
9	**d**	*t*Bu	**8c**	0	8	96	87	*M*
10[e]	**a**	Me	**10e**	20	3	85	36	*P*
11	**d**	*t*Bu	**10e**	20	5	99	36	*P*

[a] Isolated yield. [b] Determined by HPLC on chiral phase. [c] See Table 2, entry 19. [d] See Table 4, entry 6. [e] See Table 5, entry 8.

Conclusions

A series of 38 prolinamines **8**–**10**, which differ in the substituents R^1 at 5-*cis* position, R^2 at the pyrrolidine nitrogen atom, and R^3R^4 at the exocyclic amino function, were evaluated on their performance as chiral ligands in the copper-catalyzed oxidative biaryl coupling of the naphthol **1a**. Essential for good enantioselectivities were a 5-*cis*-phenyl (R^1) and an *N*-methyl group (R^2). With these two substituents given, the level and sense of the asymmetric induction can be steered by the NR^3R^4 group. Good 58–64% ee in favor of the *M*-enantiomer of **2a** were reached with the tertiary amine **8c** ($NR^3R^4 = NMe_2$) and the secondary amines **9e**–**h** ($NR^3R^4 = NHR^4$, with R^4 = secondary alkyl), while the *P*-enantiomer of **2a** was preferentially formed with the primary amine **10e** (36% ee, $NR^3R^4 = NH_2$). A mechanism, in which the steric demand of the NR^3R^4 group of the chiral ligand determines the orientation of **1a** upon complexation to the copper atom and, thus, the sense of the chirality transfer, was proposed. The 5-*cis*-phenyl group (R^1) plays the decisive role in the face-selective *C*,*C*-coupling step by shielding one side of the complexed naphthyl radical. As a consequence of the structure–enantioselectivity investigations, we concluded that naphthols with bulkier ester groups should permit better stereocontrol. And indeed, the enantiomeric excess of the oxidative coupling of **1d** (CO_2R = CO_2tBu) was improved to up to 87% ee by using CuCl•**8c** as the chiral catalyst.

Experimental

All reactions with moisture-sensitive reagents were carried out under an argon atmosphere in anhydrous solvents, prepared using standard procedures.[31] Commercially available reagents (highest quality available) were used as received. Reactions were monitored by thin layer chromatography on precoated silica gel (Macherey-Nagel, Alugram SIL G/UV254). Spots were visualized by UV light (254 nm) or by staining with aqueous $KMnO_4$, vanillin, or ceric ammonium molybdate. Silica gel (Macherey-Nagel, particle size 40–63 µm) was used for column chromatography. Melting points were measured on a Stuart SMP10 digital or a thermo scientific 9300 melting point apparatus and are uncorrected. Optical rotations were recorded on a Jasco P-1020 polarimeter (10 cm cell). NMR spectra were taken on a Bruker Avance 300, a Bruker Avance 400, or a Bruker Avance III HD 500 instrument and calibrated using the residual undeuterated solvent as an internal reference. The peak assignments in the ^{1}H and ^{13}C NMR data were made on basis of 2D NMR methods (COSY, HSQC, HMBC). Infrared spectra were recorded on a Jasco FT-IR-410 or a PerkinElmer Spectrum 100 FT-IR spectrometer, high resolution mass spectra on a Bruker Daltonics micrOTOF focus mass spectrometer using ESI (electronspray ionization). The enantiomeric excess of the binaphthols **2a**–**d** was determined by HPLC analysis (Waters Alliance HPLC; Waters 2695 Separation Module, Waters 2487 Dual λ Absorbance Detector) on chiral phase (Daicel Chiralpak AD-H).

The synthesis of **9f** and the general procedure for the oxidative biaryl coupling under optimized conditions are described here exemplary. For the preparation of all other new compounds, see Supporting Information.

(2*R*,5*S*)-1-Methyl-2-phenyl-5-((((*S*)-1-phenylethyl)amino)-methyl)pyrrolidine (9f)

NEt_3 (197 µL, 143 mg, 1.41 mmol) and MsCl (87.4 µL, 129 mg, 1.13 mmol) were added at 0°C to a solution of the alcohol **12**[19] (180 mg, 941 µmol) in anhydrous CH_2Cl_2 (8 mL). After 1 d at r.t., the solution was treated with (*S*)-1-phenylethylamine (2.40 mL, 2.28 g, 18.8 mmol) and stirring was continued for 5 d. The solvent was removed under reduced pressure and the crude material was directly subjected to column chromatography (1. silica gel, CH_2Cl_2/MeOH, 100:0–97:3, 2. silica gel, EtOAc). Filtration through a pad of basic alumina (activity I, CH_2Cl_2/MeOH, 9:1) delivered the prolinamine **9f** (205 mg, 697 µmol, 74%) as a yellowish oil.

R_f 0.65 (EtOAc). $[\alpha]_D^{21}$ 8.2 (*c* 0.50 in MeOH). IR (ATR) ν_{max}/cm^{-1} 2968w, 2784w, 1491w, 1450s, 1122w, 1041w, 1027w, 757s, 697vs. ^{1}H NMR δ_H(500 MHz; $CDCl_3$) 1.43 (3 H, d, *J* = 6.7 Hz, CHC*H*$_3$), 1.67 (1 H, m, 3-*H*H), 1.83 (1 H, m, 4-*H*H), 1.98 (1 H, m, 4-H*H*), 2.05 (1 H, m, 3-H*H*), 2.06 (3 H, s, 1-CH_3), 2.52 (1 H, dd, *J* = 11.1, 6.4 Hz, 5-C*H*H), 2.58 (1 H, m, 5-H), 2.75 (1 H, dd, *J* = 11.1, 3.1 Hz, 5-CH*H*), 3.27 (1 H, dd, *J* = 9.7, 6.7 Hz, 2-H), 3.82 (1 H, q, *J* = 6.7 Hz, C*H*CH_3), 7.26 (2 H, m, Ar-H), 7.33 (8 H, m, Ar-H) ppm. ^{13}C NMR δ_C(125 MHz, $CDCl_3$) 24.4 (CH*C*H$_3$), 28.1 (C-4), 34.3 (C-3), 39.3 (1-CH_3), 50.7 (5-CH_2), 58.8 (*C*HCH$_3$), 65.9 (C-5), 72.6 (C-2), 126.7, 127.0, 127.1, 127.4, 128.4, 128.6 (CH-Ar), 143.9, 145.9 (C_q-Ar) ppm. HRMS (ESI, pos.) *m/z* calcd for $C_{20}H_{27}N_2$ $[M + H]^+$ 295.2169, found 295.2169.

General procedure for the oxidative biaryl coupling under optimized conditions

Oxidative coupling: A solution of CuCl (4.46 mg, 45.0 µmol, 9 mol%) in MeCN (450 µL) was added to a solution of the prolinamine **8c** or **9f** (50.0 µmol, 10 mol%) in anhydrous CH_2Cl_2 (500 µL). After stirring for 20 min, the solvent was removed in vacuo and the residue was dissolved in anhydrous CH_2Cl_2 (1 mL) to give a greenish solution. The temperature was adjusted to 20 °C or 0 °C and the naphthol **1a**–**d** (500

µmol, 101 mg in the case of **1a**) and powdered mol sieves 4 Å (30 mg) were added. After 3–8 d under an O_2 atmosphere (1 bar), the reaction mixture was diluted with CH_2Cl_2 (5 mL) and directly subjected to column chromatography (for **2a**: silica gel, petroleum ether/EtOAc, 10:1–2:1; for **2b–d**: silica gel, petroleum ether/CH_2Cl_2, 3:1–1:9), delivering the product **2a–d**[8b] as a yellowish solid.

Enantiomer analysis: Sample preparation: The complete material of **2a–d** gathered from column chromatography was dissolved in CH_2Cl_2 (1 mL/10 mg). A small aliquot (50 µL) was taken, evaporated, and dissolved in MeOH (10 mL) under warming and ultra-sonification. This solution was directly used for HPLC analysis on chiral phase (Daicel Chiralpak AD-H). HPLC conditions: **2a**: *n*-hexane/*i*PrOH 8:2, 1.0 mL/min, 254 nm: t_R (*P*-enantiomer) = 8.8 min; t_R (*M*-enantiomer) = 14.3 min;[8b] **2b**: *n*-hexane/*i*PrOH 98:02, 1.0 mL/min, 254 nm: t_R (*P*-enantiomer) = 7.9 min; t_R (*M*-enantiomer) = 9.5 min; the absolute configuration of **2b** was determined after transesterification of **2b** into **2a**; **2c**: *n*-hexane/*i*PrOH 9:1, 1.0 mL/min, 254 nm: t_R (*P*-enantiomer) = 14.6 min; t_R (*M*-enantiomer) = 23.1 min;[8b] **2d**: *n*-hexane/*i*PrOH 98:02, 1.0 mL/min, 254 nm: t_R (*M*-enantiomer) = 6.8 min; t_R (*P*-enantiomer) = 7.6 min.[8b]

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Notes and references

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Copper complexes of 5-*cis*-substituted prolinamines provided up to 87% ee in the enantioselective oxidative biaryl coupling of 3-hydroxy-2-naphthoates.